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Antithrombotic agents for secondary prevention after acute coronary syndromes: A systematic review and network meta-analysis

Alexander C Fanaroff [a,b,*], Vic Hasselblad [b], Matthew T Roe [a,b], Deepak L Bhatt [c], Stefan K James [d], Ph Gabriel Steg [e,f], C Michael Gibson [g], E Magnus Ohman [a,b]

[a] Division of Cardiology, Duke University, Durham, NC, USA
[b] Duke Clinical Research Institute, Duke University, Durham, NC, USA
[c] Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA, USA
[d] Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden
[e] FACT (French Alliance for Cardiovascular Clinical Trials), DHU FIRE, INSERM Unité 1148, Université Paris-Diderot, Hôpital Bichat, Assistance-Publique-Hôpitaux de Paris, France
[f] NHLI, Imperial College, Royal Brompton Hospital, London, UK
[g] Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, MA, USA

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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 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.

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 $P2Y_{12}$ 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 $P2Y_{12}$ 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

* Corresponding author at: Duke Clinical Research Institute, 2400 Pratt Street, Durham, NC 27705, USA.
E-mail address: alexander.fanaroff@duke.edu (A.C. Fanaroff).

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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 < 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 $P2Y_{12}$ 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% 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.

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 (Fig. 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 Fig. 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,