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Antithrombotic Agents for Secondary Prevention after Acute Coronary Syndromes: A Systematic Review and Network Meta-Analysis

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Abstract

Background—Nine oral antithrombotic medications currently available in the United States and Europe have been studied in clinical trials for secondary prevention of cardiac events following acute coronary syndrome (ACS). Few combinations of these medications have been directly compared, and studies have used multiple different comparator regimens.

Methods—We performed a systematic review and network meta-analysis of randomized controlled trials evaluating one or more available oral antithrombotic therapies in patients with ACS or prior myocardial infarction (MI). Co-primary outcomes were all-cause and cardiovascular mortality compared with imputed placebo and aspirin monotherapy.

Results—Forty-seven studies (196,057 subjects) met inclusion criteria and were included in the systematic review. Almost all studies tested either aspirin monotherapy compared with placebo or a combination of antithrombotic agents that included aspirin. Nearly all regimens reduced all-cause and cardiovascular mortality compared with imputed placebo. However, compared with imputed aspirin monotherapy, only combination therapy with aspirin plus ticagrelor was associated with lower cardiovascular mortality (OR 0.80, 95% CI 0.68–0.93), and triple therapy

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with aspirin, clopidogrel, and very low dose rivaroxaban was associated with lower all-cause mortality (OR 0.67, 95% CI 0.49–0.90). Major bleeding was increased 45–95% with dual antithrombotic therapy, and 2–6-fold with triple therapy.

Conclusion—Few combinations of antithrombotic therapy were associated with a reduction in mortality compared with aspirin monotherapy, highlighting the difficulty in clinical interpretation of composite ischemic endpoints. Future studies may need to focus on limiting the number of antithrombotic therapies tested in combination to best balance ischemic event reduction and bleeding.

Keywords

acute coronary syndrome; acute myocardial infarction; antiplatelet agents; antithrombotic agents; network meta-analysis

1. Introduction

Oral antithrombotic agents are the cornerstone of secondary prevention strategies following acute coronary syndromes (ACS). Pivotal clinical trials established the benefit of long-term treatment with aspirin and P2Y₁₂ inhibitors,[1, 2] and more recently, investigators have studied the addition of direct oral anticoagulants (DOACs) and PAR-1 inhibitors to this regimen.[3, 4] Nine oral antithrombotic agents available in the United States and/or Europe – 4 P2Y₁₂ inhibitors, aspirin, vorapaxar, and 3 DOACs – have been evaluated in clinical trials in patients with ACS, and there are 64 potential combinations of up to 3 available antithrombotic agents.

While many of these strategies have been tested, others are being studied in ongoing clinical trials or have not yet been studied. Of the strategies that have been tested, few have been directly tested against one another; instead, trials have compared newer combinations against placebo, aspirin, or the combination of aspirin and clopidogrel. Furthermore, the composite of ischemic outcomes that comprise the primary endpoint in many of these trials may be driven by non-fatal outcomes of varying importance, with no significant effect on overall or cardiovascular mortality.[5] Discordance in guideline recommendations for commonly used antithrombotic medications highlight the challenges of understanding best practices from the available literature.[6, 7]

Network meta-analysis is a statistical technique that can be used to determine the relative efficacy of several treatment strategies, even when some of these strategies have not been directly compared to each other. It has been used for many applications, including studies reporting the relative efficacy of different anticoagulants for the prevention of stroke in patients with atrial fibrillation and the relative efficacy of different antiplatelet agents in patients with ST segment elevation myocardial infarction (STEMI) and those undergoing percutaneous coronary intervention (PCI).[8–10] By combining direct and indirect comparisons, network meta-analysis is able to provide estimates of treatment effect that are similar to direct comparisons.[11] As such, it enables treatments to be compared with an imputed common comparator, providing a framework to understand the relative efficacy of these treatments. Since it assumes that patients enrolled in each trial are sampled from the

same pool of potential enrollees, heterogeneity in design of included studies may make the results less reliable.

In order to properly contextualize nearly 40 years of evidence in this area, we performed a systematic review and network meta-analysis of randomized clinical trials of oral antithrombotic therapy in patients with prior ACS. We focused on all-cause and cardiovascular mortality compared with imputed placebo and aspirin monotherapy as our primary outcomes. We also explored the impact of major bleeding on these combinations. All-cause mortality accounts for both the bleeding and anti-ischemic effects of antithrombotic agents, and has been consistently defined as an endpoint in randomized controlled trials of antithrombotic medications, though it is also influenced by nonvascular causes of death; cardiovascular mortality is less prone to dilution and randomness caused by deaths unrelated to study while still representing an outcome of obvious importance.

