Supplementary material:

Title.

Efficacy and Safety of Restrictive versus Liberal Blood Transfusion Strategies for Acute Myocardial Infarction and Anemia: A Systematic Review and Meta-analysis of Randomized Controlled Trials.

Running Title.

Restrictive versus liberal blood transfusion for myocardial infarction and anemia.

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Keywords.

Blood transfusion, Liberal, Restrictive, Myocardial infarction, Acute coronary syndrome, Anemia.

Contents:

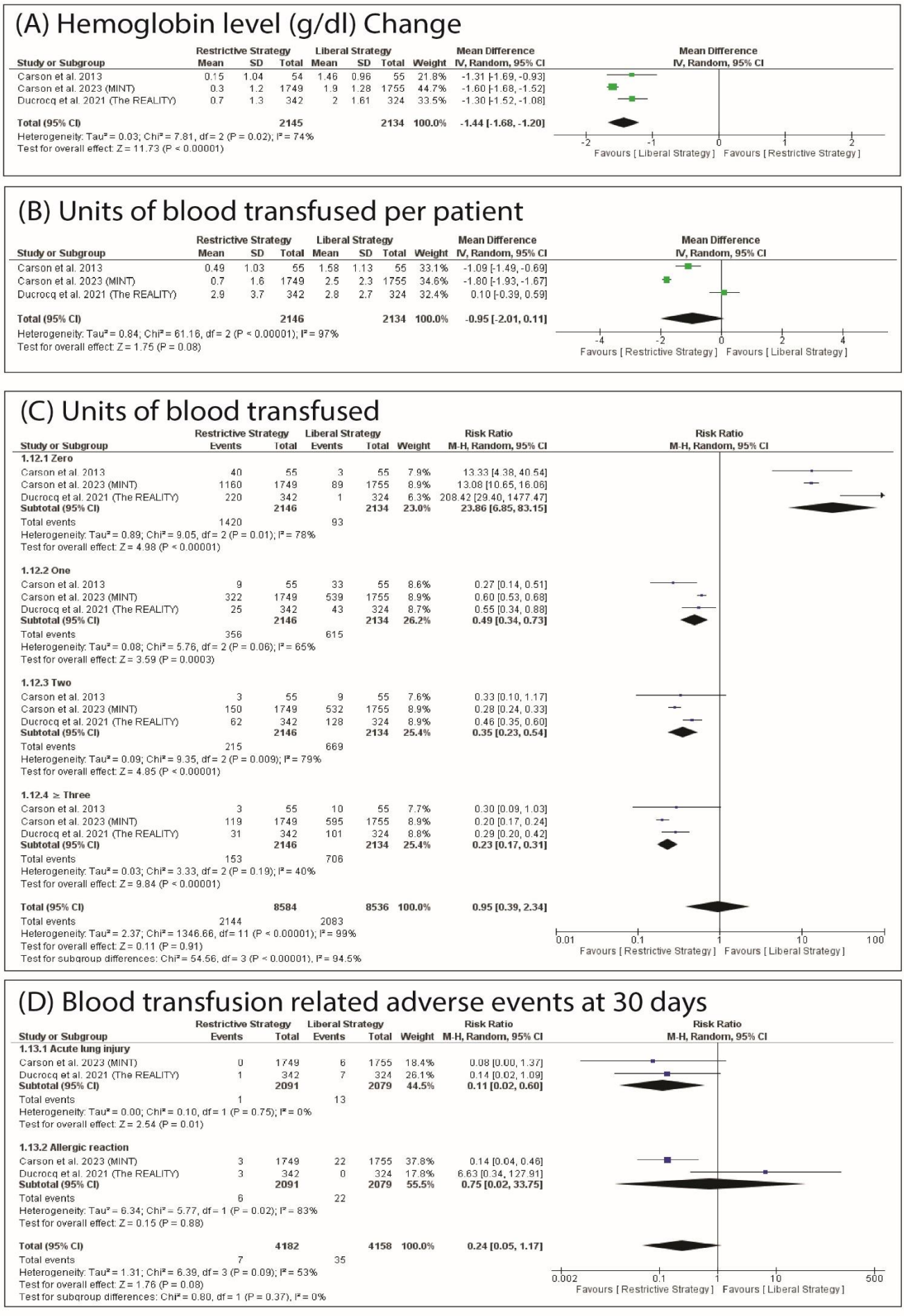

Figure S1: Forest plot of hemoglobin change, transfusion outcomes, and transfusion-related adverse events.

