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Antithrombotic treatment after coronary artery bypass graft surgery: systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE
To assess the effects of different oral antithrombotic drugs that prevent saphenous vein graft failure in patients undergoing coronary artery bypass graft surgery.

DESIGN
Systematic review and network meta-analysis.

DATA SOURCES
Medline, Embase, Web of Science, CINAHL, and the Cochrane Library from inception to 25 January 2019.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES
Randomised controlled trials of participants (aged ≥18) who received oral antithrombotic drugs (antiplatelets or anticoagulants) to prevent saphenous vein graft failure after coronary artery bypass graft surgery.

MAIN OUTCOME MEASURES
The primary efficacy endpoint was saphenous vein graft failure and the primary safety endpoint was major bleeding. Secondary endpoints were myocardial infarction and death.

RESULTS
This review identified 3266 citations, and 21 articles that related to 20 randomised controlled trials were included in the network meta-analysis. These 20 trials comprised 4803 participants and investigated nine different interventions (eight active and one placebo). Moderate certainty evidence supports the use of dual antiplatelet therapy with either aspirin plus ticagrelor (odds ratio 0.50, 95% confidence interval 0.31 to 0.79, number needed to treat 10) or aspirin plus clopidogrel (0.60, 0.42 to 0.86, 19) to reduce saphenous vein graft failure when compared with aspirin monotherapy. The study found no strong evidence of differences in major bleeding, myocardial infarction, and death among different antithrombotic therapies. The possibility of intransitivity could not be ruled out; however, between-trial heterogeneity and incoherence were low in all included analyses. Sensitivity analysis using per graft data did not change the effect estimates.

CONCLUSIONS
The results of this network meta-analysis suggest an important absolute benefit of adding ticagrelor or clopidogrel to aspirin to prevent saphenous vein graft failure after coronary artery bypass graft surgery. Dual antiplatelet therapy after surgery should be tailored to the patient by balancing the safety and efficacy profile of the drug intervention against important patient outcomes.

STUDY REGISTRATION
PROSPERO registration number CRD42017065678.

WHAT IS ALREADY KNOWN ON THIS TOPIC
Aspirin is considered the preferred antiplatelet drug to prevent saphenous vein graft failure after coronary artery bypass surgery

Uncertainty remains about the benefits of adding a P2Y12 inhibitor or direct oral anticoagulant to aspirin monotherapy after bypass surgery

WHAT THIS STUDY ADDS
Dual antiplatelet therapy with either aspirin plus ticagrelor or aspirin plus clopidogrel was more efficacious than aspirin monotherapy in preventing saphenous vein graft failure after coronary artery bypass surgery

No strong evidence was found of differences in major bleeding, myocardial infarction, and death for different antithrombotics compared with aspirin monotherapy

Future guideline updates are needed to optimise antithrombotic management of patients undergoing coronary artery bypass graft surgery

Dual antiplatelet therapy with aspirin plus ticagrelor or aspirin plus clopidogrel could be considered for most patients after surgery

Introduction
Coronary artery bypass graft surgery is the preferred treatment for many patients with multivessel coronary artery disease.[1 2] However, patients undergoing this procedure remain at risk of subsequent major adverse cardiovascular events, mainly caused by associated progression of native coronary artery disease, vascular damage, or saphenous vein graft failure.[3-7] Previous studies have shown rates of saphenous vein graft failure of up to 30-40% in the first year[8 9] and up to 70% beyond 10 years after coronary artery bypass graft surgery.[8 10-13] Despite its relatively high early failure rates, saphenous vein graft remains the most commonly used graft in contemporary coronary artery bypass graft trials.[14-17]

Aspirin is considered the preferred antiplatelet drug to prevent saphenous vein graft failure after coronary artery bypass graft (class I, level of evidence A).[18] Updated meta-analyses support this recommendation, but at a cost of increasing the risk of bleeding.[19-21] Uncertainty remains about the benefits of adding a P2Y12 inhibitor or oral anticoagulant to aspirin monotherapy. There is emerging evidence on the potential benefits of dual antiplatelet therapy with aspirin and clopidogrel or ticagrelor after coronary artery bypass graft surgery, but these combinations have not been directly

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compared with other antithrombotic therapies in randomised controlled trials. Additionally, no studies have been published to compare the effects of all available oral antithrombotic drugs (antiplatelets and anticoagulants) for the prevention of saphenous vein graft failure after coronary artery bypass graft surgery within a single analytical framework. Therefore, in this study we aimed to systematically review randomised controlled trials that assessed the effects of oral antithrombotic drugs to prevent saphenous vein graft failure in patients undergoing coronary artery bypass graft surgery. We also evaluated the comparative efficacy and harms of these drugs by using a network meta-analysis.

Methods

Literature search

This systematic review and network meta-analysis is reported following the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) extension statement for network meta-analysis[22] (fig 1). This study is registered with PROSPERO (CRD42017065678) and the protocol has been peer reviewed and published in *BMJ Open*.[23]

We conducted a search of Medline, Embase, Web of Science, CINAHL, and the Cochrane Library from their inception to 25 January 2019. We also performed a grey literature search and checked reference lists of relevant reviews and eligible randomised controlled trials to ensure a comprehensive search.[23] The full search strategy has been published in the protocol.[23]

Data selection

Studies were eligible for inclusion if they consisted of patients (≥18 years) who underwent coronary artery bypass graft surgery with at least one saphenous vein graft; if they compared oral antithrombotic regimens with each other or placebo; and if they evaluated saphenous vein graft failure, regardless of unit of analysis and drug regimens. Antithrombotic drugs included in this review were aspirin, clopidogrel, ticagrelor, vitamin K antagonists (warfarin, acenocoumarol, phenprocoumon), and rivaroxaban; dual antiplatelet therapy included aspirin plus clopidogrel or aspirin plus ticagrelor; and dual therapy included aspirin plus rivaroxaban. We did not include aspirin plus dipyridamole because this combination is no longer used in clinical practice for patients with coronary artery disease. We considered aspirin monotherapy as a single intervention regardless of whether aspirin was interrupted or continuously administered before coronary artery bypass graft surgery because a recent meta-analysis showed no difference between these two approaches.[21]

Data identification and extraction

Two investigators (KS and AAH) independently screened articles by title, abstract, and full text

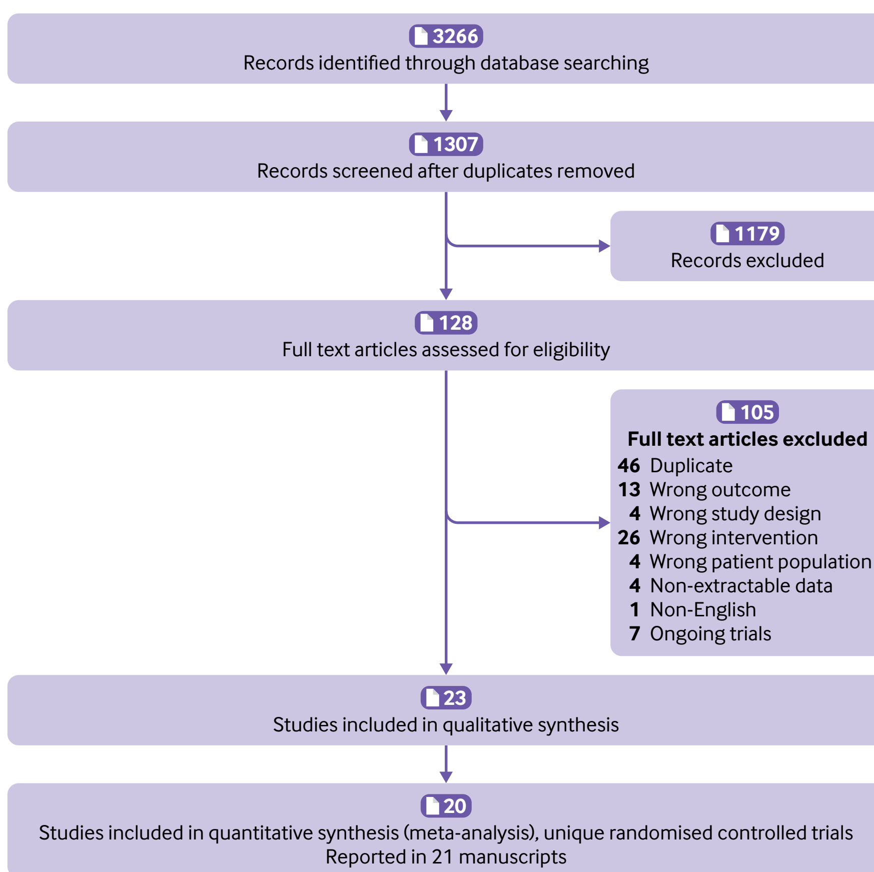

Fig 1 | PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

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Table 1 | Characteristics of the included randomised controlled trials

