Contents:

b. etable 10:Instrumental variable and conventional multivariable regression estimates of risk differences of incident upper-gastrointestinal complications per 100 patients prescribed COX-2s compared with nonselective NSAIDs. Patients with missing blood pressure or body mass index values excluded (N=37,628).

c. etable 11: Instrumental variable and conventional multivariable regression estimates of risk differences of myocardial infarction per 100 patients prescribed COX-2s compared with nonselective NSAIDs. Patients with missing blood pressure or body mass index values excluded (N= 39,478).

(v) Robustness to the exclusion of patients with less than 2 years in the database before baseline

d. etable 12:Instrumental variable and conventional multivariable regression estimates of risk differences of incident upper-gastrointestinal complications per 100 patients prescribed COX-2s compared with nonselective NSAIDs. Patients with less than two years registration prior to their index prescription excluded (N=52,189).

e. etable 13: Instrumental variable and conventional multivariable regression estimates of risk differences of myocardial infarction per 100 patients prescribed COX-2s compared with nonselective NSAIDs. Patients with less than two years registration prior to their index prescription excluded (N= 54,722).

etable 1 *Oxford* Medical Information Systems and Read codes used to detect upper-gastrointestinal complications events within 180 days of treatment

Code	Number of events	Description
1956.00	<5	Peptic ulcer symptoms
4737.11	0	Melaena - O/E of faeces
7627.00	0	Operations on duodenal ulcer
7612111	0	Balfour excision of gastric ulcer
7612500	0	Resection of gastric ulcer by cautery
7619100	0	Gastrotomy and ligation of bleeding point of stomach
7627000	0	Closure of perforated duodenal ulcer
7627100	0	Suture of duodenal ulcer not elsewhere classified
7627200	0	Oversew of blood vessel of duodenal ulcer
14C1.00	<5	H/O: peptic ulcer
14C1.11	0	H/O: duodenal ulcer
14C1.12	0	H/O: gastric ulcer
14C8.00	0	H/O: haematemesis
14C9.00	<5	H/O: melaena
19E4.12	0	C/O – melaena
761D500	0	Endoscopic injection haemostasis of duodenal ulcer
761D600	0	Endoscopic injection haemostasis of gastric ulcer
761J.00	0	Operations on gastric ulcer
761J000	0	Closure of perforated gastric ulcer
761J100	0	Closure of gastric ulcer NEC
761Jy00	0	Other specified operation on gastric ulcer
761Jz00	0	Operation on gastric ulcer NOS
7627y00	0	Other specified operation on duodenal ulcer
7627z00	0	Operation on duodenal ulcer NOS
J102000	0	Peptic ulcer of oesophagus
J11..00	17	Gastric ulcer - (GU)
J11..11	0	Prepyloric ulcer
J11..12	<5	Pyloric ulcer
J110.00	0	Acute gastric ulcer
J110000	0	Acute gastric ulcer without mention of complication
J110100	0	Acute gastric ulcer with haemorrhage
J110111	0	Bleeding acute gastric ulcer
J110200	0	Acute gastric ulcer with perforation
J110300	0	Acute gastric ulcer with haemorrhage and perforation
J110y00	0	Acute gastric ulcer unspecified
J110z00	0	Acute gastric ulcer NOS
J111.00	0	Chronic gastric ulcer
J111000	0	Chronic gastric ulcer without mention of complication
J111100	0	Chronic gastric ulcer with haemorrhage
J111111	0	Bleeding chronic gastric ulcer
J111200	0	Chronic gastric ulcer with perforation

etable 1 *Oxford* Medical Information Systems and Read codes used to detect upper-gastrointestinal complications events within 180 days of treatment

Code	Number of events	Description
J111211	<5	Perforated chronic gastric ulcer
J111300	0	Chronic gastric ulcer with haemorrhage and perforation
J111400	0	Chronic gastric ulcer with obstruction
J111y00	0	Chronic gastric ulcer unspecified
J111z00	<5	Chronic gastric ulcer NOS
J113.00	0	Non steroidal anti inflammatory drug induced gastric ulcer
J11y.00	0	Unspecified gastric ulcer
J11y000	0	Unspecified gastric ulcer without mention of complication
J11y100	0	Unspecified gastric ulcer with haemorrhage
J11y200	0	Unspecified gastric ulcer with perforation
J11y400	0	Unspecified gastric ulcer with obstruction
J11yy00	0	Unspec gastric ulcer; unspec haemorrhage and/or perforation
J11yz00	0	Unspecified gastric ulcer NOS
J11z.00	<5	Gastric ulcer NOS
J11z.11	<5	Gastric erosions
J11z.12	0	Multiple gastric ulcers
J12..00	17	Duodenal ulcer - (DU)
J120.00	0	Acute duodenal ulcer
J120000	0	Acute duodenal ulcer without mention of complication
J120100	0	Acute duodenal ulcer with haemorrhage
J120200	0	Acute duodenal ulcer with perforation
J120300	0	Acute duodenal ulcer with haemorrhage and perforation
J120400	0	Acute duodenal ulcer with obstruction
J120y00	0	Acute duodenal ulcer unspecified
J120z00	0	Acute duodenal ulcer NOS
J121.00	<5	Chronic duodenal ulcer
J121000	0	Chronic duodenal ulcer without mention of complication
J121100	0	Chronic duodenal ulcer with haemorrhage
J121111	0	Bleeding chronic duodenal ulcer
J121200	0	Chronic duodenal ulcer with perforation
J121211	<5	Perforated chronic duodenal ulcer
J121300	0	Chronic duodenal ulcer with haemorrhage and perforation
J121400	0	Chronic duodenal ulcer with obstruction
J121y00	0	Chronic duodenal ulcer unspecified
J121z00	0	Chronic duodenal ulcer NOS
J122.00	0	Duodenal ulcer disease
J123.00	0	Duodenal erosion
J124.00	0	Recurrent duodenal ulcer
J126.00	0	Non steroidal anti inflammatory drug induced duodenal ulcer
J12y.00	0	Unspecified duodenal ulcer
J12y000	0	Unspecified duodenal ulcer without mention of complication
J12y100	0	Unspecified duodenal ulcer with haemorrhage
J12y200	<5	Unspecified duodenal ulcer with perforation