2. Methods

Network meta-analysis compares multiple treatment strategies, using both direct comparisons within clinical trials, and indirect comparisons across clinical trials that used a common comparator. This network meta-analysis conforms to standards outlined in The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.[12]

2.1. Objectives and Definitions

The primary objective of this analysis was to compare outcomes of antithrombotic strategies tested in randomized clinical trials when used for long-term secondary prevention after ACS. We limited our analysis to strategies testing oral antithrombotic agents currently available in the U.S. and/or Europe that do not require routine monitoring of antithrombotic efficacy, thus excluding trials of warfarin, and are either approved by either the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for secondary prevention of ACS, or have been tested in a Phase II or III clinical trial for that indication. Trials evaluating atopaxar, darexaban, and oral glycoprotein IIb/IIIa inhibitors,[13–15] for example, were excluded because these medications are not approved for any indication in the U.S. or Europe. For the primary analysis, we evaluated either FDA/EMA approved doses or the dose evaluated in the pivotal Phase III trial. We also performed a sensitivity analysis that included all doses tested in Phase II or III trials. We defined long-term as treatment duration at least 4 weeks, and excluded studies with follow-up less than 4 weeks; we did not limit the maximum duration of therapy or follow-up. We included studies enrolling only patients with ACS or prior MI, or studies enrolling a broader population that reported outcomes specifically for the subgroup with prior MI, and we extracted data specifically for patients included in that subgroup; we excluded studies enrolling only patients with stable coronary artery disease, or studies enrolling a broader population that did not report outcomes for a subgroup with ACS or prior MI. For studies evaluating the addition of a new oral antithrombotic agent to background therapy, antithrombotic therapy in the control arm was defined as any combination of agents taken by > 80% of the study population, and therapy in the intervention arm was defined as that therapy plus the tested agent.

2.2. Outcomes

The co-primary outcomes were all-cause mortality and cardiovascular mortality; we also evaluated major bleeding. For trials that reported multiple bleeding outcomes, we preferentially recorded Thrombolysis in Myocardial Infarction (TIMI) major bleeding, if available; if TIMI bleeding was not reported, we used the study's primary major bleeding outcome.

2.3. Data Source and Inclusion/Exclusion Criteria

We performed English-language searches in MEDLINE, EMBASE, and the Cochrane Register of Controlled Trials from inception through December 31, 2016 using the following keywords: *myocardial infarction, acute coronary syndrome, unstable angina, anticoagulants, purinergic P2Y receptor antagonists, platelet aggregation inhibitors, antiplatelets, apixaban, dabigatran, rivaroxaban, aspirin, clopidogrel, prasugrel, ticlopidine, ticagrelor, and vorapaxar* (see Appendix 1 in Supplement). After identifying articles, we reviewed references from appropriate articles to identify additional references for this systematic review. One investigator (A.F.) screened titles and abstracts for all articles, and identified studies as potentially appropriate for inclusion. We subsequently reviewed the full text of these studies to make a final decision on their appropriateness for inclusion.

We included studies that met the following criteria: (1) study type: randomized controlled trial, (2) population: patients with ACS or prior MI, (3) treatment: oral antithrombotic medications as defined above (4) duration of therapy ≥ 4 weeks, (5) outcome: all-cause mortality or CV mortality.

Studies that enrolled both patients with ACS and stable coronary artery disease (CAD) without prior MI were excluded, unless specific data for those patients with ACS or prior MI could be extracted. We also excluded trials of antithrombotic strategies that did not report results stratified by the type of medication (i.e., aspirin plus P2Y₁₂ inhibitor versus aspirin alone, as in the Dual Antiplatelet Therapy [DAPT] study[16]), trials that compared different durations of the same antithrombotic strategy or different doses of the same medication, trials that tested a combination antithrombotic strategy that included an intravenous agent, and trials enrolling < 50 patients.

2.4. Data Extraction and Quality Assessment

Three authors (A.F., E.M.O., and V.H.) independently extracted data in duplicate from all included articles with discrepancies resolved by conference. Data extracted included antithrombotic treatment regimen, duration of treatment and follow-up, all-cause mortality, cardiovascular mortality, major bleeding, and the composite of all-cause death, non-fatal MI, and non-fatal stroke. Where data could not be extracted from the original manuscript, other sources (including prior meta-analyses) were searched and authors were contacted to provide data, if necessary. The quality of each study was assessed using the Cochrane Risk of Bias tool.

2.5. Statistical Analysis

The model used for the network meta-analysis is a combination of the multiple regression methods described by Hasselblad and the network method of Lumley.[11, 17] A general linear model with a random effects term was fitted using SAS Proc Genmod with over-dispersion (SAS, Cary, NC). The analysis produced maximum likelihood estimates with asymptotic 95 percent confidence limits. Forest plots were used to illustrate the relative efficacy of treatment regimens compared with imputed placebo, aspirin monotherapy, and dual antiplatelet therapy with aspirin plus clopidogrel. If a study treatment had < 25 total deaths summed across all studies included in the systematic review, it was not included in quantitative analyses for that event.

Heterogeneity was assessed for each outcome and antithrombotic treatment combination. The heterogeneity for each outcome is displayed through both the confidence interval associated with each treatment combination, and the Q-statistic and p-value associated with each network. Higher Q statistics indicate greater heterogeneity, and $p < 0.05$ indicates significant heterogeneity.

