Systematic Review

Network meta-analysis of antiplatelet therapy following coronary artery bypass grafting (CABG): none versus one versus two antiplatelet agents

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Background: Numerous agents have been trialed following coronary artery bypass grafting (CABG) to maintain long-term graft patency. While clear evidence exists for the use of aspirin in maintaining graft patency, the role of dual-antiplatelet therapy in CABG patients is not as well established. This network meta-analysis aimed to compare the short-term post-CABG graft patency outcomes for patients with none, one or two antiplatelet agents.

Methods: Electronic databases were queried for randomized controlled trials comparing CABG graft patency rates at three months and beyond using various antiplatelet agents or placebo. Drug and graft patency data were compared using a mixed treatment comparison under a Bayesian hierarchical framework. A random-effects consistency model was applied. Direct and indirect comparisons were made between drugs and used to determine the relative efficacy for graft patency.

Results: The literature search identified 16 papers fulfilling the inclusion criteria, including a total of 3,133 patients with an average of 2.43 [95% confidence interval (CI): 2.20–2.66] grafts per patient. Graft types were incompletely reported, however, saphenous vein grafts (SVGs) were predominantly used [where specifically reported: 4,490 SVG, 1,226 internal mammary artery (IMA) grafts]. In all, five different agents and placebo in various regimens were compared by results of angiographic follow-up conducted at a mean of 10.4 months (95% CI: 9.28–11.5 months). Compared to placebo, aspirin alone [odds ratio (OR) 1.9; 95% credible interval (CrI): 1.3–2.8], aspirin + dipyridamole (OR 1.9; 95% CrI: 1.3–2.6), aspirin + clopidogrel (OR 2.9; 95% CrI: 1.5–5.7) and aspirin + ticagrelor (OR 3.8; 95% CrI: 1.2–13.0) significantly improved graft patency. When compared to aspirin monotherapy, aspirin + clopidogrel (OR 1.6; 95% CrI: 0.86–2.7) and aspirin + ticagrelor (OR 2.0; 95% CrI: 0.69–6.3) had OR that suggested a trend favoring patency compared to aspirin monotherapy, however, these results did not reach significance. Sub-group analysis of SVG graft patency was unable to reach significance (only eight studies with six treatment comparisons were evaluated). Secondary endpoints of death, bleeding, myocardial infarction and cerebrovascular accident were incompletely reported and were pooled but not compared between drug treatment arms.

Conclusions: Aspirin monotherapy and dual antiplatelet therapy (DAPT) provided significant all-graft patency benefit compared to placebo at three months and beyond. A trend existed for DAPT to improve graft patency compared to aspirin, although this did not reach statistical significance. Further randomized controlled studies comparing aspirin monotherapy to DAPT are required to determine the utility of DAPT in CABG patients for maintaining graft patency.

Keywords: Antiplatelet; graft patency; dual antiplatelet therapy (DAPT); coronary artery bypass graft; network meta-analysis

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Introduction

A multitude of different agents have been used following coronary artery bypass grafting (CABG) to improve graft patency rates. These treatments have included both monotherapies (commonly aspirin) and more recently, dual therapies (aspirin in conjunction with another anti-platelet agent) (1,2). Other monotherapies have also been trialed, including the use of anti-coagulants alone (3,4), however, these have not been widely adopted.

While the use of dual anti-platelet therapy (DAPT) in coronary percutaneous intervention (PCI) patients is considered the standard of care for maintaining graft patency and reducing post-procedural ischaemic events, the role for DAPT in post-operative CABG patients is not as clearly established (1,5,6). Meta-analyses have investigated the impact on graft patency of aspirin use compared to placebo (7), as well as dual antiplatelet use compared to aspirin alone (1,8,9) in patients following CABG. These showed that aspirin monotherapy was superior to placebo and that DAPT was superior to aspirin monotherapy for saphenous vein grafts but was not significantly better when arterial grafts were included (8,9). While these meta-analyses have compared placebo with aspirin and aspirin with DAPT individually, there is a paucity of direct comparisons between all agents. This network meta-analysis aims to summarize the relative efficacies for maintaining graft patency when using none, one or two antiplatelet agents following CABG.

Methods

Literature search

Three electronic databases (MEDLINE, Embase and PubMed) were queried from their dates of inception till March 2018 using the search terms ((“CABG” OR “coronary artery bypass” OR “coronary bypass” OR “coronary artery bypass graft”) AND (“anti-platelet” OR “aspirin” OR “clopidogrel” OR “ticagrelor” OR “plavix” OR “prasugrel” OR “antiplatelet”) AND (“randomized controlled trial” OR “randomised controlled trial” OR “RCT” OR “Randomized” OR “Randomised”)). Randomized controlled trials with an intention to treat of at least 50 patients per arm and examining graft patency with at least 3-month follow-up were included. Studies which were not randomized controlled trials, were animal studies or did not have English language full texts were excluded. Non-binary patency data (such as graft patency reported by flow in milliliters/minute), unclear graft patency reporting and early study termination [incomplete randomised controlled trials (RCTs)] led to the study being excluded. Studies or study arms containing drugs not used contemporarily for graft patency and reported only in single studies (such as warfarin alone) were excluded. Where the same cohort of patients was reported in multiple articles, only the latest cohort data was included.

The primary outcome was graft patency in the (3-month or beyond) follow-up period, with secondary outcomes including mortality, bleeding, myocardial infarct and cerebrovascular accident. Literature search and data collection were performed by two independent researchers (D Jbara and K Singh). A further reference list search was conducted for the included papers. The search process is shown in supplementary *Figure S1*.

Quality analysis

Appraisal of randomized controlled trial study quality was conducted using a binary scoring system with twenty categories adapted from the Consolidated Standards of Reporting Trials statement 2010 (CONSORT 2010) (10). Using this scale, study quality was stratified as standard and high quality, with studies scoring in the range 12–16 standard quality and 16–20, high quality.

Surgical procedures, dosing and follow-up

CABG in included studies utilised both venous and arterial conduits, harvested using both open and endoscopic methods. Surgery was performed using both on-pump and off-pump (OPCAB) techniques through a median sternotomy. Minimally-invasive direct coronary artery bypass (MIDCAB) or total endoscopic coronary bypass (TECAB) was not used.