Study, year (sample size)	Time of drug initiation after CABG	Treatment duration	SVG patency assessment method (unit of analysis), time from randomisation to SVG patency assessment	Relevant study arms	No of any graft/ SVG per patient*	Age (years)	Male (%)	Effect size for SVGF, OR (95% CI)
Pantely, 1979 (n=47)	+3 days	6 months	Angiography (per patient and per graft), 6 months	VKA: warfarin (INR target: NR); C: no study medication	VKA: 2.85/2.85; C: 2.54/2.54	VKA: 56±8; C: 52±8	VKA: 69.2; C: 83.3	VKA *v* C: 1.04 (0.26 to 4.18)
McEnany, 1982 (n=216)	+3 to 4 days	12 months	Angiography (per patient and per graft), 21.5 months (range 1-47 months)	VKA: warfarin (INR target: 1.5-2); ASA: 600 mg BID; C: matching placebo	VKA: 1.91/1.91; ASA: 2.03/2.03; C: 2.00/2.00	—	VKA: 92.9; ASA: 82.0; C: 87.3	VKA *v* C: 0.55 (0.20 to 1.46); VKA *v* ASA: 0.69 (0.26 to 1.84); ASA *v* C: 0.79 (0.32 to 1.96)
Sharma, 1983 (n=116)	+3 to 5 days	12 months	Angiography (per patient and per graft), 12 months	ASA: 325 mg TID; C: no study medication	ASA: 2.20/2.20; C: 2.20/2.20	—	ASA: 100; C: 100	ASA *v* C: 0.94 (0.42 to 2.13)
Lorenz, 1984 (n=60)	+24 hours	4 months	Angiography (per patient and per graft), 4 months	ASA: 100 mg OD; C: matching placebo	ASA:1.90/1.90; C: 2.23/2.23	ASA: 55±10; C: 55±6	ASA: 82.8; C: 90.3	ASA *v* C: 0.23 (0.06 to 0.79)
Brown, 1985 (n=98)	+67± 27 hours	12 months	Angiography (per patient and per graft), 12 months	ASA: 325 mg TID; C: matching placebo	ASA: 3.10/3.10; C: 3.30/3.30	—	—	ASA *v* C: 0.52 (0.20 to 1.32)
Goldman, 1989 (n=98)	−12 hours	12 months	Angiography (per graft), 12 months (range 62-527 days)	ASA: 325 mg OD; C: matching placebo	Overall: -/3.20	ASA: 59±8; C: 58±8	ASA: 100; C: 100	ASA *v* C: 0.68 (0.39 to 1.18)
Gavaghan, 1991 (n=237)	+1 hours	12 months	Angiography (per patient and per graft), 12 months (range 222-430 days)	ASA: 324 mg OD; C: matching placebo	ASA: -/3.40; C: -/3.60	ASA:56±8; C: 56±7	ASA: 86.6; C: 83.6	ASA *v* C: 0.31 (0.15 to 0.63)
Van der Meer, 1993 (n=635)	−12 hours; 24 hours	12 months	Angiography (per patient and per graft), 12 months	VKA: 4 mg acenocoumarol or 6 mg phenprocoumon (INR target: 2.8-4.8); ASA: 50 mg OD	VKA: -/3.10; ASA: -/2.80	VKA: 58±8; ASA: 58±8	VKA: 88.0; ASA: 87.0	VKA *v* ASA: 0.99 (0.67 to 1.46)
Hockings, 1993 (n=140)	−7 days	6 months	Angiography (per patient), 6 months	ASA: 100 mg OD; C: matching placebo	ASA: 3.14/2.56; C: 3.52/2.79	ASA: 60±9; C: 60±9	ASA: 94.0; C: 92.3	ASA *v* C: 0.53 (0.16 to 1.71)
Mujanovic, 2009 (n=20)	Immediately postop	3 months	Angiography (per graft), 3 months	ASA+clopi: 100 and 75 mg OD, respectively; ASA: 100 mg OD	ASA+clopi: 2.9/2.9; ASA: 2.7/2.7	ASA+clopi: 58±8.5; ASA: 60±8.5	—	ASA+clopi *v* ASA: 0.16 (0.03 to 0.98)
Gao, 2009 (n=197)	+1 day	Unclear	64-MSCTA (per graft), 12 months	ASA+clopi: 100 and 75 mg OD, respectively; clopi: 75 mg OD	ASA+clopi: 2.66/1.71; clopi: 2.49/1.51	ASA+clopi: 61±10; clopi: 62±9.9	ASA+clopi: 82.1; clopi: 83.3	ASA+clopi *v* clopi: 0.52 (0.17 to 1.60)
Kulik, 2010 (n=113)	0 day	12 months	Angiography (per patient and per graft), 12 months	ASA+clopi: 162 and 75 mg OD, respectively; ASA: 162 mg OD and matching placebo	ASA+clopi: 3.6/2.30; ASA: 3.4/2.24	ASA+clopi: 65±7.5; ASA: 68±7.4	ASA+clopi: 91.1; ASA: 87.7	ASA+clopi *v* ASA 1.34† (0.39 to 4.62)
Gao, 2010 (n=249)	≤ +48 hours	3 months	MSCTA (per graft), 3 months	ASA+clopi: 100 and 75 mg OD, respectively; ASA: 100 mg OD	ASA+clopi: 3.18/2.14; ASA: 3.11/2.10	ASA+clopi: 58±8.3; ASA: 60±7.9	ASA+clopi: 82.3; ASA: 83.8	ASA+clopi *v* ASA: 0.55 (0.29 to 1.04)
Sun, 2010 (n=99)	+6 to 48 hours	1 month	MSCTA (per patient), 50 days	ASA+clopi: 81 and 75 mg OD, respectively; ASA: 81 mg OD	ASA+clopi: 4.03/2.35; ASA: 3.95/2.30	ASA+clopi: 66±9.4; ASA: 65±9.3	ASA+clopi: 93.9; ASA: 86.0	ASA+clopi *v* ASA: 1.20 (0.33 to 4.32)
Mannacio, 2012 (n=300)	+28± 12 hours	12 months	64-MSCTA (per graft), 12 months	ASA+clopi: 100 and 75 mg OD, respectively; ASA: 100 mg OD	ASA+clopi: 3.1/1.78; ASA: 3.2/1.87	ASA+clopi: 59±7.7; ASA: 59±8.3	ASA+clopi: 73.3; ASA: 75.3	ASA+clopi *v* ASA: 0.55 (0.29 to 1.02)
Saw, 2016 (n=70)	+58 to 59 hours	3 months	128/320-MSCTA (per graft), 12 months	ASA+tica: 81 mg OD and 90 mg BID, respectively; ASA: 81 mg OD and matching placebo	ASA+tica: 2.49/1.14; ASA: 3.43/1.69	ASA+tica: 62±7.5; ASA: 63±9.7	ASA+tica: 85.7; ASA:88.6	ASA+tica *v* ASA: 0.45 (0.13 to 1.56)
Slim, 2016 (n=20)	+6 hours	8 months	128-MSCTA (per graft), 12 months	ASA+clopi: 81 and 75 mg OD, respectively; ASA: 81 mg OD and matching placebo	ASA+clopi: 3.00/2.00; ASA: 3.38/2.38	—	—	ASA+clopi *v* ASA: 0.76 (0.20 to 2.95)
Zhao, 2018 (n=500)	+0 to 24 hours	12 months	MSCTA (per graft), 12 months	ASA+tica: 100 mg OD and 90 mg BID, respectively; tica: 90 BID; ASA: 100 OD	ASA+tica: 3.76/2.90; tica: 3.83/2.94; ASA: 3.76/2.92	ASA+tica: 64±8.2; tica: 63±8.3; ASA: 64±8.1	ASA+tica: 79.8; tica: 80.7; ASA: 84.9	ASA+tica *v* tica: 0.70 (0.44 to 1.09); ASA+tica *v* ASA: 0.47 (0.27 to 0.80); tica *v* ASA: 0.68 (0.46 to 1.01)
Xu, 2018 (n=140)	NR	1 month	MSCTA (per graft), 1 month	ASA+tica: 100 mg OD and 90 mg BID, respectively; ASA+clopi: 100 mg OD and 75 mg OD, respectively	ASA+tica: -/2.51; ASA+clopi: -/2.59	ASA+tica: 59±8.9; ASA+clopi: 60±7.5	ASA+tica: 77.1; ASA+clopi: 72.9	ASA+tica *v* ASA+clopi: 0.81 (0.24 to 2.73)
Lamy, 2018 (n=1448)	+4 to 14 days	NR	MSCTA (per graft), 12 months	ASA+riva: 100 mg OD and 2.5 mg BID, respectively; riva: 5 mg BID; ASA: 100 mg OD	ASA+riva: -/2.00; riva: -/2.00; ASA: -/2.00	ASA+riva: 66±7.8; riva: 65±7.9; ASA: 66±8.5	ASA+riva: 78.3; riva: 81.2; ASA: 82.3	ASA+riva: *v* riva: 1.24 (0.87 to 1.78); ASA+riva *v* ASA: 1.13 (0.80 to 1.62); riva *v* ASA: 0.91 (0.63 to 1.33)

