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Safety and Efficacy of Antithrombotic Strategies in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

A Network Meta-analysis of Randomized Controlled Trials

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IMPORTANCE The antithrombotic treatment of patients with atrial fibrillation (AF) and coronary artery disease, in particular with acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI), poses a significant treatment dilemma in clinical practice.

OBJECTIVE To study the safety and efficacy of different antithrombotic regimens using a network meta-analysis of randomized controlled trials in this population.

DATA SOURCES PubMed, EMBASE, EBSCO, and Cochrane databases were searched to identify randomized controlled trials comparing antithrombotic regimens.

STUDY SELECTION Four randomized studies were included (n = 10 026; WOEST, PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS).

DATA EXTRACTION AND SYNTHESIS The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used in this systematic review and network meta-analysis between 4 regimens using a Bayesian random-effects model. A pre hoc statistical analysis plan was written, and the review protocol was registered at PROSPERO. Data were analyzed between November 2018 and February 2019.

MAIN OUTCOMES AND MEASURES The primary safety outcome was Thrombolysis in Myocardial Infarction (TIMI) major bleeding; secondary safety outcomes were combined TIMI major and minor bleeding, trial-defined primary bleeding events, intracranial hemorrhage, and hospitalization. The primary efficacy outcome was trial-defined major adverse cardiovascular events (MACE); secondary efficacy outcomes were individual components of MACE.

RESULTS The overall prevalence of ACS varied from 28% to 61%. The mean age ranged from 70 to 72 years; 20% to 29% of the trial population were women; and most patients were at high risk for thromboembolic and bleeding events. Compared with a regimen of vitamin K antagonist (VKA) plus dual antiplatelet therapy (DAPT; $P2Y_{12}$ inhibitor plus aspirin), the odds ratios (ORs) for TIMI major bleeding were 0.58 (95% CI, 0.31-1.08) for VKA plus $P2Y_{12}$ inhibitor, 0.49 (95% CI, 0.30-0.82) for non-VKA oral anticoagulant (NOAC) plus $P2Y_{12}$ inhibitor, and 0.70 (95% CI, 0.38-1.23) for NOAC plus DAPT. Compared with VKA plus DAPT, the ORs for MACE were 0.96 (95% CI, 0.60-1.46) for VKA plus $P2Y_{12}$ inhibitor, 1.02 (95% CI, 0.71-1.47) for NOAC plus $P2Y_{12}$ inhibitor, and 0.94 (95% CI, 0.60-1.45) for NOAC plus DAPT.

CONCLUSIONS AND RELEVANCE A regimen of NOACs plus $P2Y_{12}$ inhibitor was associated with less bleeding compared with VKAs plus DAPT. Strategies omitting aspirin caused less bleeding, including intracranial bleeding, without significant difference in MACE, compared with strategies including aspirin. Our results support the use of NOAC plus $P2Y_{12}$ inhibitor as the preferred regimen post–percutaneous coronary intervention for these high-risk patients with AF. A regimen of VKA plus DAPT should generally be avoided.

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Supplemental content

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The combination of atrial fibrillation (AF) and coronary artery disease (CAD), and in particular acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI), poses a significant dilemma to physicians who have to decide which antithrombotic regimen provides the best balance of safety and efficacy.[1,2] Vitamin K antagonists (VKAs) and non-vitamin K antagonist oral anticoagulants (NOACs) are indicated for stroke prevention, whereas prevention from recurrent atherothrombotic events and stent thrombosis usually requires dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor and aspirin.[3]

A number of randomized controlled trials (RCTs) have compared the safety and efficacy of antithrombotic regimens in patients with AF undergoing PCI or with concomitant ACS.[4-7] In 2018, the outcomes of these RCTs were combined in a meta-analysis[8] that concluded that omitting aspirin resulted in fewer major bleeds while preserving efficacy compared with VKA or NOACs with DAPT. While the findings of this analysis are important, the sample size of approximately 5000 patients did not permit assessment of differences in less frequent but important complications such as stent thrombosis. Moreover, it also remains unclear whether different classes of anticoagulants (VKAs or NOACs) affect safety and efficacy in this high-risk population. To address these shortcomings, we performed a Bayesian network meta-analysis (NMA) that allowed for simultaneous comparisons of multiple antithrombotic strategies. This approach, with the inclusion of the 4614-patient 2019 Open-label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention (AUGUSTUS) trial,[9] presents the largest evidence base to date to inform antithrombotic decisions in this high-risk group of patients.

Key Points

Question What is the most appropriate antithrombotic regimen to manage atrial fibrillation and coronary artery disease, in particular with acute coronary syndrome and/or percutaneous coronary intervention, while balancing ischemic and bleeding risk in an understudied high-risk patient population?

Findings In this network meta-analysis, simultaneous comparisons of multiple antithrombotic strategies were performed for safety and efficacy outcomes in a study involving more than 10 000 participants. The study demonstrated that vitamin K antagonist plus dual antiplatelet therapy should be avoided, whereas the use of a non-vitamin K antagonist oral anticoagulant plus $P2Y_{12}$ inhibitor, without aspirin, should be the preferred treatment.

Meaning Meaningful information about antithrombotic regimens may help physicians in their decision making when treating this high-risk group of patients.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (eTable 1 in the Supplement) were used in this systematic review and NMA.[10] A prespecified statistical analysis plan was written, and the review protocol was registered at PROSPERO (CRD42019096584).

