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Safety and efficacy of dual vs. triple antithrombotic therapy (DAT vs. TAT) in patients with atrial fibrillation following a PCI: a systematic review and network meta-analysis

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Title:

Safety and efficacy of dual vs. triple antithrombotic therapy (DAT vs. TAT) in patients with atrial fibrillation following a PCI: a systematic review and network meta-analysis

Authors:

Renad M Altoukhi[1]

Reema A Alshouimi[1]

Shahad M Al Rammah[1]

Mohammed Y Alzahrani[1]

Abdulaali R Almutairi[2]

Abdulmajeed M Alshehri[1]

Osamah M. Alfayez[3]

Majed S Al Yami[1]

Omar A Almohammed[4]

[1] Department of Pharmacy Practice, College of pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[2] Department of Pharmacy Practice and Science; Center for Health Outcomes and Pharmacoeconomic Research, College of Pharmacy, University of Arizona, Tucson, AZ, USA

[3] Department of Pharmacy Practice, College of pharmacy, Qassim University, Qassim, Saudi Arabia

[4] Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

Corresponding author contact information:

Omar A Almohammed, B.Pharm, PharmD, PhD
Assistant Professor
Department of Clinical Pharmacy
College of Pharmacy - King Saud University
Mobile: +966555104065
E-mail: oalmohammed@ksu.edu.sa

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Abstract

Objective

Creating an appropriate antithrombotic therapy for patients with atrial fibrillation (AF) who have undergone percutaneous coronary intervention (PCI) remains a dilemma. Several clinical trials compared the use of a dual antithrombotic therapy (DAT) regimen with a direct oral anticoagulants (DOAC) including (apixaban, dabigatran, edoxaban, or rivaroxaban) and a $P2Y_{12}$ inhibitor versus a triple antithrombotic therapy (TAT) that includes a vitamin K antagonist (VKA) plus aspirin and a $P2Y_{12}$ inhibitor in AF patients who have undergone PCI. However, there are no head-to-head trials comparing the DAT regimens to each other. We aimed to compare the efficacy and safety of DAT regimens using a network meta-analysis (NMA) approach.

Design

A systematic review and network meta-analysis of randomized clinical trials

Methods:

We conducted a systematic literature review to identify relevant randomized clinical trials, and performed a Bayesian NMA for International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major (CRNM) bleeding, all-cause mortality, stroke, myocardial infarction (MI), and stent thrombosis outcomes. We used NetMetaXL 1.6.1 and WinBUGS 1.4.3 for the NMA and estimated the probability of ranking the treatments based on the surface under the cumulative ranking curve.

Results:

The comparison between DAT regimens showed no significant difference in the safety or efficacy outcomes. Apixaban regimen was ranked first preferred therapy in-terms of ISTH major or CRNM bleeding and stroke, with a probability of 52% and 54%, respectively. Rivaroxaban regimen was the preferred therapy in-terms of MI and stent thrombosis, with a probability of 34% and 27%, respectively. Dabigatran regimen was ranked first in-terms of all-cause mortality, with a probability of 28%.

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Conclusion:

The DAT regimens are as safe and effective as TAT regimens. However, the marginal superiority among the DOACs can be used to guide the selection among these agents based on different patients' conditions.

Keywords:

DAT, TAT, PCI, Anticoagulants, Atrial Fibrillation, Bleeding

Strengths and limitations of this study:

- The utilized network meta-analysis technique facilitated the comparison of dual antithrombotic therapy regimens versus triple antithrombotic therapy regimen in patients with AF who have undergone PCI.
- Only randomized clinical trials were included in this network meta-analysis
- All the included studies were of high quality with a low risk of bias
- The results were associated with wide confidence intervals, which might affect the precision of the findings.

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INTRODUCTION

Atrial fibrillation (AF) is a common comorbidity in patients with acute coronary syndrome (ACS) due to similar risk factors. The incidence rate of AF in ACS patients ranges from 5% to 23%.[1-5] Appropriate antithrombotic therapy for patients with AF who had ACS or have undergone percutaneous coronary intervention (PCI) is controversial. In patients with AF, oral anticoagulation is recommended for the prevention of cardioembolic stroke,[6] but its efficacy in preventing stent thrombosis for patients with PCI is not well established.

Dual-antiplatelet therapy (DAPT), with aspirin plus a $P2Y_{12}$ inhibitor, is recommended in patients with ACS for secondary prevention of ischemic events and stent thrombosis.[7] Triple therapy, including an oral anticoagulant on top of the DAPT, was recommended by previous guidelines and considered a standard of care for patients with AF who experienced ACS or undergone PCI.[7 8] However, the most recent AHA/ACC/HRS 2019 guidelines suggested the use of dual antithrombotic therapy (DAT: vitamin K antagonist (VKA) or a direct oral anticoagulant (DOAC) plus a $P2Y_{12}$ inhibitor) over the triple antithrombotic therapy (TAT: oral anticoagulant, aspirin and a $P2Y_{12}$ inhibitor),[6] due to the increased risk of bleeding with the triple therapy that was reported in multiple studies.[9-14]

In an attempt to clarify this controversy, six randomized control trials (WOEST, ISAR-TRIPLE, PIONEER-AF-PCI, RE-DUAL-PCI, AUGUSTUS, and ENTRUST-AF-PCI) were conducted to assess the efficacy and safety of the TAT compared to the DAT for patients with AF receiving oral anticoagulation after experiencing ACS or undergoing PCI.[9-14] Although these trials reported a higher incidence of major bleeding in patients receiving the TAT compared to the DAT without significant differences in the risk of ischemic events, it is noteworthy to recognize that these trials were underpowered to detect ischemic events.