Values are presented as mean±standard deviation or No (%) unless stated otherwise. ASA=aspirin; BID=twice a day; C=control; CABG=coronary artery bypass graft; clopi=clopidogrel; INR=international normalised ratio; MSCT=multislice computed tomography angiography; NR=not reported; OAC=oral anticoagulation; OD=once a day; OR=odds ratio; riva= rivaroxaban; SVG=saphenous vein graft; SVGF=saphenous vein graft failure; tica=ticagrelor; TID=three times a day; VKA=vitamin K antagonist.
*Data that were not reported in the original studies were calculated from total number of grafts/number of patients enrolled.
†Calculated from Hage[24] reporting long term data.

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according to prespecified inclusion criteria. The full text reports of potentially relevant studies were retrieved, and data on study and patient characteristics, treatment strategies, and results of all included studies were then independently extracted (KS and AAH/TC) using a data extraction form. Any discrepancies were resolved by consensus after consulting a third investigator (RB).

Outcome measures

The primary efficacy outcome was the incidence of saphenous vein graft failure, defined as participants with at least one occluded saphenous vein graft as assessed by either invasive angiogram or computed tomography (table 1 and supplementary table 1). We prespecified a sequence in the protocol[23] in case the overall preferred definition of total occlusion was not used. Because not all the included studies expressed saphenous vein graft failure on a per patient basis, we also included studies that reported per graft data in our base case analysis to increase the totality of evidence. We made the decision about combining per patient and per graft data after we compared the results from per patient[14-16 25-37] and per graft[14-17 24-36 38-40] (accounting for clustering effects) meta-analyses. The results for magnitude and direction of effect estimates were consistent and there were large overlapping 95% confidence intervals of effect sizes in most comparisons. Because a sensitivity analysis showed the per graft network meta-analysis and the base case network meta-analysis did not differ substantially, the inference for our base case analysis was made on per patient basis. This approach is clinically preferable given that treatments are applied to patients (and not grafts).

We calculated and used effective sample size instead of originally reported outcome data to account for clustering effects for per graft data.[41-43] The effective sample size was estimated by using a design effect that includes an intra cluster correlation coefficient.[43] We obtained the intra cluster correlation coefficient needed to calculate the effective sample size from an external source.[42] The size of the intra cluster correlation coefficient and the number of observations sampled within each cluster influence the power of the study.[43] We used an intra cluster correlation coefficient of 0.177 for this review.[42] Additionally, if studies reported the incidence of saphenous vein graft failure at multiple time points, we included the longest available follow-up period in our base case analysis.

The primary safety outcome was the incidence of major bleeding. Secondary outcomes were all cause mortality and myocardial infarction. These outcomes were binary and defined according to the definitions of the study authors (table 1 and supplementary table 1). We collected data on major adverse cardiac and cerebrovascular events, heart failure, minor bleeding, red blood cell transfusion, and admission to hospital owing to a cardiovascular cause; however, because these data were sparse, we did not report them in our study.

Risk of bias and certainty assessment

We assessed the risk of bias in included studies by using the Cochrane Collaboration tool for randomised trials 2.0[44] for each outcome. We graded the certainty of direct and network evidence by using the Grade of Recommendations Assessment, Development, and Evaluation (GRADE) for network meta-analysis.[45]

Statistical analyses

We performed a frequentist network meta-analysis of aggregate data to obtain network estimates for the aforementioned outcomes of interest. The model framework used random effects to allow for apparent heterogeneity among studies in treatment comparison effects. We conducted a pairwise meta-analysis to generate direct estimates for outcomes by using a random effects model. Transitivity assumption, the distribution of patient and study characteristics that modify treatment effects (effect modifiers) across treatment comparisons, was explored to assess whether these characteristics were sufficiently similar between comparisons. Additionally, we evaluated incoherence assumption (the statistical disagreement between direct and indirect evidence in a closed loop) locally using a loop specific approach, and globally using a design by treatment interaction model.[46] We used surface under the cumulative ranking (SUCRA)[47] to rank the intervention's hierarchy in the network meta-analysis and then we estimated mean ranks. We used the comparison adjusted funnel plot to explore the potential for publication bias.[47]

We performed sensitivity analyses to assess the robustness of the model for the primary outcomes. We visually compared the results of the base case analysis with those of the per graft and in-trial data (to exclude the legacy effect of drug interventions) analyses, and excluding trials with off pump coronary artery bypass graft only. We performed an "all missing failure" analysis to explore the impact of missing data; this analysis assumed that all missing patients had a negative event.[48] All outcomes of interest were binary and the relative treatment effects were reported as odds ratios with 95% confidence intervals. All analyses were done in Stata version 14 using the *network* command.

Patient and public involvement

There was no patient or public involvement around the research question or conception and design of the study. Because of the nature of the study, there was no patient or public involvement in any recruitment or conduction of the study. There was no patient or public involvement in measuring the outcomes, in providing interpretations of the findings, or writing of the results.

Results

Data selection

Our systematic search identified 3266 citations published between 1979 and 2019. Of these, we included 21 articles[14-17 24-40] that related to 20 unique parallel group randomised controlled trials in the network meta-analysis. These trials comprised

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4803 participants and investigated nine different interventions (eight active and one placebo) (fig 1); three trials had three eligible arms and the remaining trials had two eligible arms.[16 17 26]

The study sample size ranged from 20 to 1448 patients, patient age ranged from 44 to 83 years, 83% were male, and 83% underwent elective (stable coronary artery disease) surgery. The number of saphenous vein grafts ranged from 1.14 to 3.60 per patient, and drug interventions were started from seven days before coronary artery bypass graft surgery to 14 days after the procedure. The duration of follow-up ranged from one month to eight years. Assessment of saphenous vein graft failure was performed by either invasive angiography or computed tomography (table 1[14-17 24-40] and supplementary table 1).

Across comparisons, the distribution of baseline characteristics by treatment was generally balanced, except for the type of coronary artery bypass graft technique (on pump versus off pump coronary artery bypass graft), and the timing of drug initiation (table 2). Information on antifibrinolytic use was not reported because of limited data.