2.6. Role of the Funding Source

Statistical analysis was funded by an unrestricted statistical grant from Janssen Pharmaceutical Companies. The authors independently performed the analyses and wrote the manuscript without input from the sponsor.

3. Results

Forty-seven studies enrolling 196,057 patients compared long-term antithrombotic strategies approved for secondary prevention or tested in Phase II/III clinical trials, and reported all-cause or cardiovascular mortality (Figure 1A). Regimens evaluated in the primary analysis with doses are listed in Supplemental Appendix 2. Triple therapy with aspirin, clopidogrel, and dabigatran was evaluated in one study, and the combination of aspirin, clopidogrel, and cilostazol was evaluated in three studies, but these studies reported too few events to include in quantitative meta-analysis. Forty-three studies were thus included in quantitative meta-analysis.

The study network plot is shown in Figure 1B. All included studies were randomized controlled trials, and the majority ($n = 29$) were double blind with blinded endpoint adjudication. Q statistics and associated p values were 39.2 ($p = 0.27$) for all-cause mortality, 35.9 ($p = 0.06$) for cardiovascular mortality, and 32.2 ($p = 0.10$) for major bleeding, indicating absence of significant heterogeneity. Risk of bias using the Cochrane risk of bias tool for all included studies is reported in Supplemental Figure S1.

3.1. Study and patient characteristics

Major study characteristics, including patient population, duration from ACS/MI to study enrollment, follow-up duration, and treatment arms are summarized in Table 1. Nearly all studies ($n = 46$) enrolled only patients with ACS or prior MI; the other study reported outcomes separately for patients with prior MI. Four studies included patients that were

randomized more than 6 months after their index ACS event; the remainder enrolled patients within 30 days of their event. Twelve studies compared aspirin monotherapy with placebo, and two compared aspirin monotherapy with clopidogrel or ticlopidine; in all other studies, aspirin therapy was included both the control and experimental arms. Following the publication of the CURE trial,[18] dual antiplatelet therapy with aspirin plus clopidogrel was included in both the control and experimental arms for nearly all studies.

3.2. All-cause and cardiovascular mortality

Forty-two studies enrolling a total of 185,564 patients contributed data for the endpoint of all-cause mortality (Supplemental Table S1). The association of clopidogrel monotherapy with all-cause mortality was not evaluated since the only trial testing this therapy did not report all-cause mortality for its MI subgroup.[19] Most treatment combinations were associated with significantly lower all-cause mortality compared with imputed placebo, with odds ratios for mortality ranging from 0.80 for aspirin alone to 0.53 for the combination of aspirin, clopidogrel, and very low dose rivaroxaban (Figure 2A). When compared with imputed aspirin monotherapy and imputed aspirin plus clopidogrel dual antiplatelet therapy, only combination therapy with aspirin plus ticagrelor (OR 0.87, 95% CI 0.75–1.00, $p = 0.048$ vs. imputed aspirin monotherapy; OR 0.88, 95% CI 0.77–1.00, $p = 0.048$ vs. imputed aspirin plus clopidogrel) and combination therapy with aspirin, clopidogrel, and very low dose rivaroxaban were associated with significantly lower mortality (OR 0.67, 95% CI 0.49–0.90, $p = 0.009$ vs. imputed aspirin monotherapy; OR 0.68, 95% CI 0.49–0.93, $p = 0.02$ vs. imputed aspirin plus clopidogrel) (Figure 2B). Cardiovascular death was reported in 38 studies (190,169 patients). As with all-cause mortality, almost all evaluated treatments were associated with significantly lower risk of cardiovascular death compared with imputed placebo (Figure 3A), but only combination therapy with aspirin and ticagrelor, and combination therapy with aspirin, clopidogrel, and very low dose rivaroxaban were associated with significantly lower cardiovascular mortality than imputed aspirin monotherapy and imputed aspirin plus clopidogrel dual antiplatelet therapy (Figure 3B).

3.3. Major Bleeding

There were 32 studies enrolling 176,008 patients that contributed data to our analysis of major bleeding. The association of clopidogrel monotherapy with major bleeding is not reported, since the only trial evaluating clopidogrel monotherapy did not report major bleeding for its MI subgroup. Eighteen studies reported TIMI major bleeding; two additional studies reported TIMI major bleeding not associated with coronary artery bypass grafting. There was insufficient bleeding data reported in aspirin versus placebo trials to compare each regimen with imputed placebo. All treatments were associated with a higher risk of bleeding than imputed aspirin monotherapy, and all except combination therapy with aspirin plus ticagrelor were associated with a higher risk of bleeding than imputed aspirin plus clopidogrel (Figure 4). Numerically, triple antithrombotic therapy with aspirin, clopidogrel, and very low dose rivaroxaban was associated with the greatest risk of bleeding, though confidence intervals overlapped.