Dosing of anti-platelet (and where used, anti-coagulants) was commenced according to a number of different criteria between studies, including thresholds based on time, pericardial drain rate, drain removal and/or ability to take oral medications. Dose amount and frequency varied according to study.

Assessment of patency at follow-up was performed using either invasive angiography or non-invasive computed tomographic angiography (CTA). The degree of stenosis for each followed-up case was determined from angiography. Methods such as fractional flow reserve (FFR) were not recorded.

Table 1 Pooled patient baseline data

Parameter	Pooled data
Patients, n	3,133
Males, n (%)	2,715 (87%)
Age, mean (95% CI)	56.4 (55.7–57.1)
Smoking history, n [% (95% CI)]	1,468/2,494 [52.5 (44.1–60.9)]
Hypertension, n [% (95% CI)]	1,107/2,833 [39.0 (33.3–45.0)]
Hypercholesterolaemia, n [% (95% CI)]	648/1,476 [47.5 (37.5–57.7)]
Diabetes mellitus, n [% (95% CI)]	390/1,724 [21.9 (15.4–30.0)]
Previous myocardial infarction, n [% (95% CI)]	1,026/2,154 [46.8 (41.6–52.0)]
Angina, n [% (95% CI)]	1,609/1,883 [86.4 (74.7–93.2)]
Grafts, n	6,667
Grafts per patient, mean (95% CI)	2.43 (2.20–2.66)

Statistical methods

Baseline data was pooled using meta-analysis of means or proportions, with individual study effect size accounted for using inverse variance methods in a random-effects model. Only data present in more than 50% of included studies were included. Values that were reported as median and range or interquartile range were converted to mean and standard deviation (11,12). All data are displayed as raw values as well as percentages with 95% confidence intervals (CIs) or 95% credible intervals (CrI) (as appropriate).

Latest follow-up of per-patient, per-graft and per-anastomosis patency data was collected and the most complete dataset used for network meta-analysis comparing drugs. Where follow-up data was reported as occlusion only, patency was calculated by taking the complement of the grafts occluded.

Arm-level patency data was analysed across all studies, with direct and indirect comparisons of pooled placebo, anti-platelet and anti-coagulant regimes made using a mixed treatment comparison based on a Bayesian hierarchical model. This model was implemented using a Markov Chain Monte Carlo simulation within the *gemtc* package in R [R Foundation for Statistical Computing, Vienna, Austria (13)] (14,15). Given the range of drugs, dosing regimens, graft types and time period over which included studies were conducted, a random effects model was used. For the purposes of the mixed-treatment comparison, consistency in direct and indirect effects was assumed (16). Heterogeneity between comparisons within the network was analysed by examining I^2 values for the random-effects model and inconsistency was examined both graphically (between pair-wise and network results) and using a node-splitting analysis. Where direct comparisons were contributed to by at least two studies, I^2 was calculated to investigate heterogeneity as a source of variability in results.

Odds ratios were calculated for graft patency and findings were taken as significant where the 95% CrI did not include unity. Node-splitting analysis used within this study considered P values less than 0.05 as significant for inconsistency between included studies.

Results

The literature search identified 2,554 records, of which 16 matched the inclusion criteria. According to the CONSORT tool, 11 studies were deemed high quality and five studies standard quality. These consisted of 13 two-armed trials (3,4,17-27), two three-armed trials (28,29) and one four-armed trial (30).

Overall, 3,133 patients were included, with an average of 2.43 (95% CI: 2.20–2.66) grafts per-patient. Saphenous vein, internal mammary artery and radial artery conduits were used, however, exact numbers of each conduit type were not fully reported for all papers. Graft target vessels were also incompletely reported. Angiographic patency at follow-up was reported for all grafts and was used in the mixed treatment comparison. Mean follow-up for coronary angiography (using invasive or CTA) across studies was 10.4 (95% CI: 9.28–11.5) months (minimum follow-up of 3 months). Pooled patient data and baseline risk factors are presented in *Table 1*; individual study and patient baseline data is provided in Supplementary *Tables S1*,*S2*.

Drugs trialed to improve patency outcomes included aspirin monotherapy (ASA), aspirin + dipyridamole, aspirin + clopidogrel, aspirin + ticagrelor and clopidogrel monotherapy. Dosing amounts and regimes varied between studies and are detailed in supplementary *Table S1*. It was assumed that any impact from differences in dose amount and frequency for the same drug between studies would be visible by differences in outcomes within groups of the

network meta-analysis.

Graft details and follow-up graft patency/occlusion data is presented in supplementary *Table S3*. The network model for the mixed treatment comparison of graft patency is shown in *Figure 1*.

Summary results for all treatments' patency at follow-up is shown in *Figure 2*, with placebo and aspirin used as references. These pooled results show aspirin monotherapy and dual antiplatelet therapies (aspirin combination therapies) are superior to placebo. Aspirin in combination with dipyridamole achieved almost identical patency results to aspirin alone. Summary of relative effects is shown in *Table 2*.

Rank probability analysis for graft patency at follow-up (*Figure 3*) demonstrated dual anti-platelet therapies with ticagrelor or clopidogrel (as the agent in addition to aspirin) had higher probabilities of being the first and second most effective treatments, respectively. Aspirin with dipyridamole and aspirin monotherapy were likely to rank approximately equal third and fourth from included treatments for maintaining graft patency at follow-up. Placebo had the highest probability for ranking as least effective in maintaining graft patency at follow-up.