Study Selection and Eligibility Criteria

Two reviewers (R.D.L. and R.E.H.) performed a systematic review, and disagreements were resolved in a panel discussion of 3 reviewers (R.D.L., H.H., and R.E.H.). Study selection involved screening of titles and abstracts followed by full-text evaluation of possible eligible studies. The inclusion criteria for our study included (1) RCTs with at least 2 comparator arms; (2) study population of patients with ACS or undergoing PCI for stable CAD or ACS; (3) treatment with a combination of anticoagulation and antiplatelet therapy; (4) reported major bleeding and major adverse cardiovascular events (MACE); and (5) follow-up of at least 6 months. We excluded observational studies, crossover trials, studies where the method of allocation was not truly random, duplicate studies, and nonoriginal data studies. No language, publication date, or publication status restrictions were applied. References of prior systematic reviews and meta-analyses were also screened for related studies.

Search Strategy and Information Sources

We searched PubMed/MEDLINE, Ovid/Embase, EBSCO/CINAHL, and Cochrane databases from database inception through the final search date of April 19, 2019. We used keywords related to PCI, ACS, NOACs or VKA, antiplatelets, and atrial fibrillation. The full search strategies are provided in eTable 2 in the Supplement. Study authors were contacted to identify other relevant studies or to provide unpublished data.

Outcome Measures

The primary safety outcome was major bleeding according to the Thrombolysis In Myocardial Infarction (TIMI) criteria. The secondary safety outcomes were combined TIMI major and minor bleeding, trial-defined primary bleeding events (eTable 3 in the Supplement for trial-specific definitions), intracranial hemorrhage, and hospitalization. The primary efficacy outcome was trial-defined MACE (eTable 3 in the Supplement), which was usually defined as a combination of either all-cause or cardiovascular mortality, myocardial infarction (MI), stroke, and stent thrombosis. Secondary efficacy outcomes were individual components of this composite MACE outcome.

Data Collection Process

Two reviewers (H.H. and J.L.) independently extracted data on the study design, baseline characteristics, interventions, and outcomes. Any disagreements of collected information between the 2 reviewers were reconciled through discussion. Unpublished outcome data were provided by the principal investigators of eligible RCTs. For the AUGUSTUS trial, the lead investigator (R.D.L.) provided the necessary information shortly after database lock in December 2018.

Risk of Bias Within Individual Studies

Two independent reviewers (R.D.L. and R.E.H.) assessed the risk of bias (low, intermediate, or high) of the included studies using the Cochrane Collaboration tool (eTable 4 in the Supplement). Given the limited number of publications, we did not assess the risk of publication bias.

Statistical Analysis

We fitted a Bayesian random-effects NMA model to simultaneously compare multiple regimens. We extracted the sample size and total number of events for each of the prespecified outcomes in each treatment group from eligible RCTs. Data were analyzed between November 2018 and February 2019. The NMA model combines evidence about direct and indirect comparisons of regimens by accounting for the correlation among multiarm trials.[11,12] We assumed that the direct and indirect evidence for a treatment comparison had no discrepancy, called *evidence consistency*. To account for effect heterogeneity across trials, we allowed random effects to NMA and measured the magnitude of heterogeneity. In this model, we estimated odds ratios (ORs) of the effects of the 2 regimens and the associated 95% credible intervals using Markov chain Monte Carlo algorithms. All analyses were conducted using the gemtc package (version 0.8-2)[13] in R, version 3.5.1 (The R Foundation).[14] We used the package's default setting including noninformative prior distributions with 4 parallel chains, where each chain consists of 50 000 samples after a 20 000-sample burn-in. The gemtc package uses a normal prior for log odds of baseline or log OR parameters and a uniform prior for the standard deviation of between-study heterogeneity and then determines the specifications of the prior distributions (eg, upper bound of the uniform prior) from the data so that the prior distributions are sufficiently vague but limit bias.[15] We checked convergence of Markov chain Monte Carlo chains for all model parameters using trace plots and Gelman-Rubin diagnostic statistics.[16]

To evaluate and rank regimens, we calculated rank probabilities (ie, probability of a regimen being the best, second best, or worst for an outcome) and the Surface Under the Cumulative Ranking (SUCRA). The SUCRA is a numerical summary that accounts for both magnitude and uncertainty of the estimated effect for each regimen.[17] A larger SUCRA value indicates better performance for the outcome. We ranked regimens based on SUCRA with respect to each safety and efficacy outcome.

We assessed statistical evidence for inconsistency defined as discrepancy between direct and indirect comparisons of treatment effects using 3 methods including loop-specific approach, node-splitting approach, and comparing Bayesian model fit with and without the assumption of evidence inconsistency.[18,19] In addition, we investigated the effect of different prior distributions for the heterogeneity parameter.[20] We conducted sensitivity analyses with 4 different networks of regimens. In addition, we added the landmark study of Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE)[7] into the NMA.

All outcome data in each regimen used in the analyses (eAppendix 1 in the Supplement) and network structures for sensitivity analyses (eAppendix 3 in the Supplement) are available online.

Results

Search Results

Our database search resulted in 1448 unique studies. Of those, 1424 studies were deemed irrelevant based on title and abstract screening. Twenty-four studies were assessed in full-text for eligibility (eFigure 1 in the Supplement). Of those, 5 studies met the inclusion criteria.[4-7,9] However, 1 of these studies (ISAR-TRIPLE[7]) had a markedly different trial design, involving a randomized comparison of 2 durations of triple therapy with omitting clopidogrel after 6 weeks vs 6 months. While a landmark analysis was performed at 6 weeks, the study was not designed to compare dual-therapy vs triple-therapy regimens from time of index hospitalization (an important time window both from thromboembolic and bleeding perspective) and was included therefore only in a sensitivity analysis. As a result, the main analysis included 4 RCTs.

