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Optimal Antithrombotic Regimens for Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention
An Updated Network Meta-analysis

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IMPORTANCE Antithrombotic treatment in patients with atrial fibrillation (AF) and percutaneous coronary intervention (PCI) presents a balancing act with regard to bleeding and ischemic risks.

OBJECTIVES To evaluate the safety and efficacy of 4 antithrombotic regimens by conducting an up-to-date network meta-analysis and to identify the optimal treatment for patients with AF undergoing PCI.

DATA SOURCES Online computerized database (MEDLINE).

STUDY SELECTION Five randomized studies were included (N = 11 542; WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, ENTRUST-AF PCI).

DATA EXTRACTION AND SYNTHESIS The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this network meta-analysis, in which bayesian random-effects models were applied. The data were analyzed from September 9 to 29, 2019.

MAIN OUTCOMES AND MEASURES The primary safety outcome was thrombolysis in myocardial infarction (TIMI) major bleeding and the primary efficacy outcome was trial-defined major adverse cardiovascular events (MACE).

RESULTS The total number of participants included in the study was 11 532. The mean age of the participants ranged from 70 to 72 years, 69% to 83% were male, 20% to 26% were female, and the participants were predominantly white (>90%). Compared with vitamin K antagonists (VKA) plus dual antiplatelet therapy (DAPT) (reference), the odds ratios (ORs) (95% credible intervals) for TIMI major bleeding were 0.57 (0.31-1.00) for VKA plus $P2Y_{12}$ inhibitor, 0.69 (0.40-1.16) for non-VKA oral anticoagulant (NOAC) plus DAPT, and 0.52 (0.35-0.79) for NOAC plus $P2Y_{12}$ inhibitor. For MACE, using VKA plus DAPT as reference, the ORs (95% credible intervals) were 0.97 (0.64-1.42) for VKA plus $P2Y_{12}$ inhibitor, 0.95 (0.64-1.39) for NOAC plus DAPT, and 1.03 (0.77-1.38) for NOAC plus $P2Y_{12}$ inhibitor.

CONCLUSIONS AND RELEVANCE The findings of this study suggest that an antithrombotic regimen of VKA plus DAPT should generally be avoided, because regimens in which aspirin is discontinued may lead to lower bleeding risk and no difference in antithrombotic effectiveness. The use of a NOAC plus a $P2Y_{12}$ inhibitor without aspirin may be the most favorable treatment option and the preferred antithrombotic regimen for most patients with AF undergoing PCI.

Supplemental content

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Identifying an optimal antithrombotic regimen to prevent bleeding and ischemic events presents an unmet challenge to physicians treating patients with atrial fibrillation (AF) who require antiplatelet therapy for percutaneous coronary intervention (PCI) and/or acute coronary syndrome (ACS).[1,2] Previous studies have compared various antithrombotic regimens.[3-7] A 2019 network meta-analysis found that a regimen of non-vitamin K antagonist oral anticoagulants (NOACs) plus a $P2Y_{12}$ inhibitor without aspirin was associated with lower rates of bleeding, including intracranial hemorrhage, compared with a regimen of vitamin K antagonists (VKA) plus dual antiplatelet therapy (DAPT).[7] Since that publication, another randomized clinical trial (RCT) was completed, ENTRUST-AF PCI, which compared the safety of the use of edoxaban (trade names, Savaysa and Lixiana) plus a $P2Y_{12}$ inhibitor with VKA plus DAPT in 1506 patients with AF who underwent PCI.[8] Given the relative importance of this study, we have updated the previous literature search and network meta-analysis to provide readers with a current, state-of-the-art evidence base on antithrombotic regimens in this high-risk patient population.

Key Points

Question What is the optimal antithrombotic regimen in terms of major bleeding and ischemic risk for patients with atrial fibrillation undergoing percutaneous coronary intervention?

Findings This network meta-analysis of 5 randomized controlled trials found that the use of a combination of a non-vitamin K antagonist oral anticoagulant and a $P2Y_{12}$ inhibitor (discontinuing the aspirin regimen a few days after percutaneous coronary intervention) reduced bleeding complications, including intracranial bleeding, whereas the combination of a vitamin K antagonist and dual antiplatelet therapy resulted in the highest rates of bleeding. The risk of ischemic events was comparable among the 4 tested regimens.