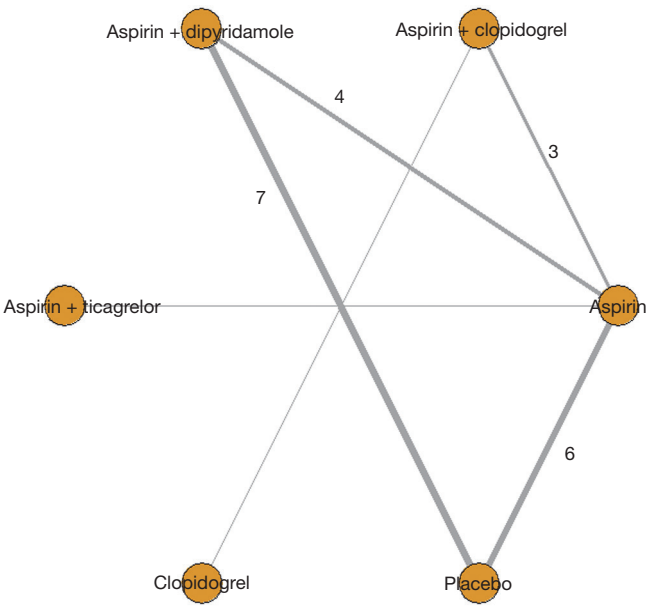

Figure 1 Network diagram of treatments and direct comparisons available from included studies. The thickness of the links between treatments reflects the number of studies in that link (annotated for all links with more than one study).

Direct, pairwise, indirect (where indirect evidence was available) and pooled/network mixed-treatment comparisons for graft patency at follow-up are shown in supplementary *Figure S2*. I^2 demonstrated heterogeneity was moderate (I^2>50%) in comparisons of placebo and aspirin + dipyridamole and was low for the placebo versus aspirin comparison (I^2>25%). Heterogeneity was minimal (I^2 =0%) for comparison of aspirin + clopidogrel and aspirin and for comparison of aspirin + dipyridamole and aspirin. Separate node splitting analysis demonstrated that inconsistency was low within treatment comparisons.

A sub-group analysis of eight included studies (containing 6 treatment comparisons) was conducted for saphenous vein graft patency. Only aspirin + dipyridamole reached significance for graft patency benefit compared to placebo (OR 2.5; 95% CrI: 1.1–5.9). The DAPT treatments were not shown as significantly better than aspirin monotherapy, however, this analysis was likely limited by sparse results (supplementary *Figure S3*).

Secondary outcomes were sparsely reported in included studies: follow-up death was reported in only 78% of studies, bleeding in 39% of studies, myocardial infarction in 47% of studies and cerebrovascular accident in 31% of studies. The pooled proportions of secondary outcomes reported are summarized in *Table 3*, individual study outcomes are reported in Supplementary *Table S4*. Network meta-analysis was not conducted for secondary outcomes.

Discussion

This network meta-analysis aimed to compare graft patency

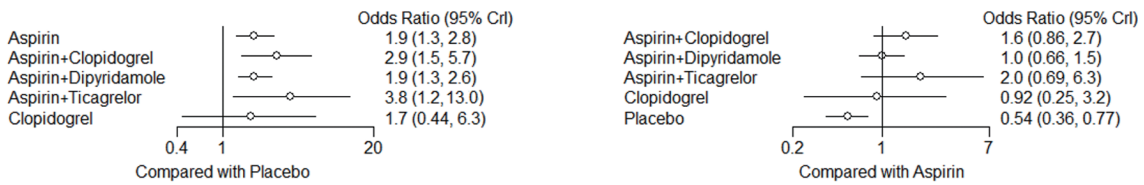

Figure 2 Network meta-analysis results for patency at follow-up with placebo and aspirin (ASA) used as reference (none versus one versus two antiplatelet agent comparison).

Table 2 Relative effects of patency drugs given post-CABG. Effect given as odds ratio (95% CrI) for patency at follow-up in experiment *vs.* control study

Patency drugs (control)	Experiment					
	Aspirin	Aspirin + clopidogrel	Aspirin + dipyridamole	Aspirin + ticagrelor	Clopidogrel	Placebo
Aspirin	–	1.56 (0.86, 2.72)	1.00 (0.66, 1.51)	2.02 (0.69, 6.26)	0.92 (0.25, 3.2)	0.54* (0.36, 0.77)
Aspirin + clopidogrel	0.64 (0.37, 1.16)	–	0.64 (0.32, 1.33)	1.3 (0.39, 4.62)	0.59 (0.18, 1.8)	0.34* (0.17, 0.69)
Aspirin + dipyridamole	1.00 (0.66, 1.51)	1.56 (0.75, 3.12)	–	2.02 (0.64, 6.74)	0.92 (0.23, 3.43)	0.54* (0.38, 0.74)
Aspirin + ticagrelor	0.49 (0.16, 1.44)	0.77 (0.22, 2.55)	0.50 (0.15, 1.55)	–	0.45 (0.08, 2.35)	0.26* (0.08, 0.82)
Clopidogrel	1.08 (0.31, 4.03)	1.7 (0.55, 5.48)	1.08 (0.29, 4.31)	2.23 (0.43, 12.48)	–	0.58 (0.16, 2.27)
Placebo	1.86* (1.29, 2.76)	2.92* (1.45, 5.74)	1.87* (1.35, 2.64)	3.79* (1.23, 12.55)	1.72 (0.44, 6.34)	–

*, odds ratios reaching significance.

results at least 3 months after CABG given the use of none, one or two anti-platelet agents to give context to the application of single or DAPT by the surgeon today. Results from 16 studies and 6,667 followed-up grafts demonstrated aspirin monotherapy, aspirin + dipyridamole and DAPT (aspirin + clopidogrel, aspirin + ticagrelor) following CABG all achieved significant patency benefit compared to placebo. A trend existed that favored DAPT over aspirin alone, although this was not statistically significant. While aspirin + ticagrelor had the highest probability being ranked the best therapeutic option, it should be noted that this was based on a single study (27).

While the superiority of DAPT over aspirin monotherapy (or aspirin + dipyridamole) did not reach significance (including in the SVG sub-analysis), this finding contrasts with recent meta-analyses of single versus dual antiplatelet therapy which showed patency benefit of DAPT over aspirin monotherapy for saphenous vein grafts (8,9). The reduced likelihood of a patency benefit for DAPT with arterial grafts likely occurs because arterial conduits are less prone to intimal hyperplasia and atherosclerosis (8). Given studies in the present analysis for DAPT included both saphenous vein and arterial conduits, it is not surprising that the inclusion of arterial conduits in pooling would attenuate the patency benefit of DAPT compared to if only SVG were being examined. Additionally, the SVG sub-group patency analysis in the present study may not have contained sufficient data to reach significance (as evidenced by wider credible intervals compared to the all-graft analysis for the same treatments and by the failure of aspirin monotherapy and DAPT to reach benefit over placebo). The pooling of arterial and venous graft patency results is appropriate given that grafting for multi-vessel disease typically involves both arterial and SVG conduits, as well as the growing trend towards total arterial revascularisation (31-33).