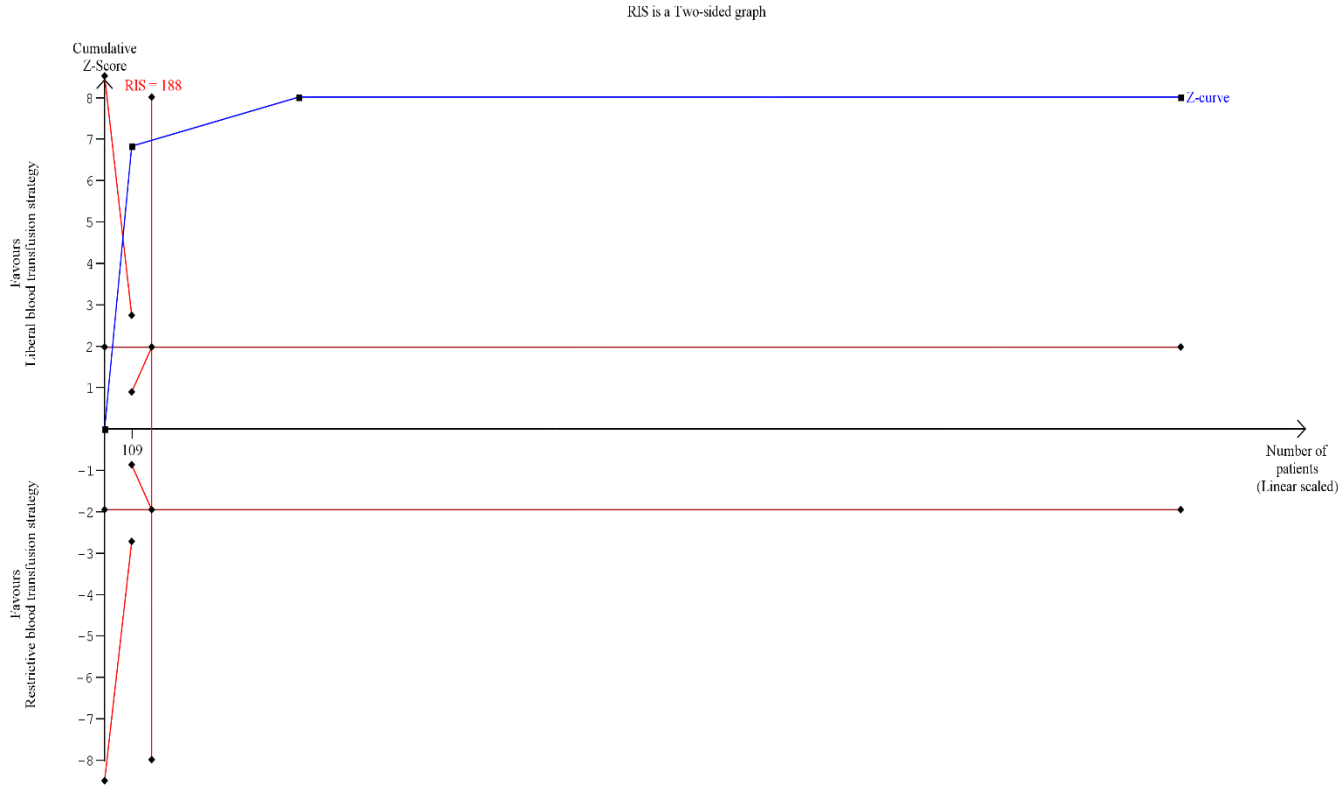

Figure S2: Trial sequential analysis of hemoglobin level change.

Database	Search Terms	Search Field	Search Results
Pubmed	("Liberal transfusion" OR "Restrictive transfusion" OR "Restrictive blood transfusion" OR "liberal blood transfusion") AND ("Myocardial infarct*" OR "Coronary artery disease" OR Angina OR "acute coronary syndrome" OR "cardiovascular stroke" OR "heart attack*" OR MI) AND anemi*	All Field	60
Cochrane	("Liberal transfusion" OR "Restrictive transfusion" OR "Restrictive blood transfusion" OR "liberal blood transfusion") AND ("Myocardial infarct*" OR "Coronary artery disease" OR Angina OR "acute coronary syndrome" OR "cardiovascular stroke" OR "heart attack*" OR MI) AND anemi*	All Field	35
WOS	("Liberal transfusion" OR "Restrictive transfusion" OR "Restrictive blood transfusion" OR "liberal blood transfusion") AND ("Myocardial infarct*" OR "Coronary artery disease" OR Angina OR "acute coronary syndrome" OR "cardiovascular stroke" OR "heart attack*" OR MI) AND anemi*	All Field	83
SCOPUS	TITLE-ABS-KEY (("Liberal transfusion" OR "Restrictive transfusion" OR "Restrictive blood transfusion" OR "liberal blood transfusion") AND ("Myocardial infarct*" OR "Coronary artery disease" OR angina OR "acute coronary syndrome" OR "cardiovascular stroke" OR "heart attack*" OR mi) AND anemi*)	Title, Abstract, Keywords	84