3.4. Sensitivity analysis

In a sensitivity analysis including all doses tested in Phase II or Phase III clinical trials, results were similar to those presented in the primary analysis. All regimens except those containing full dose apixaban or ticlopidine were associated with significantly lower all-cause mortality compared with imputed placebo, but only aspirin plus ticagrelor was associated with significantly lower all-cause and cardiovascular mortality compared with imputed aspirin monotherapy and imputed aspirin plus clopidogrel. In this analysis, combination therapy with aspirin, clopidogrel, and low-dose rivaroxaban included both the 2.5mg and 5mg twice daily rivaroxaban dosing regimens, and was not associated with lower cardiovascular mortality compared with imputed aspirin monotherapy and imputed aspirin plus clopidogrel.

4. Discussion

This systematic review and network meta-analysis represents the largest and most comprehensive comparison of the efficacy and safety of antithrombotic regimens for long-term secondary prevention in patients with ACS. It “levels the playing field” by allowing for comparison of various regimens with imputed placebo, aspirin monotherapy, and dual antiplatelet therapy with aspirin and clopidogrel. We found that treatment with almost all were associated with a lower risk of all-cause and cardiovascular mortality compared with imputed placebo. However, almost all antithrombotic regimens were also associated with a higher risk of bleeding compared with imputed aspirin monotherapy, imputed placebo, and imputed dual antiplatelet therapy with aspirin plus clopidogrel. Overall, only two regimens were associated with a lower incidence of all-cause and/or cardiovascular mortality compared with imputed aspirin monotherapy and imputed dual antiplatelet therapy with aspirin plus clopidogrel, which highlights the difficulty in clinical interpretation of composite ischemic endpoints in an era of increasingly potent antithrombotic therapy. Results for all-cause and cardiovascular mortality were broadly consistent, and these endpoints may represent an outcome of certain clinical significance relevant to future clinical trials.

Over the past 40 years, antithrombotic therapy for secondary prevention in patients with ACS has evolved considerably to its present state, where multiple drugs from several different classes are available. In clinical trials, many combinations of these agents have reduced the incidence of ischemic events;^[20] however, because of the timing of when these agents were developed, many combinations have not been tested at all, and many of the combinations that have been tested have not been directly compared with each other. Newer combinations of antithrombotic agents (those comprising three agents, and those involving aspirin and a second generation P2Y₁₂ inhibitor) have only been directly compared with dual antiplatelet therapy with aspirin and clopidogrel, and have not been compared with aspirin monotherapy or any of the other newer combinations. Moreover, even when regimens have been directly compared, treatment duration and time from index event to treatment have varied across studies. There is thus no clear consensus on which combinations of agents represent optimal care. This is further reflected by discordance in guidelines from different professional societies. For example, the European Society of

Cardiology (ESC) guidelines give a weak recommendation in favor of using very low dose rivaroxaban in patients with ACS, but the American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not comment at all on rivaroxaban, and the FDA has not approved this rivaroxaban dose for use in patients with ACS.[7, 21]

Furthermore, long-term secondary prevention in patients with ACS requires balancing the risks of ischemic and bleeding complications.[22, 23] The primary endpoint of nearly all large, recent clinical trials of antithrombotic agents is a composite of ischemic events – most frequently, cardiovascular death, myocardial infarction, or stroke, with or without urgent revascularization and/or hospitalization for unstable angina.[24–28] Recurrent ischemic events are important predictors of mortality;[29–32] however, bleeding events are also prognostically important.[33] Importantly, bleeding is associated with discontinuation of antithrombotic therapies, even among patients with minor bleeding, and worsened quality of life.[34, 35]

The risk and prognostic significance of bleeding has earned increasing attention, with several recent trials incorporating major bleeding as a “primary safety endpoint.”[16, 36] However, our systematic review highlights that the overall trend in Phase III clinical trial design has been increasing potency of antithrombotic agents – first, with the addition of clopidogrel to aspirin, then with higher potency P2Y₁₂ inhibitors, and finally the extension of dual antiplatelet therapy to lower risk groups, and the addition of a third antithrombotic agent in high risk patients. Our results demonstrate that the result of escalating antithrombotic therapy has been a reduction in ischemic events with a corresponding increase in bleeding, with little or no change in overall or cardiovascular mortality. Considerations regarding the optimal balance between bleeding and ischemia are changing dynamically, with observational studies showing that physician behavior is driven largely by safety considerations, rather than efficacy.[37] Several forthcoming Phase III clinical trials in patients with ACS seek to change this paradigm by eliminating aspirin or replacing it with an alternative agent.[38, 39] GLOBAL LEADERS will evaluate the efficacy and safety of long-term monotherapy with ticagrelor in patients undergoing coronary stenting.[40] PIONEER-AF, REDUAL PCI, and AUGUSTUS have evaluated or will evaluate the safety (in terms of bleeding events) of dropping aspirin in favor of a P2Y₁₂ inhibitor plus a DOAC in patients undergoing PCI who have atrial fibrillation.[41–43] The COMPASS trial is enrolling patients with stable coronary artery disease to evaluate the efficacy of very low dose rivaroxaban with or without aspirin compared to aspirin monotherapy for the prevention of vascular events.[44] Finally, the phase II GEMINI-ACS-1 will report on the safety of replacing aspirin with very low dose rivaroxaban as part of a dual antithrombotic strategy for patients with ACS.[45]. These trials will help fill gaps in the current evidence base by clarifying the effects of antithrombotic strategies incorporating fewer but more potent agents. However, the comparator arms differ across trials, highlighting one of the major issues with interpreting antithrombotic trials in ACS. Moreover, all of these trials have primary efficacy endpoints comprised of a composite of ischemic events and a primary bleeding endpoint. Low mortality rates following ACS in contemporary patients mandate that traditional clinical trials of antithrombotic agents are designed in this manner, but translating results into clinical practice may be difficult, especially if aspirin’s effects on cancer-related mortality cannot be taken into consideration.[46] Larger, simpler trials