Study and Patient Characteristics

Trial design, population, treatment regimens, main results, and other characteristics of the 4 included RCTs are available online (eTables 5-7 in the Supplement). The RCTs were predominantly conducted at sites in Europe and North America and were published between 2013 and 2019. Follow-up duration was 6 to 14 months. All RCTs were judged to be at low risk of bias (eTable 4 in the Supplement). eTable 8 in the Supplement shows baseline characteristics of the patients in each RCT. A total of 10 026 patients were included in the NMA, and the sample size of the individual RCTs ranged from 563 to 4614. The overall prevalence of ACS varied from 28% to 61%. Except for AUGUSTUS, all patients underwent PCI, and the use of drug-eluting stents ranged from 66% to 83%. The mean age of patients ranged from 70 to 72 years, and 20% to 29% of the trial populations were women. Patients were predominantly white (>90%). Comorbidities, such as hypertension, dyslipidemia, and diabetes, were common. Most patients had annual thromboembolic and bleeding risk exceeding 3% (CHA_2DS_2-VASc ≥3 and HAS-BLED ≥3).

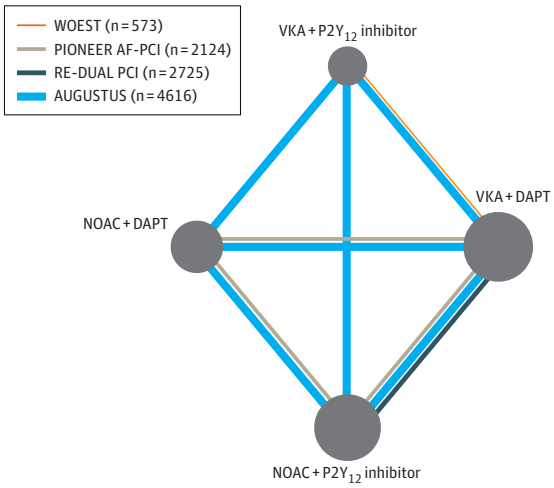
Structure of NMA

Figure 1 displays the network of treatment regimens used in the main analysis. We compared 4 treatment regimens: VKA plus DAPT; VKA plus $P2Y_{12}$ inhibitor; NOAC plus DAPT; and NOAC plus $P2Y_{12}$ inhibitor. In this network, we assumed that the 3 NOAC agents (apixaban, dabigatran, and rivaroxaban) and doses (apixaban, 5 mg, twice daily; dabigatran, 110 mg or 150 mg, twice daily; rivaroxaban, 2.5 mg, twice daily or 15 mg, once daily) included in this analysis have comparable safety and efficacy. We set VKA plus DAPT to be reference because all 4 RCTs investigated this regimen.

Network Meta-analysis Results for Safety Outcomes

Compared with VKA plus DAPT, both the NOAC plus $P2Y_{12}$ inhibitor and VKA plus $P2Y_{12}$ inhibitor regimens were

Figure 1. Network of 4 Antithrombotic Treatment Regimens



The nodes represent antithrombotic treatment regimens to be compared and the edges represent the observed direct comparisons in the included trials. The size of nodes is proportional to the number of patients assigned to the treatment regimen and the thickness of edges is proportional to the sample size of each study. AUGUSTUS indicates Open-label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; DAPT, dual antiplatelet therapy; NOAC, non–vitamin K antagonist oral anticoagulant; PIONEER AF-PCI, Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI, Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; VKA, vitamin K antagonist; WOEST, What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting.

associated with less bleeding including less TIMI major, major or minor, and trial-defined primary bleeding (**Figure 2**). For intracranial hemorrhage, the use of NOAC plus $P2Y_{12}$ inhibitor had the lowest odds among the 4 regimens. Pairwise comparisons among regimens are displayed in eFigure 2 in the Supplement. The odds for any reported bleeding outcome were lower for NOAC plus $P2Y_{12}$ inhibitor when compared with VKA plus DAPT including intracranial hemorrhage. The VKA plus $P2Y_{12}$ inhibitor regimen was also more favorable for trial-defined bleeding outcomes and any TIMI bleed compared with VKA plus DAPT. When comparing these 2 regimens, NOAC plus $P2Y_{12}$ inhibitor had more favorable odds for intracranial hemorrhage. than VKA $P2Y_{12}$ inhibitor. In addition, the combination of NOAC plus DAPT did result in numerically lower rates of all reported bleeding outcomes when compared with VKA plus DAPT.

Network Meta-analysis Results for Efficacy Outcomes

Overall, the 4 treatment regimens had comparable outcomes with respect to MACE and all-cause and cardiovascular death (**Figure 3**; eFigure 3 in the Supplement). Moreover, there were no significant differences for stroke, MI, and stent thrombosis between the antithrombotic regimens. Finally, the need for hospitalization was the same irrespective of the antithrombotic regimen used (Figure 3G; eFigure 3G in the Supplement).

Ranking of Treatment Strategies

The **Table** displays SUCRA values for safety and efficacy outcomes. The performance of the tested regimens was visualized in a 2-dimensional forest plot of ORs (**Figure 4**; eTables 9 and 10; eFigures 4 and 5 in the Supplement). The regimen with the highest SUCRA value (ie, best performance) for all bleeding outcomes was NOAC plus $P2Y_{12}$ inhibitor (SUCRA of 77-94). Most notably, this regimen was the preferred strategy for intracranial hemorrhage (94.2), followed by NOAC plus DAPT (63.5). A regimen of VKA plus $P2Y_{12}$ inhibitor was the runner-up for the other bleeding outcomes (67-79). For efficacy outcomes (MACE and its individual components), there was no treatment regimen clearly favored overall. For hospitalization, the combination of NOAC plus $P2Y_{12}$ inhibitor was equally favorable (69.2) to NOAC plus DAPT (70.0) and followed by VKA plus $P2Y_{12}$ inhibitor (50.2). All fitted models converged well (eFigure 6 in the Supplement) and we did not find evidence that indicated statistical inconsistency in our NMA (eAppendix 2 in the Supplement).