Several observational studies found a higher risk of bleeding with the triple therapy that involved vitamin K antagonist, aspirin and a $P2Y_{12}$ inhibitor.[15-17] The objective of this network meta-analysis is to assess the safety and efficacy of a DAT regimen with a DOAC versus a TAT regimen with a VKA in patients with AF who experienced ACS or undergone PCI.

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METHODS

A systemic literature search was conducted on MEDLINE and Embase through October, 2019 to identify randomized clinical trials that evaluated the use of DOACs in patients with AF who experienced ACS or undergone PCI. The search terms included percutaneous coronary intervention, PCI, atrial fibrillation, acute coronary syndrome, ACS, stent, anticoagulants, rivaroxaban, edoxaban, apixaban, dabigatran, DOACs, vitamin K antagonist, VKA, warfarin, aspirin, clopidogrel, triple therapy, double therapy, dual antithrombotic therapy, DAT, triple antithrombotic therapy, and TAT. We also searched for other systematic reviews and meta-analyses and reviewed their references to identify any relevant studies. The search was limited to studies that were published in English within the last ten years.

For each study, episodes of major or clinically relevant non-major (CRNM) bleeding events based on the International Society on Thrombosis and Haemostasis (ISTH) definition,[18] all-cause mortality, stroke, myocardial infarction (MI), stent thrombosis were extracted. Data were extracted from the published studies and assessed for eligibility by two independent investigators (RMA and RAM) and verified by a third investigator (OAA). The risk of bias assessment was conducted for each study using the Cochrane Collaboration risk of bias assessment tool.[19] A Bayesian network meta-analysis (NMA) was conducted for the pre-specified outcomes using NetMetaXL 1.6.1 (Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada)[20] and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom). We utilized the random effect binomial model with vague priors and employing Markov chain Monte Carlo simulation for 60000 iterations after discarding 30000 iteration as burn-in simulations initially. Estimates of the outcomes were presented in odds ratio (OR) and 95% credible intervals (95% CrI). Also, we estimated the probability of ranking the treatments based on the surface under the cumulative ranking curve.[21] We reported this NMA according to the preferred reporting items for systematic reviews and meta-analyses for network meta-analyses (PRISMA-NMA).[22]

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RESULTS

A total of 662 articles were identified in the systematic search. Four studies, PIONEER-AF PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI, met the inclusion criteria, and were included in the current NMA.[11-14] The flowchart in Figure 1 illustrates the process of including and excluding articles for this NMA. The risk of bias assessment of the included trials showed low risk of bias (Supplementary Table 1).

Summary of the included trials

The trials that were included demonstrated favorable results for the pre-specified outcomes towards DOACs when mainly used in a DAT regimen in combination with a $P2Y_{12}$ inhibitor only.[11-14] The PIONEER AF-PCI trial was the first to be conducted to compare the safety and efficacy of using DOACs agent in a DAT regimen to TAT regimen. A DAT regimen including low-dose rivaroxaban (15 mg once daily) in combination with a $P2Y_{12}$ inhibitor (group 1) was compared to a TAT regimen that included $P2Y_{12}$ inhibitor and aspirin in combination with either a very low dose rivaroxaban (2.5 mg twice daily; group 2) or VKA (group 3). The study found the bleeding rates were significantly reduced for groups 1 and 2 compared to group 3 (16.8%, 18.0%, and 26.7%, respectively; hazard ratio [HR] for group 1 vs. 3 =0.59; 95%CI 0.47–0.76; HR for group 2 vs. 3 =0.63; 95%CI 0.50–0.80). However, the rivaroxaban dose that was used in the trial is lower than the recommended daily dose for stroke prevention in atrial fibrillation (20 mg), and the very low dose was not included in the NMA.[11]

The RE-DUAL PCI study was conducted to compare the safety and efficacy of using dabigatran (110 or 150 mg twice daily) in a DAT regimen with a $P2Y_{12}$ inhibitor to a TAT regimen that included $P2Y_{12}$ inhibitor and aspirin in combination with a VKA. The findings of the study demonstrated a significantly lower risk of bleeding for the DAT regimen that included dabigatran to the TAT regimen (HR =0.52; 95%CI 0.42–0.63; P<0.001 for superiority).[12] However, it is to be noted that both studies, the PIONEER AF-PCI and RE-DUAL PCI, were not powered to detect any significant disparities in efficacy between the DOACs and VKA.

