

1    **Joint ACG/CAG antithrombotic CPG: evidence profiles**

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4    **A. MANAGEMENT OF PATIENTS ON ANTITHROMBOTIC (AT) AGENTS UNDERGOING ENDOSCOPY**  
5    **FOR ACUTE GIB**

6    *\*Patients hospitalized or under observation with acute overt GIB (upper and/or lower) manifesting as melena, hematochezia or hematemesis.*

7    PICOs

8    1.      GI bleeding: VKA reversal with FFP vs none

9    2.      GI bleeding: VKA reversal with PCC vs none

10   3.      GI bleeding: VKA reversal with PCC vs FFP

11   4.      GI bleeding: VKA reversal with vitamin K vs none

12   5.      GI bleeding: dabigatran reversal with idarucizumab vs none

13   6.      GI bleeding: rivaroxaban or apixaban reversal with andexanet vs none

14   7.      GI bleeding: any DOAC reversal with PCC vs none

15   8.      GI bleeding: antiplatelet reversal with platelet transfusion vs none

16   9.      GI bleeding: hold ASA vs continue ASA

17   10.     After GI bleeding: resume ASA same day as endoscopic hemostasis vs 1-7 days later

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1. GIB: FFP for reversal of VKA

## 1. GIB: Reversal of vitamin K antagonist with FFP

P: Patient with GIB currently taking warfarin

I: FFP

C: no reversal agents

O: **CRITICAL: Further** bleeding within 7 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days, transfusion-related event (congestive heart failure, pulmonary edema) within 7 days

### COMMENTS THAT RELATE TO MORE THAN ONE PICOs

**PICOs 1-9:** Further bleeding is defined as continued or recurrent bleeding that is clinically significant, i.e., with evidence of any of the following:

- Hemodynamic instability
- 2 gm or greater drop in Hg
- Necessity for endoscopic care, transfusion or hospitalization

**PICOs 1-4: Indirectness issue when assessing studies on VKA reversal in patients with intracranial bleed:** The speed of treatment is a critical factor for anticoagulated patients with intracranial hemorrhage (see intro in Vigue\_ ICM 2007<sup>11</sup>). However, the speed of (endoscopic) treatment and the speed of anticoagulant reversal seem to be less critical for anticoagulated patients with GI bleeding.

### **PICOs 1-3: Other factors (other than efficacy) influencing the choice between FFP and PCC:**

- Holbrook A et al. Evidence-based management of Anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e152S-e184S  
*"FFP has the disadvantage of potential allergic reaction or transmission of infection, preparation time, and higher volume."*  
*"Factor concentrates including PCC are expensive"*
- Sarode R et al. Rapid warfarin reversal: a 3-factor prothrombin complex concentrate and recombinant factor VIIa cocktail for intracerebral hemorrhage. J Neurosurg 2012 Mar;116(3):491-7  
*"Moreover, FFP transfusion has several disadvantages: 1) a delay in therapeutic effect because of the time required to obtain the ABO*

blood type and to thaw and transfuse several hundred milliliters of FFP; 2) the risk of transfusion-associated circulatory overload, especially in elderly patients with cardiac disease; 3) the risk of allergic reactions; 4) the risk of infection from exposure to multiple donors; and 5) transfusion-related acute lung injury, the most common cause of transfusion-related deaths in the US.”  
*“The PCCs can be reconstituted within minutes in a small volume of diluent (20–40 ml/dose) and can be infused rapidly (10 ml/minute) for partial or complete reversal of the warfarin effect without transfusion-associated circulatory overload. Importantly, there is minimal risk of transfusion-related acute lung injury, as PCCs lack anti-human leukocyte antigen/anti-granulocyte antibodies and carry a negligible risk for viral transmission due to the viral inactivation steps incorporated.”*

- Dentali F et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost* 2011; 106: 429–438 (**Dentali TH 2011**):

*“However, FFP is not optimal for immediate correction of VKA-associated coagulopathy because*

- *it may transmit infectious agents,*
- *it causes allergic reactions*
- *and volume overload,*
- *it rarely completely corrects the INR*
- *and unless a supply of thawed plasma is kept on hand, and its administration is delayed as it requires thawing and slow administration*

PCCs

- *Unlike FFP, PCCs are stored as lyophilized powders,*
- *and are not blood-group specific.*
- *In addition, PCCs contain a high clotting factor concentration which can be administered quickly in small volumes.*
- *As a result of these advantages, PCCs are thought to correct VKA-related coagulopathy more rapidly than FFP”*

- **Patient values and preferences**

#### **Patient values and preferences**

A supplementary search for patient values and preferences with regards to the critical outcomes of this guideline (GI bleeding and thromboembolic events) was conducted by one of the co-Chairs (Alan Barkun) in April 2021. The results, described in studies identified from the actual search or from a manual perusal of key cross-references, were presented and discussed in detail in the beginning the first voting meeting in May 8, 2021. A summary of the conclusions is shown below.

**Search strategy:**

Database: Embase <1996 to 2021 Week 17>, Ovid MEDLINE(R) without Revisions and Epub Ahead of Print, In-Process & Other Non-Indexed Citations <1996 to Present>

**Search Strategy:**

- 
- 1 (discrete adj25 choice adj25 experiment adj25 atrial adj25 fibrillation).tw. (10)
  - 2 (discrete adj25 choice adj25 experiment adj25 anticoagulation).tw. (8)
  - 3 (treatment adj25 preferences adj25 atrial adj25 fibrillation).tw. (76)
  - 4 (treatment adj25 preferences adj25 atrial adj25 fibrillation).tw. (76)
  - 5 (discrete adj25 choice adj25 experiment adj25 af).tw. (13)
  - 6 (discrete adj25 choice adj25 experiment adj25 ac).tw. (2)
  - 7 (dce adj25 atrial fibrillation).tw. (7)
  - 8 (dce adj25 anticoagulation).tw. (6)
  - 9 (dce adj25 atrial fibrillation).tw. (7)
  - 10 (dce adj25 anticoagulation).tw. (6)
  - 11 (treatment adj25 preference adj25 cardiac adj25 arrhythmia).tw. (0)
  - 12 (treatment adj25 preferences adj25 cardiac adj25 arrhythmia).tw. (0)
  - 13 (anticoagulant adj25 discrete adj25 choice).tw. (8)
  - 14 (anticoagulant adj25 patient adj25 preference).tw. (67)
  - 15 (discrete adj25 choice adj25 anticoagulation).tw. (12)
  - 16 (discrete adj25 choice adj25 anticoagulant).tw. (8)
  - 17 (conjoint adj25 preference adj25 anticoagulation).tw. (0)
  - 18 (trade off adj25 preference adj25 anticoagulation).tw. (0)
  - 19 (preference adj25 atrial fibrillation).tw. (171)
  - 20 (preference adj25 anticoagulation).tw. (252)
  - 21 (preference adj25 anticoagulant).tw. (151)
  - 22 or/1-21 (600)
  - 23 limit 22 to yr="2015 -Current" (366)
  - 24 remove duplicates from 23 (256)

It is critical for guideline panel members to have a good understanding of the values that patients place on the critical outcomes of this guideline (GI bleeding and thromboembolic events). This is a critical step in the Evidence to Decision Framework, prior to deciding if the balance between desirable and undesirable effects favors the intervention or the comparison. Guideline panel members need to be aware how much patients value each critical outcome (and what is their relative value/disutility: e.g., do patients place more value on the avoidance of stroke and less value on the avoidance of bleeding?). Guideline panel members also need to be aware if there is important uncertainty about or variability in how much people value the main outcomes.

Several studies have assessed values/disutilities for GI bleeding and thromboembolic events among patients on oral anticoagulation.

A well-done systematic review [Wilke 2017] included 27 studies from 12 different countries. These studies mainly assessed which benefits (mainly lower stroke risk) AF (atrial fibrillation) patients would require to tolerate harms (mainly higher bleeding risk) associated with an oral anticoagulant. “Most studies showed that patients were willing to accept higher bleeding risks if a certain threshold in stroke risk reduction could be reached”.

However, overall, there was **substantial variability** in patient values. In specific, there was substantial variability in the threshold number of bleeds observed for the acceptance of oral anticoagulation therapy (OAC) **between the different studies**:

- Alonso-Coello 2014 (Spain): “10 additional bleeds in 2 years for OAC acceptance”
- Devereaux 2001 (Canada): “17 additional bleeds in 2 years for OAC acceptance. The minimum required stroke prevention rate for the acceptance of OAC with its associated higher bleeding risk was 1.8 strokes per 100 patient years”
- Man-Son-Hing 1996 (Canada): “52% of AF patients would accept warfarin if associated with a 1 % stroke risk reduction over 2 years”
- Najafzadeh 2014 (US): “AF patients valued a 1 % increased risk of a fatal bleeding event the same as a 2 % increase in non-fatal myocardial infarction risk, a 3 % increase in non-fatal stroke risk, a 3 % increase in cardiovascular death risk, a 6 % increase in major bleeding risk, and a 16 % increase in minor bleeding risk”

Furthermore, there was **substantial variability** in the threshold number of bleeds observed for the acceptance of oral anticoagulation therapy (OAC), between participants within individual studies. Furthermore, country-specific differences exist in patients’ perceptions of atrial fibrillation, concerns about stroke, and preference for involvement in OAC treatment decisions; recent experience of stroke significantly influences patients’ values and preferences (Lane, 2018). Interestingly, in a mixed methods study of health-care providers assessing management of antithrombotic therapy after gastrointestinal bleeding, the most important factor influencing provider decision making was re-bleeding risk followed closely by thrombosis risk, although the indication For OAC was most important for a minority of respondents (Little DHW 2020).

Also, two studies showed that “methods used to elicit preferences significantly affected treatment health state valuations and treatment thresholds” (Locadia 2004; Man-Son-Hing M 2000).

These conclusions are in agreement with a previous systematic review (MacLean 2012) that concluded: “Patient values and preferences regarding thromboprophylaxis treatment appear to be highly variable. Participant responses may depend on their prior experience with the treatments or health outcomes considered as well as on the methods used for preference elicitation”.

Overall, after a discussion of the above findings, the panel members concluded that for most PICOs there is **possibly important uncertainty about or variability in how much people value the critical outcomes**.

## References

- Alonso-Coello P, Montori VM, Di’az MG, Devereaux PJ, Mas G, Diez AI, et al. Values and preferences for oral antithrombotic therapy in patients with atrial fibrillation: physician and patient perspectives. *Health Expect*. 2014;18(6):2318–27.
- Devereaux PJ, Anderson DR, Gardner MJ, Putnam W, Flowerdew GJ, Brownell BF, et al. Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ*. 2001;323:1218–22.

- Lane DA, Meyerhoff J, Rohner U, Lip GYH. Patients' Perceptions of Atrial Fibrillation, Stroke Risk, and Oral Anticoagulation Treatment: An International Survey. TH Open. 2018;2(3):e233-e241.
- Little DHW, Robertson T, Douketis J, Dionne JC, Holbrook A, Xenodemetropoulos T, Siegal DM. Management of antithrombotic therapy after gastrointestinal bleeding: A mixed methods study of health-care providers. J Thromb Haemost 2021;19(1):153-160
- Locadia M, Bossuyt PM, Stalmeier PF, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost 2004; 92 ( 6 ): 1336 - 1341 .
- MacLean S, Mulla S, Akl EA, Jankowski M, Vandvik PO, Ebrahim S, McLeod S, Bhatnagar N, Guyatt GH. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb;141(2 Suppl):e1S-e23S.
- Man-Son-Hing M, Laupacis A, O'Connor A, Wells G, Lemelin J, Wood W, et al. Warfarin for atrial fibrillation. The patient's perspective. Arch Intern Med. 1996;156:1841-8.
- Man-Son-Hing M, Laupacis A, O'Connor AM, Coyle D, Berquist R, McAlister F. Patient preference-based treatment thresholds and recommendations: a comparison of decision analytic modeling with the probability-tradeoff technique. Med Decis Making 2000; 20 ( 4 ): 394 - 403
- Najafzadeh M, Gagne JJ, Choudhry NK, Polinski JM, Avorn J, Schneeweiss SS. Patients' preferences in anticoagulant therapy: discrete choice experiment. Circ Cardiovasc Qual Outcomes. 2014;7:912-9.
- Wilke T, Bauer S, Mueller S, Kohlmann T, Bauersachs R. Patient Preferences for Oral Anticoagulation Therapy in Atrial Fibrillation: A Systematic Literature Review. Patient. 10 (1) (pp 17-37), 2017.

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75 **PICOs 1-4: Systematic search of previous clinical practice guidelines (see Appendix # 1 for methods)**

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77 **See Text box below** for an example of the approach of backwards (snowballing) citation searching for evidence in previous CPGs

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The most recent **ASGE clinical practice guideline (CPG)** was published in 2016 <sup>1</sup>

Their recommendation was *"we recommend either (1) 4-factor PCC and vitamin K or (2) fresh frozen plasma be given for life-threatening GI bleeding in patients on warfarin anticoagulant therapy. Moderate quality of evidence. Please note the ACCP only advocates option 1. The AHA/ACC supports option 1 or 2."*

The evidence profile tables were not shown but according to the main-text description of the evidence, this recommendation was based on the assessments of the evidence that were done by two previous CPGs: the **2014 AHA ACC CPG** <sup>2</sup> and the **2012 ACCP CPG** <sup>3</sup>. Both of these CPGs remain the most recent CPG versions of their respective organizations (these organizations have issued updated CPG, but the updates did not address the PICOs relevant to our CPG).

The 2016 ASGE CPG also cited 2 small studies: *"The risk of thromboembolic events was shown to be low in 2 small studies that withheld warfarin (Coumadin) for 4 to 15 days before endoscopy (1/27 patients and 0/28 patients, respectively)"*. However, these studies did not use reversal agents, therefore these studies cannot be used to estimate the risk of thromboembolic events with the use of reversal agents (as required for our PICOs).

The 2016 ASGE CPG also cited Sarode JN 2012 (Sarode R et al. Rapid warfarin reversal: a 3-factor prothrombin complex concentrate and recombinant factor VIIa cocktail for intracerebral hemorrhage. J Neurosurg 2012 Mar;116(3):491-7), that is discussed below. This study assessed the efficacy of the combination of 3F-PCC and recombinant factor VIIa in patients with intracerebral hemorrhage. No comparator cohort was used. No GIB patients.

Below we describe the evidence that the two previous CPGs (**2014 AHA ACC CPG** <sup>2</sup> and the **2012 ACCP CPG** <sup>3</sup>) used.

The **2014 AHA ACC CPG** <sup>2</sup> concluded that “*administration of FFP or PCC is reasonable in patients with mechanical valves and uncontrollable bleeding who require reversal of anticoagulation: level of evidence B (out of three levels: A, B and C)*”.

The supporting references were (a) a biochemical study on an irrelevant population and irrelevant interventions (cohort study of 19 non-bleeding patients, showing biochemical evidence of rebound hypercoagulability after planned cessation of VKA; no reversal agents were used <sup>4</sup>) and (b) a previous CPG, the 2016 French CPG <sup>5</sup>.

The **2016 French CPG** <sup>5</sup> concluded that “***besides VKA discontinuation, PCC should be administered immediately in association with 10 mg vitamin K supplement**, Grade of guidelines C (out of three grades: A, B, and C; C = low level of evidence); level of evidence 3 (out of four levels: 1, 2, 3, and 4; level 3 = case-control studies)*” and that “***FFP should be used only when PCCs are not available**. Grade of guidelines B (out of three grades: A, B, and C; B = presumption of scientific evidence); level of evidence 2 (out of four levels: 1, 2, 3, and 4; level 2 = RCTs of low power, properly conducted non-randomized controlled studies, Cohort studies)*”

The supporting references for adding Vit K to PCC were two small retrospective studies, one of which was a case report of 2 patients (Yasaka\_ AH 2003) <sup>6</sup> and the other was a retrospective cohort of 55 patients with intracerebral hemorrhage on VKA (Huttner\_ Stroke 2006) <sup>7</sup>. The latter study assessed the effect of reversal strategies (PCC, FFP, Vit K) on hematoma growth rate; however, in the PCC group, an unknown proportion of patients also received FFP or vit K, and in the FFP group an unknown proportion of patients also received FFP or vit K. Therefore, it is impossible to infer the efficacy or safety of each treatment or each combination of treatments. **In our view, these two studies do not provide any evidence either in favor of or against the recommendation to add vit K to PCC treatment. For the population of our own CPG (i.e., patients with GIB), these two studies would have been even less relevant** (due to additional serious indirectness).

The supporting references for the use of PCC were seven:

- 4 cohort studies <sup>8-11</sup> that did not have a comparator cohort of interest, but provided **evidence of rapid reversal of the INR, without documented thromboembolic events**. Total n=78 patients with major bleeding while on warfarin received PCC. 11/78 had GIB. 6/78 patients died (but this was not attributed to thromboembolic events). Possible transmission of parvovirus B-19 in 2 or 3 out of 20 pts in one study (Lubetsky\_ TR 2004) <sup>9</sup>.
- 3 comparative studies
  - two studies <sup>12,13</sup> did not use a combination of intervention/comparator that fits to the PICOs of our current CPG:
    - a 1997 cohort study (Makris\_ TH 1997) <sup>12</sup> compared FFP vs. “clotting factor concentrates”; it is unclear how similar this product is to existing PCC products
    - a small RCT (Boulis\_ NS 1999) <sup>13</sup> in 13 patients with intracranial hemorrhage and PT > 17 seconds compared FFP (n=8) vs FFP supplemented by PCC (n=5). Note that this comparator does not directly fit any of the PICOs in our CPG. There were 0/5 complications with FFP plus PCC; 5/8 experienced significant complications of fluid overload with FFP alone
  - one cohort study (Cartmill\_ BJN 2000) <sup>14</sup> of 12 patients on VKA with intracranial hemorrhage compared PCC vs FFP plus Vit K. One patient in the PCC group died, but there was no clear description of thromboembolic events

The **2012 ACCP CPG**<sup>3</sup> concluded that “For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with 4F-PCC rather than with FFP. (Grade 2C) (2 = weak recommendation; C = low quality of evidence, out of 3 levels A, B, C). We suggest the additional use of vitamin K (5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C)”

The supporting references were

- (a) three studies (2 cohort studies and 1 RCT) that compared 3F-PCC vs FFP in patients with intracranial hemorrhage
  - one cohort study (Cartmill\_ BJN 2000)<sup>14</sup>. Described above.
  - a second cohort study (Fredriksson K et al. Emergency reversal of anticoagulation after intracerebral hemorrhage. Stroke 1992;23(7):972-977), that showed that the INR faster with 3F-PCC than with FFP
  - one RCT (Boulis\_ NS 1999)<sup>13</sup>. Described above.
- (b) one RCT (Demeyere R et al. Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study. Vox Sang 2010; 99(3):251-260) that compared 4F-FFP with FFP in (non-bleeding) patients undergoing cardiopulmonary bypass surgery, and showed that the INR faster with 3F-PCC than with FFP.

79

## 80 COMMENTS SPECIFIC TO PICO 1

81 No eligible studies in patients with GI bleeding were identified by our primary literature searches:

- 82 • No RCTs
- 83 • The observational studies that were identified were cohort studies without comparator arm (the comparator needed here was a
- 84 compactor arm with no reversal agent) and/or did not report separate results for clinical outcomes in patients with GI bleeding. Such
- 85 cohort studies cannot provide any evidence on the direction (let alone the magnitude) of the effect that PPC had on clinical outcomes in
- 86 patients with GI bleeding; it is impossible to infer if PPC benefitted, harmed or made no difference in these patients compared to not
- 87 using PCC.

88

89 Therefore, we conducted additional literature searches for systematic reviews (SRs) on warfarin (not limited by GI bleeding) back to 1985, but  
90 still no evidence about clinical outcomes was found.

91

92 We also conducted a literature search of previous clinical practice guidelines (CPGs). We identified CPGs that used systematic literature searches  
93 and addressed questions similar to the PICO questions of our CPG. Initially, we had been hoping to find previous CPGs that used the full GRADE  
94 approach along with published evidence profiles that we would adopt accordingly (especially for the domain of indirectness of population).  
95 However, with a few notable exceptions, such as the American Society of Hematology (ASH)<sup>1</sup> and the American College of Chest Physicians  
96 guidelines (ACCP)<sup>2</sup>, evidence profiles were not available.

97



98 We assessed the studies that were cited as the evidence supporting recommendations to use FFP for VKA reversal in previous CPGs, in mixed  
99 populations (not restricted to GI bleeding). We reviewed the cited studies and the reference list of the cited studies. We assessed more than 60  
100 CPGs from various GI and non-GI organizations going back to 1998. No CPG cited any study that compared FFP to no reversal agent. The most  
101 recent CPGs cited comparative studies of FFP vs PCC (for a SRMA of such studies see Chai-Adisaksopha TH 2016<sup>15</sup>). The older CPGs cited  
102 previous CPGs, which cited even older CPGs, most of which did not cite any supportive studies for use of FFP. The observational study that was  
103 most frequently cited as support for the use of FFP was Makris TH 1997<sup>12</sup>. See below  
104

105 **Makris TH 1997<sup>12</sup>**

- 106 • Cohort study, unclear if it is prospective or retrospective
- 107 • N=41 patients on VKA requiring rapid reversal
- 108 • 12 patients received **FFP**
- 109 • 29 patients received **“clotting factor concentrates”** (unclear how similar this product is to current PCC products)
- 110 • All patients received intravenous vitamin K, 1-5 mg
- 111 • No clinical outcomes
- 112 • The mean pre-treatment INR of the 12 patients who received FFP was 10.2 (range 2.9-22.0). 15 min post FFP infusion the  
113 mean INR was 2.3 (range 1.6-3.8). *“In the 12 patients given FFP, the INR did not completely correct (range 1.6-3.8, mean 2.3)*  
114 *indicating an ongoing anticoagulated state in all.”*
- 115 • See table 1 in this paper, last column (INR, pre post)

116  
117  
118 The only observational study that assessed and reported clinical outcomes for the comparison of FFP vs no FFP in a mixed population of patients  
119 with VKA-related severe bleeding was Moustafa TR 2018<sup>18</sup>. As we describe below, this only provided very low certainty evidence, and only for  
120 mortality and thromboembolism, therefore there was still a need for further evidence.

121 Given that it was very unlikely that we would not find any further comparative data on the clinical efficacy of FFP use vs no use of FFP, even if we  
122 included mixed populations of patients with VKA-related severe bleeding (not limited to GI bleeding), we decided to also use single-cohort data  
123 from studies that compared FFP with PCC, and assess the results on the surrogate outcome of INR correction.

There were two options for collecting FFP arms from comparative studies (FFP vs PCC): either through a SR of observational studies or through a SR of RCTs. No recent and well-conducted SR of observational studies was available (the most recent, well-conducted SR did their search in 2015: Chai-Adisaksopha TH 2016<sup>15</sup>), while we had already conducted own updated SR of such RCTs (see PICO 3). Therefore, we decided to utilize the FFP arms of RCTs for PICO 1. The results of the observational studies with regards to the effect on INR were at the same direction as in the RCTs; for example, see above the table from Makris TH 1997.

Therefore, we included the 2 RCTs that compared FFP vs PCC in mixed populations<sup>16, 17</sup>, as well as an RCT that was excluded from PICO 3 (because there was no PCC-alone arm)<sup>13</sup>.

### Case-control studies with the comparator exposure required for this PICO

1. **Moustafa TR 2018** (Moustafa et al. Management and outcome of major bleeding in patients receiving vitamin K antagonists for venous thromboembolism. Thrombosis Research. 171 (pp 74-80), 2018)<sup>18</sup>

- Design: case-control and cohort study analyses conducted on a cohort from multi-institutional multi-national registry
  - The adjusted analyses relevant to this PICO were conducted by the authors as **case-control** analyses (reported as odds ratios)
  - The raw data were available too; however, we could not extract clean data for patients who only had FFP did not have any other reversal agents, other than vitamin K) or patients who did not have any reversal agent (other than vitamin K)
- N= 267 patients who had major bleeding while receiving VKA for VTE.
  - 78 patients had GI bleeding, but there were no separate results for the outcomes required for this PICO
- Multivariable analysis (case control analyses) showed that
  - vitamin K use was associated with lower risk of mortality (OR: 0.47; 0.24–0.92)
  - FFP use was associated with higher risk for thrombotic events (OR: 4.22; 95% CI: 1.25–14.3)
- **Indirectness concern:** Neither the exposure or the non-exposure is direct in the analyses. The exposure was FFP but some of these patients may have used other reversal agents: non-exposure was not “no reversal agent”, because some of these patients may have also used reversal agents other than FFP. Furthermore, only 2 reversal agents were included in the multivariable analysis (see next comment).
- **Serious concerns about the multivariable analysis**
  - The number of cases was too small (13 thrombotic events and 59 deaths) to allow adding all variables in the analysis.

- Several variables were captured and proposed for inclusion, but the variables that were risk factors for thromboembolism or death were not reported exhaustively -only examples were presented.
- The authors stated that “all variables achieving a significance level of  $\leq 0.1$  on univariate analysis were considered for inclusion in the logistic regression model”. Only 5 variables achieved that significance level, and eventually those 5 plus 2 additional variables were included in the multivariable model. This approach excluded important confounders from the multivariable analysis.
- The inadequate adjustment was evident when we calculated the unadjusted odds ratios from the raw data (table 4 in that paper) and found that the results were almost identical with the adjusted results in from the multivariable analysis (table 4 in that paper). For example, for the association of FFP use and risk of thromboembolism
  - Unadjusted OR: 4.3, 95% CI 1.3 - 14.1
  - Adjusted OR: 4.22, 95% CI 1.25 - 14.3

#### Cohort-type data without the comparator exposure required for this PICO

All three studies are RCTs that provided cohort-type data (we used only the FFP arm from each study)

1. **Sarode Circulation 2013** (Sarode et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: A randomized, plasma-controlled, phase IIIb study. Circulation 2013)<sup>16</sup>
  - 202 patients on VKA with **INR  $\geq 2.0$**  (within 3 hours before study treatment) and major bleeding
    - For this PICO, only the FFP arm (n=104) was used. 58/104 patients had GI bleeding
  - both arms received Vit K (5-10 mg) by slow IV infusion
  - Outcomes:
    - “**hemostatic efficacy**” at 24 hours
      - assessed by a blinded, independent Endpoint Adjudication Board: assigned a poor/none hemostatic efficacy rating if the management required administration of any hemostatic products other than study product or packed red blood cells within 24 hours after the start of study product infusion.
      - separate results for patients with GI bleeding (see suppl table 6 in suppl material in this paper)
    - **thrombotic events** at 45 days (the investigators recorded all thrombotic events up to day 10; from day 11 to day 45, they only recorded the thrombotic events that qualified as serious adverse events)

- all patients: 8/103 (PCC) vs 7/109 (FFP)
  - no separate results for patients with GI bleeding
  - **Mortality** at 30 days (mortality at 45 days was also reported)
    - all patients: 6/103 (PCC) vs 5/109 (FFP)
    - no separate results for patients with GI bleeding
  - Fluid overload (unclear timing, either at 10 days or at 45 days)
    - all patients: 5/103 (PCC) vs 14/109 (FFP)
  - “Rapid INR reduction” (proportion of patients with INR  $\leq 1.3$  at 0.5 hour after the end of infusion)
    - all patients: 61/103 (PCC) vs 10/109 (FFP)
    - See figure 2A, page 1240 in that paper
2. **Steiner LN 2016.** (Steiner T, Poli S, Griebel M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. Lancet Neurol. 2016;15(6):566-573) <sup>17</sup>
- **Serious indirectness:** 50 patients with VKA related intracranial hemorrhage who presented within 12 h after symptom onset with an INR of at least 2.0.
  - 4F-PCC vs FFP
    - If the primary endpoint was not reached (INR  $\leq 2.0$  at 3 h after the start of treatment), additional PCC was given in both arms.
  - All patients also received 10 mg of intravenous vitamin K
  - **For this PICO, only the FFP arm (n=23) was used.**
    - Thromboembolic events at 60 days: 2/23
    - Mortality at 30 days: 8/23
    - Proportion of patients with an INR  $\leq 2.0$  at 3 h after the start of treatment: 2/23
    - Proportion of patients with an INR  $\leq 1.2$  at 30 min after the start of treatment (post hoc analysis): 0/19
3. Boullis\_ NS 1999 <sup>13</sup>
- N=13 patients with intracranial hemorrhage and PT > 17 seconds
  - Compared FFP (n=8) vs FFP supplemented by PCC (n=5)

- All patients received vitamin K subcutaneously
- **For this PICO, only the FFP-alone arm (n=8) was included**
  - 5/8 experienced significant complications of fluid overload
  - 1/8 had a thromboembolic event (MI)
  - 3/8 died
  - The effect of FFP on INR can be seen in Figure 2, page 1116 in that paper.

#### Overall:

- In total the 3 cohort-type data from the 3 studies <sup>13,16,17</sup> included 135 patients treated with FFP (for safety outcomes there were 5 more patients included in the analyses). The patients had been on warfarin and experienced major bleeding.
- 58/135 had GI bleeding
- All patients received FFP (various doses and dosing protocols).
- Vitamin K was administered to all patients
- **Clinical outcomes**
  - Further bleeding: 14/58 (Sarode 2013) for the patients with GI bleeding
  - Mortality: 16/140 for the whole population (mixed, GI bleeding and other bleeding)
  - Thromboembolic events: 10/140 for the whole population (mixed, GI bleeding and other bleeding)
  - Transfusion-related events: 19/117 (Sarode 2013 and Boulis 1999)
- **Surrogate outcomes**
  - INR change. All studies showed that FFP infusion led to INR reduction (although the effect was not as consistent and large as with PCC, see PICO 2). See above for tables and figures from the included studies. Given the large body of evidence on the pharmacodynamics of warfarin treatment, is it implausible that this change in INR could have happen due to bias, confounding or chance. Of course, INR change is surrogate outcome, and furthermore it is an outcome that was included in the evidence profile by a post hoc decision.

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Risk of bias assessment of case control studies						
Study	Cases and controls similar for risk of exposure (or adjusted adequately for confounders)	Methods to determine exposure valid and similar for cases and controls	Methods to ascertain outcome of interest valid and similar for cases and controls	Incomplete/missing data addressed	Other bias	Comments
Moustafa TR 2018	Not similar, not adjusted adequately (see description of the study)	OK	OK	Unclear	OK	
<div>Low risk of bias</div> <div>Unclear risk of bias</div> <div>High risk of bias</div>						

Risk of bias assessment of cohort-type data studies							
Study	Valid methods to ascertain exposure (exposure = FFP)	<b>Prognostic factors</b> (other than exposure of interest) <b>similar</b> among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Sarode Circulation 2013		Without the comparative cohort required for this PICO		Without the comparative cohort required for this PICO	Without the comparative cohort required for this PICO		Only one of the arms of this RCT was included, as a single non-comparative cohort study.
Steiner LN 2016		Without the comparative cohort required for this PICO		Without the comparative cohort required for this PICO	Without the comparative cohort required for this PICO		Only one of the arms of this RCT was included, as a single non-comparative cohort study.
Boulis NS 1999		Without the comparative cohort required for this PICO		Without the comparative cohort required for this PICO	Without the comparative cohort required for this PICO		Only one of the arms of this RCT was included, as a single non-comparative cohort study.
<div>Low risk of bias</div> <div>Unclear risk of bias</div> <div>High risk of bias</div>							

243 Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included,  
 244 because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid  
 245 methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of  
 246 interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not  
 247 included, because it is an “indirectness” issue as per GRADE.

248 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
 249 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias.

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## 253 Evidence profile, PICO 1

Patients with GI bleeding: VKA reversal with FFP vs. no reversal agents												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	<u>Overall</u> certainty of evidence	FFP	no reversal agents	Relative (95% CI)	Absolute (95% CI)	
Further bleeding at 7 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
Single-cohort type data from one study (Sarode 2013) <sup>16</sup>	Serious <sup>a</sup>	Not applicable	Serious <sup>b</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		14/58 (24.1%)	-	-	-	
Thrombotic events within 30 days (critical outcome)												
Single-cohort type data from 3 studies <sup>13, 16, 17</sup>	Serious <sup>a</sup>	Not serious	Serious <sup>d</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		10/140 (7.1%)	-	-	-	
1 case control study (Moustafa TR 2018) <sup>18</sup>	Serious <sup>e</sup>	Not applicable	Very serious <sup>f</sup>	Serious <sup>g</sup>	None	⊕⊕⊕⊕ VERY LOW		-	-	Adjusted OR 4.22 (1.25 -14.3)	-	OR larger than 1 means that FFP use was associated with higher incidence of thrombotic events
Mortality within 30 days (important outcome, but not critical for decision making)												

Single-cohort type data from 3 studies <sup>13, 16, 17</sup>	<b>Serious</b> <sup>a</sup>	Not serious	<b>Serious</b> <sup>d</sup>	<b>Very serious</b> <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		16/140 (11.4%)	-	-	-	
<b>Transfusion-related events (fluid overload) within 7 days</b> (important outcome, not critical for decision making)												
Single-cohort type data from 2 studies (Boulis 1999, Sarode 2013) <sup>13, 16</sup>	<b>Serious</b> <sup>a</sup>	Not serious	<b>Serious</b> <sup>d</sup>	<b>Very serious</b> <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		19/117 (16.2%)	-	-	-	
<b>INR correction</b> (various target levels for INR, measured at various time points) (outcome included by <i>post hoc</i> decision; important, but not critical for decision making)												
Single-cohort type data from 3 studies <sup>13, 16, 17</sup>	<b>Serious</b> <sup>a</sup>	Not serious	<b>Serious</b> <sup>h</sup>	Not serious	None	⊕⊕⊕⊕ VERY LOW		Visual presentation (graphs)	-	-	-	-

## Footnotes

<sup>a</sup> Serious risk of bias, because the studies did not have comparator cohorts with no reversal agents.

<sup>b</sup> Serious indirectness of the outcome. The outcome of “hemostatic efficacy” as defined in Sarode 2013, was very different from the target outcome of this guideline, i.e., further bleeding. Furthermore, this outcome was only measured at 24 hours. Vitamin K was also administered to all patients, but we did not further rate down this outcome for this reason.

<sup>c</sup> Very serious imprecision, even for the event rate in the intervention group, due to small number of events. The comparative efficacy cannot be calculated.

<sup>d</sup> Serious indirectness of the population: only a small proportion of patients had GI bleeding. Vitamin K was also administered to all patients, but we did not further rate down this outcome for this reason.

<sup>e</sup> Serious risk of bias because of serious concerns about inadequate adjustment for confounders (see comments in the description of the study, above)

<sup>f</sup> Very serious indirectness of the population: patients in the FFP group could have received other reversal agents, while patients in the non-FFP group could have also received reversal agents other than FFP, and there was no reason to believe that such cointerventions were equally applied to both groups. Furthermore, only a proportion of patients had GI bleeding.

<sup>g</sup> Serious imprecision, due to small number of events.

<sup>h</sup> Serious indirectness of the outcome, because the speed of INR correction is a surrogate outcome and not a clinical outcome. The certainty of evidence was not further downrated for indirectness of population (most patients did not have GI bleeding) because the panel felt that it would be unlikely that the type of bleed would have influenced the effect of FFP on the INR. Vitamin K was also administered to all patients, but we did not further rate down this outcome for this reason.



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274 **Evidence to Decision Framework, PICO 1**

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276 01. Reversal of vitamin K antagonist with FFP

277 P: Patient with GIB currently taking warfarin

278 I: FFP

279 C: no reversal agents

280 O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein  
281 thrombosis, pulmonary embolus)

282 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days, transfusion-related events (congestive heart failure, pulmonary edema) within 7 days

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	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<b>How substantial are the desirable anticipated effects?</b> <ul style="list-style-type: none"> <li>o Trivial</li> <li>o Small</li> <li>o Moderate</li> <li>o Large</li> <li>o Varies</li> <li>● <b>Don't know</b></li> </ul>	<p>See Evidence Profile Table.</p> <p>The <u>desirable</u> anticipated effects with FFP use (compared to no treatment) are:</p> <ul style="list-style-type: none"> <li>- <b>INR correction</b> (post hoc outcome, not critical outcome) in a variable proportion of patients (post hoc outcome, not critical outcome)</li> </ul> <p>It is not possible to estimate the direction (let alone the magnitude) of the effect of FFP (vs. no FFP) on <b>clinical outcomes</b></p>	<p>There was a debate among panel members as to whether "INR correction" should be considered as a surrogate for "reduction of further bleeding" alone, vs. surrogate <b>both</b> for "reduction of further bleeding" and "increased thromboembolism".</p>
Undesirable Effects	<b>How substantial are the undesirable anticipated effects?</b> <ul style="list-style-type: none"> <li>o Large</li> <li>o Moderate</li> <li>o Small</li> <li>o Trivial</li> <li>o Varies</li> <li>● <b>Don't know</b></li> </ul>	<p>The only estimate of relative efficacy was regarding the <b>increased risk of thromboembolism (critical outcome)</b>, but the certainty of evidence for this was "extremely" low)</p> <p>With regards to the transfusion-related events (fluid overload), there are no comparative data, therefore some of the events may have not necessarily been caused by the FFP administration, however the CPG panel felt that the incidence of 16% is way higher than any decision threshold. Therefore, this outcome was also taken into consideration when the panel decided on the balance between desirable and undesirable effects.</p>	<p>The CPG panel also took into account the <b>increased risk of transmission of infectious agents with FFP administration</b> (evidence about this undesirable anticipated effect was not formally sought nor quantified, but the CPG panel acknowledged that this risk will be certainly higher compared to the zero risk of transmission of infectious agents when FFP is not administered)</p>

Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>● <b>Important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>	
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● <b>Probably favors the comparison</b></li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention (FFP)</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>● <b>Moderate costs</b></li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	The cost of FFR in Canada in 2018-19 was \$118 per Unit (300 ml)	

		<div>2018–2019 Blood Component Cost Per Unit Summary</div> <table><thead><tr><th>Blood Component</th><th>Unit of Measure</th><th>Cost Per unit</th></tr></thead><tbody><tr><td>Red Blood Cells</td><td>Unit</td><td>\$422</td></tr><tr><td>Apheresis Platelets</td><td>Dose</td><td>\$504</td></tr><tr><td>Apheresis Plasma for Transfusion</td><td>Unit (500ml)</td><td>\$449</td></tr><tr><td>Pooled Platelets</td><td>Dose</td><td>\$178</td></tr><tr><td>Frozen Plasma</td><td>Unit (300ml)</td><td>\$108</td></tr><tr><td>Cryosupernatant Plasma</td><td>Unit (280ml)</td><td>\$108</td></tr><tr><td>Concurrent Plasma</td><td>Unit (250ml)</td><td>\$114</td></tr><tr><td>Cryoprecipitate</td><td>Unit</td><td>\$122</td></tr></tbody></table>	Blood Component	Unit of Measure	Cost Per unit	Red Blood Cells	Unit	\$422	Apheresis Platelets	Dose	\$504	Apheresis Plasma for Transfusion	Unit (500ml)	\$449	Pooled Platelets	Dose	\$178	Frozen Plasma	Unit (300ml)	\$108	Cryosupernatant Plasma	Unit (280ml)	\$108	Concurrent Plasma	Unit (250ml)	\$114	Cryoprecipitate	Unit	\$122	
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Certainty of Evidence of Required Resources	<div>What is the certainty of the evidence of resource requirements (costs)?</div> <div><div><div></div><div>Very low</div></div><div><div></div><div>Low</div></div><div><div></div><div>Moderate</div></div><div><div></div><div>High</div></div></div> <div>No included studies</div>																													
Cost effectiveness	<div>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</div> <div><div><div></div><div>Favors the comparison</div></div><div><div></div><div>Probably favors the comparison</div></div><div><div></div><div>Does not favor either the intervention or the comparison</div></div><div><div></div><div>Probably favors the intervention</div></div><div><div></div><div>Favors the intervention</div></div></div> <div><div><div></div><div>Varies</div></div><div><div></div><div>No included studies</div></div></div>																													

Acceptability	<p>Is the intervention (FFP) acceptable to key stakeholders?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		
Feasibility	<p>Is the intervention (FFP) feasible to implement?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		

## Conclusions

**PICO: 01. For patients on warfarin who are hospitalized or under observation with acute GIB (upper and/or lower) should FFP administered compared to not administering reversal agents?**

**O: CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention 6/6 votes: 100%	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

<b>Recommendation</b>	For patients on warfarin who are hospitalized or under observation with acute GI bleeding, we <b>suggest against FFP</b> administration (conditional recommendation, very low certainty of evidence).
<b>Justification</b>	See EtD table above
<b>Subgroup considerations</b>	<p>Practically, a conditional recommendation against FFP use means that FFP should not be used routinely in patients with overt GI bleeding on VKA.</p> <p>It also means that FFP may still be used in a minority of such patients. Although there is no formal research evidence to guide the identification of the appropriate subgroups, the CPG panel suggested that FFP could still be administered in a minority of patients with <b>life-threatening</b> GI bleeding, especially if one or more of the following conditions is also met:</p> <ul style="list-style-type: none"> <li>• massive blood transfusion (which may worsen coagulopathy due to dilution of blood components)</li> <li>• unavailability of PCC</li> <li>• supratherapeutic INR with values substantially exceeding the therapeutic range</li> </ul>
<b>Implementation considerations</b>	
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?
<b>Research priorities</b>	Feasible research that will improve the ability of future panels to decide on this topic includes RCTs comparing FFP vs placebo in patients with acute GI bleeding on VKA. From an ethical perspective, it may be challenging to justify the inclusion of patients at the two extremes of prognosis (very high or very low risk of death from the GI bleed); for patients with life-threatening bleeding, well-designed observational studies may be the only feasible and ethical option.

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341 2. GIB: PCC for reversal of VKA

342 **2. GIB: Reversal of vitamin K antagonist with PCC vs none**

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344 P: Patient with GIB currently taking warfarin  
345 I: PCC  
346 C: no reversal agents  
347 O: **CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction,  
348 deep vein thrombosis, pulmonary embolus)  
349 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days, transfusion-related events (congestive heart failure, pulmonary edema) within 7 days  
350  
351  
352 **Note:** PCC is also referred as **factor IX complex** in older publications  
353

**Note:** The panel made an *a priori* decision to not address the issue of the comparison between 3F-PCC and 4F-PCC. In the description of the (non-comparative) studies, we made the distinction between 3F-PCC and 4F-PCC when this information is provided in the publications. However, in our recommendations the intervention is referred as “PCC”.

- A SRMA (Voils\_ TR 2012 <sup>10</sup>) that conducted a literature search in Nov 2011, did not identify any study (not even observational) that compared head-to-head 3F-PCC and 4F-PCC in any patient population.
- Our main literature search in patients with GI bleeding, did not identify any comparative studies either.
- The 2018 American Society of Hematology (ASH) guideline <sup>1</sup> refers only to 4F-PPC as intervention without any mention of 3F-PCC.
- Our backwards (snowballing) citation searching for evidence in previous guidelines identified one comparative observational study: Jones JTT 2016 <sup>11</sup>. This was a “propensity matched” cohort study in warfarin reversal in severe bleeding. It did not find a difference in the primary outcome of INR  $\leq 1.4$  between the two treatments. However, the study was underpowered. Most importantly, the planned propensity matching failed due to the small numbers of patients: 5% of patients in 3F-PCC group received FFP vs. 52% in the 4F-PCC group. Therefore, no safe conclusion can be derived from this study.

No eligible studies in patients with GI bleeding were identified by our primary literature searches:

- No RCTs
- The observational studies that were identified were cohort studies without comparator arm (we needed an arm that did not use any reversal agent, as required for this PICO question) and/or did not report separate results for clinical outcomes in patients with GI bleeding. Such cohort studies cannot provide any evidence on the direction (let alone the magnitude) of the effect that PPC had on clinical outcomes in patients with GI bleeding; it is impossible to infer if PPC benefitted, harmed or made no difference in these patients.

Therefore, we conducted a literature search of previous clinical practice guidelines (CPGs). We identified CPGs that used systematic literature searches and addressed questions similar to the PICO questions of our CPG. Initially, we had been hoping to find previous CPGs that used the full GRADE approach along with published evidence profiles that we would adopt accordingly (especially for the domain of indirectness of population). However, with a few notable exceptions, such as the American Society of Hematology (ASH) <sup>1</sup> and the American College of Chest Physicians guidelines (ACCP) <sup>2</sup>, such information was not available.

**With regards to PICO 2**, the backwards (snowballing) citation searching for evidence that was cited as support in previous CPGs led us to the 2016 French CPG <sup>3</sup>.

The **2016 French CPG** <sup>3</sup> concluded that “**besides VKA discontinuation, PCC should be administered immediately in association with 10 mg vitamin K supplement**, Grade of guidelines C (out of three grades: A, B, and C; C = low level of evidence); level of evidence 3 (out of four levels: 1, 2, 3, and 4; level 3 = case-control studies)” and that “**FFP should be used only when PCCs are not available**. Grade of guidelines B (out of three



388 *grades: A, B, and C; B = presumption of scientific evidence); level of evidence 2 (out of four levels: 1, 2, 3, and 4; level 2 = RCTs of low power,*  
389 *properly conducted non-randomized controlled studies, Cohort studies)"*

390 The supporting references **for adding Vit K to PCC** were two small retrospective studies, one of which was a case report of 2 patients (Yasaka\_ AH 2003) <sup>4</sup> and the other was a retrospective cohort of 55 patients with intracerebral hemorrhage on VKA (Huttner\_ Stroke 2006) <sup>5</sup>. The latter study assessed the effect of reversal strategies (PCC, FFP, Vit K) on hematoma growth rate; however, in the PCC group, an unknown proportion of patients also received FFP or vit K, and in the FFP group an unknown proportion of patients also received FFP or vit K. Therefore, it is impossible to infer the efficacy or safety of each treatment or each combination of treatments. **In our view, these two studies do not provide any evidence either in favor or against the recommendation to add vit K to PCC treatment. For the population of our own CPG (i.e., patients with GIB), these two studies would have been even less relevant** (due to additional serious indirectness).

397 The supporting references for the **use of PCC** were seven, four of which were cohort studies <sup>6-9</sup> that did not have the comparator cohort of interest (i.e., no treatment), but provided **compelling evidence of rapid reversal of the INR (surrogate outcome)**. These four studies were included in the evidence profile for PICO 2. See below.

400 We also included the cohort study that was identified for PICO 3 (VKA reversal with PPC vs FFP): Karaka AJRM 2014 <sup>12</sup> (see below). This study included patients with GI bleeding exclusively, and provided both clinical outcomes and results on INR reversal. However, for this PICO, this study was regarded as non-comparative cohort study. Only the PCC group was included.

403 Finally, we also included non-comparative cohort data derived from the PCC arms of the two RCTs that compared PCC vs FFP: Sarode Circulation 2013 <sup>13</sup>, Steiner LN 2016 <sup>14</sup> (see below, also see PICO 3). Such data were treated as cohort-type data without the required comparator, although they were derived from RCTs

406

#### 407 Cohort studies without the comparator cohort required for this PICO

408

409 4. **Yasaka\_TR 2005.** (Yasaka M, Sakata T, Naritomi H, Minematsu K. Optimal dose of prothrombin complex concentrate for acute reversal of oral anticoagulation. Thromb Res 2005;115:455–9) <sup>8</sup>

- 411 • N=40 patients with major bleeding on VKA (plus, 2 or 3 patients who did not have bleeding but required VKA reversal for urgent procedures)
- 412 • 2/40 patients had GI bleeding. Separate clinical outcomes were reported
- 413 • Cohort study, query prospective
- 414 • **There was no comparator (“no reversal agent”) cohort.** All patients received 4F-PCC, **with or without vit K**
- 415

- Compared different doses of PCC with/without Vit K, but no separate outcomes for GI bleeding. Also, unclear how the regimen was selected for each patient. No clear comparison between PCC plus vit K vs same dose PCC alone.
- **No** adverse effects including shock, allergy, or **thrombotic or embolic episodes** were not observed in the 42 patients
- **The effect PCC infusion on INR** was dramatic and consistent: see figure 4 in that paper.

5. **Evans\_ BJH 2001.** (Evans G, Luddington R, Baglin T. Beriplex P/N reverses severe warfarin-induced overanticoagulation immediately and completely in patients presenting with major bleeding. Br J Haematol 2001;115:998–1001) <sup>6</sup>

- N=10 patients with bleeding on VKA and INR >14
- The bleeding was stated as “major” but no definition of severity was provided. One patient had epistaxis, i.e., unlikely to have been a major bleed
- 3 patients had melena and 1 had hematemesis, but no separate outcomes were reported
- Cohort study, query prospective
- **There was no comparator (“no reversal agent”) cohort.** All patients received 4F-PCC **plus IV vit K**
- No thromboembolic complications
- The effect PCC infusion on INR was dramatic and consistent: see table 1 in that paper.

6. **Lubetsky\_ TR 2004.** (Lubetsky A, Hoffman R, Zimlichman R, Eldor A, Zvi J, Kostenko V, et al. Efficacy and safety of a prothrombin complex concentrate (Octaplex) for rapid reversal of oral anticoagulation. Thromb Res 2004;113:371–8) <sup>7</sup>

- N=10 patients with major bleeding on VKA and INR >5, (also, 10 patients who required VKA reversal for urgent medical procedures)
- 5/10 patients had GI bleeding. Separate clinical outcomes were reported
- Cohort study, prospective
- **There was no comparator (“no reversal agent”) cohort.** All patients received 4F-PCC
  - **Vit K** was administered at the discretion of the local study physician.
- No adverse events (2/20 patients died, but on both occasions, death was assessed as unrelated to Octaplex administration)
- Assessed viral safety: possible transmission of parvovirus B-19 in 2 or 3 out of 20 pts, i.e., among 10 patients with bleeding and 10 patients undergoing urgent medical procedures

- The effect PCC infusion on INR was dramatic and consistent: see figure 1 in that paper.

7. **Vigue\_ ICM 2007** (Vigue B, Ract B, Tremey B, et al. Ultra-rapid management of oral anticoagulant therapy-related surgical intracranial hemorrhage. Intensive Care Med 2007;33: 721–5) <sup>9</sup>

- N=18 patients on VKA and intracranial hemorrhage requiring urgent neurosurgical intervention
- Cohort study, prospective
- **There was no comparator (“no reversal agent”) cohort.** All patients received 4F-PCC **plus Vit K 5 mg** via NG tube.
- **No hemorrhagic or thrombotic adverse effect was observed intra- or postoperatively** following anticoagulation reversal by PCC, although systematic morphologic investigations were not performed.
- 4/18 patients died during the 6-month follow-up
- The effect PCC infusion on INR was dramatic and consistent: see figure 1 in that paper

8. **Karaka AJRM 2014.** (Karaca et al. Use and effectiveness of prothrombin complex concentrates vs fresh frozen plasma in gastrointestinal hemorrhage due to warfarin usage in the ED. American Journal of Emergency Medicine. 32 (6) (pp 660-664), 2014) <sup>12</sup>

- Design unclear. The authors describe it as “prospective cohort study of consecutive patients alternately selected by the authors”. It could also be considered a non-randomized clinical trial. The certainty of the evidence derived from this study is very low regardless of the design assigned.
- Consecutive patients with INR > 2.1 due to warfarin use, and GI bleeding that received either PCC or FFP.
- 20 each in the PCC and FFP groups. **For this PICO, we only included the PCC cohort.**
- All patients had 10 mg vitamin K1 intravenously
- n=0 with active bleeding (Forrest 1) in the PCC group
  - Note: the Forrest classification was reported as outcome, not as baseline characteristic, because “upper endoscopy was performed on patients after their INR reached an efficient level (INR <2.1)” “On average, upper endoscopy was performed 8 h (range: 6-12 h) after admission in the PCC group”
- n=0 in the PCC group underwent invasive/surgical treatment
- Thromboembolic outcomes were not mentioned
- For the PCC group, the mean INR levels at 2 hours and 6 hours dropped as shown in figure 3 in that paper

- 471
- 472 9. **Sarode Circulation 2013** (Sarode et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K
- 473 antagonists presenting with major bleeding: A randomized, plasma-controlled, phase IIIb study. Circulation 2013)<sup>13</sup>
- 474 a. 202 patients on VKA with **INR  $\geq 2.0$**  (within 3 hours before study treatment) and major bleeding
- 475 b. For this PICO, only the PCC arm (n=98) was used.
- 476 c. included **113** patients with GI bleeding (see suppl material)
- 477 i. 4F-PCC: 55 patients with GI bleeding.
- 478 ii. FFP: 58 patients with GI bleeding
- 479 d. both arms received Vit K (5-10 mg) by slow IV infusion
- 480 e. Outcomes:
- 481 i. **“hemostatic efficacy”** at 24 hours
- 482 1. assessed by a blinded, independent Endpoint Adjudication Board: assigned a poor/none hemostatic efficacy
- 483 rating if the management required administration of any hemostatic products other than study product or
- 484 packed red blood cells within 24 hours after the start of study product infusion.
- 485 2. separate results for patients with GI bleeding (see suppl table 6 in suppl material in that paper)
- 486 ii. **thrombotic events** at 45 days (the investigators recorded all thrombotic events up to day 10; from day 11 to day 45,
- 487 they only recorded the thrombotic events that qualified as serious adverse events)
- 488 1. all patients: 8/103 (PCC) vs 7/109 (FFP)
- 489 2. no separate results for patients with GI bleeding
- 490 iii. **Mortality** at 30 days (mortality at 45 days was also reported)
- 491 1. all patients: 6/103 (PCC) vs 5/109 (FFP)
- 492 2. no separate results for patients with GI bleeding
- 493 iv. Fluid overload (unclear timing, either at 10 days or at 45 days)
- 494 1. all patients: 5/103 (PCC) vs 14/109 (FFP)
- 495 v. **“Rapid INR reduction”** (proportion of patients with INR  $\leq 1.3$  at 0.5 hour after the end of infusion)
- 496 1. all patients: 61/103 (PCC) vs 10/109 (FFP)
- 497 2. Also, see Figure 2A and 2B in that paper, page 1240.
- 498
- 499 10. **Steiner LN 2016**. (Steiner T, Poli S, Griebel M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with
- 500 intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. Lancet Neurol. 2016;15(6):566-573)<sup>14</sup>

- a. **Serious indirectness:** 50 patients with VKA related intracranial hemorrhage who presented within 12 h after symptom onset with an INR of at least 2.0.
- b. 4F-PCC vs FFP
  - i. If the primary endpoint was not reached ( $\text{INR} \leq 2.0$  at 3 h after the start of treatment), additional PCC was given in both arms.
  - ii. **For this PICO, only the PCC arm (n=27) was used.**
- c. All patients also received 10 mg of intravenous vitamin K
- d. Thromboembolic events at 60 days
  - i. 7/27 (PCC) vs 2/23 (FFP)
- e. Mortality at 30 days
  - i. 3/27 (PCC) vs 8/23 (FFP)
- f. Proportion of patients with an  $\text{INR} \leq 2.0$  at 3 h after the start of treatment:
  - i. 18/27 (PCC) vs 2/23 (FFP)
- g. Proportion of patients with an  $\text{INR} \leq 1.2$  at 30 min after the start of treatment (post hoc analysis)
  - i. 17/26 (PCC) vs 0/19 (FFP)

#### Overall:

- In total the 7 studies <sup>6-9, 12-14</sup> included 223 patients who were treated with PCC (228 patients for some safety analyses). The patients had been on warfarin and experienced major bleeding.
- 86/223 had GI bleeding
- All patients received 4F-PCC (various doses and dosing protocols).
- Vitamin K was also administered to most patients
- **Clinical outcomes**
  - Further bleeding: 14/55 (Sarode 2013) and 0/20 (Karaka 2014)
  - Mortality: 16/228 for the whole population (mixed, GI bleeding and other bleeding)
  - Thromboembolic events: 15/208 for the whole population (mixed, GI bleeding and other bleeding)
  - Transfusion-related events: 5/103 (Sarode 2013)
  - Other adverse events: Possible transmission of parvovirus B-19 in 2 or 3 out of 20 pts in one study (Lubetsky\_ TR 2004) <sup>9</sup>.
- **Surrogate outcomes (included by *post hoc* decision)**
  - INR change. All studies showed that PCC infusion led to INR reduction that was consistent, rapid and of large magnitude. See above for tables and figures from the included studies. Given the large body of evidence on the pharmacodynamics of warfarin

treatment, is it implausible that this dramatic change in INR could have happen due to bias, confounding or chance. Of course, INR change is surrogate outcome, and furthermore it is an outcome that was included in the evidence profile by a post hoc decision.

Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (exposure = PCC)	Prognostic factors (other than exposure of interest) <b>similar</b> among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Yasaka TR 2005		No comparative cohort		No comparative cohort	No comparative cohort		
Evans BJH 2001		No comparative cohort		No comparative cohort	No comparative cohort		
Lubetsky TR 2004		No comparative cohort		No comparative cohort	No comparative cohort		
Vigue ICM 2007		No comparative cohort		No comparative cohort	No comparative cohort		
Karaka AJRM 2014		Without the comparative cohort required for this PICO		Without the comparative cohort required for this PICO	Without the comparative cohort required for this PICO		Only one of the two cohorts of this study could be included.
Sarode Circulation 2013		Without the comparative cohort required for this PICO		Without the comparative cohort required for this PICO	Without the comparative cohort required for this PICO		Only one of the arms of this RCT was included, as a single non-comparative cohort study.
Steiner LN 2016		Without the comparative cohort required for this PICO		Without the comparative cohort required for this PICO	Without the comparative cohort required for this PICO		Only one of the arms of this RCT was included, as a single non-comparative cohort study.
Low risk of bias							
Unclear risk of bias							
High risk of bias							

Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included, because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not included, because it is an “indirectness” issue as per GRADE.

Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias.

## Evidence profile, PICO 2

Patients with GI bleeding: VKA reversal with PCC vs. no reversal agents												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	PCC	no reversal agents	Relative (95% CI)	Absolute (95% CI)	
Further bleeding at 7 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
Single-cohort type data from 2 studies (Sarode 2013; Karaka 2014) <sup>12, 13</sup>	Serious <sup>a</sup>	Serious <sup>b</sup>	Serious <sup>c</sup>	Very serious <sup>d</sup>	None	⊕⊕⊕⊕ VERY LOW		14/55 (25.5%)	-	-	-	
Thrombotic events within 30 days (critical outcome)												
Single-cohort type data from 6 studies <sup>6-9, 13, 14</sup>	Serious <sup>a</sup>	Not serious	Serious <sup>e</sup>	Very serious <sup>d</sup>	None	⊕⊕⊕⊕ VERY LOW		15/208 (7.2%)	-	-	-	
Mortality within 30 days (important outcome, but not critical for decision making)												
Single-cohort type data from 7 studies <sup>6-9, 12-14</sup>	Serious <sup>a</sup>	Not serious	Serious <sup>e</sup>	Very serious <sup>d</sup>	None	⊕⊕⊕⊕ VERY LOW		16/228 (7.0%)	-	-	-	
Transfusion-related events (fluid overload) within 7 days (important outcome, not critical for decision making)												
Single-cohort type data from 1 study (Sarode 2013 <sup>13</sup> )	Serious <sup>a</sup>	Not applicable	Serious <sup>e</sup>	Very serious <sup>d</sup>	None	⊕⊕⊕⊕ VERY LOW	5/103 (4.9%)	-	-	-		

INR correction (various target levels for INR, measured at various time points) (outcome included by <i>post hoc</i> decision; important, but not critical for decision making)											
Single-cohort type data from 7 studies <sup>6-9, 12-14</sup>	Serious <sup>a</sup>	Not serious	Serious <sup>f</sup>	Not serious	None	⊕⊖⊖⊖ VERY LOW	78/78 (100%) in 4 studies <sup>6-9</sup>  All or almost all participants in 3 studies <sup>12-14</sup>	-	-	-	-

## Footnotes

<sup>a</sup>Serious risk of bias. The studies did not have comparator cohorts with no reversal agents.

<sup>b</sup>Serious inconsistency in the (further) bleeding rate among the two studies: 14/55 (Sarode 2013) vs. 0/20 (Karaka 2014).