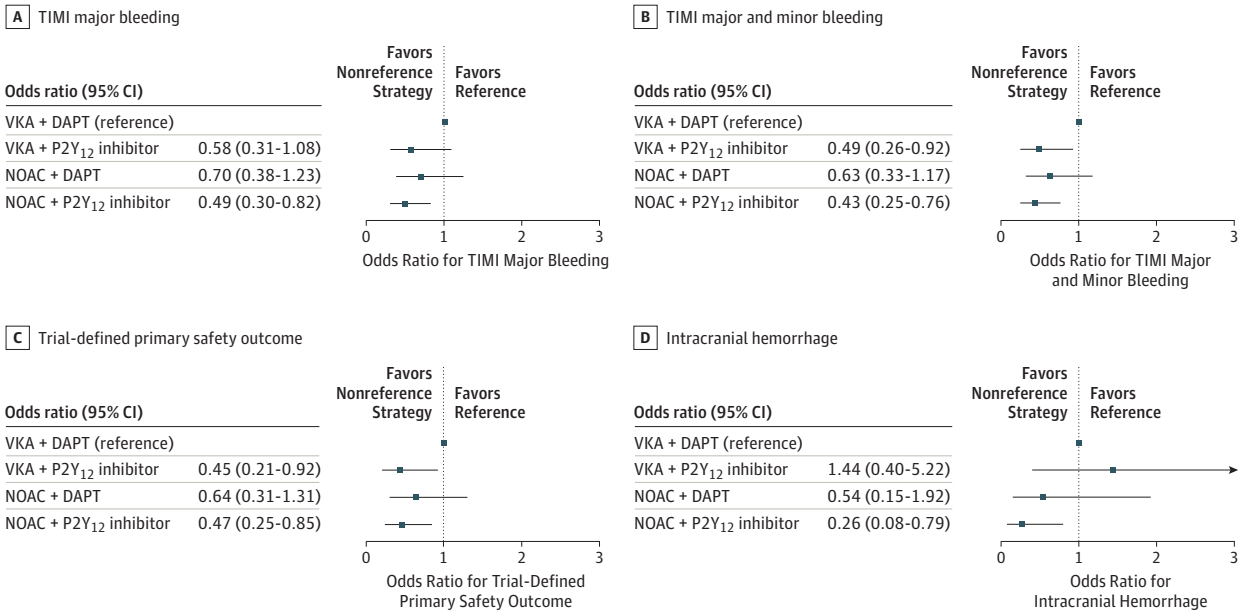
Results of Sensitivity Analyses

As shown in eAppendix 3 in the Supplement, we performed a number of additional analyses. We found similar outcomes when using an NMA in which rivaroxaban, apixaban, and dabigatran were compared with VKA plus DAPT (eAppendix 3A in the Supplement). Regimens with factor Xa inhibitors (rivaroxaban and apixaban) had similar safety and efficacy as those with a thrombin inhibitor (either as higher or lower dose of dabigatran or combined) when compared with VKA plus DAPT (eAppendix 3B and 3C in the Supplement). We found that including the results of the 6-week landmark analysis from ISAR-TRIPLE as part of a sensitivity analysis resulted in similar results compared with the main analysis (eAppendix 3E in the Supplement).

Discussion

Navigating the delicate balance between bleeding and ischemic risk is a challenge to clinicians and patients who have AF and need for antiplatelet therapy. The general consensus is to continue oral anticoagulation and to modify antiplatelet intensity and/or duration, but the optimal regimen has yet to be identified.[21,22] In our NMA of RCTs investigating the safety and efficacy of antithrombotic regimens, we found that an antithrombotic regimen of a NOAC plus $P2Y_{12}$ inhibitor results in less bleeding, including intracranial hemorrhage, compared with VKA plus DAPT. Among antiplatelet strategies, omitting aspirin caused less bleeding, without significant difference in MACE, compared with strategies including aspirin. These results support the use of a NOAC plus $P2Y_{12}$ inhibitor regimen as the preferred treatment strategy in this high-risk patient population. Routine use of regimens that include a VKA plus a $P2Y_{12}$ inhibitor plus aspirin should generally be avoided.

Figure 2. Forest Plots for Safety Outcomes



Odds ratios and 95% credible intervals (CIs) comparted with vitamin K antagonist (VKA) plus dual antiplatelet therapy (DAPT) (reference) are plotted. A total of 9924 patients were contributed to network meta-analyses for all safety outcomes. The estimated between-trial effect heterogeneity and its 95% CI (in standard deviation of the log odds ratio scale) from NMA for each outcome is 0.24 (95% CI, 0.01-0.71), 0.35 (95% CI, 0.03, 0.88), 0.46 (95% CI, 0.16, 1.03), and 0.52 (95% CI, 0.02, 1.52). A, TIMI major bleeding. B, TIMI major or minor bleeding. C, Trial-defined primary safety outcome. D, Intracranial hemorrhage. NOAC indicates non–vitamin K antagonist oral anticoagulant.