The results of the present analysis are in line with the 2016 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for duration of DAPT in patients with coronary artery disease (34), which recommend aspirin use to promote graft patency (and continuation of DAPT where it was given for acute coronary syndrome or previous coronary stents). With regard to composite (non-patency) outcomes, the ACC/AHA and European Society of Cardiologists (ESC) guidelines note that DAPT commenced for acute coronary syndrome should be recommenced post-CABG (34,35).

Further contemporary arguments for the use of DAPT include that it may confer patency benefit in off-pump CABG patients and may reduce the incidence of major adverse cardiac events, particularly in hypercoagulable or aspirin-resistant patients (5,24,36). While patency benefit has been shown with DAPT for venous grafts in off-pump patients (24), this benefit is not clear according to other DAPT versus monotherapy trials in off-pump patients (37) and a sub-analysis of 953 patients from a trial randomizing

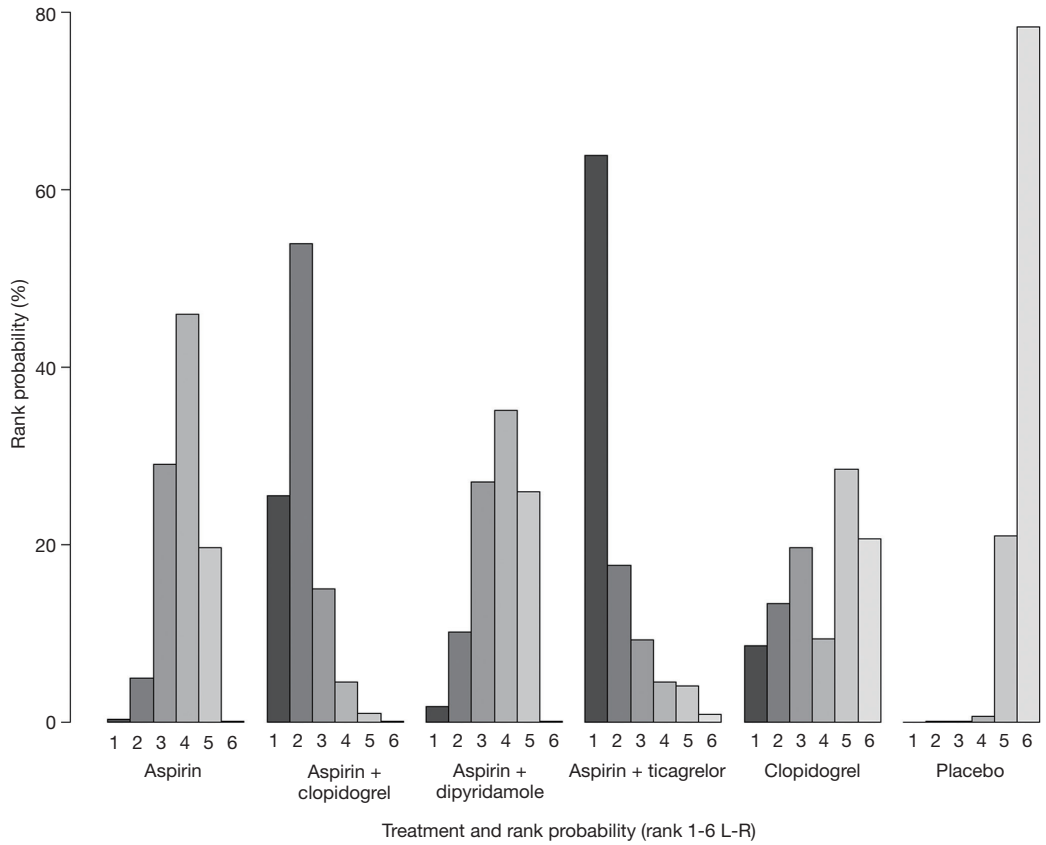

Figure 3 Rank probability for graft patency at follow-up. The probability of each treatment ranking as most effective (1st) to least effective (6th) is shown. For example, aspirin + ticagrelor has 65% probability of ranking as the most effective treatment (1st) and an approximately 1% probability as ranking as the least effective (6th best) treatment.

Table 3 Pooled proportions of secondary outcomes at follow-up across all studies

Outcomes	n [% (95% CI)]
Death	45/2,422 [2.45 (1.77–3.38)]
Bleeding	45/1,484 [3.36 (2.17–5.16)]
Myocardial infarction	64/1,575 [3.96 (2.55–6.11)]
Cerebrovascular accident	11/670 [2.28 (1.28–3.68)]

to on- and off-pump CABG (38). Reduced incidence of major adverse cardiac events (angina, myocardial infarction) was identified as a benefit of DAPT over aspirin monotherapy in a meta-analysis of RCT and institutional series, however, this may come at the expense of increased likelihood of major bleeding episodes (8). A trend towards increased major bleeding with DAPT was identified in a recent meta-analysis of bleeding from RCTs only, however, it did not reach statistical significance (risk ratio 1.28; 95% CI: 0.95–1.71), P=0.842, favoring monotherapy for reduced bleeding) (39). Other meta-analyses examining a composite endpoint (death, myocardial infarction, stroke) also identified improvement in composite endpoint outcomes with DAPT and again, a non-significant increased risk ratio for bleeding (1).

Limitations of this study included the paucity of RCT evidence for graft patency following CABG with various agents, particularly with respect to contemporary application of DAPT using aspirin + clopidogrel (three included studies) or aspirin + ticagrelor (one included study). This is a potential source of under-powering and increases heterogeneity where there is variability between patency results. Many other sources of heterogeneity

such as drug dosage and operative technique were also likely present. This study also excluded graft patency agents in studies (or arms of studies) that are not used contemporarily or only had a single contributing study (for example, warfarin, sulfinpyrazone, ticlopidine (3,4,30,40). Furthermore, as the included studies were published between 1981 and 2016, corresponding improvements in patency outcomes could be expected to vary over time due to operative improvements and differing patient selection, potentially favoring contemporary therapeutic agents.