Meaning The findings of this study may provide a rigorous and up-to-date evaluation of the safety and efficacy of available antithrombotic strategies to aid health care professionals in making informed treatment decisions.

Methods

A full description of the methodology was previously published.[7] In short, 2 of us (R.D.L. and R.E.H.) performed an updated literature review using the PubMed search engine and searched for the following: (1) RCTs with 2 or more comparator arms, (2) in patients with ACS and/or PCI, (3) a combination of anticoagulation and antiplatelet therapy, and (4) reported major bleeding and major adverse cardiovascular events (MACE) with a follow-up of 6 or more months. The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

Outcome Measures

The primary safety outcome was major bleeding according to the thrombolysis in myocardial infarction (TIMI) criteria.[9] The primary efficacy outcome was trial-defined MACE, which was usually defined as a combination of either all-cause or cardiovascular mortality, myocardial infarction (MI), stroke, and stent thrombosis (eTable 1 in the Supplement). The RCTs, WOEST,[3] AUGUSTUS,[6] and ENTRUST-AF PCI[8] reported the number of participants who had definite or probable stent thrombosis. The RCT, PIONEER AF-PCI,[5] reported the number of participants who had stent thrombosis without specifying its category, and RE-DUAL PCI[4] reported the number of participants who had definite stent thrombosis. Secondary efficacy outcomes were the individual components of this composite MACE outcome.

Data Collection Process

Two of us (H.H. and J.L.) independently extracted data on the study design, baseline characteristics, interventions, and outcomes.

Statistical Analysis

The data were analyzed from September 9 to 29, 2019. We fitted a bayesian random-effects network meta-analysis model to simultaneously compare multiple regimens. We estimated odds ratios (ORs) of the treatment effects of the 2 regimens and the associated 95% credible intervals (CrIs) using Markov chain Monte Carlo algorithms. 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). All analyses were conducted using the gemtc package (version 0.8-2) in R, version 3.6.1 (The R Foundation).

Results

Search Results

In an updated literature search, we found 38 unique studies that were published between April 19, 2019 (date of last search update) and September 14, 2019 (eTable 2 in the Supplement). Of them, 1 study (ENTRUST-AF PCI) was assessed in full-text and was found eligible.[8] These data were combined with those of the 4 RCTs previously identified (WOEST, PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS).[3-6]

Study and Patient Characteristics

Baseline characteristics of patients in each RCT are provided in the **Table**. A total of 11 542 patients were included in the network meta-analysis. The mean age of the participants ranged from 70 to 72 years, 69% to 83% were male, 20% to 26% were women, and the participants were predominantly white (>90%). The prevalence of ACS ranged from 25% to 28% and, except for AUGUSTUS, all patients underwent PCI. Most patients were at high risk for thromboembolic and bleeding complications (>3% per annum). Risk of bias assessment, characteristics of the trial design, treatment regimens, and main results are provided in the Supplement (eTables 3-6 in the Supplement).