<sup>c</sup>Serious indirectness of the outcome. The outcome of “hemostatic efficacy” as defined in Sarode 2013, as well as the outcome of active bleeding visualized at upper endoscopy as defined in Karaka 2014, were very different from the target outcome of this guideline, i.e., further bleeding. Furthermore, this outcome was only measured at 24 hours. Vitamin K was also administered to all patients, but we did not further rate down this outcome for this reason.

<sup>d</sup>Very serious imprecision, even for the event rate in the intervention group, due to small number of events. The comparative efficacy cannot be calculated.

<sup>e</sup>Serious indirectness of the population. Only a small proportion of patients had GI bleeding. Vitamin K was also administered to most patients, but we did not further rate down this outcome for this reason.

<sup>f</sup>Serious indirectness of the outcome, because the speed of INR correction is a surrogate outcome and not a clinical outcome. The certainty of evidence was not further downrated for indirectness of population (most patients did not have GI bleeding) because the panel felt that it would be unlikely that the type of bleed would have influenced the effect of PCC on the INR. Vitamin K was also administered to most patients, but we did not further rate down this outcome for this reason.

## Evidence to Decision Framework, PICO 2

### 02. Reversal of vitamin K antagonist with PCC vs none

P: Patient with GIB currently taking warfarin

I: PCC

C: no reversal agents

O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

IMPORTANT, BUT NOT CRITICAL: mortality within 30 days, transfusion-related events (congestive heart failure, pulmonary edema) within 7 days



	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<p><b>How substantial are the desirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>	<p>See Evidence Profile Table.</p> <p>The <u>desirable</u> anticipated effects with PPC (compared to no treatment) are:</p> <p>- fast and very consistent <b>INR correction</b> (post hoc outcome, not critical outcome) in all or almost all patients</p> <p>It is not possible to estimate the direction of the effect of PPC (vs. no PCC) on <b>clinical outcomes</b> because there were no comparative studies.</p> <p>The point estimate of transfusion-related events (fluid overload) was 4.9% which was below the decision threshold for the guideline panel.</p>	
Undesirable Effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>		<p>Although the risk of transmission of infectious agents with PCC infusion is considered to be lower compared to FFP infusion. However, the risk with PCC is not zero (see Lubetsky TR 2004: possible transmission of parvovirus B-19 with PCC in 2 or 3 out of 20 pts, i.e., among 10 patients with bleeding and 10 patients undergoing urgent medical procedures)</p>
Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>See Evidence Profile Table.</p>	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>● <b>Important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>	

Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention (PCC)</li> <li>○ Favors the intervention</li> </ul> <ul style="list-style-type: none"> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>		
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>● <b>Moderate costs</b></li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> </ul> <ul style="list-style-type: none"> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>In Canada: Octaplex and Beriplex are approved by Health Canada.  <a href="https://www.nacblood.ca/resources/guidelines/PCC.html">https://www.nacblood.ca/resources/guidelines/PCC.html</a> Per Canada Blood Services, Octaplex and Beriplex are both priced at \$0.57 per IU</p> <p>Therefore, if the dosing regimen of Sarode 2013 is used (see Table 2 in that paper), for a patient with a weight of 75 Kg and INR 2-4, the cost will be CAD 1,068 or approximately USD 1,500</p>	
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● <b>Moderate</b></li> <li>○ High</li> </ul> <ul style="list-style-type: none"> <li>○ No included studies</li> </ul>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> </ul> <ul style="list-style-type: none"> <li>○ Varies</li> <li>● <b>No included studies</b></li> </ul>		

Acceptability	<p>Is the intervention (PCC) acceptable to key stakeholders?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		
Feasibility	<p>Is the intervention (PCC) feasible to implement?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		

## Conclusions

**PICO 02. For patients on warfarin who are hospitalized or under observation with acute GIB (upper and/or lower) should PCC be administered compared to no reversal agents?**

**O: CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days; transfusion-related events (congestive heart failure, pulmonary edema) within 7 days

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	We could not reach a recommendation for or against 6/6 votes: 100%	Conditional recommendation for the intervention	Strong recommendation for the intervention
	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Recommendation	For patients on warfarin who are hospitalized or under observation with acute GIB, we could not reach a recommendation for or against PCC administration.				

<b>Justification</b>	
<b>Subgroup considerations</b>	<p>The guideline panel did not have adequate evidence to judge the direction of the balance between desirable and undesirable effects with PCC administration and was reluctant to issue a favorable (conditional) recommendation, especially given the moderate resource requirements. On the other hand, the guideline panel implicitly took into consideration the evidence from the next PICO question that showed a balance in favor of PCC compared to FFP, and was reluctant to issue a (conditional) recommendation against PPC administration either.</p> <p>The guideline panel felt that although the majority of patients with GI bleeding on warfarin do not require PPC administration, a subpopulation of patients with life-threatening GI bleeding could still be treated with PCC, especially if one or more of the following conditions is also met:</p> <ul style="list-style-type: none"> <li>• massive blood transfusion (which may worsen coagulopathy due to dilution of blood components)</li> <li>• supratherapeutic INR with values substantially exceeding the therapeutic range</li> </ul>
<b>Implementation considerations</b>	
<b>Monitoring and evaluation</b>	<p>Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used?</p> <p>Was this discussion and setting documented?</p>
<b>Research priorities</b>	

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614

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3. GIB: PCC vs FFP for reversal of VKA

### 3. GIB: Reversal of vitamin K antagonist with PCC vs FFP

P: Patient with GIB currently taking warfarin

I: PCC

C: FFP

O: **CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days, transfusion-related events (congestive heart failure, pulmonary edema) within 7 days

**Note:** PCC is also referred as **factor IX complex** in older publications

**Note:** Co-interventions have not been explicitly stated: holding VKA treatment; vitamin K administration

**Note:** The panel made an *a priori* decision to not address the issue of the comparison between 3F-PCC and 4F-PCC. In the description of the (non-comparative) studies, we made the distinction between 3F-PCC and 4F-PCC when this information is provided in the publications. However, in our recommendations the intervention is referred as “PCC”.

- A SRMA (Voils\_ TR 2012 <sup>10</sup>) that conducted a literature search in Nov 2011, did not identify any study (not even observational) that compared head-to-head 3F-PCC and 4F-PCC in any patient population.
- Our main literature search in patients with GI bleeding, did not identify any comparative studies either.
- The 2018 American Society of Hematology (ASH) guideline <sup>1</sup> refers only to 4F-PCC as intervention without any mention of 3F-PCC.
- Our backwards (snowballing) citation searching for evidence in previous guidelines identified one comparative observational study: Jones JTT 2016 <sup>11</sup>. This was a propensity matched cohort study in warfarin reversal in severe bleeding. It did not find a difference in the primary outcome of INR  $\leq 1.4$  between the two treatments. However, the study was underpowered. Most importantly, the planned propensity matching failed due to the small numbers of patients: 5% of patients in 3F-PCC group received FFP vs. 52% in the 4F-PCC group. Therefore, no safe conclusion can be derived from this study.

**Our review of previous guidelines** (CPGs) revealed the American Society of Hematology (ASH) 2018 guidelines (Witt\_ ASH CPG\_ Blood Adv 2018)<sup>1</sup> that addressed a PICO that was similar to PICO 2 of our guideline (although the ASH PICO included cessation of VKA and IV vitamin K as concomitant treatment for both the intervention and the comparator arms):

“Question: For patients with life-threatening bleeding during VKA treatment of VTE, should 4-factor PCC vs FFP be used, in addition to cessation of VKA and IV vitamin K?  
Recommendation 17. For patients with life-threatening bleeding during VKA treatment of VTE who have an elevated INR, the ASH guideline panel suggests using 4-factor prothrombin complex concentrates (PCCs) rather than fresh-frozen plasma (FFP) as an addition to cessation of VKA and IV vitamin K (conditional recommendation based on very low certainty in the evidence about effects)”<sup>1</sup>

The team of the 2018 ASH CPG<sup>1</sup> did comprehensive literature searches (up to March 2017) and reported detailed evidence profiles  
<https://guidelines.gradepr.org/profile/e58f8d6b-8fd6-4164-b9da-2c62605e845c>

They identified a SRMA (Chai-Adisaksopha\_ TH 2016)<sup>2</sup> that included 2 “eligible” RCTs<sup>3,4</sup>, and identified an additional RCT<sup>5</sup> when they updated the search. All three RCTs had already been identified by our literature search and our backwards citation searching of previous papers.

However, in our opinion, one of these RCTs (Boulis\_ NS 1999)<sup>3</sup> was **not eligible**. It was a small RCT 13 in 13 patients with intracranial hemorrhage and PT > 17 seconds compared FFP (n=8) vs FFP supplemented by PCC (n=5). This comparator is different from the comparators in the PICO of the ASH guideline (or our guideline). It only provides indirect evidence favoring the combination of FFP plus PCC: there were 0/5 complications with FFP plus PCC; 5/8 experienced significant complications of fluid overload with FFP alone.

A Cochrane SRMA (Johansen\_ CDSR 2015)<sup>6</sup> that compared PCC vs any control treatment for reversal of VKA treatment in bleeding and non-bleeding patients, did not identify any additional trials

None of the SRMAs or older CPGs that we assessed had included any additional RCTs, not even RCTs in non-GI bleeding. Also, they did not include any additional comparative observational studies in GI bleeding.

We performed our own focused updated search (bleeding, not limited to GI patients) from 2017 to 2020 in PubMed only on February 11, 2020. (“prothrombin complex concentrate\*” OR PCC) AND (plasma OR FFP) AND (warfarin OR coumadin OR “vitamin K antagonist\*” OR VKA OR VKAs) AND (bleed\* or re-bleed\* or rebleed\* or hemorrhag\* or haemorrhag\*). This search did not reveal any new RCTs published since 2017.

## RCTs

11. **Sarode Circulation 2013** (Sarode et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: A randomized, plasma-controlled, phase IIIb study. Circulation 2013)<sup>4</sup>
  - a. 202 patients on VKA with **INR ≥2.0** (within 3 hours before study treatment) and major bleeding
  - b. included **113** patients with GI bleeding (see suppl material). Dosing of PCC and FFP weight based and varied by initial INR

- i. 4F-PCC: 55 patients with GI bleeding
- ii. FFP: 58 patients with GI bleeding
- c. Outcomes:
  - i. **“hemostatic efficacy”** at 24 hours
    - 1. assessed by a blinded, independent Endpoint Adjudication Board: assigned a poor/none hemostatic efficacy rating if the management required administration of any hemostatic products other than study product or packed red blood cells within 24 hours after the start of study product infusion.
    - 2. separate results for patients with GI bleeding (in suppl Table 6, in suppl material in that paper)
  - ii. **thrombotic events** at 45 days (the investigators recorded all thrombotic events up to day 10; from day 11 to day 45, they only recorded the thrombotic events that qualified as serious adverse events)
    - 1. all patients: 8/103 (PCC) vs 7/109 (FFP)
    - 2. no separate results for patients with GI bleeding
  - iii. **Mortality** at 30 days (mortality at 45 days was also reported)
    - 1. all patients: 6/103 (PCC) vs 5/109 (FFP)
    - 2. no separate results for patients with GI bleeding
  - iv. Fluid overload (unclear timing, either at 10 days or at 45 days)
    - 1. all patients: 5/103 (PCC) vs 14/109 (FFP)
  - v. **“Rapid INR reduction”** (proportion of patients with INR  $\leq 1.3$  at 0.5 hour after the end of infusion)
    - 1. all patients: 61/103 (PCC) vs 10/109 (FFP)
- d. **Indirectness issues:** both arms received Vit K (5-10 mg) by slow IV infusion. More patients in the PCC group did not receive vit K (4 vs. 2 in the FFP group). More patients in the PCC group received vit K by a non-intravenous route (8 vs. 3 in the FFP group). Not reported if any of these involved the GIB subjects.

12. **Refaai EMI 2017.** (Refaai et al. Four-Factor Prothrombin Complex Concentrate Reduces Time to Procedure in Vitamin K Antagonist-Treated Patients Experiencing Gastrointestinal Bleeding: A Post Hoc Analysis of Two Randomized Controlled Trials. Emerg Med Int 2017;ID8024356) <sup>8</sup>

- Overlapping study population with Sarode Circulation 2013. A choice had to be made about which of the two studies should be included, Refaai 2017 or Sarode 2013. **We decided to include Sarode 2013 because it provided results for a larger number of patients with GI bleeding.**



- Post hoc analysis of two RCTs (Goldstein 2015 and Sarode 2013) that evaluated the subset of patients at two US sites who had GI bleeding in either of the trials. Of note, in the original publication of one of these trials (Goldstein Lancet 2015) there was no mention of GI bleeding (it included patients needing urgent surgical or invasive interventions) and was not eligible for inclusion in the evidence base for our guideline.
- 42 patients with GIB: 22 received 4F-PCC; 20 received plasma
  - 37 of the patients were derived from Sarode Circulation 2013 (already included) and 5 patients from Goldstein Lancet 2015
- Outcomes: “infusion time”, “infusion volume”, “time to procedure”, “hemostatic efficacy”, “rapid INR reduction”
- **Indirectness issue:** both arms received Vit K, protocol not standardized

13. **Steiner LN 2016.** (Steiner T, Poli S, Griebel M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. Lancet Neurol. 2016;15(6):566-573) <sup>5</sup>

- **Serious indirectness:** 50 patients with VKA related intracranial hemorrhage who presented within 12 h after symptom onset with an INR of at least 2.0.
- 4F-PCC vs FFP
  - If the primary endpoint was not reached (INR  $\leq$  2.0 at 3 h after the start of treatment), additional PCC was given in both arms.
  - Dosing of PCC and FFP was weight based but not based on initial INR
- All patients also received 10 mg of intravenous vitamin K
- Thromboembolic events at 60 days
  - 7/27 (PCC) vs 2/23 (FFP)
  - Note: Ischemic stroke included as a thromboembolic event (1 in FFP only, 1 in FFP+PPC, 1 in PPC only). This risk may be higher in a patient population with an intracranial bleed.
- Mortality at 30 days
  - 3/27 (PCC) vs 8/23 (FFP)
- Proportion of patients with an INR  $\leq$  2.0 at 3 h after the start of treatment:
  - 18/27 (PCC) vs 2/23 (FFP)
- Proportion of patients with an INR  $\leq$  1.2 at 30 min after the start of treatment (post hoc analysis)
  - 17/26 (PCC) vs 0/19 (FFP)
- Transfusion related events: 1 transfusion related event (anaphylaxis) in the FFP group

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Risk of bias assessment of RCTs							
Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Comments
Sarode Circulation 2013 <sup>4</sup>	OK	OK	Not blinded - However, outcomes were <u>blindly</u> adjudicated by an independent board.	OK	OK	The choice of timing of the INR reduction outcome (0.5 hour after the <u>end</u> of infusion) would favor the FFP arm, because FFP infusions took longer to finish.	For hemostatic efficacy there is high risk of bias (performance bias) due to lack of blinding, even with the use of a blinded adjudication committee
Refaai EMI 2017 <sup>8</sup>	OK	OK	Not blinded - However, outcomes were <u>blindly</u> adjudicated by an independent board.	OK	OK	Possible selection bias due to the post hoc decision to include patients from 2 sites	<p>This study is a post hoc analysis two RCTs (Goldstein 2015 and Sarode 2013) that evaluated the subset of patients at two US sites who had GI bleeding in either of the trials (as bleeding events were not an inclusion criterion for the Goldstein 2015 study, such events were not systematically reported by all sites in that study). Together these 2 sites enrolled 30% of the total study population for the 2 studies.</p> <p>Goldstein 2015 was conducted in 33 sites (18 US sites), and Sarode was conducted in 36 sites in the US and Europe.</p> <p>This study cannot be pooled together with Sarode Circulation 2013 because of the largely overlapping populations</p> <p>For hemostatic efficacy there is high risk of bias (performance bias) due to lack of blinding, even with the use of a blinded adjudication committee</p>

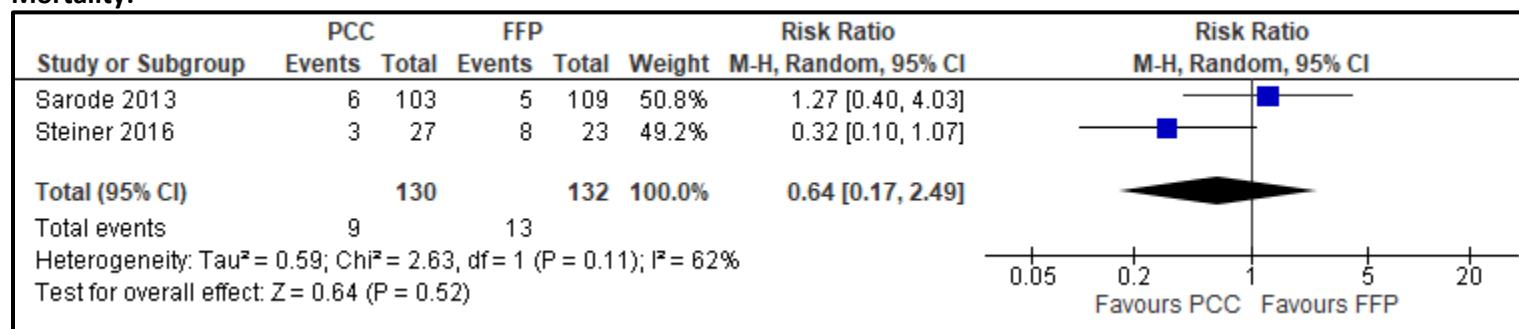
Steiner	OK	OK	Not blinded - However, outcomes were <u>blindly</u> assessed	OK	OK	OK	Serious indirectness: patients with intracranial bleeding
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Low risk of bias
Unclear risk of bias
High risk of bias

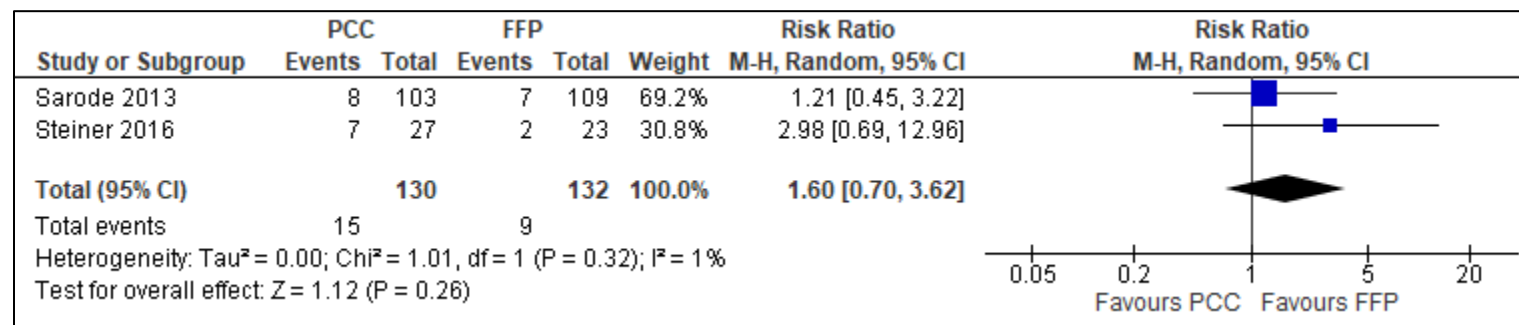
Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias

Our SRMA of 2 RCTs of mixed populations (43% of the patients had GI bleeding, 28% had intracranial hemorrhage)

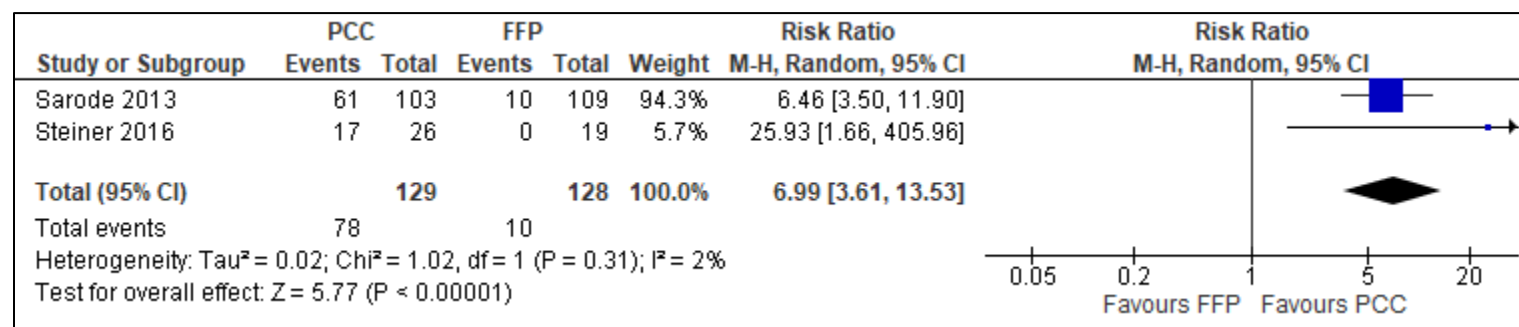
#### Mortality:



## Thrombotic events:



## INR "correction" at 30 min



Cohort studies with the control group needed for this PICO

14. **Karaka AJRM 2014.** (Karaca et al. Use and effectiveness of prothrombin complex concentrates vs fresh frozen plasma in gastrointestinal hemorrhage due to warfarin usage in the ED. American Journal of Emergency Medicine. 32 (6) (pp 660-664), 2014)<sup>9</sup>

- Design unclear. The authors describe it as "prospective cohort study of consecutive patients alternately selected by the authors". It could also be considered a non-randomized clinical trial. The certainty of the evidence derived from this study is very low, regardless of the design assigned.

- Consecutive patients with INR > 2.1 due to warfarin use, and GI bleeding that received either PCC or FFP.
- 20 each in the PCC and FFP groups.
- All patients had 10 mg vitamin K1 intravenously
- For the PCC group, the mean INR levels at 2 hours and 6 hours were lower than those for the FFP group.
- n=7 with active bleeding (Forrest 1) in the FFP group vs n=0 in the PCC group (based on Forrest; 35% vs 0%)
  - Note: the Forrest classification was reported as outcome, not as baseline characteristic, because “upper endoscopy was performed on patients after their INR reached an efficient level (INR <2.1)” “On average, upper endoscopy was performed 8 h (range: 6-12 h) after admission in the PCC group and 12 h (range: 8-24 h) in the FFP group”
- n=3 in the FFP group underwent invasive/surgical treatment (15% vs 0%)
- emergency department length of stay was also longer in FFP group (3.46 vs 1.62 days, P<.01), while total length of hospital stay was not different between the groups
- Thromboembolic outcomes were not mentioned

Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (exposures = PPC, FFP)	Prognostic factors (other than exposure of interest) similar among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Karaka AJRM 2014 <sup>9</sup>	OK	Unclear	OK	OK	OK	OK	Thrombotic events were not reported
Low risk of bias							
Unclear risk of bias							
High risk of bias							

- Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included, because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not included, because it is an “indirectness” issue as per GRADE.

- Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias

## Systematic reviews

No additional studies were identified by reviewing the SRs that were identified by our primary literature search (listed below) or the SRs and previous guidelines (that included systematic reviews) that were identified by supplemental searches

1. Johansen et al. Prothrombin complex concentrate for reversal of vitamin K antagonist treatment in bleeding and non-bleeding patients. Cochrane Database of Systematic Reviews 2015
  - Out of 4 included RCTs, only one RCT that compared PCC vs. FFP (Sarode Circulation 2013) included some patients with GI bleeding. No **separate results for patients with GI bleeding**
2. Ostermann et al. Prothrombin complex concentrate for vitamin K antagonist reversal in acute bleeding settings: efficacy and safety. Expert Review of Hematology. 12 (7) (pp 525-540), 2019.
  - Included RCTs and observational studies
  - Identified one cohort study (Karaka AJEM 2014) that assessed GI bleeding (4F-CCC vs FFP). This study had already been captured by our search for primary studies.

## Cost-effectiveness analyses

1. Guest CT 2010 (Guest et al. Modeling the Cost-Effectiveness of Prothrombin Complex Concentrate Compared with Fresh Frozen Plasma in Emergency Warfarin Reversal in the United Kingdom. Clinical Therapeutics. 32 (14) (pp 2478-2493), 2010) <sup>10</sup>
  - This CE study concluded that a typical patient with GI bleeding who is treated with PCC instead of FFP would “gain 0.2 life-year, and the cost per life-year gained with PCC would be £2100. Additionally, a typical patient would gain 0.14 QALY and the cost per QALY gained with PCC would be £2900.”

- This was based on the assumption that “use of PCC instead of FFP after a GI hemorrhage could increase survival from an estimated 97% to 98%”. The three studies from which the authors extracted evidence were: Wilcox CM et al. Am J Med 1988;84:683– 690, Rubin TA, et al. Gastrointest Endosc 2003;58:369 –373, and Thomopoulos KC, et al. World J Gastroenterol 2005;11:1365–1368. However, those 3 studies simply reported mortality rates in GI bleeding when FFP is used - they did not assess or report mortality rates with PCC, and of course, did not report any comparative efficacy (or comparative resource use) between FFP and PCC. Therefore, the efficacy data for GI bleeding that were used in the CE model were guestimates (“expert opinion”) made by 14 experts (none of which was gastroenterologist).
- Our SRMA (and previous SRMAs) on the efficacy of PCC vs FFP on mortality in patients with VKA-related bleeding has shown that there is uncertainty about the direction and magnitude of the effect on mortality. This evidence had not been published at the time of the CE analysis. Ideally, a CE should be conducted using that data.
- In conclusion, we have very low confidence in the results of this CE analysis.

## 861 Evidence profile, PICO 3

Patients with GI bleeding: VKA reversal with PCC vs. FFP												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	PCC	FFP	Relative (95% CI)	Absolute (95% CI)	
Further bleeding at 7 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
1 RCT (separate results for GI bleeding from Sarode Circulation 2013) <sup>4</sup>	Moderately serious <sup>a</sup>	Serious <sup>n</sup>	Very serious <sup>b</sup>	Serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		14/55	14/58	RR 1.05 (0.55 to 2.00)	Risk with <b>FFP</b> : 241 events per 1,000. With <b>PCC</b> : 12 <b>more</b> per 1,000 (from 108 <b>less</b> to 229 more)	
1 cohort study (Karaka AJEM 2014) <sup>9</sup>	Not serious <sup>d</sup>		Serious <sup>e</sup>	Serious <sup>f</sup>	None	⊕⊕⊕⊕ VERY LOW		0/20	7/20	RR 0.07 (0.00, 1.09)	Risk with <b>FFP</b> : 350 events per 1,000. With <b>PCC</b> : 325 <b>less</b> per 1,000 (from 350 less to 13 <b>more</b> )	
Thrombotic events within 30 days (critical outcome)												
Our SRMA of 2 RCTs (Sarode Circulation 2013; <sup>4</sup> Steiner LN 2016 <sup>5</sup> )	Not serious	Not serious	Serious <sup>g</sup>	Serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		15/130	9/132	RR 1.60 (0.70 - 3.62)	Risk with <b>FFP</b> : 68 events per 1,000. With <b>PCC</b> : 41 <b>more</b> per 1,000 (from 20 <b>less</b> to 178 more)	
Mortality within 30 days (important outcome, but not critical for decision making)												
Our SRMA of 2 RCTs (Sarode Circulation 2013; <sup>4</sup> Steiner LN 2016 <sup>5</sup> )	Not serious	Not serious	Very serious <sup>h</sup>	Serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW	11/130	13/132	RR 0.64 (0.17 - 2.49)	Risk with <b>FFP</b> : 98 events per 1,000. With <b>PCC</b> : 35 <b>less</b> per 1,000 (from 81 less to 146 <b>more</b> )		



1 cohort study (Karaka AJEM 2014) <sup>a</sup>	Not serious	Not applicable	Not serious	<b>Very serious<sup>i</sup></b>	None	⊕⊕⊕⊕ VERY LOW		1/20	1/20	RR 1.00 (0.07 - 14.90)	Risk with <b>FFP</b> : 50 events per 1,000. With <b>PCC</b> : <b>the same</b> , i.e., 50 per 1,000 (from 47 <b>less</b> to 695 <b>more</b> )	
<b>Transfusion-related events (fluid overload) within 7 days</b> (important outcome, not critical for decision making)												
1 RCT (Sarode Circulation 2013 <sup>4</sup> )	<b>Moderately serious<sup>i</sup></b>	Not applicable	<b>Moderately serious<sup>k</sup></b>	<b>Serious<sup>l</sup></b>	None	⊕⊕⊕⊖ LOW		5/103	14/109	RR 0.38 (0.14 - 1.01)	Risk with <b>FFP</b> : 128 events per 1,000. With <b>PCC</b> : 79 <b>less</b> per 1,000 (from 110 <b>less</b> to 1 <b>more</b> )	
<b>Speed of INR correction</b> (proportion of patients who reached target INR; target INR was ≤1.3 in Sarode 2013, ≤1.2 in Steiner 2016) <b>at 30 min</b> (outcome included by <i>post hoc</i> decision; important, but not critical for decision making)												
Our SRMA of 2 RCTs (Sarode Circulation 2013; <sup>4</sup> Steiner LN 2016 <sup>5</sup> )	Not serious	Not serious	<b>Serious<sup>m</sup></b>	Not Serious	None	⊕⊕⊕⊕ MODERATE		78/129	10/128	RR 6.46 (3.50 - 11.90)	Risk with <b>FFP</b> : 78 events per 1,000. With <b>PCC</b> : 427 <b>more</b> per 1,000 (from 195 <b>more</b> to 850 <b>more</b> )	<b>Desirable outcome</b>

## Footnotes

<sup>a</sup> Moderately serious risk of bias. The certainty of evidence was rated done by **half** level. For the outcome of “hemostatic efficacy”, there is moderate risk of bias (performance bias) due to lack of blinding, despite the use of a blinded adjudication committee.

<sup>b</sup> Very serious indirectness. The certainty of evidence was rated done by **one and a half** level. The outcome of “hemostatic efficacy” as defined in the study, was very different from the target outcome of this guideline, i.e., further bleeding. Furthermore, this outcome was only measured at 24 hours. The fact that vitamin K was administered in all patients (both study arms) raises further indirectness concerns (this would bias the results towards the null), but did not further rate down this outcome for this reason.

<sup>c</sup> Serious imprecision. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

<sup>d</sup> It was unclear whether prognostic factors (other than exposure of interest) were similar among cohorts. However, the certainty of evidence was not rated down for this.

<sup>e</sup> Serious indirectness. The outcome of active bleeding at upper endoscopy as defined in the study was very different from our target outcome of further bleeding. Furthermore, the timing of the outcome was at 6 to 24 hours. The fact that vitamin K was administered in all patients (both study arms) raises some indirectness concerns (this would bias the results towards the null), but did not further rate down this outcome for this reason.

876 <sup>f</sup> Serious imprecision. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm. Also, very small  
877 number of events.

878 <sup>g</sup> Serious indirectness for the outcome of thrombotic events. Mixed population: 43% of the patients had GI bleeding; 28% had intracranial hemorrhage.  
879 Patients with intracranial hemorrhage or other types of major bleeding may be very different from the target population for our guideline with regards to their  
880 risk for thrombotic events. Thrombotic events were assessed at 45 days <sup>4</sup> and at 60 days <sup>5</sup>.

881 <sup>h</sup> Very serious indirectness for the outcome of mortality. Mixed population: 43% of the patients had GI bleeding; 28% had intracranial hemorrhage. Patients  
882 with Intracranial hemorrhage are very different from the target population of this guideline, especially with regards to the mechanisms leading to death and  
883 the effect of rapid VKA reversal on the mechanisms leading to death..

884 <sup>i</sup> Very serious imprecision. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm. Also, very  
885 small number of events, only one event per study arm.

886 <sup>j</sup> Moderately serious risk of bias. The certainty of evidence was rated done by **half** level. For the outcome of fluid overload, there is moderate risk of bias  
887 (performance bias) due to lack of blinding, despite the use of a blinded adjudication committee.

888 <sup>k</sup> Moderately serious indirectness for the outcome of fluid overload. The certainty of evidence was rated done by **half** level. Mixed population: 56% of the  
889 patients had GI bleeding, while the remaining patients had intracranial, “visible”, or musculoskeletal bleeding. It is possible but not certain that this  
890 indirectness of the population could have affected the outcome. The timing of outcome assessment is unclear (either at 10 days or at 45 days).

891 <sup>l</sup> Serious imprecision. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and negligible effect. Also, small  
892 number of events.

893 <sup>m</sup> Serious indirectness of the outcome, because the speed of INR correction is a surrogate outcome and not a clinical outcome. We did not further downrate  
894 the certainty of evidence for indirectness of population, despite the fact that the population (mixed population: 43% of the patients had GI bleeding; 28% had  
895 intracranial hemorrhage) was different from the target population of this guideline. The guideline panel felt that it was unlikely that INR correction at 30 min  
896 would be expected to differ according to the type of bleed. The type of bleed would have affected the importance of this outcome (likely more important for  
897 intracranial bleed compared to GI bleed) but not the direction or the magnitude of the effect. With regards to the differences between the two studies, Sarode  
898 2013 and Steiner 2016, the target INR was very similar (1.2 and 1.3 respectively), while the timing was different: it was 30 after the end of infusion in Sarode  
899 2013 vs. 30 min after the start of infusion in Steiner 2016. In Sarode 2013, the timing of the outcome would favor the FFP arm, because FFP infusions took  
900 longer to finish, therefore it is reasonable to speculate that had the timing of the outcome been similar to the other trial, the effect size would have been even  
901 larger.

902 <sup>n</sup> There is inconsistency in the direction of effect between the two estimates

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## Evidence to Decision Framework, PICO 3

### 03. Reversal of vitamin K antagonist with PCC vs FFP

P: Patient with GIB currently taking warfarin

I: PCC

C: FFP

O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

IMPORTANT, BUT NOT CRITICAL: mortality within 30 days, transfusion-related events (congestive heart failure, pulmonary edema) within 7 days

	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<b>How substantial are the desirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>● <b>Large</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>See Evidence Profile Table.</p> <p>The <u>desirable</u> anticipated effects with PPC (compared to FFP) are:</p> <ul style="list-style-type: none"> <li>- reduced mortality: 35 less events per 1,000 patients</li> <li>- reduced fluid overload: 79 less events per 1,000 patients</li> <li>- increased speed of INR correction (post hoc outcome; proportion of patients who reached INR <math>\leq 1.2</math> or 1.3 in 30 min): 427 more per 1,000 patients</li> </ul>	
Undesirable Effects	<b>How substantial are the undesirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Large</li> <li>● <b>Moderate</b></li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Certainty of evidence	<b>What is the overall certainty of the evidence of effects?</b> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	

Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>● <b>Important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>	
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison (FFP)</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● <b>Probably favors the intervention</b> (PCC)</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>PCC would lead to large desirable anticipated effects (reduced mortality, reduced fluid overload events, more reliable INR correction) vs. moderate undesirable effects (increased thrombosis) compared to FFP.</p>	
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>● <b>Moderate costs</b></li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Per Canada Blood Services, Octaplex and Beriplex are both priced at \$0.57 per IU</p> <p>Therefore, if the dosing regimen of Sarode 2013 is used (see table 2 in that paper), for a patient with a weight of 75 Kg and INR 2-4, the cost will be CAD 1,068 or approximately USD 1,500</p> <p>The cost of FFP in Canada in 2018-19 was \$118 per Unit (300 ml)</p>	
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● <b>Moderate</b></li> <li>○ High</li> <li>○ No included studies</li> </ul>		






Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention (PCC)</li> <li>○ Favors the intervention</li> <li>● <b>Varies</b></li> <li>○ No included studies</li> </ul>	One cost-effectiveness study was identified ( <i>Guest et al. Modeling the Cost-Effectiveness of Prothrombin Complex Concentrate Compared with Fresh Frozen Plasma in Emergency Warfarin Reversal in the United Kingdom. Clinical Therapeutics. 32 (14) (pp 2478-2493), 2010</i> ), but as explained above, the guideline panel had very low confidence in the conclusions of this CE analysis.	
Acceptability	<p><b>Is the intervention (PCC) acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>● <b>Probably yes</b></li> <li>○ Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Feasibility	<p><b>Is the intervention (PCC) feasible to implement?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● <b>Yes</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

## Conclusions

**PICO 03. For patients on warfarin who are hospitalized or under observation with acute GIB (upper and/or lower) should PCC be administered compared to FFP?**

**O: CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

924 *IMPORTANT, BUT NOT CRITICAL: mortality within 30 days; transfusion-related events (congestive heart failure, pulmonary edema)*  
 925 *within 7 days*  
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Type of recommendation	Strong recommendation against the intervention 	Conditional recommendation against the intervention 	Conditional recommendation for either the intervention or the comparison 	Conditional recommendation for the intervention 6/6 votes: 100% 	Strong recommendation for the intervention 
<b>Recommendation</b>	For patients on warfarin who are hospitalized or under observation with acute GIB, we suggest PCC administration compared to FFP administration (Conditional recommendation, very low certainty of evidence)				
<b>Justification</b>					
<b>Subgroup considerations</b>	<p>The guideline panel felt that although the majority of patients with GI bleeding on warfarin do not require PPC administration, a subpopulation of patients with life-threatening GI bleeding could still be treated with PCC, especially if one or more of the following conditions is also met:</p> <ul style="list-style-type: none"> <li>• massive blood transfusion (which may worsen coagulopathy due to dilution of blood components)</li> <li>• supratherapeutic INR with values substantially exceeding the therapeutic range</li> </ul>				
<b>Implementation considerations</b>					
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?				
<b>Research priorities</b>					

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#### 931 **References to PICO 3**

- 932 1. Witt et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of  
 933 anticoagulation therapy. Blood Adv 2018;2:3257.

2. Chai-Adisaksopha C, Hillis C, Siegal DM, et al. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. *Thromb Haemost.* 2016;116(5):879-890
3. Boulis NM, Bobek MP, Schmaier A, Hoff JT. Use of factor IX complex in warfarin related intracranial hemorrhage. *Neurosurgery* 1999;45:1113–8
4. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation.* 2013;128(11):1234-1243.
5. Steiner T, Poli S, Griebel M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *Lancet Neurol.* 2016;15(6):566-573.
6. Johansen M et al. Prothrombin complex concentrate for reversal of vitamin K antagonist treatment in bleeding and non-bleeding patients. *Cochrane Database Syst Rev* 2015;2015(7):CD010555.
7. Goldstein et al. "Four factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, noninferiority, randomised trial," *The Lancet*, vol. 385, no. 9982, pp. 2077–2087, 2015
8. Refaai et al. Four-Factor Prothrombin Complex Concentrate Reduces Time to Procedure in Vitamin K Antagonist-Treated Patients Experiencing Gastrointestinal Bleeding: A Post Hoc Analysis of Two Randomized Controlled Trials. *Emerg Med Int* 2017:ID8024356
9. Karaca et al. Use and effectiveness of prothrombin complex concentrates vs fresh frozen plasma in gastrointestinal hemorrhage due to warfarin usage in the ED. *American Journal of Emergency Medicine.* 32 (6) (pp 660-664), 2014
10. Guest et al. Modeling the Cost-Effectiveness of Prothrombin Complex Concentrate Compared with Fresh Frozen Plasma in Emergency Warfarin Reversal in the United Kingdom. *Clinical Therapeutics.* 32 (14) (pp 2478-2493), 2010

4. GIB: vitamin K for reversal of VKA

#### 4. GIB: Reversal of vitamin K antagonist with vitamin K vs none

P: Patient with GIB currently taking warfarin

I: vitamin K

C: no reversal agents

O: **CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days

Our literature searches (including supplementary searches for SRMAs and previous guidelines with assessment of their references) identified only one eligible study, Moustafa TR 2018 <sup>1</sup> (see below), that included patients with VKA-related major bleeding (some of which had GI bleeding) and reported clinical outcomes. None of the previous guidelines, even guidelines dedicated to reversal of anticoagulation, reported evidence profiles for their recommendations on vitamin K as VKA reversal treatment

We decided to utilize indirect evidence: evidence on INR reduction (surrogate outcome), mortality and thromboembolic events in non-bleeding patients on VKA and elevated INR. The most recent, and by far the most rigorously conducted SRMA on vitamin K for reversal of excessive VKA anticoagulation in non-bleeding patients was Khadib Blood Adv 2019 <sup>2</sup>. See below.

No SRMA quantified the risk of anaphylactic reaction with intravenous administration of vitamin K.

#### Case-control studies with the comparator exposure required for this PICO

1. **Moustafa TR 2018** (Moustafa et al. Management and outcome of major bleeding in patients receiving vitamin K antagonists for venous thromboembolism. Thrombosis Research. 171 (pp 74-80), 2018) <sup>1</sup>
  - Design: case-control and cohort study analyses conducted on a cohort from multi-institutional multi-national registry
    - The adjusted analyses relevant to this PICO were conducted by the authors as **case-control** analyses (reported as odds ratios)
    - The raw data were available too; however, we could not extract clean data for patients who only had vitamin K and did not have any other reversal agents) or patients who did not have any reversal agent
  - N= 267 patients who had major bleeding while receiving VKA for VTE.
    - 78 patients had GI bleeding, but there were no separate results for the outcomes required for this PICO



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- Multivariable analysis (case control analyses) showed that
    - vitamin K use was associated with lower risk of mortality (OR: 0.47; 0.24–0.92)
  - **Indirectness concern:** Neither the exposure or the non-exposure is direct in the analyses. The exposure was vitamin K but some of these patients have used other reversal agents, with the non-exposure was not “no reversal agent”, as some these patients have also used reversal agents other than vitamin K. Furthermore, only 2 reversal agents were included in the multivariable analysis (see next comment).
  - **Serious concerns about the multivariable analysis**
    - The number of cases was too small (13 thrombotic events and 59 deaths) to allow for use of all variables.
    - Several variables were captured and proposed for inclusion, but the variables that were risk factors for thromboembolism or death were not reported exhaustively -only examples were presented.
    - The authors stated that “all variables achieving a significance level of  $\leq 0.1$  on univariate analysis were considered for inclusion in the logistic regression model”. Only 5 variables achieved that significance level, and eventually those 5 plus 2 additional variables were included in the multivariable model. This approach excluded important confounders from the multivariable analysis.
    - The inadequate adjustment was evident when we calculated the unadjusted odds ratios from the raw data (table 4 in that paper) and found that the results were almost identical with the adjusted results in from the multivariable analysis (table 4 in that paper). For example, for the association of vitamin K use and risk of death
      - Unadjusted OR: 0.50, 95% CI 0.27 - 0.94
      - Adjusted OR: 0.47, 95% CI 0.24 - 0.92

Risk of bias assessment of case control studies						
Study	Cases and controls similar for risk of exposure (or adjusted adequately for confounders)	Methods to determine exposure valid and similar for cases and controls	Methods to ascertain outcome of interest valid and similar for cases and controls	Incomplete/missing data addressed	Other bias	Comments
Moustafa TR 2018	Not similar, not adjusted adequately (see description of the study)	OK	OK	Unclear	OK	
Low risk of bias						
Unclear risk of bias						
High risk of bias						

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## SRMAs in non-bleeding patients

1. **Khatib BA 2019** (Khatib R et al. Vitamin K for reversal of excessive vitamin K antagonist anticoagulation: a systematic review and meta-analysis. Blood Adv 2019)
  - SRMA of 5 RCTs
  - Conducted by the highest methodological standards, including risk of bias assessments and GRADE assessments of the certainty of evidence
  - Literature search: April 2018
  - **Patients:** Adults “using VKAs with a first episode of an elevated INR value (between 4.5 and 10) that required temporary VKA cessation and without bleeding. Patients who required VKA reversal for urgent surgery or because of bleeding were excluded. Studies were included with patients taking VKA for any indication”.
  - **Intervention:** Administration of vitamin K (oral, IV, or subcutaneous) at any dose.
  - **Comparison:** Placebo or observation only
  - **Outcomes:** All-cause mortality, major bleeding, thromboembolism, and proportion of patients reaching goal INR assessed at 24 hours and at 1 week of vitamin K administration
  - **Results:**
    - nonsignificant increased risk of mortality (RR 5 1.42; 95% CI 0.62-2.47), bleeding (RR 5 2.24; 95% CI 0.81-7.27), and thromboembolism (RR 5 1.29; 95% CI 0.35-4.78) for vitamin K administration, with moderate certainty of the evidence resulting from serious imprecision as CIs included potential for benefit and harm.
    - Patients receiving vitamin K had a nonsignificant increase in the likelihood of reaching goal INR (1.95; 95% CI 0.88-4.33), with very low certainty of the evidence resulting from serious risk of bias, inconsistency, and imprecision – **see figure 4 in that paper (goal INR assessed at 24 hours)**

Risk of bias assessment of evidence derived from SRMA of RCTs							
SRMAs	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Comments
Khatib 2019 (5 RCTs)	OK	Unclear	3 studies were not blinded. For another study it was unclear if the outcome assessors were blinded	OK	OK	OK	Very serious indirectness: non-bleeding patients
<div>Low risk of bias</div> <div>Unclear risk of bias</div> <div>High risk of bias</div>							

Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of bias, the study has unclear risk of bias

## 1074 Evidence profile, PICO 4

Patients with GI bleeding: VKA reversal with vitamin K vs no treatment												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Vitamin K	No treatment	Relative (95% CI)	Absolute (95% CI)	
Further bleeding at 7 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
No studies					-	-		-	-			
Thrombotic events within 30 days (critical outcome)												
1 SRMA <sup>2</sup> of 2 RCTs in non-bleeding patients	Not serious <sup>a</sup>	Not serious	Very serious <sup>b</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		5/392	4/409	RR 1.29 (0.35- 4.78)	Risk without treatment: 10 events per 1,000 patients. With vit K: 3 more per 1,000 (from 7 less to 38 more)	
Mortality within 30 days (important outcome, but not critical for decision making)												
1 SRMA <sup>2</sup> of 3 RCTs in non-bleeding patients	Not serious <sup>d</sup>	Not serious	Very serious <sup>e</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		16/421	13/439	RR 1.24 (0.62- 2.47)	Risk without treatment: 30 events per 1,000 patients. With vit K: 7 more per 1,000 (from 11 less to 44 more)	
1 case control study (Moustafa TR 2018) <sup>1</sup>	Serious <sup>f</sup>	Not applicable	Very serious <sup>g</sup>	Serious <sup>h</sup>	None	⊕⊕⊕⊕ VERY LOW		-	-	Adjusted OR 0.47 (0.24- 0.92)	-	
INR correction (various target levels for INR, measured at 24 h) (outcome included by <i>post hoc decision</i> ; important, but not critical for decision making)												
1 SRMA <sup>2</sup> of 5 RCTs in non-bleeding patients	Serious <sup>i</sup>	Serious <sup>j</sup>	Very serious <sup>k</sup>	Serious <sup>l</sup>	None	⊕⊕⊕⊕ VERY LOW		218/507	90/518	RR 1.95 (0.88- 4.33)	Risk without treatment: 174 events per 1,000 patients. With vit K: 165 more per 1,000 (from 38 less	Beneficial outcome

											to 579 more)	
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1076 **Footnotes**

1077 <sup>a</sup> Neither of the 2 RCTs was at high risk of bias

1078 <sup>b</sup> Very serious indirectness of population, because these patients did not have bleeding. The baseline risk for thrombotic events and the effect modification of  
1079 that risk by vitamin K administration could be substantially different in hospitalized patients with a major bleed.

1080 <sup>c</sup> Very serious imprecision, because 95% CIs included potential for large benefit and large harm. Also, very small number of events

1081 <sup>d</sup> One of the 3 RCTs was at high risk of bias, but contributed only 5% of the weight of the meta-analysis

1082 <sup>e</sup> Very serious indirectness of population, because these patients did not have bleeding. The baseline risk for death and the effect modification of that risk by  
1083 vitamin K administration could be substantially different in hospitalized patients with a major bleed.

1084 <sup>f</sup> Serious risk of bias because of serious concerns about inadequate adjustment for confounders (see comments in the description of the study, above)

1085 <sup>g</sup> Very serious indirectness of the population: some patients in the vitamin K group received other reversal agents as well, while patients in the non-vitamin K  
1086 group also received reversal agents other than vitamin K, and there was no reason to believe that such cointerventions were equally applied to both groups.  
1087 Furthermore, only a proportion of patients had GI bleeding.

1088 <sup>h</sup> Serious imprecision, due to small number of events.

1089 <sup>i</sup> Serious risk of bias, mainly performance bias and ascertainment bias due to lack of blinding in most of the RCTs.

1090 <sup>j</sup> Serious inconsistency: high heterogeneity

1091 <sup>k</sup> Very serious indirectness of the outcome, because the speed of INR correction is a surrogate outcome and not a clinical outcome. The certainty of evidence  
1092 was further downrated for indirectness of population, i.e., non-bleeding patients did not have GI bleeding. The panel felt that the INR correction with and  
1093 without vitamin K administration could follow a different course in patients with substantial loss of blood (often requiring blood transfusions) from a major GI  
1094 bleeding

1095 <sup>l</sup> Serious imprecision, because 95% CIs included potential for large benefit and small harm.

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1099 **Evidence to Decision Framework, PICO 4**

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1101 04. Reversal of vitamin K antagonist with vitamin K

1102 P: Patient with GIB currently taking warfarin

1103 I: Vitamin K

1104 C: no treatment

1105 O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein  
1106 thrombosis, pulmonary embolus)

1107 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days, transfusion-related events (congestive heart failure, pulmonary edema) within 7 days

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	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<p><b>How substantial are the desirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>o Trivial</li> <li>o Small</li> <li>o Moderate</li> <li>o Large</li> <li>● <b>Varies</b></li> <li>o Don't know</li> </ul>	<p>See Evidence Profile Table. Most of the evidence is derived from research on non-bleeding patients.</p> <p>The <u>desirable</u> anticipated effects with vitamin K use (compared to no treatment) are:</p> <ul style="list-style-type: none"> <li>● <b>INR correction</b> (post hoc outcome, not critical outcome) in a larger proportion of patients compared to no treatment</li> </ul> <p>The experts noted that the effect on INR varies based on baseline INR.</p> <p>The panel considered the INR correction as a desirable effect (i.e., surrogate for reduced further bleeding), and did not consider the INR correction as a big concern for thrombotic risk acutely- however, this also depends on the patient's indication for antithrombotics.</p>	Pros/cons of route of administration were discussed
Undesirable Effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>o Large</li> <li>o Moderate</li> <li>● <b>Small</b></li> <li>o Trivial</li> <li>o Varies</li> <li>o Don't know</li> </ul>	<p>However, vitamin K can lead to increased time to return to an anticoagulated state if given liberally. This may lead to an increased time of bridging and/or hospitalization to get the patient back to a therapeutic level.</p> <p>The <u>undesirable</u> anticipated effects with vitamin K use (compared to no treatment) are:</p> <ul style="list-style-type: none"> <li>● <b>increased risk of thromboembolism (critical outcome)</b>: 3 more events per 1,000 patients</li> </ul> <p>It is not possible to estimate the direction (let alone the magnitude) of the effect of vitamin K (vs. no vitamin K) on <b>other clinical outcomes</b></p> <p>Also, the <b>risk of anaphylaxis</b> could not be systematically quantified.</p>	

Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>● <b>Important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>	
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● <b>Probably favors the comparison</b></li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention (vitamin K)</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Variable desirable anticipated effects (INR correction) vs. small undesirable anticipated effects (increased thrombosis). Very low certainty of evidence. Given that patients place high disutility on thrombosis, the guideline panel judged that the balance probably favors the comparison.	
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>● <b>Negligible costs and savings</b></li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Negligible cost	Mode of use increases cost (personnel needed for IV/ pump)

Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● <b>Moderate</b></li> <li>○ High</li> <li>○ No included studies</li> </ul>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● <b>No included studies</b></li> </ul>		
Acceptability	<p><b>Is the intervention (vitamin K) acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● <b>Yes</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Feasibility	<p><b>Is the intervention (vitamin K) feasible to implement?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● <b>Yes</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

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1111 **Conclusions**

1112 *PICO: 04. For patients on warfarin who are hospitalized or under observation with acute GIB (upper and/or lower) should vitamin*






1113 *K administered (compared to not)?*

1114 *O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial*

1115 *infarction, deep vein thrombosis, pulmonary embolus)*

1116 *IMPORTANT, BUT NOT CRITICAL: mortality within 30 days*

1117

Type of recommendation	Strong recommendation against the intervention 	Conditional recommendation against the intervention 6/6 votes: 100% 	Conditional recommendation for either the intervention or the comparison 	Conditional recommendation for the intervention 	Strong recommendation for the intervention 
<b>Recommendation</b>	For patients on warfarin who are hospitalized or under observation with acute GIB (upper and/or lower) we suggest against the use of vitamin K (Conditional recommendation, very low certainty of evidence)				
<b>Justification</b>					
<b>Subgroup considerations</b>	Practically, this recommendation means that the majority of patients with acute GI bleeding on warfarin will not require administration of vitamin K. However, a minority of patients should be given vitamin K, especially when GI bleeding is severe and the INR is supratherapeutic. Another situation where vitamin K could be used, is when the intention is to fully reverse an INR and don't plan to resume warfarin therapy.				
<b>Implementation considerations</b>	Route of administration considerations.				
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?				
<b>Research priorities</b>					

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1123 **References, PICO 4**

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- 1125 1. Moustafa et al. Management and outcome of major bleeding in patients receiving vitamin K antagonists for venous thromboembolism.  
1126 Thrombosis Research. 171 (pp 74-80), 2018  
1127 2. Khatib R et al. Vitamin K for reversal of excessive vitamin K antagonist anticoagulation: a systematic review and meta-analysis. Blood Adv  
1128 2019.

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1141 5. GIB: idarucizumab for dabigatran reversal

1142 **5. GIB: Reversal of dabigatran with idarucizumab**

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1145 P: Patient with GIB currently taking dabigatran

1146 I: idarucizumab

1147 C: no reversal agent

1148 O: **CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction,  
1149 deep vein thrombosis, pulmonary embolus)

1150 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days, infusion-related events within 7 days

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Cohort studies with the comparator cohort needed for this PICO

1. **Singh AJCD 2019** (Singh et al. Real World Outcomes Associated with Idarucizumab: Population-Based Retrospective Cohort Study. American Journal of Cardiovascular Drugs. 2019) <sup>1</sup>
  - Retrospective cohort study in the US
  - Included patients hospitalized for dabigatran-associated major non-traumatic GI bleeding or intracranial bleeding
  - Analyzed separately the 1283 patients with GI bleeding
    - N= 159 patients on dabigatran with GIB who received idarucizumab
    - N= 1124 patients on dabigatran with GIB who **did not receive** idarucizumab
  - Mortality:
    - idarucizumab: 9 deaths/159 (5.7%)
    - no idarucizumab: 37 deaths/1124 (3.3%)
    - Adjusted OR 1.39, 95% CI 0.51–3.45
  - Venous thromboembolism:
    - idarucizumab: 2/159 (1.3%)
    - no idarucizumab: 47/1124 (4.2%)
    - Adjusted OR 0.35, 95% CI 0.08–1.58
  - Did not report results on further bleeding or infusion AEs
  - Multiple mistakes with inversed groups in the manuscript
  - See discussion about higher mortality in the idarucizumab group, including the **FDA rationale for dropping the requirement for a phase IV cohort study with “comparator” arm**  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2015/761025Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/761025Orig1s000SumR.pdf)

Cohort studies without the comparator cohort needed for this PICO

1. **Pollack NEJM 2017** (Pollack et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017;377(5):431-441) <sup>2</sup>
  - Single cohort study (RE-VERSE AD study)
  - Patients on dabigatran who had uncontrolled bleeding (group A) or were about to undergo an urgent procedure (group B)

- All patients received 5 g of intravenous idarucizumab
- **No comparator cohort (i.e., no cohort receiving another treatment or no treatment)**
- Group A included **137 patients GI bleeding**, for which separate safety outcomes were reported:
  - 30-day **mortality**: 11.1% (15/137)
  - 30-day **thrombotic events** (figure 2 in the article): (3.6%) 5/137 (note: van der Wall 2019 reported 4/137)
- Reported “bleeding cessation” within 24 hours, but not separately for GI bleeding
- Reported hypersensitivity events in the whole cohort (N=503): 3 events, all classified as “potential”: 1 rash; 1 vomiting and loss of consciousness; 1 hypotension
- Reported surrogate outcomes (not separate for patients with GI bleeding):
  - For the whole group A (301 patients): reversal of the anticoagulant effect of dabigatran before and up to 24 hours after the administration of idarucizumab, on the basis of the diluted thrombin time or ecarin clotting time. **See Figure 1 in that article.**
  - For the whole cohort (group A and B together: 503 patients) concentration of unbound dabigatran before and up to 24 hours after the administration of idarucizumab (**see Figure 1C in that paper**)
  - Note that there was recurrent elevation in diluted thrombin time and in unbound dabigatran concentration at 12 and 24 hours in some patients. The suggested explanation was the redistribution of unbound dabigatran from the extravascular to the intravascular compartment. *“Unbound-dabigatran concentrations remained below 20 ng per milliliter for 24 hours in the majority of patients; however, reappearance of levels above 20 ng per milliliter was observed in 114 of 497 patients (23.0%), mainly after 12 hours, with 67 patients having elevated levels only at the 24-hour measurement. These recurrent elevations were associated with recurrent or continued bleeding in 10 patients in group A and in no patients in group B”*
  - Of note, this recurrent elevation was noted 2 years earlier in Pollack NEJM 2015 <sup>3</sup> (preliminary report of 90 patients) but there was no modification of the sampling protocol to collect data beyond 24 hours and assess the shape of the curves beyond 24 h. How long do these elevations last, do they raise higher after 24 hours?
    - Suppl Figure 3 in van der Wall 2019 <sup>4</sup> shows that in patients (with renal insufficiency) the “12 to 24 hour elevations” of dTT and dabigatran concentration were sustained well beyond 24 hours. See below.
- Also, see Idarucizumab\_ Center of Drug Evaluation review\_ 2015  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2015/761025Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/761025Orig1s000SumR.pdf)

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1209  
1210 2. **Pollack NEJM 2015** (Pollack et al. Idarucizumab for dabigatran reversal. New England Journal of Medicine. 373 (6) (pp 511-520), 2015) <sup>3</sup>  
1211     • Interim analysis of the RE-VERSE AD study.  
1212     • **No comparator cohort (i.e., no cohort receiving another treatment or no treatment)**  
1213     • The full report has already been published (Pollack NEJM 2017 <sup>2</sup>, see above)  
1214     • It does not report additional info compared to the full report  
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1216 3. **van der Wall\_ Circulation 2019** (Van der Wall et al. Idarucizumab for Dabigatran Reversal in the Management of Patients with  
1217 Gastrointestinal Bleeding. Circulation. 139 (6) (pp 748-756), 2019) <sup>4</sup>  
1218     • Separate analyses on the **137 GI bleeding patients from the RE-VERSE AD study** <sup>2</sup>  
1219     • **No comparator cohort (i.e., no cohort receiving another treatment or no treatment)**  
1220     • 84% was adjudicated as major or life-threatening, 48 (35.0%) was upper GI tract in origin, 43 (31.4%) was lower GI in origin, 4  
1221 patients (2.9%) had both upper and lower GI bleeding, and the bleeding site remained unidentified in 42 patients (30.7%).  
1222     • Many patients had additional comorbidities, including 114 (83.2%) with hypertension, 68 (49.6%) with chronic heart failure, and  
1223 39 (28.5%) with prior stroke or transient ischemic attack.  
1224     • Gastric and duodenal ulcers were common in those with upper GI bleeding (25.0%), whereas polyps and diverticular disease  
1225 were identified frequently in patients with lower GI bleeding (9.3% and 16.3%, respectively). Newly diagnosed luminal GI cancer  
1226 was reported in at least 2 patients in source documentation, 1 patient with a GI stromal tumor, and 1 patient with pancreatic  
1227 carcinoma involving the stomach. This information reporting was not mandatory and may represent underreporting; it was also  
1228 not captured in the clinical database.  
1229     • Complete reversal of dabigatran was observed in 118 of 121 patients (97.5%) with an elevated diluted thrombin time at  
1230 presentation and 95 of 131 patients (72.5%) with an elevated ecarin clotting time and was similar for upper and lower GI  
1231 bleeding.  
1232     • Post-reversal rebleeding: 10/137. However, the reporting is not clear on this. It reads: *“A re-elevation of dTT above the ULN*  
1233 *occurred in 25 patients (20.7%) within 12 hours and in 50 patients (41.3%) within 24 hours. In 10 of these 50 patients (20.0%),*  
1234 *rebleeding was reported within 48 hours after idarucizumab administration.”* Unclear if there were any rebleeds among the  
1235 remaining 87 patients  
1236     • Time to bleeding cessation was as assessed by the treating physician and defined by stabilization of pulse, blood pressure, or  
1237 hemoglobin values or, if the site was endoscopically evaluable, visible determination. Bleeding cessation occurred in 9.5% of

patients at time points >25 hours and could not be confirmed in 14.3% of patients. In the upper GI location, 82.6% were assessable within 24(+1) hours, with a median time of 2.7 hours (IQR, 1.5–9.6 hours); 4.3% of patients stopped bleeding >25 hours; and 13.0% were not assessable. In patients with lower GI bleeding, 76.2% were assessable within 24(+1) hours, with a time of 2.1 hours (IQR, 1.3–7.9 hours) to bleeding cessation. In patients with an unknown location of GI bleed, 52.4% were assessable within 24(+1) hours, with a median of 3.2 hours (IQR, 2.0–6.5 hours); 14.3% stopped bleeding at times >25 hours; and 33.3% were not confirmed. In patients with >1 location, bleeding cessation occurred within 24(+1) hours in 100% of patients after 6.4 hours (IQR, 0.8– 16.0 hours).