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The AUGUSTUS trial compared the use of apixaban to a VKA along with clopidogrel and aspirin to a placebo using a 2x2 factorial design. The study concluded that a DAT regimen with apixaban and clopidogrel only was both non-inferior and superior to a TAT regimen in-terms of reducing the risk of major or CRNM bleeding (HR =0.69; 95%CI 0.58–0.81; p<0.001 for both non-inferiority and superiority), while there was no difference in the ischemic event outcomes.[13]

The most recent, ENTRUST-AF PCI trial was designed to assess a DAT regimen, that included edoxaban plus a $P2Y_{12}$ inhibitor, to a TAT regimen, that included a VKA plus $P2Y_{12}$ inhibitor and aspirin. Similar to the previous trials, they found a lower rate of bleeding in the DAT regimen in comparison to the TAT regimen (HR =0.83, 95%CI 0.65–1.05; p=0·0010 for non-inferiority). However, unlike other DOACs, the trial found the edoxaban regimen to be non-inferior, but not superior to the TAT regimen.[14]

Network meta-analysis

Demographic characteristics

A total of 7,890 patients were included in the NMA. The mean age for the included patients ranged between 68 and 71 years, and about 22 to 30% of participants were females. The detailed patients' demographics and outcomes from the included studies were presented in Table 1.

ISTH major or CRNM bleeding

There were no significant differences between all DOACs when used in DAT regimens as well as when compared to TAT regimen, using VKA. Among all, DAT regimen containing apixaban was the preferred one, with a probability of 52%, followed by regimens containing dabigatran or rivaroxaban, with a probability of 18% and 17.9%, respectively (Figure 2).

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All-cause mortality

The NMA showed no differences between all DAT regimens containing DOACs as well as between DAT and TAT regimens in regard to all-cause mortality. However, the ranking of DAT regimens showed that dabigatran regimen was the preferred agent, followed by apixaban regimen, and rivaroxaban regimen with a probability of 28%, 21.5%, and 20.8%, respectively (Figure 3 [A], Supplementary Figure 1).

Stroke

Similar to all-cause mortality, the results of the NMA showed no significant difference between the DOACs when used in DAT regimen, and when compared to the TAT regimen, with VKA. Apixaban DAT regimen was ranked first, followed by regimens of edoxaban and rivaroxaban with a probability of 54%, 19.5%, and 12.4%, respectively (Figure 3 [B], Supplementary Figure 2).

Myocardial infarction (MI)

There were no significant differences between all DOACs in the DAT regimens compared to each other or to the TAT regimen, with VKA. Rivaroxaban DAT regimen was the preferred regimen, followed by apixaban regimen and edoxaban regimen, with a probability of 34%, 22%, and 18%, respectively (Figure 4 [A], Supplementary Figure 3).

Stent thrombosis

The odds of stent thrombosis were similar across all DAT regimens with DOACs and TAT regimen, with rivaroxaban DAT regimen being the preferred regimen with a probability of 27% and followed by edoxaban regimen with a probability of 23% (Figure 4 [B], Supplementary figure 4).

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DISCUSSION

For patients with atrial fibrillation who experienced ACS or undergone PCI, the selection of a regimen that is both effective in preventing stroke and stent thrombosis while minimizing the risk of bleeding remains a challenge for prescribers. The main focus of this NMA was to estimate the efficacy and safety of different DOACs in DAT regimens compared to each other and to VKA in a TAT regimen for patients with AF who undergone PCI, and to rank the DOACs in terms of difference in the efficacy and safety outcomes. We looked at five main end points, which were ISTH major or CRNM bleeding, all-cause mortality, stroke, MI, and stent thrombosis.

Our results showed no significant difference between a DAT regimen with a DOAC compared to a TAT regimen with a VKA for all the specified outcomes. This demonstrates that the DAT regimen with DOACs is just as safe and effective as the TAT regimen with a VKA. However, apixaban regimen was the preferred option in reducing the risk of major or CRNM bleeding and stroke, dabigatran regimen was ranked as first option in the reduction of all-cause mortality, and rivaroxaban regimen was the preferred in-term of reducing the risk of MI and stent thrombosis. Based on this ranking, VKA was ranked the lowest in comparison to all DOACs' DAT regimens in terms of bleeding, all-cause mortality, and MI. A previous NMA by Lopes et al. presented similar results, but in their NMA, there was a significant difference between the DAT and the TAT regimens with a more favorable outcome in terms of safety for the regimen that includes a DOAC and a $P2Y_{12}$ inhibitor.[23]

The 2016 European Society of Cardiology (ESC) guidelines for the management of AF recommended to initiate the patients' management on the triple therapy that includes an oral anticoagulant (OAC) with aspirin and clopidogrel in the first month of treatment after PCI, or to an extended period of 6 months in case of lower risk of bleeding; then, to continue with a dual therapy (OAC plus aspirin or clopidogrel) for 6 to 12 months, and lifetime therapy on an OAC.[8] Only aspirin and clopidogrel were recommended as antiplatelet therapy as opposed to third generation $P2Y_{12}$ inhibitors due to the increased risk of bleeding and lack of evidence. If