Table. Baseline Characteristics in Each Study

Characteristic	Treatment Regimen													
	WOEST		PIONEER AF-PCI			RE-DUAL PCI			AUGUSTUS				ENTRUST-AF PCI	
	VKA + $P2Y_{12}$ Inhibitor	VKA + DAPT	NOAC + $P2Y_{12}$ Inhibitor	NOAC + DAPT	VKA + DAPT	NOAC (L) + $P2Y_{12}$ Inhibitor[a]	NOAC (H) + $P2Y_{12}$ Inhibitor[a]	VKA + DAPT	NOAC + DAPT	NOAC + $P2Y_{12}$ Inhibitor	VKA + DAPT	VKA + $P2Y_{12}$ Inhibitor	NOAC + $P2Y_{12}$ Inhibitor	VKA + DAPT
No. of participants (randomization)	279	284	709	709	706	981	763	981	1153	1153	1154	1154	751	755
Age, mean (SD), y	70.3 (7.0)	69.5 (8.0)	70.4 (9.1)	70.0 (9.1)	69.9 (8.7)	71.5 (8.9)	68.6 (7.7)	71.7 (8.9)	70.7 (9.11)	69.8 (9.31)	70.5 (9.07)	70.5 (9.13)	69 (63-77)[b]	70 (64-77)[b]
Male, %	76.7	82.4	74.5	75.5	73.4	74.2	69.3	76.5	69.0	72.9	70.6	71.6	74.2	74.6
BMI, mean (SD)	27.5 (4.3)	27.9 (4.2)	28.6 (25.7-32.4)[b]	28.4 (25.6-32.1)[b]	29.0 (25.8-32.8)[b]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Diabetes, %	24.3	25.4	28.8	28.1	31.3	36.9	34.1	37.9	37.1	35.9	35.9	36.6	34.5	34.2
History, %														
Myocardial infarction	34.4	35.2	19.7	25.4	22.2	24.2	25.4	27.3	NA	NA	NA	NA	25.0	23.4
PCI	30.8	35.6	NA	NA	NA	33.2	31.3	35.4	NA	NA	NA	NA	26.5	25.8
Coronary artery bypass graft	20.1	26.1	NA	NA	NA	9.9	10.4	11.3	NA	NA	NA	NA	6.1	6.5
Gastrointestinal bleeding	5.0	4.9	1.0	1.3	0.7	NA	NA	NA	NA	NA	NA	NA	NA	NA
CHA_2DS_2-VASc score, %[c]														
≤2	NA	NA	26.7	23.7	20.8	23.4	32.4	19.7	20.8	21.5	20.8	19.1	NA	NA
≥3	NA	NA	73.3	76.3	79.2	76.6	67.6	80.3	79.2	78.5	79.2	80.9	NA	NA
HAS-BLED score, %[d]														
≤2	NA	NA	27.6	32.0	29.5	33.2	40.5	29.4	50.5	51.7	50.9	49.6	31.8	27.0
≥3	NA	NA	72.3	68.0	70.5	66.8	59.5	70.6	49.5	48.3	49.1	50.4	62.2	66.6
Arterial access, %														
Radial	26.5	25.0	NA	NA	NA	63.0	65.8	62.3	NA	NA	NA	NA	77.5	80.5
Femoral	73.1	73.2	NA	NA	NA	36.6	33.0	36.8	NA	NA	NA	NA	22.4	19.3
Stent type, %														
None	1.8	1.4	0.0	0.0	0.0	0.0	0.0	0.0	NA	NA	NA	NA	NA	NA
Bare metal	31.9	30.3	32.6	31.2	31.8	15.2	16.1	13.6	NA	NA	NA	NA	NA	NA
Drug eluting	64.9	64.4	65.4	66.8	66.5	82.1	81.5	84.6	NA	NA	NA	NA	NA	NA
Bare metal and drug eluting	1.1	3.9	2.0	2.0	1.7	1.9	1.3	1.2	NA	NA	NA	NA	NA	NA
Other	NA	NA	NA	NA	NA	0.8	1.0	0.5	NA	NA	NA	NA	NA	NA
Creatinine clearance, mL/min/1.73 m^2, mean (SD)	NA	NA	78.3 (31.3)	77.5 (31.8)	80.7 (30.0)	76.3 (28.9)	83.7 (31.0)	75.4 (29.1)	78.5 (31.5)	79.4 (31.7)	78.7 (30.2)	80.0 (36.8)	71.8 (53.7-91.1)[b]	71.7 (54.0-90.9)[b]

(continued)

Table. Baseline Characteristics in Each Study (continued)

Characteristic	Treatment Regimen												
	WOEST		PIONEER AF-PCI			RE-DUAL PCI			AUGUSTUS			ENTRUST-AF PCI	
	VKA + $P2Y_{12}$ Inhibitor	VKA + DAPT	NOAC + $P2Y_{12}$ Inhibitor	NOAC + DAPT	VKA + DAPT	NOAC (L) + $P2Y_{12}$ Inhibitor[a]	NOAC (H) + $P2Y_{12}$ Inhibitor[a]	VKA + DAPT	NOAC + DAPT	NOAC + $P2Y_{12}$ Inhibitor	VKA + DAPT	VKA + $P2Y_{12}$ Inhibitor	NOAC + $P2Y_{12}$ Inhibitor	VKA + DAPT
Type of index event, %														
NSTEMI	NA	NA	18.5	18.3	17.8	20.7	23.5	21.0	NA	NA	NA	NA	21.7	20.8
STEMI	NA	NA	12.3	13.8	10.7	14.7	14.9	14.6	NA	NA	NA	NA	17.7	17.5
Unstable angina	NA	NA	20.7	21.1	23.7	19.9	16.5	16.9	NA	NA	NA	NA	14.9	16.3
Type of AF, %														
Persistent	NA	NA	20.7	20.6	21.1	17.7	17.3	18.2	NA	NA	NA	NA	18.6	19.3
Permanent	NA	NA	37.4	33.6	34.5	32.6	32.8	32.4	NA	NA	NA	NA	27.8	33.1
Paroxysmal	NA	NA	42.8	46.1	44.4	49.6	49.8	49.4	NA	NA	NA	NA	53.5	47.4