- A total of 117 patients (85.4%) in this cohort also received blood products: 113 (82.5%) received packed red blood cell transfusions; 6 (4.4%) received PCCs; 2 (1.5%) received activated PCCs; and 1 received recombinant activated factor VII (0.7%).
- A total of 6 patients (4.4%) experienced 7 thromboembolic events during the 90-day follow-up period, 4 of which occurred within 30 days (2.9%; Table 2). Five of these events in 4 patients occurred in the absence of anticoagulation. Overall, patients were discharged from hospital after a median of 7 days (IQR, 4–12 days).
- The 30-day and 90-day mortality was 15 patients and 20 patients, respectively, including myocardial infarction (3 patients), and hemorrhage (2 patients).
  - The high mortality (10.9% at 30 days) was discussed in the accompanying editorial (Siegal\_ Circulation 2019)
- Suppl Figure 3 in this article shows the surrogate outcomes (dTT and dabigatran concentration) in 3 patients who rebled and had repeat idarucizumab infusions. These patients had a creatinine clearance at enrollment of 26, 43, and 29 mL/min. The shaded (missing) areas been the two parts if the graphs were 38, 17 and 1.5 hours respectively for the 3 patients. These graphs show that in these patients (with renal insufficiency) the “12 to 24 hour elevations” of dTT and dabigatran concentration were sustained well beyond 24 hours.

Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (exposure = idarucizumab)	Prognostic factors (other than exposure of interest) <b>similar among cohorts</b> – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and <b>similar among cohorts</b>	Follow up complete and <b>similar among cohorts</b>	Free of other bias	Results/Comments
Singh AJCD 2019 <sup>1</sup>	OK	No adjustment for severity of GI bleeding, treatments for GI bleeding, or PCC use.	OK	OK	OK	OK	
Pollack NEJM 2017 <sup>2</sup>	OK	No comparative cohort	OK	Outcome detection methods valid, but there was <b>no comparative cohort</b>	Follow up complete but there was <b>no comparative cohort</b>	OK	
van der Wall_Circulation 2019 <sup>4</sup>	OK	No comparative cohort	OK	Outcome detection methods valid, but there was <b>no comparative cohort</b>	Follow up complete but there was <b>no comparative cohort</b>	OK	Sub-analysis of Pollack NEJM 2017
Low risk of bias							
Unclear risk of bias							
High risk of bias							

- Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included, because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not included, because it is an “indirectness” issue as per GRADE.
- Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias

## 1278 Evidence profile, PICO 5

Patients with GI bleeding: Dabigatran reversal with idarucizumab vs. no idarucizumab												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Idarucizumab	No idarucizu mab	Relative (95% CI)	Absolute (95% CI)	
Further bleeding at 7 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
1 cohort study without comparator cohort (van der Wall 2019) <sup>4</sup>	Serious <sup>a</sup>	Not applicable	Moderately serious <sup>b</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		10/50 (20%)	-	-	-	
Thrombotic events within 30 days (critical outcome)												
1 cohort study (Singh 2019) <sup>1</sup>	Serious <sup>d</sup>	Not applicable	Serious <sup>e</sup>	Serious <sup>f</sup>	None	⊕⊕⊕⊕ VERY LOW		2/159 (1.3%)	47/1124	Adjusted OR 0.35 (0.08 - 1.58)  Adjusted RR <sup>g</sup> 0.36 (0.08 - 1.54)	Risk <u>without</u> idarucizumab: 42 events per 1,000. <u>With idarucizumab</u> : 26 less per 1,000 (from 39 less to 23 more)	
1 cohort study without comparator cohort (van der Wall 2019) <sup>4</sup>	Serious <sup>a</sup>	Not applicable	Not serious	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		15/137 (10.9%)	-	-	-	
Mortality within 30 days (important outcome, but not critical for decision making)							⊕⊕⊕⊕ VERY LOW					
1 cohort study (Singh 2019) <sup>1</sup>	Serious <sup>d</sup>	Not applicable	Not serious	Serious <sup>f</sup>	None	⊕⊕⊕⊕ VERY LOW		9/159	37/1124	Adjusted OR 1.39 (0.51 - 3.45)  Adjusted RR <sup>g</sup> 1.37 (0.52 - 1.51)	Risk <u>without</u> idarucizumab: 33 events per 1,000. <u>With idarucizumab</u> : 12 more per 1,000 (from 16 less to 17 more)	



1 cohort study without comparator cohort (van der Wall 2019) <sup>4</sup>	<b>Serious</b> <sup>a</sup>	Not applicable	Not serious	<b>Very serious</b> <sup>c</sup>	None	⊕⊖⊖⊖ VERY LOW		4/137	-	-	-	
<b>Infusion-related events within 7 days</b> (important outcome, not critical for decision making)												
1 cohort study without comparator cohort (van der Wall 2019) <sup>4</sup>	<b>Serious</b> <sup>a</sup>	Not applicable	Not serious	<b>Very serious</b> <sup>c</sup>	None	⊕⊖⊖⊖ VERY LOW		3/137	-	-	-	
<b>Correction of diluted thrombin time</b> (measured up to 24 hours) (outcome included by <i>post hoc</i> decision; important, but not critical for decision making)												
1 cohort study without comparator cohort (Pollack NEJM 2017; van der Wall 2019) <sup>1,4</sup>	<b>Serious</b> <sup>a</sup>	Not applicable	<b>Serious</b> <sup>h</sup>	<b>Serious</b> <sup>i</sup>	None	⊕⊖⊖⊖ VERY LOW		Visual presentation (graphs)	-	-	-	-

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## 1280 Footnotes

1281 <sup>a</sup> Serious risk of bias, because the study did not have comparator cohort with no use of idarucizumab.

1282 <sup>b</sup> Moderately severe indirectness of the outcome. The outcome of post-reversal rebleeding was reported for 48 hours and only among the 50/137 patients with  
1283 “a re-elevation of dTT above the ULN within 24 hours of the outcome”.

1284 <sup>c</sup> Very serious imprecision, even for the event rate in the intervention group, due to small number of events. The comparative efficacy cannot be calculated.

1285 <sup>d</sup> Serious risk of bias because of no adjustment for severity of GI bleeding, treatments for GI bleeding, or PCC use.

1286 <sup>e</sup> Serious indirectness of the outcome, because only venous (not arterial) thrombotic events were reported

1287 <sup>f</sup> Serious imprecision. Lower and upper bounds of the 95% CI for the anticipated effect include important benefit and important harm

1288 <sup>g</sup> The RR was calculated from the adjusted OR (<https://clincalc.com/stats/convertor.aspx>) using the following formula

$$RR = \frac{OR}{(1 - P_{ref}) + (P_{ref} * OR)} = 1.368$$

RR = risk ratio; OR = odds ratio  
P<sub>ref</sub> = Prevalence of the outcome in the reference group

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1290 <sup>h</sup> Serious indirectness of the outcome, because the correction of diluted thrombin time (or unbound dabigatran concentration) is surrogate outcome and not a  
 1291 clinical outcome.

1292 <sup>i</sup> Serious imprecision, due to the rebound of diluted thrombin time in a proportion of patients: “Unbound-dabigatran concentrations remained below 20 ng per  
 1293 milliliter for 24 hours in the majority of patients; however, reappearance of levels above 20 ng per milliliter was observed in 114 of 497 patients (23.0%), mainly  
 1294 after 12 hours, with 67 patients having elevated levels only at the 24-hour measurement” <sup>2</sup>

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## 1297 Evidence to Decision Framework, PICO 5

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1299 05. Reversal of dabigatran with idarucizumab

1300 P: Patient with GIB currently taking dabigatran

1301 I: idarucizumab

1302 C: no idarucizumab

1303 O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein  
 1304 thrombosis, pulmonary embolus)

1305 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days, infusion-related events within 7 days

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	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<b>How substantial are the desirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>	See Evidence Profile Table.  The <u>desirable</u> anticipated effects with idarucizumab use (compared to no idarucizumab) are:  • <b>• dTT correction</b> in a proportion of patients (post hoc outcome, not critical outcome), but the duration of effect is unclear The guideline panel could not decide on the direction of the effect of the intervention on 30-day thrombotic events ( <b>critical outcome</b> ): one comparative cohort study that did not adjust for confounders showed a reduction in thrombotic events (26 less events per 1,000 patients), but a single-arm cohort study found a concerning high rate of thrombosis (11%) with the use of the intervention	
Undesirable Effects	<b>How substantial are the undesirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>● <b>Small</b></li> <li>○ Trivial</li> </ul>		

	<ul style="list-style-type: none"> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>The <u>undesirable</u> anticipated effects with idarucizumab use (compared to no idarucizumab) are:</p> <ul style="list-style-type: none"> <li>▪ increased 30-day <b>mortality</b>: 12 more events per 1,000 patients</li> </ul> <p>It is not possible to estimate the direction (let alone the magnitude) of the <b>relative</b> effect of idarucizumab (vs. no idarucizumab) on <b>further bleeding</b> or <b>infusion reactions</b></p>	
Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>● <b>important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>	
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>	There were small undesirable effects (increased mortality). Given that the direction of desirable effects was unclear, the guideline panel could not decide on the balance between desirable and undesirable effects.	

Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>• Large costs</li> <li>○ Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Cost of idarucizumab treatment in the US: around \$3,500 per 2 g dose (but varies considerably based on pharmacy coverage, insurance co-pays, government or privately paid insurance etc.)	
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>• Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>• No included studies</li> </ul>		
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>• Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

Feasibility	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Widely available; however, some institutions may not stock it because of its cost
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### Conclusions

**PICO: 05. For patients on dabigatran who are hospitalized or under observation with acute GIB (upper and/or lower) should idarucizumab administered compared to not?**

**O: CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days, infusion reactions

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention 6/6 votes: 100%	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	●	○	○	○
<b>Recommendation</b>	For patients on dabigatran who are hospitalized or under observation with acute GIB we suggest against the administration of idarucizumab (Conditional recommendation, very low certainty of evidence)				
<b>Justification</b>	Large cost of the intervention; uncertainty about whether the balance between desirable and effects favors the intervention or the comparator				
<b>Subgroup considerations</b>	Practically, this conditional recommendation against the intervention means that most patients with GI bleeding on dabigatran should not be given idarucizumab. However, idarucizumab could be used in a minority of patients with life threatening GI bleeding who had taken dabigatran within the past 24 hours, after considering potential thrombotic risk associated with underlying condition and cost of infusion.				

<b>Implementation considerations</b>	
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?
<b>Research priorities</b>	

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# 1321 **References, PICO 5**

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1323 1. Singh et al. Real World Outcomes Associated with Idarucizumab: Population-Based Retrospective Cohort Study. American Journal of  
1324 Cardiovascular Drugs. 2019

1325 2. Pollack et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017 Aug 3;377(5):431-441

1326 3. Pollack et al. Idarucizumab for dabigatran reversal. New England Journal of Medicine. 373 (6) (pp 511-520), 2015

1327 4. Van der Wall et al. Idarucizumab for Dabigatran Reversal in the Management of Patients with Gastrointestinal Bleeding. Circulation. 139  
1328 (6) (pp 748-756), 2019.

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1335 6. GIB: andexanet alfa for rivaroxaban/apixaban reversal

1336 **6. GIB: Reversal of rivaroxaban/apixaban with andexanet alfa**

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1339 P: Patient with GIB currently taking factor Xa inhibitor (rivaroxaban or apixaban)

1340 I: andexanet alfa

1341 C: no reversal agent

1342 O: **CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction,  
1343 deep vein thrombosis, pulmonary embolus)

1344 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days, infusion-related events within 7 days

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1346 Cohort studies without the comparator cohort required for this PICO

1347 1. **Connolly NEJM 2019** (Connolly et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. New England  
1348 Journal of Medicine. 380 (14) (pp 1326-1335), 2019) <sup>1</sup>

1349 • **ANNEXA-4 trial**

1350 • It is an interesting epistemological question whether this study should be regarded a prospective single-group cohort study  
1351 (as the authors call it) or a single arm interventional trial: the certainty of the evidence is very low with either approach.

1352 • 352 patients who had acute major bleeding within 18 hours after administration of a factor Xa inhibitor: rivaroxaban  
1353 (n=128), apixaban (n=194), enoxaparin (n=20), or edoxaban (n=10)

1354 ○ 227 patients with intracranial bleeding

1355 ○ 35 patients with other (non-GI, non-intracranial) bleeding

1356 ○ 90 patients with GIB. All 90 contributed to the "safety group". 62 patients contributed to the "efficacy group" (those  
1357 with baseline anti-Xa activity of at least 75 ng per milliliter and confirmed major bleeding)

1358 • Intervention: Andexanet. All patients received andexanet. **There was no comparator cohort/arm.**

- 1359 • Follow up: 30 days
- 1360 • Report outcomes for GIB separately only for hemostatic efficacy at 12 hours, and infusion reactions
- 1361 • Two co-primary efficacy outcomes:
  - 1362 ○ percent **change from baseline in anti-factor Xa activity** after andexanet treatment (see Figure 1A and 1B in this
  - 1363 paper)
  - 1364     ▪ Apixaban group: the median anti-factor Xa activity decreased from 149.7 ng/ml to 11.1 ng/ml
  - 1365     (92% reduction; 95% CI 91 to 93)
  - 1366     ▪ Rivaroxaban group: the median value decreased from 211.8 ng/ml to 14.2 ng/ml
  - 1367     (92% reduction; 95% CI 88 to 94).
  - 1368 ○ percentage of patients with **excellent or good hemostatic efficacy 12 hours after** the andexanet infusion, with
  - 1369 hemostatic efficacy assessed by an independent adjudication committee on the basis of prespecified criteria (see
  - 1370 comments below)
    - 1371     ▪ Excellent or good hemostatic efficacy occurred in 204 of 249 patients (82%) who could be evaluated
    - 1372     ▪ For the GIB "efficacy" group (n=62): excellent or good hemostatic efficacy at 12 hours: 85% (95% CI 76 to 94)
    - 1373     ▪ No report on recurrent GIB
- 1374 • Infusion reactions
  - 1375 ○ All patients: 2 non-severe reactions (2/352)
  - 1376 ○ GIB patients: none (0/90)
- 1377 • Thrombotic events
  - 1378 ○ All patients: 34/352 (9.7%)
  - 1379 ○ GIB patients: no separate results
- 1380 • Mortality
  - 1381 ○ All patients: 49/352 (14%)
  - 1382 ○ GIB patients: no separate results
- 1383 • **Concerns**



1384                   ○ The clinical outcome (“hemostatic efficacy at 12 hours”) was neither adequately relevant (“indirectness”, 12 hours is  
1385 too short; of note, it was changed from 24 to 12 hours by a post hoc decision), nor specific and nor sensitive for  
1386 assessment of a GI bleeding

1387                   ▪ **Hemostatic efficacy** for GIB was evaluated based on corrected hemoglobin and hematocrit **at 12 hours**  
1388 compared to baseline, with “excellent” hemostasis having a < 10% decrease and “good” hemostasis with a ≤  
1389 20% decrease (correction done by subtracting 1 g/dL from the hemoglobin or 3% from the hematocrit for  
1390 each unit of packed red blood cells given); and no more than 2 additional units of coagulation intervention  
1391 required.

1392                   ○ ITT results for efficacy outcomes were not reported. In clinical practice, baseline anti-Xa activity of at least 75 ng/ml  
1393 will not be determined for patients who have taken their last dose of factor Xa inhibitor within 18 hours

1394                   ○ Unclear criteria for volume resuscitation and use of inotropes – these would affect hemoglobin values

1395                   ○ Unclear etiology of GIB; unclear if /when the patients were scoped and what were the findings

1396                   ○ No description of co-interventions: PPIs, somatostatin analogs, endoscopic hemostasis (banding, thermocoagulation,  
1397 clips, injection treatment), interventional radiology, surgery

1398                   ○ Surprisingly, *“there was no significant relationship between hemostatic efficacy and a reduction in anti-factor Xa*  
1399 *activity during andexanet treatment (Fig. 3)”*. Of note, andexanet alpha was approved by FDA and Health Canada  
1400 based on evidence of reduction in anti-factor Xa activity with andexanet treatment in volunteers. In other words,  
1401 this study attempted to validate this surrogate endpoint, but unfortunately failed to do so. This means that either  
1402 “hemostatic efficacy” is not a valid outcome measure, or the reduction in anti-factor Xa activity is not a valid  
1403 surrogate endpoint (or both are not valid).

1404                   ○ There will be a post-marketing RCT, but it will not include GIB patients:  
1405 <https://clinicaltrials.gov/ct2/show/NCT03661528> A Randomized Clinical Trial of Andexanet Alfa [Andexanet Alfa for  
1406 Injection] in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor. Actual Study Start Date:  
1407 January 18, 2019. Estimated Study Completion Date: November 1, 2023. Only short-term outcomes: hemostatic  
1408 efficacy at 12 hours (blinded assessors), neurological outcomes at 24 h. Open label. No placebo, compared to “usual  
1409 care”.

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Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (exposure = andexanet)	Prognostic factors (other than exposure of interest) <b>similar among cohorts</b> – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and <b>similar among cohorts</b>	Follow up complete and <b>similar among cohorts</b>	Free of other bias	Results/Comments
Connolly NEJM 2019 <sup>1</sup>	OK	No comparative cohort	OK	Outcome detection methods valid, but there was <b>no comparative cohort</b>	Follow up complete but there was <b>no comparative cohort</b>	OK	
<div>Low risk of bias</div> <div>Unclear risk of bias</div> <div>High risk of bias</div>							

- Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included, because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not included, because it is an “indirectness” issue as per GRADE.
- Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias

Patients with GI bleeding: rivaroxaban/apixaban reversal with andexanet vs. no andexanet												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Andexanet	No andexanet	Relative (95% CI)	Absolute (95% CI)	
Further bleeding at 7 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
1 cohort study without comparator cohort (Connolly NEJM 2019) <sup>1</sup>	Serious <sup>a</sup>	Not applicable	Very serious <sup>b</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		9/62	-	-	-	
Thrombotic events within 30 days (critical outcome)												
1 cohort study without comparator cohort (Connolly NEJM 2019) <sup>1</sup>	Serious <sup>a</sup>	Not applicable	Serious <sup>d</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		34/352	-	-	-	
Mortality within 30 days (important outcome, but not critical for decision making)												
1 cohort study without comparator cohort (Connolly NEJM 2019) <sup>1</sup>	Serious <sup>a</sup>	Not applicable	Serious <sup>e</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		49/352	-	-	-	
Infusion-related events within 7 days (important outcome, not critical for decision making)												
1 cohort study without comparator cohort (Connolly NEJM 2019) <sup>1</sup>	Serious <sup>a</sup>	Not applicable	Not serious <sup>f</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		2/352 (for GI bleeding patients: 0/90)	-	-	-	
Change from baseline in anti-factor Xa activity (outcome included by <i>post hoc</i> decision; important, but not critical for decision making)												
1 cohort study without comparator	Serious <sup>a</sup>	Not applicable	Very serious <sup>h</sup>	Not serious	None	⊕⊕⊕⊕ VERY LOW	Apixaban users: 92% (91% - 93%) reduction	-	-	-	-	

cohort (Connolly NEJM 2019) <sup>1</sup>								Rivaroxaban users: 92% (88% - 94%) reduction				
								Also, visual presentation (graphs)				

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# 1436 **Footnotes**

1437 <sup>a</sup> Serious risk of bias, because the study did not have comparator cohort with no use of andexanet.

1438 <sup>b</sup> Very serious indirectness of the outcome. The outcome of not having “excellent or good hemostatic efficacy 12 hours after the andexanet infusion” is very  
1439 different from and does not correspond well to the definitions of further bleeding in studies in patients with GI bleeding. Furthermore, the timing of outcome  
1440 measurement (12 hours after the andexanet infusion) is much shorter than the desired timing at 7 days. Also, there is indirectness of the population: ITT  
1441 results were not reported. This is the “efficacy population” of 69% (62/90) of the patients with GI bleeding, i.e., “those with baseline anti-Xa activity of at least  
1442 75 ng/ml and confirmed major bleeding”. In real life, patients with major GI bleeding while on rivaroxaban or apixaban will not be tested for “baseline anti-Xa  
1443 activity of at least 75 ng/ml”. Finally, 20/352 patients were in treatment with enoxaparin.

1444 <sup>c</sup> Very serious imprecision, even for the event rate in the intervention group, due to small number of events. The relative efficacy cannot be calculated.

1445 <sup>d</sup> Serious indirectness of the population. Mixed population: only 25.6% patients had GI bleeding; 64.5% had intracranial hemorrhage; and the remaining had  
1446 other bleeds. Patients with intracranial hemorrhage are very different from the target population of this guideline, especially with regards to their risk for  
1447 thrombotic events. Also, 20/352 patients were in treatment with enoxaparin.

1448 <sup>e</sup> Serious indirectness of the population. Mixed population: only 25.6% patients had GI bleeding; 64.5% had intracranial hemorrhage; and the remaining had  
1449 other bleeds. Patients with intracranial hemorrhage are very different from the target population of this guideline, especially with regards to the mechanisms  
1450 leading to death and the influence of the speed of rapid anticoagulant reversal on the mechanisms leading to death. Also, 20/352 patients were in treatment  
1451 with enoxaparin.

1452 <sup>f</sup> There was no serious indirectness, even if the total results (for total, mixed study population) are included. It is not plausible that the risk of infusion reactions  
1453 will differ according to the type of bleed.

1454 <sup>h</sup> Very serious indirectness of the outcome, because the change from baseline in anti-factor Xa activity is surrogate outcome and not a clinical outcome. Also,  
1455 there is indirectness of the population: ITT results were not reported. This is the “efficacy population” of 69% (62/90) of the patients with GI bleeding, i.e.,  
1456 “those with baseline anti-Xa activity of at least 75 ng/ml and confirmed major bleeding”. In real life, patients with major GI bleeding while on rivaroxaban or  
1457 apixaban will not be tested for “baseline anti-Xa activity of at least 75 ng/ml”.

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1460 **Evidence to Decision Framework, PICO 6**

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1462 06. Rivaroxaban or apixaban reversal with andexanet

1463 P: Patient with GIB currently taking rivaroxaban or apixaban

1464 I: andexanet alfa

1465 C: no andexanet alfa

1466 O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

1468 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days, infusion-related events within 7 days

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	<b>Judgement</b> (Panel's judgments highlighted in yellow color)	<b>Research evidence</b>	<b>Additional considerations</b>
<b>Desirable Effects</b>	<b>How substantial are the desirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>	<p>See Evidence Profile Table. No comparative results for clinical outcomes.</p> <p>The <u>desirable</u> anticipated effects with andexanet alfa use (compared to no andexanet alfa) are:</p> <ul style="list-style-type: none"> <li>▪ <b>reduction of anti-factor Xa activity</b> (post hoc outcome, not critical outcome), but the duration of effect is unclear</li> </ul> <p>It is not possible to estimate the direction (let alone the magnitude) of the <b>relative</b> effect of andexanet alfa (vs. no andexanet alfa) on <b>any of the clinical outcomes of interest for this guideline</b></p>	
<b>Undesirable Effects</b>	<b>How substantial are the undesirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>		

Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>• <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>• <b>Important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>	
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention (andexanet alfa)</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>• <b>Don't know</b></li> </ul>	Unknown magnitude of desirable anticipated effects vs. unknown magnitude of undesirable anticipated effects. Very low certainty of evidence.	
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>• <b>Large costs</b></li> <li>○ Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<i>"Treatment with the high dose would cost \$49 500 for the drug alone. The low-dose regimen would cost half as much" <sup>2</sup></i>	

Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● <b>Moderate</b></li> <li>○ High</li> <li>○ No included studies</li> </ul>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● <b>No included studies</b></li> </ul>		
Acceptability	<p><b>Is the intervention (andexanet alfa) acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● <b>Yes</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Feasibility	<p><b>Is the intervention (andexanet alfa) feasible to implement?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● <b>Yes</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

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1474 **Conclusions**

1475 **PICO: 06. For patients on rivaroxaban or apixaban who are hospitalized or under observation with acute GIB (upper and/or lower)**  
 1476 **should andexanet alpha administered compared to not?**

1477 **O: CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial  
 1478 infarction, deep vein thrombosis, pulmonary embolus)

1479 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days, infusion reactions

1480

Type of recommendation	Strong recommendation against the intervention 	Conditional recommendation against the intervention 6/6 votes: 100% 	Conditional recommendation for either the intervention or the comparison 	Conditional recommendation for the intervention 	Strong recommendation for the intervention 
<b>Recommendation</b>	For patients on rivaroxaban or apixaban who are hospitalized or under observation with acute GIB, we suggest against andexanet alpha administration (Conditional recommendation, very low certainty of evidence)				
<b>Justification</b>	Large cost of the intervention; uncertainty about whether the balance between desirable and effects favors the intervention or the comparator				
<b>Subgroup considerations</b>	<p>Practically, this conditional recommendation against the intervention means that most patients with GI bleeding on rivaroxaban or apixaban should not be given andexanet alpha.</p> <p>However, andexanet alpha could be used in a minority of patients with life threatening GI bleeding, after considering potential thrombotic risk associated with underlying condition and cost of infusion.</p>				
<b>Implementation considerations</b>					
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?				
<b>Research priorities</b>					

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## References, PICO 6

1. Connolly et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. New England Journal of Medicine. 380 (14) (pp 1326-1335), 2019
2. Anonymous. Andexxa: an antidote for apixaban and rivaroxaban. JAMA 2018;60:99-100.

7. GIB: PCC for DOAC reversal

## 7. GIB: Reversal of DOAC with PCC

P: Patient with GIB currently taking any DOAC

I: PCC

C: no reversal agent

O: **CRITICAL:** Further bleeding within 7 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days, transfusion-related event (congestive heart failure, pulmonary edema) within 7 days

**Overall remarks:** The main literature search identified only 2 cohort studies that had comparator arms, Schulman TR 2017 <sup>1</sup> and Smythe JTT 2015 <sup>2</sup>, both of which have very serious limitations (see descriptions below).

Though our main literature search, and well as through the additional searches (not confined to GI bleeding) of systematic reviews (SRs) and guidelines, we identified several SRs (such as refs <sup>3</sup> and <sup>4</sup>) that assessed the role of PPC in patients on DOACs, but none had identified any additional comparative cohort studies. A SR <sup>5</sup> that was published after the formal date of our search, confirmed the low quality of these single arm cohort studies that do not allow the reader to draw any conclusions about whether PCC improved or worsened clinical outcomes.

1511 The most recent guideline that used the GRADE approach and reported detailed evidence profiles was the ASH 2018 guideline <sup>6</sup>, the authors of  
1512 which conducted their own SR in March 2017 and were only able to identify 8 non-comparative cohort studies (see  
1513 <https://dbep.gradeapro.org/profile/2ec6099d-9b00-4bac-bc31-34653ee10737>).

1514 We included 4 RCTs in healthy volunteers (see description below): one RCT <sup>7</sup> that assessed bleeding following punch biopsy and clotting assays,  
1515 and three RCTs <sup>8, 9, 13</sup> that only assessed clotting assays. We need to emphasize that we did not conduct a formal systematic literature search for  
1516 studies assessing surrogate outcomes on healthy volunteers. Our *a priori* decision was to only include comparative studies in patients with GI  
1517 bleeding that reported our pre-determined clinical outcomes. The healthy volunteer studies were included by a *post hoc* decision, in a non-  
1518 formal fashion, as examples of the underlying physiology and pharmacodynamics.

1519 We did not include RCTs that assessed the effect of (human) PPC on the reversal of DOACs in animal models, even those that measured clinical  
1520 outcomes (for example two RCTs that used the rabbit kidney incision model <sup>10, 11</sup>, and showed reversal of dabigatran anticoagulation and  
1521 edoxaban anticoagulation) because of the critically serious indirectness of the population (non-human) and the outcomes (duration of minutes,  
1522 limited similarity to the mechanism of GI bleeding)

1523

1524 Cohort studies with the comparator cohort needed for this PICO

1525 1. **Schulman TR 2017** (Schulman et al. Reversal of dabigatran-associated major bleeding with activated prothrombin concentrate: A  
1526 prospective cohort study. Thrombosis Research. 152 (pp 44-48), 2017) <sup>1</sup>

- 1527
- 1528 • N=14 (5 patients with GIB). Acute active major bleeding while on **dabigatran** and treated with aPCC (i.e., 4-Factor PCC that  
contains coagulation factors II, IX, and X, and activated VII (FVIIa))
  - 1529 • Should not have received additional hemostatic agents (tranexamic acid was allowed).
  - 1530 • **Compared to matched patients** (N=28) **from 5 phase III trials** <sup>12</sup> (“cases suffering major bleeding on dabigatran in the phase III  
1531 trials on treatment of venous thromboembolism or stroke prophylaxis in atrial fibrillation”).
    - 1532 ○ Majeed TR 2016 <sup>12</sup>: Reports on 1034 individuals experiencing 1121 MBEs (696 on dabigatran, and 425 on warfarin) in 5  
1533 phase III randomized controlled trials were assessed independently by two investigators.
    - 1534 ○ “After matching for type of bleed and age, it was not possible to find matches for sex for 4 of the 28 historical cases and  
1535 this criterion was violated”
  - 1536 • The “effectiveness” rating was assessed at 24 h by the treating physicians for GI bleeding (“The study staff contacted the treating  
1537 physician for assessment of the effectiveness of the aPCC treatment within 7 days from the event”; however, the rating was  
1538 assessed at 24 hours). The criteria were not necessarily clinically relevant for patients with GIB (see suppl material)

- **Good:**  $\leq 10\%$  decrease in both Hb/Hct at 24 hours compared to baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb  $\leq 80 \pm 1$  g/L [i.e. transfuse PRBCs if the Hb  $\leq 80 \pm 1$  g/L])
- **Moderate:**  $>10$  to  $\leq 20\%$  decrease in both Hb/Hct at 24 hours compared with baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb  $\leq 80 \pm 1$  g/L [i.e. transfuse PRBCs if the Hb  $\leq 80 \pm 1$  g/L])
- **Poor/None:**  $>20\%$  decrease in both Hb/Hct at 24 hours compared to baseline (initial correction of decrease in hemoglobin with PRBCs, with a transfusion trigger of a Hb  $\leq 80 \pm 1$  g/L [i.e. transfuse PRBCs if the Hb  $\leq 80 \pm 1$  g/L])
- **For the 5 GIB patients**
  - Effectiveness: 4 good, 1 moderate (“not good” = 20%). In the matched historical cohort: 9 good, 1 moderate (“not good” = 101%) P=0.6 (the paper reports P=1.0, but we calculated it as 0.6)
  - 30-day mortality: 0/5 (for the whole study: 1/14 on aPCC vs 7/28)
  - 30-day venous arterial thromboembolic events: 0/5 (for the whole study: 0/14 on aPCC vs 1/28)

2. **Smythe JTT 2015** (Smythe MA, et al. Dabigatran versus warfarin major bleeding in practice: an observational comparison of patient characteristics, management and outcomes in atrial fibrillation patients. J Thromb Thrombolysis. 2015;40(3):280-287) <sup>2</sup>

- 28 patients with GIB on **dabigatran**
  - 2 received 4F PCC, and both (100%) died within 30 days
  - Among the remaining 26 patients who did not receive PCC, it is not clear how many died.
    - at best 0/27 died during the index admission
    - at worse 3/27 (11.1%) died during the index admission).
- Results not adjusted for confounders. The comparison is at very high risk of bias because of confounding by (severity of) indication.

Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (exposure = PCC)	Prognostic factors (other than exposure of interest) <b>similar</b> among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Schulman TR 2017	OK	No. The comparative cohort was historical (collected from the dabigatran arms of 5 previous RCTs). The cohorts were not adequately matched or adjusted (they were only matched for age and type of bleed)	OK	Unclear	Unclear	OK	Reported separate outcomes for GIB  Indirectness issues: - activated PCC - outcome of “effectiveness”
Smythe JTT 2015	OK	No. The cohorts were not adjusted for confounders	OK	OK	OK	OK	Reported separate outcomes for GIB
Low risk of bias							
Unclear risk of bias							
High risk of bias							

1569 Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included,  
1570 because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid  
1571 methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of  
1572 interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not  
1573 included, because it is an “indirectness” issue as per GRADE.

1574 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
1575 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias.

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## 1577 RCTs in healthy volunteers

- 1578 1. **Zahir Circulation 2015** (Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-  
1579 factor prothrombin complex concentrate. Circulation 2015;131:82-90) <sup>7</sup>

- A double-blind, randomized, placebo controlled, 2-way crossover study that assessed the effects of **edoxaban** on **bleeding following punch biopsy** on healthy volunteers (n=110) and reversal by 4F-PCC.
- Single dose edoxaban, then “infusions were administered at the maximum rate of 210 IU/min, lasted 15 to 20 minutes, and were timed to end 2.25 hours after the dose of edoxaban”.
- The three doses of PCC were not administered randomly or in a blinded fashion – they were administered consecutively in a dose-descending order. *“Three doses of 4F-PCC (50, 25, and 10 IU/kg) were investigated in 3 separate cohorts in a dose-descending manner. Descending doses of 4F-PCC were studied until no reversal was observed.”*
  - Therefore results regarding the differences in efficacy between the 3 doses of PCC were unblinded, non-randomized, observational type data
- A punch biopsy (5 mm diameter, 5 mm depth) on the back of the thigh, was performed 30 minutes after the end of 4F-PCC or placebo infusion.
- The observation period was short, given that mean bleeding times were less than 20 min.
- Primary outcome: bleeding duration
- Secondary outcomes: bleeding volume and clotting assays
- Conclusion of the authors: *“The 4F-PCC dose-dependently reversed the effects of edoxaban (60 mg), with complete reversal of bleeding duration and endogenous thrombin potential and partial reversal of prothrombin time following 50 IU/kg”*
- **However, as seen in Figure 3 in the article, the 95% CI (which extend to an equal length downwards too) between placebo and PCC overlap widely for every dose of PCC.**
- The effect on endogenous thrombin potential is shown in Figure 3C in this paper: 50 IU/Kg PCC was different (statistically significant) from placebo
- The effect of PCC on prothrombin time was not different from placebo.

2. **Eerenberg Circulation 2011** (Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124:1573-1579)<sup>8</sup>
  - placebo controlled RCT in healthy male volunteers (n=12) that assessed reversal of anticoagulation of **rivaroxaban or dabigatran** as measured by clotting assays.
  - Treated for 2.5 days with DOAC
  - Subjects were unblinded to the anticoagulant but blinded to placebo or 4F-PCC (50 IU/kg).
  - Assessors were blinded to the treatment administered.

- “Rivaroxaban induced a significant prolongation of the prothrombin time (15.8±1.3 versus 12.3±0.7 seconds at baseline; P<0.001) that was immediately and completely reversed by PCC (12.8±1.0; P<0.001). The endogenous thrombin potential was inhibited by rivaroxaban (51±22%; baseline, 92±22%; P=0.002) and normalized with PCC (114±26%; P<0.001), whereas saline had no effect”.
- “Dabigatran increased the activated partial thromboplastin time, ecarin clotting time, and thrombin time. Administration of PCC did not restore these coagulation tests”.

3. **Levi JTH 2014.** (Levi M, Moore K, Castillejos C, Kubitz D, Berkowitz S, Goldhaber S, Raghoobar M, Patel, Weitz J, Levy J. Comparison of three- and four-factor prothrombin complex concentrates on the anticoagulant effects of rivaroxaban in healthy volunteers. J Thromb Haemost. 2014;12:1428–1436) <sup>9</sup>
  - placebo controlled RCT in healthy volunteers (n=35) that assessed reversal of anticoagulation of **rivaroxaban** as measured by clotting assays.
  - 4.5 days of rivaroxaban 20 mg twice daily to obtain supratherapeutic steady-state concentration
  - Randomized to saline or 3F-PCC (50IU/kg) or 4F-PCC (50 IU/kg).
  - Apparently not blinded
  - Prothrombin time
    - According to the authors “Within 30 min, four-factor PCC reduced mean prothrombin time by 2.5–3.5 s, whereas three-factor PCC produced only a 0.6–1.0-s reduction”. However, the study was not designed to compare 3F-PCC with 4F-PCC.
    - See Figures 2 and 3 in the article: only 4F-PCC had statistically significant differences in PT compared to saline, and only between 4 and 6 hours
    -
  - Endogenous thrombin potential
    - According to the authors “In contrast, three-factor PCC reversed rivaroxaban- induced changes in thrombin generation [endogenous thrombin potential] more than four-factor PCC”. However, the study was not designed to compare 3F-PCC with 4F-PCC.
    - See Figure 4 in the article: both 4F-PCC and 3F-PCC had non-significant (borderline significant) differences in ETP compared to saline, between 12 and 28 hours
4. **Song JTH 2017.** Song JTH 2017 Song et al. Reversal of apixaban anticoagulation by four-factor prothrombin complex concentrates in healthy subjects: a randomized three-period crossover study. J Thromb Haemost 2017; 15:2125-2137

- placebo controlled RCT in healthy volunteers (n=15) that assessed reversal of anticoagulation of apixaban as measured by clotting assays.
- three-period crossover study (11 day washout between periods)
- 3 days of apixaban 10 mg twice daily
- Randomized to
  - i. saline
  - ii. 4F-PCC: Cofact (50 IU/ kg)
  - iii. 4F-PCC: Beriplex (50 IU/ kg),
- Not blinded
- Outcomes
  - i. ETP (endogenous thrombin potential, measured with a thrombin generation assay) change from pre-PCC baseline: both 4F-PPCs were better than saline
    - Both PCCs returned ETP to pre-apixaban baseline levels 4 h after PCC infusion, versus 45 h for placebo.
    - For both PCCs, mean ETP peaked 21 h after PCC initiation, and then slowly decreased over the following 48 h.  
See figure 2A in the paper
  - ii. Prothrombin time: both 4F-PPCs were better than saline
  - iii. anti-FXa activity: neither of the 2 4F-PCCs had an effect on anti-FXa activity (AFA), see figure 3C in that paper

Risk of bias assessment of RCTs							
Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Comments
Zahir 2015 <sup>7</sup>	Unclear	Unclear	Blinded for the comparison of PCC vs placebo. However, note that the 3 doses of PCC were not administered randomly or blinded – they were administered consecutively in a dose-descending order.	OK	OK	OK	
Eerenberg 2011	Unclear	Unclear	OK	OK	OK	OK	
Levi 2014	Unclear	Unclear	Apparently not blinded	OK	OK	OK	
Song 2017	OK		Not blinded				
Low risk of bias							
Unclear risk of bias							
High risk of bias							

Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias



## 1679 Evidence profile, PICO 7

Patients with GI bleeding: DOAC reversal with PCC vs. none												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	PCC	no reversal agents	Relative (95% CI)	Absolute (95% CI)	
Further bleeding at 7 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
1 cohort study (Schulman 2017) <sup>1</sup> on <b>dabigatran</b>  (only patients with GI bleeding)	Very serious <sup>a</sup>	Not applicable	Serious <sup>b</sup>	Very serious <sup>d</sup>	None	⊕⊕⊕⊕ VERY LOW		1/5	1/10	RR 2.00 (0.16 - 25.75)	Risk <u>without</u> PCC: 100 events per 1,000. With PCC: 100 <b>more</b> per 1,000 (from 84 <b>less</b> to <b>noncalculable more</b> )	Remark: the direction of the effect is opposite of the theoretically predicted direction
1 RCT (Zahir 2015) <sup>7</sup> on <b>edoxaban</b>  (Healthy volunteers; bleeding following punch biopsy of skin)	Moderately serious <sup>e</sup>	Not applicable	Critically serious <sup>f</sup>	Serious <sup>g</sup>	None	⊕⊕⊕⊕ VERY LOW		Continuous outcome		No statistically significant difference between PCC and placebo	Not calculable	
Thrombotic events within 30 days (critical outcome)												
1 cohort study (Schulman 2017) <sup>1</sup> on <b>dabigatran</b>  (mixed population: GI and non-GI bleeding)	Very serious <sup>a</sup>	Not applicable	Serious <sup>g</sup>	Very serious <sup>d</sup>	None	⊕⊕⊕⊕ VERY LOW		0/14	1/28	RR 0.67 (0.03 - 15.40)	Risk <u>without</u> PCC: 36 events per 1,000. With PCC: 12 <b>less</b> per 1,000 (from 35 <b>less</b> to 518 <b>more</b> )	Remark: the direction of the effect is opposite of the theoretically predicted direction
Mortality within 30 days (important outcome, but not critical for decision making)												
1 cohort study (Smythe 2015) <sup>2</sup> on <b>dabigatran</b> (only patients with GI bleeding)	Very serious <sup>h</sup>	Serious <sup>i</sup>	Moderately serious <sup>j</sup>	Very serious <sup>k</sup>	None	⊕⊕⊕⊕ VERY LOW	2/2	Worst case scenario 3/27	RR From 28.00 (1.57 - 500.53) To 5.00	Risk <u>without</u> PCC: 0 to 111 events per 1,000. With PCC: 444 to <b>noncalculable more</b> per 1,000		

									Best case scenario 0/27	(1.17 - 21.39)	(from 19 more to <b>noncalculable</b> more)	
1 cohort study (Schulman 2017) <sup>1</sup> on <b>dabigatran</b>  <b>(only patients with GI bleeding)</b>	<b>Very serious <sup>a</sup></b>		<b>Serious <sup>l</sup></b>	<b>Very serious <sup>d</sup></b>	None	⊕⊖⊖⊖ <b>VERY LOW</b>		1/14	7/28	RR 0.33 (0.04 - 2.48)	Risk <u>without</u> PCC: 250 events per 1,000. With PCC: 167 <b>less</b> per 1,000 (from 245 <b>less</b> to 370 more)	
<b>Transfusion-related events (fluid overload) within 7 days</b> (important outcome, not critical for decision making)												
No comparative studies						-		-	-	-	-	
<b>Correction of anticoagulation measured by clotting assays</b> (measured within 24 or 28 hours) (outcome included by <b>post hoc decision</b> ; important, but not critical for decision making)												
4 RCTs in healthy volunteers on direct Xa inhibitors (rivaroxaban <sup>8,9</sup> , edoxaban <sup>7</sup> , apixaban <sup>13</sup> )	<b>Moderately serious <sup>e</sup></b>	<b>Serious <sup>m</sup></b>	<b>Very serious <sup>n</sup></b>	<b>Serious <sup>o</sup></b>	None	⊕⊖⊖⊖ <b>VERY LOW</b>		Prothrombin time (continuous outcome)	4F-PCC better than saline <sup>8, 9, 13</sup>  4F-PCC <u>not</u> different from saline <sup>7</sup>  3F-PCC <u>not</u> different from saline <sup>9</sup>	Not calculable	-	
								Endogenous thrombin potential (continuous outcome)	4F-PCC better than saline <sup>7, 8, 13</sup>  4F-PCC <u>not</u> different from saline <sup>9</sup>			
1 RCT in healthy volunteers on dabigatran <sup>8</sup>	<b>Moderately serious <sup>e</sup></b>	<b>Serious <sup>m</sup></b>	<b>Very serious <sup>n</sup></b>	Not serious <sup>p</sup>	None	⊕⊖⊖⊖ <b>VERY LOW</b>		Activated partial thromboplastin time; ecarin clotting time; thrombin time (continuous outcomes)	4F-PCC <u>not different</u> from saline <sup>8</sup>	Not calculable	-	

1681 <sup>a</sup>Very serious risk of bias. The cohorts were only matched for age (and type of bleeding, but in the analysis for “further bleeding” we only included patients  
1682 with GI bleeding), without adjustment for confounders. Very serious confounding by severity (of indication) is expected in this study design and in this setting.

1683 <sup>b</sup>Serious indirectness of the outcome. The outcome of “effectiveness in 24 h”, as defined in this study, is very different from the target outcome of this  
1684 guideline, i.e., further bleeding in 7 days. Also, the intervention was activated PCC. Note: the population had been taking dabigatran (no other DOACs)

1685 <sup>c</sup>Very serious imprecision. Very few events. Very wide 95% CI that include both large benefit and large harm.

1686 <sup>d</sup>Very serious risk of bias. The cohorts were only matched for age and type of bleeding, without adjustment for confounders. Very serious confounding by  
1687 severity (of indication) is expected in this study design and in this setting.

1688 <sup>e</sup>Moderately serious risk of bias for the comparisons between each dose of PCC and placebo (unclear sequence generation, unclear allocation concealment).  
1689 Two of the RCTs (Song 2017, Levi 2014) were not blinded, but the outcomes were relatively objectively measured.

1690 <sup>f</sup>Critically serious indirectness overall. Very serious indirectness of the population. These were healthy volunteers who only took a single dose of edoxaban.  
1691 Furthermore, the type of bleeding (punch biopsy of the skin) and the outcome (bleeding duration, with a timeframe of minutes) are only marginally relevant to  
1692 the pathophysiology of GI bleeding and the predetermined outcome of clinically severe further bleeding within 7 days. Remark: the population took edoxaban  
1693 (no other DOACs)

1694 <sup>g</sup>Serious indirectness of the population. Only 27% of patients had GI bleeding. Also, the intervention was activated PCC. Remark A: We could not extract  
1695 comparative results for the subpopulation with GI bleeding. The only comparative results available referred to the total study population. Remark B: the  
1696 population had been taking dabigatran (no other DOACs)

1697 <sup>h</sup>Very serious risk of bias. The cohorts were not matched or adjusted for confounders. Very serious confounding by severity (of indication) is expected in this  
1698 study design and in this setting.

1699 <sup>i</sup>Serious inconsistency between the results of the two studies

1700 <sup>j</sup>Moderately serious indirectness: the intervention was activated PCC. Remark: the population had been taking dabigatran (no other DOACs)

1701 <sup>k</sup>Very serious imprecision. Very few events. Very high fragility index for the comparative results. Wide range of possible event rates in the comparator cohort.

1702 <sup>l</sup>Serious indirectness of the population. Only 27% of patients had GI bleeding. Remark: We could not extract comparative results for the subpopulation with GI  
1703 bleeding. The only comparative results available referred to the total study population. Note: the population had been taking dabigatran (no other DOACs)

1704 <sup>m</sup>Inconsistent results among the three studies

1705 <sup>n</sup>Very serious indirectness of the population. Healthy volunteers who only took a few doses of DOAC. Not experiencing spontaneous serious bleeding. Remark:  
1706 the population took rivaroxaban (no other DOACs)

1707 <sup>o</sup>Serious imprecision. Small number of participants. The 95% CI widely overlap for most time-points for most comparisons between PCC and saline.

1708 <sup>p</sup> No serious imprecision. The results are precise enough to rule out a clinically important difference between PCC and saline.

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## 1714 Evidence to Decision Framework, PICO 7

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### 1716 07. DOAC reversal with PCC vs none

1717 P: Patient with GIB currently taking DOAC

1718 I: PCC

1719 C: no reversal agents

1720 O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

1722 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days, transfusion-related events (congestive heart failure, pulmonary edema) within 7 days

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	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<b>How substantial are the desirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>● Don't know</li> </ul>	See Evidence Profile Table. <b>In patients on direct thrombin inhibitors (dabigatran):</b> <ul style="list-style-type: none"> <li>• The <u>desirable</u> anticipated effects with PPC (compared to no treatment) are: Reduced thrombotic events (critical outcome): 12 less per 1,000 patients.</li> <li>•</li> <li>• The <u>undesirable</u> anticipated effects with PPC (compared to no treatment) are: Increased further bleeding (critical outcome): 100 more per 1,000 patients.</li> <li>• It is not possible to estimate the direction of the effect of PPC on the other clinical outcomes (mortality, transfusion related events)</li> <li>• PCC had an inconsistent effect on clotting assays (surrogate outcome, post-hoc outcome)</li> </ul>	Dabigatran: The two cohort studies reported diametrically opposed results for mortality.
Undesirable Effects	<b>How substantial are the undesirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>● Don't know</li> </ul>	<b>In patients on Xa inhibitors (apixaban, edoxaban, or rivaroxaban):</b> <ul style="list-style-type: none"> <li>• PCC may have <b>trivial</b> effect on further bleeding.</li> <li>• It is not possible to estimate the direction of the effect of PPC on other clinical outcomes (further bleeding, mortality, transfusion related events)</li> </ul>	

		<ul style="list-style-type: none"> <li>It is not possible to estimate the magnitude of the effect of PPC on clotting assays (surrogate outcome, post-hoc outcome).</li> </ul>	
<b>Certainty of evidence</b>	<b>What is the overall certainty of the evidence of effects?</b> <ul style="list-style-type: none"> <li>Very low</li> <li>Low</li> <li>Moderate</li> <li>High</li> <li>No included studies</li> </ul>	See Evidence Profile Table.	
<b>Values and Preferences</b>	<b>Is there important uncertainty about or variability in how much people value the main outcomes?</b> <ul style="list-style-type: none"> <li>Important uncertainty or variability</li> <li>Possibly important uncertainty or variability</li> <li>Probably no important uncertainty or variability</li> <li>No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>	
<b>Balance of effects</b>	<b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b> <ul style="list-style-type: none"> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> <li>Varies</li> <li>Don't know</li> </ul>	<p>Patients on direct thrombin inhibitors (dabigatran): the balance between desirable and undesirable effects is unknown</p> <p>Patients on Xa inhibitors (apixaban, edoxaban, or rivaroxaban): the balance between desirable and undesirable effects is unknown</p>	

Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"><li>○ Large costs</li><li>● <b>Moderate costs</b></li><li>○ Negligible costs and savings</li><li>○ Moderate savings</li><li>○ Large savings</li> <li>○ Varies</li><li>○ Don't know</li></ul>	<p>Per Canada Blood Services, Octaplex and Beriplex are both priced at \$0.57 per IU</p> <table><tr><th colspan="3">Table 2. Dose of Study Treatment per Baseline INR</th></tr><tr><th>Baseline INR</th><th>4F-PCC Dose, IU of Factor IX per kg Body Weight*</th><th>Plasma Dose, mL per kg Body Weight*</th></tr><tr><td>2 to &lt;4</td><td>25</td><td>10</td></tr><tr><td>4–6</td><td>35</td><td>12</td></tr><tr><td>&gt;6</td><td>50</td><td>15</td></tr></table> <p>4F-PCC indicates 4-factor prothrombin complex concentrate; and INR, international normalized ratio. *Dose calculation based on 100 kg body weight for patients weighing &gt;100 kg. Maximum dose ≤5000 IU of factor IX (4F-PCC) or ≤1500 mL (plasma).</p> <p>Therefore, if the dosing regimen of Sarode 2013 is used, for a patient with a weight of 75 Kg and INR 2-4, the cost will be CAD 1,068 or approximately USD 1,500</p>	Table 2. Dose of Study Treatment per Baseline INR			Baseline INR	4F-PCC Dose, IU of Factor IX per kg Body Weight*	Plasma Dose, mL per kg Body Weight*	2 to <4	25	10	4–6	35	12	>6	50	15	
Table 2. Dose of Study Treatment per Baseline INR																		
Baseline INR	4F-PCC Dose, IU of Factor IX per kg Body Weight*	Plasma Dose, mL per kg Body Weight*																
2 to <4	25	10																
4–6	35	12																
>6	50	15																
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"><li>○ Very low</li><li>○ Low</li><li>● <b>Moderate</b></li><li>○ High</li> <li>○ No included studies</li></ul>																	
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"><li>○ Favors the comparison</li><li>○ Probably favors the comparison</li><li>○ Does not favor either the intervention or the comparison</li><li>○ Probably favors the intervention</li><li>○ Favors the intervention</li> <li>○ Varies</li><li>● <b>No included studies</b></li></ul>																	

Acceptability	<p>Is the intervention (PCC) acceptable to key stakeholders?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		
Feasibility	<p>Is the intervention (PCC) feasible to implement?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		

## Conclusions

**PICO 07. For patients on DOACs who are hospitalized or under observation with acute GIB (upper and/or lower) should PCC be administered compared to no reversal agents?**

**O: CRITICAL:** Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days; transfusion-related events (congestive heart failure, pulmonary edema) within 7 days

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention 6/6 votes: 100%	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

<b>Recommendation</b>	For patients on DOACs who are hospitalized or under observation with acute GIB, we suggest against PCC administration (Conditional recommendation, very low quality of evidence)
<b>Justification</b>	
<b>Subgroup considerations</b>	Practically, this conditional recommendation against the intervention means that most patients with GI bleeding on DOACs should not be given PCC. However, PCC could be used in a minority of patients with life threatening GI bleeding, after considering potential thrombotic risk associated with underlying condition and cost of infusion.
<b>Implementation considerations</b>	
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?
<b>Research priorities</b>	

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#### 1738 **References for PICO 7**

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1764 strategies for dabigatran- or warfarin related major bleeding events. *Thromb. Res.* 140 (2016) 81–88.
- 1765 13. Song et al. Reversal of apixaban anticoagulation by four-factor prothrombin complex concentrates in healthy subjects: a randomized  
1766 three-period crossover study. *J Thromb Haemost* 2017; 15:2125-2137

1782 8. GIB: platelet transfusion for antiplatelet reversal

1783 **8. GIB: Reversal of antiplatelet with platelet transfusion**

1784

1785 P: Patients with GIB currently taking antiplatelet agents

1786 I: platelet transfusion

1787 C: no platelet transfusion

1788 O: **CRITICAL:** Further bleeding within 7 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction,  
1789 deep vein thrombosis, pulmonary embolus)

1790 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days, transfusion-related event (congestive heart failure, pulmonary edema) within 7 days

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1792

1793 **Overall comments:** through our main literature search, supplementary searches of non-GI systematic reviews and older guidelines, and  
1794 backward and forward citation searching, we identified two cohort studies: Zakko CGH 2017 <sup>1</sup> and Victor CCM 2014 <sup>2</sup>.

1795 A 2012 SR by Razzaghi & Barkun <sup>3</sup>, did not identify any study specifically assessing patients with active GI bleeding.

1796 A 2020 SR by Maida et al <sup>4</sup>, identified only Zakko CGH 2017.

1797 A 2019 narrative review by Nagalla et al <sup>5</sup>, that was not restricted to GI bleeding, identified Zakko CGH 2017 and two RCTs in patients with  
1798 intracranial hemorrhage (ICH):

- 1799       • Li JNS 2013 <sup>6</sup>. We did not include this RCT (on patients with acute hypertensive basal ganglia hemorrhage undergoing craniotomy),  
1800       because only the patients on ASA therapy who based on a platelet aggregation test were “ASA-sensitive” entered the randomized part  
1801       of the study (randomized to 2 regimens of platelet transfusions or no transfusion)  
1802       • Baharoglu Lancet 2016 <sup>7</sup>. See below.

1803 The cohort study by Ramos et al <sup>8</sup>, reported platelet transfusions in inpatients who underwent endoscopy within 24 hours of presentation for  
1804 overt GIB with a platelet count of 20-50 × 103/mL, but did not assess how platelet transfusions were associated with subsequent clinical  
1805 outcomes.

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1808 Cohort studies with the comparator cohort required for this PICO

1809 1. **Zakko CGH 2017** (Zakko L, Rustagi T, Douglas M, Laine L. No Benefit from Platelet Transfusion for Gastrointestinal Bleeding in Patients  
1810 Taking Antiplatelet Agents. Clin Gastroenterol Hepatol. 2017 Jan;15(1):46-52) <sup>1</sup>

1811 • Retrospective **cohort study** (it is not case control study as other articles have described it; it is a **matched cohort study**)

1812 • Included patients on antiplatelets, with GIB, with platelet counts higher than 100 x10<sup>9</sup>/L.

1813 i. GIB that developed in patients already hospitalized was excluded.

1814 • **204** patients received platelet transfusions

1815 • **204** matched (on age, sex and GIB location) did not receive platelet transfusions

1816 • Reported clinical outcomes (multivariable analyses and sensitivity analyses of the multivariable analyses) during hospital  
1817 admission. See Table 4 in that paper.

1818 • Note: mortality was the only outcome with an effect size that increased after adjustment – all other outcomes had effect sizes  
1819 that decreased after adjustment

1820 • As the authors stated “*this difference in mortality could be due to residual bias from unmeasured and unknown factors and*  
1821 *reflect the increased severity of GIB in patients receiving platelet transfusion. On the other hand, the adjusted ORs for mortality*  
1822 *(4.5–6.8 with different sensitivity analyses) are large, increasing the likelihood of a cause-and-effect relationship.*”

1823 • Interesting indirect evidence, as stated by the authors: “*Platelet transfusions have also been reported to increase bleeding and*  
1824 *mortality in other settings. A retrospective analysis of data collected in double-blind placebo-controlled trials of patients*  
1825 *undergoing coronary artery bypass graft surgery showed more bleeding and higher mortality in patients receiving platelet*  
1826 *transfusions than in those not receiving platelets (Kaufman RM, et al. Platelet transfusion: a clinical practice guideline from the*  
1827 *AABB. Ann Intern Med 2015;162:205–213). Subsequent analysis by using propensity scoring revealed the OR for death with*  
1828 *platelet transfusion to be 4.76 (1.65–13.73).*”

1829

1830 2. **Victor CCM 2014** (Victor N, Umakanthan J, Gandhi A, et al. Role of platelet transfusion in gastrointestinal bleeding in patients on  
1831 antiplatelet therapy. Crit Care Med 2014;42:A1461) <sup>2</sup>

1832 • Retrospective cohort study.

- 1833 • Published only as conference abstract.
- 1834 • Included patients on antiplatelets, with GIB (non-variceal upper GIB, or lower GIB) and normal platelet count.
- 1835 • 35 patients received platelet transfusions.
- 1836 • 48 patients did not receive platelet transfusions.
- 1837 • No adjustment was mentioned.
- 1838 • **None of the outcomes of interest for this guideline were reported; therefore, it cannot be included in the Evidence Profile.**
- 1839
- 1840 • Duration of bleeding and length of stay in ICU were significantly longer in the platelet transfused group.
- 1841 • No statistically significant difference was found in the total length of stay, amount of packed red cells, hemoglobin levels at
- 1842 8, 16 and 24 hours, or diagnostic and therapeutic procedures.