Conclusions

The present network meta-analysis showed clear evidence for improved patency compared to placebo at follow-up beyond three months exists for aspirin monotherapy and dual antiplatelet therapies with aspirin. The results also demonstrated that while DAPT may confer some patency benefit over aspirin monotherapy, this was not statistically significant. Results from further randomized controlled trials are required to evaluate the relative benefit of DAPT over aspirin monotherapy.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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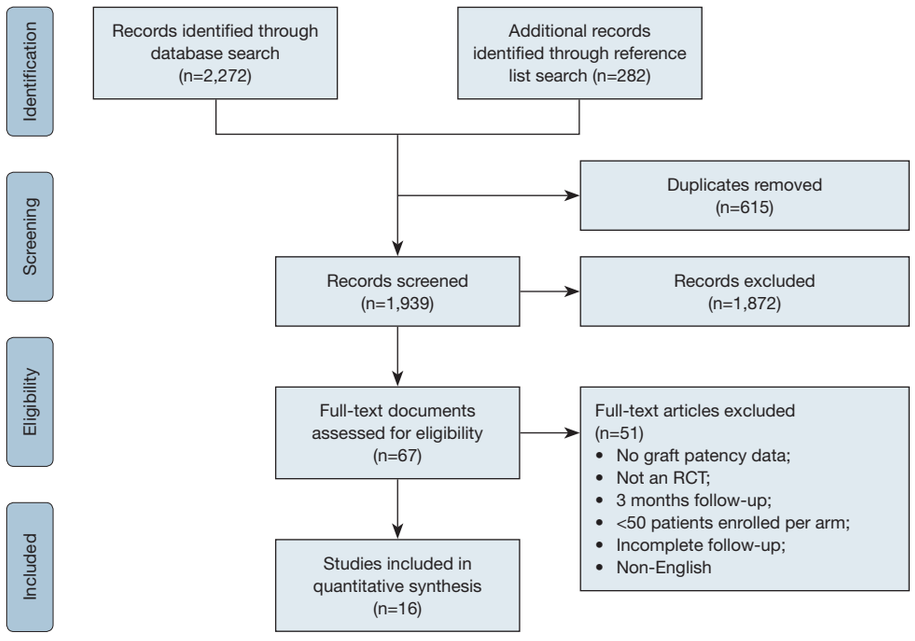

Figure S1 PRIMSA flow chart detailing the literature search process for randomized controlled trials comparing graft patency between placebo or drug arms. RCT, randomized controlled trial.

Table S1 Study details

Author, year published	Country	Recruitment period	RCT design	Quality	Mean f/u (months)	RCT arms	Post-op dose regimen	Graft type	On-pump (CCABG), off-pump (OPCAB)	Patients (n)
Brooks, 1985	England	1978–1982	S	SQ	12.4	Placebo	Placebo**	SVG	CCABG	160
						ASA + dipyridamole	ASA 330 mg TDS + dipyridamole 75 mg TDS	SVG	CCABG	160
Brown, 1985	USA	1976–1980	S	HQ	12	ASA + dipyridamole	ASA 325 mg TDS + 75 mg dipyridamole TDS	SVG	CCABG	45
						ASA	ASA 325 mg TDS	SVG	CCABG	38
						Placebo	–	SVG	CCABG	44
Chesebro, 1984	USA	1977–1981	S	HQ	13.3±2.1*	ASA + dipyridamole	ASA 325 mg TDS	SVG	CCABG	171
						Placebo	NA	SVG	CCABG	172
Gao, 2009	China	2005–2007	S	HQ	12	Clopidogrel	75 mg clopidogrel OD	SVG, RA, LIMA	OPCAB, CCABG	102
						ASA + clopidogrel	ASA 100 mg OD + 75 mg clopidogrel OD	SVG, RA, LIMA	OPCAB, CCABG	95
Gao, 2010	China	2007–2008	S	HQ	3	ASA	ASA 100 mg OD	LIMA, RA, SVG	OPCAB, CCABG	111
						ASA + clopidogrel	ASA 100 mg OD + clopidogrel 75 mg OD	LIMA, RA, SVG	OPCAB, CCABG	113
Goldman, 1989	USA	1983–1986	M	HQ	12	Placebo	–	SVG	–	107
						ASA	ASA 325 mg OD	SVG	–	104
						ASA	ASA 325 mg TDS	SVG	–	96
						ASA + dipyridamole	ASA 325 mg TDS + dipyridamole 75 mg TDS	SVG	–	99
Guiteras, 1989	Spain	1984–1986	S	SQ	6	Placebo	–	LIMA, SVG	–	68
						ASA + dipyridamole	ASA 50 mg TDS + dipyridamole 75 mg TDS	LIMA, SVG	–	72
Kulik, 2010	Canada	2006–2009	M	HQ	12	ASA + clopidogrel	162 mg ASA OD + 75 mg clopidogrel OD	SVG, LIMA, RIMA	CCABG, OPCAB	56
						ASA	ASA 162 mg OD	SVG, LIMA, RIMA	CCABG, OPCAB	57
Lorenz, 1984	W. Germany	1980–1982	S	SQ	4	Placebo	–	SVG	CCABG	31
						ASA	ASA 100 mg OD	SVG	CCABG	29
Mannacio, 2012	Italy	2006–2009	S	HQ	12	ASA	ASA 100 mg OD	LIMA, RIMA, RA, SVG	CCABG, OPCAB	150
						ASA + clopidogrel	ASA 100 mg OD + Clopidogrel 75 mg OD	LIMA, RIMA, RA, SVG	CCABG, OPCAB	150
Mayer Jr, 1981	USA	1973–1975	S	SQ	4.5	ASA + dipyridamole	ASA 650 mg BD + dipyridamole 50 mg BD	LIMA, SVG	CCABG	47
						Placebo	–	LIMA, SVG	CCABG	66
McEnany, 1982	USA	NR	S	HQ	22.8±13.3*	Placebo	–	SVG	CCABG	77
						ASA	ASA 600 mg BD	SVG	CCABG	71
Meister, 1984	W. Germany	1980–1982	S	HQ	4	Placebo	–	Unclear	CCABG	31
						ASA	ASA 100 mg OD	Unclear	CCABG	29
Saw, 2016	Canada	2011–2014	M	HQ	3	ASA + ticagrelor	ASA 81 mg OD + ticagrelor 90 mg BD	IMA, SVG, Radial	Unclear	35
						ASA	ASA 81 mg OD	IMA, SVG, Radial	Unclear	35
Sharma, 1983	USA	1977–1979	S	SQ	12	Placebo	–	SVG	CCABG	52
					–	ASA	ASA 325 mg TDS	SVG	CCABG	64
					12	ASA + dipyridamole	ASA 325 mg TDS + dipyridamole 75 mg TDS	SVG	CCABG	60
Van Der Meer, 1994	Netherlands	1987-1990	M	HQ	–	ASA	ASA 50 mg OD	IMA, SVG	NS	173
					12	ASA + dipyridamole	ASA 50 mg OD + dipyridamole 200 mg BD	IMA, SVG	NS	163