powered to detect differences in patient-centered outcomes like all-cause mortality and hospital re-admission may help overcome these challenges.[47]

The lack of an observed decrease in mortality with more potent combinations of antithrombotic therapy seen in this analysis may reflect the effect of changing epidemiology of cardiovascular disease. Non-cardiovascular death competes with cardiovascular death in a traditional Kaplan-Meier framework, as patients who die of non-cardiovascular causes are censored, reducing power to detect a difference between groups.[48] The effects of factors like potent background secondary prevention, patient age, coronary anatomy, and type of presentation on the relative risks of cardiovascular and non-cardiovascular death over long-term follow-up are unknown, but may play an important role in successful trial design.

4.1. Limitations

Our study includes the limitations of all studies included in the network meta-analysis; though many studies limited bias through the use of effective randomization, concealed allocation, double-blind design, blinded outcome ascertainment, and intention-to-treat analysis with low loss to follow-up, not all studies reported on these key study design principles and some studies were not blinded. Furthermore, network meta-analysis assumes that patients in the included studies were sampled from the same global patient population, and that background treatment outside of the therapy being tested is the same. Due to the time span across which these studies were completed, patient population changed substantially, as did concomitant therapy, which may interact with the efficacy of antithrombotic treatment.[49] Important sources of heterogeneity include different times from index ACS event to trial enrollment; the advent of fibrinolysis and PCI; and the use of statins, beta blockers, and ACE inhibitors in both the acute and chronic settings following MI. These limitations are inescapable, and detract from the precision of our estimates. Our use of random effects analysis takes this heterogeneity into account and is reflected in the relatively broad confidence intervals of our results. Furthermore, there are instances where our results comparing a treatment strategy to imputed aspirin monotherapy differ from the results of well-done clinical trials directly comparing a treatment strategy to aspirin, such as the comparison of clopidogrel monotherapy to aspirin monotherapy, which reduced cardiovascular events in CAPRIE (though not in the prior MI subgroup, the only patients from CAPRIE included in our analysis) but was not associated with a lower incidence of cardiovascular events in our network meta-analysis. Due to these limitations, our results are not intended to supersede the results of well-done clinical trials or directly inform clinicians' antithrombotic choices. Rather, these results should inform future clinical trials, by helping investigators determine appropriate control populations, treatment comparators, and cardiovascular endpoints of interest.

5. Conclusions

In this network meta-analysis, we compared available antithrombotic regimens to the same imputed placebo and aspirin monotherapy controls and evaluated all-cause mortality, enabling the indirect comparison of regimens that have not been directly tested. Though nearly all regimens were associated with a lower incidence of cardiovascular and all-cause

mortality compared with imputed placebo, all were also associated with a higher incidence of bleeding, and few regimens were associated with lower all-cause mortality compared with imputed aspirin monotherapy, highlighting the difficulty in clinical interpretation of composite ischemic endpoints when evaluating antithrombotic therapies. These results should inform the interpretation of ongoing clinical trials and the design of future trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Article Flow (A) and Study Network (B)

Figure 2.

All-cause mortality

Panel A shows the listed treatment compared with imputed placebo; Panel B shows the listed treatment compared with imputed aspirin monotherapy; Panel C shows the listed treatment compared with imputed dual antiplatelet therapy with aspirin + clopidogrel. Odds ratios < 1 favor imputed treatment (aspirin or placebo); odds ratios > 1 favor comparator. ASA, aspirin. Medication doses included: aspirin, all doses; ticlopidine, 250mg twice daily; clopidogrel, 75mg daily; ticagrelor 90mg twice daily; prasugrel, 5 or 10mg daily; vorapaxar, 2.5mg daily; rivaroxaban 2.5mg twice daily; apixaban 5mg twice daily.

Figure 3.
Cardiovascular mortality

Panel A shows the listed treatment compared with imputed placebo; Panel B shows the listed treatment compared with imputed aspirin monotherapy; Panel C shows the listed treatment compared with imputed dual antiplatelet therapy with aspirin + clopidogrel. Odds ratios < 1 favor imputed treatment (aspirin or placebo); odds ratios > 1 favor comparator. Abbreviations and doses per Figure 2.