1843

Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (exposure = platelet transfusion)	Prognostic factors (other than exposure of interest) similar among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Zakko CGH 2017	OK	The cohorts were matched (for age, sex, and GIB location) and statistically adjusted for confounders (with sensitivity analyses on the selection of confounders)	OK	OK	OK	OK	
Victor CCM 2014	Unclear	The cohorts were not adjusted for confounders	Unclear	Unclear	Unclear	Unclear	Available as abstract only
Low risk of bias							
Unclear risk of bias							
High risk of bias							

- 1844 Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included,
- 1845 because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid

1846 methods to ascertain exposure". The NOS domain "Comparability of cohorts on the basis of design or analysis" was renamed "Prognostic factors (other than exposure of  
1847 interest) similar among cohorts – or cohorts were adjusted adequately for confounders". The NOS domain "Was Follow-Up Long Enough for Outcomes to Occur" was not  
1848 included, because it is an "indirectness" issue as per GRADE.

1849 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
1850 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias.

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1853 RCTs in patients with non-GI bleeding

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1855 1. **Baharoglu Lancet 2016** (Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, et al. Platelet transfusion  
1856 versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a  
1857 randomised, open-label, phase 3 trial. Lancet 2016;387:2605–13) <sup>7</sup>

- 1858 • RCT, multicentre, open-label, masked-endpoint
- 1859 • 190 patients with intracerebral haemorrhage while antiplatelet therapy
- 1860 • Randomized to either standard care (n=93) or standard care with platelet transfusion (n=97) within 90 min of diagnostic brain  
1861 imaging.
- 1862 • The odds of "death or dependence" at 3 months were higher in the platelet transfusion group than in the standard care group  
1863 (adjusted common odds ratio 2.05, 95% CI 1.18–3.56).
- 1864 • 40 (42%) participants who received platelet transfusion had a serious adverse event during their hospital stay, vs 28 (29%) who  
1865 received standard care.
- 1866 • Mortality during hospital stay: 23/97 (24%) participants assigned to platelet transfusion vs 16/93 (17%) assigned to standard  
1867 care
- 1868 • Thromboembolism (at 3 months): 4/97 vs 1/93

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Risk of bias assessment of RCTs							
Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Comments
Baharoglu 2016 <sup>7</sup>	OK	OK	The outcome assessors were masked; therefore, the study is at low risk for <u>detection</u> bias for the outcomes of death and thromboembolism. However, the clinicians treating the patients were not masked; therefore, the study is at high risk for <u>performance</u> bias.	OK	OK	OK	Indirectness: patients with ICH
<div>Low risk of bias</div> <div>Unclear risk of bias</div> <div>High risk of bias</div>							

1875 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
1876 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias

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Patients with GI bleeding on antiplatelets: platelet transfusion vs none												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	platelet transfusion	none	Relative (95% CI)	Absolute (95% CI)	
Further bleeding at 7 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
1 cohort study (Zakko 2017) <sup>1</sup>	Not serious	Not applicable	Not serious	Serious <sup>a</sup>	None	⊕⊕⊕⊕ VERY LOW		29/204	16/204	Adjusted OR 1.47 (0.73-3.05)	Risk <u>without</u> platelet transfusion: 78 events per 1,000 patients. <u>With</u> platelet transfusion: 33 <b>more</b> per 1,000 (from 20 <b>less</b> to 95 more)	
Thrombotic events within 30 days (critical outcome)												
1 cohort study (Zakko 2017) <sup>1</sup>	Not serious	Not applicable	Serious <sup>b</sup>	Serious <sup>a</sup>	None	⊕⊕⊕⊕ VERY LOW		47/204	26/204	Adjusted OR 1.35 (0.74-2.49)	Risk <u>without</u> platelet transfusion: 78 events per 1,000 patients. <u>With</u> platelet transfusion: 38 <b>more</b> per 1,000 (from 29 <b>less</b> to 102 more)	
1 RCT (Baharoglu 2016) <sup>7</sup>	Serious <sup>c</sup>	Not applicable	Very serious <sup>d</sup>	Very serious <sup>e</sup>	None	⊕⊕⊕⊕ VERY LOW		4/97	1/93	RR 3.84 (0.44-33.68)	Risk <u>without</u> platelet transfusion: 31 events per 1,000 patients. <u>With</u> platelet transfusion: 88 <b>more</b> per 1,000 (from 17 <b>less</b> to inestimable more)	
Mortality within 30 days (important outcome, but not critical for decision making)												

1 cohort study (Zakko 2017) <sup>1</sup>	Not serious	Not applicable	Not serious	Serious <sup>f</sup>	None	⊕⊖⊖⊖ VERY LOW		14/204	3/204	Adjusted OR 5.57 (1.52-27.1)	Risk <u>without</u> platelet transfusion: 15 events per 1,000 patients. <u>With</u> platelet transfusion: 52 <b>more</b> per 1,000 (from 7 more to 273 more)	
1 RCT (Baharoglu 2016) <sup>7</sup>	Serious <sup>c</sup>	Not applicable	Very serious <sup>g</sup>	Serious <sup>h</sup>	None	⊕⊖⊖⊖ VERY LOW		23/97	16/93	RR 1.38 (0.78-2.44)	Risk <u>without</u> platelet transfusion: 31 events per 1,000 patients. <u>With</u> platelet transfusion: 65 <b>more</b> per 1,000 (from 103 <b>less</b> to 183 more)	

1894

#### 1895 Footnotes

1896 <sup>a</sup> Serious imprecision, because 95% CIs included potential for small benefit and large harm. Also, small number of events

1897 <sup>b</sup> Serious indirectness of the outcome. Venous thromboembolism was not included. This study assessed included MACE (myocardial infarction, stroke, arterial  
1898 thromboembolic event, or cardiovascular death) during the hospital admission. Of note, all but one of the MACE events were myocardial infarction.

1899 <sup>c</sup> Serious risk of bias (performance bias)

1900 <sup>d</sup> Very serious indirectness of population, because these patients had intracranial bleeding. The baseline risk for thrombotic events and the effect modification  
1901 of that risk by platelet transfusions could be substantially different in patients with GI bleeding. Also, the timeframe for assessment of the outcome was 3  
1902 months.

1903 <sup>e</sup> Very serious imprecision, because 95% CIs included potential for large benefit and large harm. Also, very small number of events

1904 <sup>f</sup> Serious imprecision, due to small number of events

1905 <sup>g</sup> Very serious indirectness of population, because these patients had intracranial bleeding. The baseline risk for death, the mechanism of death and the effect  
1906 modification of that risk by platelet transfusions could be substantially different in patients with GI bleeding.

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1909 **Evidence to Decision Framework, PICO 8**

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1911 **08. Reversal of antiplatelet with platelet transfusion vs none**

1912 P: Patient with GIB currently taking antiplatelet

1913 I: platelet transfusion

1914 C: none

1915 O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

1917 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days, transfusion-related events (congestive heart failure, pulmonary edema) within 7 days

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	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<p><b>How substantial are the desirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> <li>● Not applicable (all clinical effects were undesirable; no desirable effects)</li> </ul>	See Evidence Profile Table.	
Undesirable Effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>● Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>The <u>undesirable</u> anticipated effects of platelet transfusion are:</p> <ul style="list-style-type: none"> <li>• Increased further bleeding (critical outcome): 33 more events per 1,000 patients.</li> <li>• Increased thrombotic events (critical outcome): 38-88 more events per 1,000 patients.</li> <li>• Increased mortality: 52-65 more events per 1,000 patients.</li> </ul>	

Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"><li>● <b>Very low</b></li><li>○ Low</li><li>○ Moderate</li><li>○ High</li><li>○ No included studies</li></ul>	See Evidence Profile Table.																												
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"><li>● <b>Important uncertainty or variability</b></li><li>○ Possibly important uncertainty or variability</li><li>○ Probably no important uncertainty or variability</li><li>○ No important uncertainty or variability</li></ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>																												
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"><li>● <b>Favors the comparison</b></li><li>○ Probably favors the comparison</li><li>○ Does not favor either the intervention or the comparison</li><li>○ Probably favors the intervention</li><li>○ Favors the intervention (platelet transfusion)</li><li>○ Varies</li><li>○ Don't know</li></ul>	Large undesirable effects vs. no desirable effects																												
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"><li>○ Large costs</li><li>● <b>Moderate costs</b></li><li>○ Negligible costs and savings</li><li>○ Moderate savings</li><li>○ Large savings</li><li>○ Varies</li><li>○ Don't know</li></ul>	<p><b>2018–2019 Blood Component Cost Per Unit Summary</b></p> <table><tr><th>Blood Component</th><th>Unit of Measure</th><th>Cost Per unit</th></tr><tr><td>Red Blood Cells</td><td>Unit</td><td>\$422</td></tr><tr><td>Apheresis Platelets</td><td>Dose</td><td>\$504</td></tr><tr><td>Apheresis Plasma for Transfusion</td><td>Unit (500ml)</td><td>\$449</td></tr><tr><td>Pooled Platelets</td><td>Dose</td><td>\$178</td></tr><tr><td>Frozen Plasma</td><td>Unit (300ml)</td><td>\$108</td></tr><tr><td>Cryosupernatant Plasma</td><td>Unit (280ml)</td><td>\$108</td></tr><tr><td>Concurrent Plasma</td><td>Unit (250ml)</td><td>\$114</td></tr><tr><td>Cryoprecipitate</td><td>Unit</td><td>\$122</td></tr></table>		Blood Component	Unit of Measure	Cost Per unit	Red Blood Cells	Unit	\$422	Apheresis Platelets	Dose	\$504	Apheresis Plasma for Transfusion	Unit (500ml)	\$449	Pooled Platelets	Dose	\$178	Frozen Plasma	Unit (300ml)	\$108	Cryosupernatant Plasma	Unit (280ml)	\$108	Concurrent Plasma	Unit (250ml)	\$114	Cryoprecipitate	Unit	\$122
Blood Component	Unit of Measure	Cost Per unit																												
Red Blood Cells	Unit	\$422																												
Apheresis Platelets	Dose	\$504																												
Apheresis Plasma for Transfusion	Unit (500ml)	\$449																												
Pooled Platelets	Dose	\$178																												
Frozen Plasma	Unit (300ml)	\$108																												
Cryosupernatant Plasma	Unit (280ml)	\$108																												
Concurrent Plasma	Unit (250ml)	\$114																												
Cryoprecipitate	Unit	\$122																												

Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● <b>Moderate</b></li> <li>○ High</li> <li>○ No included studies</li> </ul>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● <b>No included studies</b></li> </ul>		
Acceptability	<p><b>Is the intervention (platelet transfusion) acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● <b>Yes</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Feasibility	<p><b>Is the intervention (platelet transfusion) feasible to implement?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● <b>Yes</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

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1922 **Conclusions**

1923 **PICO 08. For patients on antiplatelets who are hospitalized or under observation with acute GIB (upper and/or lower) should**

1924 **platelet transfusions be administered compared to none?**

1925 *O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial*

1926 *infarction, deep vein thrombosis, pulmonary embolus)*

1927 *IMPORTANT, BUT NOT CRITICAL: mortality within 30 days; transfusion-related events (congestive heart failure, pulmonary edema)*

1928 *within 7 days*

1929

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention 6/6 votes: 100% ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
<b>Recommendation</b>	For patients on antiplatelets who are hospitalized or under observation with acute GIB, we suggest against platelet transfusions. (Conditional recommendation, very low certainty of evidence)				
<b>Justification</b>					
<b>Subgroup considerations</b>					
<b>Implementation considerations</b>					
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?				
<b>Research priorities</b>					

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## References for PICO 8

1. Zakko L, Rustagi T, Douglas M, Laine L. No Benefit from Platelet Transfusion for Gastrointestinal Bleeding in Patients Taking Antiplatelet Agents. *Clin Gastroenterol Hepatol*. 2017 Jan;15(1):46-52.
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1963 9. GIB: Hold ASA vs continue ASA

1964 **9. GIB: Hold ASA vs continue ASA**

1965

1966 P: Patient with GIB currently taking cardiac ASA (81 - 325 mg/day) for secondary prevention

1967 I: hold ASA

1968 C: continue ASA

1969 O: **CRITICAL:** Further bleeding within 7 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction,  
1970 deep vein thrombosis, pulmonary embolus)

1971 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days

1972 **Overall comments about the evidence:**

1973 We did not identify any comparative study (RCT or observational) that addressed the question of whether cardiac ASA should be continued or  
1974 interrupted in patients with GI bleeding for the period that it is uncertain if hemostasis has been achieved or not.

1975 The landmark RCT by Sung et al (Sung AIM 2010) <sup>1</sup> covers the period that responds to PICO question #10, i.e., the period after confirmation of  
1976 hemostasis.

1977 PICO #9 covers the period that spans from admission to (endoscopic) confirmation of hemostasis, i.e., during the period of active bleeding,  
1978 which may last from a few hours to few days, usually less than 3 days.

1979 We included one cohort study (Cheung CJG 2009)<sup>2</sup> with indirectness of the population, that did not provide adjusted results (see description  
1980 below)

1981 We sought indirect evidence from observational studies on the incidence of thrombosis when cardiac ASA is held for 1 to 3 days (in lieu of the  
1982 question that we cannot answer: what is the relative risk of thrombosis in bedridden inpatients with GI bleeding when cardiac ASA is held for 1  
1983 to 3 days vs. when it is continued?). However, not even the “simple” question of the incidence of thrombosis when cardiac ASA is held for 1 to 3  
1984 days could be answered with the evidence that we identified (see discussion regarding Burger JIM 2005 <sup>3</sup>)

1985 As explained in the ACCF/ACG/AHA 2008 Expert Consensus Document <sup>8</sup>: “*Hemodynamic instability and hemostatic changes induced by acute*  
1986 *bleeding may further increase the risk of thrombosis in the absence of antiplatelet therapy. On the other hand, continuation of ASA in the setting*  
1987 *of acute ulcer bleeding may provoke recurrent bleeding*”.

1988 However, as explained in Sung AIM 2010 <sup>1</sup>: “despite rapid clearance of aspirin from the circulation, the antiplatelet effects of aspirin last for at  
1989 least a few days because of the permanent inactivation of the platelets’ cyclooxygenase activity on prostaglandin synthase 1 and synthase 2.”

1990

1991 Cohort studies with the comparator cohort needed for this PICO

- 1992 1. **Cheung CJG 2009** (Cheung et al. Acetylsalicylic acid use in patients with acute myocardial infarction and peptic ulcer bleeding. Canadian  
1993 Journal of Gastroenterology. 23 (9) (pp 619-623), 2009) <sup>2</sup>
- 1994 • Retrospective cohort study
  - 1995 • Indirectness of the population: included patients (n= 104) with acute myocardial infarction who subsequently (at least 24 hours  
1996 later) developed peptic ulcer bleeding during the same hospitalization
  - 1997 • The study aimed to assess predictors of the primary outcome of “continued ASA use during PUD bleeding”
  - 1998 • Reported further bleeding and mortality for patients who had ASA discontinued or continued: unadjusted results (see table 4 in  
1999 the paper)
  - 2000 • The authors did not attempt to assess these comparisons; they acknowledged the selection bias, and the lack of power  
2001 to assess this comparison (a much larger sample would have been required to perform multivariable adjustment for  
2002 confounders)
  - 2003 • We did not include the rate of recurrent MI in lieu of thrombotic events because this was a population who had a recent  
2004 MI already.

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2015

Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (exposure = cardiac ASA)	Prognostic factors (other than exposure of interest) similar among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Cheung CJG 2009	OK	The cohorts were not matched or adjusted for the outcomes of interest for this guideline	OK	Unclear	OK	OK	

Low risk of bias
Unclear risk of bias
High risk of bias

2016 Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included,  
2017 because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid  
2018 methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of  
2019 interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not  
2020 included, because it is an “indirectness” issue as per GRADE.

2021 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
2022 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias.

2023

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## 2025 Observational studies and SRMA of observational studies on the risk of thrombosis after ASA discontinuation

- 2026 1. **Sibon Neurol 2004** (Sibon I et al. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. Neurology. 2004;62:1187) <sup>9</sup>
- 2027 • Case series
- 2028 • In 11/289 patients with an ischemic stroke, a discontinuation of aspirin was reported during the month before the stroke
- 2029 episode.
- 2030 • In 6 cases, the disruption was ordered by the patient’s physician in charge before a surgical operation.
- 2031 • In 5 patients, the disruption was performed by the patients or the patients’ physicians out of negligence or because they
- 2032 thought that this treatment was without clinical relevance.





In this Box we provide the **information Dr. Laine has put together** for the time after aspirin withdrawal for the studies from Burger and from Biondi-Zoccai SRs that provided information on specific number of days after withdrawal. Also included Sibon et al). In addition, he determined the days for bleeding and death after randomization in the Sung et al study of re-introduction of aspirin in Annals.

**Burger et al:**

**Reference 3 Collet JP, Himbet F, Steg PG. Myocardial infarction after aspirin cessation in stable coronary artery disease patients. Int J Cardiol 2000; 76: 257– 8.** retrospective analysis, we reviewed 475 consecutive patients admitted for acute myocardial infarction (MI) between December 1992 and September 1996, and found 11 patients who had discontinued aspirin therapy within 15 days prior to admission (Table 1). All patients had been on chronic aspirin for symptomatic coronary artery disease.

11 events; 1 at day 3, 1 day 6, 1 day 7; others 9-15 days

**Ref 4 (abstract):** 1236 patients with coronary syndromes were hospitalized in our center. Among these, 51 occurred less than 1 week after aspirin withdrawal. This represents an incidence of 4.1% of all hospitalized coronary events.

Subsequently published: Ferrari E, et al. Coronary syndromes following aspirin withdrawal: A special risk for late stent thrombosis JACC 2005;45:456-9

During the 32-month study-period, 1,236 patients with coronary syndrome (non–ST-segment elevation or ST-segment elevation) were hospitalized in our center. Among these, 383 (31%) were known coronary disease patients and, consequently, should have been taking aspirin regularly. Fifty-one new coronary events occurred <1 month after aspirin withdrawal. These 51 cases represent 4.1% (51 of 1,236) of all patients hospitalized for a coronary event, and 13.3% (51 of 383) of those who relapsed.

The coronary history that had required the prescription of aspirin in these patients consisted of a previous myocardial infarction in 15 cases (29%) and stable angina in 36 cases (71%). Mean delay between diagnosis of the initial coronary disease requiring aspirin prescription and the recurrent coronary event after aspirin withdrawal was  $4.1 \pm 1.2$  years. Coronary syndrome following aspirin withdrawal involved ST-segment elevation coronary syndrome in 19 cases (37%) and non–ST-segment elevation coronary syndrome in 32 cases (63%). Mean delay between aspirin withdrawal and the acute coronary event was  $10 \pm 1.9$  days (**range 4 to 17 days**).

**Ref 7 Bachman DS. Discontinuing chronic aspirin therapy: another risk factor for stroke? Ann Neurol 2002; 51: 137– 8:**

Over the last 3 years, I have prospectively noted 11 patients with cerebrovascular events occurring within a few weeks of stopping chronic aspirin intake (Table). One of my colleagues saw 2 additional cases during the same time period (A and B in Table). The indication for chronic aspirin use is included in the table under the heading of additional diagnoses, if indeed there was any specific indication. Unfortunately, the dosage of aspirin that was being taken by each patient was not recorded.

13 patients off aspirin developed TIA or CVA: **1 at 2 days (CVA) , 1 5days (TIA), 1 “several days” (CVA), 2 “recent” (CVAs); others, 1 11 days (CVA), 6 2-3 weeks, 1 6-8 wks .**

**Ref 8 Kovich O, Otley CC. Thrombotic complications related to discontinuation of warfarin and aspirin therapy perioperatively for cutaneous operation. J Am Acad Dermatol 2003; 48: 233– 7.:**

Our aim was to present a large case series of thrombotic complications resulting from this practice and to estimate the incidence of these events. Methods: A total of 504 members of the American College of Mohs Micrographic Surgery and Cutaneous Oncology were surveyed regarding thrombotic complications when blood thinners were withheld perioperatively to ascertain the frequency of these complications and to describe associated morbidity and mortality.

46 valid case reports of patients experiencing thrombotic events. Of thrombotic events, 54% (25/46) occurred when warfarin was withheld, 39% (18/46) when aspirin was withheld, and 4% (2/46) when both aspirin and warfarin were withheld. Aspirin was withheld for a median of 7 days (range, 3-14 days) and was resumed at a median of 2 days postoperatively (range, 1-30 days). Thrombotic complications resulting from cessation of aspirin therapy occurred postoperatively at a median of 2.5 days (range, 0-30 days).

**CAN'T TELL NUMBER OF DAYS WITHHELD—HAD TO BE MINIMUM OF 3 DAYS BUT PROBABLY HIGHER.**

**Ref. 9 Matsuzaki K, Matsui K, Haraguchi N, Nagano I, Okabe H, Asou T. Ischemic heart attacks following cessation of aspirin before coronary artery bypass surgery: a report of two cases. Ann Thorac Cardiovasc Surg 1999; 5: 121– 2.**

We couldn't get the full text

**Ref. 10 Mitchell SM, Sethia KK. Hazards of aspirin withdrawal before transurethral prostatectomy. BJU Int 1999; 84: 530.:**

5 case reports of people having aspirin stopped before TURP. 1) aspirin was stopped 10 days preoperatively. Two days before his admission he developed unilateral weakness and dysphasia which recovered within 24h (Dx TIA): **?8 days**

2) stopped 10 days before an uneventful TURP. On the first postoperative day he developed an acutely painful right arm. A 6cm thrombus was removed at brachial embolectomy. **11 days**. 3) Stopped aspirin 10 days preop. CVA 7 days after TURP: **17 days**; 4) MI and death, but **don't say duration** of withdrawal; 5) Aspirin stopped 8 days before admission; day after admission—CVA and death. **9 days**

**Biondi-Zoccai GGL, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50 279 patients at risk for coronary artery disease. Eur Heart J 2006;27:2667-74**

Whereas this work was not designed to address this topic (already extensively covered by Burger et al.13), pooling available data showed that on an average 10.66 (95% CI 10.25–11.07) days elapsed between drug withdrawal and thrombotic events. These results appear in line with the half-life of platelets, and suggest that in case of mandatory aspirin discontinuation for highly invasive interventions in patients at high risk of bleeding, the drug should be resumed well before that 8–10 days have elapsed. **References from this SR are below**

**Collet JP, et al. Impact of Prior Use or Recent Withdrawal of Oral Antiplatelet Agents on Acute Coronary Syndromes. Circulation 2004;110:2361-7**

Among ACS admissions: Recent withdrawers were admitted  $11.9 \pm 0.8$  days after OAA cessation (aspirin, n=70; ticlopidine, n=3) **Don't give individual times.**

**Mangano DT et al. Aspirin and mortality from coronary bypass surgery. NEJM 2002;347:1309-17.** At 70 centers in 17 countries, we prospectively studied 5065 patients undergoing coronary bypass surgery, of whom 5022 survived the first 48 hours after surgery. We gathered data on 7500 variables per patient and adjudicated outcomes centrally. The primary focus was to discern the relation between early aspirin use and fatal and nonfatal outcomes.

Results: During hospitalization, 164 patients died (3.2 percent), and 812 others (16.0 percent) had nonfatal cardiac, cerebral, renal, or gastrointestinal ischemic complications. Among patients who received aspirin (up to 650 mg) within 48 hours after revascularization, subsequent mortality was 1.3 percent (40 of 2999 patients), as compared with 4.0 percent among those who did not receive aspirin during this period (81 of 2023,  $P < 0.001$ ). Aspirin therapy was associated with a 48 percent reduction in the incidence of myocardial infarction (2.8 percent vs. 5.4 percent,  $P < 0.001$ ), a 50 percent reduction in the incidence of stroke (1.3 percent vs. 2.6 percent,  $P = 0.01$ ), a 74 percent reduction in the incidence of renal failure (0.9 percent vs. 3.4 percent,  $P < 0.001$ ), and a 62 percent reduction in the incidence of bowel infarction (0.3 percent vs. 0.8 percent,  $P = 0.01$ ). **Risk in CABG increased with 48 hrs interruption.**

**McFadden P, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:23-9** four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paclitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. **4, 5, 7, 14 days after aspirin stopped**

**Albaladejo P, et al. Aspirin withdrawal and acute lower limb ischemia. Anesh Analg 2004;99:440-3.**

Among a retrospective cohort of 181 patients admitted for acute lower limb ischemia for 4 yr, we studied 11 patients who had recently stopped taking aspirin. Aspirin was administered for vascular event prevention. The median duration of aspirin treatment without vascular events was 12 mo (range, 6-60 mo). The median time between aspirin withdrawal and lower limb ischemia was 23 days (**range, 7-60 days**)

**Sibon I, Orgogozo JM. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. Neurology 2004;62:1187-9.** The survey was carried out in three periods of 1.5 month each in the three neurologic wards of the University Hospital (CHU) Pellegrin in Bordeaux, France. All patients hospitalized for a TIA or an ischemic or hemorrhagic stroke during each period were included. When an APD treatment had been modified before stroke onset, we recorded the delay between treatment change and stroke onset. In 13 (4.5%) patients with an ischemic stroke, a discontinuation of APD was reported during the month before the stroke episode. Clinical characteristics of these patients are summarized in the table. ASA was the most frequent (n = 11; 85%) of the APD discontinued before a stroke. In the 11 with aspirin alone: **7, 9, 8, 6, 8, 6, 7, 8, 8, 6, 6 days. 6 days was shortest interruption before a stroke.**

**Sung AIM 2010:** Placebo deaths: ACS: days 1 and 7; recurrent CVA day 12; CHF days 20, 39. Perforated ulcer: days 15, 16; bleeding day 2. Aspirin 1 death: died of CHF at day 30 after recurrent bleeding DU with successful hemostasis.

FROM FIGURE LOOKS LIKE REPEAT BLEEDING IN ASA GROUP AT DAY 2, 2, 3, 4, AND 6—5 OF 8 CONFIRMED REBLEEDS THUS IN 1ST 6 DAYS AND 3 OF 8 IN FIRST 3 DAYS. IN PLACEBO GROUP ONLY 1 RECURRENT IN 1ST WEEK—APPEARS TO BE DAY 1.

**We probably want to discuss issue of primary prevention and secondary prevention.** There is a recent SRMA, but I tend not to like it for 2 reasons: 1) many people feel that patients in modern studies are very different than patients in studies in the past (e.g., statins, better BP control, less smoking, etc). In addition, 3 very large high-quality studies were recently published (2 in NEJM, one in Lancet) regarding primary prevention and I thought a priori it is more reasonable to pool them together but separately from old studies (although it turns out the difference is quite similar in my SRMA of these 3 and the old Berger meta-analysis) and also because the newer SRMA got one of the recent study's data wrong [...] I was able to get the correct data by personal communication).

Berger JS et al. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: A meta-analysis of randomized trials. Am Heart J 2011;162:115-24.

The number needed to treat to prevent 1 MCE over a mean follow-up of 6.9 years was 253 (95% CI 163-568), which was offset by the number needed to harm to cause 1 major bleed of 261 (95% CI 182-476). For every 1,000 subjects treated with aspirin over a 5-year period, aspirin would prevent 2.9 MCE and cause 2.8 major bleeds. 0.06% absolute risk/yr NNT 1yr = 1667

3 recent more modern RCTs (ARRIVE, ASCEND, ASPREE) that I like to look at separately. But when I do my own meta-analysis, I find RR=0.92, 0.85-1.00 for reduction in CV events (p=0.04) with annual risk difference 0.07% and **NNT 1429**.

Meta-analysis of serious GIB (transfusion, hospitalization, death): RR=1.53, 1.30-1.82 Pooled increase annually 0.09%, **NNH 1112** (GIB <50% of all major bleeding events).

The SRMA from Oxford group (Lancet 2009;373:1849) I generally quote for **secondary prevention** is somewhat old perhaps but it shows the following: ARR 1.49% per yr; annual **NNT=67**.

I did want to share the recent SRMA from JAMA about primary prevention. I mentioned some problems with it—and also that it didn't have the number exactly right for GI bleeding in the ARRIVE study. In addition, here are 2 letters to the editor about other shortcomings:

Shah R. Meta-analysis of Aspirin for Primary Prevention of Cardiovascular Events. JAMA 2019 32:2244.

authors excluded the Prevention and Progression of Arterial Disease and Diabetes (POPADAD) trial and the Thrombosis Prevention Trial (TPT) from the estimate of the pooled effect for the composite cardiovascular outcome. Although POPADAD, TPT, the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial, and the Aspirin for Asymptomatic Atherosclerosis (AAA) trial did not report the event rate for the composite cardiovascular outcome, it seems that for the JPAD and AAA trials, Dr Zheng and Mr Roddick calculated the composite outcome by adding events for individual outcomes (stroke/cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke). The POPADAD and TPT investigators also reported event rates for

individual outcomes, which the authors could have added to calculate the composite outcome. To maintain consistency, the authors either should have used only trials that reported event rates for the composite outcome or should have included all trials by calculating the composite outcome from individual outcome events in the trials that did not report a composite outcome. Their selective use of data from some trials while excluding other relevant data could have introduced bias and potentially compromised the validity of their analysis and conclusions

Syn NL, Wee IJY. Meta-analysis of Aspirin for Primary Prevention of Cardiovascular Events. JAMA 2019 32:2243-4.

The investigators required randomized trials to enroll at least 1000 participants to be eligible for inclusion in the analyses. The basis for imposing such a study eligibility criteria was not explicitly justified, but a plausible motivation could be related to the perception that small randomized trials are neither adequately powered nor generalizable.

The exclusion of studies based on small sample size has been clarified in a meeting presentation by the Cochrane Collaboration.<sup>2</sup> During a poll of statisticians and methodologists from the Cochrane Statistical Methods Group, 26 of 26 representatives voted that it is inappropriate to exclude studies simply on the basis of sample size.<sup>2</sup> Intentionally excluding studies because of small sample size may exacerbate the “file drawer” problem and introduce publication bias. In addition, including only large or representative studies in meta-analyses defeats the very purpose of a meta-analysis, which is to aggregate evidence where it is lacking or where clinical questions have not been clearly answered because of small sample sizes within individual studies.

The Cochrane Statistical Methods Group also recommended that small studies could be excluded in sensitivity analyses because smaller studies are often at higher risk of bias.

For some reason I thought we were looking for study to give **risk with prior UGIB in low-dose aspirin users**. Here is such a study from NEJM:

Lanas A et al. Nitrovasodilators, Low-Dose Aspirin, Other Nonsteroidal Antiinflammatory Drugs, and the Risk of Upper Gastrointestinal Bleeding N Engl J Med 2000;343:834-9 Risk of UGIB in low-dose aspirin users with hx of UGIB: adjusted OR = 6.5, 2.0-21.2

**Finally, a study about anti-platelet activity:** It suggests activity returns more quickly than measures of thromboxane synthesis that are typically used to suggest 5-7 days to hold aspirin: **Santilli G, et al. Platelet Cyclooxygenase Inhibition by Low-Dose Aspirin Is Not Reflected Consistently by Platelet Function Assays. Implications for Aspirin “Resistance”.** J Am Coll Cardiol 2009;53:667—77

Recovery of platelet function by optical aggregation and VerifyNow Aspirin followed first-order kinetics and reached approximately 70% of the relative function at day 3 post-aspirin. Whereas values obtained with platelet functional assays had largely recovered by day 3 post-aspirin, day 3 TXB2 values still average 45% of baseline; full recovery occurred by day 7 post aspirin. Virtually complete suppression of the biosynthetic capacity of platelets is required to have a measurable impact on TX-dependent platelet function. Inhibition of platelet COX activity, explored both on and off treatment, was nonlinearly related to inhibition of TX-dependent platelet function, leading to faster functional recovery following aspirin withdrawal than predicted by the rate of platelet turnover. Thus, 3 days after stopping aspirin, AA-induced platelet aggregation and VerifyNow Aspirin had recovered approximately 60% and 80% of baseline values, respectively. This finding may have clinical implications for the adequacy of recommended timing of drug withdrawal before surgical/invasive procedures in aspirin-treated patients (30,31). The nonlinearity of the relationship between inhibition of the TX biosynthetic capacity and inhibition of TX-dependent platelet function enables some recovery of platelet function at 48 hours after drug withdrawal, a phenomenon that may be substantial in some subjects because of the interindividual variability.

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2059 Evidence profile, PICO 9

Patients with active GI bleeding: hold ASA vs continue ASA												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Hold ASA	Continue ASA	Relative (95% CI)	Absolute (95% CI)	
Further bleeding at 7 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					Remark: the direction of the effect is opposite of the theoretically predicted direction
1 cohort study (Cheung 2009) <sup>2</sup>	Critically serious <sup>a</sup>	Not applicable	Serious <sup>b</sup>	Serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		10/64	4/38	RR 1.48 (0.50-4.41)	Risk with continued ASA: 105 events per 1,000 patients. Held ASA: 50 more per 1,000 (from 52 less to 358 more)	
Thrombotic events within 30 days (critical outcome)												
No studies						-		-	-	-		
Mortality within 30 days (important outcome, but not critical for decision making)												
1 cohort study (Cheung 2009) <sup>2</sup>	Serious <sup>a</sup>	Not applicable	Serious <sup>b</sup>	Serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		10/64	4/38	RR 1.48 (0.50-4.41)	Risk with continued ASA: 105 events per 1,000 patients. Held ASA: 50 more per 1,000 (from 52 less to 358 more)	

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2061 Footnotes

2062 <sup>a</sup> Critically serious risk of bias. Further bleeding was not a main outcome of the study; the authors did not attempt to adjust for confounders. However, for this  
2063 research question it is certain that the decision to hold ASA and the outcome of further bleeding were strongly confounded by severity of indication (severity of  
2064 index bleeding).

2065 <sup>b</sup>Serious indirectness of the population. All patients had already had a recent MI and developed GIB subsequently as in-patients. Minor issue: further bleeding  
 2066 was reported at 30 days, not 7 days.

2067 <sup>c</sup>Serious imprecision, because 95% CIs included potential for large benefit and large harm. Also, small number of events.

2068 <sup>d</sup>Serious risk of bias. Mortality was not a main outcome of the study; the authors did not attempt to adjust for confounders.

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## 2071 Evidence to Decision Framework, PICO 9

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### 2073 09. Patient with active GI bleeding: hold ASA vs continue ASA

2074 P: Patient with GIB currently taking cardiac ASA (81 - 325 mg/day) for secondary prevention

2075 I: hold ASA

2076 C: continue ASA

2077 O: CRITICAL: Further bleeding within 7 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein  
 2078 thrombosis, pulmonary embolus)

2079 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

2080

	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<b>How substantial are the desirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> <li>● Not applicable (all clinical effects were undesirable; no desirable effects)</li> </ul>	See Evidence Profile Table. <b>Intervention: hold ASA</b> Comparator: continue ASA  The <u>undesirable</u> anticipated effects with holding ASA (compared to continuing ASA) are: - Increased further bleeding (critical outcome): 12 more events per 1,000 patients. - Increased mortality: 12 more events per 1,000 patients.  It is not possible to estimate the direction of the effect of holding ASA (compared to continuing ASA) on the risk of thrombosis.	
Undesirable Effects	<b>How substantial are the undesirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Large</li> <li>● Moderate</li> <li>○ Small</li> <li>○ Trivial</li> </ul>		



	<ul style="list-style-type: none"> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
<b>Certainty of evidence</b>	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	
<b>Values and Preferences</b>	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>● <b>Important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>	
<b>Balance of effects</b>	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● <b>Probably favors the comparison</b></li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention (holding ASA)</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	The intervention (holding ASA) would lead to moderate undesirable effects and no known desirable effects. Very low certainty of evidence.	
<b>Resources required</b>	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>● <b>Negligible costs and savings</b></li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Aspirin is inexpensive, so holding it for a few days means negligible savings.	

Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>● High</li> <li>○ No included studies</li> </ul>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>		
Acceptability	<p><b>Is the intervention (holding ASA) acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Feasibility	<p><b>Is the intervention (holding ASA) feasible to implement?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

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## **Conclusions**

2083 **PICO 09. For patients with GI bleeding on cardiac ASA, should ASA be held until (endoscopic) confirmation of hemostasis or should**  
 2084 **ASA be continued (without interruption)?**  
 2085 **O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial**  
 2086 **infarction, deep vein thrombosis, pulmonary embolus)**  
 2087 **IMPORTANT, BUT NOT CRITICAL: mortality within 30 days**  
 2088

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention (holding ASA) 6/6 votes: 100%	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	●	○	○	○
<b>Recommendation</b>	For patients with GI bleeding on cardiac aspirin for secondary prevention, we suggest that aspirin is not held. (Conditional recommendation, very low certainty of evidence) <b>Note: In the final guideline document the wording was reversed to avoid double negative wording:</b> <b>“We suggest that patients who present with GIB while taking low-dose aspirin for secondary cardiovascular protection continue rather than interrupt their aspirin”</b>				
<b>Justification</b>					
<b>Subgroup considerations</b>	This recommendation does not apply to patients with GI bleeding while on cardiac aspirin for primary prevention (cardiology guidelines make it clear that if patient has a risk factor for GIB, primary ASA prevention should not be used)				
<b>Implementation considerations</b>					
<b>Monitoring and evaluation</b>					
<b>Research priorities</b>					

2089  
 2090  
 2091 **References for PICO 9**

- 2092  
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2100 operation. J Am Acad Dermatol 2003; 48: 233–7.

2101 6. Matsuzaki K, Matsui K, Haraguchi N, Nagano I, Okabe H, Asou T. Ischemic heart attacks following cessation of aspirin before coronary  
2102 artery bypass surgery: a report of two cases. Ann Thorac Cardiovasc Surg 1999; 5: 121–2.

2103 7. Mitchell SM, Sethia KK. Hazards of aspirin withdrawal before transurethral prostatectomy. BJU Int 1999; 84: 530.

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2106 9. Sibon I et al. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. Neurology. 2004;62:1187

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2122 10. Post-GIB: when to resume ASA

2123 **10. Post-GIB: resume ASA same day as hemostasis is confirmed endoscopically vs 1-7 days later**

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2125 P: Patient with GIB currently taking cardiac ASA (81 mg or 325 mg/day) for secondary prevention

2126 I: Resume same day as endoscopic hemostasis is confirmed endoscopically

2127 C: Resume 1 to 7 days after endoscopic hemostasis

2128 O: **CRITICAL:** Further bleeding within 7 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction,  
2129 deep vein thrombosis, pulmonary embolus)

2130 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days

2131

2132 **RCTs**

2133 1. **Sung AIM 2010** (Sung et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Annals of Internal  
2134 Medicine 2010 Jan 5;152(1):1-90) <sup>1</sup>

- 2135 • Double-blind RCT
- 2136 • **Patients** (N=156)
  - 2137 i. PU bleeding (active bleeding, NBVV, adherent clots) successfully treated with endoscopic therapy (and IV PPI)
  - 2138 ii. continuing indication for low-dose ASA for secondary prevention
- 2139 • **Randomized** (after endoscopy) to **aspirin (n=78)**, 80 mg/d or **placebo (n=78)** for 8 weeks
- 2140 • All patients took oral pantoprazole 40 mg OD for 8 weeks
- 2141 • **Results: ASA vs. placebo:**
- 2142 • 30-day confirmed recurrent ulcer **bleeding (see Figure 2 in the paper):**  
2143 8/78 (**10.3%**) vs. 4/78 (**5.4%**); difference 4.9 percentage points (95% CI - 3.6 to 13.4)
- 2144 •
- 2145
- 2146 • **8-week all-cause mortality:**  
2147 1/78 (**1.3%**) vs. 10/78 (**12.9%**); difference 11.6 percentage points (95% CI 3.7 to 19.5)

- 30-day **all-cause mortality**:  
1/78 (1.3%) vs 7/78 (9%)
- 8-week **mortality attributable to cardiovascular, cerebrovascular, or GI complications** (see Figure 3 in the paper):  
1.3% vs. 10.3%; difference 9 percentage points (95% CI 1.7 to 16.3)
- Six nonfatal, recurrent acute ischemic events were reported (2 in the aspirin group and 4 in the placebo group)

Risk of bias assessment of RCTs							
Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Comments
Sung 2010 <sup>1</sup>	OK	OK	OK	OK	OK	OK	Indirectness of the compactor intervention: duration of 8 weeks
Low risk of bias							
Unclear risk of bias							
High risk of bias							

Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias

#### Observational studies on the risk of thrombosis after ASA discontinuation

1. **Sibon Neurol 2004** (Sibon I et al. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. Neurology. 2004;62:1187) <sup>4</sup>
  - Case series
  - In 11/289 patients with an ischemic stroke, a discontinuation of aspirin was reported during the month before the stroke episode.
    - In 6 cases, the disruption was ordered by the patient's physician in charge before a surgical operation.
    - In 5 patients, the disruption was performed by the patients or the patients' physicians out of negligence or because they thought that this treatment was without clinical relevance.

- 2168 • The delay range between the treatment disruption and the cerebral infarct was remarkably narrow, between 6 and 8  
2169 days in all 11 patients.

2170

2171

2172 Cohort studies without the comparator needed for this PICO

2173 Cohort studies that compared a cohort of patients who continued ASA following GIB vs a cohort who discontinued ASA and did not resume ASA  
2174 for years, were not included.

- 2175 • The study by Derogar et al (Derogar CGH 2013) <sup>2</sup>
- 2176 ○ Retrospective cohort study, Sweden
  - 2177 ○ Patients (n=118) with PU bleeding while receiving low-dose ASA therapy
  - 2178 ○ Median follow up 2 years post-discharge
  - 2179 ○ Outcome: death or acute cardiovascular events
  - 2180 ○ Results (adjusted for confounders):
    - 2181 ▪ Among patients with baseline cardiovascular comorbidities, those who discontinued ASA at discharge vs. those who
    - 2182 continued ASA at discharge: HR: 6.9, 95% CI 1.4- 34.8
    - 2183 ▪ Among patients without baseline cardiovascular comorbidities: no such association
    - 2184 ▪ Figure 2 from that article shows the Kaplan-Maier curve for the whole study population (with or without baseline
    - 2185 cardiovascular comorbidities). **There is a separation of the two curves at the start of the study, but it is not possible to**
    - 2186 **extract accurate results for the first 1-7 days (the timeframe of interest for this guideline).**

2187

- 2188 • The study by Chan et al (Chan Gastro 2016) <sup>3</sup> had a follow up of 5 years following lower GIB. Furthermore, the two cohorts were not ASA  
2189 users vs. non-users. Instead “Study subjects were allocated to 1 of 2 groups according to their cumulative duration of aspirin use: <20%  
2190 of the follow-up period (nonuser group) vs ≥ 50% of the observation period (aspirin group)”. Kaplan-Meier curves were reported in this  
2191 article too, but they cannot be interpreted, given that it is unclear when along the x-axis each patient was on or off ASA.

2192

2193 **Also, please see Box in PICO#9 with the relevant information provided by Dr. Laine**

2194

Patients with GI bleeding: resume ASA on day of hemostasis vs 1-7 days later												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Resume ASA on day of hemostasis	Resume ASA 1-7 days after hemostasis	Relative (95% CI)	Absolute (95% CI)	
Further bleeding at 7 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
1 RCT (Sung 2010) <sup>1</sup>	Not serious	Not applicable	Serious <sup>a</sup>	Very serious <sup>b</sup>	None	⊕⊕⊕⊕ VERY LOW		8/78	4/78	RR 2.00 (0.63-6.37)	Risk with <u>delayed resumption</u> : 51 events per 1,000 patients. <u>ASA on day of hemostasis</u> : 51 <b>more</b> per 1,000 (from 29 <b>less</b> to 274 more)	
Thrombotic events within 30 days (critical outcome)												
1 RCT (Sung 2010) <sup>1</sup>	Not serious	Not applicable	Very serious <sup>c</sup>	Very serious <sup>b</sup>	None	⊕⊕⊕⊕ VERY LOW		3/78	9/78	RR 0.33 (0.09-1.19)	Risk with <u>delayed resumption</u> : 130 events per 1,000 patients. <u>ASA on day of hemostasis</u> : 87 <b>less</b> per 1,000 (from 118 less to 3 <b>more</b> )	Fatal and non-fatal cardiovascular complications
Mortality within 30 days (important outcome, but not critical for decision making)												
1 RCT (Sung 2010) <sup>1</sup>	Not serious	Not applicable	Very serious <sup>d</sup>	Very serious <sup>b</sup>	None	⊕⊕⊕⊕ VERY LOW		1/78	7/78	RR 0.14 (0.02-1.13)	Risk with <u>delayed resumption</u> : 90 events per 1,000 patients. <u>ASA on day of hemostasis</u> : 77 <b>less</b> per 1,000 (from 88 less to 12 <b>more</b> )	<u>Note</u> : some of the deaths were also included in the analysis of thrombotic events



2196 **Footnotes**

2197 <sup>a</sup> Serious indirectness of the comparator intervention. The study held ASA for 8 weeks as opposed to the duration of 1-7 days defined in this PICO question.

2198 <sup>b</sup> Very serious imprecision, because 95% CIs included potential for large benefit and large harm. Also, very small number of events.

2199 <sup>c</sup> Very serious indirectness of the comparator intervention. The study held ASA for 8 weeks as opposed to the duration of 1-7 days defined in this PICO question  
2200 and this would have substantially increased the difference in cardiovascular complications between the two treatments in the study as opposed to the  
2201 interventions required for this PICO question.

2202 <sup>d</sup> Very serious indirectness of the comparator intervention. The study held ASA for 8 weeks as opposed to the duration of 1-7 days defined in this PICO question  
2203 and this would have substantially increased the difference in deaths (esp. cardiovascular deaths) between the two treatments in the study as opposed to the  
2204 interventions required for this PICO question.

2205

2206

2207 **Evidence to Decision Framework, PICO 10**

2208

2209 **10. Post-GIB: resume ASA same day as endoscopic hemostasis vs 1-7 days later**

2210

2211 P: Patient with GIB currently taking cardiac ASA (81 mg or 325 mg/day) for secondary prevention

2212 I: Resume same day as hemostasis is confirmed endoscopically

2213 C: Resume 1 to 7 days after hemostasis is confirmed endoscopically

2214 O: CRITICAL: Further bleeding within 7 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein  
2215 thrombosis, pulmonary embolus)

2216 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

2217

Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
---	-------------------	---------------------------

Desirable Effects	<p><b>How substantial are the desirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>● <b>Large</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>See Evidence Profile Table.</p> <p>Intervention: Resume ASA on day of hemostasis Comparator: Resume ASA 1-7 days after hemostasis</p> <p>The <u>desirable</u> anticipated effects with resuming ASA on day of hemostasis (compared to resuming ASA 1-7 days after hemostasis) are:</p> <ul style="list-style-type: none"> <li>- Reduced thrombotic events (critical outcome): 87 less events per 1,000 patients.</li> <li>- Reduced mortality: 77 less events per 1,000 patients.</li> </ul>	
Undesirable Effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Large</li> <li>● <b>Moderate</b></li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>The <u>undesirable</u> anticipated effects with resuming ASA on day of hemostasis (compared to resuming ASA 1-7 days after hemostasis) are:</p> <ul style="list-style-type: none"> <li>- Increased further bleeding (critical outcome): 51 more events per 1,000 patients.</li> </ul>	
Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>See Evidence Profile Table.</p>	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>● <b>Important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>	

Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● <b>Probably favors the intervention</b></li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	The intervention (resuming ASA on the day hemostasis is endoscopically confirmed) would lead to large desirable effects and moderate undesirable effects. Very low certainty of evidence.	
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>● <b>Negligible costs and savings</b></li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Aspirin is inexpensive, so resuming it early means negligible costs.	
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>● <b>High</b></li> <li>○ No included studies</li> </ul>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● <b>No included studies</b></li> </ul>		

Acceptability	<p>Is the intervention (resuming ASA on day of hemostasis) acceptable to key stakeholders?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		
Feasibility	<p>Is the intervention (resuming ASA on day of hemostasis) feasible to implement?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		

2218

2219

2220

## Conclusions

2221 **PICO 10. For patients with GI bleeding on cardiac ASA, whose ASA treatment has been held (since admission), should ASA be**

2222 **resumed on the same day as hemostasis is (endoscopically) confirmed compared to later?**

2223 *O: CRITICAL: Further bleeding within 7 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial*

2224 *infarction, deep vein thrombosis, pulmonary embolus)*

2225 *IMPORTANT, BUT NOT CRITICAL: mortality within 30 days*

2226

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention 6/6 votes: 100%	Strong recommendation for the intervention
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
<b>Recommendation</b>	For patients with GI bleeding on aspirin for secondary cardiovascular prevention whose aspirin was held, we suggest the aspirin be resumed on the day hemostasis is confirmed endoscopically.				

<b>Justification</b>	
<b>Subgroup considerations</b>	In patients in whom endoscopy is not performed, clinical assessment of hemostasis may be sufficient.
<b>Implementation considerations</b>	
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?
<b>Research priorities</b>	

#### References for PICO 10

1. Sung et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Annals of Internal Medicine* 2010 Jan 5;152(1):1-90
2. Derogar M, et al. Discontinuation of low-dose aspirin therapy after peptic ulcer bleeding increases risk of death and acute cardiovascular events. *Clin Gastroenterol Hepatol*. 2013 Jan;11(1):38-42.
3. Chan F.K.L. et al. Risks of Bleeding Recurrence and Cardiovascular Events With Continued Aspirin Use After Lower Gastrointestinal Hemorrhage. *Gastroenterology*. 151 (2) (pp 271-277), 2016.
4. Sibon I et al. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. *Neurology*. 2004;62:1187

2248 **B. MANAGEMENT OF ANTITHROMBOTIC AGENTS IN PATIENTS UNDERGOING**  
2249 **ELECTIVE ENDOSCOPY**

2250  
2251 \*Patients undergoing elective/planned endoscopic procedures. This excludes patients at high-risk of thromboembolic events in whom  
2252 elective procedures should be deferred.

2253 - Patients at high risk of thromboembolic event:

2254 1. Patients within 3 months of venous thromboembolism, pulmonary embolism, stroke or TIA.

2255 2. Patients within 3 months of ACS event, 12 months of drug eluting stent placement or 2 months of bare metal stent placement.

2256

2257 11. Continuous anticoagulation of Warfarin

2258 **11. Continuous anticoagulation of Warfarin**

2259 P: Patient on Warfarin (undergoing elective/planned endoscopic procedures)

2260 I: Continuous anticoagulation

2261 C: Temporary interruption of warfarin X up to 7 days

2262 O: **CRITICAL:** Bleeding within 30 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep  
2263 vein thrombosis, pulmonary embolus)

2264 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days

2265

2266

2267 Cohort studies with the comparator cohort needed for this PICO

2268

2269 1. Ara et al. Prospective analysis of risk for bleeding after endoscopic biopsy without cessation of antithrombotics in Japan. *Digestive*  
2270 *Endoscopy* 2015; 27:458-464

2271 • Design: prospective cohort study

2272 • Population: Consecutive patients who underwent **upper GI endoscopic biopsy** at a hospital in Japan, 2011-2014

2273 • **Indirectness:** the “exposure” was limited to endoscopic biopsies and also limited to Upper GI endoscopy

2274 • Intervention: temporary interruption of warfarin

2275 • Comparator: no interruption of warfarin

2276 • Outcomes: major bleeding within 4 weeks (no results on thrombotic events or mortality)

2277                   • Results:

2278                   • **Continued** warfarin = 92; events (bleeding) = 0 (95% CI calculated with the rule of 3/n for zero events (**Govani. AJG 2013;**

2279                   **108:1831**) is 0%- 3.3%)

2280                   • **Interrupted** warfarin = 19; events (bleeding) = 0 (95% CI 0% - 15.8%)

2281                   • RR: **not meaningful**

2282                   • only unadjusted results

2283                   • Notes regarding risk of bias:

2284                   • The decision to interrupt or continue warfarin was made by the “prescribing physicians”

2285                   • Only patients who had endoscopic biopsies taken were included in the study, i.e., it is unclear how many patients had

2286                   UGI endoscopy without biopsies and how many patients had their biopsies avoided (or UGI endoscopy deferred

2287                   altogether) because of their anticoagulation status

2288                   • Therefore, the decision to interrupt or continue warfarin could have been influenced by the strength of indication for

2289                   endoscopy and endoscopic biopsies, whereas the decision to scope could have been influenced by the comfort level of

2290                   the physicians in interrupting warfarin for a specific patient, and the decision to biopsy could have been influenced by

2291                   whether warfarin had been interrupted or continued.

2292                   • Furthermore, **the number of biopsies taken per procedure, the size of biopsy forceps and treatment of the biopsy site**

2293                   **with thrombin spray were shown to have been influenced by whether antithrombotics had been interrupted or**

2294                   **continued** (no results were reported for patients on warfarin, but for the overall study population on any anticoagulant

2295                   or any antiplatelet, number of biopsies per case was significantly lower in the patients who continued antithrombotic

2296                   treatment ( $1.9 \pm 1.1$  vs  $2.4 \pm 1.6$ ;  $P < 0.01$ ); use of mini cup biopsy forceps (15.4% vs 3.7%;  $P < 0.01$ ), and thrombin spray

2297                   (19.6% vs 5.6%;  $P < 0.01$ ) were significantly higher in the group that did not interrupt antithrombotics use than in the

2298                   group that did).

2299                   • Overall, the choice of peri-procedural management of anticoagulation was influenced by factors (confounders) that also

2300                   influenced the risk of the outcomes of interest.

2301                   • The study also assessed an **indirect** comparator: 3364 patients undergoing diagnostic endoscopy without antithrombotics

2302                   • Events (bleeding) = 4 (0.12%)

2303

2304

2. Gerson et al. Adverse events associated with anticoagulation therapy in the periendoscopic period. *Gastrointestinal Endoscopy* 2010;71:1211-7.

- Design: prospective cohort study (outcomes assessed by telephone questionnaire)
- Population: Consecutive patients (n=483) on warfarin who underwent GI endoscopic procedures at 13 US sites, 2004-2006
  - Indirectness: **several types of GI endoscopic procedures were included and pooled together**. Colonoscopy = 347 (72%); Colonoscopic “polypectomy (snare, hot or cold biopsy)” = 161.
- Intervention (for PICO 11): no interruption of warfarin (n= 46)
- Intervention (for PICO 12): Interrupted warfarin, heparin bridging (n = 114)
- Comparator: interruption of warfarin without heparin bridging (n= 323)
- Outcomes: bleeding, thrombotic events, mortality
- Results (no adjustment for confounders):
  - Major bleeding (at 30-45 days), among all 483 patients, n=10
    - PICO 11:
      - 0/46 (0%) in patients who did not interrupt warfarin.
      - 5/323 (1.5%) in patients who interrupted warfarin without bridging. **We calculated the RR for not interrupting vs interrupting warfarin (without bridging): RR = 0.63, 95% CI 0.04 – 11.15**
    - PICO 12:
      - 5/114 (4.4%) among patients who interrupted warfarin with bridging with LMWH or enoxaparin.
      - 5/323 (1.5%) in patients who interrupted warfarin without bridging. **We calculated the RR for interrupting warfarin with bridging vs interrupting warfarin without bridging: RR = 2.83, 95% CI 0.84 – 9.6**
  - Major bleeding, among 161 who had colonoscopic polypectomy, 6/161= 3.7%. Of these, 2 patients held warfarin (without bridging) and 4 patients were bridged with LMWH or enoxaparin. However, denominators cannot be calculated (how many of the 161 patients had held warfarin, and how many had been bridged; we only know the denominators for the total study population).
  - Thrombotic events, n=1 (fatal stroke). However, it was not clear which group this patient belonged to; **therefore, no comparative results can be calculated.**



- 2332                   • Deaths, n=11 (timing ranged from 7 days to 8 months post procedure). However, it was not clear which group these  
2333                   patients belonged to; **therefore, no comparative results can be calculated.**
- 2334           • Notes regarding risk of bias:
- 2335                   • Six of the patients received pre-procedure vitamin K, unclear how many in each group
- 2336                   • The decision to interrupt or continue warfarin could have been influenced by the strength of indication for endoscopy  
2337                   and endoscopic interventions, whereas the decision to scope could have been influenced by the comfort level of the  
2338                   physicians in interrupting warfarin for a specific patient, and the decision to perform an intervention (and the type of  
2339                   intervention) could have been influenced by whether warfarin had been interrupted or continued. This means that the  
2340                   choice of peri-procedural management of anticoagulation was influenced by factors (confounders) that also influenced  
2341                   the risk of the outcomes of interest.

2342

2343   **3. Yanagisawa et al. Post-polypectomy bleeding and thromboembolism risks associated with warfarin vs direct oral anticoagulants.**  
2344   **World Journal of Gastroenterology 2018;24:1540-1549**

2345

- 2346           • Design: retrospective cohort study
- 2347           • PICO 11, PICO 12, PICO 13
- 2348           • Population: patients on warfarin on DOACs who underwent colonoscopic polypectomy at a center in Japan. 145 patients on  
2349           warfarin
- 2350                   • After polypectomy, patients routinely underwent prophylactic clipping
- 2351                   • Apparently, all polypectomies were hot snare polypectomies: they used "(SnareMaster, Olympus Co.) [which is  
2352                   electrocautery snare], and electrosurgical device (ERBE ICC-350, Somo Technology Inc., Tokyo, Japan or ESG-100,  
2353                   Olympus Co.)".
- 2354           • Cohort 1: no interruption of warfarin (n=43)
- 2355           • Cohort 2: temporary interruption of warfarin without heparin bridging (n=19)
- 2356           • Cohort 3: temporary interruption of warfarin with heparin bridging (n=83)
- 2357           • Outcomes: bleeding (30 days), thrombotic events (timing unclear), mortality (30 days)
- 2358           • Results (unadjusted):
- 2359                   • **Bleeding**
- 2360                       • No interruption of warfarin: 2/43 (4.7%)

- 2361 • Temporary interruption of warfarin (without heparin bridging): 0/19 (0%). For PICO 11, we calculated the RR (no  
 2362 interruption vs. temporary interruption of warfarin without heparin bridging): **2.27, 95% CI 0.11 – 45.20**
- 2363 • Temporary interruption of warfarin with heparin bridging: 18/83 (21.7%). For PICO 12, we calculated the RR  
 2364 (temporary interruption of warfarin with heparin bridging vs. temporary interruption of warfarin without  
 2365 heparin bridging): **8.81, 95% CI 0.55 – 140.1**
- 2366 • **Thrombotic events**
- 2367 • No interruption of warfarin: 0/43 (0%)
- 2368 • Temporary interruption of warfarin (without heparin bridging): 1/19 (5.3%). For PICO 11, we calculated the RR  
 2369 (no interruption vs. temporary interruption of warfarin without heparin bridging): **0.15, 95% CI 0.01 – 3.56**
- 2370 • Temporary interruption of warfarin with heparin bridging: 1/83 (1.2%). For PICO 12, we calculated the RR  
 2371 (temporary interruption of warfarin with heparin bridging vs. temporary interruption of warfarin without  
 2372 heparin bridging): **0.23, 95% CI 0.02 – 3.50**
- 2373
- 2374 • Mortality: no deaths in any group. Mortality for this PICO was 0% vs 0%. **The RR is not meaningful.**
- 2375 • No interruption of warfarin: 0/43 = 0% (95% CI 0% - 7%)
- 2376 • Temporary interruption of warfarin (without heparin bridging): 0/19 = 0% (95% CI 0% - 15.8%)
- 2377 • Temporary interruption of warfarin with heparin bridging: 0/83 (95% CI 0% - 3.6%)
- 2378 • Notes regarding risk of bias: the decision to interrupt or continue warfarin or use bridging could have been influenced by the  
 2379 strength of indication for endoscopy and polypectomy, whereas the decision to scope could have been influenced by the  
 2380 comfort level of the physicians in interrupting warfarin for a specific patient, and the decision to perform polypectomy (and the  
 2381 type of polypectomy) could have been influenced by whether warfarin had been interrupted or continued. This means that the  
 2382 choice of peri-procedural management of anticoagulation was influenced by factors (confounders) that also influenced the risk  
 2383 of the outcomes of interest.