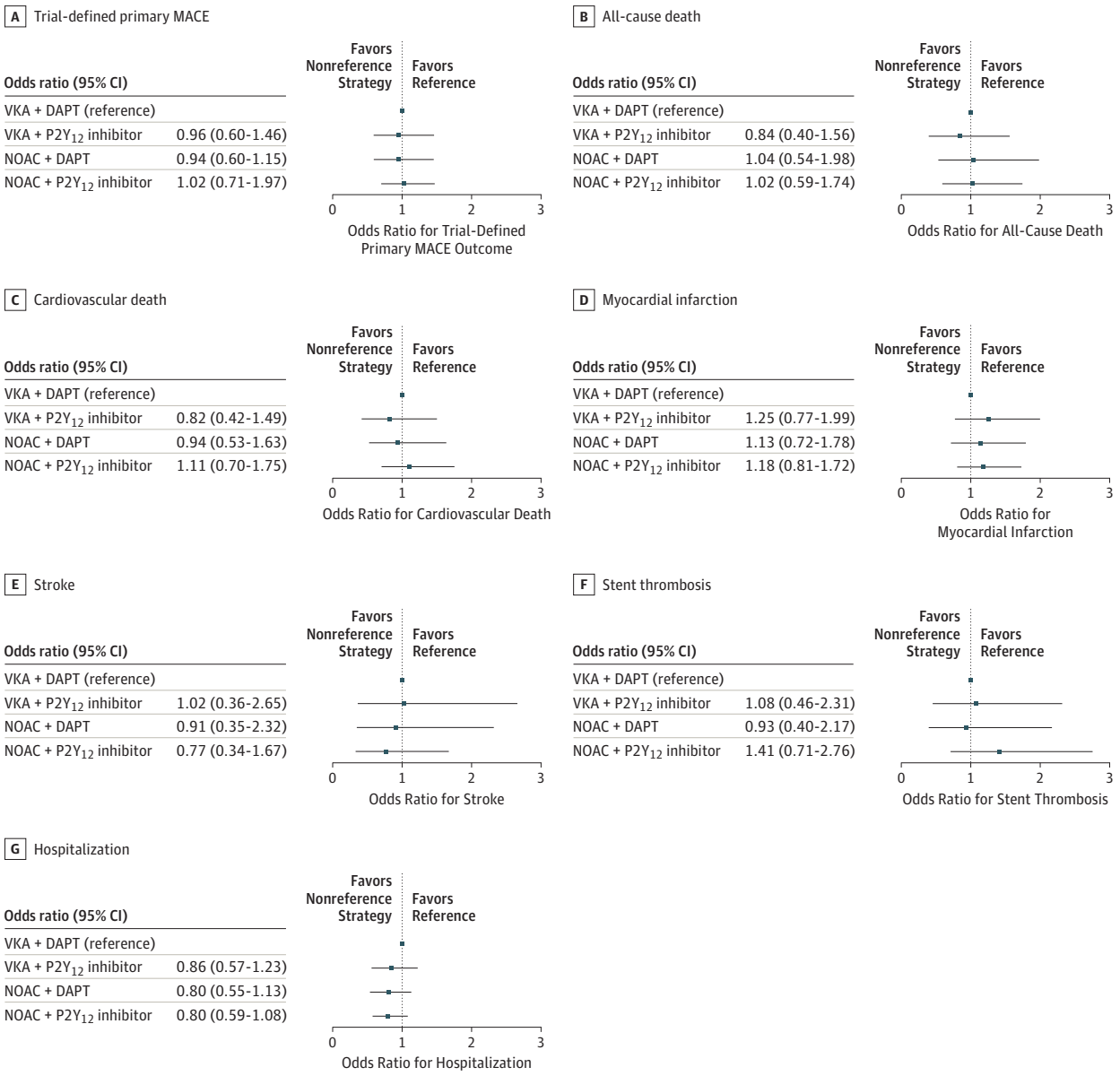
Antithrombotic Strategies With NOACs vs VKAs

A prior NMA[23] investigated antithrombotic strategies in patients with AF and ACS and/or PCI. The authors found that the combination of VKA and a single antiplatelet agent provided the best choice in terms of safety and efficacy, with a very low dose of rivaroxaban, 2.5 mg, twice daily plus DAPT as an acceptable alternative. These findings are of interest because they confirm that conventional triple therapy with VKA, $P2Y_{12}$ inhibitor, and aspirin should be avoided. However, the study also found that triple therapy with a low dose of NOAC in combination with $P2Y_{12}$ inhibitor and aspirin could be considered and was preferable vs a standard dose of NOAC plus $P2Y_{12}$ inhibitor. A 2018 study[24] using a bivariate analysis based on an Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) and Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) found that all tested NOAC combinations were superior in terms of bleeding and noninferior in efficacy when compared with VKA plus DAPT.

Antithrombotic Strategies With or Without Aspirin

During the last decade, the role of aspirin in combination antithrombotic regimens had been questioned. A 2018 meta-analysis,[8] restricted to data from high-quality randomized clinical trials (n = 5317), concluded that dual antithrombotic therapy with an oral anticoagulant and $P2Y_{12}$ inhibitor may be a better option than triple therapy in many patients with AF following PCI, based on a 47% reduction in major or minor bleeding with comparable outcomes of MACE. Our meta-analysis, which adds almost 5000 patients, confirms these findings. This is particularly relevant for more rare events, such as stent thrombosis, which is an important reason to use DAPT in the month(s) following PCI prior to re-endothelialization of the stent struts and/or polymer material and is particularly of concern when PCI occurs in the (prothrombotic) setting of ACS.[25] A systematic review[26] that included observational data suggested comparable outcomes of $P2Y_{12}$ inhibitor with and without aspirin in terms of stent thrombosis and other MACE outcomes. In our NMA, we also found no clear signal of increased stent thrombosis in the groups taking antithrombotic regimens without aspirin. In patients who underwent PCI, a loading dose of aspirin followed by a few days of aspirin was typically administered, irrespective of subsequent regimen. It is therefore possible that, following PCI, dual antithrombotic therapy with an oral anticoagulant and a $P2Y_{12}$ inhibitor might be comparable with triple therapy for prevention of thrombotic events, including stent thrombosis, and should be preferred vs triple therapy for most patients owing to its better safety profile. Other studies in patients with ACS without AF have demonstrated the bleeding risk associated with full-dose triple therapy with a NOAC, P2Y12 inhibitor, and aspirin.[27,28]