etable 1 *Oxford* Medical Information Systems and Read codes used to detect upper-gastrointestinal complications events within 180 days of treatment

Code	Number of events	Description
J12y300	0	Unspecified duodenal ulcer with haemorrhage and perforation
J12y400	0	Unspecified duodenal ulcer with obstruction
J12yy00	0	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
J12yz00	0	Unspecified duodenal ulcer NOS
J12z.00	0	Duodenal ulcer NOS
J13..00	5	Peptic ulcer - (PU) site unspecified
J13..11	0	Stress ulcer NOS
J130.00	0	Acute peptic ulcer
J130000	0	Acute peptic ulcer without mention of complication
J130100	0	Acute peptic ulcer with haemorrhage
J130200	0	Acute peptic ulcer with perforation
J130300	0	Acute peptic ulcer with haemorrhage and perforation
J130y00	0	Acute peptic ulcer unspecified
J130z00	0	Acute peptic ulcer NOS
J131.00	0	Chronic peptic ulcer
J131000	0	Chronic peptic ulcer without mention of complication
J131100	0	Chronic peptic ulcer with haemorrhage
J131200	0	Chronic peptic ulcer with perforation
J131400	0	Chronic peptic ulcer with obstruction
J131y00	0	Chronic peptic ulcer unspecified
J131z00	0	Chronic peptic ulcer NOS
J13y.00	0	Unspecified peptic ulcer
J13y000	0	Unspecified peptic ulcer without mention of complication
J13y100	0	Unspecified peptic ulcer with haemorrhage
J13y200	0	Unspecified peptic ulcer with perforation
J13y300	0	Unspecified peptic ulcer with haemorrhage and perforation
J13y400	0	Unspecified peptic ulcer with obstruction
J13yz00	0	Unspecified peptic ulcer NOS
J13z.00	0	Peptic ulcer NOS
J17y800	0	Healed gastric ulcer leaving a scar
J68..00	10	Gastrointestinal haemorrhage
J680.00	27	Haematemesis
J681.00	31	Melaena
J68z.00	0	Gastrointestinal haemorrhage unspecified
J68z.11	19	GIB - Gastrointestinal bleeding
J68z100	0	Intestinal haemorrhage NOS
J68z200	0	Upper-gastrointestinal haemorrhage
J68zz00	0	Gastrointestinal tract haemorrhage NOS
ZV12711	0	[V]Personal history of peptic ulcer
ZV12712	0	[V]Personal history of duodenal ulcer
ZV12C00	0	[V] Personal history of gastric ulcer

etable 2: *Oxford* Medical Information Systems and Read codes used to define myocardial infarction events within 180 days of treatment

Code	Number of events	Description
Gyu3400	0	[X]Acute transmural myocardial infarction of unspecif site
Gyu3600	0	[X]Subsequent myocardial infarction of unspecified site
G301000	0	Acute anteroapical infarction
G300.00	0	Acute anterolateral infarction
G301100	<5	Acute anteroseptal infarction
G30y000	0	Acute atrial infarction
G302.00	0	Acute inferolateral infarction
G303.00	0	Acute inferoposterior infarction
G30..00	80	Acute myocardial infarction
G30z.00	26	Acute myocardial infarction NOS
G307000	0	Acute non-Q wave infarction
G307100	<5	Acute non-ST segment elevation myocardial infarction
G30y100	0	Acute papillary muscle infarction
G30B.00	0	Acute posterolateral myocardial infarction
G309.00	0	Acute Q-wave infarct
G30y200	0	Acute septal infarction
G30X000	<5	Acute ST segment elevation myocardial infarction
G307.00	<5	Acute subendocardial infarction
G30X.00	0	Acute transmural myocardial infarction of unspecif site
G301z00	0	Anterior myocardial infarction NOS
G361.00	0	Atrial septal defect/curr comp folow acut myocardal infarct
G30..11	<5	Attack - heart
G30..13	0	Cardiac rupture following myocardial infarction (MI)
G36..00	0	Certain current complication follow acute myocardial infarct
889A.00	0	Diab mellit insulin-glucose infus acute myocardial infarct
G310.11	0	Dressler's syndrome
3233.00	0	ECG: antero-septal infarct.
3236.00	0	ECG: lateral infarction
323Z.00	0	ECG: myocardial infarct NOS
323..00	0	ECG: myocardial infarction
3232.00	0	ECG: old myocardial infarction
3235.00	0	ECG: subendocardial infarct
3234.00	0	ECG:posterior/inferior infarct
14A3.00	0	H/O: myocardial infarct <60
14A4.00	0	H/O: myocardial infarct >60
14AH.00	0	H/O: Myocardial infarction in last year
G360.00	<5	Haemopericardium/current comp folow acut myocard infarct
G32..11	0	Healed myocardial infarction
G30..14	0	Heart attack
G308.00	<5	Inferior myocardial infarction NOS
G305.00	0	Lateral myocardial infarction NOS

etable 2: *Oxford* Medical Information Systems and Read codes used to define myocardial infarction events within 180 days of treatment