2384

2385

2386 Cohort studies without the comparator cohort needed for this PICO

2387

- 2388 1. Horiuchi et al. Removal of small colorectal polyps in anticoagulated patients: a prospective randomized comparison of cold snare and  
 2389 conventional polypectomy. *Gastrointest Endosc* 2014;79:417-23

- Design: this is an RCT that compared cold vs hot polypectomy for removal of colorectal polyps up to 10 mm in patients **on warfarin, which was not interrupted** in a center in Japan. For this PICO this paper provides cohort-type data on the risk of post-polypectomy bleeding when warfarin is not interrupted.
  - However, it is difficult to identify study sub-population with direct and unbiased results. The cold polypectomy group is the best choice, but is still indirect and biased. See below
- **No comparator** (patients on temporary interruption of warfarin were excluded from the study)
- Results:
  - Immediate bleeding (>30 sec): 2/35 (5.7%) with cold polypectomy vs. 8/35 (23%) with hot polypectomy
  - **Delayed bleeding (within 14 days): 0/35 (0%, 95% CI 0% - 8.7%) with cold polypectomy** vs. 5/35 (14%) with hot polypectomy
- Notes of risk of bias
  - The RCT (comparison of cold vs hot polypectomy) was of high risk of bias, because of lack of blinding of the endoscopist (performance bias for both outcomes and ascertainment bias for immediate bleeding), lack of blinding of assessors of delayed bleeding (ascertainment bias), lack of concealment of allocation (selection bias) for a proportion of the patients (with fixed block size of 4, and unblinded endoscopists, it was easy to predict the allocation of the last 1-2 patients in each block). Therefore, the results of each of the two groups could be biased.
    - The results on immediate bleeding and histology (injured arteries) may be indicators of the above-mentioned biases:
      - a. Other studies (although they had not included exclusively patients on warfarin) have consistently shown that immediate bleeding is more frequent with CSP compared to hot snare polypectomy. This study showed inverse results.
      - b. The presence of histologically demonstrated injured arteries in the submucosal layer with cold snare was significantly less than with conventional snare (22% vs 39%,  $P = 0.023$ ). This is unlikely to be caused by the choice of snare, most likely reflecting selection bias or chance (favoring CSP)
  - As cohort study, there is serious selection bias (as expected when one of the arms of an RCT is used as cohort study, further exaggerated here because there was no flow diagram for participants: it is not known how many patients were excluded because they had interrupted warfarin or because of other reasons)

2419 **2. Arimoto J et al. Safety of Cold Snare Polypectomy in Patients Receiving Treatment with Antithrombotic Agents. Digestive diseases and**  
 2420 **sciences. 2019.**

- 2421 • Design: The main study was a retrospective cohort study on 501 patients who underwent CSP (Cold Snare Polypectomy) for polyps up to  
 2422 10 mm at a center in Japan. For this PICO, we extracted data from the cohort of patients on **uninterrupted warfarin** (the number of  
 2423 patients is unclear; the number of **polypectomies** in patients on warfarin is 23). In this center no antithrombotics were discontinued for  
 2424 CSP.
- 2425 • The comparator (patients to have not been taking any antithrombotics) is not the comparator required for this PICO. Therefore, this  
 2426 study is included as a **cohort study without comparator**
- 2427 • Results (unclear results per patient- reported results per polypectomy (more than one polypectomy per patient)):  
 2428 - **Delayed bleeding: 0/23 (0%) polypectomies** among for patients on uninterrupted warfarin (in fact it was 0% for the whole study  
 2429 population)  
 2430 - Immediate bleeding: 4/23 (17.4%) **polypectomies** among for patients on uninterrupted warfarin
- 2431
- 2432 • Note: clipping was applied for “immediate bleeding” (clipping was applied in 13.9% of polypectomies in patients on uninterrupted  
 2433 antithrombotics (the results for patients on warfarin were not reported)
- 2434
- 2435
- 2436

Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (here, exposure vs non-exposure is the difference in antithrombotic management between the intervention and the comparator for this PICO)	Prognostic factors (other than exposure of interest) <b>similar</b> among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Ara. Dig End 2015 <sup>1</sup>	OK	No, the two cohorts were not similar for prognostic factors	OK	OK	OK	OK	P: patients who had upper GI endoscopic biopsy <b>DELAYED BLEEDING (30 days):</b> • Continuous warfarin treatment:

		for bleeding: confounding was favoring the non-interruption group. No adjustment.					0/92 = 0% (0% - <b>3.3%</b> ) • <b>interrupted</b> warfarin: 0/19 = 0% (0% - 15.8%) • RR is not meaningful
Gerson. GIE 2010 <sup>2</sup>	OK	No, the two cohorts were not similar for prognostic factors for the outcomes of interest. No adjustment	OK	OK	Unclear if follow up was complete. Unclear if no-response was non-differential among the two cohorts	OK	P: patients who had <b>various GI procedures</b> <b>DELAYED BLEEDING</b> (30-45 days) with <b>continuous warfarin RR 0.63 (0.04 – 11.15)</b> • <b>Continuous:</b> 0/46 = 0% (0% - <b>6.5%</b> ) • <b>Interrupted:</b> 5/323 (1.5%)
Yanagisawa. WJG 2018 <sup>3</sup>	OK	No, the two cohorts were not similar for prognostic factors for the outcomes of interest. No adjustment for the comparison of interest for this PICO (whereas, other analyses were adjusted)	OK	OK	OK	OK	P: patients who had <b>hot snare colonic polypectomy</b> <b>DELAYED BLEEDING</b> (30 days) with <b>continuous warfarin: RR 2.27 (0.11 - 45.20)</b> • <b>Continuous warfarin:</b> 2/43 = 4.7% (0% - <b>16.7%</b> ) • <b>Interrupted:</b> 0/19 (0%) <b>THROMBOTIC EVENTS</b> (timing unclear, likely 30 days), with <b>continuous warfarin: RR 0.15 (0.006 – 3.56)</b> • <b>Continuous:</b> 0/43 (0%) • <b>Interrupted:</b> 1/19 (5.3%) <b>DEATHS</b> (30 days; RR not meaningful) • <b>Continuous:</b> 0/43 = 0% (0% - 7%) • <b>Interrupted:</b> 0/19 = 0% (0% - 15.8%)
Horiuchi. GIE 2014 <sup>4</sup>	OK	<b>Very</b> serious risk of bias: <b>no comparator</b> (only patients who continued warfarin treatment were included)	OK	Very serious risk of bias: <b>no comparator</b> (only patients who continued warfarin treatment were included)	Very serious risk of bias: <b>no comparator</b> (only patients who continued warfarin treatment were included)		- Cohort type data ( <b>without</b> the <b>comparator</b> that is required for this PICO) extracted from an RCT at high risk of bias. - Bias is further exaggerated when <b>only the cold polypectomy group is considered</b> (see notes in the description of the study) - Provides estimates for outcomes for the <b>continuous warfarin cohort</b> P: patients who had <b>colonic polypectomy</b> ( $\leq 10$ mm) - We used the results for the <b>cold snare cohort</b> , the least indirect results (most

							applicable, given that nowadays such polyps (i.e., up to 10 mm) are usually removed with cold snare), instead of the results for both cohorts (cold and hot snare) pooled together. <b>DELAYED BLEEDING</b> (within 14 days): • <b>Continuous</b> warfarin, cold snare: 0/35 = 0% (0% - <b>8.7%</b> )
Arimoto. DDS 2019 <sup>5</sup>	OK	<b>Very</b> serious risk of bias: <b>no comparator</b> of interest	OK	Very serious risk of bias: <b>no comparator</b> of interest	Very serious risk of bias: <b>no comparator</b> of interest		- Cohort type data ( <b>without</b> the <b>comparator</b> that is required for this PICO) extracted from a wider cohort study <b>P</b> : patients undergoing <b>cold snare colonic polypectomy</b> ( $\leq 10$ mm) <b>DELAYED BLEEDING</b> (within 14 days): • <b>Continuous</b> warfarin, cold snare: 0/23 = 0% (0% - <b>13%</b> ). The denominator (n=23) is the number of <b>polypectomies</b> (each patient could have had 1 or more polypectomies)
Low risk of bias							
Unclear risk of bias							
High risk of bias							

2437 Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included,  
2438 because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid  
2439 methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of  
2440 interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not  
2441 included, because it is an “indirectness” issue as per GRADE.

2442 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
2443 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias.

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## 2448 Evidence profile for PICO 11

No interruption of warfarin vs. temporary interruption													
Certainty Assessment								Summary of Findings				Comments	
								Events / participants		Effect			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Continuous warfarin	Interrupted warfarin	Relative (95% CI)	Absolute (95% CI)		
Bleeding within 30 days (critical outcome)							⊕⊕⊕⊕ VERY LOW						
3 cohort studies with control cohort <sup>1-3</sup>	Serious <sup>a</sup>	Not serious <sup>b</sup>	Serious <sup>c</sup>	Very serious <sup>d</sup>	None	⊕⊕⊕⊕ VERY LOW		Not estimable <sup>e</sup>	Not estimable <sup>e</sup>	RR ranged from 0.63 (0.04-11.15) to 2.27 (0.11-45.20) <sup>e</sup>	Not estimable <sup>e</sup>	If continuous warfarin arms from all 5 studies are pooled: 0/239 events (95% CI 0% to 12.5%)	
2 cohort studies without control cohort <sup>4,5</sup>	Very serious <sup>f</sup>	Not serious	Serious <sup>c, g</sup>	Very serious <sup>h</sup>	None	⊕⊕⊕⊕ VERY LOW		0/58 (0%, 95% CI 0%-5.2%)	-	-	-		
Thrombotic events within 30 days (critical outcome)													
1 cohort study <sup>3</sup>	Serious <sup>a</sup>	Not applicable	Not serious	Very serious <sup>i</sup>	None	⊕⊕⊕⊕ VERY LOW			0/43 (0%)	1/19 (5.3%)	RR 0.15 (0.006-3.56)	Risk with interrupted warfarin: 53 events per 1,000. With continuous warfarin: 45 fewer per 1,000 (from 53 fewer to 137 more)	
Mortality within 30 days (important outcome, but not critical for decision making)													
1 cohort study <sup>3</sup>	Serious <sup>a</sup>	Not applicable	Not serious	Very serious <sup>i</sup>	None	⊕⊕⊕⊕ VERY LOW		0/43 (0%, 95% CI 0% - 7%)	0/19 (0%, 95% CI 0% - 15.8%)	-	-		

2449

2450 **Footnotes:**

2451 <sup>a</sup> Serious risk of bias, mainly because prognostic factors (other than exposure of interest) were not similar and not adjusted among the two cohorts (see risk of  
2452 bias table, above)

2453 <sup>b</sup> Inconsistency between Gerson GIE 2010 and Yanagisawa WJG 2018, but this could be explained by the differences in population

2454 <sup>c</sup> No study assessed outcomes in patients who were **prospectively** (i.e. at the time of procedure scheduling) **instructed** to continue vs. interrupt warfarin  
2455 treatment, which is how decisions have to be made in clinical practice: **before** the endoscopic procedure, usually without knowledge of whether a diagnostic or  
2456 therapeutic intervention will be required – and for many patients no intervention will be required. The populations of the included studies were different, in  
2457 that the participants were the ones who **had** an intervention (e.g. biopsy or polypectomy); these studies excluded those who had the endoscopic procedure  
2458 but who did not need an intervention and those who needed an intervention but the endoscopist deferred, or called off the intervention due to  
2459 anticoagulation status.  
2460 Also, large variability in the study populations (i.e. the endoscopic procedures the patients were undergoing: from simple biopsies to polypectomy to ERCP).

2461 <sup>d</sup> Sample sizes were very small and events were very few (2 vs 6). Very fragile results with very wide confidence intervals compatible with both large benefit  
2462 and large harm

2463 <sup>e</sup> Included studies were too heterogeneous to be pooled via meta-analysis

2464 <sup>f</sup> Very serious risk of bias due to lack of comparator cohort

2465 <sup>g</sup> The outcome was measured at 2 weeks

2466 <sup>h</sup> Very small sample sizes (n=58 in total). Zero events overall.

2467 <sup>i</sup> Very small sample size (n=62 in total). Only 1 event in total. Very fragile results with very wide confidence intervals compatible with both large benefit and  
2468 large harm

2469 <sup>j</sup> Very small sample size (n=62 in total). Zero events overall.

2470

2471 **Evidence to Decision Table**

2472

2473 11. Continuous anticoagulation with Warfarin vs. temporary interruption

2474 P: Patient on Warfarin (undergoing elective/planned endoscopic procedures)

2475 I: Continuous anticoagulation

2476 C: Temporary interruption of warfarin X up to 7 days



2477 O: CRITICAL: Bleeding within 30 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis,  
 2478 pulmonary embolus)  
 2479 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days  
 2480  
 2481

	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<p><b>How substantial are the desirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>● <b>Moderate</b></li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>See Evidence Profile Table</p> <p>The <u>desirable</u> anticipated effect with continued warfarin (compared to interrupted warfarin) are</p> <ul style="list-style-type: none"> <li>▪ reduced <b>thromboembolic events (critical outcome)</b>: 45 fewer per 1,000 patients (from 53 fewer to 137 more)</li> </ul>	<p>We have don't conducted a formal literature search for non-GI ambulatory procedures. The guideline panel noted that of all the studies on non-GI procedures, the literature on cardiac device procedures provides the best indirect evidence in estimating bleeding/thrombotic risks for this PICO: it suggests that continued vs interrupted warfarin does not substantially impact bleeding or thrombosis risks; this has lent support to continuing warfarin for most "standard" cardiac device procedures.</p>
Undesirable Effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>	<p>It is not possible to estimate the direction (let alone the magnitude) of the effect uninterrupted warfarin (compared to interrupted warfarin) on <b>bleeding (critical outcome) or mortality</b></p> <p>Our best estimate of the bleeding incidence with continued warfarin has an upper bound of 95% CI of 12.5%</p>	<p>The panel acknowledged our inability to estimate bleeding risk for GI procedures: the bleeding risk is unknown and is a <b>moving target</b> due to heterogeneity in patient populations and type of procedures. The is no evidence for advanced procedures with high baseline risk of bleeding. Also, there is a difference in the consequences of the bleed between luminal and extra-luminal GI procedures. It was also noted that the incremental risk of bleeding with continued warfarin is unknown (the baseline risk may not be as relevant as the incremental risk of bleeding)</p>

Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>See Evidence Profile Table.</p> <p>The certainty of the evidence from studies in patients undergoing GI endoscopic procedures is very low.</p>	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>● <b>Important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p> <p>Review of the evidence of the value (disutility) that patients place on the outcomes of GI bleeding and thromboembolism, revealed both important <b>uncertainty</b> (due to limitations of the research and indirectness: different populations, less evidence on thromboembolism other than stroke) and important <b>variability</b> in patient values within each study.</p> <p>However, in general, patients placed more weight (more disutility) on stroke rather than GI bleeding (unless they had just had a GI bleed)</p>	<p>These are patients who have not bled yet. So, thrombosis has even higher disutility value (weight) than GI bleeding.</p>
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● <b>Probably favors the intervention (continuous anticoagulation)</b></li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>○ Negligible costs and savings</li> <li>● <b>Moderate savings</b></li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>More costly to interrupt than to continue. Cost of the process of restarting/lab tests/consultation etc</p>	

<b>Certainty of Evidence of Required Resources</b>	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● <b>Moderate</b></li> <li>○ High</li> <li>○ No included studies</li> </ul>		
<b>Cost effectiveness</b>	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● <b>No included studies</b></li> </ul>		
<b>Acceptability</b>	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● <b>Yes</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Continuing warfarin in acceptance to patients and HCP (it is inconvenient to stop and restart warfarin)	
<b>Feasibility</b>	<p><b>Is the intervention feasible to implement?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● <b>Yes</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

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**Conclusions**

2484 **PICO: 11. For patients on warfarin who are undergoing elective/planned endoscopic GI procedures, should warfarin be continued**  
 2485 **or temporarily interrupted for up to 7 days?**  
 2486 *O: CRITICAL: Bleeding within 30 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial*  
 2487 *infarction, deep vein thrombosis, pulmonary embolus)*  
 2488 *IMPORTANT, BUT NOT CRITICAL: mortality within 30 days*  
 2489

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention (continuous warfarin) 6/6 votes: 100%	Strong recommendation for the intervention
	○	○	○	●	○
<b>Recommendation</b>	For patients on warfarin who are undergoing elective/planned endoscopic GI procedures, we suggest that warfarin be continued, as opposed to temporarily interrupted (1-7 days). (Conditional recommendation, very low certainty of evidence)				
<b>Justification</b>					
<b>Subgroup considerations</b>	The (anticipated) type of procedure and the baseline risk of thromboembolism will influence the recommendation. See grit in main-text paper.				
<b>Implementation considerations</b>					
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?				
<b>Research priorities</b>					

2490  
 2491 **References for PICO 11**

- 2492 1. Ara et al. Prospective analysis of risk for bleeding after endoscopic biopsy without cessation of antithrombotics in Japan. Digestive Endoscopy 2015;  
 2493 27:458-464  
 2494 2. Gerson et al. Adverse events associated with anticoagulation therapy in the periendoscopic period. Gastrointestinal Endoscopy 2010;71:1211-7.  
 2495 3. Yanagisawa et al. Post-polypectomy bleeding and thromboembolism risks associated with warfarin vs direct oral anticoagulants. World Journal of  
 2496 Gastroenterology 2018;24:1540-1549

- 2497 4. Horiuchi et al. Removal of small colorectal polyps in anticoagulated patients: a prospective randomized comparison of cold snare and conventional  
2498 polypectomy. *Gastrointest Endosc* 2014;79:417-23  
2499 5. Arimoto J et al. Safety of Cold Snare Polypectomy in Patients Receiving Treatment with Antithrombotic Agents. *Digestive diseases and sciences*.  
2500 2019;64:3247–3255  
2501

2502

2503 [12. Bridging anticoagulation for patients on warfarin](#)

2504 **12. Bridging anticoagulation for patients on warfarin**

2505 P: Patients on warfarin **whose warfarin is held peri-operatively**

2506 I: Use of peri-procedural low-molecular heparin or IV heparin (i.e., bridging anticoagulation)

2507 C: No heparin/low-molecular weight heparin bridge

2508 O: **CRITICAL:** Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep  
2509 vein thrombosis, pulmonary embolus)

2510 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days  
2511

2511

2512 **RCTs**

2513 • **Douketis JD, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med* 2015;373:823-33**

2514 • RCT: bridging (LMWH) vs placebo in perioperative discontinuation of warfarin

2515 • Double-blind study

2516 • Arterial thromboembolism: very serious **imprecision** (high fragility, due to small number of events: 3 vs. 4 events with bridging  
2517 vs no bridging)

2518 • The results for minor bleeding (secondary outcome) are at the same direction as the results for major bleeding

2519 • **Indirectness issues**

2520 • There isn't indirectness for the outcome of arterial thromboembolism

2521 • The indirectness affects the outcome of bleeding

2522 • Did not report separate results for patients who underwent GI procedures (n= 758, i.e. 44.0%) or separate results for the  
2523 outcome of GI bleeding, in the main article or the suppl appendix.

2524 • **The vast majority (n= 748, i.e. 98.7%) of the GI procedures were “minor or low-bleeding risk procedures”** (described as  
2525 “GI endoscopy with or without biopsy” = 748). There were 10 major GI procedures (described as “e.g., colonic polyp  
2526 resection”, but the size of polyps is not known), i.e. 1.3% of the GI procedures.

2527

2528 Of note, another large RCT (Kovacs MJ et al. **Double Blind Randomized Control Trial of Postoperative Low Molecular Weight Heparin Bridging**  
2529 **Therapy for Patients Who Are at High Risk for Arterial Thromboembolism (PERIOP 2). Blood (2018) 132 (Supplement 1): 424**

2530 <https://doi.org/10.1182/blood-2018-99-109964>) has only been available as an abstract publication, and as such it was not included in the  
2531 evidence profile. Nevertheless, this study showed results similar to Douketis NEJM 2015.

2532

2533 • **Takeuchi et al. Continuous Anticoagulation and Cold Snare Polypectomy Versus Heparin Bridging and Hot Snare Polypectomy in**  
2534 **Patients on Anticoagulants with Subcentimeter Polyps. Ann Intern Med 2019; 171:229-237**

2535 **Population:** N = 184 patients on anticoagulant therapy (warfarin or DOACs) requiring polypectomy for least 1 nonpedunculated  
2536 subcentimeter colorectal polyp. Undergoing hot-snare polypectomy (HSP) or cold-snare polypectomy (CSP).

2537 **Intervention:** n = 90 patients: interruption of anticoagulation with heparin bridging (HB) **plus** hot snare polypectomy (HSP)

2538 **Comparator:** n = 92 patients: **continuous** anticoagulation (CA) **plus** cold snare polypectomy (CSP)

2539 **Outcome:** Polypectomy-related major bleeding (did not assess thromboembolic events)

2540 **Results:** Polypectomy-related major bleeding occurred in 12% (n=10) in the HB+HSP group and 4.7% (n=4) in the CA+CSP group

2541 Comments:

2542 • Sub-centimeter polyp resection during colonoscopy: 100%

2543 • Not blinded

2544 • Provided separate results for warfarin and DOAC users for polypectomy-related major bleeding

2545 • Did not assess thromboembolic events

2546 • **Indirectness issues**

2547 • The comparator (**continuous** anticoagulation) is different from the comparator required for this PICO question  
2548 (interrupted anticoagulation without bridging): **therefore, the study is included in a separate Evidence Profile**

2549 • The polypectomy technique was different among the two arms

2550 • The study population is unusual. Patients “*had at least 1 sub centimeter nonpedunculated polyp detected during*  
 2551 *colonoscopy in the past 3.5 years*”. The investigators had to know this information several days prior to the  
 2552 polypectomy. This means that the patients had previous colonoscopies during which the polyps were simply observed  
 2553 and documented without any action taken for up to 3.5 years. No explanation was provided for this unusual practice.  
 2554 Only a small proportion of patients (5 patients, 2.7%) were excluded post-randomization because the study colonoscopy  
 2555 showed different findings than the previous colonoscopy.

2556  
 2557 • Of note <https://ashpublications.org/blood/article/132/Supplement%201/424/275575/Double-Blind-Randomized-Control-Trial-of>  
 2558

Risk of bias assessment of RCTs							
Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Comments
Douketis NEJM 2015 <sup>1</sup>	OK	OK	OK (double-blind)	OK	OK	OK	
Takeuchi AIM 2019 <sup>2</sup>	OK	Unclear	Not blinded	OK	Did not report thromboembolic events	OK	
Low risk of bias							
Unclear risk of bias							
High risk of bias							

2559 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
 2560 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias

2561

2562 Cohort studies **with** the comparator cohort needed for this PICO

2563

## 2564 2. Gerson et al. Adverse events associated with anticoagulation therapy in the periendoscopic period. Gastrointestinal Endoscopy 2010

- 2565 • Design: prospective cohort study (outcomes assessed by telephone questionnaire)
- 2566 • Population: Consecutive patients (n=483) on warfarin who underwent GI endoscopic procedures at 13 US sites, 2004-2006
- 2567 • Indirectness: **several types of GI endoscopic procedures were included and pooled together**. Colonoscopy = 347 (72%);
- 2568 Colonoscopic “polypectomy (snare, hot or cold biopsy)” = 161.

- 2569 • Intervention (for PICO 11): no interruption of warfarin (n= 46)
- 2570 • Intervention (for PICO 12): Interrupted warfarin, heparin bridging (n = 114)
- 2571 • Comparator: interruption of warfarin without heparin bridging (n= 323)
- 2572 • Outcomes: bleeding, thrombotic events, mortality
- 2573 • Results (no adjustment for confounders):
  - 2574 • Major bleeding (at 30-45 days), among all 483 patients, n=10
    - 2575 • PICO 11:
      - 2576 • 0/46 (0%) in patients who did not interrupt warfarin.
      - 2577 • 5/323 (1.5%) in patients who interrupted warfarin without bridging. **We calculated the RR for not**
      - 2578 **interrupting vs interrupting warfarin (without bridging): RR = 0.63, 95% CI 0.04 – 11.15**
    - 2579 • PICO 12:
      - 2580 • 5/114 (4.4%) among patients who interrupted warfarin with bridging with LMWH or enoxaparin.
      - 2581 • 5/323 (1.5%) in patients who interrupted warfarin without bridging. **We calculated the RR for**
      - 2582 **interrupting warfarin with bridging vs interrupting warfarin without bridging: RR = 2.83, 95% CI 0.84 –**
      - 2583 **9.6**
  - 2584 • Major bleeding, among 161 who had colonoscopic polypectomy, 6/161= 3.7%. Of these, 2 patients held warfarin
  - 2585 (without bridging) and 4 patients were bridged with LMWH or enoxaparin. However, denominators cannot be calculated
  - 2586 (how many of the 161 patients had held warfarin, and how many had been bridged; we only know the denominators for
  - 2587 the total study population.
  - 2588 • Thrombotic events, n=1 (fatal stroke). However, it was not clear which group this patient belonged to; **therefore, no**
  - 2589 **comparative results can be calculated.**
  - 2590 • Deaths, n=11 (timing ranged from 7 days to 8 months post procedure). However, it was not clear which group these
  - 2591 patients belonged to; **therefore, no comparative results can be calculated.**
  - 2592 • Notes regarding risk of bias:
    - 2593 • Six of the patients received pre-procedure vitamin K, unclear how many in each group
    - 2594 • The decision to interrupt or continue warfarin could have been influenced by the strength of indication for endoscopy
    - 2595 and endoscopic interventions, whereas the decision to scope could have been influenced by the comfort level of the
    - 2596 physicians in interrupting warfarin for a specific patient, and the decision to perform an intervention (and the type of



intervention) could have been influenced by whether warfarin had been interrupted or continued. This means that the choice of peri-procedural management of anticoagulation was influenced by factors (confounders) that also influenced the risk of the outcomes of interest.

**3. Yanagisawa et al. Post-polypectomy bleeding and thromboembolism risks associated with warfarin vs direct oral anticoagulants. World Journal of Gastroenterology. 24 (14) (pp 1540-1549), 2018.**

- Design: retrospective cohort study
- PICO 11, PICO 12, PICO 13
- Population: patients on warfarin on DOACs who underwent colonoscopic polypectomy at a center in Japan. 145 patients on warfarin
  - After polypectomy, patients routinely underwent prophylactic clipping
  - Apparently, all polypectomies were hot snare polypectomies: they used “(SnareMaster, Olympus Co.) [which is electrocautery snare], and electrosurgical device (ERBE ICC-350, Somo Technology Inc., Tokyo, Japan or ESG-100, Olympus Co.)”.
- Cohort 1: no interruption of warfarin (n=43)
- Cohort 2: temporary interruption of warfarin without heparin bridging (n=19)
- Cohort 3: temporary interruption of warfarin with heparin bridging (n=83)
- Outcomes: bleeding (30 days), thrombotic events (timing unclear), mortality (30 days)
- Results (unadjusted):
  - **Bleeding**
    - No interruption of warfarin: 2/43 (4.7%)
    - Temporary interruption of warfarin (without heparin bridging): 0/19 (0%). For PICO 11, **we calculated the RR (no interruption vs. temporary interruption of warfarin without heparin bridging): 2.27, 95% CI 0.11 – 45.20**
    - Temporary interruption of warfarin with heparin bridging: 18/83 (21.7%). For PICO 12, **we calculated the RR (temporary interruption of warfarin with heparin bridging vs. temporary interruption of warfarin without heparin bridging): 8.81, 95% CI 0.55 – 140.1**
  - **Thrombotic events**
    - No interruption of warfarin: 0/43 (0%)

- 2625                   • Temporary interruption of warfarin (without heparin bridging): 1/19 (5.3%). For PICO 11, **we calculated the RR**  
 2626                   **(no interruption vs. temporary interruption of warfarin without heparin bridging): 0.15, 95% CI 0.01 – 3.56**  
 2627                   • Temporary interruption of warfarin with heparin bridging: 1/83 (1.2%). For PICO 12, **we calculated the RR**  
 2628                   (temporary interruption of warfarin with heparin bridging vs. temporary interruption of warfarin without  
 2629                   heparin bridging): **0.23, 95% CI 0.02 – 3.50**  
 2630  
 2631                   • Mortality: no deaths in any group. Mortality for this PICO was 0% vs 0%. **The RR is not meaningful.**  
 2632                   • No interruption of warfarin: 0/43 = 0% (95% CI 0% - 7%)  
 2633                   • Temporary interruption of warfarin (without heparin bridging): 0/19 = 0% (95% CI 0% - 15.8%)  
 2634                   • Temporary interruption of warfarin with heparin bridging: 0/83 (95% CI 0% - 3.6%)  
 2635  
 2636                   • Notes regarding risk of bias: the decision to interrupt or continue warfarin or use bridging could have been influenced by the  
 2637                   strength of indication for endoscopy and polypectomy, whereas the decision to scope could have been influenced by the  
 2638                   comfort level of the physicians in interrupting warfarin for a specific patient, and the decision to perform polypectomy (and the  
 2639                   type of polypectomy) could have been influenced by whether warfarin had been interrupted or continued. This means that the  
 2640                   choice of peri-procedural management of anticoagulation was influenced by factors (confounders) that also influenced the risk  
 2641                   of the outcomes of interest.  
 2642  
 2643                   **4. Nagata N et al. Therapeutic endoscopy-related GI bleeding and thromboembolic events in patients using warfarin or direct oral**  
 2644                   **anticoagulants: Results from a large nationwide database analysis. Gut 2018;67(10):1805-1812**  
 2645                   • Design: retrospective cohort  
 2646                   • Population: N = 10,092 patients on warfarin or DOACs who underwent 13 types of **high-risk endoscopic procedures**  
 2647                   • Not explicitly mentioned, but it seems that there were only 2 options: either bridging or temporary interruption; no patient  
 2648                   remained on oral anticoagulants in the peri-procedural period  
 2649                   • Used unfractionated heparin for bridging  
 2650                   • For the bridging group the typical protocol was provided, but the protocol for temporary interruption and assumption was not  
 2651                   described  
 2652                   • Propensity score matching for various factors (age category, sex, BMI category, 13 comorbidities, annual hospital volume for  
 2653                   therapeutic endoscopy, 7 types of drugs used and 13 types of endoscopic procedures). Not matched for CHADS<sub>2</sub> score. This

means that the choice of peri-procedural management of anticoagulation was influenced by factors (confounders) that also influenced the risk of the outcomes of interest.

- **Indirectness** concern: about 25% of the study population had endoscopy so as to have emergency endoscopic hemostasis (endoscopic variceal ligation, endoscopic injection sclerotherapy, upper GI hemostasis, lower GI hemostasis). These patients (who contributed disproportionally to the post-endoscopic events) are different from the population of this PICO question, because they could have post-endoscopic bleeding because of unsuccessful hemostasis, not because of the endoscopic intervention.
- The comparison of interest for this PICO question (temporary interruption of warfarin with heparin bridging vs. temporary interruption of warfarin without heparin bridging) was not assessed in this paper. All interventions were compared to “DOACs alone” which was the reference for all analyses (see Table 4 from this paper). **We are able to calculate the odds ratios (ORs) of interest**, but the 95% CIs cannot be easily estimated.
  - Bleeding: OR 1.48
  - Thromboembolism: OR 1.94
  - Death: OR 1.42

5. Inoue T et al. Clinical features of post-polypectomy bleeding associated with heparin bridge therapy. *Digestive Endoscopy*. 26 (2) (pp 243-249), 2014.

**Design:** retrospective cohort study

**Population:** patients on anticoagulants undergoing colonoscopic polypectomy. 45 patients had been on warfarin

- Prophylactic clipping was made by each primary doctor individually to prevent PPB
- Hot snare polypectomy

**Intervention:** Interruption of warfarin with heparin bridging (unfractionated heparin continuous administration in-hospital), n= 33

**Comparator:** Interruption of warfarin without heparin bridging, n= 13

**Outcome:** post-polypectomy bleed (by 30 days). The outcomes of interest as only available as unadjusted results (other analyses were adjusted, but not these). This means that the choice of peri-procedural management of anticoagulation was influenced by factors (confounders) that also influenced the risk of the outcomes of interest.

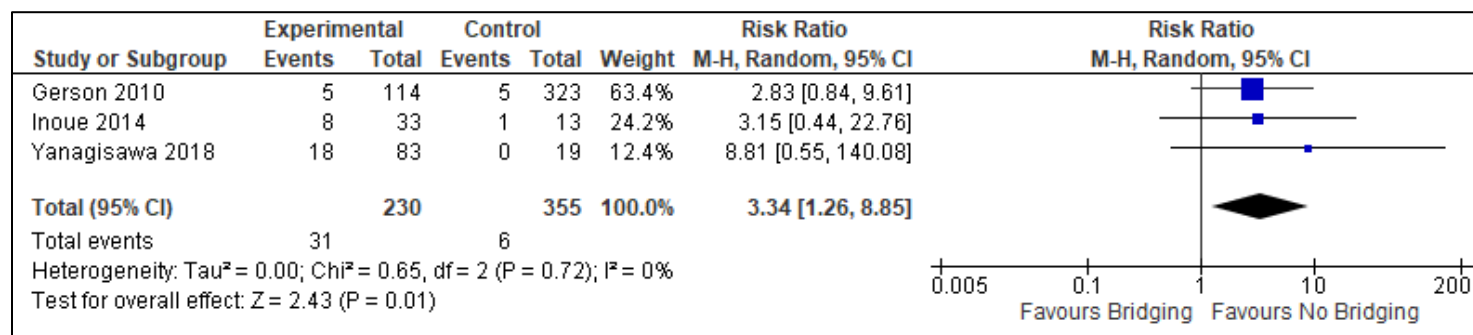
- Interruption of warfarin with heparin bridging: 8/33 (24.2%)
- Interruption of warfarin without heparin bridging: 1/13 (7.7%)

**We calculated the RR** (temporary interruption of warfarin with heparin bridging vs. temporary interruption of warfarin without heparin bridging): **3.15, 95% CI 0.44 -22.77**

2688 **Our meta-analysis of cohort studies**

2689 Three of the above cohort studies (on GI procedures) could be pooled via meta-analysis for the outcome of bleeding. Nagata et al could not be  
 2690 pooled because neither the raw data, nor the 95% CI could be extracted or calculated. For the outcomes of thromboembolic events and death  
 2691 only one study reported granular data

2692 **Delayed bleeding:**



Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (here, Exposure vs non-exposure is the difference in antithrombotic management between the intervention and the comparator for this PICO)	Prognostic factors (other than exposure of interest) <b>similar</b> among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Comments
Gerson. GIE 2010 <sup>3</sup>	OK	No, the two cohorts were not similar for prognostic factors for the outcomes of interest. No adjustment.	OK	OK	Unclear if follow up was complete. Unclear if no-response was non-differential among the two cohorts	OK	P: patients who had <b>various GI procedures</b> <b>DELAYED BLEEDING</b> (30-45 days) • Interrupted warfarin plus <b>bridging</b> : 5/114 (4.4%) • Interrupted warfarin <b>without</b> bridging: 5/323 (1.5%) <b>RR 2.83, 95% CI 0.84 - 9.6</b>
Yanagisawa. WJG 2018 <sup>4</sup>	OK	No, the two cohorts were not similar for prognostic factors for the outcomes of interest. No adjustment for the comparison of interest for this PICO (whereas, other analyses were adjusted)	OK	OK	OK	OK	P: patients who had hot snare <b>colonic polypectomy</b> <b>DELAYED BLEEDING</b> (30 days) • Interrupted warfarin plus <b>bridging</b> : 18/83 (21.7%) • Interrupted warfarin <b>without</b> bridging: 0/19 (0%) <b>RR 8.81, 95% CI 0.55-140.1</b> <b>THROMBOTIC EVENTS</b> (timing unclear, likely 30 days) • Interrupted warfarin plus <b>bridging</b> : 1/83 (1.2%)

							<ul style="list-style-type: none"> <li>• Interrupted warfarin <b>without</b> bridging: 1/19 (5.3%) <b>RR 0.23, 95% CI 0.02-3.50</b></li> <li><b>DEATHS</b> (30 days; RR not meaningful)</li> <li>• Interrupted warfarin plus <b>bridging</b>: 0/83 (0%; 95% CI 0% - 3.6%)</li> <li>• Interrupted warfarin <b>without</b> bridging: 0/19 (0%; 95% CI 0% - 15.8%)</li> </ul>
Nagata Gut 2018 <sup>5</sup>	OK	Incomplete adjustment. Propensity score matching for various factors, but not matched for CHADS2 score.	High risk of bias for the outcome of bleeding, because for 25% of the patients the outcome of interest was present at the start of the study (i.e. they were bleeding before the endoscopy)	OK	OK	OK	<p>P: patients on anticoagulants who underwent high-risk endoscopic procedures</p> <p><b>DELAYED BLEEDING</b> (30 d) Interrupted warfarin plus <b>bridging</b> vs. interrupted warfarin <b>without</b> bridging: <b>OR 1.48</b> (95% CI and absolute risk could not be estimated)</p> <p><b>THROMBOEMBOLISM</b> (30 d) <b>OR 1.94</b> <u>Deaths</u> (in-hospital) <b>OR 1.42</b></p>
Inoue DE 2014 <sup>6</sup>	OK	No, the two cohorts were not similar for prognostic factors for the outcomes of interest. No adjustment for the comparison of interest for this PICO (whereas, other analyses were adjusted)	OK	OK	OK	OK	<p>P: patients who had hot snare <b>colonic polypectomy</b></p> <p><b>DELAYED BLEEDING</b> (30 days) • Interrupted warfarin plus <b>bridging</b>: 8/33 (24.2%)</p> <ul style="list-style-type: none"> <li>• Interrupted warfarin <b>without</b> bridging: 1/13 (7.7%)</li> </ul> <p><b>RR 3.15, 95% CI 0.44-22.77</b></p>
Low risk of bias							

Unclear risk of bias
High risk of bias

2705 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e. if one domain has unclear risk of  
 2706 bias, the study has unclear risk of bias overall. If one domain has high risk of bias, the study has high risk of bias overall.

2707 **Notes about the above tool:** Modified Newcastle-Ottawa Scale (NOS). For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed  
 2708 cohort) was not included, because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort)  
 2709 was replaced with “valid methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other  
 2710 than exposure of interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to  
 2711 Occur” was not included, because it is an “indirectness” issue as per GRADE.

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## 2737 Evidence profile for PICO 12

Interrupted warfarin <u>with</u> heparin bridging vs. interrupted warfarin <u>without</u> heparin bridging																
Certainty Assessment								Summary of Findings								
								Events / participants		Effect						
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Interrupt ed warfarin and heparin bridging	Interrupt ed warfarin <u>without</u> heparin bridging	Relative (95% CI)	Absolute (95% CI)					
Bleeding within 30 days (critical outcome)							⊕⊕⊕⊕ LOW									
1 RCT (Douketis NEJM 2015) <sup>1</sup>	Not serious	Not applicable	Serious <sup>a</sup>	Serious <sup>b</sup>	None	⊕⊕⊕⊕ LOW		29/895	12/918	RR 2.48 (1.27 - 4.83)	Risk <b>without</b> heparin bridging: 13 events per 1,000. <b>With</b> heparin bridging: 19 <b>more</b> per 1,000 (from 4 more to 50 more)					
4 Cohort studies <sup>3-6</sup> (3 studies <sup>3,4,6</sup> could be pooled via meta-analysis)	Serious <sup>c</sup>	Not serious	Serious <sup>d</sup>	Serious <sup>e</sup>	None	⊕⊕⊕⊕ VERY LOW		Meta-analysis: 31/230	Meta-analysis: 6/355	Meta-analysis: RR 3.34 (1.26 - 8.85) Nagata 2018: <b>OR</b> 1.48	Meta-analysis: Risk <b>without</b> heparin bridging: 17 events per 1,000. <b>With</b> heparin bridging: 40 <b>more</b> per 1,000 (from 5 more to 133 more)					
Thrombotic events within 30 days (critical outcome)																
1 RCT (Douketis NEJM 2015) <sup>1</sup>	Not serious	Not applicable	Not serious <sup>f</sup>	Very serious <sup>g</sup>	None	⊕⊕⊕⊕ LOW			3/895	4/918	RR 0.77 (0.17 - 3.43)	Risk <b>without</b> heparin bridging: 4 events per 1,000. <b>With</b> heparin bridging: 1 <b>less</b> per 1,000 (from 3 less to 11 <b>more</b> )				



2 Cohort studies <sup>4,5</sup>	<b>Serious <sup>c</sup></b>	Not serious	<b>Serious <sup>d</sup></b>	<b>Very serious <sup>h</sup></b>	None	⊕⊖⊖⊖ VERY LOW		1/83 <sup>4</sup>	1/19 <sup>4</sup>	RR 0.23 (0.02-3.50) <sup>4</sup> <b>OR 1.94 <sup>5</sup></b>	Not calculable	
<b>Mortality within 30 days (important outcome, but not critical for decision making) –</b>												
2 Cohort studies <sup>4,5</sup>	<b>Serious <sup>c</sup></b>	Not serious	<b>Serious <sup>i</sup></b>	<b>Very Serious <sup>j</sup></b>	None	⊕⊖⊖⊖ VERY LOW		0/83 <sup>4</sup>	0/19 <sup>4</sup>	RR not meaningful <sup>4</sup> <b>OR 1.42 <sup>5</sup></b>	Not calculable	

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## 2739 Footnotes

2740 <sup>a</sup> Serious indirectness: No separate results for bleeding for GI procedures (44% of all procedures). Furthermore, the vast majority of GI procedures were low risk  
2741 procedures such as endoscopy with/without biopsy); only 1.3% of the GI procedures may have had significant risk of bleeding (defined as “e.g., colonic polyp  
2742 resection”, but the size of polyps is not known; 4 procedures in the no bridging group, 6 procedures in the bridge group).

2743

2744 <sup>b</sup> Serious imprecision, due to small number of events: 29 vs. 12 events

2745

2746 <sup>c</sup> Serious risk of bias, mainly due to residual confounding (see table: risk of bias assessment for cohort studies)

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2748 <sup>d</sup> Serious indirectness, because of the diversity of different GI endoscopic procedures that were included. Also, one study (Nagata 2028) included endoscopy for  
2749 emergency endoscopic hemostasis.

2750

2751 <sup>e</sup> Serious imprecision, due to small number of events: 31 vs. 6 events

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2753 <sup>f</sup> Reported arterial thromboembolism rates: no serious indirectness. Only 44% of the procedures were GI procedures, but this did not introduce serious  
2754 indirectness. The outcome of arterial thromboembolism wouldn’t have been substantially influenced by the type of procedure

2755

2756 <sup>g</sup> Very serious imprecision, due to very small number of arterial thromboembolism events (3 vs. 4 events).

2757

2758 <sup>h</sup> Very serious imprecision, due to very small number of thromboembolism events (1 vs. 1) in the only study <sup>4</sup> that allowed calculation of RR with 95% CI

2759

2760 <sup>i</sup> Serious indirectness, because of the diversity of different GI endoscopic procedures that were included. Also, one study (Nagata 2028) included endoscopy for  
2761 emergency endoscopic hemostasis. One study (Nagata 2008) only measured in-hospital mortality.

2762

2763 <sup>j</sup> Very serious imprecision, due to zero events in only study <sup>4</sup> that allowed calculation of RR with 95% CI

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2766 **Additional Evidence Profile for a PICO question related but different than what is required for recommendation #12**

Discontinued warfarin <u>with heparin bridging</u> vs. <b>continued</b> warfarin ( <u>without</u> heparin bridging)												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Interrupted warfarin and heparin bridging	<b>Continued</b> warfarin	Relative (95% CI)	Absolute (95% CI)	
<b>Bleeding</b> within 30 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
1 RCT (Takeuchi 2019) <sup>2</sup>	<b>Serious<sup>a</sup></b>	Not applicable	<b>Very Serious<sub>b</sub></b>	<b>Very serious<sup>c</sup></b>	None	⊕⊕⊕⊕ VERY LOW		3/25  [if DOACs users are included as well: 10/83]	0/30  [if DOACs users are included as well: 5/85]	<b>RR 8.3 (0.5 -154.3)</b>  [if DOACs users are included as well: RR 2.0 (0.7-5.7)]	Risk with <b>continued warfarin</b> : 0 events per 1,000. <b>With heparin bridging</b> : 120 <b>more</b> per 1,000 (from 0 fewer to 880 more)	
<b>Thrombotic events</b> within 30 days (critical outcome)												
No studies <sup>d</sup>	-	-	-	-	-	-		-	-	-	-	
<b>Mortality</b> within 30 days (important outcome, but not critical for decision making) –												
No studies <sup>e</sup>	-	-	-	-	-	-		-	-	-	-	

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2768 <sup>a</sup> Serious risk of bias due to a lack of blinding.

2769 <sup>b</sup> Very serious indirectness. Even if patients on DOACs are excluded, there was indirectness of intervention as a different technique of polypectomy was used  
2770 amongst the two arms.

2771 <sup>c</sup> Very serious imprecision due to wide confidence intervals and very few events (very serious imprecision remains even if the DOACs patients are included)

2772

2773 <sup>d</sup> This RCT (Takeuchi 2019) did not specifically assess or report thromboembolic events.

2774

2775 <sup>e</sup> This RCT (Takeuchi 2019) did not specifically assess or report on mortality. One patient was lost to FU, so at worst case scenario there was one death but we  
2776 do not know in which arm

2777

2778

2779 **Evidence to Decision Table**

2780

2781 12. Bridging anticoagulation for patients on warfarin

2782 P: Patients on warfarin whose warfarin is held peri-operatively

2783 I: Use of peri-procedural low-molecular heparin or IV heparin (i.e., bridging anticoagulation)

2784 C: No heparin/low-molecular weight heparin bridge

2785 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

2787 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

2788

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2790

	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<b>How substantial are the desirable anticipated effects?</b> <ul style="list-style-type: none"> <li>● Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	See Evidence Profile Table:  The <u>desirable</u> anticipated effects with interrupted warfarin with heparin bridging (vs. interrupted warfarin without heparin bridging) are - reduction of <b>thromboembolic events (critical outcome)</b> : 1 less per 1,000 patients	See additional considerations in PICO#11
Undesirable Effects	<b>How substantial are the undesirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Large</li> <li>● Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	The <u>undesirable</u> anticipated effects with interrupted warfarin with heparin bridging (vs. interrupted warfarin without heparin bridging) are:  - increased <b>delayed bleeding (critical outcome)</b> : 19 to 40 more per 1,000 patients  It is not possible to estimate the direction (let alone the magnitude) of the effect uninterrupted warfarin (compared to interrupted warfarin) on <b>mortality</b>	

Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>● <b>Low</b></li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>See Evidence Profile Table.</p> <p>The certainty of the evidence is low.</p>	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>● <b>Important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p>	
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>● <b>Favors the comparison</b> (no heparin bridging)</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>● <b>Moderate costs</b></li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<ul style="list-style-type: none"> <li>• Bridging heparin treatment cost about \$1000 in the US</li> </ul>	






Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● <b>Moderate</b></li> <li>○ High</li> <li>○ No included studies</li> </ul>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● <b>No included studies</b></li> </ul>		
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>● <b>Probably yes</b></li> <li>○ Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Feasibility	<p><b>Is the intervention feasible to implement?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● <b>Yes</b></li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

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## Conclusions

2793 **PICO: 12. For patients on warfarin, who hold warfarin in the periprocedural period for elective/planned endoscopic GI procedures,**  
 2794 **should bridging anticoagulation (peri-procedural low-molecular heparin or IV heparin) be used?**  
 2795 **O: CRITICAL: Bleeding within 30 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial**  
 2796 **infarction, deep vein thrombosis, pulmonary embolus)**  
 2797 **IMPORTANT, BUT NOT CRITICAL: mortality within 30 days**  
 2798

Type of recommendation	Strong recommendation against the intervention 	Conditional recommendation against the intervention 6/6 votes: 100% 	Conditional recommendation for either the intervention or the comparison 	Conditional recommendation for the intervention 	Strong recommendation for the intervention 
<b>Recommendation</b>	For patients on warfarin, who hold warfarin in the periprocedural period for elective/planned endoscopic GI procedures, we suggest against bridging anticoagulation. (Conditional recommendation, <b>low</b> certainty of evidence)				
<b>Justification</b>					
<b>Subgroup considerations</b>	<p>Practically, the two conditional recommendations (#11 and 12) mean, that in patients undergoing elective/planned endoscopic GI procedures warfarin should not be interrupted in the majority of situations, but in the minority of situations where warfarin is held, heparin bridging rather not be used.</p> <p>Exceptions: Mechanical heart valves, atrial fibrillation with CHADS2 score &gt;5, patients with prior thromboembolism during temporary interruption of VKAs, or those patients undergoing certain types of surgery (e.g., cardiac valve replacement, carotid endarterectomy, major vascular surgery).</p>				
<b>Implementation considerations</b>					
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?				
<b>Research priorities</b>					

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2803 **References for PICO 12**

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- 2806 2. Takeuchi et al. Continuous Anticoagulation and Cold Snare Polypectomy Versus Heparin Bridging and Hot Snare Polypectomy in Patients
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- 2808 3. Gerson et al. Adverse events associated with anticoagulation therapy in the periendoscopic period. Gastrointestinal Endoscopy
- 2809 2010;71:1211-7.
- 2810 4. Yanagisawa et al. Post-polypectomy bleeding and thromboembolism risks associated with warfarin vs direct oral anticoagulants. World
- 2811 Journal of Gastroenterology 2018;24:1540-1549
- 2812 5. Nagata N et al. Therapeutic endoscopy-related GI bleeding and thromboembolic events in patients using warfarin or direct oral
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- 2814 6. Inoue T et al. Clinical features of post-polypectomy bleeding associated with heparin bridge therapy. Digestive Endoscopy. 26 (2) (pp
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2822 13. Continuous anticoagulation with DOACS

2823 **13. Continuous anticoagulation vs. temporary interruption of DOACS**

2824 P: Patient on DOAC

2825 I: Continuous anticoagulation:

2826 C: Temporary interruption of DOACs for 1 to 5 days

2827 O: **CRITICAL:** Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep

2828 vein thrombosis, pulmonary embolus)

2829 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days

2830

2831 Cohort studies **with** the comparator cohort needed for this PICO

2832 1. Ara et al. Prospective analysis of risk for bleeding after endoscopic biopsy without cessation of antithrombotics in Japan. Digestive  
2833 Endoscopy. 27 (4) (pp 458-464), 2015

2834 • Design: prospective cohort study

2835 • Population: Consecutive patients who underwent **upper GI endoscopic biopsy** at a hospital in Japan, 2011-2014

2836 • **Indirectness**: the “exposure” was limited to endoscopic biopsies and also limited to Upper GI endoscopy

2837 • Intervention: no interruption of DOACs (dabigatran or rivaroxaban)

2838 • Comparator: temporary interruption of DOACs (dabigatran or rivaroxaban): **the interruption protocol is unclear**

2839 • Outcomes: major bleeding within 4 weeks (no results on thrombotic events or mortality)

2840 • Results:

2841 • **Continued** DOACs: dabigatran =15; rivaroxaban =3; total = 18; events (bleeding at 30 days) = 0 (95% CI calculated with  
2842 the rule of 3/n for zero events (**Govani. AJG 2013; 108:1831**) is 0%- 17%)

2843 • **Interrupted** DOACs: dabigatran =2; rivaroxaban =2; total = 4; events (bleeding at 30 days) = 0 (95% CI 0% - 75%)

2844 • **RR: not meaningful**

2845 • only unadjusted results are available

2846 • Notes regarding risk of bias:

2847 • The decision to interrupt or continue warfarin was made by the “prescribing physicians”

2848 • Only patients who had endoscopic biopsies taken were included in the study, i.e. it is unclear how many patients had  
2849 UGI endoscopy without biopsies and how many patients had their biopsies avoided (or UGI endoscopy deferred  
2850 altogether) because of their anticoagulation status

2851 • Therefore, the decision to interrupt or continue warfarin could have been influenced by the strength of indication for  
2852 endoscopy and endoscopic biopsies, whereas the decision to scope could have been influenced by the comfort level of  
2853 the physicians in interrupting warfarin for a specific patient, and the decision to biopsy could have been influenced by  
2854 whether warfarin had been interrupted or continued.

2855 • Furthermore, the number of biopsies taken per procedure, the size of biopsy forceps and treatment of the biopsy site  
2856 with thrombin spray were shown to have been influenced by whether antithrombotics had been interrupted or  
2857 continued (no results were reported for patients on warfarin, but for the overall study population on any anticoagulant



or any antiplatelet, number of biopsies per case was significantly lower in the patients who continued antithrombotic treatment ( $1.9 \pm 1.1$  vs  $2.4 \pm 1.6$ ;  $P < 0.01$ ), use of mini cup biopsy forceps (15.4% vs 3.7%;  $P < 0.01$ ), and thrombin spray (19.6% vs 5.6%;  $P < 0.01$ ) were significantly higher in the group that did not interrupt antithrombotics use than in the group that did).

- Overall, the choice of peri-procedural management of anticoagulation was influenced by factors (confounders) that also influenced the risk of the outcomes of interest.

**2. Heublein et al. Gastrointestinal endoscopy in patients receiving novel direct oral anticoagulants: results from the prospective Dresden NOAC registry. Journal of Gastroenterology. 53 (2) (pp 236-246), 2018.**

- Prospective cohort study
- Included all types of procedures
  - 499 Scheduled procedures
  - 214 Unscheduled procedures (Diagnostic or therapeutic endoscopies in patients with (a) acute GI bleeding or (b) acute GI infections, sepsis, or other emergency situations)
- Reported (unadjusted) outcomes at 30 days (also stratified by scheduled /unscheduled procedures) for:
  - No preinterventional DOAC therapy interruption ( $n = 119$ );
  - Preinterventional DOAC therapy interruption  $<24$  h ( $n = 45$ );
  - Preinterventional DOAC therapy interruption  $> 24$  h ( $n = 549$ )

For the total population: scheduled and unscheduled procedures

1. 713 endoscopy procedures (44.5% EGD, 53% CY, 2.5% ERCP) – 119/713 didn't stop, 45/713 last intake  $<24$ , 336 stopped 24-48 h, 213 cases stopped  $>48$ h
2. **Outcome: Cardiovascular events** within 30days = 10 (five strokes, 3 PV thrombosis, 1 MI, 1 TIA)

i. 1/119

ii. 1/45

iii. 8/549 CV events

2885 3. **Outcome: Major bleeding-** overt bleeding with any of the following: transfusion of at least 2 units PRBC, drop in Hgb of 2g/l, surgery  
2886 for bleeding, bleeding into critical sites, fatal bleeding

2887 i. 0/119

2888 ii. 1/45

2889 iii. 4/549

2890 4. **Outcome: Non-Major Clinically Relevant Bleeding**

2891 i. 3/119

2892 ii. 0/45

2893 iii. 11/549

2894 5. **Outcome: Death**

2895 i. 0/119

2896 ii. 0/45

2897 iii. 5/549

2898 **However, the detailed extracted data (see above) are inaccurate for several reasons:**

2899 • Category iii (Preinterventional NOAC therapy interruption > 24 h) contains patients who permanently discontinued DOAC  
2900 therapy (n=51), as well as an unknown number of patients who temporarily discontinued DOAC therapy for unusually large  
2901 periods, longer than 5 days (see Suppl Appendix Table S6 and S7, where this period was up to 28 days in some patients)

2902 • Categories ii and iii, contain 180 patients who received heparin bridging therapy (in prophylactic, semitherapeutic or therapeutic  
2903 doses)

2904 • The unscheduled procedures for acute GI bleeding should not be counted for the outcome of bleeding because it is not possible  
2905 to differentiate between bleeding that occurred because of endoscopic intervention vs. further bleeding from the primary  
2906 bleeding lesion.

2907 • Even after reconciling all tables in the main paper and the supplement, it is impossible to obtain granular data for outcomes for  
2908 clean categories:

- 2909 • patients who did not interrupt DOAC therapy and underwent scheduled endoscopic procedures
- 2910 • Patients who interrupted DOAC therapy for 1-5 days (without heparin bridging) and underwent scheduled endoscopic
- 2911 procedures
- 2912 • **The best data we could extract are as follows:**
- 2913 • patients who did not interrupt DOAC therapy and underwent scheduled endoscopic procedures, n= 91
- 2914 • major bleeding: 0/91 (0%, 95% CI 0% - 3.3%)
- 2915 • CV events: 1/91 (1.1%, 95% CI 0% – 5.5%)
- 2916 • Patients who interrupted DOAC therapy for 1-5 days (without heparin bridging) and underwent scheduled endoscopic
- 2917 procedures, n= **unknown**
- 2918 • major bleeding: 0, denominator unknown (less than n= 298)
- 2919 • CV events: 3, denominator unknown (less than n= 298)
- 2920 • We cannot calculate relative risks
- 2921
- 2922 **3. Yanagisawa et al. Post-polypectomy bleeding and thromboembolism risks associated with warfarin vs direct oral anticoagulants.**
- 2923 **World Journal of Gastroenterology. 24 (14) (pp 1540-1549), 2018.**
- 2924 • Design: retrospective cohort study
- 2925 • Population: patients on warfarin or DOACs who underwent colonoscopic polypectomy at a center in Japan. 73 patients on
- 2926 DOACs
- 2927 • After polypectomy, patients routinely underwent prophylactic clipping
- 2928 • Apparently, all polypectomies were hot snare polypectomies: they used “(SnareMaster, Olympus Co.) [which is
- 2929 electrocautery snare], and electrosurgical device (ERBE ICC-350, Somo Technology Inc., Tokyo, Japan or ESG-100,
- 2930 Olympus Co.)”.
- 2931 • Cohort 1: no interruption of DOACs (n=50)
- 2932 • Cohort 2: temporary interruption of DOACs without heparin bridging (n=4)
- 2933 • Cohort 3: temporary interruption of DOACs with heparin bridging (n=19)
- 2934 • Outcomes: bleeding (30 days), thrombotic events (timing unclear), mortality (30 days)
- 2935 • Results (unadjusted):
- 2936 • **Bleeding**
- 2937 • No interruption of DOACs: 8/50 (16%)

- Temporary interruption of DOACs (without heparin bridging): 0/4 (0%). **RR 1.67, 95% CI 0.11 - 24.81**
- **Thrombotic events**
  - No interruption of DOACs: 0/50 (0%)
  - Temporary interruption of DOACs (without heparin bridging): 0/4 (0%). RR not meaningful.
- **Mortality**
  - No interruption of DOACs: 0/50 (0%)
  - Temporary interruption of DOACs (without heparin bridging): 0/4 (0%). RR not meaningful.
- Notes regarding risk of bias: the decision to interrupt or continue DOACs could have been influenced by the strength of indication for endoscopy and polypectomy, whereas the decision to scope could have been influenced by the comfort level of the physicians in interrupting warfarin for a specific patient, and the decision to perform polypectomy (and the type of polypectomy) could have been influenced by whether DOACs had been interrupted or continued. This means that the choice of peri-procedural management of anticoagulation was influenced by factors (confounders) that also influenced the risk of the outcomes of interest.