Mixed treatment meta-analyses

Primary efficacy outcome

The network of treatment comparisons for saphenous vein graft failure included nine individual nodes (fig 2, top panel). Each of the nodes represents placebo or different drug interventions; aspirin was the most well connected intervention with all other interventions directly linked to it, except for clopidogrel monotherapy. Figure 3 (top panel) shows network estimates of treatment effect on saphenous vein graft failure for different interventions compared with aspirin monotherapy. Network meta-analysis showed that dual antiplatelet therapy with either aspirin plus ticagrelor (odds ratio 0.50, 95% confidence interval 0.31 to 0.79, number needed to treat 10) or aspirin plus clopidogrel (0.60, 0.42 to 0.86, 19) was more efficacious than aspirin monotherapy to prevent saphenous vein graft failure. Pooled effect sizes also suggested that all active interventions reduced saphenous vein graft failure compared with placebo. However, the evidence does not support the efficacy of clopidogrel monotherapy in reducing saphenous vein graft failure compared with placebo (fig 3, top panel). According to SUCRA values, the top two ranked interventions for the reduction of saphenous vein graft failure were dual antiplatelet therapy with aspirin plus ticagrelor (94.4) and aspirin plus clopidogrel (85.3; table 3).

In our sensitivity analyses we used per graft data, excluded off pump only trials,[35 36] and accounted for missing outcome data. The study effect estimates (supplementary table 2) and SUCRA values (supplementary table 3) did not substantially change. One of the included studies in our network meta-analysis reported post-trial[24] (used in the base case analysis) and in-trial[37] data. We performed a sensitivity analysis to explore the legacy effect of drug interventions by using in-trial data. Effect estimates and SUCRA values did not substantially change compared with the base case analysis (supplementary tables 2 and 3, respectively).

Primary safety outcome

Eleven randomised controlled trials[15-17 24 26 31 33 34 35 39 40] comprising 3745 patients reported the incidence

Table 2 | Summary of baseline and procedural characteristics of patients across different treatment comparisons

	Treatment comparison (No of RCTs)											
Characteristics (No of RCTs*)	**ASA *v* placebo (n=7)**	**VKA *v* control (n=2)**	**VKA *v* ASA (n=2)**	**Tica *v* ASA (n=1)**	**Riva *v* ASA (n=1)**	**ASA+riva *v* aspirin (n=1)**	**ASA+riva *v* riva (n=1)**	**ASA+clopi *v* ASA (n=6)**	**ASA+clopi *v* clopi (n=1)**	**ASA+tica *v* ASA (n=2)**	**ASA+clopi *v* ASA+tica (n=1)**	**ASA+tica *v* tica (n=1)**
Age (n=17)	58±7.7	53±8	58±8	64±8.2	65±8.2	66±8.1	66±7.8	61±8.16	62±9.94	63±8.24	60±8.2	64±8.3
Male (n=16)	1212/1278 (95)	129/148 (87)	632/722 (88)	275/332 (83)	773/946 (82)	774/965 (80)	785/985 (80)	599/736 (81)	163/197 (83)	336/404 (83)	105/140 (75)	183/217 (84)
Diabetes (n=14)	45/560 (8)	18/111 (16)	74/722 (10)	142/332 (43)	412/946 (44)	413/965 (43)	393/985 (40)	168/756 (22)	108/197 (55)	163/404 (40)	94/140 (67)	124/217 (57)
Hypertension (n=15)	528/1218 (43)	20/111 (18)	250/722 (35)	242/332 (73)	NR	NR	NR	417/756 (55)	125/197 (64)	301/404 (75)	92/140 (66)	176/217 (81)
Dyslipidaemia (n=9)	27/116 (23)	NR	271/616 (44)	243/332 (73)	NR	NR	NR	426/736 (58)	41/197 (21)	299/404 (74)	NR	245/292 (84)
Prior MI (n=13)	703/1076 (65)	74/111 (67)	401/722 (56)	103/332 (31)	351/946 (37)	350/965 (36)	355/985 (36)	253/623 (41)	105/197 (53)	108/404 (27)	53/140 (38)	102/217 (47)
Prior PCI (n=5)	NR	NR	NR	NR	NR	NR	NR	77/524 (15)	24/197 (12)	8/70 (11)	18/140 (13)	NR
Prior CVA (n=3)	NR	NR	NR	35/332 (11)	29/946 (3.1)	36/965 (4.0)	37/985 (3.8)	16/436 (3.7)	NR	48/334 (14)	NR	75/217 (35)
OPCABG (n=16)	862/862 (100)	37/37 (100)	616/616 (100)	82/332 (25)	235/946 (25)	228/965 (24)	245/985 (25)	321/776 (41)	124/197 (63)	85/334 (25)	26/140 (19)	88/217 (41)
Elective surgery (n=16)	932/1006 (93)	73/145 (50)	695/755 (92)	332/332 (100)	582/946 (61)	599/965 (62)	601/985 (61)	776/776 (100)	186/197 (94)	381/404 (94)	140/140 (100)	217/217 (100)
Time of drug initiation (range) (n=20)	14 preop to 5 postop days	3-4 postop days	12 preop hours to 4 postop days	Within 24 postop hours	4-14 postop days	4-14 postop days	4-14 postop days	Immediately postop to 48 hours	1 day	Within 24-59 postop hours	NR	Within 24 postop hours

Values presented as mean±standard deviation or No (%) unless stated otherwise. ASA=aspirin; clopi=clopidogrel; CVA=cerebrovascular accident; MI=myocardial infarction; NR=not reported; OPCABG=off pump coronary artery bypass graft; PCI=percutaneous coronary intervention; RCT=randomised controlled trial; riva=rivaroxaban; tica=ticagrelor; VKA=vitamin K antagonist.
*Number of RCTs reporting data.

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of major bleeding. The network diagram of eligible treatment comparisons included eight individual nodes (fig 2, bottom panel). Each of the nodes represents different active interventions or placebo, in which aspirin monotherapy was the most well connected intervention with all other interventions directly linked to it. Figure 3 (bottom panel) shows network estimates of treatment effect on major bleeding for different interventions compared with aspirin monotherapy. Network meta-analyses showed no evidence of differences among all possible treatment comparisons. Pooled effect sizes also suggested that all active interventions increased bleeding compared with placebo, although without substantial statistical evidence (fig 3, bottom panel). According to SUCRA values, after placebo (84.4), the top ranked intervention associated with fewer major bleeding events was dual antiplatelet therapy with aspirin plus clopidogrel (66.5; table 3).

Sensitivity analyses that excluded one off pump only trial,[35] accounted for missing outcome data, and used in-trial data did not show substantial changes in study effect estimates (supplementary table 4) and SUCRA values (supplementary table 5). When we used in-trial data for analysis, aspirin monotherapy and its combination with rivaroxaban obtained a higher rank (supplementary table 5).