Abbreviations: AF, atrial fibrillation; BMI, body mass index (calculated as the weight in kilograms divided by height in meters); CHA2DS2-VASc score, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke [double weight], vascular disease, age 65 to 74 years, and female sex; DAPT, dual antiplatelet therapy; HAS-BLED, hypertension, abnormal renal and liver function, stroke–bleeding, labile international normalized ratio, elderly, drugs or alcohol; NA, not available; NOAC, non-VKA oral anticoagulant; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; VKA, vitamin K antagonist.

SI conversion factor: To convert creatinine clearance to milliliter/second/meter squared, multiply by 0.0167.

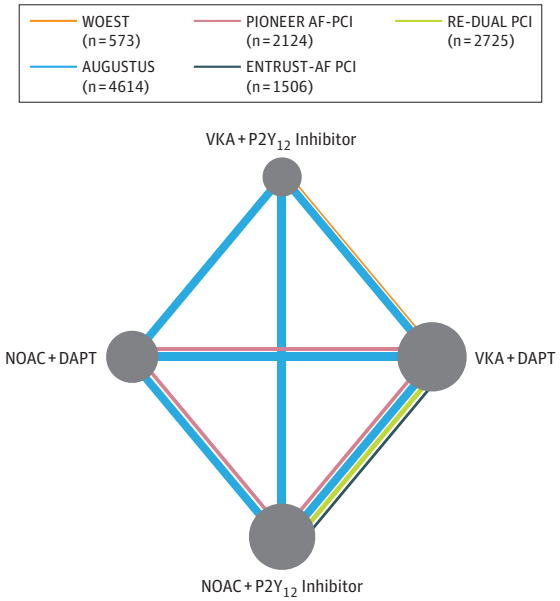
[a] (L) and (H) indicate low- and high-dose schemes of NOAC used in the RE-DUAL PCI trial.

[b] Median (IQR).

[c] CHA2DS2-VASc scores reflect the risk of stroke, with values ranging from 0 to 9 and with higher scores indicating greater risk.

[d] HAS-BLED scores reflect the risk of major bleeding, with values ranging from 0 to 9 and with higher scores indicating greater risk.

Figure 1. Network of 4 Antithrombotic Treatment Regimens



The nodes represent the antithrombotic treatment regimens that were compared, and the edges represent the observed direct comparisons in the included randomized clinical 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. AF indicates atrial fibrillation; DAPT, dual antiplatelet therapy; NOAC, non-VKA oral anticoagulant; PCI, percutaneous coronary intervention; VKA, vitamin K antagonists.

Structure of Network Meta-analysis

We simultaneously compared the following 4 treatment regimens: VKA plus DAPT (reference), VKA plus $P2Y_{12}$ inhibitor, NOAC plus DAPT, and NOAC plus $P2Y_{12}$ inhibitor (**Figure 1**). We assumed a class effect, that is, all 4 NOAC agents and respective doses had comparable safety and efficacy.

Safety Outcomes

Compared with the ORs for VKA plus DAPT, those for all safety outcomes, including intracranial hemorrhage, were significantly lower for NOAC plus $P2Y_{12}$ inhibitor (**Figure 2**A-D). Compared with VKA plus DAPT (reference), the ORs for TIMI major bleeding were 0.57 (95% CrI, 0.31-1.00) for VKA plus $P2Y_{12}$ inhibitor, 0.69 (95% CrI, 0.40-1.16) for NOAC plus DAPT, and 0.52 (95% CrI, 0.35-0.79) for NOAC plus $P2Y_{12}$ inhibitor. For MACE, compared with VKA plus DAPT the ORs were 0.97 (95% CrI, 0.64-1.42) for VKA plus $P2Y_{12}$ inhibitor, 0.95 (95% CrI, 0.64-1.39) for NOAC plus DAPT, and 1.03 (95% CrI, 0.77-1.38) for NOAC plus $P2Y_{12}$ inhibitor. Discontinuing the aspirin regimen (either with NOAC or VKA) was associated with a lower risk of trial-defined bleeding compared with regimens including aspirin. Compared with VKA plus DAPT, the ORs for trial-defined bleeding were 0.46 (95% CrI, 0.22-0.95) for VKA plus $P2Y_{12}$ inhibitor and 0.53 (95% CrI, 0.31-0.90) for NOAC plus $P2Y_{12}$ inhibitor.