EMBASE	#4. #1 AND #2 AND #3 29 #3. anemia:ti,ab,kw 221,554 #2. 'heart infarction':ti,ab,kw OR 'coronary artery disease':ti,ab,kw OR 'angina pectoris':ti,ab,kw OR 'acute coronary syndrome':ti,ab,kw OR 'cardiovascular stroke':ti,ab,kw OR mi:ti,ab,kw 341,000 #1. 'liberal transfusion':ti,ab,kw OR 'restrictive transfusion':ti,ab,kw OR 'restrictive blood transfusion':ti,ab,kw OR 'liberal blood transfusion':ti,ab,kw 1,444	All Field	29

Table S1: Search Strategy.

Study ID	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Main Inclusion Criteria
Carson et al. 2013	Patients were permitted to receive blood for symptoms from anemia or for a hemoglobin < 8 g/dL.	Patients received one or more units of blood to raise the hemoglobin level ≥ 10 g/dL.	1) greater than 18 years of age; 2) had either a) ST segment elevation myocardial infarction,b) Non ST segment elevation myocardial infarction, c) unstable angina, or d) stable coronary artery disease undergoing a cardiac catheterization; and 3) had a hemoglobin concentration less than 10 g/dL at the time of random allocation.
Carson et al. 2023 (MINT)	Transfusion was permitted but not required when the hemoglobin level was less than 8 g per deciliter and was strongly recommended when the level was less than 7 g per deciliter or when anginal symptoms were not controlled with medications	One unit of packed red cells was administered after randomization and red cells were transfused to maintain the hemoglobin level at or above 10 g per deciliter until the time of hospital discharge or 30 days	Adults (≥18 years of age) with ST-segment elevation or non–ST-segment elevation myocardial infarction, defined in accordance with the Third Universal Definition of Myocardial Infarction,along with anemia (hemoglobin level, <10 g per deciliter within 24 hours before randomization).
Cooper et al. 2011 (The CRIT)	RBC transfusion when their hematocrit decreased 24% with the goal of maintaining a hematocrit from 24% to 27%.	RBC transfusion when their hematocrit decreased 30% with the goal of maintaining a hematocrit from 30% to 33%.	Patients in whom the hematocrit was 30% within 72 hours of symptom onset with AMI
Ducrocq et al. 2021, Gonzalez-Juanatey et al. 2022 (The REALITY)	No transfusion was to be performed unless hemoglobin level decreased to less than or equal to 8 g/dL, with a target range for posttransfusion hemoglobin of 8 to 10 g/dL (the initial protocol used a threshold of 7 g/dL but this was changed to 8 g/dL to maximize investi-gator adherence to the protocol before inclusion of the first patient).	Transfusion was to be per-formed after randomization on all patients with a hemoglobin level less than or equal to 10 g/dL, with a target posttransfusion hemoglobin level of at least 11g/dL.	Patients had to be aged at least 18 years and have AMI (with or without ST-segment elevation with a combination of ischemic symptoms occurring in the 48 hours before admission and elevation of biomarkers of myocardial injury) and a hemoglobin level between 7 and 10 g/dL.

Table S2: Summary characteristics (Restrictive and liberal blood transfusion strategy description and the inclusion criteria).

AMI: Acute myocardial infarction.