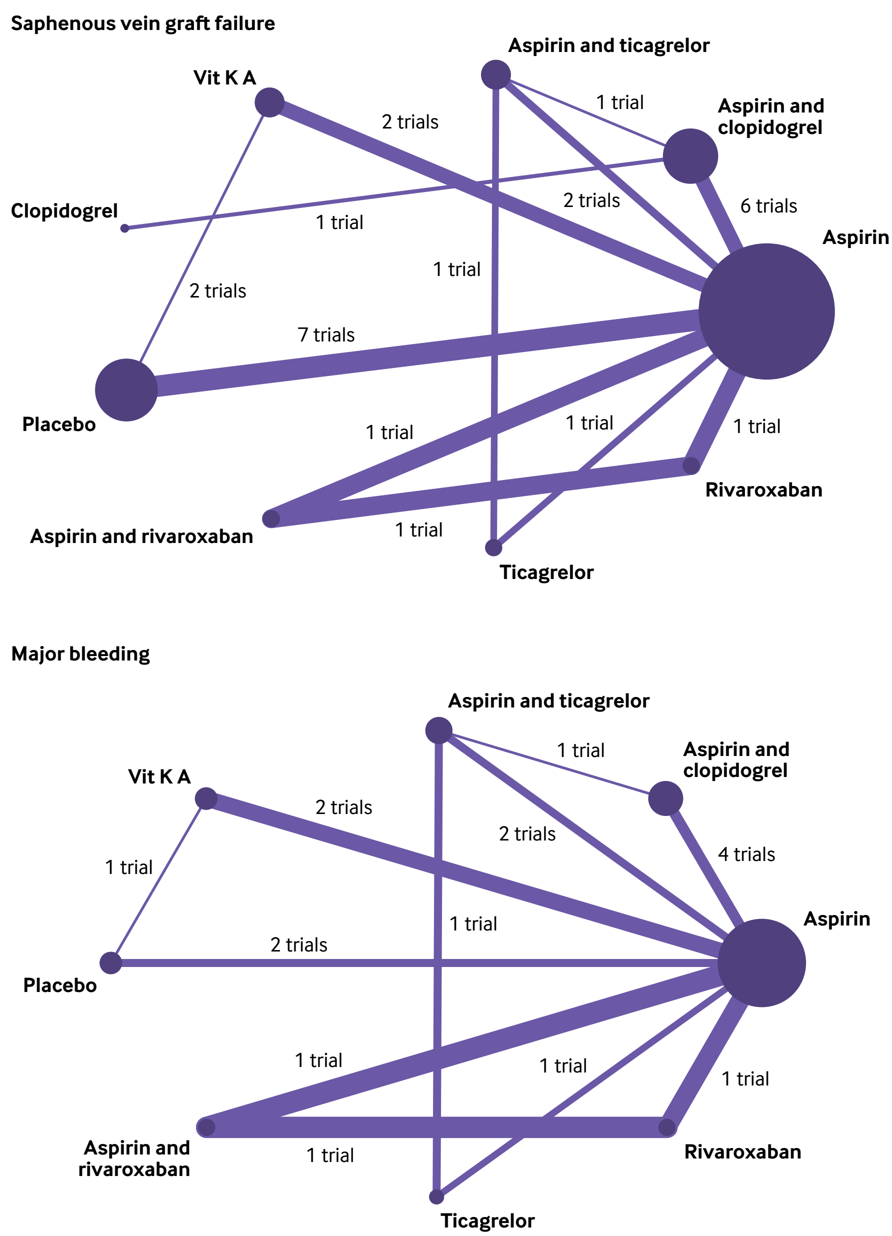

Fig 2 | Network of treatment comparisons for saphenous vein graft failure (primary efficacy outcome) and major bleeding (primary safety outcome). Each node represents different active interventions or placebo. Size of nodes is proportional to number of studies comparing respective nodes. Increasing thickness of lines between nodes is proportional to number of randomly assigned patients contributing to direct comparisons. Vit K A=vitamin K antagonist

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Secondary outcomes

Ten randomised controlled trials[14 15 25 26 29 30 31 33 37 39] comprising 1921 patients reported all cause mortality, and 12 randomised controlled trials[14-17 24 26 31 33 34 35 39 40] comprising 3994 patients reported myocardial infarction. Figure 4 shows networks of treatment comparisons for secondary outcomes. Figure 5 summarises results for secondary outcomes. Network meta-analyses showed no evidence of differences among all possible comparisons for secondary outcomes (all cause mortality and myocardial infarction). Supplementary table 6 presents SUCRA values. The included randomised controlled trials sparsely reported other prespecified secondary outcomes; therefore, network meta-analyses were not conducted for these outcomes.

Risk of bias and certainty of evidence

We judged two randomised controlled trials[27 39] to have a high risk of bias arising from the randomisation process and five randomised controlled trials[24-26 30 40] to have a high risk of bias because of missing outcome data (supplementary table 7). Five of the trials[26 29 36 38 39] had some concerns about measurement of the outcome and three randomised controlled trials[27 36 38] had some concerns about bias from selective reporting of outcomes. We judged only five unique trials[15 16 35 37 40] to have a low risk of bias due to deviation from intended interventions. Overall, we judged eight trials (40%)[24-28 30 39 40] to have a high risk of bias, primarily owing to failure to blind and missing outcome data. Of trials reporting incomplete outcome data, 10 trials[14-17 27 33-35 37 39] performed intention to treat

Saphenous vein graft failure

Placebo	0.64 (0.19 to 2.16)	**0.56 (0.42 to 0.76)**	**0.56 (0.37 to 0.86)**	**0.45 (0.26 to 0.79)**	**0.48 (0.30 to 0.77)**	**0.28 (0.16 to 0.48)**	**0.60 (0.38 to 0.98)**	**0.34 (0.21 to 0.54)**
	Clopidogrel	0.88 (0.27 to 2.84)	0.88 (0.26 to 2.98)	0.70 (0.20 to 2.47)	0.75 (0.22 to 2.55)	0.44 (0.13 to 1.52)	0.93 (0.27 to 3.16)	0.52 (0.17 to 1.60)
		Aspirin	1.00 (0.71 to 1.41)	0.80 (0.49 to 1.29)	0.85 (0.59 to 1.23)	**0.50 (0.31 to 0.79)**	1.06 (0.75 to 1.50)	**0.60 (0.42 to 0.86)**
			Vitamin K antagonists	0.80 (0.44 to 1.44)	0.85 (0.51 to 1.41)	**0.50 (0.28 to 0.88)**	1.06 (0.65 to 1.73)	**0.60 (0.36 to 0.98)**
				Ticagrelor	1.07 (0.58 to 1.95)	0.62 (0.37 to 1.05)	1.33 (0.73 to 2.40)	0.75 (0.42 to 1.35)
					Rivaroxaban	0.58 (0.32 to 1.05)	1.25 (0.87 to 1.78)	0.70 (0.42 to 1.18)
						Aspirin + Ticagrelor	**2.13 (1.20 to 3.85)**	1.20 (0.69 to 2.09)
							Aspirin + Rivaroxaban	**0.56 (0.34 to 0.93)**
								Aspirin + Clopidogrel

Major bleeding

Placebo	2.98 (0.31 to 28.2)	5.31 (0.56 to 50.2)	4.86 (0.20 to 119)	4.45 (0.42 to 47.0)	2.96 (0.28 to 31.8)	5.74 (0.31 to 106)	2.53 (0.21 to 30.0)
	Aspirin	1.78 (0.95 to 3.34)	1.63 (0.17 to 15.9)	1.50 (0.73 to 3.04)	0.99 (0.46 to 2.14)	1.93 (0.30 to 12.4)	0.85 (0.30 to 2.37)
		Vitamin K antagonists	0.91 (0.09 to 9.69)	0.84 (0.32 to 2.16)	0.56 (0.21 to 1.50)	1.08 (0.15 to 7.69)	0.48 (0.14 to 1.59)
			Ticagrelor	0.92 (0.08 to 9.93)	0.61 (0.06 to 6.71)	1.18 (0.24 to 5.91)	0.52 (0.05 to 5.39)
				Rivaroxaban	0.66 (0.33 to 1.33)	1.29 (0.18 to 9.42)	0.57 (0.16 to 1.98)
					Aspirin + Rivaroxaban	1.94 (0.26 to 14.5)	0.86 (0.24 to 3.08)
						Aspirin + Ticagrelor	0.44 (0.07 to 2.97)
							Aspirin + Clopidogrel

Fig 3 | Network meta-analysis and certainty of evidence for saphenous vein graft failure (primary efficacy outcome) and major bleeding (primary safety outcome). Results are odds ratios (95% confidence intervals) from the network meta-analysis between the column defining intervention and row defining intervention. Significant results are in bold. Certainty of evidence is also given: green=moderate certainty evidence, yellow=low certainty evidence, red=very low certainty evidence

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Table 3 | Summary of network meta-analysis estimates of effects, confidence intervals, and certainty of evidence for the comparison of different antithrombotic drugs in patients undergoing coronary artery bypass graft surgery