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a DOAC is chosen for anticoagulation, then the lowest effective dose for stroke prevention should be used. However, a regimen of low-dose rivaroxaban plus clopidogrel and aspirin is not recommended for stroke prevention in atrial fibrillation.[8] In the recent AHA/ACC/HRS 2019 guidelines for the management of AF in patients who had undergone PCI, the guidelines favored the DAT over the TAT; for patients with an increased risk of stroke based on their CHA_2DS_2-VASc who should be initiated on triple therapy (OAC plus $P2Y_{12}$ inhibitor plus aspirin), it is recommended to transition them to double therapy at the 4^{th} to 6^{th} week of treatment.[6] However, no recommendations were made in such population regarding the use of apixaban and edoxaban due to the lack of data on these agents at that time.

The results of this NMA align with the findings of previous studies that demonstrates the sufficiency of the DAT regimen for the prevention of stroke in patients with AF who experienced ACS or undergone PCI, with the added benefit of having a reduced risk of bleeding in those patients.[12 9 11 13 10 14] There are some limitations to this NMA. The prominent variation in the design, the length of follow-up period, and sample sizes between the included trials could have possibly contributed to the wide confidence interval and the lack of significance in our analysis. Therefore, the findings should be used with caution until a large direct comparison studies among DOACs are conducted or findings from retrospective studies become available to support this evidence. Perhaps future studies could look more into patient specific outcomes that could be based on differences in terms of sex, age group, presence of other comorbidities, genetic variations, and other $P2Y_{12}$ inhibitors.

Conclusion

The DAT regimens with DOACs are as safe and effective as the TAT regimen with VKA. Moreover, DOACs in DAT regimens were associated with a marginal superiority over VKA in a TAT regimen. This marginal benefit can be used to guide the selection among different DOACs agents based on patients' conditions, until evidence from large and direct comparison studies become available.

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Footnotes:

- **Contributors** RMA, RAA, SMA conducted the systematic literature search, extracted the data and participated in drafting the manuscript. MYA, AMA, ARA, OMA, MSA, and OAA contributed to the study design, as well as the analysis and interpretation of the results, drafting the manuscript and approving the final manuscript.
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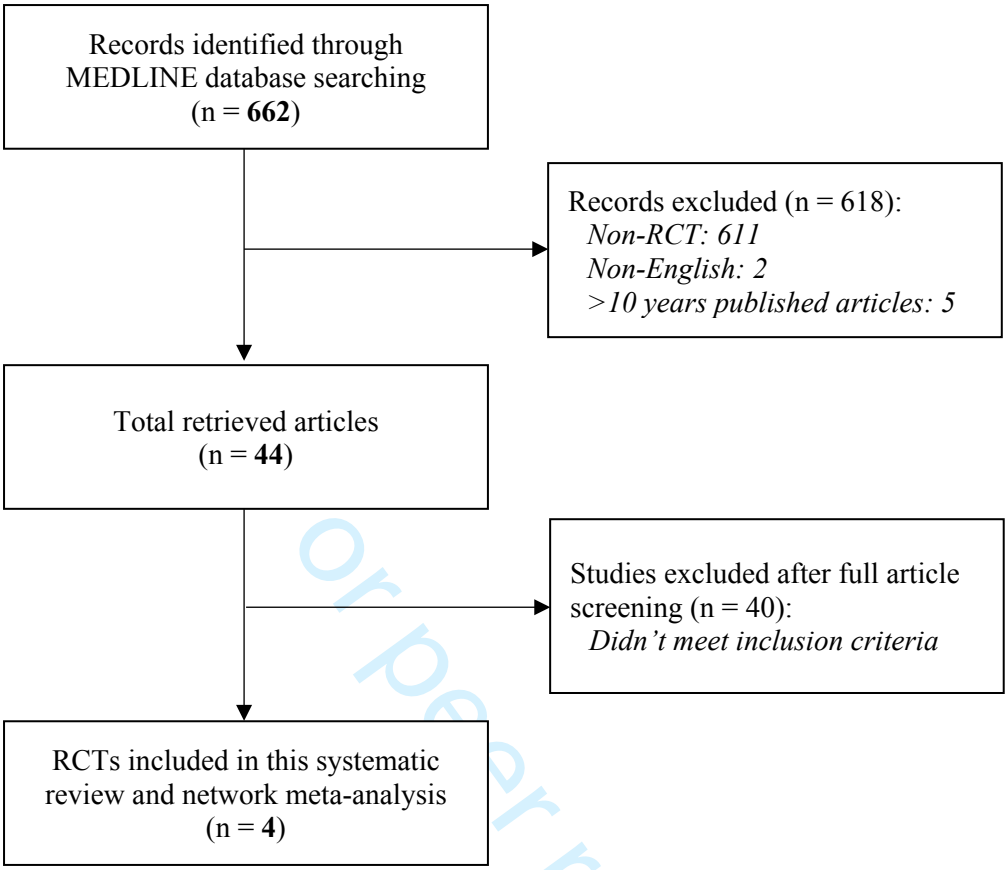