Study ID	Killip Class N. (%)								Comorbidities N.(%)															
	1		2		3		4		Prior myocardial infarction		Percutaneous coronary intervention		Coronary artery bypass graft		Congestive heart failure		Hypertension		Dislipidemia		Diabetes mellitus		Bleeding	
	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy	Restrictive blood transfusion strategy	Liberal blood transfusion strategy
Carson et al. 2013	NA	NA	NA	NA	NA	NA	NA	NA	17 (30.9)	13 (23.6)	22 (40)	24 (43.6)	18 (32.7)	16 (29.1)	13 (23.6)	12 (21.8)	45 (81.8)	47 (85.5)	36 (65.5)	38 (69.1)	29 (52.7)	34 (61.8)	9 (16.4)	6 (10.9)
Carson et al. 2023 (MINT)	NA	NA	NA	NA	NA	NA	NA	NA	589 (33.7)	549 (31.3)	623 (35.6)	577 (32.9)	372 (21.3)	390 (22.2)	NA	NA	NA	NA	NA	NA	948(54.2)	948(54)	246 (14.1)	213 (12.1)
Cooper et al. 2011 (The CRIT)	16(67)	11(52)	2(8)	5(24)	3(13)	0	3(13)	5(25)	NA	NA	6(25)	5(24)	4(17)	6(29)	NA	NA	18(75)	19(91)	15(63)	16(76)	13(54)	17(81)	NA	NA
Ducrocq et al. 2021, Gonzalez-Juanatey et al. 2022 (The REALITY)	189 (56.3)	183 (57.0)	87 (25.9)	88 (27.4)	54 (16.1)	39 (12.1)	6 (1.8)	11 (3.4)	121 (35.4)	119 (36.7)	114 (33.3)	111 (34.3)	44 (12.9)	42 (13.0)	44 (12.9)	38 (11.7)	272 (79.5)	256 (79.0)	189 (55.3)	201 (62.0)	176 (51.5)	158 (48.8)	36 (10.5)	49 (15.1)

Table S3: Baseline characteristics (Killip class and patients comorbidities).

NA: not available

Study ID	Domain	Decision	Description
Carson et al. 2013	Randomization process	Low risk	Treatment group randomization was done by using an automated telephone system. They were unable to blind the treating physician or patient to the transfusion strategy, and there were no apparent differences between the two groups.
	Deviations from intended interventions	Low risk	They were unable to blind the treating physician or patient to the transfusion strategy. There was no deviation from the intended interventions because of the trial context. Additionally, the analysis was done by the intention to treat analysis.
	Missing outcome data	Low risk	Outcome data of nearly all randomized patients were available.
	Measurement of the outcome	Low risk	Appropriate tools were used to measure the outcome without difference between the two group arms.
	Selection of the reported result	Low risk	All outcomes, measurement tools, and analysis plans were pre-specified in the study protocol.
	OVERALL	**LOW RISK**	
Carson et al. 2023 (MINT)	Randomization process	Low risk	The patients were randomly assigned in a 1:1 ratio to a restrictive or liberal transfusion strategy by means of a Web-based system and there were no apparent differences between the two groups.
	Deviations from intended interventions	Low risk	This study was an open-label study. There was no deviation from the intended interventions because of the trial context. Additionally, the analysis was done by the intention to treat analysis.
	Missing outcome data	Low risk	Outcome data were available for nearly all participants.
	Measurement of the outcome	Low risk	Appropriate tools were used to measure the outcome without difference between the two group arms.
	Selection of the reported result	Low risk	No information about whether the outcomes and the analysis methods were pre-specified.
	OVERALL	**LOW RISK**	
Cooper et al. 2011 (The CRIT)	Randomization process	Low risk	This study was open-label, and the patients were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups by the coordinating center using consecutively numbered opaque envelopes and there were no apparent differences between the two groups.
	Deviations from intended interventions	Low risk	This study was an open-label study. There was no deviation from the intended interventions because of the trial context. Additionally, the analysis was done by the intention to treat analysis.
	Missing outcome data	Low risk	Outcome data were available for nearly all participants.
	Measurement of the outcome	Low risk	Appropriate tools were used to measure the outcome without difference between the two group arms.
	Selection of the reported result	Low risk	data that produced this result analysed in accordance with a pre-specified analysis plan.
	OVERALL	**LOW RISK**	
Ducrocq et al. 2021, Gonzalez-Juanatey et al. 2022	Randomization process	Low risk	A web-based randomization system was used for the randomization process and there were no apparent differences between the two groups.
	Deviations from intended interventions	Low risk	This study was an open-label study. There was no deviation from the intended interventions because of the trial context. Additionally, the analysis was done by the intention to treat analysis.
	Missing outcome data	Low risk	Outcome data were available for nearly all participants.

(The REALITY)	Measurement of the outcome	Low risk	Appropriate tools were used to measure the outcome without difference between the two group arms.
	Selection of the reported result	Low risk	data that produced this result analysed in accordance with a pre-specified analysis plan.
	OVERALL	**LOW RISK**	

Table S4: Description of risk of bias (ROB) assessment.