Comparator (reference): ASA monotherapy	Relative effect, odds ratio (95% CI)*	Anticipated absolute effect, per 1000 patients† (95% CI)			Certainty of evidence*	NNT/NNH (95% CI)	SUCRA‡
		ASA monotherapy	Other strategies	Difference			
SVGF§ (total studies: 20 RCTs; total participants: 4803):							
ASA+tica (2 RCTs; 420 participants)	**0.50 (0.31 to 0.79)**, network estimate	230	130	100 fewer (145 to 39 fewer)	⊕⊕⊕○**, moderate**, due to indirectness	NNT: 10 (7 to 26)	**94.4**
ASA+clopi (6 RCTs; 1118 participants)	**0.60 (0.42 to 0.86)**, network estimate	150	96	54 fewer (81 to 18 fewer)	⊕⊕⊕○**, moderate**, due to indirectness	NNT: 19 (13 to 55)	**85.3**
ASA+riva (1 RCT; 1401 participants)	1.06 (0.75 to 1.50), network estimate	99	104	5 more (23 fewer to 43 more)	⊕⊕○○, low, due to indirectness and imprecision	Not calculated (non-statistically significant)	32.9
Tica monotherapy (1 RCT; 332 participants)	0.80 (0.49 to 1.29), network estimate	283	240	43 fewer (121 fewer to 54 more)	⊕⊕○○, low, due to indirectness and imprecision	Not calculated (non-statistically significant)	61.3
Riva monotherapy (1 RCT; 1351 participants)	0.85 (0.59 to 1.23), network estimate	99	85	14 fewer (38 fewer to 20 more)	⊕⊕○○, low, due to indirectness and imprecision	Not calculated (non-statistically significant)	58.3
VKA (2 RCTs; 601 participants)	1.00 (0.71 to 1.41), network estimate	284	284	0 fewer (64 fewer to 75 more)	⊕○○○, very low, due to risk of bias, indirectness, and imprecision	Not calculated (non-statistically significant)	39.7
Clopi monotherapy (no direct evidence, indirect evidence only)	1.14 (0.35 to 3.69)	100¶	112	12 more (63 fewer to 191 more)	⊕○○○, very low, due to intransitivity, indirectness, and imprecision	Not calculated (non-statistically significant)	36.2
Placebo (7 RCTs; 831 participants)	1.77 (1.31 to 2.39), network estimate	255	377	122 more (55 to 195 more)	⊕⊕⊕○, moderate, due to indirectness	NNH: 9 (6 to 19)	3.3
Major bleeding (total studies: 11 RCTs; total participants: 3745):							
Placebo (2 RCTs; 385 participants)	0.34 (0.04 to 3.23), network estimate	8	3	5 fewer (7 fewer to 16 more)	⊕⊕○○, low, due to indirectness and imprecision	Not calculated (non-statistically significant)	**84.4**
ASA+clopi (5 RCTs; 518 participants)	0.85 (0.30 to 2.37), network estimate	33	28	5 fewer (23 fewer to 42 more)	⊕⊕○○, low, due to indirectness and imprecision	Not calculated (non-statistically significant)	**66.5**
ASA+riva (1 RCT; 965 participants)	0.99 (0.46 to 2.14), network estimate	28	28	0 fewer (15 fewer to 30 more)	⊕⊕⊕○, moderate, due to imprecision	Not calculated (non-statistically significant)	61.1
Riva (1 RCT; 946 participants)	1.50 (0.73 to 3.04), network estimate	28	41	13 more (7 fewer to 53 more)	⊕⊕⊕○, moderate, due to imprecision	Not calculated (non-statistically significant)	33.6
Tica (1 RCT; 332 participants)	1.63 (0.17 to 15.9), network estimate	3	5	2 more (2 fewer to 43 more)	⊕⊕⊕○, moderate, due to imprecision	Not calculated (non-statistically significant)	38.6
ASA+tica (2 RCTs; 404 participants)	1.93 (0.30 to 12.4), network estimate	12	23	11 more (9 fewer to 123 more)	⊕⊕⊕○, moderate, due to imprecision	Not calculated (non-statistically significant)	29.8
VKA (2 RCTs; 755 participants)	1.78 (0.95 to 3.34), network estimate	42	74	31 more (2 fewer to 88 more)	⊕○○○, very low, due to risk of bias, indirectness and imprecision	Not calculated (non-statistically significant)	24.4

ASA=aspirin; clopi=clopidogrel; NNH=number needed to harm; NNT=number needed to treat; RCT=randomised controlled trial; riva=rivaroxaban; SUCRA=surface under the cumulative ranking; SVGF=saphenous vein graft failure; tica=ticagrelor; VKA=vitamin K antagonist.
*Significant results are in bold.
†Data obtained directly from study sample (studies reporting outcome data), unless stated otherwise.
‡Larger SUCRA values indicate better interventions and higher hierarchy ranks are in bold.
§Saphenous vein graft failure (base case analysis), range of follow-up between one month and eight years.
¶Assumed risk (risk was assumed because of lack of direct evidence).

analysis, and two of these[16 27] clearly reported the use of intention to treat analysis with worst case assumptions for imputation of missing data. It was unclear how the remaining trials with incomplete data handled missing outcome data.

Figure 3 (top panel) also provides the certainty of evidence of network estimates for saphenous vein graft failure. We downgraded evidence certainty to low or very low for most comparisons, mainly because of study limitations owing to incomplete outcome data, imprecision, indirectness, and the possibility of intransitivity. Supplementary tables 8 and 9 summarise certainty of evidence for direct, indirect, and network estimates. The network evidence for dual antiplatelet therapy with aspirin plus ticagrelor and aspirin plus clopidogrel was of moderate certainty compared with aspirin monotherapy. The symmetrical comparison adjusted funnel plot shows neither evidence of publication bias for placebo controlled trials nor small study effects (supplementary figure 1). When we performed a sensitivity analysis that excluded studies considered at serious risk of bias, the effect estimates did not change substantially, except for aspirin plus clopidogrel versus vitamin K antagonist, which became non-significant (supplementary figure 2).

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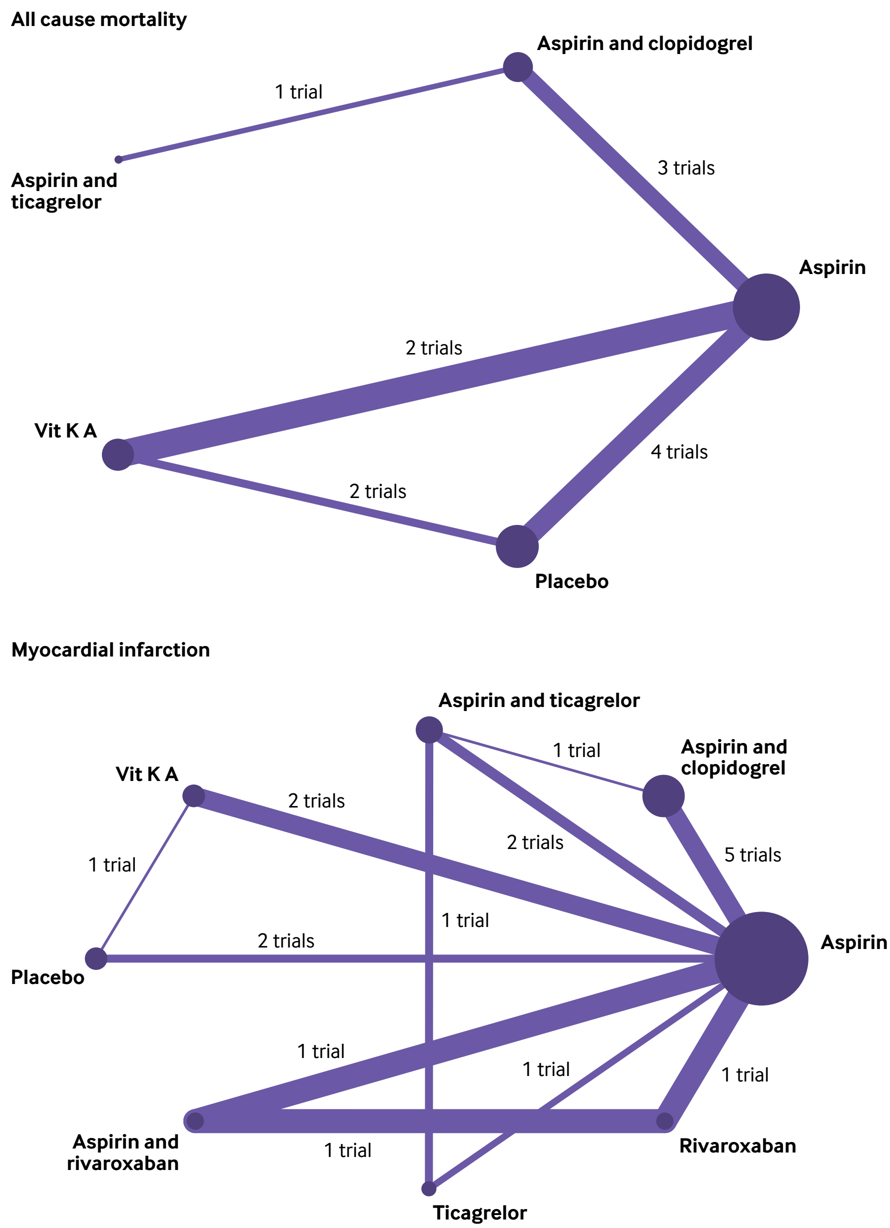