Figure 3. Forest Plots for Efficacy Outcomes



Odds ratios and 95% credible intervals (CIs) compared with vitamin K antagonist (VKA) plus dual antiplatelet therapy (DAPT) (reference) are plotted. A total of 9995 patients were contributed to network meta-analyses for all efficacy outcomes except the hospitalization outcome. The network meta-analysis for the hospitalization outcome included 10 001 patients. The estimated between-trial effect heterogeneity and its 95% credible interval (in standard deviation of the log odds ratio scale) from the NMA for each outcome is 0.23 (0.01-0.50), 0.31 (0.01, 0.83), 0.22 (0.01, 0.66), 0.17 (0.01, 0.37), 0.47 (0.03, 0.94), 0.34 (0.01, 0.72), and 0.22 (0.05, 0.43). MACE indicates major adverse cardiac event; NOAC, non–vitamin K antagonist oral anticoagulant.

Mechanistic Insights Into Antithrombotic Regimens

The scientific basis for VKA therapy to prevent arterial thrombosis in the setting of AF is not platelet dependent but includes interference with effects of tissue-factor expressed by activated endothelial cells and monocytes.[29] Prior research has demonstrated that oral anticoagulation is more effective in preventing reinfarction and stroke than aspirin plus clopidogrel in patients with AF.[30] Moreover, temporary discontinuation of oral anticoagulants or omission of $P2Y_{12}$ inhibitors in patients with AF undergoing PCI is associated with increased risk for ischemic events without reducing the risk of bleeding complications.[31,32] In addition, studies that have added aspirin to VKA vs VKA monotherapy did not clearly demonstrate an additional benefit in patients following MI while increasing the risk of bleeding.[33,34] While the exact underlying mechanisms may not be fully elucidated, it is known that oral anticoagulants, including NOACs, exert antiplatelet effects that result in prevention of both stroke and recurrent MI and that are further synergized by $P2Y_{12}$ inhibition.[35-38] Thus, a dual pathway of platelet

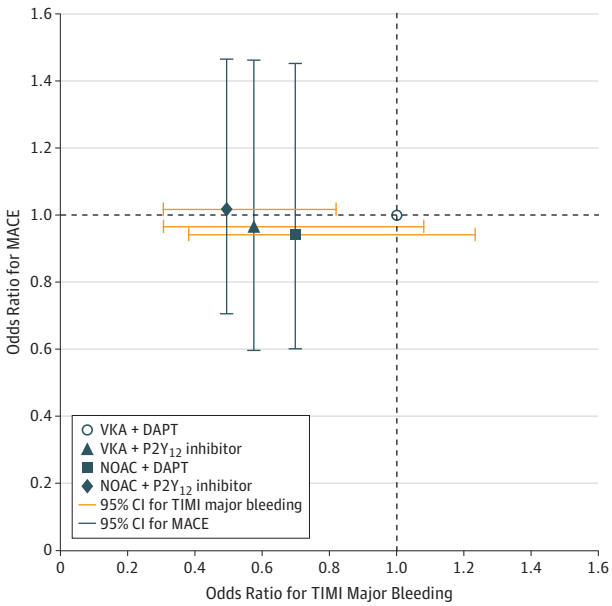
Table. SUCRA Values for Each Treatment Regimen and Outcomes[a]

Value	VKA Plus DAPT	VKA Plus $P2Y_{12}$ Inhibitor	NOAC Plus DAPT	NOAC Plus $P2Y_{12}$ Inhibitor
Safety outcome				
TIMI				
Major	4.6	66.6	43.8	85.1
Major and minor	2.7	70.6	41.9	84.9
Trial-defined bleeding outcome	3.6	79.1	40.6	76.7
Intracranial hemorrhage	30.0	12.1	63.5	94.2
Efficacy outcome				
Trial-defined MACE	45.7	53.5	60.7	40.0
All-cause death	46.2	71.8	39.9	42.2
Cardiovascular death	45.2	74.8	56.6	23.5
MI	79.1	30.1	51.0	39.9
Stroke	39.4	38.6	51.1	70.9
Stent thrombosis	62.9	51.0	68.2	17.8
Hospitalization	10.5	50.2	70.0	69.2

Abbreviations: DAPT, dual antiplatelet therapy; MACE, major adverse cardiac events; MI, myocardial infarction; NOAC, non–vitamin K antagonist oral anticoagulant; SUCRA, Surface Under the Cumulative Ranking; TIMI, thrombolysis in myocardial infarction; VKA, vitamin K antagonist.

[a] SUCRA values are presented as percentage of area under the cumulative rank probability curve (eFigures 4 and 5 in the Supplement) and the entire plane of the plot. The larger the SUCRA value, the better the treatment regimen performance with respect to the outcome.

Figure 4. Odds Ratios for TIMI Major Bleeding and MACE



Odds ratios compared with vitamin K antagonist (VKA) plus dual antiplatelet therapy (DAPT) (reference) and associated 95% credible intervals are plotted: TIMI major bleeding (orange) on the x-axis and major adverse cardiac event (MACE) (blue) on the y-axis. Network meta-analyses for the TIMI major bleeding and MACE outcomes included 9924 and 9995 patients, respectively.

inhibition with oral anticoagulants plus $P2Y_{12}$ inhibition might be enough for most patients with AF and ACS and/or PCI and adding aspirin might only increase the risk of bleeding, including intracranial bleeding, without a significant additional benefit in efficacy outcomes.