Outcome	No. of Participants (/)	No. of trials	Quantitative data synthesis				Heterogeneity analysis		
			MD	95% CI	Z value	p-value	df	p-value	I2 (%)
MACE at 30 days.									
Carson et al. 2013	2115/2100	3	0.77	[0.46, 1.29]	0.98	0.33	2	0.007	80%
Carson et al. 2023 (MINT)	420/400	3	0.84	[0.34, 2.08]	0.37	0.71	2	0.007	80%
Cooper et al. 2011 (The CRIT)	2145/2134	3	1.11	[0.75, 1.64]	0.51	0.61	2	0.05	66%
Ducrocq et al. 2021 (The REALITY)	1827/1831	3	0.98	[0.42, 2.25]	0.05	0.96	2	0.005	81%
Cardiac death at 30 days.									
Carson et al. 2013	2091/2079	2	1.05	[0.36, 3.04]	0.10	0.92	1	0.004	88%
Carson et al. 2023 (MINT)	396/379	2	1.69	[0.14, 20.08]	0.68	0.42	1	0.02	81%
Ducrocq et al. 2021 (The REALITY)	1803/1810	2	2.41	[0.75, 7.77]	1.47	0.14	1	0.18	44%
New or exacerbating heart failure at 30 days.									
Carson et al. 2013	2115/2100	3	0.76	[0.43, 1.33]	0.97	0.33	2	0.15	47%
Carson et al. 2023 (MINT)	420/400	3	0.86	[0.23, 3.22]	0.22	0.82	2	0.03	71%
Cooper et al. 2011 (The CRIT)	2145/2134	3	1.02	[0.63, 1.65]	0.09	0.93	2	0.22	33%
Ducrocq et al. 2021 (The REALITY)	1827/1831	3	0.88	[0.28, 2.80]	0.21	0.83	2	0.03	71%
Hemoglobin level (g/dl) Change.									
Carson et al. 2013	2091/2079	2	-1.47	[-1.76, -1.18]	9.87	<0.00001	1	0.01	84%
Carson et al. 2023 (MINT)	396/379	2	-1.30	[-1.49, -1.11]	13.31	<0.00001	1	0.96	0%
Ducrocq et al. 2021 (The REALITY)	1803/1810	2	-1.52	[-1.77, -1.26]	11.50	<0.00001	1	0.14	54%
Units of blood transfused per patient.									
Carson et al. 2013	2091/2079	2	-0.87	[-2.73, 1.00]	0.91	0.36	1	0.00001	98%
Carson et al. 2023 (MINT)	397/379	2	-0.50	[-1.67, 0.66]	0.85	0.40	1	0.0002	93%
Ducrocq et al. 2021(The REALITY)	1804/1810	2	-1.47	[-2.17, -0.78]	4.16	<0.0001	1	0.001	91%
Number of patients who transfused zero units of red blood cells.									
Carson et al. 2013	2091/2079	2	44.99	[2.35, 861.22]	2.53	0.01	1	0.003	89%
Carson et al. 2023 (MINT)	397/379	2	48.72	[1.69, 1402.96]	2.27	0.02	1	0.003	89%

Ducrocq et al. 2021 (The REALITY)	1804/1810	2	13.09	[10.70, 16.01]	24.98	<0.00001	1	0.97	0%
Number of patients who transfused one unit of red blood cells.									
Carson et al. 2013	2091/2079	2	0.60	[0.53, 0.67]	8.64	<0.00001	1	0.73	0%
Carson et al. 2023 (MINT)	397/379	2	0.40	[0.20, 0.80]	2.61	0.009	1	0.08	67%
Ducrocq 2021, Gonzalez-Juanatey 2022 (The REALITY)	1804/1810	2	0.43	[0.20, 0.92]	2.16	0.03	1	0.02	82%
Number of patients who transfused two units of red blood cells.									
Carson et al. 2013	2091/2079	2	0.36	[0.22, 0.57]	4.24	<0.0001	1	0.002	89%
Carson et al. 2023 (MINT)	397/379	2	0.45	[0.35, 0.59]	6.05	<0.00001	1	0.62	0%
Ducrocq et al. 2021 (The REALITY)	1804/1810	2	0.28	[0.24, 0.34]	14.77	<0.00001	1	0.80	0%

Table S5: Sensitivity analysis

MD: mean difference; CI: confidence interval; df: degrees of freedom.