Code	Number of events	Description
G30..15	35	MI - acute myocardial infarction
G30A.00	0	Mural thrombosis
G32..00	<5	Old myocardial infarction
G30y.00	0	Other acute myocardial infarction
G30yz00	<5	Other acute myocardial infarction NOS
G301.00	0	Other specified anterior myocardial infarction
G32..12	0	Personal history of myocardial infarction
G501.00	0	Post infarction pericarditis
G304.00	0	Posterior myocardial infarction NOS
G310.00	0	Postmyocardial infarction syndrome
G38..00	<5	Postoperative myocardial infarction
G38z.00	0	Postoperative myocardial infarction, unspecified
G384.00	0	Postoperative subendocardial myocardial infarction
G380.00	0	Postoperative transmural myocardial infarction anterior wall
G381.00	0	Postoperative transmural myocardial infarction inferior wall
G311.00	0	Preinfarction syndrome
G363.00	0	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	0	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	0	Rupture papillary muscle/curr comp fol acute myocard infarct
G30..17	<5	Silent myocardial infarction
G35..00	0	Subsequent myocardial infarction
G350.00	0	Subsequent myocardial infarction of anterior wall
G351.00	0	Subsequent myocardial infarction of inferior wall
G353.00	0	Subsequent myocardial infarction of other sites
G35X.00	0	Subsequent myocardial infarction of unspecified site
G366.00	0	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G306.00	0	True posterior myocardial infarction
G362.00	0	Ventric septal defect/curr comp fol acut myocardal infarctn

etable 3: Risk and mean differences of observed confounders by a joint test of the association between a count of the 20 prior NSAID prescriptions that were COX-2s and the observed confounders adjusted for physician fixed effects

		Indicators of 20 prior prescriptions		Predicted exposure indicators for 20 prior prescriptions		Indicators of 20 prior prescriptions adjusted for physician fixed effects	
		F -test*	p -value	Risk difference *100	p -value	F -test*	p-value
Male	56,908	1.1	0.36	-1.5	0.83	1.34	0.23
Aged 70 or over at index date	56,908	14.2	<0.001	-16.3	<0.001	15.10	<0.001
≤5 doctor visits in previous year	56,908	2.5	0.01	6.2	<0.001	1.18	0.31
≤5 prescription drugs in previous year	56,908	5.6	<0.001	10.2	<0.001	2.51	0.01
Hospitalized in previous year	56,908	2.5	0.01	11.3	<0.001	0.22	0.98
History of							
hemorrhagic stroke	56,908	1.2	0.28	-0.2	0.28	1.24	0.27
renal complications	56,908	0.7	0.68	0.9	0.26	0.87	0.53
ischemic heart disease	56,908	0.8	0.56	-0.2	0.92	1.71	0.10
myocardial infarction	56,908	0.9	0.47	0.0	0.92	0.99	0.44
arrhythmia	56,908	0.3	0.97	0.7	0.47	0.33	0.94
upper-gastrointestinal complication	56,908	1.2	0.32	2.1	0.05	0.85	0.55
gastritis	56,908	0.7	0.68	1.3	0.25	0.57	0.78
endoscopy	56,908	1.4	0.20	3.6	0.03	1.49	0.17
gastroprotective drug use	56,908	5.2	<0.001	12.0	<0.001	1.49	0.17
warfarin drug use	56,908	1.7	0.11	0.6	0.44	1.40	0.20
glucocorticoids use	56,908	0.5	0.86	0.9	0.73	0.83	0.56
Moderate exercise	21,976	0.4	0.88	-5.9	0.22	0.49	0.84
Heavy exercise	21,976	1.1	0.35	3.1	0.11	0.79	0.59
Light exercise	21,976	1.0	0.41	-0.6	0.89	0.65	0.72
Has diabetes	56,908	0.5	0.81	-0.5	0.63	0.92	0.49
Current smoker	50,157	0.7	0.69	-3.1	0.14	0.53	0.81
Ever smoked	50,157	1.9	0.07	-6.1	0.03	0.51	0.82
Mean systolic blood pressure(mmHg)	46,117	1.1	0.35	0.3**	0.77	0.51	0.83
Mean body mass index (kg/m^2)	45,490	2.1	0.04	-0.7**	0.002	0.75	0.63

Risk or mean differences estimated using ordinary least squares regression of confounder on exposure or instrument (COX-2s minus nonselective NSAIDs), adjusted for age, gender and year of prescription and in the right-hand column physician fixed effects. P-values are robust to heteroskedasticity and allow for clustering by physician. *F-test of joint hypothesis that 20 prior prescriptions are not associated with observed covariates. **Mean difference based on ordinary least squares regression, adjusted for age, gender and year of prescription. All associations adjusted for indicator variables for prescribing physician.

etable 4: Balke Pearl non-parametric bounds of the risk difference per 100 patients treated