Figure 1: Flow diagram for studies included in the network meta-analysis

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Table 1: Patients' demographics and outcomes from the included randomized controlled trials

Name of the Study	PIONEER AF-PCI* [11]		RE-DUAL PCI[12]		AUGUSTUS*[13]		ENTRUST-AF-PCI[14]	
Relevant Groups in the Study	**DAT** Riva+P2Y$_{12}$i	**TAT** VKA+ P2Y$_{12}$i + ASA	**DAT** Dabi+P2Y$_{12}$i	**TAT** VKA+ P2Y$_{12}$i + ASA	**DAT** Apix+P2Y$_{12}$i	**TAT** VKA+ P2Y$_{12}$i + ASA	**DAT** Edox+P2Y$_{12}$i	**TAT** VKA+ P2Y$_{12}$i + ASA
n	696	697	1744	981	1143	1123	751	755
Baseline Characteristics								
Age (years, SD or IQR)	70.4 (9.1)	69.9 (8.7)	70.2 (8.4)	71.7 (8.9)	70.6 (64 - 77)	70.8 (64 - 77)	69 (63 – 77)	70 (64 – 77)
Female (%)	25.5%	26.6%	24.3%	23.5%	27.8%	30.2%	26.0%	25.4%
Risk Factors:								
Diabetes (%)	28.8%	31.3%	35.7%	37.9%	36.2%	36.5%	34.5%	34.2%
Hypertension (%)	73.3%	75.4%	NR	NR	88.5%	88.0%	90.0%	91.0%
Dyslipidemia (%)	42.6%	44.8%	NR	NR	NR	NR	66.2%	64.1%
History of MI (%)	19.8%	22.2%	24.7%	27.3%	NR	NR	25.0%	23.4%
Type of index event (%)								
ACS	51.5%	52.2%	51.6%	48.4%	61.7%	60.7%	51.7%	51.5%
Non-ACS	48.5%	47.8%	48.4%	51.6%	38.3%	39.3%	48.3%	48.5%
Outcomes								
Major or CRNM bleeding (ISTH)	16.8%	25.5%	17%	27%	7.3%	18.7%	17%	20%
Death from any cause	2.3%	1.9%	4.9%	4.9%	3.4%	2.9%	6.1%	4.9%
MI	3.0%	3.5%	4.0%	3.0%	3.3%	2.9%	3.9%	3.0%
Stroke	1.3%	1.2%	1.5%	1.3%	0.4%	1.0%	1.3%	1.6%
Stent thrombosis	0.8%	0.7%	1.3%	0.8%	1.8%	1.0%	1.7%	1.3%

*The patients' baseline characteristics for these studies are based on the overall population in the studies

DAT: Dual antithrombotic therapy, TAT: Triple antithrombotic therapy, Riva: Rivaroxaban, Dabi: Dabigatran, Apex: Apixaban, Edox: Edoxaban, VKA: Vitamin K antagonist, P2Y12i: P2Y12 inhibitors, ASA: Aspirin, MI: Myocardial infarction, CRNM: Clinically relevant non-major, ISTH: International Society on Thrombosis and Haemostasis, NR: Not reported

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Apixaban + $P2Y_{12}i$				
0.59 (0.02 – 20.88)	**Dabigatran (110/150 mg) + $P2Y_{12}i$**			
0.58 (0.02 – 20.55)	0.98 (0.03 – 34.48)	**Rivaroxaban (LD) + $P2Y_{12}i$**		
0.42 (0.01 – 14.90)	0.71 (0.02 – 25.50)	0.73 (0.02 – 25.58)	**Edoxaban + $P2Y_{12}i$**	
0.34 (0.03 – 4.34)	0.58 (0.05 – 7.13)	0.59 (0.05 – 7.46)	0.81 (0.07 – 10.28)	**VKA + $P2Y_{12}i$ + Aspirin**