Figure 4.**Major bleeding**

Panel A shows the listed treatment compared with imputed aspirin monotherapy; Panel B shows the listed treatment compared with imputed dual antiplatelet therapy with aspirin + clopidogrel.. There was insufficient data for major bleeding in placebo-controlled trials to compare with imputed placebo. Odds ratios > 1 indicate a higher incidence of bleeding with comparator; odds ratios < 1 indicate a higher incidence of bleeding with imputed aspirin. Abbreviations and doses per Figure 2.

Table 1

Included studies

Study #	Study; journal, publication year	Patient population	Years enrolling	Treatment arms (number of patients enrolled)	Time from MI to enrollment	Follow-up duration	Primary endpoint
1	Cardiff-1; British Medical Journal, 1974	Patients recovered from MI	February 1971–July 1973	Aspirin (615) vs. placebo (624)	9.8 weeks (mean)	12 months (median)	Overall mortality
2	Cardiff-2; Lancet, 1979	Patients hospitalized with MI	NR	Aspirin (832) vs. placebo (850)	25% within 3 days; 50% within 7 days	12 months	Overall mortality
3	PARIS-1; Circulation, 1980	Patients recovered from MI	May 1975–August 1976	Aspirin (810) vs. placebo (406)	8 weeks to 5 years; 78% > 6 months	41 months	Overall mortality, coronary mortality, and coronary mortality plus nonfatal MI
4	AMIS; JAMA, 1980	Patients recovered from MI	1975–1976	Aspirin (2,267) vs. placebo (2,257)	8 weeks to 5 years; mean 25 months	36 months	Total mortality
5	CDP-A; Circulation, 1980	Patients with previous MI	1972–1974	Aspirin (758) vs. placebo (771)	75% > 5 years	10–28 months (mean 22)	Total mortality
6	GAMIS; Circulation, 1980	Patients hospitalized with MI	1970–1977	Aspirin (317) vs. placebo (309)	30–42 days	24 months	Overall mortality, coronary mortality, and coronary mortality plus nonfatal MI
7	Lewis et al.; N Engl J Med, 1983	Patients with unstable angina	November 1974–August 1981	Aspirin (625) vs. placebo (641)	< 48 hours from hospital admission	12 weeks	Total mortality, MI
8	Cairns et al; N Engl J Med, 1985	Patients with unstable angina	July 1979–December 1983	Aspirin (139) vs. placebo (139)	< 8 days from hospital admission	18 months (median)	Cardiac death or non-fatal MI
9	ISIS-2; Lancet, 1988	Patients with suspected acute MI	March 1985–December 1987	Aspirin (8,587) vs. placebo (8,600)	< 24 hours from symptom onset	28 days	Vascular mortality

Study #	Study; journal, publication year	Patient population	Years enrolling	Treatment arms (number of patients enrolled)	Time from MI to enrollment	Follow-up duration	Primary endpoint
10	Theroux et al.; N Engl J Med, 1988	Patients with unstable angina	October 1986–March 1988	Aspirin (121) vs. placebo (118)	7.7 hours from symptom onset (mean)	3 months	Refractory angina, MI, death
11	Husted et al.; Journal of Internal Medicine, 1989	Patients with probable acute myocardial infarction	NR	Aspirin (196) vs. placebo (97)	4 hours from symptom onset (median)	3 months	Cardiac death or non-fatal MI
12	Balsano et al.; Circulation, 1990	Patients with acute unstable angina	December 1986–October 1987	Ticlopidine (314) vs. conventional therapy (338)	< 48 hours from hospital admission	6 months	Vascular death, non-fatal MI
13	RISC; JACC, 1991	Patients with acute unstable angina or NSTEMI	May 1985–June 1988	Aspirin (399) vs. placebo (397)	< 72 hours from hospital admission	12 months	Total mortality or MI
14	CAPRIE; Lancet, 1996	Patients with recent MI	March 1992–February 1995	Aspirin (3159) vs. clopidogrel (3143)	35 days	1.91 years (median)	Composite of stroke, MI, or vascular death
15	JAMIS; Am J Cardiol, 1999	Patients hospitalized with acute MI	October 1994–March 1996	Aspirin (250) vs. placebo (230)	< 30 days; mean 1 day	1.3 years (mean)	Recurrent MI
16	Ochiai et al.; Am J Cardiol, 1999	Patients with acute MI with total occlusion of the infarct-related artery	September 1995–May 1997	Aspirin + ticlopidine (25) vs. Aspirin + cilostazol (25)	< 12 hours	6 months	Not specified
17	STAMI; JACC, 2001	Patients recovered from MI	March 1995–January 1997	Aspirin (736) vs. ticlopidine (734)	< 30 days; mean 12.8 days	6 months	Composite of total mortality, non-fatal MI, non-fatal stroke, or recurrent angina
18	CURE; N Engl J Med, 2001	Patients with acute NSTEMI or unstable angina	December 1998–November 2000	Aspirin (6303) vs. aspirin + clopidogrel (6259)	< 24 hours from symptom onset	9 months (mean)	Composite of cardiovascular death, nonfatal MI, stroke
19	Cin et al.; Turk J Med Sci, 2002	Patients with acute MI	January 1998–June 1998	Aspirin (46) vs. aspirin +	NR	6 months	Composite of death and MI