Cohort studies without the comparator cohort that is needed for this PICO

**Arimoto J et al. Safety of Cold Snare Polypectomy in Patients Receiving Treatment with Antithrombotic Agents. Digestive diseases and sciences. 2019. 64:3247–3255**

- Design: The main study was a retrospective cohort study on 501 patients who underwent CSP (Cold Snare Polypectomy) for polyps up to 10 mm at a center in Japan. For this PICO, we extracted data from the cohort of patients on uninterrupted DOACs (the number of patients is unclear; the number of **polypectomies** in patients on DOACs is 65). In this center all CSP were performed without discontinuing antithrombotics.
- The comparator (patients to have not been taking any antithrombotics) is not the comparator needed for this PICO. Therefore, this study is included as a cohort study without comparator
- Results (unclear results per patient- reported results per polypectomy (more than one polypectomy per patient)):
  - **Delayed bleeding: 0/65 (0%) polypectomies** among for patients on uninterrupted DOACs (in fact it was 0% for the whole study population)
- Note: clipping was applied for “immediate bleeding” (clipping was applied in 13.9% of polypectomies in patients on uninterrupted antithrombotics (separate results for patients on DOACs were not reported)

**Douketis JAMA IM 2019**<sup>5</sup>: the PAUSE study (Douketis et al. Perioperative Management of Patients with Atrial Fibrillation Receiving a Direct Oral Anticoagulant. JAMA IM 2019)

- Prospective, multicenter cohort study without comparator arm
  - This is one of very few studies that provided rationale for not having comparator. In fact, the design and rationale were published *a priori* as a separate paper (Douketis Thromb Haemost 2017<sup>13</sup>).
- Included n= 3007 patients with AF, long-term users of apixaban, dabigatran, or rivaroxaban who were scheduled for an elective surgery or procedure and followed a well-defined DOAC therapy interruption protocol.
  - 1007 patients had a high-bleeding-risk procedure.
  - 2000 patients had a low-bleeding-risk procedure. Of these, 627 (31.4%) had GI procedures. **No separate results for GI procedures in the original publication (but we were able to extract GI data from the raw data of the study; see below)**
    - The GI procedure group was highly diverse: it included procedures such as VCE, EGD, colonoscopy, flex sig, ERCP, push enteroscopy and Barrett's ablation.
    - Unclear if any of these patients underwent snare polypectomy, sphincterotomy or EMR
- Consecutive patients were enrolled, and a flow chart of patient flow was published (83% of the approached patients were recruited), but the recruitment per center varied substantially, ranging from 853 patients (i.e., convincingly consecutive recruitment) to 4, 6, 20 and 23 patients in four other centers (i.e., likely non-consecutive recruitment, given that the enrolment period was 4 years)
- DOAC resumption: after the operation, DOAC regimens were resumed 1 day (approximately 24 hours) after a low-bleeding-risk procedure and 2 to 3 days (48-72 hours) after a high-bleeding-risk procedure, provided that hemostasis was achieved.
- Note: Patients at high risk for venous thromboembolism could receive a prophylactic dose of heparin after the operation until DOAC therapy resumption.
- See figure (the only figure) in page 1471 in the paper for the full perioperative DOAC management protocol was as follows:
- Note: this protocol is different than the intervention of this PICO (DOAC resumption on day 0). It falls within the range of timing of the comparator of this PICO (DOAC resumption on day 1 to day 7)
- The authors mentioned two previous clinical studies that informed the design of the perioperative protocol that was used in this study:
  - *"The only previous studies suggested a high post-procedural bleeding risk if therapeutic-dose heparins are uniformly re-initiated approximately 24 hours after a procedure irrespective of procedural bleeding risk"*. Reference: Dunn et al. Bridging therapy in patients on long-term oral anticoagulants who require surgery: the Prospective Peri-operative Enoxaparin Cohort Trial (PROSPECT). J Thromb Haemost 2007;5(11):2211–2218)

2998 • Also: Schulman S, Carrier M, Lee AY, et al; Periop Dabigatran Study Group. Perioperative management of dabigatran: a  
 2999 prospective cohort study. Circulation. 2015;132(3):167-173. (see Excluded studies document)  
 3000 • Also, the authors explained that in order to design their perioperative protocol they also utilized indirect evidence from  
 3001 DOAC pharmacokinetic properties, and they had “2 broad aims: (1) to have the shortest duration of DOAC therapy  
 3002 interruption before and after the procedure so as to minimize the risks for bleeding and thromboembolism, and (2) to  
 3003 have a simple interruption and resumption protocol for each DOAC that would be easy to use by clinicians and easily  
 3004 understood by patients”.

- 3005 • Outcomes were well defined and described:
  - 3006 • Major postoperative bleeding (at 30 days). The low-bleeding-risk procedures (the category that included the GI  
 3007 procedures) is the cohort that fits best the population of this PICO: 20/2000 = 1.0%, 95% CI 0.63% to 1.57% (calculated  
 3008 from table 4 in the paper)
  - 3009 • Thrombotic events (at 30 days). Total (arterial and venous) for the whole cohort (separate results could not be extracted  
 3010 for the low-bleeding-risk group): 21/3007 = 0.70%, 95% CI 0.45% to 1.09%
  - 3011 • Mortality (at 30 days). Total, for the whole cohort (separate results could not be extracted for the low-bleeding-risk  
 3012 group): 9/3007 = 0.30%, 95% CI 0.15% to 0.59%.
  - 3013 • **Feasibility outcomes:** adherence to the resumption protocol ranged from 87.5% to 99.6% in various sub-cohorts. For  
 3014 the low-bleeding risk group (that included the GI procedures) adherence was 1811/2000 = 90.6%
- 3015 • **Separate results on GI procedures (Jim Douketis, Alan Barkun; personal communication):**
  - 3016 • Only patients who had GI endoscopic procedures were included
  - 3017 • Results provided in the last column of the Risk of Bias table

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Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (exposure vs non-exposure is the difference in antithrombotic management between the intervention and the comparator for this PICO)	Prognostic factors (other than exposure of interest) <b>similar</b> among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Ara. Dig End 2015 <sup>1</sup>	OK	No, the two cohorts were not similar for prognostic factors for bleeding: confounding was favoring the non-interruption group. No adjustment.	OK	OK	OK	OK	P: patients on DOACs (dabigatran or rivaroxaban) having upper GI endoscopic <b>biopsy</b> <b>DELAYED BLEEDING</b> (30 days): <ul style="list-style-type: none"> <li>• <b>Continuous</b> DOAC: 0/18 = 0% (0% - 17%)</li> <li>• <b>interrupted</b> DOAC: 0/4 = 0% (0% - 75%)</li> <li>• RR not meaningful</li> </ul>
Heublein JG 2018 <sup>2</sup>	OK	No, the two cohorts were not similar for prognostic factors for bleeding: confounding was favoring the non-interruption group. No adjustment.	OK	OK	OK	OK	P: patients on DOACs having various <b>scheduled</b> upper GI endoscopic procedures <b>DELAYED BLEEDING</b> (30 days): <ul style="list-style-type: none"> <li>• <b>Continuous</b> DOAC: 0/91 (0%, 95% CI 0% - 3.3%)</li> <li>• <b>interrupted</b> DOAC: 0 (denominator unknown, but less than n= 298)</li> <li>• RR cannot be calculated</li> </ul> <b>THROMBOTIC EVENTS</b> (30 days) <ul style="list-style-type: none"> <li>• <b>Continuous</b>: 1/91 (1.1%, 95% CI 0% – 5.5%)</li> <li>• <b>Interrupted</b>: 3 (denominator unknown, but less than n= 298)</li> </ul>
Yanagisawa. WJG 2018 <sup>3</sup>	OK	No, the two cohorts were not similar for prognostic factors	OK	OK	OK	OK	P: patients who had hot snare <b>colonic polypectomy</b>

		for the outcomes of interest. No adjustment for the comparison of interest for this PICO (whereas, other analyses were adjusted)					<p><b>DELAYED BLEEDING</b> (30 days) with continuous DOACs: RR 1.67 (0.11 - 24.81)</p> <ul style="list-style-type: none"> <li>• Continuous DOACs: 8/50 (16%)</li> <li>• Interrupted: 0/4 (0%)</li> </ul> <p><b>THROMBOTIC EVENTS</b> (timing unclear, likely 30 days)</p> <ul style="list-style-type: none"> <li>• Continuous: 0/50 (0%)</li> <li>• Interrupted: 0/4 (5.3%)</li> </ul> <p><b>DEATHS</b> (30 days)</p> <ul style="list-style-type: none"> <li>• Continuous: 0/50 (0%)</li> <li>• Interrupted: 0/4 (0%)</li> </ul>
Arimoto. DDS 2019 <sup>4</sup>	OK	<b>Very</b> serious risk of bias: <b>no comparator</b> of interest	OK	Very serious risk of bias: <b>no comparator</b> of interest	Very serious risk of bias: <b>no comparator</b> of interest		<p>- Cohort type data (<b>without</b> the <b>comparator</b> that is required for this PICO) extracted from a wider cohort study</p> <p>P: patients undergoing <b>cold snare colonic polypectomy</b> (<math>\leq 10</math> mm)</p> <p><b>DELAYED BLEEDING</b> (within 14 days):</p> <ul style="list-style-type: none"> <li>• Continuous DOAC treatment: 0/65 = 0% (0% - 5%).</li> </ul> <p>The denominator (n=65) is the number of <b>polypectomies</b> (each patient could have had 1 or more polypectomies)</p>
Douketis 2019 (PAUSE study) <sup>12</sup>	OK	No comparator cohort with a different timing of DOAC resumption	OK	Outcome detection methods were valid, but there was no comparator cohort of interest for this PICO	Follow up was complete and similar among cohorts, but there was no comparator cohort of interest for this PICO		<p>P: patients who had endoscopic GI procedures after interrupting NOACs</p> <p><b>Extra analyses: results on GI procedures only</b> (Jim Douketis, Alan Barkun; personal communication):</p> <ul style="list-style-type: none"> <li>• <b>DELAYED BLEEDING</b> (1 month) 14/554 = 2.5%, 95% CI 1.4% to 4.2% Of note 5/14 of the bleeding events were major bleeds</li> <li>• <b>THROMBOEMBOLIC EVENTS</b> (1 month) 4/552 = 0.7%, 95% CI 0.3% to 1.8%</li> <li>• <b>MORTALITY</b> (1 month) 3/552 = 0.5%, 95% CI 0.2% to 1.6%</li> </ul>



Low risk of bias
Unclear risk of bias
High risk of bias

3027 Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included,  
3028 because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid  
3029 methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of  
3030 interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not  
3031 included, because it is an “indirectness” issue as per GRADE.

3032 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
3033 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias.

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### 3035 **Our attempted meta-analysis**

3036 The studies could not be meaningfully synthesized via meta-analysis. For the outcome of bleeding, of the 3 studies that had comparator cohorts,  
3037 one study had zero events in both arms <sup>1</sup>, one had zero events in both arms and also the denominator for one arm was unknown <sup>2</sup>, and the third  
3038 study had zero events in one of the two arms. Continuity correction approaches could not be used, because they could lead to seriously  
3039 misleading results because (a) only one arm that had events, (b) the number of events was extremely small and (c) arm sizes were not balanced.  
3040 For the other two outcomes, there was even less data.

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## 3050 Evidence profile for PICO 13

Continuous anticoagulation with DOACs vs Temporary Interruption of DOACs (1-5 days)												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Continuous DOAC treatment	Interrupted DOAC for 1-5 days	Relative (95% CI)	Absolute (95% CI)	
Bleeding within 30 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
3 cohort studies with control arm <sup>1-3</sup> and  2 cohort studies without control arm <sup>4,5</sup>	Serious <sup>a</sup>	Serious <sup>b</sup>	Serious <sup>c</sup>	Very serious <sup>d</sup>	None	⊕⊕⊕⊕ VERY LOW		0/18 <sup>1</sup> 0/91 <sup>2</sup> 8/50 <sup>3</sup> 0/65 <sup>4</sup>  Total <sup>1-4</sup> : 8/224	0/4 <sup>1</sup> 0/ (denominator smaller than 298) <sup>2</sup> 0/4 <sup>3</sup>  14/554 (2.5%) <sup>5</sup>	RR 1.67 (0.11 - 24.81) <sup>3e</sup>	Calculation not meaningful, given the zero event rate in the control group in the comparative studies	
Thrombotic events within 30 days (critical outcome)												
2 cohort studies with control arm <sup>2,3</sup> and  1 cohort study without control arm <sup>5</sup>	Serious <sup>f</sup>	Not serious	Serious <sup>g</sup>	Very serious <sup>h</sup>	None	⊕⊕⊕⊕ VERY LOW		1/91 <sup>2</sup> 0/50 <sup>3</sup>	3/(denominator smaller than 298) <sup>2</sup> 0/4 <sup>3</sup>  4/552 (0.7%) <sup>5</sup>	NC	NC	
Mortality within 30 days (important outcome, but not critical for decision making) –												
1 cohort study with control cohort <sup>3</sup> and  1 cohort study without control arm <sup>5</sup>	Serious <sup>f</sup>	Not applicable	Not serious	Very serious <sup>i</sup>	None	⊕⊕⊕⊕ VERY LOW	0/50 <sup>3</sup>	0/4 <sup>3</sup>  3/552 (0.5%) <sup>5</sup>	NC	NC		

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3052 NC: not calculable

3053 <sup>a</sup> Serious risk of bias. The three controlled cohort studies did not adjust for known confounders, while the other two studies did not have a control arm.

3054 <sup>b</sup> Serious inconsistency because among the three controlled studies, two studies had no events in any arm, while the third study had events only in one arm

3055 <sup>c</sup> Serious indirectness because of diversity among studies in the type of GI procedures, the time horizon for outcome measurement, and the interruption

3056 protocol for DOACs

3057 <sup>d</sup> Very serious imprecision due to the very small number of events, with most study arms having zero events.

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3059 <sup>e</sup> Only one study allowed for calculation of the relative effect

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3061 <sup>f</sup> Serious risk of bias, due to lack of adjustment for known confounders in the controlled cohort studies, while the 4<sup>th</sup> study did not have a control arm.

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3063 <sup>g</sup> Serious indirectness because of diversity among studies in the type of GI procedures, and the interruption protocol for DOACs

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3065 <sup>h</sup> Very serious imprecision due to the very small number of events, with one of the 2 studies having zero events.

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3067 <sup>i</sup> Very serious imprecision due to a single small study with zero events.

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## 3074 Evidence to Decision Table

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3076 13. Continuous anticoagulation vs temporary interruption of DOACS

3077 P: Patient on DOAC

3078 I: Continuous anticoagulation with DOACs:

3079 C: Temporary interruption of DOACs for 1-5 days

3080 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis,

3081 pulmonary embolus)

3082 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

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	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<p><b>How substantial are the desirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>	<p>The <u>desirable</u> anticipated effects with continuous DOAC treatment (vs interrupted DOAC treatment) could not be estimated</p> <p>The <u>undesirable</u> anticipated effects with continuous DOAC treatment (vs interrupted DOAC treatment) are:</p> <p>- increased <b>delayed bleeding (critical outcome)</b>: absolute effect could not be calculated</p>	<p>The incidence on bleeding with continuous DOAC can be indirectly estimated as 5.2% by multiplying the incidence of bleeding (3.1%) from Douketis 2019 with the RR (1.67) from <b>another</b> study, i.e., Yanagisawa 2018.</p>
Undesirable Effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Large</li> <li>● <b>Moderate</b></li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>It is not possible to estimate the direction (let alone the magnitude) of the effect uninterrupted DOAC (compared to interrupted DOAC) on <b>thrombotic events (critical outcome)</b> or <b>mortality</b></p>	<p>The panel discussed whether holding DOAC for 1-5 days could a trigger for pro-thrombotic state that will cause thrombosis after a delay of several additional days. It was argued that the pro-thrombotic risks seem to be more due to the peri-procedural milieu (vascular surgery vs. non-vascular surgery, patient characteristics) rather than interruption of DOAC. Furthermore, when DOAC is interrupted, it is only for a short period of time (quick on, quick off). The thrombotic risk of interruption of DOAC is anticipated to be lower than interruption of warfarin.</p>
Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>See Evidence Profile Table.</p> <p>The certainty of the evidence from studies in patients undergoing GI endoscopic procedures is very low.</p>	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>● <b>Important uncertainty or variability</b></li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p>	

Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● <b>Probably favors the comparison</b></li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> </ul> <p>○ Varies</p> <p>○ Don't know</p>	The certainty of the evidence from studies in patients undergoing GI endoscopic procedures is very low.	
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>● <b>Negligible costs and savings</b></li> <li>○ Moderate savings</li> <li>○ Large savings</li> </ul> <p>○ Varies</p> <p>○ Don't know</p>		
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● <b>Moderate</b></li> <li>○ High</li> </ul> <p>○ No included studies</p>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> </ul> <p>○ Varies</p> <li>● <b>No included studies</b></li>		

Acceptability	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		
Feasibility	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		

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## Conclusions

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**PICO: 13. For patients on DOACs who are undergoing elective/planned endoscopic GI procedures, should DOACs be continued or temporarily interrupted for 1-5 days?**

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**O: CRITICAL: Bleeding within 30 days; thrombotic events within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)**

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**IMPORTANT, BUT NOT CRITICAL: mortality within 30 days**

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Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention (continued DOAC) 5/5 votes: 100% (1 panel member was absent for vote)	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

<b>Recommendation</b>	For patients on DOACs who are undergoing elective/planned endoscopic GI procedures, we suggest temporarily interrupting DOAC rather than continuing DOAC (conditional recommendation, very low certainty of evidence)
<b>Justification</b>	
<b>Subgroup considerations</b>	Should the (anticipated) type of procedure influence the recommendation? Should the risk of thromboembolism influence the recommendation?
<b>Implementation considerations</b>	
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?
<b>Research priorities</b>	

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#### 3096 **References for PICO 13**

- 3097 1. Ara et al. Prospective analysis of risk for bleeding after endoscopic biopsy without cessation of antithrombotics in Japan. Digestive  
3098 Endoscopy 2015; 27:458-464
- 3099 2. Heublein et al. Gastrointestinal endoscopy in patients receiving novel direct oral anticoagulants: results from the prospective Dresden  
3100 NOAC registry. Journal of Gastroenterology. 53 (2) (pp 236-246), 2018.
- 3101 3. Yanagisawa et al. Post-polypectomy bleeding and thromboembolism risks associated with warfarin vs direct oral anticoagulants. World  
3102 Journal of Gastroenterology. 24 (14) (pp 1540-1549), 2018
- 3103 4. Arimoto J et al. Safety of Cold Snare Polypectomy in Patients Receiving Treatment with Antithrombotic Agents. Digestive diseases and  
3104 sciences. 2019;64:3247–3255
- 3105 5. Douketis JD et al. Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant. JAMA IM 2019

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14a. DAPT: Temporary interruption of thienopyridine agents with continuation of cardiac ASA

#### 14.a. DAPT: Temporary interruption of thienopyridine agents with continuation of cardiac ASA

P: Patient on DAPT (P2Y12 thienopyridine agent (clopidogrel, prasugrel, or ticagrelor) and ASA 81 to 325 mg/day (i.e, cardiac ASA)) for secondary prevention

I: Temporary interruption of thienopyridine X up to 10 days with continuation of cardiac ASA

C: Continuous thienopyridine antiplatelet drug use and cardiac ASA use

O: **CRITICAL:** Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, cardiac stent occlusion, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days

#### RCTs

1. **Chan Gastro 2019**<sup>1</sup> (Chan et al. Risk of Postpolypectomy Bleeding with Uninterrupted Clopidogrel Therapy in an Industry-Independent, Double-Blind, Randomized Trial. Gastro 2019)
  - RCT
  - Double blinded
  - Patients receiving clopidogrel for cardiovascular disease undergoing elective colonoscopies
  - Randomized to either clopidogrel 75 mg or placebo for 7 days before colonoscopy
  - All patients resumed their usual prescriptions of clopidogrel after colonoscopy (apparently on the next day).
  - 387 underwent colonoscopy
  - 216 received colonoscopic polypectomy (106 patients in the clopidogrel group and 110 patients in the placebo group)
    - Method of polypectomy was cold snare, hot snare, cold biopsy and hot biopsy
    - No prophylactic clipping or endoloop
  - Members of an independent masked adjudication committee confirmed the study end points occurred according to prespecified criteria
  - Reported bleeding outcomes for the 216 patients
    - i. **Delayed postpolypectomy bleeding** at 30 days = significant rectal bleeding (hypotension, a decrease in hemoglobin of  $\geq 2$  g/dL from baseline or a decrease in hematocrit  $\geq 10$  percentage points, requirement of transfusion, prolonged hospitalization, hospitalization, and/or hemostatic interventions using endoscopic therapy, angiographic embolization, or surgery).



- ii. **Immediate postpolypectomy bleeding** = bleeding at the time of polypectomy that persisted despite continuous irrigation with diluted epinephrine solution for 5 minutes. Interventions for immediate postpolypectomy bleeding included epinephrine injection alone or in combination with endoclip application.
  - iii. Serious cardio-thrombotic events = nonfatal myocardial infarction, nonfatal stroke, or death from a vascular cause
- Reported **serious cardio-thromboembolic events at 6 months** (nonfatal myocardial infarction, nonfatal stroke, or death from a vascular cause) for the 390 patients who received at least 1 study medication
  - i. 3 in clopidogrel group (n=194, see suppl figure 1)
  - ii. 4 in placebo group (n= 196)
- Death was not reported (the strokes were reported as nonfatal, but the MIs had no descriptor, therefore some of the MIs could have been fatal)
- Concomitant aspirin therapy (about 78.5% of patients) was uninterrupted
- Reported **stratified results (suppl Table 1) according to concomitant aspirin use.**
- Timing of delayed postpolypectomy bleeding: see Table 3 and suppl Table 1 in the paper.

#### **Concomitant ASA Use : Clopidogrel group 84/106, placebo 86 /110**

Delayed postpolypectomy bleeding with concomitant ASA: Clopidogrel 4/84, Placebo 4/86

Immediate postpolypectomy bleeding with concomitant ASA: Clopidogrel 8/84, Placebo 3/86

Serious cardio-thromboembolic events:

- Clopidogrel 1.3% (95% CI 0.3% – 5.0%), estimated 2/156
- Placebo 2.7% (95% CI 1.0% – 7.0%), estimated 4/148

#### **Nonconcomitant ASA Use: Clopidogrel group 22/106, placebo 24/110**

Delayed postpolypectomy bleeding: Clopidogrel 0/22, Placebo 0/24

Immediate postpolypectomy bleeding: Clopidogrel 1/22, Placebo 3/24

Serious cardio-thromboembolic events:

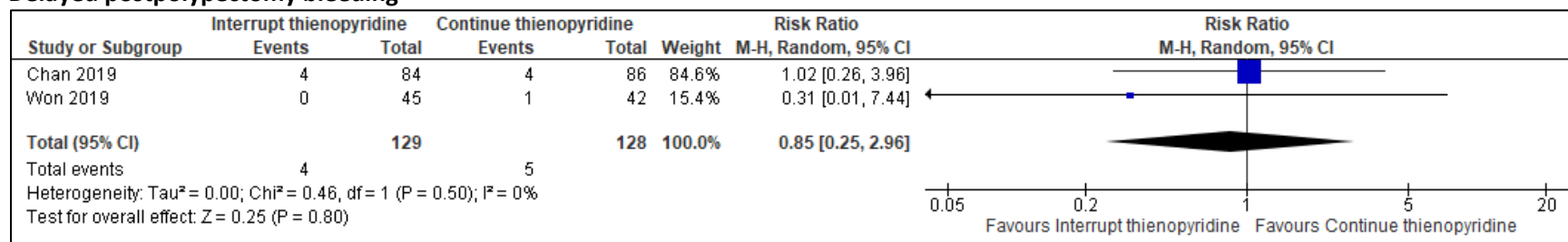
- Clopidogrel 2.6% (95% CI 0.4% - 17.3%), estimated 1/38
- Placebo 0%, estimated 0/58

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3173 2. **Won CTG 2019** <sup>2</sup> (Won D., Kim J.S., Ji J.-S., Kim B.-W., Choi H. Cold Snare Polypectomy in Patients Taking Dual Antiplatelet Therapy: A  
3174 Randomized Trial of Discontinuation of Thienopyridines. Clinical and translational gastroenterology. 10 (10) (pp e00091), 2019).
- 3175 • **Design: RCT**
    - 3176 ○ The endoscopist was blinded
  - 3177 • **Population:** N = 87 patients receiving DAPT “scheduled to undergo cold snare polypectomy” (polyp size ≤ 10mm)
    - 3178 ○ Implausible design: it was not possible for the investigators to predict 1 week prior to the colonoscopy which
    - 3179 patients will be found to have polyps ≤ 10 mm when they have their colonoscopy. According to the flowchart
    - 3180 only 4 patients was excluded post-randomization for “protocol violation”. We would expect a large proportion
    - 3181 (probably the majority) of patients to have been excluded post-randomization for not having polyps eligible for
    - 3182 cold snare polypectomy
  - 3183 • **Intervention:** n = 45 patients in the ASA-only group (aspirin was not interrupted; discontinued thienopyridines for 1
  - 3184 week prior to colonoscopy; re-started thienopyridines on the day after colonoscopy)
  - 3185 • **Comparator:** n = 42 patients in the DAPT group (neither of the two medications was interrupted)
  - 3186 • **Outcomes:**
    - 3187 ○ Clinically significant postpolypectomy bleeding (at 2 weeks)
      - 3188 ▪ ASA-only: 0/45
      - 3189 ▪ DAPT: 1/42 (2.4%)
    - 3190 ○ Thromboembolic events (at 1 month):
      - 3191 ▪ ASA-only: 0/45
      - 3192 ▪ DAPT: 0/42
    - 3193 ○ Death: not mentioned
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3203 **Our meta-analysis of the two RCTs:**

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3205 **Delayed postpolypectomy bleeding**



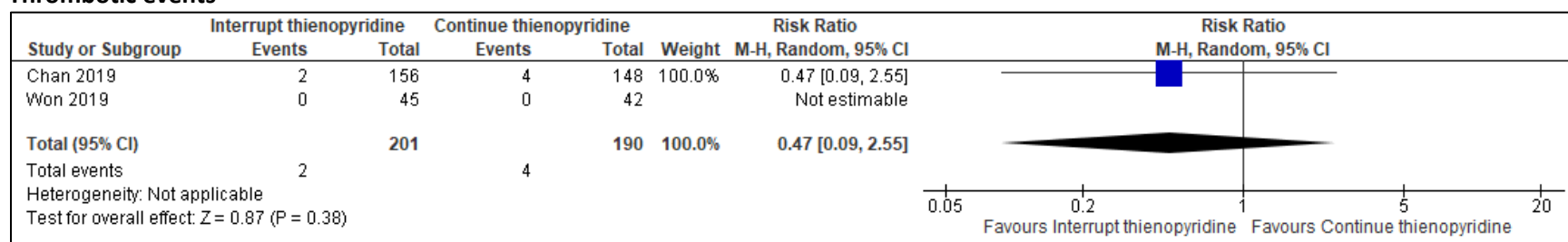
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**Thrombotic events**



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RCTs							
Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Comments
Chan 2019 <sup>1</sup>	OK – computer generated	OK - independent staff member assigned the treatments according to consecutive numbers that were kept in sealed opaque envelopes	OK (double blinded)	OK	OK	OK	
Won 2019 <sup>2</sup>	OK	OK	The endoscopist was blinded (low risk for performance bias), but patients and outcome assessors were not blinded (high risk for detection bias)	Unclear follow up of patients after 1 week (patients were assessed via a visit 1 week post colonoscopy)	No mention about mortality	Implausible flowchart: it was not possible for the investigators to predict 1 week prior to the colonoscopy which patients will be found to have polyps ≤ 10 mm when they have their colonoscopy.	

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1. **Eisenberg Circulation 2019**<sup>3</sup> (Eisenberg et al. Safety of Short-Term Discontinuation of Antiplatelet Therapy in Patients With Drug-Eluting Stents Circulation. 2009;119:1634-1642)
  - Systematic review of case reports, registries, and RCTs (84 articles with total of 161 cases)
  - Assessed time to event (late stent thrombosis = stent thrombosis occurring between 30 days and 1 year after stent implantation) in patients with **drug eluding stents** on dual antiplatelet therapy after discontinuing thienopyridine alone or discontinuing both drugs
  - It does not provide comparative data eligible for this PICO
  - The absolute risk of stent thrombosis within 10 days when thienopyridine is discontinued and ASA is maintained cannot be calculated because the denominator (patients at risk) is unknown. The statement in the abstract is misleading “Among the 94 patients who discontinued a thienopyridine but continued acetylsalicylic acid, only 6 cases (6%) occurred within 10 days”. This should have been “Among the 94 patients **with stent thrombosis** after discontinuing a thienopyridine but continuing acetylsalicylic acid, only 6 cases (6%) occurred within 10 days”.
  - We cannot extract any results that could fit into the Evidence Profile. The only evidence (very low certainty) that can be extracted relevant to this PICO is that in this high-risk population, there were no events in the first 3-4 days. See figures 1B and 2 in the paper.

## 3265 Evidence profile for PICO 14a

Temporary interruption of thienopyridine for up to 10 days with continuation of cardiac ASA vs. Continuous thienopyridine use and cardiac ASA use													
Certainty Assessment								Summary of Findings				Comments	
								Events / participants		Effect			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Interrupted thienopyridine	Continued thienopyridine	Relative (95% CI)	Absolute (95% CI)		
Bleeding within 30 days (critical outcome)								⊕⊕⊕⊕ VERY LOW					
SRMA of 2 RCTs (Chan 2019 <sup>1</sup> ; Won 2019 <sup>2</sup> )	Not serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW	4/129		5/128	RR 0.85 (0.25 - 2.96)	Risk with continued thienopyridine: 39 events per 1,000. With interrupted thienopyridine: 6 less per 1,000 (from 29 less, to 77 more)	Chan 2019: We only included patients on DAPT who did not interrupt ASA	
Thrombotic events within 30 days (critical outcome)													
SRMA of 2 RCTs (Chan 2019 <sup>1</sup> ; Won 2019 <sup>2</sup> )	Not serious <sup>a</sup>	Not serious	Serious <sup>d</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW	2/201		4/190	RR 0.47 (0.09 - 2.55)	Risk with continued thienopyridine: 21 events per 1,000. With interrupted thienopyridine: 11 less per 1,000 (from 19 less, to 32 more)	Won 2019 had zero events in both arms.  Chan 2019: We only included patients on DAPT who did not interrupt ASA. There is some uncertainty about the absolute numbers for denominators	
Mortality within 30 days (important outcome, but not critical for decision making)													

No data	-	-	-	-	-	-		-	-	-	-	-
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## Footnotes

<sup>a</sup> The certainty of evidence was not rated down for the outcomes of further bleeding and thrombosis, despite the fact that one of the two RCTs was at high risk of bias (Won 2019). If Won 2019 is excluded (by sensitivity analysis that retains of low risk of bias studies) nothing changes in the estimates and the certainty of evidence

<sup>b</sup> Serious indirectness for the outcome of delayed bleeding, given that this PICO covers all GI procedures, not only colonic polypectomy (if the PICO was restricted to colonic polypectomy, there would be no indirectness). Note: no data for thienopyridines other than clopidogrel

<sup>c</sup> Very serious imprecision due to very wide confidence intervals (compatible with large benefit and large harm) and the very small number of events

<sup>d</sup> Serious indirectness for the outcome of thrombotic events, because this study did not assess deep vein thrombosis, or pulmonary embolus (the outcome was cardio-thromboembolic events, defined as “nonfatal myocardial infarction, nonfatal stroke, or death from a vascular cause”, although the results were reported as “myocardial infarctions” and “nonfatal strokes”). Also, this outcome was measured at 6 months, rather than in the 1-month timeframe required for this PICO. Note: no data for thienopyridines other than clopidogrel. This outcome was not further downrated for indirectness for being restricted to colonic polypectomy, because it is unlikely that is outcome would be substantially different in other GI procedures.

## Evidence to Decision Table

14a. DAPT: Temporary interruption of thienopyridine agents with continuation of cardiac ASA

P: Patient on DAPT (P2Y12 thienopyridine agent (clopidogrel, prasugrel, or ticagrelor) and ASA 81 to mg/day (i.e, cardiac ASA)) for secondary prevention

I: Temporary interruption of thienopyridine X up to 10 days with continuation of cardiac ASA

C: Continuous thienopyridine antiplatelet drug use and cardiac ASA use

O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, cardiac stent occlusion, deep vein thrombosis, pulmonary embolus)

IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<p><b>How substantial are the desirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>● <b>Small</b></li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>See Evidence Profile Table</p> <p>The desirable anticipated effects of interruption of thienopyridine agents was a small decrease in bleeding (critical outcome).</p> <p>Theoretically, <b>interruption of</b> thienopyridine would tend to increase <b>thrombotic events (critical outcome)</b> compared to non-interrupted thienopyridine. However, the direction of the effect for thrombotic events was opposite to the theoretically anticipated.</p> <p>No data on <b>mortality</b></p>	
Undesirable Effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>		
Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>● <b>Possibly important uncertainty or variability</b></li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	See Box on Patient Values and Preferences, at the beginning of PICO 1.	



Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● <b>Probably favors the intervention</b> (interruption)</li> <li>○ Favors the intervention</li> </ul> <p>○ Varies</p> <p>○ Don't know</p>		
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>● <b>Negligible costs and savings</b></li> <li>○ Moderate savings</li> <li>○ Large savings</li> </ul> <p>○ Varies</p> <p>○ Don't know</p>		
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● <b>Moderate</b></li> <li>○ High</li> </ul> <p>○ No included studies</p>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> </ul> <p>○ Varies</p> <li>● <b>No included studies</b></li>		

Acceptability	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		
Feasibility	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		

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## Conclusions

3300 14A. DAPT: Temporary interruption of thienopyridine agents with continuation of cardiac ASA

3301 P: Patient on DAPT (P2Y12 thienopyridine agent (clopidogrel, prasugrel, or ticagrelor) and ASA 81 to 325 mg/day (i.e, cardiac ASA))  
 3302 for secondary prevention

3303 I: Temporary interruption of thienopyridine X up to 10 days with continuation of cardiac ASA

3304 C: Continuous thienopyridine antiplatelet drug use and cardiac ASA use

3305 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial  
 3306 infarction, cardiac stent occlusion, deep vein thrombosis, pulmonary embolus)

3307 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

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Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention 6/6 votes: 100%	Strong recommendation for the intervention
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	○ ○ ○ ● ○
<b>Recommendation</b>	For patients on dual antiplatelet therapy for secondary prevention, who are undergoing elective endoscopic GI procedures while continuing ASA, we suggest temporary interruption of the thienopyridine (conditional recommendation, very low certainty of evidence)
<b>Justification</b>	
<b>Subgroup considerations</b>	This recommendation applies only to elective procedures, not emergency procedures  Remarks: mention the duration of discontinuation; mention what DAPT means = P2Y12 thienopyridine agents (clopidogrel, prasugrel, ticagrelor) and ASA 81 to 325 mg/day (i.e, cardiac ASA)
<b>Implementation considerations</b>	
<b>Monitoring and evaluation</b>	Quality indicators: Did the physician talk to the patient or elicit the conditions under which the intervention should be used? Was this discussion and setting documented?
<b>Research priorities</b>	<u>Ongoing study:</u> Ket S, Metz A, Moss A, Ogra R, Tam W, Secomb R, Reynolds J, Gibson PR, Brown G. Study design of endoscopic polypectomy on clopidogrel (EPOC): a randomised controlled trial. Contemporary clinical trials communications. Vol.16, 2019.

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3313 **References, PICO 14a**

3314 1. Chan et al. Risk of Postpolypectomy Bleeding with Uninterrupted Clopidogrel Therapy in an Industry-Independent, Double-Blind, Randomized  
3315 Trial. Gastroenterology 2019 Mar;156(4):918-925

3316 2. Won D., Kim J.S., Ji J.-S., Kim B.-W., Choi H. Cold Snare Polypectomy in Patients Taking Dual Antiplatelet Therapy: A Randomized Trial of  
3317 Discontinuation of Thienopyridines. Clinical and translational gastroenterology. 10 (10) (pp e00091), 2019)

3318 3. Eisenberg et al. Safety of Short-Term Discontinuation of Antiplatelet Therapy in Patients With Drug-Eluting Stents Circulation. 2009;119:1634-  
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14.b. Temporary interruption of thienopyridine agents

## 14.B. Temporary interruption of thienopyridine agents

P: Patient on (**single antiplatelet therapy with**) P2Y12 thienopyridine agents (clopidogrel, prasugrel, ticagrelor)

I: Temporary interruption of thienopyridine X up to 10 days

C: Continuous thienopyridine antiplatelet drug use

O: **CRITICAL:** Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, cardiac stent occlusion, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days

## SRs of mixed study designs

1. Li et al. Colonoscopic post-polypectomy bleeding in patients on uninterrupted clopidogrel therapy: A systematic review and meta-analysis. Exp Ther Med. 2020 May;19(5):3211-3218.
  - Serious methodological limitations (one of the two “RCTs” (Feagins CGH 2013) is in fact a retrospective observational study, RCTs and observational studies were pooled together, the x-axis in the forest plot was inverted, RR was used for case-control studies, the assessment of study quality has serious mistakes, adjusted data were not use, etc.). Therefore, we could not include this SR as is. Instead, we checked the studies included in this SRMA.
    - Feagins CGH 2013 is not an RCT as the authors of the systematic review stated. It is a prospective cohort study, that compared patients who did not discontinue thienopyridine for more than 2 days, vs. those who were not taking thienopyridines at all. Some patients were on ASA. Not eligible for PICO 14 or 14b.
    - Feagins DDS 2011: retrospective cohort study (not a case-control study as its own authors and the SR authors stated). Compared patients who did not discontinue thienopyridine vs. those who were not taking thienopyridines at all.
    - Grossman GEI 2010: abstract publication. Case-control study. Compared clopidogrel use vs non-use.
    - Singh GIE: retrospective cohort study (not a case-control study as the SR authors stated). Compared patients who did not discontinue thienopyridine vs. those who were not taking thienopyridines at all.
    - Chan Gastro 2019: we have included this RCT already

## RCTs

1. **Chan Gastro 2019**<sup>1</sup> (Chan et al. Risk of Postpolypectomy Bleeding with Uninterrupted Clopidogrel Therapy in an Industry-Independent, Double-Blind, Randomized Trial. Gastro 2019)

- 3355 • RCT
- 3356 • Double blinded
- 3357 • Patients receiving clopidogrel for cardiovascular disease undergoing elective colonoscopies
- 3358 • Randomized to either clopidogrel 75 mg or placebo for 7 days before colonoscopy
- 3359 • All patients resumed their usual prescriptions of clopidogrel after colonoscopy (apparently on the next day).
- 3360 • 387 underwent colonoscopy
- 3361 • 216 received colonoscopic polypectomy (106 patients in the clopidogrel group and 110 patients in the placebo group)
- 3362 • Method of polypectomy was cold snare, hot snare, cold biopsy and hot biopsy
- 3363 • No prophylactic clipping or endoloop
- 3364 • Members of an independent masked adjudication committee confirmed the study end points occurred according to prespecified
- 3365 criteria
- 3366 • Reported bleeding outcomes for the 216 patients
  - 3367 i. **Delayed postpolypectomy bleeding** at 30 days = significant rectal bleeding (hypotension, a decrease in hemoglobin of
  - 3368 \_2 g/dL from baseline or a decrease in hematocrit \_10 percentage points, requirement of transfusion, prolonged
  - 3369 hospitalization, hospitalization, and/or hemostatic interventions using endoscopic therapy, angiographic embolization,
  - 3370 or surgery).
  - 3371 ii. **Immediate postpolypectomy bleeding** = bleeding at the time of polypectomy that persisted despite continuous
  - 3372 irrigation with diluted epinephrine solution for 5 minutes. Interventions for immediate postpolypectomy bleeding
  - 3373 included epinephrine injection alone or in combination with endoclip application.
  - 3374 iii. Serious cardio-thrombotic events = nonfatal myocardial infarction, nonfatal stroke, or death from a vascular cause
- 3375 • Reported **serious cardio-thromboembolic events at 6 months** (nonfatal myocardial infarction, nonfatal stroke, or death from a
- 3376 vascular cause) for the 390 patients who received at least 1 study medication
  - 3377 i. 3 in clopidogrel group (n=194, see suppl figure 1)
  - 3378 ii. 4 in placebo group (n= 196)
- 3379 • Death was not reported (the strokes were reported as nonfatal, but the MIs had no descriptor, therefore some of the MIs could
- 3380 have been fatal)
- 3381 • Polyp characteristics favoured the placebo group – smaller and fewer pedunculated.
- 3382 • Did not report proportion of cecal/proximal polyps
- 3383 • Concomitant aspirin therapy (about 78.5% of patients) was uninterrupted

- 3384
- Reported **stratified results (suppl Table 1 in the paper)** according to concomitant aspirin use.
- 3385
- Timing of delayed postpolypectomy bleeding (Table 3 in the paper)
- 3386

3387 **Concomitant ASA Use : Clopidogrel group 84/106, placebo 86 /110**

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- 3389 Delayed postpolypectomy bleeding with concomitant ASA: Clopidogrel 4/84, Placebo 4/86
- 3390 Immediate postpolypectomy bleeding with concomitant ASA: Clopidogrel 8/84, Placebo 3/86
- 3391 Serious cardio-thromboembolic events:
- 3392 • Clopidogrel 1.3% (95% CI 0.3% – 5.0%), estimated 2/156
  - 3393 • Placebo 2.7% (95% CI 1.0% – 7.0%), estimated 4/148
- 3394

3395 **Non-concomitant ASA Use: Clopidogrel group 22/106, placebo 24/110**

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- 3396 Delayed postpolypectomy bleeding: Clopidogrel 0/22, Placebo 0/24
- 3397 Immediate postpolypectomy bleeding: Clopidogrel 1/22, Placebo 3/24
- 3398 Serious cardio-thromboembolic events:
- 3399 • Clopidogrel 2.6% (95% CI 0.4% - 17.3%), estimated 1/38
  - 3400 • Placebo 0%, estimated 0/58
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RCTs							
Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Comments
Chan 2019 <sup>1</sup>	OK – computer generated	OK - independent staff member assigned the treatments according to consecutive numbers that were kept in sealed opaque envelopes	OK (double blinded)	OK	OK	OK	

Cohort studies with the comparator cohort needed for this PICO

1. **Watanabe SE 2020** <sup>3</sup> (Watanabe K., Nagata N., Yanagisawa N., Shimbo T., Okubo H., Imbe K., Yokoi C., Yanase M., Kimura A., Akiyama J., Uemura N. Effect of antiplatelet agent number, types, and pre-endoscopic management on post-polypectomy bleeding: validation of endoscopy guidelines. Surgical Endoscopy. 2020).

- Retrospective cohort study (this is not a case-control study, even though the authors refer to “cases and controls”)
- **Population:** N = 1050 patients on various AP therapies undergoing colonoscopy polypectomy: All hot snare. Cold snare polypectomies were excluded. Prophylactic clip placement “in most cases”.
- **Intervention:** n = 525 AP users, of which;
  - n = 271 low-dose ASA
  - n = 45 thienopyridines
  - n = 50 thienopyridines with ASA

- Of the 525 on antiplatelet therapy, 289 continued therapy, 8 switched, and presumably the others stopped. Bleeding rates in thienopyridine monotherapy continuing (n=19 only) was 0/19. We do not have direct data on the cessation group, however by extrapolation: 19 continued,

3438 8 switched, 18 must have stopped since there were 45 in total in that group. Since 0 bled in those two groups, then 3/18 in the stopped  
 3439 group must have bled. Therefore, post-polypectomy bleeding was:

- 3440
- 3441 • Continued thienopyridine: 0/19
- 3442 • Interrupted thienopyridine: 3/18
- 3443

3444 No thromboembolic events at 30 days. No deaths at 30 days.

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Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (Exposure vs non-exposure refers to whether the thienopyridine was interrupted or not)	Prognostic factors (other than exposure of interest) <b>similar</b> among cohorts – or cohorts were adjusted adequately for confounders	Demonstrati on that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Watanabe SE 2020 <sup>2</sup>	OK	The two cohorts were likely different in prognostic factors, and no adjustment was made for confounders <b>for the outcomes that we extracted</b>	OK	OK	Unclear	OK	
Low risk of bias							
Unclear risk of bias							
High risk of bias							



3448 Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included,  
3449 because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid  
3450 methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of  
3451 interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not  
3452 included, because it is an “indirectness” issue as per GRADE.

3453 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
3454 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias.

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3482 Evidence Profile for PICO 14b  
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Patients on thienopyridine alone: temporary interruption of thienopyridine for up to 10 days vs. continuous thienopyridine use														
Certainty Assessment								Summary of Findings				Comments		
								Events / participants		Effect				
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Interrupted thienopyridine	Continued thienopyridine	Relative (95% CI)	Absolute (95% CI)			
Bleeding within 30 days (critical outcome)														
1 RCT on colonic polypectomy (Chan 2019) <sup>1</sup>	Not serious	Not serious	Serious <sup>a</sup>	Very serious <sup>b</sup>	None	⊕⊕⊕⊕ VERY LOW	⊕⊕⊕⊕ VERY LOW	0/22 (95% CI 0% to 13.6%)	0/24 (95% CI 0% to 12.5%)	Not calculable	Not calculable	We only included patients on single antiplatelet therapy with thienopyridine		
1 cohort study on hot snare colonic polypectomy (Watanabe 2020) <sup>2</sup>	Serious <sup>c</sup>		Serious <sup>d</sup>	Very serious <sup>b</sup>	None	⊕⊕⊕⊕ VERY LOW		3/18 (16.7%, 95% CI 4.4% to 42.3%)	0/19	RR 7.37 (0.41 - 133.37)	Risk with <b>continued thienopyridine</b> : 0 events per 1,000. With <b>interrupted thienopyridine</b> : 167 <b>more</b> per 1,000 (from 44 more, to 423 more)			
Thrombotic events within 30 days (critical outcome)														
1 RCT on cold snare colonic polypectomy (Chan 2019) <sup>1</sup>	Not serious	Not serious	Serious <sup>e</sup>	Very serious <sup>b</sup>	None	⊕⊕⊕⊕ VERY LOW		<b>Reported</b> 2.6% (95% CI 0.4% - 17.3%) <b>Estimated</b> 1/38	<b>Reported</b> 0% <b>Estimated</b> 0/58	RR 4.54 (0.19 - 108.59)	Risk with <b>continued thienopyridine</b> : 0 events per 1,000. With <b>interrupted thienopyridine</b> : 26 <b>more</b> per 1,000 (from 4 more, to 17 more)	We only included patients on single antiplatelet therapy with thienopyridine		
1 cohort study on hot snare colonic polypectomy (Watanabe 2020) <sup>2</sup>	Serious <sup>c</sup>		Serious <sup>f</sup>	Very serious <sup>b</sup>	None	⊕⊕⊕⊕ VERY LOW		0/18	0/19	Not calculable	Not calculable			

Mortality within 30 days (important outcome, but not critical for decision making)											
1 cohort study on hot snare colonic polypectomy (Watanabe 2020) <sup>2</sup>	Serious <sup>c</sup>		Serious <sup>f</sup>	Very serious <sup>b</sup>	None	⊕⊖⊖⊖ VERY LOW		0/18	0/19	Not calculable	Not calculable

### Footnotes

<sup>a</sup> Serious indirectness for the outcome of delayed bleeding, given that this PICO covers all GI procedures, while Chan 2019 included only colonic polypectomy. Note: no data for thienopyridines other than clopidogrel

<sup>b</sup> Very serious imprecision due to very wide confidence intervals (compatible with large benefit and large harm) and the very small number of events

<sup>c</sup> Serious risk of bias due to lack of adjustment for confounders

<sup>d</sup> Serious indirectness for the outcome of delayed bleeding, given that this PICO covers all GI procedures, while Watanabe 2020 included only colonic polypectomy (hot snare). Furthermore, routine prophylactic clip placement was performed in most cases.

<sup>e</sup> Serious indirectness for the outcome of thrombotic events, because this study did not assess deep vein thrombosis, or pulmonary embolus (the outcome was cardio-thromboembolic events, defined as “nonfatal myocardial infarction, nonfatal stroke, or death from a vascular cause”, although the results were reported as “myocardial infarctions” and “nonfatal strokes”). Also, this outcome was measured at 6 months, rather than in the 1-month timeframe required for this PICO. Note: no data for thienopyridines other than clopidogrel. This outcome was not further downrated for indirectness for being restricted to colonic polypectomy, because it is unlikely that this outcome would be substantially different in other GI procedures.

<sup>f</sup> Serious indirectness, given that this PICO covers all GI procedures, while Watanabe 2020 included only colonic polypectomy (hot snare).

### Evidence to Decision Table

P: Patient on **single antiplatelet therapy with** P2Y12 thienopyridine agents (clopidogrel, prasugrel, ticagrelor)

I: Temporary interruption of thienopyridine for up to 10 days

C: Continuous thienopyridine antiplatelet drug use

O: **CRITICAL:** Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, cardiac stent occlusion, deep vein thrombosis, pulmonary embolus)

3514 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days  
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	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<p><b>How substantial are the desirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>	<p>See Evidence Profile Table</p> <p>Theoretically, interruption of thienopyridine would tend to decrease <b>bleeding (critical outcome)</b> compared to continued thienopyridine use.</p> <p>However, the direction of the effect for bleeding events was found opposite to the theoretically anticipated (interrupted thienopyridines caused less bleeding, which seems implausible). The panel felt that the available evidence did not allow a judgment on the direction of the effect with regards to bleeding.</p>	
Undesirable Effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>● <b>Small</b></li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>There were small undesirable anticipated effects with interrupted thienopyridine use: small increase in thrombotic events (critical outcome).</p> <p>No data on <b>mortality</b></p>	
Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>See Evidence Profile Table.</p>	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>● <b>Possibly important uncertainty or variability</b></li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<p>See Box on Patient Values and Preferences, at the beginning of PICO 1.</p>	

Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> </ul> <p>○ Varies</p> <p>● <b>Don't know</b></p>	Given that the effect on bleeding was unknown, it was not possible to judge the balance between desirable and undesirable effects.	
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>● <b>Negligible costs and savings</b></li> <li>○ Moderate savings</li> <li>○ Large savings</li> </ul> <p>○ Varies</p> <p>○ Don't know</p>		
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● <b>Moderate</b></li> <li>○ High</li> </ul> <p>○ No included studies</p>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> </ul> <p>○ Varies</p> <p>● <b>No included studies</b></p>		

Acceptability	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		
Feasibility	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		

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## Conclusions

3518 P: Patient on single antiplatelet therapy with P2Y12 thienopyridine agents (clopidogrel, prasugrel, ticagrelor)

3519 I: Temporary interruption of thienopyridine X up to 10 days

3520 C: Continuous thienopyridine antiplatelet drug use

3521 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, cardiac stent occlusion, deep vein thrombosis, pulmonary embolus)

3523 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

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Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Neither in favor nor against 6/6 votes: 100%	Conditional recommendation for the intervention	Strong recommendation for the intervention
	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>

<b>Recommendation</b>	For patients on single antiplatelet therapy with P2Y12 thienopyridine agents who are undergoing elective endoscopic GI procedures, we could not reach a recommendation for or against temporary interruption of the thienopyridine
<b>Justification</b>	
<b>Subgroup considerations</b>	Remark: P2Y12 thienopyridine agents = clopidogrel, prasugrel, or ticagrelor
<b>Implementation considerations</b>	
<b>Monitoring and evaluation</b>	
<b>Research priorities</b>	<u><b>Ongoing study:</b></u> Ket S, Metz A, Moss A, Ogra R, Tam W, Secomb R, Reynolds J, Gibson PR, Brown G. Study design of endoscopic polypectomy on clopidogrel (EPOC): a randomised controlled trial. Contemporary clinical trials communications. Vol.16, 2019.

## References, PICO 14b

1. Chan et al. Risk of Postpolypectomy Bleeding with Uninterrupted Clopidogrel Therapy in an Industry-Independent, Double-Blind, Randomized Trial. *Gastroenterology* 2019 Mar;156(4):918-925'
2. Watanabe K., Nagata N., Yanagisawa N., Shimbo T., Okubo H., Imbe K., Yokoi C., Yanase M., Kimura A., Akiyama J., Uemura N. Effect of antiplatelet agent number, types, and pre-endoscopic management on post-polypectomy bleeding: validation of endoscopy guidelines. *Surgical Endoscopy*. 2020

## 15. Interruption of cardiac ASA

### 15. Interruption of cardiac ASA

P: Patient on ASA 81 mg/day or 325 mg/day (i.e, cardiac ASA) for secondary prevention

I: Interruption of cardiac ASA X 5-7 days

C: No temporary interruption of cardiac ASA

O: **CRITICAL:** Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, cardiac stent occlusion, deep vein thrombosis, pulmonary embolus)

**IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days

#### Overall remarks

Our literature search identified a large number of comparative observational studies that seemed eligible judging from the information provided in the abstracts. However, careful assessment of the full-text of these articles revealed that the vast majority of these studies were not eligible for this PICO. The most common reason for exclusion was that they did not provide (and did not allow for calculation of) “clean” data for groups that were similar other than the interruption vs. non-interruption of ASA prior to the endoscopic procedure: either one or both of the groups contained a proportion of patients were on a second antithrombotic (usually more potent than ASA) and in most studies the handling of the second antithrombotic was not clear. We needed both groups (interrupted and noninterrupted ASA) to be taking only ASA, or at least to be taking the same second antithrombotic with known periprocedural management. Only 4 retrospective observational studies allowed for such data extractions. See below.

Given the very low quality of evidence from the 4 eligible studies, we (a) assessed previous GI guidelines to identify any missed studies, (b) looked at indirect evidence from studies that assessed the risk of thrombotic events when cardiac ASA is interrupted for 5-7 days for any reason, and (c) looked at non-GI guidelines in an attempt to find indirect evidence on non-GI procedures.

#### SRMA of observational studies

1. **Burger JIM 2005**<sup>1</sup> (Burger et al. Low-dose aspirin for secondary cardiovascular prevention – cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation – review and meta-analysis. JIM 2005)
  - See figure 1 in the paper for time between aspirin withdrawal and vascular event.
  - Also informs PICO 9 (hold vs continue ASA in GI bleeding)
  - It included **4 observational studies on GI endoscopy** (page 404 in the paper): no meta-analysis, no risk of bias assessment. See our assessment below.



- This SRMA can also provide indirect evidence on the timing of the cardiovascular events after ASA discontinuation (page 400-401)
  - “Randomized studies or observational retrospective or prospective studies comparing the cardiovascular risks of preprocedural aspirin withdrawal directly against aspirin continuation were not obtained”. “However, we found three retrospective studies reporting on the frequency of aspirin withdrawal preceding acute cardiovascular syndromes in consecutive series of patients”.
  - These studies were case series of patients all of whom had the cardiovascular outcome. The studies reported the proportion of patients who had discontinued aspirin prior the event among those who experienced the event. They did not report what proportion of patients had the event among those who discontinued aspirin, therefore we cannot extract relative or absolute risks
  - Burger et al “also found four case reports covering a total of 38 patients, who, after discontinuation of low dose aspirin, experienced cerebrovascular events (n = 29), myocardial infarctions (n = 8), or an arterial embolus (n = 1). Five of these patients died” 4-7
  - Burger et al summarized the **time interval between aspirin discontinuation and the cardiovascular event in figure 1 in the paper**
    - acute peripheral vascular event  $25.8 \pm 18.1$  days (mean  $\pm$  standard deviation)
    - acute coronary syndromes  $8.5 \pm 3.6$  days
    - acute cerebral events  $14.3 \pm 11.3$  days after withdrawal of aspirin
- With regards to the **4 observational studies on GI endoscopy** that were included in Burger, we excluded 3 of them.
  - Hui AJ, Wong RM, Ching JY, Hung LC, Chung SC, Sung JJ. Risk of colonoscopic polypectomy bleeding with anticoagulants and antiplatelet agents: analysis of 1657 cases. Gastrointest Endosc 2004; 59: 44–8.
    - **Excluded**
    - there is a mention that patients in NSAIDs were excluded, but it is not clear if all patients were on aspirin monotherapy or if some patients were taking a second antithrombotic agent.
    - In this paper the term “antiplatelet agent” includes NSAIDs too
    - intervention = colonic polypectomy
    - n= 127 with use of aspirin (and another 7 with use of aspirin and NSAID) within 1 week before colonoscopy. Events (bleeding): 6

3605                   ▪ The definition of exposure in this study (“use of aspirin within 1 week before colonoscopy”) does not fit to our  
3606                   PICO question: “use of aspirin within 1 week before colonoscopy” would be compatible with both continuous  
3607                   anticoagulation and temporary interruption of 6 or less days  
3608           ○ Sorbi D, Norton I, Conio M, Balm R, Zinsmeister A, Gostout CJ. Postpolypectomy lower GI bleeding: descriptive analysis.  
3609           Gastrointest Endosc 2000; 51: 690–6.  
3610                   ▪ Excluded  
3611                   ▪ Describes 83 patients with post-polypectomy bleeding  
3612                   ▪ 32.5% had taken ASA within 3 days of the presentation of the bleeding (unclear if they were on ASA at the time  
3613                   of polypectomy)  
3614                   ▪ No comparative cohort, no comparative control group. Impossible to assess the contribution of ASA to the  
3615                   bleeding  
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3617           ○ **Hui APT 2002** <sup>2</sup> (Hui CK, Lai KC, Yuen MF, Wong WM, Lam SK, Lai CL. Does withholding aspirin for one week reduce the  
3618           risk of post-sphincterotomy bleeding? Aliment Pharmacol Ther 2002; 16: 929–36)  
3619                   ▪ Excluded  
3620                   ▪ Retrospective cohort study  
3621                   ▪ Over an 11-year period, 240 patients on ASA underwent endoscopic sphincterotomy  
3622                         • 124 (51.7%) continued to take aspirin until the day of endoscopic sphincterotomy (Group 1)  
3623                         • 116 (48.3%) had their aspirin discontinued for 1 week before endoscopic sphincterotomy (Group 2)  
3624                   ▪ Outcome: Delayed post-sphincterotomy bleeding (timing of assessment was not stated)  
3625                         • Mild = hemoglobin drop of less than 3 g/dL and no need for blood transfusion  
3626                         • Moderate = transfusion of four units or less with no angiographic intervention or surgery  
3627                         • Severe = transfusion of five units or more in those requiring intervention (angiographic or surgical)  
3628                         • We included moderate and severe, pooled together, as outcome  
3629                                 ○ Continued aspirin: 3/124  
3630                                 ○ Interrupted aspirin 4/116  
3631                   ▪ Analysis not adjusted for differences in the procedure between the two groups (only “repeat cannulation” was  
3632                   assessed, but not any of: indication for ERCP, urgent vs elective procedure, reason for sphincterotomy, size of  
3633                   sphincterotomy, type of current used, sphincteroplasty, pre-cut, other interventions such as stone extraction,  
3634                   stent insertion, individual endoscopist skill, etc.)

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- The denominators (number of patients who had ERCP with/without sphincterotomy) were not reported: it is possible that under similar circumstances, patients on aspirin were less likely to have sphincterotomy
  - **Excluded** because clean data for patients on ASA monotherapy could not be extracted, as the patients may have been on other anti-thrombotics. Dr. Laine contacted the author who said he didn't know and that it was possible.
- **Yousfi AJG 2004**<sup>3</sup> (Yousfi M, Gostout CJ, Baron TH et al. Postpolypectomy lower gastrointestinal bleeding: potential role of aspirin. Am J Gastroenterol 2004; 99: 1785–9)
    - Excluded
    - Case control study: 81 patients with post-polypectomy bleeding matched (for age, gender, history of CAD) with 81 patients with uneventful polypectomy
    - Indirectness of the exposure: this study did not compare patients who continued vs interrupted ASA for 5-7 days. Instead compared those who used ASA within 3 days of colonoscopy (this group could include patients who interrupted ASA for 2 days) vs. those who did not use ASA within 3 days of colonoscopy (this group would include patients who were never on ASA (different population, likely healthier, with healthier vessels) as well as patients who discontinued ASA for 3 days or longer). Furthermore, it is not clear that dual antiplatelet therapy was excluded.
    - High risk of bias
      - the cases were derived from two databases, and the controls from a different third database (unknown timeframe)
      - Used retrospective evaluation of medical records to establish ASA exposure
      - Did not adjust for factors that affect bleeding risk post-polypectomy, even though there was an obvious imbalance in the total number of polyps removed: in the cases, the number of polyps removed was twice the number in controls. The imbalance in such an important factor is so large, that it makes it possible for the results to reverse direction if the results are appropriately adjusted - of course, a “protective effect” of ASA for post-polypectomy bleeding is implausible biologically and would simply mean that strong residual confounding (for example, the endoscopists may have acted differently when they scoped and removed polyps in patients on ASA vs patients not on ASA). We cannot do the statistical adjustment ourselves because we would need access to individual raw data.