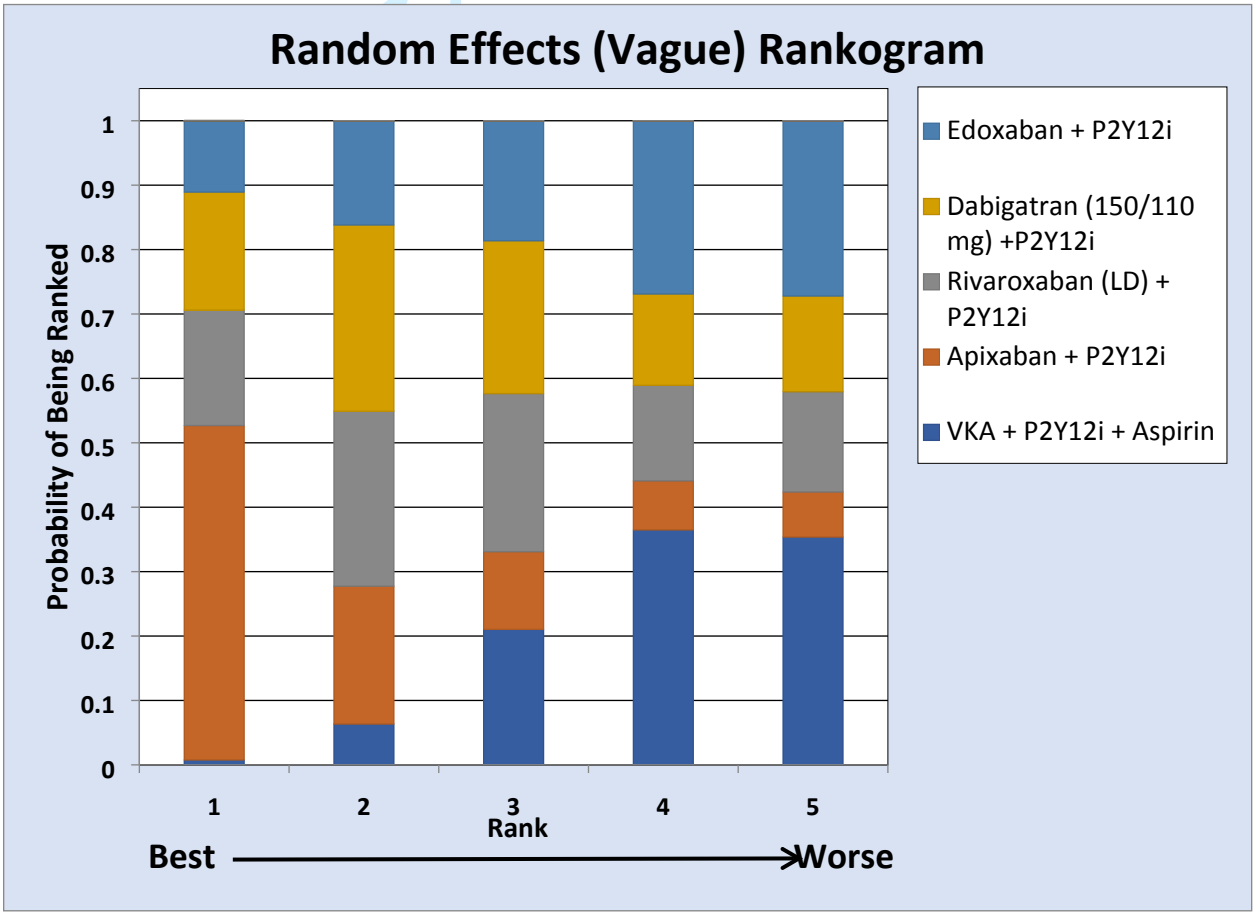

Figure 2: The network meta-analysis and the rankogram results for the International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major (CRNM) bleeding.

Estimates are presented in odds ratio (OR) and 95% credible intervals (95% CrI). VKA: Vitamin K antagonist, $P2Y_{12}i$: $P2Y_{12}$ inhibitor, LD: Low dose

VKA + P2Y$_{12}$i + Aspirin				
1.00 (0.08 – 12.33)	**Dabigatran (110/150 mg) + P2Y$_{12}$i**			
0.87 (0.07 – 11.19)	0.87 (0.02 – 31.42)	**Apixaban + P2Y$_{12}$i**		
0.80 (0.06 – 11.00)	0.80 (0.02 – 30.36)	0.93 (0.03 – 35.56)	**Rivaroxaban (LD) + P2Y$_{12}$i**	
0.79 (0.06 – 10.21)	0.79 (0.02 – 29.03)	0.91 (0.02 – 33.73)	0.99 (0.03 – 37.82)	**Edoxaban + P2Y$_{12}$i**

(A) All-cause mortality

Apixaban + P2Y$_{12}$i				
0.48 (0.01 – 19.86)	**Edoxaban + P2Y$_{12}$i**			
0.40 (0.03 – 5.70)	0.83 (0.06 – 11.41)	**VKA + P2Y$_{12}$i + Aspirin**		
0.34 (0.01 – 14.68)	0.71 (0.02 – 30.36)	0.86 (0.06 – 12.35)	**Rivaroxaban (LD) + P2Y$_{12}$i**	
0.34 (0.01 – 13.86)	0.72 (0.02 – 28.15)	0.88 (0.07 – 11.33)	1.02 (0.02 – 40.06)	**Dabigatran (110/150 mg) + P2Y$_{12}$i**

(B) Stroke

Figure 3: The network meta-analysis results for (A) all-cause mortality, and (B) stroke.

Estimates are presented in odds ratio (OR) and 95% credible intervals (95% CrI). VKA: Vitamin K antagonist, P2Y$_{12}$i: P2Y$_{12}$ inhibitor, LD: Low dose.