	N events	Lower bound	Upper bound
Incident upper-gastrointestinal complications n=53,352			
60 Days	73	-7.57	64.56
120 Days	112	-7.62	64.51
180 Days	143	-7.65	64.48
Incident myocardial infarction n=55,915			
60 Days	54	-7.94	63.58
120 Days	113	-8.02	63.50
180 Days	158	-8.09	63.43

fweights used with stata command bpbounds. These bounds are not 95% confidence intervals, but point estimates of the lower and upper bound of the causal effect assuming physicians prescribing preference is a valid instrument. 95% confidence intervals were derived by a non-parametric bootstrap. However, the standard error on the bounds were very small, (0.5) and the confidence with which the bounds were estimated was very high (t~20-40), so they have not been included in the table.

etable 5: Instrumental variable regression estimates of risk differences of upper-gastrointestinal complications and myocardial infarction per 100 patients prescribed COX-2s compared with nonselective NSAIDs adjusted for physician fixed effects and estimated with average of instruments

Timing of event	Events	Unadjusted risk difference (95% confidence interval)	p-value	Adjusted risk difference (95% confidence interval)	p-value
Incident upper-gastrointestinal complications (n=53,352)					
Instrumental variable estimated risk differences per 100 patients; physicians' 20 prior prescription physician fixed effects:					
60 Days	73	-0.28 (-0.64,0.08)	0.13	-0.04 (-0.63,0.55)	0.89
120 Days	112	-0.58 (-1.05,-0.12)	0.01	-0.44 (-1.22,0.34)	0.27
180 Days	143	-0.23 (-0.76,0.31)	0.40	0.13 (-0.74,1.00)	0.77
Instrumental variable estimated risk differences per 100 patients; physicians' 20 prior prescription averaged:					
60 Days	73	-0.08 (-0.37,0.20)	0.57	-0.05 (-0.40,0.30)	0.78
120 Days	112	-0.17 (-0.49,0.15)	0.30	-0.16 (-0.55,0.22)	0.41
180 Days	143	-0.08 (-0.45,0.28)	0.65	-0.01 (-0.44,0.42)	0.95
Incident myocardial infarction (n=55,915)					
Instrumental variable estimated risk differences per 100 patients; physicians' 20 prior prescription physician fixed effects:					
60 Days	54	-0.15 (-0.38,0.09)	0.22	0.06 (-0.31,0.44)	0.74
120 Days	113	-0.55 (-0.93,-0.17)	<0.001	-0.71 (-1.34,-0.07)	0.03
180 Days	158	-0.74 (-1.19,-0.28)	<0.001	-1.02 (-1.80,-0.23)	0.01
Instrumental variable estimated risk differences per 100 patients; physicians' 20 prior prescription averaged:					
60 Days	54	-0.06 (-0.21,0.09)	0.40	-0.05 (-0.24,0.15)	0.65
120 Days	113	-0.18 (-0.40,0.05)	0.12	-0.23 (-0.51,0.05)	0.11
180 Days	158	-0.19 (-0.49,0.11)	0.22	-0.15 (-0.54,0.23)	0.43

Confidence intervals allow for clustering by physician. The instrumental variable results were estimated using generalized method of moments. Adjusted results are conditional on the following variables measured at baseline: year of prescription, gender, aged over 75 years, made more than five general physician visits in year before prescription, five prescriptions in last year, number of referrals to hospital in previous year, prescriptions of gastroprotective drugs in prior year, warfarin prescriptions in prior year, glucocorticoid prescription in the prior year, light, moderate or heavy exercise, diabetes status, current or ever smoker, systolic blood pressure and body mass index. Missing values were replaced with the mean and indicator variables are included for missing values.

etable 6: Instrumental variable regression estimates of risk difference of myocardial infarction per 100 patients prescribed rofecoxib, celecoxib, naproxen and diclofenac compared with ibuprofen, (N=42,332):