- Indirectness of the polypectomy technique: 85% and 88% hot polypectomy in each group, although >95% of the polyps were  $\leq 10$  mm (this approach is not applicable to current practice; nowadays, most of these polyps would have been removed by cold snaring)
- 2. **Wu TJG 2017**<sup>4</sup> (Wu W., Chen J., Ding Q., Yang D., Yu H., Lin J. Continued use of low-dose aspirin may increase risk of bleeding after gastrointestinal endoscopic submucosal dissection: A meta-analysis. Turkish Journal of Gastroenterology. 28 (5) (pp 329-336), 2017)
  - SRMA of 5 studies (4 retrospective cohort studies and 1 case-control study) that compared continued ASA vs interrupted ASA for patients undergoing ESD. See figure 2a in the paper.
  - We could not use the results due to multiple errors, but we assessed each individual study
  - Data-extraction and/or eligibility errors in all 5 studies:
    - **Cho 2012**: the data used by Wu et al are not clean; these results include patients taking a second antithrombotic. For clean data, see our comments below
    - **Lim 2012**: the data used by Wu et al are wrong; these are the results for patients on any antithrombotic or combination of antithrombotics. Data on ASA users (or ASA-alone users) are not extractable. Furthermore, the univariate and analysis on ASA alone users is uninterpretable. See comments on Lim 2012 below
    - **Matsumura 2014**: the comparator data used by Wu et al are wrong. 5/41 are the bleeding episodes in patients on any antithrombotic (warfarin or various antiplatelets) who discontinued treatment perioperatively. This study does not report rate of bleeding for patients on ASA who discontinued ASA perioperatively.
    - **Nimomiya 2015**: the data used by Wu et al are not clean; these results include patients taking a second antithrombotic. Clean data are not extractable
    - **Sanomura 2012**: the data used by Wu et al are not clean; these results include patients taking a second antithrombotic. Clean data are not extractable
  - **Comments on those 5 studies**
    - Cho SJ, Choi IJ, Kim CG, et al. Aspirin use and bleeding risk after endoscopic submucosal dissection in patients with gastric neoplasms. Endoscopy 2012;44:114-21.<sup>5</sup>
      - **INCLUDED**
      - Retrospective cohort study of patients on cardiac ASA who underwent gastric ESD.
        - Interrupted ASA (held for 7 days prior and 28 days post procedure) n=56
          - ASA alone (no second antiplatelet) **n=53**
        - Uninterrupted ASA n =19
          - ASA alone (no second antiplatelet) **n=12**

- Post-ESD bleeding was defined as a “decrease in blood hemoglobin level of more than 2g/dL that was accompanied by the occurrence of hematemesis, melena, or the combination of unstable vital signs with fresh blood or clots upon Levin tube irrigation within 4 weeks after ESD”
  - We extracted “clean” data for ASA-alone users (different from the data used in the previous SRMA)
    - Interrupted ASA: 1/53
    - Uninterrupted ASA: 2/12
  - No results on thrombotic events or mortality
- Lim JH, Kim SG, Kim JW, et al. Do antiplatelets increase the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms? *Gastrointest Endosc* 2012; 75: 719-27 <sup>6</sup>
  - Retrospective cohort study of patients on various antiplatelets who underwent gastric ESD.
  - Definitions were different than usual: “Patients who had continued antiplatelet therapy or had it interrupted <7 days before ESD were counted as continuous users, and those who had never used antiplatelet therapy or had it discontinued 30 days or more before the procedure were counted as non-users. Others were counted in the withdrawal group.”
  - Included in a SRMA (Wu 2017) but with wrong data extractions. Data on ASA users cannot be extracted.
  - The univariate and analysis on “single-ASA users” seems relevant at first sight, but at close inspection it becomes obvious that it is uninterpretable. See table 7 in that paper. The comparator is not defined, but the numbers don’t add up unless this analysis includes all patients on single ASA (including patients who permanently discontinued ASA). This is not an analysis comparing uninterrupted single ASA vs interrupted <7 days single ASA
  - Excluded
- Matsumura T, Arai M, Maruoka D, et al. Risk factors for early and delayed post-operative bleeding after endoscopic submucosal dissection of gastric neoplasms, including patients with continued use of antithrombotic agents. *BMC Gastroenterol* 2014;14:172.<sup>7</sup>
  - Retrospective cohort study of patients on various antithrombotics who underwent gastric ESD.
  - It has been erroneously included in previous SRMAs, no data for this comparison can be extracted (previous SRMAs did different mistakes in their interpretation of the extractable data)
  - Excluded

- Ninomiya Y, Oka S, Tanaka S, et al. Risk of bleeding after endoscopic submucosal dissection for colorectal tumors in patients with continued use of low-dose aspirin. J Gastroenterol 2015; 50:1041-6.<sup>8</sup>

  - Retrospective cohort study of patients on various antithrombotics who underwent colonic ESD.
  - Results on patients taking ASA-alone (interrupted ASA-alone vs continued ASA-alone) cannot be extracted. 10/41 patients were also taking warfarin (n=3, managed with IV heparin bridging) or a second or third antiplatelet. The paper reports that 5 (out of 7 total) bleeds occurred among the 31 patients (34 procedures) on ASA-alone, but we don't know the number of bleeds according to whether these patients continued or interrupted ASA.
  - Excluded
- Sanomura Y, Oka S, Tanaka S, et al. Continued use of low-dose aspirin does not increase the risk of bleeding during or after endoscopic submucosal dissection for early cancer. Gastric Cancer 2014;17:489-96.<sup>9</sup>

  - Retrospective cohort study of patients on cardiac ASA who underwent gastric ESD.
  - During the first period of the study patients interrupted ASA for 5-7 days before the procedure (n = 66 procedures, 53 patients)
  - During the second period of the study, due to change in guidelines, all patients continued cardiac ASA perioperatively (n= 28 procedures, 25 patients)
  - Post-operative bleeding
    - Interrupted ASA: 3/66
    - Uninterrupted: ASA 1/28
  - Thrombotic events (perioperatively = pre- or post-operatively)
    - Interrupted ASA: 4/53
    - Uninterrupted: ASA 0/25
  - Mortality
    - Interrupted ASA: 1/53
    - Uninterrupted: ASA 0/25
  - **However, it is not possible to extract “clean” data for aspirin-only users: 25/78 patients were taking a second antithrombotic (warfarin or another antiplatelet) in addition to ASA**, and it is not clear how the second antithrombotic was handled perioperatively and how soon it was re-started (other than that “warfarin was replaced with heparin”)
  - Excluded

3. Dong J; Wei K; Deng J; Zhou X; Huang X; Deng M; Lu M. Effects of antithrombotic therapy on bleeding after endoscopic submucosal dissection. *Gastrointestinal Endoscopy*. 86(5):807-816, 2017 <sup>10</sup>
- SRMA of 3 cohort studies that compared continued ASA vs interrupted ASA for patients undergoing ESD
  - Results on delayed bleeding: see Figure 6B in the paper.
  - We could not use the results due to multiple errors that we found in this SRMA, but we assessed each individual study
  - Data-extraction and/or eligibility errors in all 3 studies
    - Cho 2012: the data are not clean; they include patients taking a second antithrombotic. For clean data, see comments above.
    - Matsumura 2014: the data for the comparator are wrong. 5/21 are the bleeding episodes in patients who were on bridging therapy with heparin. This study does not report rate of bleeding for patients on ASA who discontinued ASA perioperatively.
    - Sanomura 2012: the data are not clean; they include patients taking a second antithrombotic. Clean data are not extractable
4. Kimchi N.A., Broide E., Scapa E., Birkenfeld S. Antiplatelet therapy and the risk of bleeding induced by gastrointestinal endoscopic procedures: A systematic review of the literature and recommendations. *Digestion*. 75 (1) (pp 36-45), 2007
- Narrative review (not a SR, and not MA), so we assessed the 3 studies they identified
    - Hui GIE 2004. See above. Excluded
    - Yousfi AJG 2004. See above. Included.
    - Shiffman GIE 1994 <sup>12</sup>. Retrospective cohort study. Excluded. There is no comparator of patients who did not hold ASA.

Cohort studies **with** the comparator cohort that is needed for this PICO

1. Ara DE 2015 <sup>13</sup> (Ara et al. Prospective analysis of risk for bleeding after endoscopic biopsy without cessation of antithrombotics in Japan. *Digestive Endoscopy*. 27 (4) (pp 458-464), 2015)
- Procedure: endoscopic biopsy during EGDs
  - **Continued** ASA = 166; events (bleeding): 1 (however, was patient was on both ASA and clopidogrel continued use)
  - **Interrupted** ASA = 67; events (bleeding): 1

- We cannot extract clean data for patients who were on ASA-alone. The best **approximation** we can make is as follows:
  - Continued ASA-alone  $\approx 166 \times 85.7\% = 142$ . Bleeding 0/142
  - Interrupted ASA-alone  $\approx 67 \times 90.7\% = 61$ . Bleeding 1/61

- Cho S.-J., Choi I.J., Kim C.G., Lee J.Y., Nam B.-H., Kwak M.H., Kim H.J., Ryu K.W., Lee J.H., Kim Y.-W. Aspirin use and bleeding risk after endoscopic submucosal dissection in patients with gastric neoplasms. Endoscopy. 44 (2) (pp 114-121), 2012. <sup>5</sup>

- Included. See comments above

Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (for this PICO, exposure vs non-exposure refers to whether the ASA was interrupted or not)	Prognostic factors (other than exposure of interest) <b>similar</b> among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Cho Endo 2012 <sup>5</sup>	OK	The two cohorts were likely very different in prognostic factors. No adjustment was made for confounders <b>for the outcomes that we extracted</b>	OK	OK	Unclear	OK	P: ASA users who had gastric ESD (endoscopic mucosal resection)  Post-ESD bleeding (at 4 weeks): <ul style="list-style-type: none"> <li>Continued aspirin: 2/12</li> <li>Interrupted aspirin: 1/53</li> </ul>
Ara. Dig End 2015 <sup>13</sup>	OK	No, the two cohorts were not similar for prognostic factors for bleeding: confounding was favoring the non-interruption group. No adjustment.	OK	OK	OK	OK	P: patients who had upper GI endoscopic biopsy <u>Delayed bleeding (30 days) approximate data</u> <ul style="list-style-type: none"> <li><b>Continuous</b> aspirin treatment: 0/142 = 0% (0% - 2.1%)</li> <li><b>interrupted</b> aspirin: 1/61 = 1.6% (0% - 9.1%)</li> </ul>



Low risk of bias
Unclear risk of bias
High risk of bias

3798 Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included,  
3799 because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid  
3800 methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of  
3801 interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not  
3802 included, because it is an “indirectness” issue as per GRADE.

3803 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
3804 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias

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## 3806 **ASSESSMENT OF PREVIOUS GUIDELINES**

- 3807 • **2016 ASGE guidelines** <sup>15</sup>
  - 3808 ○ “We suggest that continuation of low doses of ASA and nonsteroidal anti-inflammatory drugs may be continued safely in the
  - 3809 peri-endoscopic period. Moderate quality of evidence”
    - 3810 ▪ However, not a single study was cited as supportive evidence
    - 3811
- 3812 • **Bhatt ACCF/ACG/AHA expert consensus\_ AJG 2008** <sup>16</sup>
  - 3813 ○ This guideline did not address this question (interruption vs non-interruption of cardiac ASA prior to procedures) and did not cite
  - 3814 any relevant studies
  - 3815
- 3816 • **Levine 2016 ACC/AHA Focused Update\_ JACC 2016** <sup>17</sup>
  - 3817 ○ This guideline did not address this question (interruption vs non-interruption of cardiac ASA prior to procedures) and did not cite
  - 3818 any relevant studies
  - 3819 ○ The whole guideline addressed patients DAPT. They issued a “Class I (strong recommendation)” based on level of evidence C-EO
  - 3820 (expert consensus based on clinical experience): *“In patients treated with DAPT after coronary stent implantation who must*
  - 3821 *undergo surgical procedures that mandate the discontinuation of P2Y12 inhibitor therapy, it is recommended that aspirin be*
  - 3822 *continued if possible and the P2Y12 platelet receptor inhibitor be restarted as soon as possible after surgery.”*
  - 3823 ○ No studies relevant to our PICO were cited
  - 3824
- 3825 • **Chan APAGE/APSDE CPG Gut 2018** <sup>18</sup>

- Elective endoscopy, Low-risk procedures, patients on single antiplatelet agent: “We do not recommend withholding antiplatelet agents. (strong recommendation; moderate-quality evidence)”
- Elective endoscopy, High-risk/ultra-high risk procedures, patients on single antiplatelet agent: “We do not recommend discontinuation of aspirin except in ultra-high risk procedures. (strong recommendation; low-quality evidence)”
- Several studies were cited, but only one (Yousfi AJG 2004, already included in our Evidence Profile) provides evidence relevant to one of these recommendations (in fact it provides evidence contradicting the recommendation). The cited studies are:
  - Hui GIE 2004.
    - Not eligible. See our comments further up (discussion of the studies included in previous SRMAs)
  - Shiffman GIE.
    - Not eligible. See our comments further up (discussion of the studies included in previous SRMAs)
  - **Yousfi AJG 2004.**
    - Already included in our evidence profile
  - Whitson MJ, Dikman AE, von Althann C, et al. Is gastroduodenal biopsy safe in patients receiving aspirin and clopidogrel? A prospective, randomized study involving 630 biopsies. J Clin Gastroenterol 2011;45:228–33.
    - Compared ASA and clopidogrel in healthy volunteers who underwent duodenal and antral biopsies.

**TABLE 2.** Probability of Endoscopic and Clinical Bleeding Events (First and Second Endoscopies are Combined)

Drug	Biopsies	Endoscopic Bleeding Events	Upper Confidence Limit (Endoscopic Bleeding)	Clinical Bleeding Events	Upper Confidence Limit (Clinical Bleeding)
CPG	350	0	0.0085	0	0.0085
ASA	280	1	0.0169	0	0.0106

The upper confidence limit reflects the highest probability consistent with the data of bleeding at a single gastroduodenal biopsy site. ASA indicates aspirin; CPG, clopidogrel.

- 
- There were no clinical bleeds in any arm
- Not eligible. It did not have the comparator required for our PICO. Furthermore, antral and duodenal biopsies are considered among the safest of the GI endoscopic interventions, so there is no equipoise as to whether ASA should be held.
- Ono S, Fujishiro M, Kodashima S, et al. Evaluation of safety of endoscopic biopsy without cessation of antithrombotic agents in Japan. J Gastroenterol 2012;47:770–4.
  - Not eligible. No comparator of interrupted ASA.

- 3849       ▪ Burgess NG, Metz AJ, Williams SJ, et al. Risk factors for intraprocedural and clinically significant delayed bleeding after  
3850 wide-field endoscopic mucosal resection of large colonic lesions. Clin Gastroenterol Hepatol 2014;12:651–61.
- 3851             • Not eligible. No comparator of interrupted ASA (the comparator for patients on ASA was the pooled group of all  
3852 other patients, some on warfarin, some on no antithrombotics)
- 3853       ▪ Metz AJ, Bourke MJ, Moss A, et al. Factors that predict bleeding following endoscopic mucosal resection of large colonic  
3854 lesions. Endoscopy 2011;43:506–11.
- 3855             • Not eligible. Some of the included patients interrupted ASA but these were pooled together with those who  
3856 were never on ASA (this makes a big difference because those who interrupted ASA, resumed ASA 5 days after  
3857 the procedure and this affected their risk of post-procedural bleeding). Also, those who continued ASA included  
3858 those who inadvertently took at least 1 dose of ASA within the 7 days prior to the procedure (they started ASA 5  
3859 days after the procedure) and those who, for medical reasons, were asked to not interrupt ASA (and did not  
3860 interrupt ASA post-procedurally either). Clean numerators and clean denominators could not be extracted for  
3861 our PICO. Also, in the multivariable analyses the comparator for patients on ASA was the pooled group of all  
3862 other patients, some on warfarin, some on no antithrombotics, etc.
- 3863       ▪ Lim GIE 2012.
- 3864             • Not eligible. See our comments further up (discussion of the studies included in previous SRMAs)
- 3865       ▪ Cho Endo 2012.
- 3866             • Not eligible. See our comments further up (where the studies included in previous SRMAs are discussed)
- 3867       ▪ Tounou S, Morita Y, Hosono T. Continuous aspirin use does not increase postendoscopic dissection bleeding risk for  
3868 gastric neoplasms in patients on antiplatelet therapy. Endosc Int Open 2015;3:E31–8.
- 3869             • Not eligible. See document of Excluded studies
- 3870       ▪ Tsuji Y, Ohata K, Ito T, et al. Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. World J  
3871 Gastroenterol 2010;16:2913–7.
- 3872             • Not eligible. No separate results for ASA users (all of whom held ASA for 3 days).
- 3873       ▪ Jeon SW, Jung MK, Cho CM, et al. Predictors of immediate bleeding during endoscopic submucosal dissection in gastric  
3874 lesions. Surg Endosc 2009;23:1974–9.
- 3875             • Not eligible. No separate results for ASA users (all of whom held ASA for 5 days).
- 3876       ▪ Sanomura Y, Oka S, Tanaka S, et al. Continued use of low-dose aspirin does not increase the risk of bleeding during or  
3877 after endoscopic submucosal dissection for early gastric cancer. Gastric Cancer 2014;17:489–96.
- 3878             • Not eligible. See our comments further up (discussion of the studies included in previous SRMAs)
- 3879       ▪ Hamada T, Yasunaga H, Nakai Y, et al. Bleeding after endoscopic sphincterotomy or papillary balloon dilation among  
3880 users of antithrombotic agents. Endoscopy 2015;47:997–1004

- Not eligible. They report results for aspirin users (page 999) “when analyzed with adjustment for the same collection of variables, 3/354 patients and 415 of 51325 patients (0.8% in each group) experienced severe bleeding with the continuation of and the non-use of aspirin, respectively and the continuation of aspirin was not associated with a statistically significant increase in severe bleeding (OR 0.91; 95%CI 0.29–2.89)”. However, these results include patients on dual and triple antithrombotic treatment (see table 3 in that paper). We could not extract clean data for our PICO. Interestingly, this study found some implausible results (increased bleeding with discontinuation of anticoagulants) which suggest serious confounding.
  - Kien-Fong Vu C, Chang F, Doig L, et al. A prospective control study of the safety and cellular yield of EUS-guided FNA or Trucut biopsy in patients taking aspirin, nonsteroidal anti-inflammatory drugs, or prophylactic low molecular weight heparin. *Gastrointest Endosc* 2006;63:808–13.
    - Not eligible. No separate results on ASA users (pooled together with NSAID users) and no comparison of interruption vs no interruption
  - Richter JA, Patrie JT, Richter RP, et al. Bleeding after percutaneous endoscopic gastrostomy is linked to serotonin reuptake inhibitors, not aspirin or clopidogrel. *Gastrointest Endosc* 2011;74:22–34.
    - Not eligible. Exposure was defined as ASA administered within 48 or 72 hours before or after PEG. Neither the exposed nor the non-exposed definition fits into the interventions required for this PICO. Some ASA users were using second antithrombotic. The comparator included patients on no antithrombotics or non-ASA antithrombotics. We were unable to extract clean data for our PICO.
- **Veitch\_ BSG/ESGE CPG\_ Endo 2016** <sup>19</sup>
  - For all endoscopic procedures we recommend continuing aspirin (**moderate evidence, strong recommendation**), with the exception of ESD, large colonic EMR (>2cm), upper gastrointestinal EMR and ampullectomy. In the latter cases, aspirin discontinuation should be considered on an individual patient basis depending on the risks of thrombosis vs haemorrhage (**low quality evidence, weak recommendation**).
  - Several studies were cited:
    - Hui GIE 2004.
      - Not eligible. See above.
    - Shiffman GIE 1994
      - Not eligible. See above.
    - Nelson DB, Freeman ML. Major hemorrhage from endoscopic sphincterotomy: risk factor analysis. *J Clin Gastroenterol* 1994; 19: 283–287
      - Not eligible. Did not separate ASA from NSAID use, no comparator of discontinued ASA

3913       ▪ **Yousfi AJG 2004**  
3914           • Already included in our Evidence Profile  
3915       ▪ Cho Endo 2012  
3916           • Not eligible. See above.  
3917       ▪ Takeuchi T, Ota K, Harada S et al. The postoperative bleeding rate and its risk factors in patients on antithrombotic  
3918       therapy who undergo gastric endoscopic submucosal dissection. BMC Gastroenterol 2013; 13: 136  
3919           • Not eligible. Compared patients with interrupted ASA vs patients who were never on ASA.  
3920       ▪ Bahin FF, Naidoo M, Williams SJ et al. Prophylactic endoscopic coagulation to prevent bleeding after wide-field  
3921       endoscopic mucosal resection of large sessile colon polyps. Clin Gastroenterol Hepatol 2015; 13: 724–730 e1–e2  
3922           • RCT, but the randomization is not relevant to whether ASA should be held or not. Results on “ASA users” (use of  
3923       ASA less than 7 days before the EMR) vs “non-users” can be calculated in each group, but there is no comparison  
3924       between those who held ASA vs those who continued ASA.  
3925       ▪ Burgess NG, Metz AJ, Williams SJ et al. Risk factors for intraprocedural and clinically significant delayed bleeding after  
3926       wide-field endoscopic mucosal resection of large colonic lesions. Clin Gastroenterol Hepatol 2014; 12: 651–661 e1–e3  
3927           • Not eligible. See above.  
3928       ▪ Metz AJ, Bourke MJ, Moss A et al. Factors that predict bleeding following endoscopic mucosal resection of large colonic  
3929       lesions. Endoscopy 2011; 43: 506–511  
3930           • Not eligible. See above.  
3931       ▪ **Biondi-Zoccai GG, Lotrionte M, Agostoni P et al. A systematic review and meta-analysis on the hazards of**  
3932       **discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J 2006;**  
3933       **27: 2667–2674**  
3934           • SRMA of observational studies that assessed the effect of discontinuing or not adhering to ASA  
3935           • Moderate to high risk for CAD:  
3936           ○ One study on 31,750 patients (Newby LK, et al. Long-term adherence to evidence-based secondary  
3937       prevention therapies in coronary artery disease. Circulation 2006;113:203–212) focused on **adherence**  
3938       **to aspirin therapy in the secondary prevention of CAD** in patients with documented CAD (at least 1  
3939       documented coronary stenosis of > 50% or coronary bypass surgery). "Consistent use was then defined  
3940       as reporting a medication use on at least 2 consecutive occasions and continuing to do so until death,  
3941       withdrawal from follow-up, or the end of the study period. Patients were considered inconsistent users  
3942       if they met criteria for none of these patterns" These surveys were separated by 6 or 12-month  
3943       intervals. Therefore, this study assessed long term (several months) adherence rather than few days of  
3944       interruption of aspirin.

- two studies (2594) on aspirin discontinuation in acute CAD
    - Infarction occurred  $11.9 \pm 0.8$  days and  $10.0 \pm 1.9$  days after aspirin withdrawal, respectively, in this high-risk population
  - two studies (13 706) on adherence to aspirin therapy before or shortly after coronary artery bypass grafting,
  - and another (2229) on aspirin discontinuation among patients undergoing drug-eluting stenting
- Maulaz AB, Bezerra DC, Michel P et al. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Neurol 2005; 62: 1217–1220
  - Not eligible. Case-control study at high risk of bias. Assessed longer durations of ASA discontinuation (4 weeks)
- **Oscarsson A, Gupta A, Fredrikson M et al. To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. Br J Anaesth 2010; 104: 305–312**
  - RCT. Serious indirectness because the procedures were non-cardiac surgeries, rather than endoscopic procedures
  - Included in SRMAs of RCTs in non-GI procedures (see below)
- **Becker JACC “overview” AJG 2009** <sup>20</sup>
  - It is not a true guideline, but provided recommendations in **Table 3 in the paper**.
  - Several studies were cited, most of which are discussed above in this section (including Yousfi AJG 2004, that we have included), except from the following three:
    - Williams EJ, Taylor S, Fairclough P, et al. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. Endoscopy 2007;39:793–801.
      - Not eligible. It does not report data on aspirin separate from other antiplatelets
    - Sawhney MS, Salfiti N, Nelson DB, et al. Risk factors for severe delayed postpolypectomy bleeding. Endoscopy 2008;40:115–9.
      - Not eligible. Case-control study. Aspirin use was defined as “at least one dose of aspirin within 1 week prior and within 1 week after polypectomy” which would include both the definition of ASA interruption and the definition of ASA non-interruption required for this PICO.
    - Hussain N, Alsulaiman R, Burtin P, et al. The safety of endoscopic sphincterotomy in patients receiving antiplatelet agents: a case-control study. Aliment Pharmacol Ther 2007;25:579–84.

- Not eligible. Case-control study. The definition of ASA exposure was having taken ASA in the 10 days prior to the procedure, which would include both the definition of ASA interruption and the definition of ASA non-interruption required for this PICO.

- **Boustiere ESGE CPG Endoscopy** <sup>21</sup>

- Large number of studies cited – most of them have been discussed already above. No new eligible studies for our PICO

- **Fleisher ACC/AHA CPG JACC 2014** <sup>22</sup>

- This guideline recommended **against** continuation of ASA in patients undergoing elective noncardiac noncarotid surgery who have not had previous coronary stenting (Level of Evidence: B), unless the risk of ischemic events outweighs the risk of surgical bleeding. (Level of Evidence: C)  
see section 6.2.6. Antiplatelet Agents: Recommendations (page e107) in the paper
- The supportive evidence is two RCTs
  - Devereaux NEJM 2014 (POISE-2) <sup>24</sup>
  - PEP trial Lancet 2000 <sup>25</sup>

- **Duceppe CCVS CPG 2017** <sup>23</sup>

- This guideline recommended **against** continuation of ASA in patients undergoing elective noncardiac noncarotid surgery: “We recommend against the continuation of ASA to prevent perioperative cardiac events, except in patients with a recent coronary artery stent and patients who undergo carotid endarterectomy (Strong Recommendation; High-Quality Evidence)”.
- The supportive evidence is two RCTs, although the evidence profile used only the POISE-2.
  - Devereaux NEJM 2014 (POISE-2) <sup>24</sup>
  - PEP trial Lancet 2000 <sup>25</sup>

## RCTs and SRMAs of RCTs on **non-GI** procedures

1. **Devereaux NEJM 2014 (POISE-2)** <sup>24</sup>

- RCT, 2x2 factorial trial design
- N= 10,010 patients who were preparing to undergo noncardiac surgery and were at risk for vascular complications
  - Procedures: orthopedic, general, urologic, gynecologic, vascular, thoracic, “other”.
- Randomized in a 1:1:1:1 ratio to receive
  - clonidine and aspirin

- 4008                   • clonidine and aspirin placebo
- 4009                   • clonidine placebo and aspirin
- 4010                   • clonidine placebo and aspirin placebo.
- 4011           • Aspirin “dimension” of the trial: patients were stratified according to whether they had not been taking aspirin before the study
- 4012                   (initiation stratum, with 5628 patients) or they were already on an aspirin regimen (continuation stratum, with 4382 patients).
- 4013                   • Initiation stratum: patients started taking aspirin (at a dose of 200 mg) or placebo just before surgery and continued it
- 4014                   daily (at a dose of 100 mg) for 30 days
- 4015                   • Continuation stratum (existing ASA users): patients stopped taking aspirin at least 3 days before surgery; patients started
- 4016                   taking aspirin (at a dose of 200 mg) or placebo just before surgery and continued it for 7 days, after which patients
- 4017                   resumed their regular aspirin regimen.
- 4018                   • The continuation stratum is the most relevant to our PICO, but still there is serious indirectness: both arms
- 4019                   discontinued ASA for “at least 3 days” prior to surgery; the difference between those 2 arms was that one arm
- 4020                   took ASA just before surgery and for the first 7 postoperative days, while the second arm stayed off ASA for the
- 4021                   first 7 postoperative days. Therefore, neither of these arms fits well within the description of preoperative
- 4022                   interruption vs. non-interruption of ASA that is required for our PICO.
- 4023           • The results for ASA and for clonidine were reported as separate papers
- 4024                   • Regarding clonidine: it did not reduce the rate of the composite outcome of death or nonfatal MI; it did, however,
- 4025                   increase the risk of clinically important hypotension and nonfatal cardiac arrest.
- 4026                   • No “clean data” on ASA (excluding the patients who took clonidine) were reported. No test for interaction between the
- 4027                   two treatments was reported in this paper. The second paper on clonidine (Devereaux NEJM 2014; 370:1504-13)
- 4028                   assessed the inverse interaction: “Status with respect to receipt of the aspirin study drug had no significant effect on the
- 4029                   results of the comparison of clonidine with placebo ( $P \geq 0.12$  for all interactions)”, however, the actual results were not
- 4030                   shown (such tests in 2x2 factorial design studies are almost always underpowered, so it is important to also report the
- 4031                   results for each of the 4 cells)
- 4032           • The primary outcome was a composite of death or nonfatal MI at 30 days. For the whole study (patients previously on ASA and
- 4033                   patients not on ASA previously):
- 4034                   • ASA: 351/4998 (7.0%)
- 4035                   • Placebo: 355/5012 (7.1%)
- 4036                   • HR 0.99 (0.86 -1.15)
- 4037           • Death (for the whole study):
- 4038                   • ASA: 65/4998 (1.3%)



- Placebo: 62/5012 (1.2%)
  - HR 1.05 (0.74–1.49)
  - The RR for the inverse (i.e., interruption vs continuation) is 0.95 (0.67-1.34)
- We calculated the composite of nonfatal MI, cardiac revascularization, nonfatal PE or nonfatal DVT (for the whole study):
  - ASA: 286/4998 (5.7%)
  - Placebo: 293/5012 (5.9%)
  - The RR for the inverse (i.e., interruption vs continuation) is 1.02 (0.87 - 1.20)
- Note: definitions of bleeding
  - A life-threatening bleed was defined as a bleeding event that was fatal or led to: significant hypotension that required inotrope or vasopressor therapy, emergent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage
  - A major bleed was defined as a bleeding event that was not specified under life- threatening bleeding and resulted in any one of the following:
    1. a hemoglobin  $\leq 70$  g/L and the patient received a transfusion of  $\geq 2$  units of red blood cells;
    2. a hemoglobin drop of  $\geq 50$  g/L and the patient received a transfusion of  $\geq 2$  units of red blood cells;
    3. the patient received a transfusion of  $\geq 4$  units of red blood cells within a 24 hour period;
    4. any one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); or
    5. retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging) bleeding.
  - Life threatening bleeding or Major bleeding (for the whole study):
    - ASA: 317/4998 (6.3%)
    - Placebo: 261/5012 (5.2%)
    - OR 0.81 (0.69-0.96); RR 0.82 (0.70-0.96)
- The bleeding outcomes were also reported separately for the continuation stratum (i.e., patients who were previously on cardiac ASA and were randomized to ASA or placebo perioperatively).
  - Life-threatening or major bleed:
    - ASA: 136/2191 (6.2)
    - Placebo: 113/2191 (5.2)
    - OR (not HR) = 1.20 (0.94-1.55)
    - The inverse (i.e., interruption vs continuation) is OR 0.82 (0.64-1.06); RR 0.83 (0.65-1.06)

- 4070 2. **Lewis CDSR 2018** <sup>26</sup> (Lewis SR, et al. Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in  
4071 adults undergoing non-cardiac surgery. Cochrane Database of Systematic Reviews 2018)
- 4072 • SRMA (Cochrane review) of 5 RCTs, one of which dealt with clopidogrel. The 4 ASA studies were:
- 4073 • **Oscarsson BJA 2010** <sup>27</sup> (Oscarsson A, et al. To continue or discontinue aspirin in the perioperative period: a randomized,  
4074 controlled clinical trial. Br J Anaesth 2010)
- 4075 • Type of surgery: Abdominal, Urologic, Orthopaedic, Gynaecologic
- 4076 • Prior to surgery: 90% of participants were on aspirin. We could not extract “clean” data for patients on ASA prior  
4077 to surgery.
- 4078 • Continuation group (n = 109): participants discontinued any existing dose of aspirin at 7 days prior to surgery,  
4079 then given 75 mg aspirin, until third postoperative day
- 4080 • Discontinuation group (n=111): participants discontinued any existing dose of aspirin at 7 days prior to surgery,  
4081 then given placebo until third postoperative day
- 4082
- 4083 • **Antolovic BMCS 2011** <sup>28</sup> (Antolovic, et al. A randomised controlled trial to evaluate and optimize the use of antiplatelet  
4084 agents in the perioperative management in patients undergoing general and abdominal surgery: the APAP trial. BMC  
4085 Surgery 2011;11:7)
- 4086 • Type of surgery: elective general and abdominal surgery (inguinal hernia repair, cholecystectomy,  
4087 colonic/colorectal, laparoscopic)
- 4088 • Prior to surgery all participants were on cardiac ASA
- 4089 • Continuation group (n = 26): participants continued on usual prescribed antiplatelet dose (25 participants = 100  
4090 mg a day, 1 participant = 50 mg) during whole study period
- 4091 • Discontinuation group (n=26): participants discontinued antiplatelet medication 5 days prior to surgery. Study  
4092 period for 5 days postoperatively. No placebo treatment.
- 4093
- 4094 • **Mantz BJA 2011** <sup>29</sup> (Mantz et al. Impact of preoperative maintenance or interruption of aspirin on thrombotic and  
4095 bleeding events after elective non-cardiac surgery: the multicentre, randomized, blinded, placebo-controlled,  
4096 STRATAGEM trial. British Journal of Anaesthesia 2011;107(6):899-910)
- 4097 • Type of surgery: All types of elective procedures were considered (orthopaedic, abdominal, urologic, thoracic,  
4098 oncologic, ENT)
- 4099 • Prior to surgery 73% of participants were on cardiac ASA, the remaining were on other antiplatelets. We could  
4100 not extract “clean” data for patients on ASA prior to surgery.

- Continuation group (n = 145): existing antiplatelet therapy discontinued 10 days prior to study and switched to aspirin 75 mg which was continued up to morning of surgery. Participants resumed initial anti-platelet therapy after surgery as soon as medical staff felt it was clinically appropriate
    - Discontinuation group (n= 146): existing antiplatelet therapy discontinued 10 days prior to study and switched to a placebo. Participants resumed initial anti-platelet therapy after surgery as soon as medical staG felt it was clinically appropriate.
  - **Nielsen SJUN 2000** <sup>30</sup> (Nielsen et al. The effect of low-dose acetylsalicylic acid on bleeding after transurethral prostatectomy: a prospective, randomized, double-blind, placebo-controlled study. Scandinavian Journal of Urology and Nephrology 2000;34(3):194-8)
    - Type of surgery: TURP
    - Prior to surgery all participants were on cardiac ASA
    - Continuation group (n = 26): usual dose of aspirin was discontinued 10 days before surgery and participant given 150 mg aspirin. Participants resumed usual dose after catheter removal
    - Discontinuation group (n= 27): usual antiplatelet therapy discontinued 10 days prior to study and participant given placebo. Participants resumed usual antiplatelet therapy after catheter removal
  - See Figure 3 (Risk of bias summary) in Lewis 2018 for risk of bias assessment of these 4 trials. We made one correction: in our opinion, Antolovic 2021 should have been high risk of bias for performance bias.
3. **Wolff IJC 2018** <sup>31</sup> (Wolff G, et al. Perioperative aspirin therapy in non-cardiac surgery: A systematic review and meta-analysis of randomized controlled trials. Int J Cardiol. 2018;258:59-67)
- SRMA of RCTs
  - Included both discontinuation and initiation trials on perioperative ASA
  - No additional eligible trials for our PICO, other than the four ones that we described under Lewis CDSR 2018.
  - The POISE-2 trial <sup>24</sup> (see above) is also potentially eligible for our PICO
  - The PEP trial Lancet 2000 <sup>25</sup>, should be mentioned because it was a large RCT on 17,444 patients
    - Not eligible. It was essentially a peri-operative ASA initiation trial. Aspirin or other NSAIDs had been taken within 48 h before randomisation by 9% of patients. Separate results for prior ASA users were not reported (in fact, there is a

4130 mention in another paper (Mantz BJA 2011) that the PEP trial authors were contacted for results on the subgroup of  
4131 prior ASA users but “did not have the data to allow them to determine the outcome for this subgroup of patients”)  
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4134 **Our SRMA of non-GI RCTs**

4135 We included 4 RCTs and extracted the outcomes from the SRMA by Lewis 2018

- 4136 • Oscarsson BJA 2010  
4137 • Antolovic BMCS 2011  
4138 • Mantz BJA 2011  
4139 • Nielsen SJUN 2000

4140 We also included Devereaux NEJM 2014 (POISE-2) in sensitivity analyses (our own data extraction), due to the additional indirectness concerns.  
4141 After discussions with the panel, we included Devereaux NEJM 2014 for the outcome of bleeding but not for the outcomes of thrombotic events  
4142 and mortality (because for the last two outcomes we could not extract separate results for prior ASA users who discontinued ASA).

Risk of bias assessment of RCTs							
Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Comments
Devereaux NEJM 2014 (POISE-2)	OK	OK	OK (double-blind)	OK	OK	OK	
Low risk of bias							
Unclear risk of bias							
High risk of bias							

4143 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
4144 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias

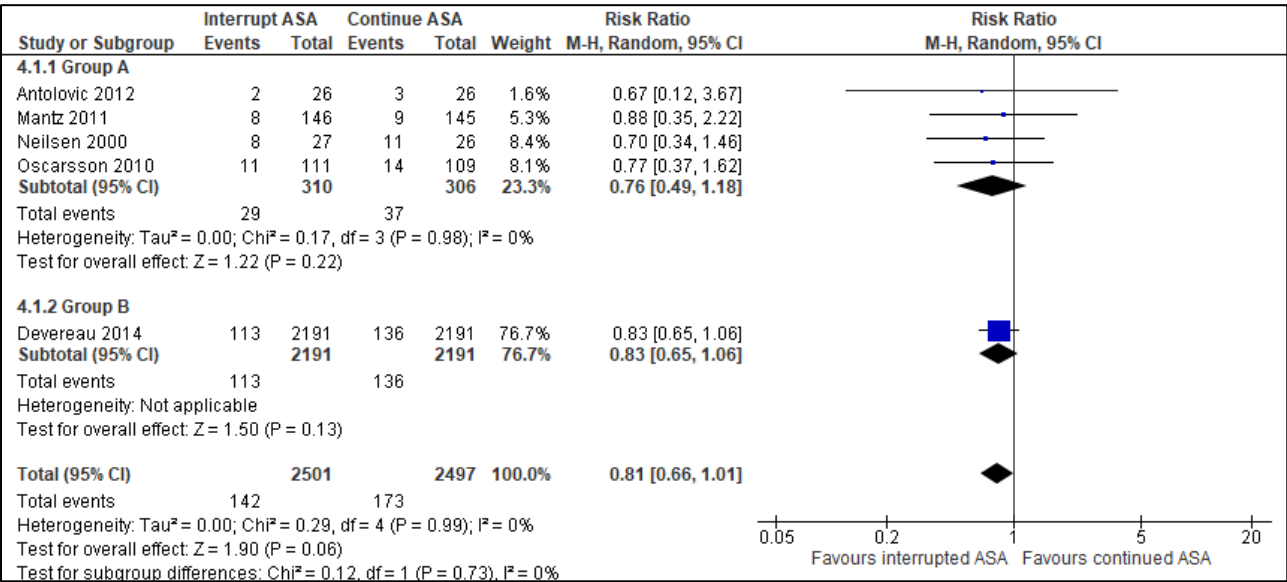
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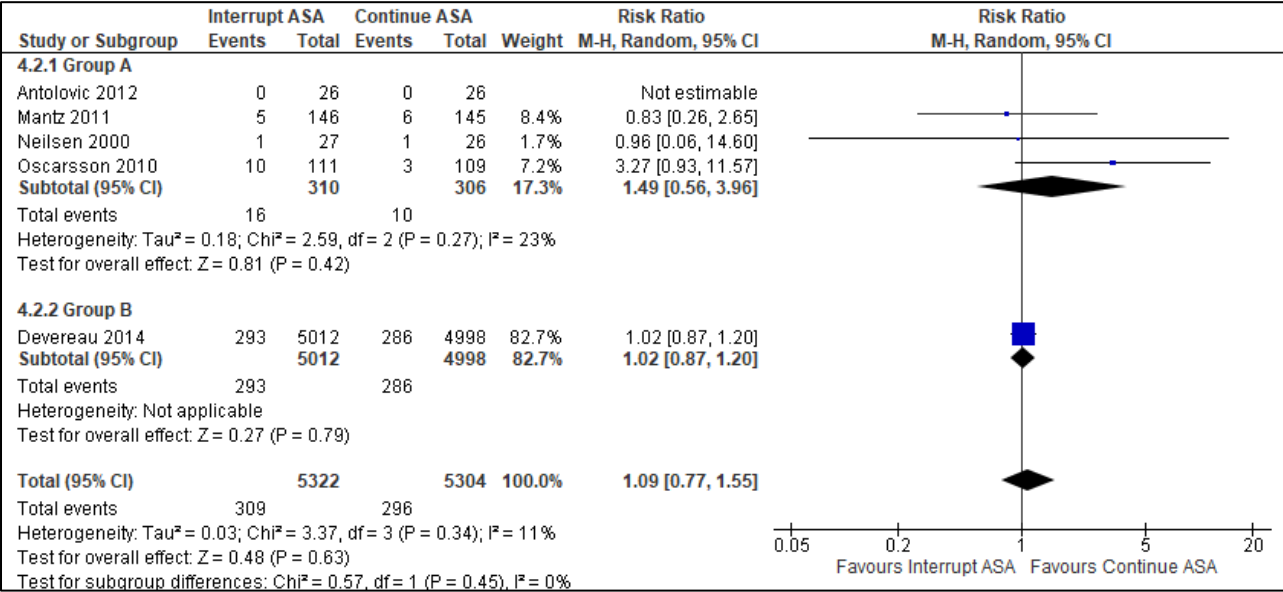
4148     **Results:**

4149     •    Bleeding (requiring transfusion of blood products intraoperatively or postoperatively).



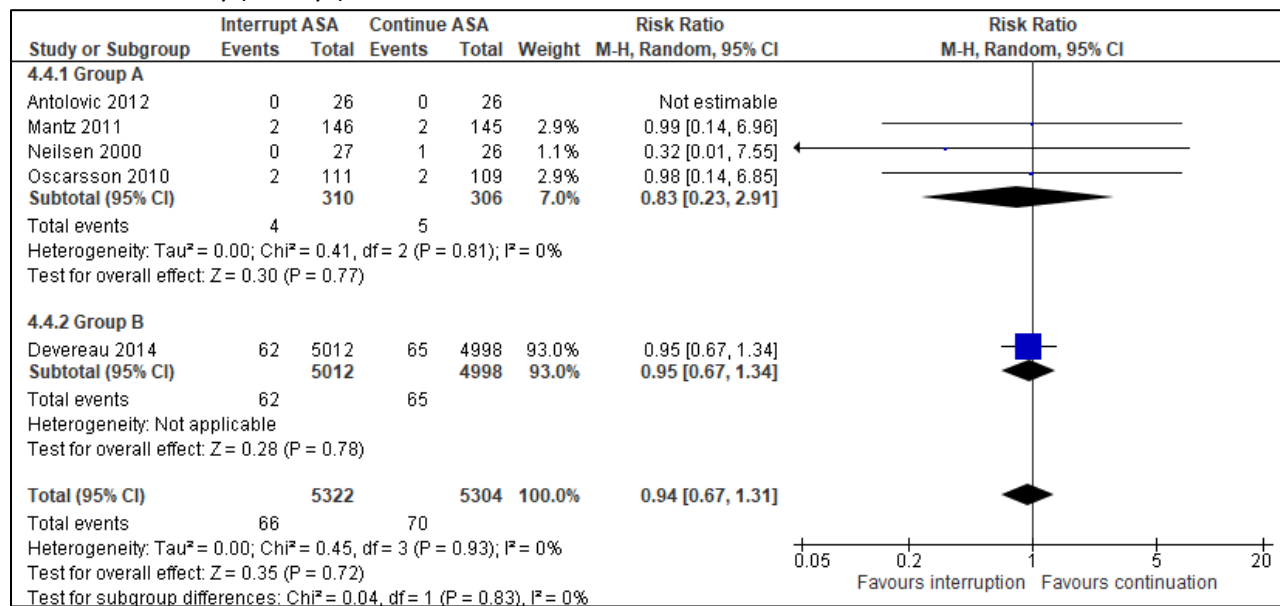
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- Thrombotic and ischemic events (peripheral thrombosis, cerebral infarction, myocardial infarction within 30 days)



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- All-cause mortality (30 days):



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## 4189 Evidence profile for PICO 15

Temporary interruption of cardiac ASA for 5-7 days vs. continuous ASA use												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Interrupted ASA	Continued ASA	Relative (95% CI)	Absolute (95% CI)	
Bleeding within 30 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
Gastric ESD: 1 cohort study (Cho 2012 <sup>5</sup> )	Serious <sup>a</sup>	Not applicable	Serious <sup>b</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		1/53	2/12	RR 0.11 (0.01 – 1.15)	Risk with continued ASA: 166 events per 1,000. With interrupted ASA: 148 less per 1,000 (from 164 less, to 25 more)	
Biopsies at upper GI endoscopy 1 cohort study (Ara. Dig End 2015 <sup>13</sup> )	Serious <sup>a</sup>	Not applicable	Serious <sup>d</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		1/61	0/142	RR 6.91 (0.29- 167.52)	Risk with continued ASA: 0 events per 1,000. With interrupted ASA: 16 more per 1,000 (from 0 more, to 91 more)	
Non-GI procedures  SRMA of 5 RCTs (Antolovic 2012, Mantz 2011, Neilsen 2000, Osxarsson 2010, Devereaux 2014)	Not serious	Not Serious	Very serious <sup>e</sup>	Serious <sup>f</sup>	None	⊕⊕⊕⊕ VERY LOW		142/2501	173/2397	RR 0.81 (0.66 -1.01)	Risk with continued ASA: 72 events per 1,000. With interrupted ASA: 14 less per 1,000 (from 24 less, to 1 more)	



<b>Thrombotic events within 30 days (critical outcome)</b>												
<b>Non-GI procedures</b>												
SRMA of 4 RCTs (Antolovic 2012, Mantz 2011, Neilsen 2000, Osxarsson 2010)	Not serious	Not Serious	<b>Very serious<sup>g</sup></b>	<b>Very serious<sup>c</sup></b>	None	⊕⊕⊕⊕ <b>VERY LOW</b>		16/310	10/306	<b>RR 1.49</b> (0.56 -3.96)	Risk with <b>continued ASA:</b> 33 events per 1,000. With <b>interrupted ASA:</b> 16 <b>more</b> per 1,000 (from 15 <b>less</b> , to 98 <b>more</b> )	Range of interruption 4-10 days
<b>Mortality within 30 days (important outcome, but not critical for decision making)</b>												
<b>Non-GI procedures</b>												
SRMA of 5 RCTs (Antolovic 2012, Mantz 2011, Neilsen 2000, Osxarsson 2010)	Not serious	Not Serious	<b>Very serious<sup>h</sup></b>	<b>Very serious<sup>c</sup></b>	None	⊕⊕⊕⊕ <b>VERY LOW</b>		3/310	5/306	<b>RR 0.83</b> (0.23 -2.91)	Risk with <b>continued ASA:</b> 16 events per 1,000. With <b>interrupted ASA:</b> 3 <b>less</b> per 1,000 (from 12 <b>less</b> , to 31 <b>more</b> )	

## Footnotes

<sup>a</sup> Serious risk of bias due to results not adjusted for known major confounders

<sup>b</sup> Serious indirectness for the outcome of bleeding, given that this PICO covers all GI procedures, not only gastric ESD (if the PICO had been restricted to gastric ESD, there would be no indirectness)

<sup>c</sup> Very serious imprecision due to very wide confidence intervals (compatible with large benefit as well as large harm) and the very small number of events

<sup>d</sup> Serious indirectness for the outcome of bleeding, given that this PICO covers all GI procedures, not only upper GI endoscopy biopsies (if the PICO had been restricted to upper GI endoscopy biopsies, there would be no indirectness). Also, indirectness because the paper did not allow for extraction of “clean” data for patients on aspirin monotherapy; instead, we calculated approximate results

<sup>e</sup> Very serious indirectness because the baseline risk of bleeding and the effect on ASA on the risk of bleeding is likely very different in these surgeries as opposed to GI endoscopy. Also, the timing of interruption and initiation was different than the timing required for our PICO. Also, two of the studies included a small proportion of patients who were not on cardiac ASA treatment prior to surgery. Of note, we were able to extract data for prior ASA users from Devereauz 2012 (only for this outcome)

4204 <sup>f</sup> Serious impression because the 95% CI is compatible with serious harm and no (or negligible) difference  
 4205 <sup>g</sup> Very serious indirectness because the baseline risk of thrombosis and the effect on ASA on the risk of thrombosis is likely very different in these  
 4206 surgeries as opposed to GI endoscopy. Also, the timing of interruption and initiation was different than the timing required for our PICO. Also, two of  
 4207 the studies included a small proportion of patients who were not on cardiac ASA treatment prior to surgery.  
 4208 <sup>h</sup> Very serious indirectness because the baseline risk of death and the effect on ASA on the risk of death is likely very different in these surgeries as  
 4209 opposed to GI endoscopy. Also, the timing of interruption and initiation was different than the timing required for our PICO. Also, two of the studies  
 4210 included a small proportion of patients who were not on cardiac ASA treatment prior to surgery.

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## Evidence to Decision Table

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### 15. Interruption of cardiac ASA

4218 P: Patient on ASA 81 mg/day or 325 mg/day (i.e, cardiac ASA)  
 4219 I: Interruption of cardiac ASA X 5-7 days  
 4220 C: No temporary interruption of cardiac ASA  
 4221 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, cardiac stent occlusion,  
 4222 deep vein thrombosis, pulmonary embolus)  
 4223 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days  
 4224

	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<b>How substantial are the desirable anticipated effects?</b> ○ Trivial ○ Small ○ Moderate ○ Large ● <b>Varies</b> ○ Don't know	See Evidence Profile Table  The desirable anticipated effects of ASA interruption are: reduction in delayed bleeding (critical outcome), however, there are comparative studies only on patients who had gastric endoscopic mucosal resection, i.e., a population with extreme baseline bleeding risk. The panel could not make a blanket judgment for all GI procedures, and felt more appropriate to state that the effect on bleeding risk varies according to the type of procedure. Non-GI literature showed a reduction in bleeding as well, although the panel considered that data as very indirect (bleeding location is important: GI vs. non-GI location- access to GIB site is easier than some of the non-GI sites of internal bleeding).	
Undesirable Effects	<b>How substantial are the undesirable anticipated effects?</b> ○ Large ○ Moderate		

	<ul style="list-style-type: none"> <li>● <b>Small</b></li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	but the committee felt that results on thrombosis from non-GI procedures could be used for decision making in GI procedures	
<b>Certainty of evidence</b>	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>● <b>Very low</b></li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	
<b>Values and Preferences</b>	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>● <b>Possibly important uncertainty or variability</b></li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	See Box on Patient Values and Preferences, at the beginning of PICO 1.	
<b>Balance of effects</b>	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● <b>Probably favors the comparison</b></li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>● Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	The cost of cardiac ASA for 5-7 days is negligible	
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>● High</li> <li>○ No included studies</li> </ul>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>		
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

Feasibility	Is the intervention feasible to implement? <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes  <input type="radio"/> Varies <input type="radio"/> Don't know		
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## Conclusions

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### 15. Interruption of cardiac ASA

4228 P: Patient on ASA 81 to 325 mg/day (i.e, cardiac ASA) for secondary prevention

4229 I: Interruption of cardiac ASA X 5-7 days

4230 C: No temporary interruption of cardiac ASA

4231 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial

4232 infarction, cardiac stent occlusion, deep vein thrombosis, pulmonary embolus)

4233 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

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Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention (interruption) 6/6 votes: 100%	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Recommendation</b>	For patients on ASA 81 to 325 mg/day (i.e, cardiac ASA) for secondary prevention, we suggest against interruption of ASA				
<b>Justification</b>					
<b>Subgroup considerations</b>					
<b>Implementation considerations</b>					

Monitoring and evaluation	
Research priorities	

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4311 16. Timing of warfarin resumption following endoscopy

4312 **16. Timing of warfarin resumption following endoscopy**

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4314 P: Patient on warfarin who underwent endoscopy

4315 I: Resumption on the same day of the procedure

4316 C: Resumption 1 to 7 days after the procedure

4317 O: **CRITICAL:** Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep  
4318 vein thrombosis, pulmonary embolus)

4319 **IMPORTANT, BUT NOT CRITICAL:** mortality within 30 days

4320

4321 **Overall remarks:**

- 4322
- Very little evidence for patients undergoing GI procedures
  - The wording of the Intervention and Comparator (“resumption”) implies that the patient interrupts warfarin therapy for the procedure.
    - We also searched for studies that included patients who did not hold warfarin prior to the procedure and compared the efficacy and safety of holding warfarin for 1-7 days after the procedure vs continuing warfarin therapy without any interruptions: we did not identify such studies.
  - SRMA of 3 cohort studies Chai-Adisaksopha TH 2015 <sup>1</sup> (Chai-Adisaksopha et al. Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding. Thromb Haemost 2015; 114: 819–825) was not eligible. See Excluded Studies Appendix.
  - Given the paucity of comparative data (resumption on the same day of the procedure vs resumption 1 to 7 days after the procedure) we assessed the evidence base that informed previous guidelines that addressed the question of timing of resumption:
    - **ASGE 2016 guideline** <sup>2</sup>: two cohort studies were cited:  
4332 *“In 1 study involving 94 patients who had undergone 109 colonoscopies (including hot biopsy or snare polypectomy in 47%),*  
4333 *patients were instructed to restart warfarin (Coumadin) therapy on the day after endoscopy [Timothy DCR 2001] <sup>3</sup>. Only 1 case*  
4334 *(0.9%) of procedure-related bleeding occurred after 7 days of warfarin (Coumadin) therapy and required hospitalization and*  
4335 *transfusion. None of the patients undergoing diagnostic colonoscopy experienced bleeding. Conversely, a second study involving*  
4336

4337 173 patients found that resuming warfarin (Coumadin) or heparin within 1 week after polypectomy was associated with an  
4338 increased risk of bleeding (OR 5.2; 95% CI, 2.2-12.5) [Sawhney Endo 2008] <sup>4</sup>.”

4339 We did not include these studies for the following reasons:

- 4340     ▪ Both studies were single-arm studies (they did not have a comparator cohort), and did not allow for extraction of non-  
4341 comparative data either.
- 4342     ▪ With regards to the first study (Timothy DCR 2001 <sup>3</sup>), the authors stated that “*patients were asked to restart warfarin*  
4343 *(using their previous dose) the day after the examination*”. However, this protocol was not necessarily adhered to, given  
4344 that the only patient who bleed post-colonoscopy was a patient who restarted warfarin 3 days after the procedure and  
4345 no data on the timing of resumption were reported for the remaining patients. Therefore, this study cannot even  
4346 provide non-comparative data: it cannot inform the rate for a single intervention/comparison in this PICO. Furthermore,  
4347 complications may have been missed (especially VTEs) given that “*patients were followed up by chart review of the two*  
4348 *months after the colonoscopy to identify complications*”, i.e., patients may have presented to other hospitals or to  
4349 primary care providers.
- 4350     ▪ With regards to the second study (Sawhney Endo 2008 <sup>4</sup>), the reported OR cannot be used to support decision-making,  
4351 because both the “cases group” and “controls groups” included patients on anticoagulation prior to the procedure and  
4352 patients who had not been on anticoagulation prior to the procedure. The variable “anticoagulation” was defined as  
4353 “heparin or warfarin use within 1 week after a polypectomy”. This means that it is unknown how many patients in each  
4354 group had been on anticoagulation prior to the procedure, held it and did not resume anticoagulation within 7 days  
4355 after the procedure. Similarly, any patients on anticoagulation who held it peri-procedurally and resumed it more than 7  
4356 days post procedure would have been classified as non-anticoagulated patients. For the PICO of our guideline, we  
4357 cannot extract any relevant comparative data. We cannot extract any relevant non-comparative data either.
- 4358 ○ The ASGE 2016 guideline <sup>2</sup> also cited two previous guidelines
- 4359     ▪ The **2014 AHA/ACC guideline** <sup>5</sup> (that addressed the management of valvular heart disease), which “*recommends that*  
4360 *warfarin (Coumadin) be restarted within 24 hours of the procedure in patients with valvular heart disease and a low-risk*  
4361 *for thromboembolism. In patients at high risk for thromboembolism, UFH or LMWH should be restarted as soon as*  
4362 *“bleeding stability allows” and continued until the INR reaches an appropriate therapeutic level.*” However, the two  
4363 studies that were cited in the 2014 AHA/ACC guideline do not provide any evidence that supports any of the two  
4364 recommendations:
  - 4365         • Tinker JAMA 1978 <sup>6</sup>: retrospective cohort study on 159 patients with mechanical valves who underwent  
4366 noncardiac operations between 1962 and 1975. 10% of the patients had thromboembolic complications and  
4367 13% had “various difficulties with hemostasis”. The authors concluded “*that there is minimal risk to patients*  
4368 *with cardiac valve prostheses who are receiving anticoagulants when the drug regimen is stopped for one to*  
4369 *three days preoperatively and one to seven days postoperatively*”, but this was a mixed population with 23  
4370 patients not discontinuing anticoagulation and 7 patients delaying resumption for more than 7 days.

4371 Furthermore, for some patients the indication for noncardiac surgery was bleeding while on anticoagulation,  
4372 either intracranial bleeding or GI bleeding. Results for clean denominators cannot be extracted. These results  
4373 can neither support or refute the AHA/ACC recommendation.

- 4374 • Kearon NEJM 1997 <sup>7</sup>: This a narrative review that also provided recommendations that were based on risk  
4375 estimates that were clearly stated in tables, that were derived via prorated extrapolation from the annual rates  
4376 of events (but see comments below (Dunn JTH 2006) about the uncertainty with such prorated extrapolations).  
4377 There were no data supporting a specific timing for warfarin resumption vs a different timing for warfarin  
4378 resumption.

- 4379 ▪ The 2012 ACCP guideline <sup>8</sup>, which cited several cohort studies and a narrative review:

- 4380 • **Douketis Arch IM 2004** <sup>9</sup> (included in our Evidence Profile). Single-arm prospective single-center cohort study of  
4381 consecutive patients who interrupted warfarin therapy because of an invasive procedure. All patients were  
4382 managed according to a standardized periprocedural anticoagulation regimen. See description below in included  
4383 studies.
- 4384 • **Kovacs Circulation 2004** <sup>10</sup>. Single-arm prospective multi-center cohort study. Apparently non-consecutive  
4385 patients (given that 11 tertiary academic centers enrolled only 224 patients over 9-10 months) who interrupted  
4386 warfarin therapy because of an invasive procedure. All patients resumed warfarin on the day of the procedure,  
4387 and had pre-operative and post-operative bridging with dalteparin. The invasive procedures were diverse,  
4388 including 19 “endoscopies” (no further description was available, no separate outcomes for those patients), 25  
4389 major orthopedic surgeries and 25 dental procedures. The indirectness concerns are similar to the ones related  
4390 to the above-mentioned study (Douketis Arch IM 2004). Furthermore, given that patients were unlikely to be  
4391 consecutive, the results cannot be used as to prove feasibility (we don’t know the denominator)
- 4392 • **Spyropoulos JTH 2006** <sup>11</sup>. Prospective multi-center cohort study. Compared unfractionated heparin (UFH) with  
4393 low-molecular-weight heparin (LMWH) for the perioperative bridging of patients at risk of thromboembolism  
4394 requiring temporary interruption of long-term warfarin therapy. No separate outcomes for GI procedures. This  
4395 study cannot answer the PICO of this guideline, especially since results on outcomes were not reported  
4396 according to the timing of the warfarin resumption (started < 24 h postoperatively: 38% in the UFH group, 63%  
4397 in the LMWH group).
- 4398 • Dunn JTH 2006 <sup>12</sup>. Narrative review that commented on four cohort studies: the 3 above-mentioned cohort  
4399 studies (including the abstract publication of Spyropoulos JTH 2006 <sup>11</sup>) plus another abstract publication that was  
4400 published one year later as Dunn JHT 2007 <sup>16</sup> (see below). No results on the comparison of different timings for  
4401 warfarin resumption.
  - 4402 ○ **Dunn JHT 2007** <sup>16</sup> (Included in our Evidence profile, see below). Single-arm cohort study on 260 patients  
4403 at 20 sites in North America requiring invasive or surgical procedures, whose treating physician felt that  
4404 bridging therapy was required. Warfarin was withheld, and once-daily s.c. enoxaparin (1.5 mg/kg) was

given peri-operatively. Patients apparently non-consecutive. Separate results for patients who had GI invasive procedures were extracted. *“The bleeding risk varied markedly by extensiveness of procedure: the incidence of major bleeding for invasive procedures, minor surgery and major surgery was 0.7% (95% CI: 0.02–3.7), 0% (95% CI: 0–5.0), and 20.0% (95% CI: 9.1–35.7), respectively.”*

- The 2018 ASH guidelines<sup>13</sup> did not address this PICO.