Fig 4 | Network of treatment comparisons for secondary outcomes all cause mortality and myocardial infarction. Each node represents different active interventions or placebo. Size of nodes is proportional to number of studies comparing respective nodes. Increasing thickness of lines between nodes is proportional to number of randomly assigned patients contributing to direct comparisons. Vit K A=vitamin K antagonist

We also downgraded the certainty of evidence to low or very low for most comparisons of clinical outcomes, including major bleeding, myocardial infarction, and mortality (fig 3, bottom panel, fig 5, and supplementary tables 8 and 9). However, comparisons with moderate certainty evidence should be interpreted with caution mainly because of inconsistency and publication bias. We could not thoroughly assess inconsistency because many of the comparisons consisted of a single study. Additionally, we could not assess publication bias for secondary outcomes because this network meta-analysis was designed to exclude studies that did not evaluate our primary efficacy outcome (saphenous vein graft failure), regardless of reported secondary outcomes (supplementary tables 8 and 9).

Network assumptions

The distribution of potential effect modifiers was not balanced across comparisons; however, the evidence of intransitivity was inconclusive because of missing data in several comparisons (table 2). While we could not rule out the possibility of intransitivity (lack of similar characteristics across the studies and treatment comparisons), between-trial heterogeneity (τ^2) was low in all included analyses compared with the expected value reported in the literature.[49] Supplementary table 9 shows direct and indirect estimates, and τ^2. Loop specific approach (supplementary table 10) and design by treatment interaction models (supplementary table 11) showed no evidence of incoherence between direct and indirect comparisons for all analyses.

All cause mortality

Placebo	1.77 (0.52 to 5.99)	1.04 (0.23 to 4.72)	1.24 (0.01 to 114)	1.24 (0.13 to 11.5)
	Aspirin	0.59 (0.19 to 1.87)	0.70 (0.01 to 54.3)	0.70 (0.11 to 4.50)
		Vitamin K antagonists	1.19 (0.01 to 107)	1.19 (0.13 to 10.6)
			Aspirin + Ticagrelor	1.00 (0.02 to 51.1)
				Aspirin + Clopidogrel

Myocardial infarction

Placebo	0.49 (0.11 to 2.11)	0.45 (0.10 to 2.00)	0.33 (0.03 to 3.28)	0.47 (0.08 to 2.84)	0.34 (0.04 to 2.84)	0.25 (0.04 to 1.73)	0.34 (0.06 to 2.05)
	Aspirin	0.92 (0.52 to 1.63)	0.68 (0.12 to 3.97)	0.96 (0.33 to 2.75)	0.70 (0.15 to 3.22)	0.52 (0.15 to 1.80)	0.71 (0.26 to 1.96)
		Vitamin K antagonists	0.74 (0.12 to 4.71)	1.04 (0.31 to 3.45)	0.76 (0.15 to 3.88)	0.57 (0.15 to 2.21)	0.77 (0.24 to 2.46)
			Ticagrelor	1.40 (0.18 to 10.93)	1.03 (0.16 to 6.80)	0.77 (0.09 to 6.58)	1.04 (0.14 to 7.68)
				Rivaroxaban	0.74 (0.12 to 4.68)	0.55 (0.16 to 1.88)	0.74 (0.17 to 3.20)
					Aspirin + Ticagrelor	0.74 (0.10 to 5.27)	1.00 (0.18 to 5.74)
						Aspirin + Rivaroxaban	1.35 (0.27 to 6.70)
							Aspirin + Clopidogrel

Fig 5 | Network meta-analysis and certainty of evidence for secondary outcomes all cause mortality and myocardial infarction. Results are odds ratios (95% confidence intervals) from the network meta-analysis between the column defining intervention and the row defining intervention. Certainty of evidence is also given: green=moderate certainty evidence, yellow=low certainty evidence, red=very low certainty evidence

Discussion

Principal findings

This systematic review included 20 parallel group randomised controlled trials of 4803 patients undergoing coronary artery bypass graft. The review compared eight active antithrombotic interventions in a single framework to assess saphenous vein graft failure. The results of this network meta-analysis suggest that among active interventions and based on moderate certainty evidence, dual antiplatelet therapies with aspirin plus ticagrelor or aspirin plus clopidogrel were the most efficacious treatment regimens to prevent saphenous vein graft failure compared with aspirin monotherapy. However, the tradeoff was an increased risk of major bleeding, although the risk did not differ among the drug interventions.

Strengths and limitations of the study

The strength of our analysis is its robust design and transparency. We prespecified the research question and published a peer reviewed protocol[23] for this systematic review of published randomised controlled trials of drug interventions to prevent saphenous vein graft failure after coronary artery bypass graft surgery. To increase the totality of evidence, we accounted for clustering effects of data expressed on a per graft basis, and made an inference at the patient level, which improved the applicability of the results in light of a newer P2Y12 inhibitor (ticagrelor) and direct factor Xa inhibitor (rivaroxaban). Our analysis adds new data on the use of dual antiplatelet therapy with aspirin plus ticagrelor and direct oral anticoagulation with rivaroxaban, thereby providing a better understanding of the role of these drug interventions to prevent saphenous vein graft failure after coronary artery bypass graft surgery.

The certainty of evidence for the saphenous vein graft failure endpoint was considered low or moderate for making a recommendation for most treatments compared with aspirin. Therefore, additional well designed research might change the findings.

For clinical (secondary) outcomes, the results of our network meta-analysis show no differences in effect estimates among multiple treatment comparisons; nonetheless, these were not our prespecified primary outcomes. Interestingly, the recently published and prematurely terminated trial that compared ticagrelor with aspirin after coronary artery bypass graft surgery showed no important differences in major adverse cardiovascular events or bleeding between the

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monotherapies.[50] These findings support the need for studies that evaluate dual antiplatelet therapy after coronary artery bypass graft surgery. Although our study might be underpowered to detect differences in clinical outcomes, further and larger randomised controlled trials that compare all the relevant antithrombotic strategies after coronary artery bypass graft surgery will be difficult to undertake with a mixed treatment comparison design. Therefore, our study is clinically meaningful and contributes up to date data to guide future directions in preventing saphenous vein graft failure after coronary artery bypass graft surgery.

In this study, we used a frequentist framework to perform the analysis as opposed to a Bayesian approach because the results of Bayesian analysis with non-informative priors are numerically equivalent to frequentist results. Although informative priors would make Bayesian methods more appealing than a frequentist framework, especially when dealing with small studies, such priors were not available. Therefore, the risk of using inaccurate informative priors can cause even more damage to the validity of the results.

Our study has several limitations. First, the quality of our analysis is limited by the inherent limitations of individual included trials. In particular, patient level data were not available, which precluded adjustment for any differences in clinical setting; for example, stable coronary artery disease versus acute coronary syndromes, elective versus urgent surgery, and on pump versus off pump coronary artery bypass graft surgery. In this study, more than 80% of the patients underwent elective coronary artery bypass graft surgery; moreover, in the acute coronary syndrome setting, there is consensus among international guidelines that dual antiplatelet therapy is resumed soon after surgery and continued for one year (class I).[2 51 52] Also, we were unable to perform competing risk analysis. If we had reported measures of effects that reflect time to event (that is, hazard ratio), the results would have been more informative. However, the studies that were eligible for this review did not report these measures.