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VKA + P2Y$_{12}$i + Aspirin				
0.77 (0.05 – 12.50)	**Rivaroxaban (LD) + P2Y$_{12}$i**			
0.73 (0.05 – 10.81)	0.95 (0.02 – 48.03)	**Edoxaban + P2Y$_{12}$i**		
0.62 (0.05 – 8.52)	0.81 (0.02 – 36.90)	0.85 (0.02 – 36.67)	**Dabigatran (110/150 mg) + P2Y$_{12}$i**	
0.56 (0.04 – 7.52)	0.72 (0.02 – 32.96)	0.76 (0.02 – 32.03)	0.90 (0.02 – 35.85)	**Apixaban + P2Y$_{12}$i**

A) Myocardial infarction

Rivaroxaban (LD) + P2Y$_{12}$i				
0.90 (0.07 – 11.95)	**VKA + P2Y$_{12}$i + Aspirin**			
0.80 (0.02 – 29.72)	0.89 (0.07 – 11.55)	**Apixaban + P2Y$_{12}$i**		
0.71 (0.02 – 26.93)	0.79 (0.06 – 10.33)	0.89 (0.02 – 33.59)	**Edoxaban + P2Y$_{12}$i**	
0.65 (0.02 – 25.35)	0.72 (0.06 – 9.49)	0.81 (0.02 – 30.88)	0.92 (0.02 – 35.80)	**Dabigatran (110/150 mg) + P2Y$_{12}$i**

B) Stent thrombosis

Figure 4: The network meta-analysis results for (A) myocardial infarction, and (B) stent thrombosis.

Estimates are presented in odds ratio (OR) and 95% credible intervals (95% CrI). VKA: Vitamin K antagonist, P2Y$_{12}$i: P2Y$_{12}$ inhibitor, LD: Low dose.

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Supplementary Table 1: Risk of bias for the included randomized controlled trials

	PIONEER AF-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST AF-PCI
Random sequence generation *(Selection bias)*	⊕	⊕	⊕	⊕
Allocation concealment *(Selection bias)*	⊕	⊕	⊕	⊕
Blinding of participants and personnel *(Performance bias)*	⊕	⊕	⊕	⊕
Incomplete outcome data *(Attrition bias)*	⊕	⊕	⊕	⊕
Selective reporting *(Reporting bias)*	⊕	⊕	⊕	⊕
Other sources of bias	⊕	⊕	⊕	⊕

(+) denotes low risk of bias, blank denotes unclear risk of bias, and (−) denotes high risk of bias.

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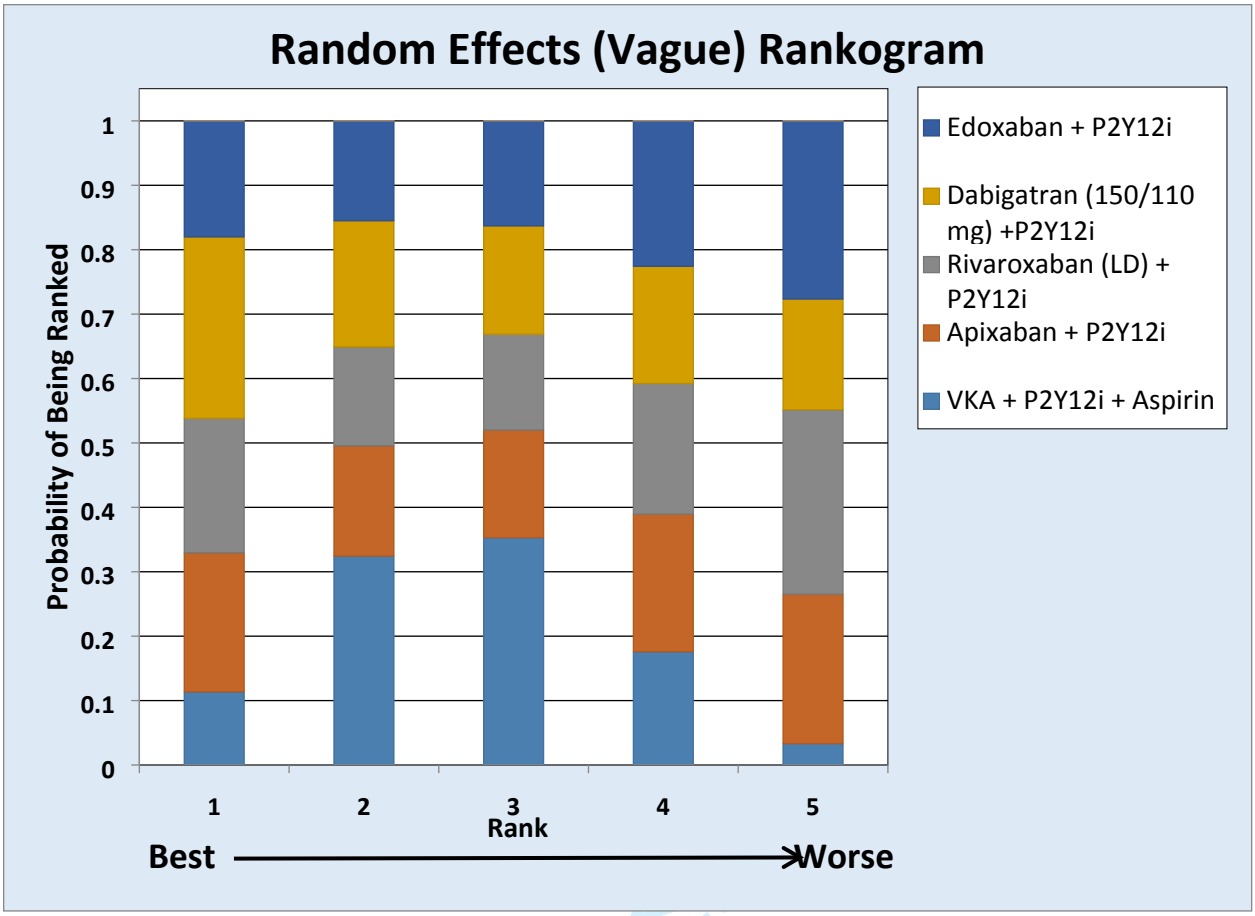