Efficacy Outcomes

No differences were found among the antithrombotic regimens in terms of the composite of MACE as well as its individual components of (cause-specific) death, MI, stroke, or stent thrombosis (Figure 2E-H and eFigure 1 in the Supplement).

Ranking of Antithrombotic Regimens

The SUCRA values for safety and efficacy outcomes are presented in eTable 7 in the Supplement. The performance of the tested regimens is shown in a forest plot of ORs (eFigure 2 in the Supplement). Regimens in which aspirin was omitted had the best performance (ie, highest SUCRA value) for treating bleeding complications. The combination of NOAC plus $P2Y_{12}$ inhibitor was the best regimen for treating major bleeding (SUCRA value, 81.9), and any regimen with NOAC (plus DAPT [SUCRA value, 67.3] or plus $P2Y_{12}$ inhibitor [SUCRA value, 91.8]) was preferred to using VKA (plus DAPT [SUCRA value, 28.8] or plus $P2Y_{12}$ inhibitor [SUCRA value, 12.9]) for treating intracranial hemorrhage. No treatment regimen was clearly favored overall for efficacy outcomes.

Discussion

In this updated, comprehensive network meta-analysis an antithrombotic regimen in which aspirin is discontinued a few days after PCI appears to be associated with fewer bleeding complications while preserving antithrombotic efficacy. The findings of the present study suggest that a regimen of NOAC plus $P2Y_{12}$ inhibitor without aspirin had the best safety profile, with the lowest rates of intracranial bleeding and similar rates of ischemic events compared with other antithrombotic regimens that included persistent use of aspirin.

Most guideline recommendations in cardiology are based on low-quality evidence, and the field of antithrombotic therapy for AF and ACS and PCI is no exception.[10,11] The recommendation for traditional antithrombotic triple therapy mostly relied on extrapolation and findings from observational studies.[1,2,12-15] Remarkable advances have been made over the past few years, starting with the initial findings from WOEST followed by PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI.[3-6,8] Combined, these studies encompass high-quality data from more than 11 000 patients that allow for meaningful observations with regard to bleeding and ischemic outcomes.

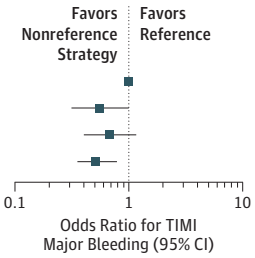
Limitations

A question that remains is whether this network meta-analysis provides definitive answers for infrequent outcomes, such as stent thrombosis. Although we did not observe a statistically significant difference in the rates of stent thrombosis between regimens with and without aspirin, the numerical excess of stent thrombosis in patients when aspirin therapy was discontinued may be important, particularly for patients at high risk of stent thrombosis and those in whom the consequences of this condition would be severe. Clear guidance on how to identify such patients based on the available evidence is lacking, and we do not foresee the data to do so becoming available in the future.[11] Although the use of a network meta-analysis allows for simultaneous comparisons and

Figure 2. Forest Plots for Safety and Efficacy Outcomes

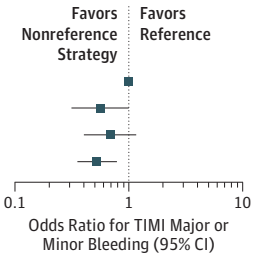
A Thrombolysis in myocardial infarction (TIMI) major bleeding

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	0.57 (0.31-1.00)
NOAC + DAPT	0.69 (0.40-1.16)
NOAC + $P2Y_{12}$ inhibitor	0.52 (0.35-0.79)