Exposure:	Unadjusted risk difference (95% confidence interval)	p-value	Adjusted risk difference (95% confidence interval)	p-value
Ordinary least squares estimated risk differences at 60 days per 100 patients				
rofecoxib	0.05 (-0.05,0.15)	0.31	0.07 (-0.03,0.17)	0.18
naproxen	0.02 (-0.11,0.15)	0.78	0.02 (-0.11,0.15)	0.78
celecoxib	0.10 (-0.01,0.21)	0.08	0.12 (0.00,0.24)	0.04
diclofenac	0.01 (-0.06,0.08)	0.78	0.02 (-0.06,0.09)	0.67
Ordinary least squares estimated risk differences 120 days per 100 patients				
rofecoxib	0.02 (-0.11,0.15)	0.73	0.05 (-0.08,0.18)	0.47
naproxen	-0.01 (-0.20,0.17)	0.89	-0.01 (-0.20,0.17)	0.89
celecoxib	0.06 (-0.08,0.21)	0.39	0.09 (-0.06,0.24)	0.22
diclofenac	0.02 (-0.09,0.13)	0.69	0.03 (-0.08,0.14)	0.57
Ordinary least squares estimated risk differences at 180 days per 100 patients				
rofecoxib	0.08 (-0.07,0.23)	0.30	0.10 (-0.05,0.25)	0.20
naproxen	-0.01 (-0.21,0.20)	0.95	-0.01 (-0.22,0.20)	0.93
celecoxib	0.13 (-0.05,0.30)	0.15	0.16 (-0.02,0.34)	0.08
diclofenac	0.06 (-0.06,0.17)	0.37	0.06 (-0.06,0.18)	0.31
Instrumental variable estimated risk differences at 60 days per 100 patients				
rofecoxib	-0.05 (-0.14,0.05)	0.33	-0.03 (-0.14,0.07)	0.51
naproxen	-0.02 (-0.15,0.12)	0.81	-0.02 (-0.15,0.11)	0.71
celecoxib	-0.06 (-0.12,0.00)	0.07	-0.05 (-0.14,0.03)	0.23
diclofenac	0.09 (-0.06,0.24)	0.24	0.08 (-0.05,0.22)	0.24
Instrumental variable estimated risk differences at 120 days per 100 patients				
rofecoxib	-0.45 (-0.65,-0.26)	<0.001	-0.37 (-0.58,-0.17)	<0.001
naproxen	-0.42 (-0.70,-0.15)	<0.001	-0.44 (-0.72,-0.17)	<0.001
celecoxib	-0.38 (-0.57,-0.20)	<0.001	-0.33 (-0.56,-0.10)	<0.001
diclofenac	0.11 (-0.25,0.46)	0.56	0.14 (-0.22,0.49)	0.45
Instrumental variable estimated risk differences at 180 days per 100 patients				
rofecoxib	-0.62 (-0.84,-0.40)	<0.001	-0.55 (-0.79,-0.31)	<0.001
naproxen	-0.61 (-0.93,-0.30)	<0.001	-0.62 (-0.93,-0.30)	<0.001
celecoxib	-0.50 (-0.73,-0.27)	<0.001	-0.43 (-0.71,-0.14)	<0.001
diclofenac	-0.01 (-0.42,0.40)	0.96	0.03 (-0.38,0.45)	0.88

Confidence intervals allow for clustering by physician. Instrumental variable estimated using generalized method of moments. Adjusted results are conditional on the following variables measured at baseline: year of prescription, gender, aged over 75, made more than five general physician visits in year before prescription, five prescriptions in last year, number of referrals to hospital in previous year, prescriptions of gastroprotective drugs in prior year, warfarin prescriptions in prior year, glucocorticoid prescription in the prior year, light, moderate or heavy exercise, diabetes status, current or ever smoker, systolic blood pressure and body mass index. Missing values were replaced with the mean and indicator variables are included for missing values. Patients whose physicians' 20 previous prescriptions were not completely observed and patients not prescribed celecoxib, rofecoxib, naproxen, diclofenac or ibuprofen were dropped from the analysis (14,576 of 56,908 eligible patients). There were 41, 89 and 117 events after 60 days, 120 and 180 days respectively. Instruments were seven variables indicating the number of each NSAID each physician prescribed to their previous 20 patients.

etable 7: Instrumental variable and conventional multivariable regression estimates of risk differences of myocardial infarction per 100 patients prescribed COX-2s compared with nonselective NSAIDs. 13,228 Patients prescribed diclofenac excluded (N= 42,687).

Timing of event	No. of Events #	Unadjusted Risk difference (95% confidence interval)	p-value	Adjusted Risk difference (95% confidence interval)	p-value
Ordinary least squares					
60 Days	44	0.04 (-0.03,0.11)	0.21	0.03 (-0.05,0.11)	0.48
120 Days	87	0.02 (-0.07,0.11)	0.66	0.02 (-0.08,0.12)	0.65
180 Days	121	0.04 (-0.07,0.15)	0.47	0.07 (-0.06,0.19)	0.29
Instrumental variable (physicians' prior prescription)					
60 Days	44	-0.11 (-0.26,0.05)	0.17	-0.20 (-0.44,0.04)	0.11
120 Days	87	0.01 (-0.37,0.40)	0.95	0.05 (-0.51,0.62)	0.85
180 Days	121	-0.03 (-0.47,0.41)	0.90	0.08 (-0.58,0.73)	0.82
Instrumental variable (physicians' 20 prior prescriptions)					
60 Days	44	0.15 (0.03,0.27)	0.02	0.24 (0.08,0.40)	<0.001
120 Days	87	-0.13 (-0.30,0.03)	0.11	-0.06 (-0.30,0.18)	0.63
180 Days	121	-0.33 (-0.54,-0.12)	<0.001	-0.28 (-0.58,0.03)	0.08

Confidence intervals allow for clustering by physician. The instrumental variable results were estimated using generalized method of moments. 993 patients with records indicating a diagnosis of MI prior to prescription were excluded. Adjusted results are conditional on the following variables measured at baseline: year of prescription, gender, aged over 75 years, made more than five GP visits in year before prescription, five prescriptions in last year, number of referrals to hospital in previous year, prescriptions of gastroprotective drugs in prior year, warfarin prescriptions in prior year, glucocorticoids prescription in the prior year, light, moderate or heavy exercise, diabetes status, current or ever smoker, systolic blood pressure and body mass index.

etable 8: Strength of the instruments in subgroups defined by observed covariates, and test of imbalance in covariates across levels of the instrument:

Covariate	N	Risk difference in exposure *100	95% confidence intervals	p-values	OLS bias> IV bias	% of bootstrap samples[a] OLS>IV
All	56,908	27.33	(25.57,29.08)	<0.001		
Male	56,908	-6.87	(-8.90,-4.84)	<0.001	Yes	99.9%
Aged 70 or over at index date	56,908	14.35	(12.12,16.57)	<0.001	Yes	76.9%
<<5 doctor visits in previous year	56,908	6.93	(4.26,9.59)	<0.001	Yes	97.8%
<<5 prescription drugs in previous year	56,908	8.83	(6.64,11.03)	<0.001	Yes	100.0%
Hospitalised in previous year	56,908	4.79	(2.44,7.15)	<0.001	Yes	88.0%
History of						
haemorraghic stroke	56,908	8.98	(-13.61,31.56)	0.44	No	1.4%
renal complications	56,908	2.60	(-5.50,10.71)	0.53	No	39.3%
ischaemic heart disease	56,908	3.27	(-0.32,6.87)	0.07	No	3.9%
myocardial infarction	56,908	-0.44	(-8.33,7.45)	0.91	No	3.5%
arrhythmia	56,908	-0.14	(-5.56,5.28)	0.96	Yes	70.1%
upper-gastrointestinal complication	56,908	9.20	(4.41,13.99)	<0.001	Yes	99.4%
gastritis	56,908	5.34	(-0.08,10.76)	0.05	Yes	77.0%
endoscopy	56,908	8.26	(4.32,12.19)	<0.001	Yes	78.1%
gastroprotective drug use	56,908	10.84	(8.42,13.27)	<0.001	Yes	100.0%
warfarin drug use	56,908	3.38	(-2.85,9.61)	0.29	Yes	49.9%
glucocorticoids use	56,908	6.60	(3.92,9.28)	<0.001	Yes	100.0%
Takes moderate exercise at baseline	21,976	0.49	(-2.30,3.28)	0.73	No	0.0%
Takes heavy exercise at baseline	21,976	-8.78	(-14.07,-3.50)	<0.001	No	6.3%
Takes light exercise at baseline	21,976	3.02	(0.10,5.95)	0.04	No	1.2%
Diabetic at baseline	56,908	2.21	(-3.45,7.87)	0.44	No	1.8%
Current smoker	50,157	-1.26	(-3.79,1.26)	0.33	Yes	55.6%
Ever smoked	50,157	0.10	(-1.98,2.17)	0.93	No	2.1%
Systolic blood pressure (mmHg) [b]	46,117	0.10[c]	(0.02,0.17)	0.01	NA	NA
Body mass index (kg/m^2) [d]	45,490	0.04[c]	(-0.20,0.29)	0.72	NA	NA

Notes: [a] 1,000 bootstrap samples were generated with replacement. OLS ordinary least squares, IV instrumental variable. Risk difference in column 2 is the coefficient on an interaction of the prior prescription with each covariate. Each row is estimated in a separate regression. [b] Based on a sample of 46,117. [c] mean differences. [d] Based on a sample of 45,490.

COX-2 selective non-steroidal anti-inflammatory drugs and risk of gastrointestinal tract complications and myocardial infarction: an instrumental variables analysis

Appendix and sensitivity analyses:

(vi) Robustness to variation in the algorithm used to define the outcome

We investigated whether our results changed when we used an extra nine Read codes identified by Margulis et al. (2009)[1] to define upper-gastrointestinal complications. The extra codes were:

4A24.11 "Coffee ground vomit"

1994.11 "blood in vomit – symptom"

J680.11 "vomiting of blood"

1994.00 "vomiting blood – fresh"

J681.00 "GI bleeding NEC"

J681.11 "blood in stool"

J14..15 "stomal ulcer"

J14..11 "anastomotic ulcer"

J14..00 "gastrojejunal ulcer (GJU)"

If we had included these codes, we would have excluded 74 patients who had these codes in their medical record prior to their first prescription. One of the excluded codes detected fewer than five further cases of upper-gastrointestinal complications. However, including these cases into the analysis makes no difference to the results (**eTable 9**):

[1] 1. Margulis A, Rodríguez L, Hernández-Díaz S. Positive predictive value of computerized medical records for uncomplicated and complicated upper gastrointestinal ulcer. *Pharmacoepidemiol Dr S*. 2009;18(10):900–909.

etable 9: Instrumental variable and conventional multivariable regression estimates of risk differences of incident upper-gastrointestinal complications per 100 patients prescribed COX-2s compared with nonselective NSAIDs. 3 extra cases found with Margulis et al. code list included. (N=53,278).

Timing of event	No. of Events	Unadjusted Risk difference (95% confidence interval)	p-value	Adjusted Risk difference (95% confidence interval)	p-value
Ordinary least squares					
60 Days	74	-0.02 (-0.09,0.05)	0.59	-0.06 (-0.14,0.03)	0.18
120 Days	113	-0.02 (-0.11,0.07)	0.64	-0.08 (-0.18,0.03)	0.14
180 Days	146	-0.02 (-0.12,0.08)	0.67	-0.08 (-0.20,0.04)	0.18
Instrumental variable (physicians' prior prescription)					
60 Days	74	-0.35 (-0.65,-0.05)	0.02	-0.45 (-0.84,-0.06)	0.02
120 Days	113	-0.49 (-0.85,-0.13)	0.01	-0.63 (-1.13,-0.14)	0.01
180 Days	146	-0.38 (-0.85,0.08)	0.11	-0.46 (-1.07,0.16)	0.14
Instrumental variable (physicians' 20 prior prescriptions)					
60 Days	74	-0.26 (-0.49,-0.04)	0.02	-0.25 (-0.52,0.03)	0.08
120 Days	113	-0.45 (-0.71,-0.20)	<0.001	-0.45 (-0.78,-0.12)	0.01
180 Days	146	-0.17 (-0.53,0.18)	0.34	-0.11 (-0.53,0.31)	0.59