*, data given as median and interquartile range or range. Mean and standard deviation calculated according to methods of Wan *et al.* and Hozo *et al.* (11,12); **, Brooks 1985 used 3 months post-operative Warfarin (to international normalised ratio 2–3) in both control and experiment groups. RCT, randomised controlled trial; f/u, follow-up; HQ, high-quality; SQ, standard quality; CCABG, conventional coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass grafting; S, single centre; M, multi-centre; ASA, acetylsalicylic acid (aspirin); OD, once-daily; BD, twice daily; TDS, three times daily; IMA, internal mammary (thoracic) artery; LIMA, left internal mammary (thoracic) artery; RIMA, right internal mammary (thoracic) artery; RA, radial artery; NS, not specified.

Table S2 Patient characteristics

Author, year published	Population	RCT arms	Patients (n)	Males (n)	Age (mean ± SD)	Smoking history (n)	HTN (n)	HC (n)	DM (n)	Prior MI (n)	Angina (n)
Brooks, 1985	SVG CABG	Placebo	160	143	51.3±12.8*	93	35	–	6	87	154
		ASA + dipyridamole	160	139	52.6±10.4*	107	32	–	15	87	156
Brown, 1985	SVG CABG	ASA + dipyridamole	45	45	52*	–	–	–	–	–	–
		ASA	38	38	52*	–	–	–	–	–	–
		Placebo	44	44	52*	–	–	–	–	–	–
Chesebro, 1984	Primary cardiac CABG	ASA + dipyridamole	171	155	53.3±10.2*	137	57	–	–	–	157
		Placebo	172	153	54.3±9.7*	140	54	–	–	–	166
Gao, 2009	Elective primary CABG	Clopidogrel	102	85	62.4±9.85	48	66	20	51	49	–
		ASA + clopidogrel	95	78	60.5±10.11	44	59	21	57	56	–
Gao, 2010	Isolated CABG with >1 SVG	ASA	111	93	59.8±7.92	66	63	44	45	49	–
		ASA + clopidogrel	113	93	57.9±8.25	59	70	40	45	56	–
Goldman, 1989	Elective male CABG	Placebo	107	107	58±8	80	57	–	–	65	104
		ASA	104	104	59±8	85	49	–	–	57	99
		ASA	96	96	59±7	68	35	–	–	55	90
		ASA + dipyridamole	99	99	59±7	105**	48	–	–	60	93
Guiteras, 1989	SVG CABG	Placebo	68	47	56±8	42	24	–	14	24	15
		ASA + dipyridamole	72	55	55±7	42	20	–	19	31	14
Kulik, 2010	Isolated CABG with ≥2 SVG	ASA + clopidogrel	56	51	64.9±7.5	6	27	49	14	7	–
		ASA	57	50	68.1±7.4	9	30	50	19	13	–
Lorenz, 1984	Elective CABG	Placebo	31	28	54.6±6.2	23	–	–	–	–	27
		ASA	29	24	55.1±10.3	17	–	–	–	–	26
Mannacio, 2012	OPCAB patients with at least 1 SVG	ASA	150	113	58.9±8.3	–	68	86	–	52	–
		ASA + clopidogrel	150	110	59.4±7.7	–	71	82	–	57	–
Mayer Jr, 1981	CABG for refractory angina pectoris	ASA + dipyridamole	47	36	56.2	–	–	–	–	–	–
		Placebo	66	57	52	–	–	–	–	–	–
McEnany, 1982	1–4 SVG CABG	Placebo	77	48	50.3±14.4*	12	11	–	7	35	47
		ASA	71	41	47.8±14.4*	20	13	–	7	29	45
Meister, 1984	All institute's patients enrolled	Placebo	31	28	55	23	6	19	–	24	15
		ASA	29	24	55	17	6	12	–	17	11
Saw, 2016	18–80 yo isolated ACS or stable CAD	ASA + ticagrelor	35	30	61.7±7.5	2	26	31	11	5	26
		ASA	35	31	62.5±9.7	1	28	28	10	7	28
Sharma, 1983	<75 yo for isolated SVG CABG	Placebo	52	52	52.5±11.6	19	12	13	10	35	–
		ASA	64	64	52.5±11.6	23	16	14	15	37	–
		ASA + dipyridamole	60	60	52.5±11.6	21	14	11	13	32	–
Van Der Meer, 1994	Elective CABG for angina	ASA	173	154	58±9	137	55	71	17	–	173
		ASA + dipyridamole	163	140	58±8	127	55	57	15	–	163

*, data given as median and interquartile range or range. Mean and standard deviation calculated according to methods of Wan *et al.* and Hozo *et al.* (11,12); **, current and previous smokers add up to more than the total number in the ASA + dipyridamole group in Goldman 1989. Excluded from pooling. HTN, hypertension; HC, hypercholesterolaemia; DM, diabetes mellitus; MI, myocardial infarction; SVG, saphenous vein graft; CABG, coronary artery bypass grafting; yo, years old; ASA, acetylsalicylic acid (aspirin); ACS, acute coronary syndrome; CAD, coronary artery disease.