So how can we explain the favorable safety profile of NOACs plus $P2Y_{12}$ inhibition vs VKA-based regimens? Unlike VKAs, the NOACs exert their anticoagulant directly by either targeting factor Xa (apixaban, rivaroxaban, and edoxaban) or as a direct thrombin inhibitor (dabigatran). Thus, NOACs offer simplification of long-term anticoagulation therapy by promoting optimal thromboembolic protection with less bleeding complications. Finally, our main conclusions are based on the significance of the ORs and 95% credible intervals as well as ranking of treatment strategies using SUCRA values for best performance. Both VKA plus $P2Y_{12}$ inhibitor and NOAC plus $P2Y_{12}$ inhibitor have less TIMI major bleeding, TIMI major or minor bleeding, and trial-defined primary safety than VKA plus DAPT; however, NOAC plus $P2Y_{12}$ inhibitor had lower odds of intracranial hemorrhage compared with VKA plus $P2Y_{12}$ inhibitor and lower odds of TIMI major bleeding than VKA plus $P2Y_{12}$ inhibitor compared with VKA plus DAPT. The AUGUSTUS trial had an arm that included 1126 patients treated with VKA plus $P2Y_{12}$ inhibitor, which was much larger than the 279 patients receiving VKA plus $P2Y_{12}$ inhibitor in WOEST. Given these results and the other well-known advantages of NOACs over VKA, we concluded that NOAC plus P2Y12 inhibitor is the preferred treatment option for this patient population.

Limitations and Future Directions

Although an NMA overcomes some of the limitations of routine pairwise meta-analyses and allows for evidence-based grading, our NMA also has limitations. First, the estimated between-study heterogeneity as a standard deviation on the log OR scale is close to or smaller than the standard deviation of the estimated log ORs, which could not be ignored. Although there is no definite cut point to determine small or large heterogeneity; in our analysis, between-study heterogeneity exists and the potential sources include design, indication, type, dose and duration of antithrombotic therapy, and duration of follow-up, which may potentially affect the interpretation of our results. Although the sample size was sufficient to draw firm conclusions on the overall populations for the primary safety and efficacy outcomes, it may still be insufficient to ascertain more modest effects on rare but serious events, such as stent thrombosis. A few other ongoing studies, including the Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF-PCI) trial with 1508 participants, may add some information on the safety (and efficacy) of (standard dose) edoxaban vs VKA both in combination with a $P2Y_{12}$ inhibitor.[39] However, the relatively small sample size of these studies is unlikely to change the results of our NMA. In addition, to further explore which patients would benefit most from a given treatment combination, an individual patient-level data analysis is warranted. This analysis could shed further light on whether adjustments need to be made by sex, race/ethnicity, age, clinical presentation (ACS and

stable CAD), thromboembolic risk, bleeding risk, stent placement, stent type, and other procedural characteristics. Most patients used clopidogrel as a $P2Y_{12}$ inhibitor; as such, we do not know whether the use of other more potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) have the same effects on safety and efficacy in combination with oral anticoagulant therapyDirect comparisons between NOACs may also be warranted because it is possible that not all NOACs or doses of NOACs perform the same in terms of the balance of safety and efficacy when combined with platelet inhibitors in the setting of ACS and/or PCI. Mechanistic studies into the role of platelet function and genetic testing in patients treated with VKA or NOAC and antiplatelet therapy after PCI to develop personalized antithrombotic regimens is another area that remains poorly explored and warrants investigation. Genome-wide pharmacogenomics data suggest that several polymorphisms affect the response of VKA or NOACs.[40] In the future, a personalized medicine approach based on pharmacogenetics could be helpful in this complex heterogeneous patient population.

Conclusions

In patients with AF undergoing PCI, a regimen of NOAC plus $P2Y_{12}$ inhibitor was associated with fewer bleeding complications, including intracranial bleeding, without a significant difference in ischemic events compared with VKA plus DAPT. Although further data on outcomes of patients receiving VKA plus $P2Y_{12}$ inhibitor are needed for definitive conclusions, our results support the use of an NOAC and $P2Y_{12}$ inhibitor as the preferred treatment option for this high-risk patient population. In the absence of future trials showing incremental efficacy with acceptable bleeding resulting in a favorable net clinical benefit of triple therapy, regimens that include a VKA plus a $P2Y_{12}$ inhibitor plus aspirin should generally be avoided.

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REFERENCES

1. Michniewicz E, Mlodawska E, Lopatowska P, Tomaszuk-Kazberuk A, Malyszko J. Patients with atrial fibrillation and coronary artery disease:

double trouble. *Adv Med Sci*. 2018;63(1):30-35. doi:10.1016/j.advms.2017.06.005

2. Jabre P, Jouven X, Adnet F, et al. Atrial fibrillation and death after myocardial infarction: a community study. *Circulation*. 2011;123(19):2094-2100. doi:10.1161/CIRCULATIONAHA.110.990192

3. Cho JR, Angiolillo DJ. Percutaneous coronary intervention and atrial fibrillation: the triple therapy dilemma. *J Thromb Thrombolysis*. 2015;39(2):203-208. doi:10.1007/s11239-014-1132-z

4. Dewilde WJM, Oirbans T, Verheugt FWA, et al; WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381(9872):1107-1115. doi:10.1016/S0140-6736(12)62177-1

5. Cannon CP, Bhatt DL, Oldgren J, et al; RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377(16):1513-1524. doi:10.1056/NEJMoa1708454

6. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375(25):2423-2434. doi:10.1056/NEJMoa1611594

7. Fiedler KA, Maeng M, Mehilli J, et al. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial. *J Am Coll Cardiol*. 2015;65(16):1619-1629. doi:10.1016/j.jacc.2015.02.050

8. Golwala HB, Cannon CP, Steg PG, et al. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J*. 2018;39(19):1726-1735a. doi:10.1093/eurheartj/ehy162

9. Lopes RD, Heizer G, Aronson R, et al; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380(16):1509-1524. doi:10.1056/NEJMoa1817083

10. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777-784. doi:10.7326/M14-2385

11. Dias S, Welton SJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomized controlled trials. http://nicedsu.org.uk/wp-content/uploads/2017/05/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf. Published August 2011. Updated September 2016. Accessed April 30, 2019.

12. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23(20):3105-3124. doi:10.1002/sim.1875

13. Package 'gemtc.' Version 0.8-2. https://cran.r-project.org/web/packages/gemtc/gemtc.pdf. Published December 23, 2016. Accessed April 30, 2019.

14. R Core Team. R: a language and environment for statistical computing. https://www.r-project.org/. Published 2018. Accessed April 30, 2019.

15. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Res Synth Methods*. 2012;3(4):285-299. doi:10.1002/jrsm.1054

16. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Stat Sci*. 1992;7:457-472. doi:10.1214/ss/1177011136

17. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol*. 2011;64(2):163-171. doi:10.1016/j.jclinepi.2010.03.016

18. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. 2010;29(7-8):932-944. doi:10.1002/sim.3767

19. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 6: embedding evidence synthesis in probabilistic cost-effectiveness analysis. *Med Decis Making*. 2013;33(5):671-678. doi:10.1177/0272989X13487257

20. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol*. 2012;41(3):818-827. doi:10.1093/ije/dys041

21. Kirchhof P, Benussi S, Kotecha D, et al; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210

22. Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention. *Circulation*. 2018;138(5):527-536. doi:10.1161/CIRCULATIONAHA.118.034722

23. Gong X, Tang S, Li J, Zhang X, Tian X, Ma S. Antithrombotic therapy strategies for atrial fibrillation patients undergoing percutaneous coronary intervention: a systematic review and network meta-analysis. *PLoS One*. 2017;12(10):e0186449. doi:10.1371/journal.pone.0186449

24. Chi G, Kerneis M, Kalayci A, et al. Safety and efficacy of non-vitamin K oral anticoagulant for atrial fibrillation patients after percutaneous coronary intervention: a bivariate analysis of the PIONEER AF-PCI and RE-DUAL PCI trial. *Am Heart J*. 2018;203:17-24. doi:10.1016/j.ahj.2018.06.003

25. Claessen BE, Henriques JPS, Jaffer FA, Mehran R, Piek JJ, Dangas GD. Stent thrombosis: a clinical perspective. *JACC Cardiovasc Interv*. 2014;7(10):1081-1092. doi:10.1016/j.jcin.2014.05.016

26. Khan SU, Khan MU, Ghani AR, Lone AN, Arshad A, Kaluski E. Meta-analysis of antithrombotic therapy in atrial fibrillation after percutaneous coronary intervention. *Am J Cardiol*. 2018;121(10):1200-1206. doi:10.1016/j.amjcard.2018.01.036

27. Alexander JH, Lopes RD, James S, et al; APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med*. 2011;365(8):699-708. doi:10.1056/NEJMoa1105819

28. Mega JL, Braunwald E, Wiviott SD, et al; ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366(1):9-19. doi:10.1056/NEJMoa1112277

29. Hoffman M, Monroe DM III. A cell-based model of hemostasis. *Thromb Haemost*. 2001;85(6):958-965. doi:10.1055/s-0037-1615947

30. Connolly S, Pogue J, Hart R, et al; ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367(9526):1903-1912. doi:10.1016/S0140-6736(06)68845-4

31. Ruiz-Nodar JM, Marín F, Hurtado JA, et al. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation implications for bleeding risk and prognosis. *J Am Coll Cardiol*. 2008;51(8):818-825. doi:10.1016/j.jacc.2007.11.035

32. Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *Eur Heart J*. 2007;28(6):726-732. doi:10.1093/eurheartj/ehl488

33. van Es RF, Jonker JJC, Verheugt FWA, Deckers JW, Grobbee DE; Antithrombotics in the Secondary Preventionof Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet*. 2002;360(9327):109-113. doi:10.1016/S0140-6736(02)09409-6

34. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med*. 2002;347(13):969-974. doi:10.1056/NEJMoa020496

35. Steppich B, Dobler F, Brendel LC, Hessling G, Braun SL, Steinsiek AL, Deisenhofer I, Hyseni A, Roest M, Ott I. Effect of the FXa inhibitors Rivaroxaban and Apixaban on platelet activation in patients with atrial fibrillation. *J Tromb Thrombolysis*. 2017;43:490-497.

36. Nakase T, Moroi J, Ishikawa T. Anti-inflammatory and antiplatelet effects of non-vitamin K antagonist oral anticoagulants in acute phase of ischemic stroke patients. *Clin Transl Med*. 2018;7(1):2. doi:10.1186/s40169-017-0179-9

37. Jiang X, Wong PC. Comparative effects of the direct factor Xa inhibitor, apixaban, and the direct inhibitors of factor VIIa, XIa and thrombin on tissue factor-induced human platelet aggregation. *Blood*. 2008;112(11):2021. http://www.bloodjournal.org/content/112/11/2021. Accessed April 30, 2019.

38. Perzborn E, Heitmeier S, Laux V. Effects of rivaroxaban on platelet activation and platelet-coagulation pathway interaction: in vitro and in vivo studies. *J Cardiovasc Pharmacol Ther*. 2015;20(6):554-562.

39. Vranckx P, Lewalter T, Valgimigli M, et al. Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement: rationale and design of the ENTRUST-AF PCI trial. *Am Heart J*. 2018;196:105-112. doi:10.1016/j.ahj.2017.10.009

40. Cullell N, Carrera C, Muiño E, Torres N, Krupinski J, Fernandez-Cadenas I. Pharmacogenetic studies with oral anticoagulants: genome-wide association studies in vitamin K antagonist and direct oral anticoagulants. *Oncotarget*. 2018;9(49):29238-29258. doi:10.18632/oncotarget.25579