- See discussion in Dunn JTH 2006<sup>12</sup> on why a prorated extrapolation from the annual rates of thromboembolism may be underestimating the peri-operative risk

“Potential arterial hypercoagulable state: Given the lack of randomized trials, clinicians typically use a general sense of the perioperative stroke risk if bridging anticoagulation is not given to estimate the perioperative stroke risk. **This method assumes that the perioperative stroke rate can be considered a prorated portion of the annual stroke rate and discounts the possibility that patients may be hypercoagulable during the perioperative period.** A perioperative hypercoagulable state that dramatically increases the risk of venous events is well established, however, and an impact on arterial events has not been excluded by trial data. Several potential mediators have been noted, including increased levels of antithrombin III and decreased levels of endogenous tissue plasminogen activator. In addition, rebound hypercoagulability after OAC is withdrawn has also been demonstrated, which may further increase the incidence of perioperative thromboembolism. The results of recent trials have found a substantially greater than expected incidence of arterial thromboembolism, suggesting that a hypercoagulable state affecting the risk of arterial events may exist. As an **example**, the expected stroke rate if bridging therapy is not administered for a patient with atrial fibrillation who has a 5% annual stroke rate without anticoagulation is approximately 0.2% (i.e., 1 in 500 patients). Though the data is not definitive, the clinical event rate in studies is approximately 1.0% (1 in 100 patients). Given the catastrophic nature of thromboembolic stroke, this difference is clinically important and could potentially impact whether bridging anticoagulation is indicated.”

#### Cohort studies without the comparator needed for this PICO

1. **Douketis Arch IM 2004<sup>9</sup>** (Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. Arch Intern Med. 2004; 164 (12):1319-1326).
  - Single-arm prospective single-center cohort study of consecutive patients who interrupted warfarin therapy because of an invasive procedure. All patients were managed according to a standardized periprocedural anticoagulation regimen. All patients had pre-procedural dalteparin bridging.

- i. Patients who had “high-bleeding-risk” procedure (such as coronary artery bypass, abdominal aortic aneurysm repair, neurosurgical cancer surgery, etc.), resumed warfarin on the evening after the procedure, but did not receive post-procedural dalteparin.
  - ii. Patients (n=542) who had “non-high-bleeding-risk” procedure (including colonoscopic polypectomy (n=5), GI endoscopy ± biopsy (n=65), cholecystectomy, arthroscopy, etc.) who had adequate postprocedural hemostasis, resumed warfarin on the evening of procedure, and resumed dalteparin (100 IU/kg twice daily) 24 hours after the procedure (dalteparin was continued until the INR was 2.0 or more)
  - iii. Patients who had “non-high-bleeding risk” procedure who had inadequate postprocedural hemostasis, delayed resumption of warfarin was delayed until the first postprocedural day, and dalteparin was delayed until the second or third postprocedural day when hemostasis was secured.
- Although there was no comparator cohort, this study showed that this standardized approach was associated with a low risk of thromboembolic and major bleeding complications (mean FU 13.8 days, range, 10-18 days): See Table 5 in the paper.
- For this PICO, there is serious indirectness:
  - Indirectness of population (we cannot extract separate results for the patients who underwent GI procedures)
    - The incidence of “**major bleeding**” in this study (defined as clinical evidence (hematemesis) and hgb decrease of more than 2 g/dL or transfusion) may be different than the incidence of bleeding in patients undergoing GI procedures.
    - The incidence of **thromboembolism** in this study (**if we use the data from the group that underwent ambulatory procedures with minimal tissue destruction**) should be similar to the incidence thromboembolism patients undergoing ambulatory GI procedures,
  - Indirectness of co-intervention: most of the patients in the “non-high-bleeding-risk” group received post-procedural dalteparin
    - Major bleeding. Post-procedural dalteparin would tend to increase the risk of bleeding compared to no dalteparin bridging (as shown in Douketis NEJM 2015, BRIDGE study <sup>14</sup>). Therefore, we can assume that if post-procedural dalteparin had not been used, the incidence of major bleeding would have been similar or lower (and not higher) than the observed incidence in this study.
    - Regarding the incidence of **thromboembolism**, the use of post-procedural dalteparin has probably led to lower incidence of thromboembolism in this study, compared to our PICO. However, we cannot be confident about the direction of the difference because, on the other hand, dalteparin would cause additional cases of bleeding or minor/suspected bleeding, that would alarm patients and HCPs and lead to further deferral of resumption of anticoagulation, thus causing more thromboembolism (as seen in Kovacs Circulation 2004 <sup>10</sup>, where 6 out of 8 episodes of thromboembolism, 6 occurred in patients who had warfarin deferred or withdrawn because of bleeding).
- Outcomes for patients in the “non-high-bleeding-risk” group (mean FU 13.8 days, range 10-18 days) for
  - Major bleeding: 4/542 = 0.74%, 95% CI 0.20% - 1.87%

- Remark: Major bleeding in the non-high risk bleeding procedure group: 3 wound hematomas and 1 rectus sheath hematoma. Highly unlikely these occurred in those patients undergoing endoscopic procedures.
    - Thromboembolism:  $2/542 = 0.37\%$ , 95% CI 0.04% - 1.32%
      - Remark: Table 6. Only 1 patient with a thromboembolic event had a GI endoscopy. Event occurred 5 days after the procedure. The patient did have pre and post-procedural LMWH
    - Death:  $0/542 = 0\%$ , 95% CI 0% - 0.5% (95% CI calculated with the rule of 3/n for zero events (Govani. AJG 2013; 108:1831))
  - Also, this study was included in the Evidence-to-Decision Framework to provide evidence that early resumption of warfarin is feasible: very low certainty of evidence, given that it was observational study and it was not designed as feasibility study (which has very specific requirements), although some feasibility outcomes were actually reported.
2. **Paik SE 2018**<sup>15</sup> (Paik W.H., Lee S.H., Ahn D.W., Jeong J.B., Kang J.W., Son J.H., Ryu J.K., Kim Y.-T. Optimal time of resuming anticoagulant after endoscopic sphincterotomy in patients at risk for thromboembolism: a retrospective cohort study. Surgical Endoscopy. 32 (9) (pp 3902-3908), 2018)
- **Population:** N = 96 patients on heparin bridging due to interruption of warfarin therapy, who underwent endoscopic sphincterotomy (EST)
  - This ERCP practice may not be generalizable. 72 (75%) had a biliary stent placed, including 40 patients undergoing ERCP for CBD stones. 22 (23%) had a pre-cut. 15 (16%) had treatment of bleeding during ERCP
  - **NOTE:** It is unclear when warfarin was resumed. There is no description of the protocol that was used for warfarin resumption. The fact that the authors note in their introduction that “the consensus of discontinuing warfarin is fundamentally unchanged from 2008 guideline of the British Society of Gastroenterology” and use the 2016 BSG guideline (Veitch Gut 2016;65:374) as citation to support this, implies that they may have aimed to follow the 2016 BSG recommendations (according to which “*warfarin can be resumed on the day of the procedure with the usual dose that night; restart the daily therapeutic dose of LMWH on the day after the procedure*”). However, this represents a very serious uncertainty for this guideline if these results are used to inform the incidence of outcomes for the “intervention” of this PICO, that is, for patients who resume warfarin on the day of the procedure. We will have to make this decision based on an assumption of intention: even if our assumption is correct, the execution could have been different than the intention (i.e., it is unclear if any and how many patients actually resumed warfarin in 1-7 days)
  - Authors’ comparisons
    - intervention: n = 56 patients resumed heparin < 24 h (very early group)
    - comparator 1: n = 23 patients resumed heparin at 24-48 hours (early group)
    - comparator 2: n = 17 resumed heparin > 48 hours (late group)
  - For this PICO:
    - Intervention: 96 patients assumed to have resumed warfarin on the day of the procedure

- Comparator: none
- Therefore, for the needs of this PICO, this study can only be used as a single-arm cohort study (all patients assumed to have resumed warfarin on the day of the procedure)
- **Outcomes:**
  - **Post-EST delayed bleeding** (at 14 days)
    - very early (< 24 h): 3/56 patients (5%) had delayed bleeding; 1/56 patients (2%) had significant delayed bleeding.
    - early (24–48 h): 2/23 patients (9%) had delayed bleeding; 1/23 (4%) had significant delayed bleeding.
    - late (> 48 h): 0/17 patients
    - Overall: 5/96 (5%) had delayed bleeding; 2/96 (2%) had significant delayed bleeding
  - **Thromboembolic events** (at 90 days)
    - 0 thromboembolic events in very early and early group
    - 4/17 patients (24%) had thromboembolic events in late group
    - Overall: 4/96 (4%)
      - Remark: Evaluated at 90 days but reported time from procedure for all events. 3 occurred before 30 days and 1 occurred after 30 days (33 days). None occurred in patients with post-EST bleeding treated during ERCP.
  - **Mortality:** not reported

#### Remarks

- Serious indirectness, because all patients received both pre-procedural and post-procedural heparin (type of heparin, dose and route of administration were not reported). As discussed above in the Overall Remarks regarding Douketis Arch IM 2004, the direction of the effect of postprocedural heparin use on bleeding and VTE cannot be confidently predicted.
- Patients (n=6) with post-EST bleeding before heparin resumption and were excluded

3. **Dunn JHT 2007** <sup>16</sup> (Dunn AS, Spyropoulos AC, Turpie AGG. Bridging therapy in patients on long-term oral anticoagulants who require surgery: the Prospective Peri-operative Enoxaparin Cohort Trial (PROSPECT). J Thromb Haemost 2007 Nov;5(11):2211-8)
  - Single-arm cohort study on 260 patients at 20 sites in North America requiring invasive or surgical procedures, whose treating physician felt that bridging therapy was required.
  - Warfarin was withheld, and once-daily s.c. enoxaparin (1.5 mg/kg) was given peri-operatively.
  - Patients apparently non-consecutive.

- Separate results for patients who had “GI invasive procedures” (n = 46) were extracted. These 46 procedures were included in the category of “invasive procedures” and most likely they represented endoscopic procedures (not clear what type) although it is possible that some of them were non-endoscopic, such as laparoscopic ones. In a separate category, “Minor Surgery”, there were 8 “gastrointestinal”, but these were likely true surgical procedures and not endoscopic ones (this is not certain, as another study (Douketis Arch IM 2004), had classified “bowel polypectomy” as “surgical procedure, and “GI endoscopy ± biopsy” as nonsurgical procedure; however, the results for our PICO would not change substantially)
  - i. Bleeding (during follow up = 28 days after INR reached therapeutic target):  
1/46 (a patient who had “colonoscopy”) = 2%, 95% CI 0% to 13%
  - ii. Thromboembolic events (during follow up = 28 days after INR reached therapeutic target)  
0/46= 0%, 95% CI 0% to 6.5% (95% CI calculated with the rule of 3/n for zero events (Govani. AJG 2013; 108:1831))
  - iii. Death (during follow up = 28 days after INR reached therapeutic target)  
0/46= 0%, 95% CI 0% to 6.5% (95% CI calculated with the rule of 3/n for zero events)
- Note: Among all patients “*the bleeding risk varied markedly by extensiveness of procedure: the incidence of major bleeding for invasive procedures, minor surgery and major surgery was 0.7% (95% CI: 0.02–3.7), 0% (95% CI: 0–5.0), and 20.0% (95% CI: 9.1–35.7), respectively.*”



Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (exposure vs non-exposure is the difference in timing of warfarin resumption between the intervention and the comparator for this PICO)	Prognostic factors (other than exposure of interest) <b>similar</b> among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Paik SE 2018 <sup>1</sup>	Unclear. We assumed that all patients resumed warfarin on the day of the procedure, but this is unclear	For the needs of this PICO, this is a single-arm cohort study (no comparator group that resumed warfarin later)	OK	No comparator eligible for this PICO. Unclear how outcomes were identified, especially after hospital discharge.	No comparator eligible for this PICO.	OK	<p>P: patients who had endoscopic sphincterotomy with heparin bridging after discontinuing warfarin</p> <p><b>DELAYED BLEEDING (14 days):</b></p> <ul style="list-style-type: none"> <li>• 5/96 (5%) had delayed bleeding; 2/96 (2%) had significant delayed bleeding</li> <li>• Also, 6 patients (in addition to the 96) had with post-EST bleeding before heparin resumption and were excluded from the study.</li> <li>• Therefore, the overall bleeding rate was: 11/102 (11%, 95% CI 6% – 19%)</li> </ul> <p><b>THROMBOEMBOLIC EVENTS (90 days)</b></p> <ul style="list-style-type: none"> <li>• 4/96 (4%, 95% CI 1% - 11%)</li> </ul> <p><b>MORTALITY:</b> not reported</p>
Dunn JTH 2007	OK	No comparator eligible for this PICO	OK	No comparator eligible for this PICO	No comparator eligible for this PICO		<p>P: patients who had “GI invasive procedure” with heparin bridging after discontinuing warfarin</p> <p><b>BLEEDING (28 days after INR reached therapeutic target):</b></p> <p>1/46 = 2%, 95% CI 0% to 13%</p> <p><b>THROMBOEMBOLIC EVENTS (28 days after INR reached therapeutic target)</b></p> <p>0/46= 0%, 95% CI 0% to 6.5%</p>

							<b>MORTALITY</b> (28 days after INR reached therapeutic target) 0/46 = 0%, 95% CI 0% to 6.5%
Douketis Arch IM 2004	OK	No comparator eligible for this PICO	OK	No comparator eligible for this PICO	No comparator eligible for this PICO		<p>P: patients who had “non-high-bleeding-risk procedure” with heparin bridging after discontinuing warfarin</p> <p><b>BLEEDING</b> (mean FU 13.8 days, range 10-18): 4/542 = 0.74%, 95% CI 0.20% - 1.87%</p> <p><b>THROMBOEMBOLIC EVENTS</b> (mean FU 13.8 days, range 10-18) 2/542 = 0.37%, 95% CI 0.04% - 1.32%</p> <p><b>MORTALITY</b> (mean FU 13.8 days, range 10-18) 0/542 = 0%, 95% CI 0% - 0.5%</p>
Low risk of bias							
Unclear risk of bias							
High risk of bias							

4565 Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included,  
4566 because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid  
4567 methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of  
4568 interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not  
4569 included, because it is an “indirectness” issue as per GRADE.

4570 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
4571 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias.

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Resumption of warfarin: on the same day of the procedure vs. 1-7 days after the procedure												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	Warfarin resumed on same day	Warfarin resumed on day 1-7	Relative (95% CI)	Absolute (95% CI)	
Bleeding within 30 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
1 cohort study on endoscopic sphincterotomy (Paik 2018 <sup>15</sup> )	Serious <sup>a</sup>	Serious <sup>e</sup>	Serious <sup>b</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		11/112 (11%, 95% CI 6% - 18%)	-	Not estimable	Not estimable	
1 cohort study on “GI invasive procedures” (Dunn 2017 <sup>16</sup> )	Serious <sup>d</sup>		Serious <sup>f</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		1/46 (2%, 95% CI 0% - 13%)	-	Not estimable	Not estimable	
1 cohort study on “non-high-bleeding-risk” procedures (Douketis 2004 <sup>8</sup> )	Serious <sup>d</sup>		Serious <sup>g</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		4/542 (0.74%, 95% CI 0.20% - 1.87%)	-	Not estimable	Not estimable	
Thrombotic events within 30 days (critical outcome)												
1 cohort study on endoscopic sphincterotomy (Paik SE 2018 <sup>15</sup> )	Serious <sup>a</sup>	Serious <sup>e</sup>	Serious <sup>h</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		4/96 (4%, 95% CI 1% - 11%)	-	Not estimable	Not estimable	
1 cohort study on “GI invasive procedures” (Dunn 2017 <sup>16</sup> )	Serious <sup>d</sup>		Serious <sup>i</sup>	Very serious <sup>j</sup>	None	⊕⊕⊕⊕ VERY LOW		0/46 (0%, 95% CI 0% to 6.5%)	-	Not estimable	Not estimable	
1 cohort study on “non-high-bleeding-risk” procedures (Douketis 2004 <sup>8</sup> )	Serious <sup>d</sup>		Serious <sup>i</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		2/542 (0.37%, 95% CI 0.04% - 1.32%)	-	Not estimable	Not estimable	
Mortality within 30 days (important outcome, but not critical for decision making)												
1 cohort study on “GI invasive procedures” (Dunn 2017 <sup>16</sup> )	Serious <sup>d</sup>		Serious <sup>f</sup>	Very serious <sup>j</sup>	None	⊕⊕⊕⊕ VERY LOW		0/46 (0%, 95% CI 0% to 6.5%)	-	Not estimable	Not estimable	

1 cohort study on "non-high- bleeding-risk" procedures (Douketis 2004 <sup>g</sup> )	<b>Serious</b> <sup>d</sup>	Not serious	<b>Serious</b> <sup>g</sup>	<b>Very serious</b> <sup>i</sup>	None	⊕⊕⊕⊕ VERY LOW		0/542 (0%, 95% CI 0% - 0.5%)	-	Not estimable	Not estimable	
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4580 **Footnotes:**

4581 <sup>a</sup> Serious risk of bias. This study was designed as a comparative cohort study but it addressed a research question different than the PICO of this guideline.  
4582 There is no eligible comparator for this PICO, therefore it is included as a single-arm cohort study providing non-comparative data for the "Intervention arm".

4583 <sup>b</sup> Serious indirectness because all patients received both pre-procedural and post-procedural heparin. Also, bleeding was assessed at 14 days. All patients had  
4584 endoscopic sphincterotomy.

4585 <sup>c</sup> Very serious imprecision, even for the event rate in the intervention group, due to small number of events. The comparative efficacy cannot be calculated.

4586 <sup>d</sup> Serious risk of bias. There is no eligible comparator for this PICO, therefore it is included as a single-arm cohort study providing non-comparative data for the  
4587 "Intervention arm".

4588 <sup>e</sup> Serious inconsistency. The 95% CIs of Paik 2018 and Douketis 2004 are discrepant (do not overlap).

4589 <sup>f</sup> Serious indirectness because all patients received both pre-procedural and post-procedural heparin. Also, the "non-high-bleeding-risk" procedure group  
4590 (n=542) consisted of a very diverse procedures (including colonoscopic polypectomy (n=5), GI endoscopy ± biopsy (n=65), cholecystectomy, arthroscopy, etc.)

4591 <sup>g</sup> Serious indirectness because all patients received both pre-procedural and post-procedural heparin. Also, it is unclear what these "GI invasive procedures"  
4592 were.

4593 <sup>h</sup> Serious indirectness because all patients received both pre-procedural and post-procedural heparin. Also, thromboembolism was assessed at 90 days.

4594 <sup>i</sup> Serious indirectness because all patients received both pre-procedural and post-procedural heparin.

4595 <sup>j</sup> Very serious imprecision, even for the event rate in the intervention group, due to zero events. The comparative efficacy cannot be calculated.

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4600 **Evidence to Decision Table**

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4602 16. Timing of warfarin resumption following endoscopy

4603 P: Patient on warfarin who underwent endoscopy

4604 I: Resumption on the same day of the procedure

4605 C: Resumption 1 to 7 days after the procedure

4606 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

4607 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

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	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<b>How substantial are the desirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>● Don't know</li> </ul>	<p>See Evidence Profile Table</p> <p>No comparative data can be calculated. Three single-arm cohort studies provided estimates for the incidence of outcomes with the intervention (same-day resumption of warfarin), but we were not able to estimate the incidence with the comparator (resumption in 1-7 days)</p> <p>Desirable: reduction in thrombosis</p> <p>The <u>desirable</u> anticipated effect with same-day resumption of warfarin (compared to resumption in 1-7 days) cannot be estimated.</p>	
Undesirable Effects	<b>How substantial are the undesirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	<p>Theoretically, earlier resumption of warfarin after the procedure would tend to reduce <b>thromboembolic events (critical outcome)</b> and increase <b>bleeding (critical outcome)</b> compared to delayed resumption of warfarin. Whoever, we did not identify within-study comparative evidence to quantify the magnitude of the effect.</p> <p>It is not possible to estimate the direction (let alone the magnitude) of the effect on <b>mortality</b></p>	
Certainty of evidence	<b>What is the overall certainty of the evidence of effects?</b> <ul style="list-style-type: none"> <li>● Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	

Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>● <b>Possibly important uncertainty or variability</b></li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	See Box on Patient Values and Preferences, at the beginning of PICO 1.	
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● <b>Don't know</b></li> </ul>		
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>● <b>Negligible costs and savings</b></li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>● <b>High</b></li> <li>○ No included studies</li> </ul>		

Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>		
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Feasibility	<p><b>Is the intervention feasible to implement?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

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## Conclusions

4612 16. Timing of warfarin resumption following endoscopy

4613 P: Patient on warfarin who underwent endoscopy

4614 I: Resumption on the same day of the procedure

4615 C: Resumption 1 to 7 days after the procedure

4616 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

4617 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

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Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Neither for nor against 6/6 votes: 100%	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	●	○	○
Recommendation	In patients who are undergoing elective endoscopic GI procedures whose warfarin was interrupted, we cannot make a recommendation whether to resume same day vs. 1-7 days after the procedure.				
Justification					
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

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**References for PICO 16**

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## 17. Timing of DOAC resumption following endoscopy

P: Patient on an anticoagulant (DOAC)

I: DOAC Resumption on the same day of the procedure

C: DOAC Resumption 1 to 7 days after the procedure

O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

### Overall Comments

Due to the paucity of primary studies through our literature search, we investigated what evidence was cited in **previous guidelines** as justification for their recommendations on this question. None of the previous guidelines had included any clinical studies that assessed the timing of DOAC resumption after a procedure:

- **Veitch\_ BSG/ESGE CPG\_ Endo 2016**<sup>1</sup>. This guideline did not issue a formal (“numbered and bolded-text”) recommendation for the timing of DOAC resumption after endoscopy. However, an “informal” recommendation was included in the text. See below.
  - “It is of the utmost importance that clinicians are aware that unlike reintroduction of warfarin, which results in delayed anticoagulation for several days, a therapeutic intensity of anticoagulation is restored within 3 hours of taking a therapeutic dose of a DOAC. **Because of the high risk of bleeding associated with therapeutic intensity anticoagulation after an invasive procedure, we suggest a delay in reintroducing a DOAC after a high-risk procedure.** This delay will depend on the risk of hemorrhage specific to the procedure and will usually be 24–48 hours. For procedures with a significant risk of delayed haemorrhage such as EMR or ESD, a longer period of discontinuation may be considered in the context that DOAC patients are in a relatively low thrombotic risk category”.
  - No study was cited to justify this informal recommendation. Further up in this guideline article, a narrative review was cited with regards to the pharmacokinetics and pharmacodynamics of dabigatran and rivaroxaban (Baglin 2013<sup>2</sup>). The statement that “high risk of bleeding [is] associated with therapeutic intensity anticoagulation after an invasive procedure” was also mentioned further up in the text of this guideline, but no reference was cited to support this.
- **Acosta ASGE CPG 2016**<sup>3</sup>. This guideline issued a conditional recommendation on the timing of DOAC resumption with Low quality of evidence. Low quality evidence requires comparative cohort or case control studies, without indirectness, without study limitations,

without imprecision, without inconsistency – but as noted in the text, “there are no data to inform optimal timing of resumption of NOACs after endoscopic procedures”.

- We **suggest** that the reinitiation of NOACs after high-risk endoscopic procedures be delayed until adequate hemostasis is ensured, given their rapid onset of action and lack of reversal agents. If therapeutic doses of NOACs cannot be restarted within 12 to 24 hours after a high-risk endoscopic procedure, thromboprophylaxis (ie, UFH bridge) should be considered to decrease risk of thromboembolism, given the short half-life of the NOAC agent, in those with a high risk for thromboembolism. ⊕⊕⊕⊕
- At the beginning of the section on re-initiation of antithrombotic agents after elective endoscopy, it is stated that “there is consensus that antithrombotic therapy should be resumed upon completion of the procedure”, but the two cited papers (Becker RC, Scheiman J, Dauerman HL, et al. Management of platelet directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures. Am J Gastroenterol 2009;104:2903-17; Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. Circulation 2008;118:1894-909.) did not address DOACs.
- Two other studies were cited in the text:
  - Weitz JI, Quinlan DJ, Eikelboom JW. Periprocedural management and approach to bleeding in patients taking dabigatran. Circulation 2012;126:2428-32 <sup>4</sup>. This paper is not a formal guideline and did not include a systematic review. The authors noted that “*the timing for reinitiating dabigatran after surgery depends on the bleeding risk. Dabigatran should be restarted when hemostasis is secure and the risk of bleeding is deemed to be acceptably low. [...] If therapeutic doses of dabigatran cannot be restarted within 24 hours of surgery, thromboprophylaxis should be considered according to usual practice*”. It was implied that this recommendation was based on an included plot of the expected pharmacodynamic effect of dabigatran over time: [see Figure 1 in the paper](#).
  - The wording of the ASGE recommendation (“given the rapid onset of action”) implies that similar pharmacokinetic and pharmacodynamic data were the rationale for the timing of DOAC resumption
  - Dzik WS. Reversal of drug-induced anticoagulation: old solutions and new problems. Transfusion 2012;52(Suppl 1):25S-55S. 55. This paper deals with reversal of anticoagulation. It does not contain any data or discussion relevant to resumption after discontinuation for procedures.
- **Chan APAGE/APSDE CPG Gut 2018** <sup>5</sup>. This guideline noted that “No studies are available to guide the optimal time for discontinuation or resumption of DOACs for endoscopic procedures”, but it issued a strong recommendation based on low quality of evidence (of note, low quality evidence requires comparative cohort or case control studies, without indirectness, without study limitations, without imprecision, without inconsistency):
  - “37. We recommend resuming DOACs after adequate haemostasis has been achieved. (A+ 45%, A 55%; strong recommendation; low-quality evidence)”

- Specific timelines (as days or hours post-procedurally) were not given. The definition of adequate hemostasis was not provided.

- **Raval\_ AHA CPG\_ Circulation 2017** <sup>6</sup>. This guideline did not provide guidance on the timing of DOAC resumption following procedures, with the exception of a statement that after cardiac surgery DOACs should be “restarted after clinical hemostasis has been established”. Also, there was discussion on restarting DOACs after GI bleeding, however, there was no guidance on the timing of DOAC resumption: *“Reinitiating NOAC therapy after gastrointestinal bleeding should take into account the patient’s underlying risk of bleeding and thrombosis risk. In a retrospective study of >4600 patients with NVAF who suffered gastrointestinal bleeding on anticoagulation (primarily warfarin), resumption of a single anticoagulant was associated with the lowest risk of mortality and thromboembolism compared with nonresumption of antithrombotic treatment. The risk of recurrent gastrointestinal bleeding was also low in the anticoagulated patients. Patients on NOACs comprised a very small subset of the entire cohort; therefore, it remains uncertain whether NOAC resumption after gastrointestinal bleeding would be similarly linked to these favorable outcomes (Staerk L, Lip GY, Olesen JB, et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. BMJ. 2015;351:h5876).”*
- **Witt\_ ASH guidelines\_ Blood Adv 2017** <sup>7</sup>. This guideline addressed only two PICOs regarding “Invasive procedure management”, and the timing of DOAC resumption was not included among them.
- **Narouze ASRA RAPM 2018** <sup>8</sup>. This guideline dealt with interventional pain procedures. They stated “we could not provide strength and grading of these recommendations because there are not enough well-designed large studies concerning interventional pain procedures to support such grading”
  - “We recommend a 24-hour interval after interventional pain procedures before resumption of rivaroxaban. If the risk of VTE is very high, half the usual dose may be given 12 hours after the pain intervention. The decision regarding timing of drug resumption should be shared with the patient's treating physician(s).”
  - The supporting evidence was indirect evidence from a study suggesting that clots become stable at 8 hours in neuraxial anesthesia and studies on the time window of efficacy of thrombolytics: *“Although thrombolytics are still effective when given within 6 hours of a cerebral embolic clot, thrombolytics are more effective when given within 3 hours after the onset of stroke. These studies imply that anticoagulants (not thrombolytics) may have a hard time lysing a clot if given after 6 hours and most probably will not lyse a clot if given 24 to 48 hours after a neuraxial injection”*
  - No other primary studies were cited. Three opinion papers (not formal guidelines) were cited, that recommended longer intervals: *“Liew and Douketis (Intern Emerg Med. 2013;8: 477–484) recommended a minimum of 24 hours in patients with low bleeding risk and 48 hours in those with a high bleeding risk, before resuming dabigatran, rivaroxaban, or apixaban. Baron et al (N Engl J Med. 2013; 368: 2113–2124) recommended 48 hours, while Connolly and Spyropoulos (J Thromb Thrombolysis 2013; 36:*

212–222) recommended 24 hours but at half the usual dose.”

- **Kaye ASIPP GPG PP 2019**<sup>9</sup>. This guideline dealt with interventional pain procedures. They recommended resumption of DOACs in 24 hours, but did not provide a justification for the timing.
- **Lip CHEST CPG\_ Chest 2018**<sup>10</sup>. This guideline dealt with peri-procedural management of DOACs but did not address the question of timing of DOAC resumption.

Cohort studies with the comparator cohort needed for this PICO

1. **Radaelli Gut 2019**<sup>11</sup> (Radaelli et al. Periendoscopic management of direct oral anticoagulants: A prospective cohort study. Gut. 68 (6) (pp 969-976), 2019)
  - Prospective cohort study. 13 open-access GI endoscopy centers in Italy, over 15 months
  - Outpatients on DOACs scheduled for elective GI endoscopy. Excluded urgent endoscopy (i.e., GIB, cholangitis, acute obstruction). No prespecified protocol for periprocedural management of DOAC. On day of endoscopy, pt recruited in project. After procedure pt contact by phone (or visit for inpts still in hospital) 1 wk and 1 mo later. Double-checked by searching hospital records.
  - Primary outcome was incidence of major and clinically relevant non-major bleeding during or within 30 days after endoscopy. Secondary: thromboembolic arterial events and venous events. Intraprocedural only if required intervention.
  - 529 patients. 327 had low bleeding risk procedure; 202 had high risk procedure (18/202 had LMWH bridging)
  - The study was not powered to compare outcomes in sub-cohorts according to whether the patients were managed according to BSG/ESGE guidelines or not. In fact, the pre-registered protocol includes as secondary outcome this comparison of VTE events but there was not a priori intent to compare bleeding among these cohorts
  - Resumption “as recommended” (by the 2016 BSG/ESGE guidelines) was defined as: **DOAC resumption is about 48 hours after a high-risk procedure (i.e., 2 days after endoscopy), except for procedures with a significant risk of delayed haemorrhage such as large endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), for which a longer period of discontinuation (72 hours; i.e., 3 days after endoscopy) may be considered at the discretion of the endoscopist.**
  - DOAC resumption for a low risk procedure was the same day

- Supplementary tables provide the specifics for the 17 major bleeding and 2 thromboembolic cases (e.g, timing of event, timing of resumption) but don't provide that level of detail on all of the other patients.
- Multiple typos and mistakes in the numerical results. Table 5 in the paper, which summarizes the results relevant to this PICO has mistakes in four out of six results, as compared to the detailed supplementary tables:
  - First row, third column reads 1/139 (0.7). Should be corrected to 0/0
  - First row, forth column reads "-". Should be corrected to 1/139
  - Third row, second column reads 9/136 (6.6). Should be corrected to 7/136 (5.1)
  - Third row, third column reads 4/52 (7.7). Should be corrected to 6/52 (11.5), but 3 bleeds in patients on LMWH bridging
- Detailed statistics are shown in the Results column of the Risk of Bias table below.
- We could not calculate results for the comparisons required for this PICO (same day vs 1-7 days)
- Furthermore, results for the 184 (out of 202) patients with high-risk procedures who did not have post-procedural LMWH bridging were not reported separately. The detailed suppl tables show that among the 6 delayed major bleeds in patients with high-risk procedures who resumed DOACs "later", 3 patients had been on LMWH bridging. The problem is that we do not know how many of the 52 patients in the denominator had LMWH bridging, so we cannot calculate "clean" results for patients who did not have LMWH bridging (or clean results for those on LMWH according to timing of resumption). Obviously, LMWH bridging is an important confounder that can affect the results substantially.

2. **Douketis JAMA IM 2019** <sup>12</sup>: the PAUSE study (Douketis et al. Perioperative Management of Patients with Atrial Fibrillation Receiving a Direct Oral Anticoagulant. JAMA IM 2019)

- Prospective, multicenter cohort study without comparator arm
  - This is one of very few studies that provided rationale for not having comparator. In fact, the design and rationale were published *a priory* as a separate paper (Douketis Thromb Haemost 2017 <sup>13</sup>).
- Included n= 3007 patients with AF, long-term users of apixaban, dabigatran, or rivaroxaban who were scheduled for an elective surgery or procedure and followed a well-defined DOAC therapy interruption protocol.
  - 1007 patients had a high-bleeding-risk procedure.
  - 2000 patients had a low-bleeding-risk procedure. Of these, 627 (31.4%) had GI procedures. No separate results for GI procedures in the original publication
    - The GI procedure group was highly diverse: it included procedures such as VCE, EGD, colonoscopy, flex sig, ERCP, push enteroscopy and Barrett's ablation.
    - Unclear if any of these patients underwent snare polypectomy, sphincterotomy or EMR

- Consecutive patients were enrolled, and a flow chart of patient flow was published (83% of the approached patients were recruited), but the recruitment per center varied substantially, ranging from 853 patients (i.e., convincingly consecutive recruitment) to 4, 6, 20 and 23 patients in four other centers (i.e., likely non-consecutive recruitment, given that the enrolment period was 4 years)
- DOAC resumption: after the operation, DOAC regimens were resumed 1 day (approximately 24 hours) after a low–bleeding-risk procedure and 2 to 3 days (48-72 hours) after a high–bleeding-risk procedure, provided that hemostasis was achieved.
- Note: Patients at high risk for venous thromboembolism could receive a prophylactic dose of heparin after the operation until DOAC therapy resumption.
- The full perioperative DOAC management protocol is shown in the (only) Figure in the paper.
- Note: this protocol is different than the intervention of this PICO (DOAC resumption on day 0). It falls within the range of timing of the comparator of this PICO (DOAC resumption on day 1 to day 7)
- The authors mentioned two previous clinical studies that informed the design of the perioperative protocol that was used in this study:
  - *“The only previous studies suggested a high post-procedural bleeding risk if therapeutic-dose heparins are uniformly re-initiated approximately 24 hours after a procedure irrespective of procedural bleeding risk”*. Reference: Dunn et al. Bridging therapy in patients on long-term oral anticoagulants who require surgery: the Prospective Peri-operative Enoxaparin Cohort Trial (PROSPECT). J Thromb Haemost 2007;5(11):2211–2218)
  - Also: Schulman S, Carrier M, Lee AY, et al; Periop Dabigatran Study Group. Perioperative management of dabigatran: a prospective cohort study. Circulation. 2015;132(3):167-173. (see Excluded studies document)
  - Also, the authors explained that in order to design their perioperative protocol they also utilized indirect evidence from DOAC pharmacokinetic properties, and they had “2 broad aims: (1) to have the shortest duration of DOAC therapy interruption before and after the procedure so as to minimize the risks for bleeding and thromboembolism, and (2) to have a simple interruption and resumption protocol for each DOAC that would be easy to use by clinicians and easily understood by patients”.
- Outcomes were well defined and described:
  - Major postoperative bleeding (at 30 days). The low-bleeding-risk procedures (the category that included the GI procedures) is the cohort that fits best the population of this PICO: 20/2000 = 1.0%, 95% CI 0.63% to 1.57% (calculated from table 4 in the paper)
  - Thrombotic events (at 30 days). Total (arterial and venous) for the whole cohort (separate results could not be extracted for the low-bleeding-risk group): 21/3007 = 0.70%, 95% CI 0.45% to 1.09%

- 4841 • Mortality (at 30 days). Total, for the whole cohort (separate results could not be extracted for the low-bleeding-risk  
 4842 group): 9/3007 = 0.30%, 95% CI 0.15% to 0.59%.
- 4843 • **Feasibility outcomes:** adherence to the resumption protocol ranged from 87.5% to 99.6% in various sub-cohorts. For  
 4844 the low-bleeding risk group (that included the GI procedures) adherence was 1811/2000 = 90.6%
- 4845 • **Separate results on GI procedures (Jim Douketis, Alan Barkun; personal communication):**
- 4846 • Only patients who had GI endoscopic procedures were included
- 4847 • Results provided in the last column of the Risk of Bias table

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Risk of bias assessment of Cohort studies							
Study	Valid methods to ascertain exposure (for this PICO, exposure vs non-exposure is the difference in timing of DOAC resumption between the intervention and the comparator)	Prognostic factors (other than exposure of interest) <b>similar</b> among cohorts – or cohorts were adjusted adequately for confounders	Demonstration that outcome of interest was not present at the start of the study	Outcome detection methods valid and similar among cohorts	Follow up complete and similar among cohorts	Free of other bias	Results/Comments
Radaelli 2019 <sup>11</sup>	OK	No adjustment for confounders. The cohorts were not powered to show statistically significant differences in prognostic factors between cohorts; LMWH bridging was an important prognostic factor and confounder (because patients on LMWH bridging were	OK	OK	OK	OK	<p>P: patients who had endoscopic GI procedures after interrupting NOACs <b>[corrected results]</b></p> <p><b><u>DELAYED MAJOR BLEEDING (1 month):</u></b></p> <p><b>Low-risk procedures</b></p> <ul style="list-style-type: none"> <li>• DOAC resumption “as recommended”: 1/188 (0.5%)</li> <li>• DOAC resumption “later”: 0/0</li> <li>• DOAC resumption “earlier”: 1/139 (0.7%)</li> </ul> <p><b>High-risk procedures</b></p> <ul style="list-style-type: none"> <li>• DOAC resumption “as recommended”: 7/136 (5.1%)</li> <li>• DOAC resumption “later”: 6/52 (11.5%)</li> <li>• DOAC resumption “earlier”: 2/14 (14.3%)</li> </ul>



		more likely to have delayed NOAC resumption); the proportion of patients on LMWH bridging according to the timing of NOAC resumption was not reported (and no adjustment was performed for LMWH bridging)					<p>- as recommended vs later: RR 0.44, 95% CI 0.16 - 1.51  - as recommended vs earlier: RR 0.36, 95% CI 0.08 - 1.57</p> <p><b>All procedures</b></p> <ul style="list-style-type: none"> <li>• DOAC resumption "as recommended": 8/324 (2.5%)</li> <li>• DOAC resumption "later": 6/52 (11.5%)</li> <li>• DOAC resumption "earlier": 3/153 (2.0%)</li> </ul> <p>- as recommended vs later: <b>RR 0.21, 95% CI 0.08 - 0.59</b>  - as recommended vs earlier: RR 1.24, 95% CI 0.33 - 4.62</p> <p>• <b>DOAC resumption on same day: not reported</b>  • <b>DOAC resumption on day 1-7: not reported</b></p> <ul style="list-style-type: none"> <li>• DOAC resumption "as recommended" or "earlier": 11/477 (2.3%)</li> <li>• DOAC resumption "later": 6/52 (11.5%)</li> </ul> <p>- as recommended/earlier vs later: <b>RR 0.20, 95% CI 0.08 - 0.52</b></p> <p><b>THROMBOEMBOLIC EVENTS (1 month)</b></p> <p><b>Low-risk procedures</b></p> <ul style="list-style-type: none"> <li>• DOAC resumption "as recommended": 1/188 (0.5%)</li> <li>• DOAC resumption "later": 0/0</li> <li>• DOAC resumption "earlier": 0/139</li> </ul> <p><b>High-risk procedures</b></p> <ul style="list-style-type: none"> <li>• DOAC resumption "as recommended": 0/136</li> <li>• DOAC resumption "later": 1/52 (1.9%)</li> <li>• DOAC resumption "earlier": 0/14</li> </ul> <p>- as recommended vs later: RR 0.44, 95% CI 0.16 - 1.51  - as recommended vs earlier: RR 0.36, 95% CI 0.08 - 1.57</p> <p><b>All procedures</b></p> <ul style="list-style-type: none"> <li>• DOAC resumption "as recommended": 1/324 (0.03%)</li> <li>• DOAC resumption "later": 1/52 (1.9%)</li> <li>• DOAC resumption "earlier": 0/153</li> </ul> <p>- as recommended vs later: RR 0.16, <b>95% CI 0.01 - 2.52</b>  - as recommended vs earlier: RR 1.42, 95% CI 0.06 - 34.70</p> <p>• <b>DOAC resumption on same day: not reported</b></p>
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						<ul style="list-style-type: none"> <li>• <b>DOAC resumption on day 1-7: not reported</b></li> <li>• DOAC resumption “as recommended” or “earlier”: 1/477 (0.2%)</li> <li>• DOAC resumption “later”: 1/52 (1.9%)</li> <li>- as recommended/earlier vs later: RR 0.11, 95% CI 0.007 - 1.57</li> </ul> <p><b>MORTALITY</b> (1 month) No deaths occurred</p>
Douketis 2019 (PAUSE study) <sup>12</sup>	OK	No comparator cohort with a different timing of DOAC resumption	OK	Outcome detection methods were valid, but there was no comparator cohort of interest for this PICO	Follow up was complete and similar among cohorts, but there was no comparator cohort of interest for this PICO	<p>P: patients who had procedures (including endoscopic GI procedures) after interrupting NOACs</p> <p><b>DELAYED MAJOR BLEEDING (1 month):</b>  <b>Low-risk procedures</b> (the category that included the GI procedures)</p> <ul style="list-style-type: none"> <li>• DOAC resumption in 1 day: 20/2000 = 1.0%, 95% CI 0.63% to 1.57%</li> </ul> <p><b>Extra analyses: GI procedures only</b>  14/554 = 2.5%, 95% CI 1.4% to 4.2%  Of note 5/14 of the bleeding events were major bleeds</p> <p><b>THROMBOEMBOLIC EVENTS (1 month)</b>  <b>All procedures</b></p> <ul style="list-style-type: none"> <li>• DOAC resumption in 1, 2 or 3 days: 21/3007 = 0.70%, 95% CI 0.45% to 1.09%</li> </ul> <p><b>Extra analyses: GI procedures only</b>  4/552 = 0.7%, 95% CI 0.3% to 1.8%</p> <p><b>MORTALITY (1 month)</b>  <b>All procedures</b></p> <ul style="list-style-type: none"> <li>• DOAC resumption in 1, 2 or 3 days: 9/3007 = 0.30%, 95% CI 0.15% to 0.59%</li> </ul> <p><b>Extra analyses: GI procedures only</b>  3/552 = 0.5%, 95% CI 0.2% to 1.6%</p>
Low risk of bias						
Unclear risk of bias						
High risk of bias						

4850 Modified from the Newcastle-Ottawa Scale. For the purpose of GRADE assessments, the first domain of NOS (representativeness of the exposed cohort) was not included,  
 4851 because it relates to “indirectness” which is separate from risk of bias as per GRADE. The second NOS domain (selection of the non-exposed cohort) was replaced with “valid  
 4852 methods to ascertain exposure”. The NOS domain “Comparability of cohorts on the basis of design or analysis” was renamed “Prognostic factors (other than exposure of  
 4853 interest) similar among cohorts – or cohorts were adjusted adequately for confounders”. The NOS domain “Was Follow-Up Long Enough for Outcomes to Occur” was not  
 4854 included, because it is an “indirectness” issue as per GRADE.

4855 Note: the overall risk of bias for a study (for a specific outcome) is determined by the worse risk of bias assessment, even in one domain, i.e., if one domain has unclear risk of  
 4856 bias, the study has unclear risk of bias; if one domain has high risk of bias, the study has high risk of bias.

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4859 **Evidence profile, PICO 17**

Resumption of DOAC: on the same day of the procedure vs. 1-7 days after the procedure												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	DOAC resumed on same day	DOAC resumed on day 1-7	Relative (95% CI)	Absolute (95% CI)	
Bleeding within 30 days (critical outcome)							⊕⊕⊕⊕ VERY LOW					
1 cohort study on GI endoscopic procedures (Radaelli 2019 <sup>11</sup> )	Serious <sup>a</sup>	Not applicable	Very serious <sup>b</sup>	Very serious <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		DOAC resumed on day 0, 1, 2, or 3  11/477 (2.3%)	DOAC resumed on day 3 or later  6/52 (11.5%)	RR 0.20 (0.08- 0.52)	Risk with DOAC resumed on day 3 or later: 115 events per 1,000. With DOAC resumed on day 0, 1, 2, or 3: 92 less per 1,000 (from 106 less, to 55 less)	
1 single-arm cohort study on GI endoscopic and non-GI	Serious <sup>d</sup>	Not applicable	Serious <sup>e</sup>	Serious <sup>f</sup>	None	⊕⊕⊕⊕ VERY LOW			DOAC resumed on day 1	-	-	

procedures (Douketis 2019 <sup>12</sup> )								20/2000 (1.0%, 95% CI 0.63% - 1.57%)			
<b>ALTERNATIVE LINE OF EVIDENCE</b> 1 single-arm cohort study on GI endoscopic procedures (post hoc analysis from Douketis 2019 <sup>12</sup> )	<b>Serious</b> <sup>d</sup>	Not applicable	<b>Serious</b> <sup>e</sup>	<b>Serious</b> <sup>f</sup>	None	⊕⊕⊕⊕ <b>VERY LOW</b>		14/554 (2.5%, 95% CI 1.4% - 4.2%)	-	-	
<b>Thrombotic events</b> within 30 days (critical outcome)											
1 cohort study on GI endoscopic procedures (Radaelli 2019 <sup>11</sup> )	<b>Serious</b> <sup>a</sup>	Not applicable	<b>Very serious</b> <sup>b</sup>	<b>Very serious</b> <sup>c</sup>	None	⊕⊕⊕⊕ <b>VERY LOW</b>		DOAC resumed on day 0, 1, 2, or 3  1/477 ( <b>0.2%</b> )	DOAC resumed on day 3 or later  1/52 ( <b>1.9%</b> )	RR 0.11 (0.01- 1.57)	Risk with <b>DOAC resumed on day 3 or later</b> : 19 events per 1,000. With <b>DOAC resumed on day 0, 1, 2, or 3</b> : 17 less per 1,000 (from 19 less, to 11 more)
1 single-arm cohort study on GI endoscopic and non-GI procedures (Douketis 2019 <sup>12</sup> )	<b>Serious</b> <sup>d</sup>	Not applicable	<b>Serious</b> <sup>e</sup>	<b>Serious</b> <sup>f</sup>	None	⊕⊕⊕⊕ <b>VERY LOW</b>		-	DOAC resumed on day 1, 2 or 3  21/3007 (0.70%, 95% CI 0.45% - 1.09%)	-	-
<b>ALTERNATIVE LINE OF EVIDENCE</b> 1 single-arm cohort study on GI endoscopic procedures (post hoc analysis from Douketis 2019 <sup>12</sup> )	<b>Serious</b> <sup>d</sup>	Not applicable	<b>Serious</b> <sup>e</sup>	<b>Serious</b> <sup>f</sup>	None	⊕⊕⊕⊕ <b>VERY LOW</b>		-	4/552 (0.7%, 95% CI 0.3% - 1.8%)	-	-

<b>Mortality</b> within 30 days (important outcome, but not critical for decision making)												
1 cohort study on GI endoscopic procedures (Radaelli 2019 <sup>11</sup> )	<b>Serious</b> <sup>a</sup>	Not applicable	<b>Very serious</b> <sup>b</sup>	<b>Very serious</b> <sup>c</sup>	None	⊕⊕⊕⊕ VERY LOW		DOAC resumed on day 0, 1, 2, or 3  0/477 (0%)	DOAC resumed on day 3 or later  0/52 (0%)	RR not meaningful	Not calculable	
1 single-arm cohort study on GI endoscopic and non-GI procedures (Douketis 2019 <sup>12</sup> )	<b>Serious</b> <sup>d</sup>	Not applicable	<b>Serious</b> <sup>e</sup>	<b>Serious</b> <sup>f</sup>	None	⊕⊕⊕⊕ VERY LOW		-	DOAC resumed on day 1, 2 or 3  9/3007 (0.30%, 95% CI 0.15% - 0.59%)	-	-	
<b>ALTERNATIVE LINE OF EVIDENCE</b> 1 single-arm cohort study on GI endoscopic procedures (post hoc analysis from Douketis 2019 <sup>12</sup> )	<b>Serious</b> <sup>d</sup>	Not applicable	<b>Serious</b> <sup>e</sup>	<b>Serious</b> <sup>f</sup>	None	⊕⊕⊕⊕ VERY LOW		-	3/552 (0.5%, 95% CI 0.2% - 1.6%)	-	-	

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4861 **Footnotes:**

4862 <sup>a</sup> Serious risk of bias mainly because prognostic factors (other than exposure of interest) were not proven to be similar among cohorts, and cohorts were not  
4863 adjusted for confounders.

4864 <sup>b</sup> Very serious indirectness because the intervention and comparator are different from the ones required for this PICO. Also, some of the patients (18/202) in  
4865 the high-risk procedure group had LMWH bridging after the procedure.

4866 <sup>c</sup> Very serious imprecision, due to small number of events.

4867 <sup>d</sup> Serious risk of bias, due to lack of eligible comparator cohort arm

4868 <sup>e</sup> Serious indirectness because patients at high risk for venous thromboembolism could receive a prophylactic dose of heparin after the operation until DOAC  
 4869 therapy resumption (16% of the total population received such prophylactic heparin)

4870 <sup>f</sup> Serious imprecision, due to small number of events.

4871 <sup>g</sup> Very serious imprecision, due to zero events with a relatively small sample size.

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## 4876 Evidence to Decision Table

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4878 17. Timing of DOAC resumption following endoscopy

4879 P: Patient on DOAC who underwent endoscopy

4880 I: Resumption on the same day of the procedure

4881 C: Resumption 1 to 7 days after the procedure

4882 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis,  
 4883 pulmonary embolus)

4884 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

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	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<b>How substantial are the desirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	See Evidence Profile Table  We did not identify within-study comparisons of the intervention proposed in this recommendation (i.e., DOAC resumption on Day 0) with more delayed resumption. No comparative data relevant to this PICO can be calculated. One comparative cohort study (Radaelli 2019) assessed interventions that are different (both were more delayed) than the comparison required for this PICO.	
Undesirable Effects	<b>How substantial are the undesirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> </ul>	One additional single-arm cohort study (Douketis 2019) provided data on the event rates for DOAC resumption slightly later than the intervention required for this PICO (very low certainty evidence showing low rates of major bleeding and thrombotic events) and also provided sufficient data on the feasibility of that protocol	

	<ul style="list-style-type: none"> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Certainty of evidence	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	
Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	See Box on Patient Values and Preferences, at the beginning of PICO 1.	
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		

Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		
Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ No included studies</li> </ul>		
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>○ Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Feasibility	<p><b>Is the intervention feasible to implement?</b></p>		



<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes  <input type="radio"/> Varies <input type="radio"/> Don't know		
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### **Conclusions**

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17. Timing of DOAC resumption following endoscopy

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P: Patient on DOAC who underwent endoscopy

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I: Resumption on the same day of the procedure

4891

C: Resumption 1 to 7 days after the procedure

4892

O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial

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infarction, deep vein thrombosis, pulmonary embolus)

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IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

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Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Neither for nor against 6/6 votes: 100%	Conditional recommendation for the intervention	Strong recommendation for the intervention
	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Recommendation</b>	In patients who are undergoing elective endoscopic GI procedures whose DOAC was interrupted, we cannot make a recommendation whether to resume DOAC on the same day of the procedure vs. 1-7 days after the procedure				
<b>Justification</b>					
<b>Subgroup considerations</b>					
<b>Implementation considerations</b>					
<b>Monitoring and evaluation</b>					

Research priorities	
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## References for PICO 17

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4928 18. Timing of thienopyridine resumption following endoscopy

4929 **18. Timing of thienopyridine resumption following endoscopy**

4930

4931 P: Patient on thienopyridine agents

4932 I: Resumption on the same day of the procedure

4933 C: Resumption 1 to 7 days after the procedure

4934 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep  
4935 vein thrombosis, pulmonary embolus)

4936 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

4937

4938 **OVERALL COMMENTS**

4939 **No relevant studies for PICO 18 (on GI procedures) were identified by our literature search.** It is possible that there are some relevant  
4940 observational data provided as secondary results within the main text, tables or supplementary material in some observational study reports

4941 that have not mentioned the relevant terms in the title/abstract/keywords and therefor have been missed by our literature search. However, to  
4942 systematically identify such papers would require an investment of several thousand human-hours of work in order to search the full text, tables  
4943 and appendixes of thousands of papers; such investment would not be worthy, given that such secondary results are unlikely to be adjusted or  
4944 matched comparative results.

4945 We assessed previous guidelines for evidence that was used to support their recommendations, but no guideline has cited any relevant studies.

4946 • **Bhatt ACCF/ACG/AHA expert consensus\_ AJG 2008** <sup>1</sup>

4947 ○ This guideline did not address this question (timing of thienopyridine resumption following endoscopy) and did not include any  
4948 relevant studies

4949 • **Levine 2016 ACC/AHA Focused Update\_ JACC 2016** <sup>2</sup>

4950 ○ This guideline addressed this question, and issued a “Class I (strong recommendation)” based on level of evidence C-EO (expert  
4951 consensus based on clinical experience): *“In patients treated with DAPT after coronary stent implantation who must undergo  
4952 surgical procedures that mandate the discontinuation of P2Y12 inhibitor therapy, it is recommended that aspirin be continued if  
4953 possible and the P2Y12 platelet receptor inhibitor be restarted as soon as possible after surgery.”*

4954 ○ No studies relevant to the timing of the resumption of the P2Y12 platelet receptor inhibitor were cited in the main publication or  
4955 in the online data supplement that listed the evidence supporting these recommendations

4956 • **Chan APAGE/APSDE CPG Gut 2018** <sup>3</sup>

4957 ○ In this guideline it was stated that “there are no data on the optimal timing of resuming antiplatelet drugs after elective  
4958 endoscopic procedures” and, as such, no relevant studies were cited. Still, two strong recommendations were issued on the  
4959 timing of resumption of antiplatelet drugs, and the quality of evidence described as low quality evidence (whereas low quality  
4960 evidence would require comparative cohort or case control studies, without indirectness, without study limitations, without  
4961 imprecision, without inconsistency)

4962 ■ High-risk/ultra-high risk procedures, patients on single antiplatelet agent: “We recommend resuming P2Y12 receptor  
4963 inhibitor once adequate haemostasis has been achieved (strong recommendation; low-quality evidence)”

4964 ■ High-risk/ultra-high risk procedures, patients on dual antiplatelet agent (aspirin continued): “we recommend resuming  
4965 P2Y12 receptor inhibitor once adequate haemostasis has been achieved (strong recommendation; low-quality  
4966 evidence)”

4967 • **Acosta ASGE CPG 2016** <sup>4</sup>

4968 ○ This guideline stated: “Cardiac ASA should not be discontinued in most cases. Other APAs should be resumed once hemostasis  
4969 has been achieved”. The reader is directed to a table reprinted from Becker AJG 2009 <sup>5</sup> (this was a paper that included narrative  
4970 review and “informal recommendations procedures”). In the table it reads “Resume thienopyridine and ASA drug therapy after

the procedure once hemostasis is achieved. A loading dose of the former should be considered among patients at risk for thrombosis.”

- Becker et al <sup>5</sup> did not provide any specific papers to support the timing of resumption of thienopyridines (there was a discussion of the pharmacodynamics of discontinuation of thienopyridines but there was no discussion on the pharmacodynamics of resumption of thienopyridines)

- **Veitch\_ BSG/ESGE CPG\_ Endo 2016 <sup>6</sup>**

- This guideline issued a recommendation on the timing of resumption: “Post endoscopic procedure: If antiplatelet or anticoagulant therapy is discontinued, then we recommend this should be resumed up to 48 hours after the procedure depending on the perceived bleeding and thrombotic risks (moderate quality evidence, strong recommendation)”

- However, no studies were cited to support the timing of resumption of antiplatelets

## Evidence profile, PICO 18

Resumption of thienopyridine: on the same day of the procedure vs. 1-7 days after the procedure												
Certainty Assessment								Summary of Findings				Comments
								Events / participants		Effect		
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of Evidence	Overall certainty of evidence	thienopyridine resumed on same day	thienopyridine resumed on day 1-7	Relative (95% CI)	Absolute (95% CI)	
Bleeding within 30 days (critical outcome)							-					
No studies	-	-	-	-	-	-		-	-	-	-	
Thrombotic events within 30 days (critical outcome)												
No studies	-	-	-	-	-	-		-	-	-	-	
Mortality within 30 days (important outcome, but not critical for decision making)												
No studies	-	-	-	-	-	-		-	-	-	-	

4986 **Evidence to Decision Table**

4987

4988 18. Timing of thienopyridine resumption following endoscopy

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4992 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial infarction, deep vein thrombosis, pulmonary embolus)

4994 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days

4995

	Judgement (Panel's judgments highlighted in yellow color)	Research evidence	Additional considerations
Desirable Effects	<b>How substantial are the desirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	No included studies  Theoretically, earlier resumption of thienopyridine after the procedure would tend to reduce <b>thromboembolic events (critical outcome)</b> and increase <b>bleeding (critical outcome)</b> compared to delayed resumption of thienopyridine. Whoever, we did not identify any studies providing relevant data	
Undesirable Effects	<b>How substantial are the undesirable anticipated effects?</b> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Certainty of evidence	<b>What is the overall certainty of the evidence of effects?</b> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	See Evidence Profile Table.	

Values and Preferences	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>○ <b>Possibly important uncertainty or variability</b></li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>		
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ <b>Don't know</b></li> </ul>		
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>○ <b>Negligible costs and savings</b></li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
Certainty of Evidence of Required Resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ <b>Moderate</b></li> <li>○ High</li> <li>○ No included studies</li> </ul>		

Cost effectiveness	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> </ul> <p>○ Varies</p> <p>○ No included studies</p>		
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>○ Yes</li> </ul> <p>○ Varies</p> <p>○ Don't know</p>		
Feasibility	<p><b>Is the intervention feasible to implement?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>○ Yes</li> </ul> <p>○ Varies</p> <p>○ Don't know</p>		

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## **Conclusions**

5000 18. Timing of thienopyridine resumption following endoscopy

5001 P: Patient on thienopyridine who underwent endoscopy

5002 I: Resumption on the same day of the procedure

5003 C: Resumption 1 to 7 days after the procedure



5004 O: CRITICAL: Bleeding within 30 days; thrombotic event within 30 days (ischemic stroke, TIA, systemic embolism, myocardial  
 5005 infarction, deep vein thrombosis, pulmonary embolus)  
 5006 IMPORTANT, BUT NOT CRITICAL: mortality within 30 days  
 5007

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Neither for or against 6/6 votes: 100%	Conditional recommendation for the intervention	Strong recommendation for the intervention
	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Recommendation</b>	In patients who are undergoing elective endoscopic GI procedures whose thienopyridine was interrupted, we cannot make a recommendation whether to resume it on the same day of the procedure vs. 1-7 days after the procedure				
<b>Justification</b>					
<b>Subgroup considerations</b>					
<b>Implementation considerations</b>					
<b>Monitoring and evaluation</b>					
<b>Research priorities</b>					

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- 5022 4. Acosta et al. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc. 2016 Jan;83(1):3-16
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