Table S3 Graft details and patency outcomes. Data for individual graft types was not completely reported, hence, for patency, overall figures are given

Author, year published	RCT arms	Total grafts (n)	Total grafts/ patient (n)	SVG (n)	LIMA (n)	RIMA (n)	Targets, RA (n)	LAD (n)	Diag (n)	Circ (n)	RCA (n)	Per-GRAFT patency		Total patency (N/n)	Total occluded (N/n)
												Latest f/u (mo)	Assessment method		
Brooks, 1985	Placebo	352	2.2	349	3	–	–	–	–	–	–	12	CA	306/352	–
	ASA + dipyridamole	360	2.25	358	2	–	–	–	–	–	–	12	CA	321/360	–
Brown, 1985	ASA + dipyridamole	138	3.1	138	–	–	–	–	–	–	–	12	CA	–	19/138
	ASA	114	3.1	114	–	–	–	–	–	–	–	12	CA	–	14/114
	Placebo	147	3.3	147	–	–	–	–	–	–	–	12	CA	–	31/147
Chesebro, 1984	ASA + dipyridamole	355	2.1	171	–	–	–	98*	9	70	92	12	CA	–	24/270
	Placebo	345	2	172	–	–	–	93	5	72	85	12	CA	–	75/256
Gao, 2009	Clopidogrel	252	2.49±0.72	154	98	–	–	98	–	–	–	12	CTA	239/252	–
	ASA + clopidogrel	253	2.66±0.75	163	90	–	–	90	–	–	–	12	CA	245/253	–
Gao, 2010	ASA	340	3.11	233	109	–	3	110	56	131	119	3	CTA	305/340	35/340
	ASA + clopidogrel	353	3.18	242	112	–	5	112	61	133	121	3	CTA	330/353	23/353
Goldman, 1989	Placebo	345	3.22*	345	–	–	–	–	–	–	–	12	CA	–	78/345
	ASA	340	3.27*	340	–	–	–	–	–	–	–	12	CA	–	45/340
	ASA	315	3.28*	315	–	–	–	–	–	–	–	12	CA	–	53/315
	ASA + dipyridamole	315	3.18*	315	–	–	–	–	–	–	–	12	CA	–	55/315
Guiteras, 1989	Placebo	94	2.3±0.8	–	–	–	–	–	–	–	–	6	CA	–	12/94/
	ASA + dipyridamole	116	2.4±0.8	–	–	–	–	–	–	–	–	6	CA	–	10/116
Kulik, 2010	ASA + clopidogrel	136	2.96*	57	57	14	–	–	–	–	–	12	CA	–	7/136*
	ASA	121	2.75*	87	85	12	–	–	–	–	–	12	CA	–	5/121*
Lorenz, 1984	Placebo	53	2.23	–	–	–	–	23	–	15	15	4	CA	–	17/53
	ASA	40	1.9	–	–	–	–	19	–	13	8	4	CA	–	4/40/
Mannacio, 2012	ASA	267	3.2±0.6	267	141	35	24	144	51	137	135	12	CTA	–	35/267
	ASA + clopidogrel	257	3.1±0.6	257	142	28	28	144	40	141	130	12	CTA	–	19/257
Mayer Jr, 1981	ASA + dipyridamole	93	1.9	75	–	–	–	–	–	–	–	3–6	CA	87/93	–
	Placebo	120	1.9	92	–	–	–	–	–	–	–	3–6	CA	98/120	–
McEnany, 1982	Placebo	74	1.34*	–	–	–	–	–	–	–	–	12–24	CA	54/74	–
	ASA	81	1.44*	–	–	–	–	–	–	–	–	12–24	CA	65/81	–
Meister, 1984	Placebo	53	1.71*	–	–	–	–	–	–	–	–	4	CA	36/53	–
	ASA	40	1.38*	–	–	–	–	–	–	–	–	–	CA	36/40	–
Saw, 2016	ASA + Ticagrelor	87	2.49*	40	40	–	7	–	–	–	–	3	CTA	–	9/87
	ASA	120	3.43*	59	51	–	10	–	–	–	–	3	CTA	–	22/120
Sharma, 1983	Placebo	95	2.2	–	–	–	–	30	10	–	27	12	CA	76/95	–
	ASA	111	2.2	–	–	–	–	36	12	–	30	12	CA	87/111	–
	ASA + dipyridamole	89	1.9	–	–	–	–	29	13	–	24	12	CA	74/89	–
Van Der Meer, 1994	ASA	157	1.05*	–	157	–	–	144	57	10	0	12	CA	–	10/157
	ASA + dipyridamole	139	1.12*	–	139	–	–	126	33	18	0	12	CA	–	7/139

*, specific graft/patient data not given for these studies- number required calculation from total number of grafts/number of patients enrolled. mo, month; SVG, saphenous vein graft; LIMA, left internal mammary (thoracic) artery; RIMA, right internal mammary (thoracic) artery; RA, radial artery; LAD, left anterior descending artery; Diag, diagonal branch; Circ, circumflex; RCA, right coronary artery; f/u, follow-up; CA, catheter/conventional angiography; CTA, computed tomographic angiography; ASA, acetylsalicylic acid (aspirin).