Confidence intervals allow for clustering by physician. The instrumental variable results were estimated using generalized method of moments. 3,630 patients with records indicating a diagnosis of an upper-gastrointestinal complication prior to prescription were excluded. Adjusted results are conditional on the following variables measured at baseline: year of prescription, gender, aged over 75 years, made more than five GP visits in year before prescription, five prescriptions in last year, number of referrals to hospital in previous year, prescriptions of gastroprotective drugs in prior year, warfarin prescriptions in prior year, glucocorticoids prescription in the prior year, light, moderate or heavy exercise, diabetes status, current or ever smoker, systolic blood pressure and body mass index.

(vii) Robustness to exclusion of individuals with missing data on body mass index and blood pressure.

We repeated the analysis presented in Tables 4 and 5 in the paper, restricted to patients without missing blood pressure or body mass index values. This excluded 15,724 from the upper-gastrointestinal complications analysis and 16,437 patients from the myocardial infarction analysis. The only results to meaningfully change were the instrumental variable results using 20 prior prescriptions. However, this difference was evident in the unadjusted results, suggesting this is due to changes to the sample, rather than reflecting a problem with the adjustment. (See eTable 10 and eTable 11 below):

etable 10:Instrumental variable and conventional multivariable regression estimates of risk differences of incident upper-gastrointestinal complications per 100 patients prescribed COX-2s compared with nonselective NSAIDs. Patients with missing blood pressure or body mass index values excluded (N=37,628).

Timing of event	No. of Events	Unadjusted Risk difference (95% confidence interval)	p-value	Adjusted Risk difference (95% confidence interval)	p-value
Ordinary least squares					
60 Days	46	-0.01 (-0.08,0.07)	0.88	-0.06 (-0.15,0.04)	0.24
120 Days	74	-0.01 (-0.11,0.08)	0.79	-0.07 (-0.19,0.04)	0.21
180 Days	94	-0.01 (-0.11,0.10)	0.93	-0.08 (-0.22,0.05)	0.22
Instrumental variable (physicians' prior prescription)					
60 Days	46	-0.33 (-0.66,0.01)	0.06	-0.38 (-0.81,0.05)	0.08
120 Days	74	-0.45 (-0.88,-0.02)	0.04	-0.51 (-1.08,0.07)	0.08
180 Days	94	-0.22 (-0.80,0.37)	0.47	-0.20 (-0.95,0.55)	0.60
Instrumental variable (physicians' 20 prior prescriptions)					
60 Days	46	-0.22 (-0.45,0.02)	0.07	-0.12 (-0.38,0.14)	0.35
120 Days	74	-0.41 (-0.71,-0.12)	0.01	-0.36 (-0.71,-0.00)	0.05
180 Days	94	-0.46 (-0.79,-0.12)	0.01	-0.37 (-0.78,0.05)	0.08

Confidence intervals allow for clustering by physician. The instrumental variable results were estimated using generalized method of moments. Adjusted results are conditional on the following variables measured at baseline: year of prescription, gender, aged over 75 years, made more than five GP visits in year before prescription, five prescriptions in last year, number of referrals to hospital in previous year, prescriptions of gastroprotective drugs in prior year, warfarin prescriptions in prior year, glucocorticoids prescription in the prior year, light, moderate or heavy exercise, diabetes status, current or ever smoker, systolic blood pressure and body mass index.

etable 11: Instrumental variable and conventional multivariable regression estimates of risk differences of myocardial infarction per 100 patients prescribed COX-2s compared with nonselective NSAIDs. Patients with missing blood pressure or body mass index values excluded (N= 39,478).

Timing of event	No. of Events #	Unadjusted Risk difference (95% confidence interval)	p-value	Adjusted Risk difference (95% confidence interval)	p-value
Ordinary least squares					
60 Days	37	0.03 (-0.04,0.10)	0.38	0.03 (-0.05,0.11)	0.42
120 Days	89	-0.00 (-0.11,0.10)	0.98	-0.00 (-0.11,0.11)	1.00
180 Days	123	0.02 (-0.11,0.14)	0.80	0.04 (-0.09,0.18)	0.53
Instrumental variable (physicians' prior prescription)					
60 Days	37	-0.11 (-0.38,0.16)	0.44	-0.09 (-0.47,0.30)	0.65
120 Days	89	-0.07 (-0.62,0.49)	0.82	-0.02 (-0.79,0.74)	0.95
180 Days	123	-0.26 (-0.86,0.34)	0.39	-0.16 (-0.98,0.66)	0.70
Instrumental variable (physicians' 20 prior prescriptions)					
60 Days	37	0.00 (-0.05,0.05)	0.98	0.05 (-0.05,0.16)	0.33
120 Days	89	-0.67 (-0.88,-0.45)	<0.001	-0.62 (-0.96,-0.29)	<0.001
180 Days	123	-0.98 (-1.24,-0.71)	<0.001	-0.90 (-1.30,-0.50)	<0.001

Confidence intervals allow for clustering by physician. The instrumental variable results were estimated using generalized method of moments. Adjusted results are conditional on the following variables measured at baseline: year of prescription, gender, aged over 75 years, made more than five GP visits in year before prescription, five prescriptions in last year, number of referrals to hospital in previous year, prescriptions of gastroprotective drugs in prior year, warfarin prescriptions in prior year, glucocorticoids prescription in the prior year, light, moderate or heavy exercise, diabetes status, current or ever smoker, systolic blood pressure and body mass index.