Study #	Study; journal, publication year	Patient population	Years enrolling	Treatment arms (number of patients enrolled)	Time from MI to enrollment	Follow-up duration	Primary endpoint
				ticlopidine (44)			
20	Parodi et al.; Am Heart J, 2005	Patients with STEMI undergoing PCI	December 2003–August 2004	Aspirin + clopidogrel (66) vs. aspirin + ticlopidine (67)	< 12 hours from symptom onset	1 month	Scintigraphic infarct size
21	Di Pasquale et al.; HeartDrug 2005	Patients with NSTEMI undergoing PCI	May 2002–December 2003	Aspirin + clopidogrel (214) vs. aspirin + ticlopidine (214)	< 72 hours from admission	6 months	Ischemic events and reocclusions in treated vessels
22	CLARITY; N Engl J Med 2005	Patients with acute STEMI	February 2003–October 2004	Aspirin (1739) vs. aspirin + clopidogrel (1752)	< 12 hours from symptom onset	30 days	Composite of occluded infarct-related artery, or death/MI before angiography
23	CHARISMA; JACC, 2007	Patients with prior MI	October 2002–November 2003	Aspirin (1903) vs. aspirin + clopidogrel (1943)	23.6 months (median)	28 months (median)	Composite of cardiovascular death, MI, and stroke
24	DISPERSE-2; JACC, 2007	Patients with acute NSTEMI or unstable angina	October 2004–April 2005	Aspirin + clopidogrel (327) vs. aspirin + ticagrelor (334)	< 48 hours from hospital admission	28 days	TIMI major or minor bleeding
25	TRITON-TIMI 38; N Engl J Med, 2007	Patients with ACS scheduled for revascularization	November 2004–January 2007	Aspirin + clopidogrel (6,795) vs. aspirin + prasugrel (6,813)	< 72 hours from symptom onset	14.5 months (median)	Composite of cardiovascular death, nonfatal MI, nonfatal stroke
26	PLATO; N Engl J Med, 2009	Patients with ACS	October 2006–July 2008	Aspirin + clopidogrel (9291) vs. aspirin + ticagrelor (9333)	< 24 hours from symptom onset	12 months	Composite of vascular death, MI, and stroke

Study #	Study; journal, publication year	Patient population	Years enrolling	Treatment arms (number of patients enrolled)	Time from MI to enrollment	Follow-up duration	Primary endpoint
27	APPRAISE; Circulation, 2009	Patients stabilized after hospitalization for ACS	May 2006–October 2007	Aspirin + clopidogrel (599) vs. aspirin + clopidogrel + apixaban (1104)	7 days from symptom onset; median 4 days	21.7 weeks	ISTH major bleeding
28	ATLAS-1; Lancet, 2009	Patients with ACS	November 2006–September 2008	Aspirin + clopidogrel (1160) vs. aspirin + clopidogrel + rivaroxaban (153)	1–7 days after hospital admission	6 months	Clinically significant bleeding
29	Han et al.; Am Heart J, 2009	Patients with ACS undergoing PCI	December 2004–February 2006	Aspirin + clopidogrel (608) vs. aspirin + clopidogrel + cilostazol (604)	NR	12 months	Composite of cardiac death, nonfatal MI, stroke, or target vessel revascularization
30	Goto et al.; J Atheroscler Thromb, 2010	Patients with acute NSTEMI or unstable angina	NR	Aspirin + clopidogrel (21) vs. aspirin + clopidogrel + vorapaxar (31 patients)	< 24 hours from symptom onset	2 months	TIMI major and minor bleeding
31	Min Ahn et al.; Heart Vessels, 2011	Patients with ACS undergoing PCI	August 2005–September 2006	Aspirin + clopidogrel (66) vs. aspirin + clopidogrel + cilostazol (64)	NR	24 months	Carotid intima media thickness progression
32	TRILOGY; N Engl J Med, 2012	Patients with acute NSTEMI or unstable angina not undergoing revascularization	June 2008–September 2011	Aspirin + clopidogrel (4663) vs. aspirin + prasugrel (4663)	< 10 days from hospital admission; median 4 days	17 months (median)	Composite of cardiovascular death, MI, or stroke
33	APPRAISE-2; New Engl J Med, 2011	Patients stabilized after hospitalization for ACS	March 2009–November 2010	Aspirin + clopidogrel (3687) vs. aspirin +	7 days from symptom onset; median 6 days	241 days (median)	Efficacy: Composite of cardiovascular death, MI, or ischemic stroke Safety: TIMI major bleeding