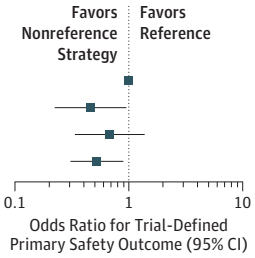
B TIMI major or minor bleeding

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	0.50 (0.24-1.04)
NOAC + DAPT	0.66 (0.32-1.34)
NOAC + $P2Y_{12}$ inhibitor	0.53 (0.30-0.89)



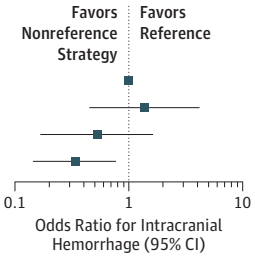
C Trial-defined primary safety outcome

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	0.46 (0.22-0.95)
NOAC + DAPT	0.68 (0.34-1.38)
NOAC + $P2Y_{12}$ inhibitor	0.53 (0.31-0.90)



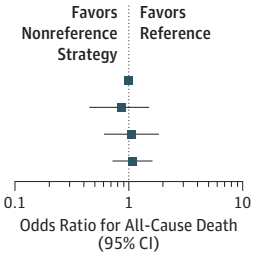
D Intracranial hemorrhage

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	1.38 (0.45-4.18)
NOAC + DAPT	0.54 (0.17-1.63)
NOAC + $P2Y_{12}$ inhibitor	0.34 (0.14-0.77)



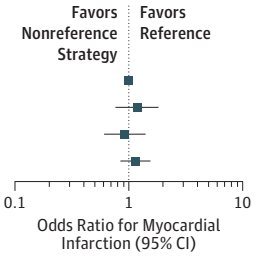
E All-cause death

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	0.88 (0.45-1.51)
NOAC + DAPT	1.06 (0.61-1.84)
NOAC + $P2Y_{12}$ inhibitor	1.08 (0.72-1.62)



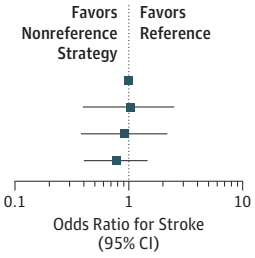
F Myocardial infarction

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	1.20 (0.76-1.82)
NOAC + DAPT	0.93 (0.61-1.40)
NOAC + $P2Y_{12}$ inhibitor	1.15 (0.84-1.55)



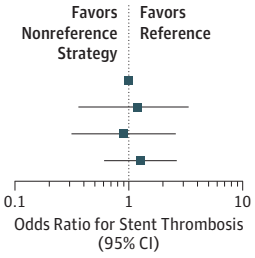
G Stroke

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	1.03 (0.39-2.51)
NOAC + DAPT	0.92 (0.38-2.18)
NOAC + $P2Y_{12}$ inhibitor	0.79 (0.40-1.46)



H Stent thrombosis

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	1.21 (0.36-3.35)
NOAC + DAPT	0.92 (0.31-2.59)
NOAC + $P2Y_{12}$ inhibitor	1.30 (0.61-2.64)



The safety outcomes assessed were thrombolysis in myocardial infarction (TIMI) major bleeding, TIMI major or minor bleeding, trial-defined primary safety outcome, and intracranial hemorrhage. A total of 11 430 patients were included in the network meta-analyses for all safety outcomes. The efficacy outcomes assessed were all-cause death, myocardial infarction, stroke, and stent thrombosis. A total of 11 501 patients were included in the network meta-analyses for all efficacy outcomes. Odds ratios and 95% credible intervals compared with vitamin K antagonist plus dual antiplatelet therapy (VKA+DAPT) (reference) were plotted for all outcomes. NOAC indicates non-VKA oral anticoagulant.

evidence-based grading to facilitate overall conclusions, we believe that it does not have the granularity to address specific subgroups of patients. Future studies with individual patient-level data analyses, whether trial-specific or pooled, may help to further refine which patients would benefit most from longer-term aspirin use in combination with a NOAC and a $P2Y_{12}$ inhibitor.

Conclusions

Selecting the optimal antithrombotic regimen for patients with AF undergoing PCI presents an important unmet clinical need. We believe that the findings of this study support the use of regimens in which aspirin therapy is discontinued

a few days after PCI. A regimen that includes a NOAC plus a $P2Y_{12}$ inhibitor seems to be the most favorable treatment option and may be the preferred antithrombotic regimen for most of these patients.

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