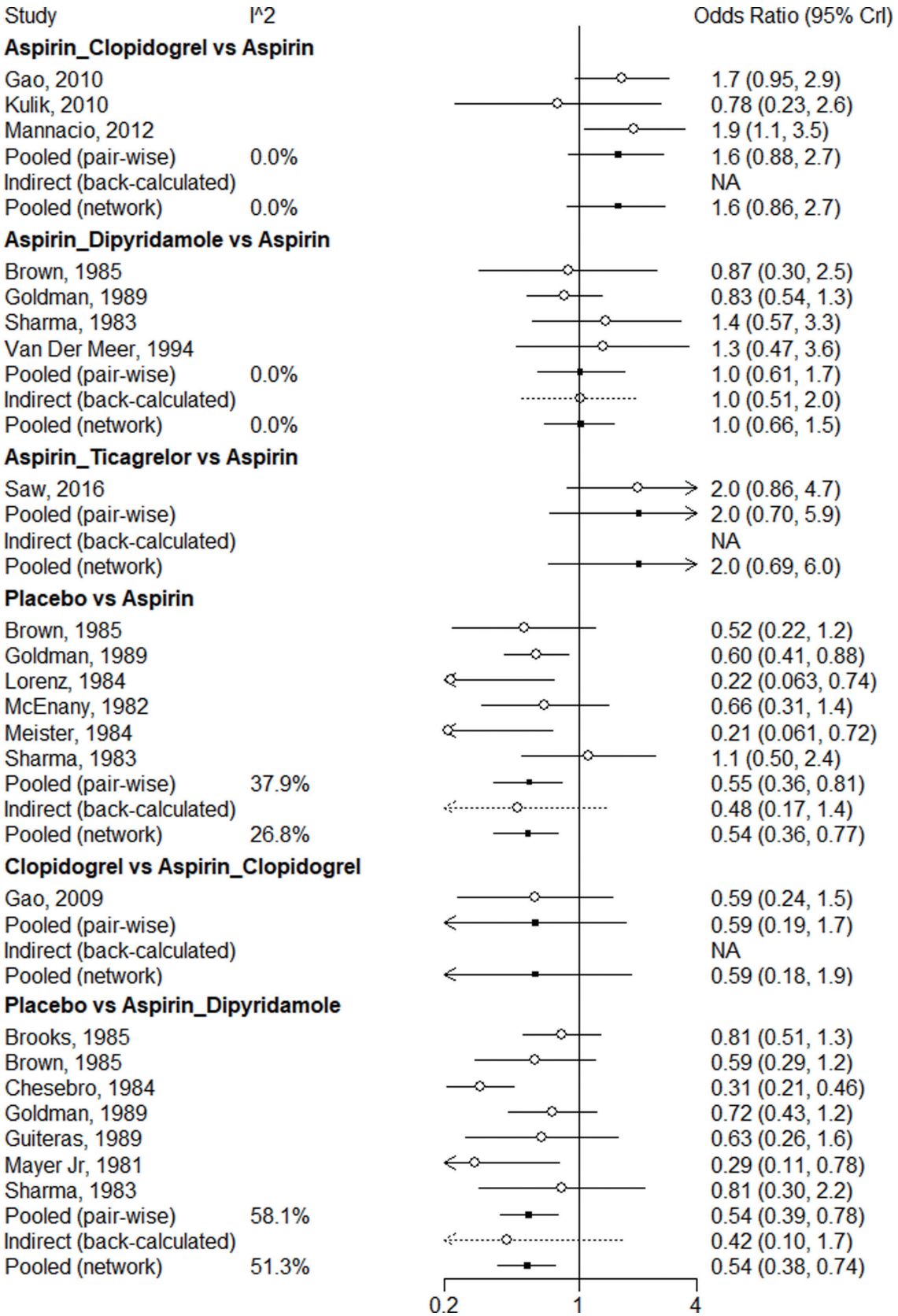

Figure S2 Direct, indirect and pooled network comparisons between treatments using a random effects model. Heterogeneity is shown for comparisons with at least 2 sets of direct evidence. ASA, aspirin; CrI, credible interval.

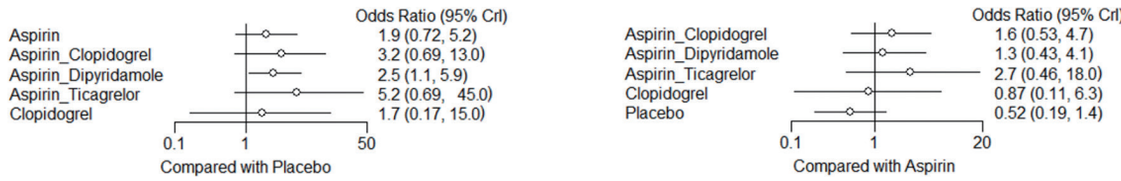

Figure S3 Sub-group analysis of saphenous vein graft (SVG) patency between different agents from 8 of 16 included studies. Placebo and aspirin used as reference.

Table S4 Non-patency (secondary) outcome data

Author, year published	RCT arms	Patients (n)	Death (n)	Bleeding (n)	MI (n)	CVA (n)
Brooks, 1985	Placebo	160	3	2	–	–
	ASA + dipyridamole	160	2	3	–	–
Brown, 1985	ASA + dipyridamole	45	1	–	–	0
	ASA	38	1	–	–	1
	Placebo	44	1	–	–	1
Chesebro, 1984	ASA + dipyridamole	171	–	–	–	–
	Placebo	172	–	–	–	–
Gao, 2009	Clopidogrel	102	0	0	0	–
	ASA + clopidogrel	95	0	0	0	–
Gao, 2010	ASA	111	1	–	–	–
	ASA + clopidogrel	113	0	–	–	–
Goldman, 1989	Placebo	107	2	–	1	–
	ASA	104	9**	–	12**	–
	ASA	96	–	–	–	–
	ASA + dipyridamole	99	–	–	–	–
Guiteras, 1989	Placebo	68	3	–	0	–
	ASA + dipyridamole	72	3	–	0	–
Kulik, 2010	ASA + clopidogrel	56	0	4	4	0
	ASA	57	1	3	1	2
Lorenz, 1984	Placebo	31	–	–	–	–
	ASA	29	–	–	–	–
Mannacio, 2012	ASA	150	2	4	6	4
	ASA + clopidogrel	150	1	5	3	2
Mayer Jr, 1981	ASA + dipyridamole	47	–	–	–	–
	Placebo	66	–	–	–	–
McEnany, 1982	Placebo	77	3	0	5	–
	ASA	71	1	0	1	–
Meister, 1984	Placebo	31	2	–	1	1
	ASA	29	2	–	0	0
Saw, 2016	ASA + ticagrelor	35	0	1	0	0
	ASA	35	1	0	0	0
Sharma, 1983	Placebo	52	0	–	–	–
	ASA	64	0	–	–	–
	ASA + dipyridamole	60	0	–	–	–
Van Der Meer, 1994	ASA	173	3	10	15	–
	ASA + dipyridamole	163	3	13	15	–

**, 9 events across all ASA groups in Goldman 1989. ASA, acetylsalicylic acid (aspirin); MI, myocardial infarction; CVA, cerebrovascular accident.