Study #	Study; journal, publication year	Patient population	Years enrolling	Treatment arms (number of patients enrolled)	Time from MI to enrollment	Follow-up duration	Primary endpoint
				clopidogrel + apixaban (3705)			
34	RE-DEEM; Eur Heart J, 2011	Patients with MI	March 2008–September 2009	Aspirin + clopidogrel (373) vs. aspirin + clopidogrel + dabigatran (1505)	14 days after hospital admission	6 months	ISTH major or clinically relevant non-major bleeding
35	TRA 2°P-TIMI 50; Lancet, 2012	Patients with prior MI	September 2007–November 2009	Aspirin + clopidogrel (8881) vs. aspirin + clopidogrel + vorapaxar (8898 patients)	2 weeks–12 months	30 months (median)	Composite of cardiovascular death, MI, and stroke
36	TRACER; N Engl J Med, 2012	Patients with acute NSTEMI or unstable angina	December 2008–June 2010	Aspirin + clopidogrel (6471) vs. aspirin + clopidogrel + vorapaxar (6473 patients)	< 24 hours from symptom onset	502 days (median)	Composite of cardiovascular death, MI, and stroke
37	ATLAS-2; N Engl J Med, 2012	Patients with ACS	November 2008–September 2011	Aspirin + clopidogrel (5114) vs. aspirin + clopidogrel + rivaroxaban (5113)	< 7 days after hospital admission; median 4.7 days	13.1 months (median)	Composite of cardiovascular death, MI, or stroke
38	Dasbivass et al.; J Assoc Physicians India 2013	Patients with ACS undergoing PCI	January 2010–August 2010	Aspirin + clopidogrel (109) vs. aspirin + prasugrel (111)	< 14 hours from symptom onset	14.5 weeks	Percent ADP-induced platelet aggregation
39	APPRAISE-J; Circ J, 2013	Patients stabilized after hospitalization for ACS	April 2009–November 2010	Aspirin + clopidogrel (52) vs. aspirin + clopidogrel	7 days from symptom onset	24 weeks	ISTH major or clinically relevant non-major bleeding

Study #	Study; journal, publication year	Patient population	Years enrolling	Treatment arms (number of patients enrolled)	Time from MI to enrollment	Follow-up duration	Primary endpoint
				+ apixaban (99)			
40	PRASFIT; Circ J, 2014	Patients with ACS scheduled for revascularization	December 2010–June 2012	Aspirin + clopidogrel (678) vs. aspirin + prasugrel (685)	< 72 hours from symptom onset	24 weeks	Composite of cardiovascular death, MI, and stroke
41	PEGASUS-TIMI 54; N Engl J Med, 2015	Patients with prior MI	October 2010–May 2013	Aspirin (7067) vs. aspirin + ticagrelor (14,095)	1.7 years (median)	33 months (median)	Efficacy: Composite of cardiovascular death, MI, and stroke Safety: TIMI major bleeding
42	PHILO; Circ J, 2015	Patients with ACS	NR	Aspirin + clopidogrel (400) vs. aspirin + ticagrelor (401)	< 24 hours from symptom onset	12 months	Efficacy: Composite of vascular death, MI, and stroke Safety: Major bleeding
43	Bonello et al.; Am J Cardiol, 2015	Patients with NSTEMI or unstable angina	January 2014–September 2014	Aspirin + prasugrel (107) vs. aspirin + ticagrelor (106)	NR	1 month	Periprocedural myonecrosis
44	ACCEL-LOADING ACS; Int J Cardiol, 2015	Patients with acute NSTEMI or unstable angina	November 2009–September 2011	Aspirin + clopidogrel (127) vs. aspirin + clopidogrel + cilostazol (127 patients)	NR	1 month	Composite of cardiovascular death, MI, and ischemia-driven target vessel revascularization
45	Wang et al.; Ther Clin Risk Manag, 2015	Patients with acute NSTEMI undergoing PCI	October 2010–August 2012	Aspirin + clopidogrel (79) vs. aspirin + clopidogrel + cilostazol (74)	< 48 hours from symptom onset	30 days	Not specified
46	PRAGUE-18; Circulation, 2016	Patients with MI undergoing emergency PCI	April 2013–May 2016	Aspirin + prasugrel (634) vs. aspirin +	< 2 hours from hospital arrival	30 days	All-cause death, re-infarction, stroke, serious bleeding, urgent target vessel revascularization

Study #	Study; journal, publication year	Patient population	Years enrolling	Treatment arms (number of patients enrolled)	Time from MI to enrollment	Follow-up duration	Primary endpoint
				ticagrelor (596)			
47	Wang et al.; Ther Clin Risk Manag, 2016	Patients with ACS	August 2013–November 2014	Aspirin + clopidogrel (100) vs. aspirin + ticagrelor (100)	NR	12 months	Efficacy: Composite of CV death, MI, stroke Safety: PLATO major bleeding

ACS, acute coronary syndrome; NSTEMI, non-ST segment elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; NR, not reported. Study number corresponds to the study number in Supplemental Table S1, and the full citation for each study can be found in the Supplemental materials.