Second, although we presented full details about the risk of bias of all included trials (supplementary table 7), many trials did not report adequate information about allocation sequence concealment, proportions of and reasons for missing outcome data, and how trials handled missing data. This lack of information could have led to inaccurate interpretation of the certainty of evidence. Third, different trials used different outcome definitions and also various imaging follow-up protocols, which could have threatened the internal validity of our network meta-analysis. Although our sensitivity analysis showed no substantial differences in effect estimates between per graft and per patient analyses for most comparisons, the credibility of this data driven approach remains unclear. Fourth, we combined studies using different doses of the same drug intervention in the same node, and assumed that there would be no systematic differences in treatment effects across doses. Fifth, the trials in which most of patients underwent off pump coronary artery bypass graft surgery,[16 35 36] the dose of aspirin (monotherapy or dual antiplatelet therapy) was 81-100 mg daily. However, we were unable to compare and confirm the potential benefit of higher doses (such as 160-325 mg) of aspirin in patients undergoing off pump procedures because of a lack of off pump trials using these doses of aspirin. Nevertheless, when combined with a P2Y12 inhibitor, the recommended dose of aspirin is less than 100 mg daily.

Sixth, our network meta-analysis included trials published over a 39 year period, which might not reflect the current clinical practice; for example, patient characteristics, surgical techniques (eg, off pump coronary artery bypass graft), drug regimens (early trials were more likely to compare against placebo and later trials were more likely to be active comparator trials), and secondary prevention strategies[18] (statins, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers and β blockers). Therefore, changes in adjunct medical treatment over time could potentially affect treatment estimates. Post hoc meta-regression analysis did not show evidence of an association between treatment effect and year of publication for some treatments. However, it was not possible to estimate the effect of publication year for all treatments owing to multicollinearity and missing linkage (supplementary table 12). We performed a sensitivity analysis stratified by publications before and after the year 2000 (supplementary figure 3), and the findings did not change the treatment effect when the results were split by more recent trials. Finally, legacy or post trial persistent treatment effect was explored. While the sensitivity analysis did not change the effect estimates, this was based on a single study that reported saphenous vein graft failure at one[37] and eight[24] years.

Comparison with other studies

Aspirin monotherapy is currently recommended for patients with stable coronary artery disease after coronary artery bypass graft surgery to reduce saphenous vein graft failure.[18] In patients who present with acute coronary syndromes, dual antiplatelet therapy is recommended to be resumed soon after coronary artery bypass graft surgery.[2 51 52] However, there is a lack of evidence that dual antiplatelet therapy is associated with a decrease in thromboembolic complications or mortality in patients with stable coronary artery disease undergoing coronary artery bypass graft surgery.[53] Few observational and randomised data suggest that additional drug intervention with dual antiplatelet therapy reduces the risk of saphenous vein graft failure. This effect appears to be more pronounced in patients undergoing off pump coronary artery bypass graft surgery than on pump coronary artery bypass graft surgery, or for arterial graft recipients.[54 55]

The 2016 American guidelines[51] recommend that in patients with stable coronary artery disease, aspirin

81 mg (75-100 mg) plus clopidogrel (started early after surgery) for 12 months after coronary artery bypass graft might be reasonable to improve saphenous vein graft patency (class IIb, level of evidence B). Conversely, the 2017 European guidelines state that there is insufficient evidence to generally recommend dual antiplatelet therapy to reduce saphenous vein graft failure.[53] To mitigate the relative hypercoagulable state that off pump patients experience, the 2015 American Heart Association scientific statement[18] recommends the combination of aspirin and clopidogrel after off pump coronary artery bypass graft surgery (class I, level of evidence A). However, the European guidelines state that there is weak evidence to support dual antiplatelet therapy in this subset of patients,[53] and the American guidelines[51] do not comment on this.

The clinical benefits of adding a P2Y12 inhibitor to aspirin originate from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial. Participants with non-ST elevation acute coronary syndromes who were allocated to receive aspirin plus clopidogrel experienced a major reduction in the composite outcome of death from cardiovascular causes, non-fatal myocardial infarction, or stroke, and a range of related ischaemic events.[56] However, there was a tradeoff of increased risk of bleeding, and most of the major bleeding events were gastrointestinal and arterial access site bleeds.[56] In our analysis, although the occurrence of major bleeding with aspirin plus ticagrelor was not statistically significant compared with aspirin alone, the network estimates showed an odds ratio of 1.93, and wide 95% confidence intervals (0.30 to 12.4) compared with aspirin plus clopidogrel (0.85, 0.30 to 2.37). The lack of different doses of clopidogrel precludes further analysis. Notably, the combination of aspirin plus rivaroxaban 2.5 mg twice daily or rivaroxaban 5 mg twice daily alone did not reduce saphenous vein graft failure compared with aspirin alone in the COMPASS (Cardiovascular OutcoMes for People Using Anticoagulation StrategieS) coronary artery bypass graft trial.[17] However, the combination of aspirin plus rivaroxaban 2.5 mg twice daily was associated with similar reductions in major adverse cardiovascular events, and this was consistent with the findings of the main COMPASS trial.[57] Therefore, because major bleeding has been associated with increased morbidity and mortality,[58 59] the risk of bleeding should be carefully balanced against the benefits when planning long term (>12 months) dual antiplatelet therapy in patients undergoing coronary artery bypass graft surgery.

Unanswered questions and future research

We did not have enough power to detect significance for clinical outcomes because we restricted the inclusion to trials that reported saphenous vein graft failure (our primary outcome), hence reducing statistical power in this regard. However, the eligibility criteria were purposefully stringent to reduce heterogeneity and risk of bias. Saphenous vein graft failure is not a clinical outcome in itself; it is considered a surrogate endpoint of myocardial infarction or repeat revascularisation. However, not all saphenous vein grafts are the same because of individual graft quality or technical (that is, anastomoses) matters. Additionally, the grafts depend on which are the target vessels, the severity of stenosis and ischemia,[60] and the territory and amount of myocardium being supplied by a given graft. Hence, saphenous vein graft failure will occur because of physiological or functional causes rather than saphenous vein graft driven thrombotic mechanisms, yet without apparent clinical consequence.[60 61] Lopes and colleagues[61] showed that saphenous vein graft failure was associated with an increased risk for the composite of death, myocardial infarction, or repeat revascularisation at four years after the angiogram. However, this association was mainly because of repeat revascularisation; there were no differences in terms of death or the composite of death and myocardial infarction among individuals with and without saphenous vein graft failure.[61] These findings highlight the confounded association between saphenous vein graft failure and major adverse cardiovascular events. Therefore, when saphenous vein graft failure is accompanied by clinical symptoms,[61] for example new onset angina and progressive symptoms of angina, or hospital admission for acute coronary syndromes leading to revascularisation, this could be more relevant for prognosis and patient preferences and values.

Not all the included trials reported the actual data on duration of treatment. Therefore, patients might have received different durations of antithrombotic treatments, which resulted in patient level covariate effects. Post hoc meta-regression analysis did not show evidence of an association between duration of treatment (originally prespecified by the trial authors, not actual duration) and treatment effect for some drug interventions; however, it was not possible to estimate the effect of treatment duration for all treatments because of multicollinearity and missing linkage (supplementary table 13). Moreover, this meta-regression probably had low power to detect such an association, and its credibility is questionable owing to the lack of patient level data; therefore, it is subject to ecological bias.

Further research is needed to improve strategies to optimise saphenous vein graft patency after coronary artery bypass graft surgery. We need studies of adequate duration and sample size that report saphenous vein graft failure at different time points to determine the potential legacy effect of dual antiplatelet therapy during the first year after coronary artery bypass graft surgery. Additionally, these studies should report long term (that is, five or 10 years) incidence of saphenous vein graft failure, and patient important outcomes (mortality, ischaemic, or bleeding events).

Conclusion and policy implications

The results of this network meta-analysis suggest an important absolute benefit of adding ticagrelor or clopidogrel to aspirin to prevent saphenous vein graft

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failure after coronary artery bypass graft surgery. Dual antiplatelet therapy after surgery should be tailored to the patient by balancing the safety and efficacy profile of the drug intervention against important patient outcomes. Future guideline updates are needed to optimise antithrombotic management of patients undergoing coronary artery bypass graft surgery. Meanwhile, dual antiplatelet therapy with aspirin plus ticagrelor or aspirin plus clopidogrel could be considered for most patients after surgery.

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The lead author (RB) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned in the peer-reviewed published protocol have been explained.

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Web appendix: Supplementary material

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