(viii) Robustness to the exclusion of patients with less than 2 years in the database before baseline

We reran the results excluding 1,225 (of 56,908 i.e. 2%) patients with less than two years continuous recording at baseline. As with the results reported in the paper, each analysis excludes prevalent cases and the diagnosis history was defined using a patient's entire medical record, not just their last six months of records.

The results of this sensitivity analysis (of Tables 4 and 5 in the paper), on the 55,683 patients with at least two years of up-to-standard registration prior to their index prescription are shown below (**eTables 12** and **13)**. There were no meaningful differences in the results.

etable 12:Instrumental variable and conventional multivariable regression estimates of risk differences of incident upper-gastrointestinal complications per 100 patients prescribed COX-2s compared with nonselective NSAIDs. Patients with less than two years registration prior to their index prescription excluded (N=52,189).

Timing of event	No. of Events	Unadjusted Risk difference (95% confidence interval)	p-value	Adjusted Risk difference (95% confidence interval)	p-value
Ordinary least squares					
60 Days	71	-0.02 (-0.09,0.05)	0.61	-0.06 (-0.14,0.03)	0.17
120 Days	109	-0.02 (-0.11,0.07)	0.66	-0.08 (-0.18,0.02)	0.13
180 Days	139	-0.02 (-0.12,0.08)	0.70	-0.08 (-0.20,0.04)	0.17
Instrumental variable (physicians' prior prescription)					
60 Days	71	-0.35 (-0.65,-0.05)	0.02	-0.45 (-0.84,-0.06)	0.02
120 Days	109	-0.49 (-0.85,-0.12)	0.01	-0.63 (-1.13,-0.14)	0.01
180 Days	139	-0.38 (-0.84,0.09)	0.12	-0.46 (-1.07,0.16)	0.14
Instrumental variable (physicians' 20 prior prescriptions)					
60 Days	71	-0.26 (-0.49,-0.04)	0.02	-0.25 (-0.52,0.03)	0.08
120 Days	109	-0.45 (-0.71,-0.19)	<0.001	-0.45 (-0.78,-0.12)	0.01
180 Days	139	-0.16 (-0.52,0.19)	0.37	-0.11 (-0.53,0.31)	0.60

Confidence intervals allow for clustering by physician. The instrumental variable results were estimated using generalized method of moments. 3,556 patients with records indicating a diagnosis of an upper-gastrointestinal complication prior to prescription were excluded. Adjusted results are conditional on the following variables measured at baseline: year of prescription, gender, aged over 75 years, made more than five GP visits in year before prescription, five prescriptions in last year, number of referrals to hospital in previous year, prescriptions of gastroprotective drugs in prior year, warfarin prescriptions in prior year, glucocorticoids prescription in the prior year, light, moderate or heavy exercise, diabetes status, current or ever smoker, systolic blood pressure and body mass index. 1,163 patients with less than two years follow up excluded.

etable 13: Instrumental variable and conventional multivariable regression estimates of risk differences of myocardial infarction per 100 patients prescribed COX-2s compared with nonselective NSAIDs. Patients with less than two years registration prior to their index prescription excluded (N= 54,722).

Timing of event	No. of Events #	Unadjusted Risk difference (95% confidence interval)	p-value	Adjusted Risk difference (95% confidence interval)	p-value
Ordinary least squares					
60 Days	53	0.05 (-0.02,0.12)	0.16	0.05 (-0.02,0.12)	0.17
120 Days	111	0.02 (-0.07,0.11)	0.65	0.02 (-0.07,0.11)	0.66
180 Days	155	0.04 (-0.07,0.14)	0.50	0.06 (-0.05,0.17)	0.31
Instrumental variable (physicians' prior prescription)					
60 Days	53	-0.10 (-0.32,0.12)	0.37	-0.10 (-0.41,0.20)	0.50
120 Days	111	0.06 (-0.40,0.52)	0.81	0.11 (-0.52,0.75)	0.72
180 Days	155	-0.07 (-0.58,0.44)	0.79	0.01 (-0.70,0.72)	0.97
Instrumental variable (physicians' 20 prior prescriptions)					
60 Days	53	-0.02 (-0.16,0.13)	0.82	0.07 (-0.11,0.25)	0.43
120 Days	111	-0.31 (-0.53,-0.09)	0.01	-0.27 (-0.57,0.02)	0.07
180 Days	155	-0.56 (-0.82,-0.30)	<0.001	-0.53 (-0.89,-0.17)	<0.001

Confidence intervals allow for clustering by physician. The instrumental variable results were estimated using generalized method of moments. 993 patients with records indicating a diagnosis of MI prior to prescription were excluded. Adjusted results are conditional on the following variables measured at baseline: year of prescription, gender, aged over 75 years, made more than five GP visits in year before prescription, five prescriptions in last year, number of referrals to hospital in previous year, prescriptions of gastroprotective drugs in prior year, warfarin prescriptions in prior year, glucocorticoids prescription in the prior year, light, moderate or heavy exercise, diabetes status, current or ever smoker, systolic blood pressure and body mass index. 1,193 further patients with less than two years follow up excluded.