Supplementary Figure 1: The rankogram for different agents in the all-cause mortality outcome

VKA: Vitamin K antagonist, P2Y12i: $P2Y_{12}$ inhibitor, LD: Low dose.

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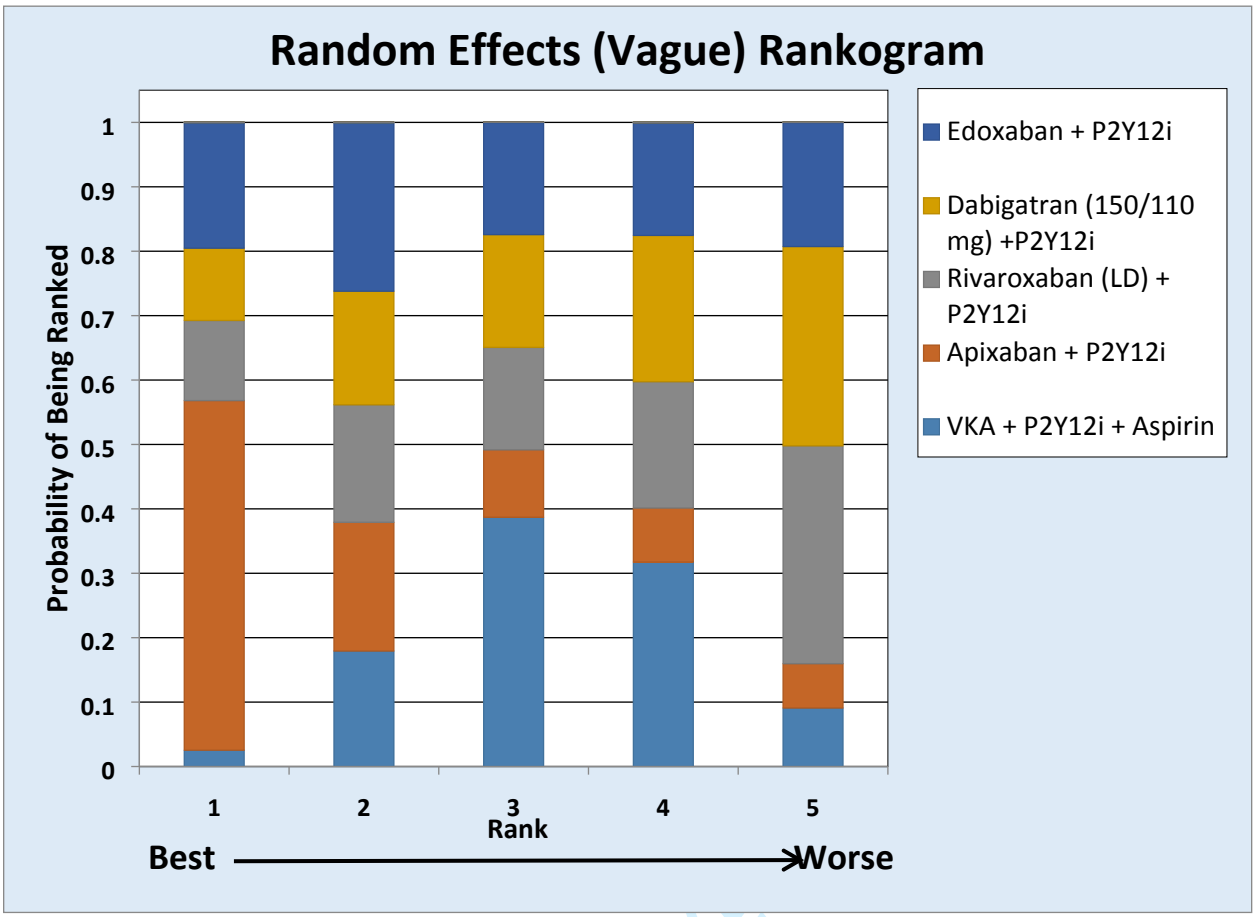

Supplementary Figure 2: The rankogram for different agents in the stroke outcome

VKA: Vitamin K antagonist, P2Y12i: $P2Y_{12}$ inhibitor, LD: Low dose.

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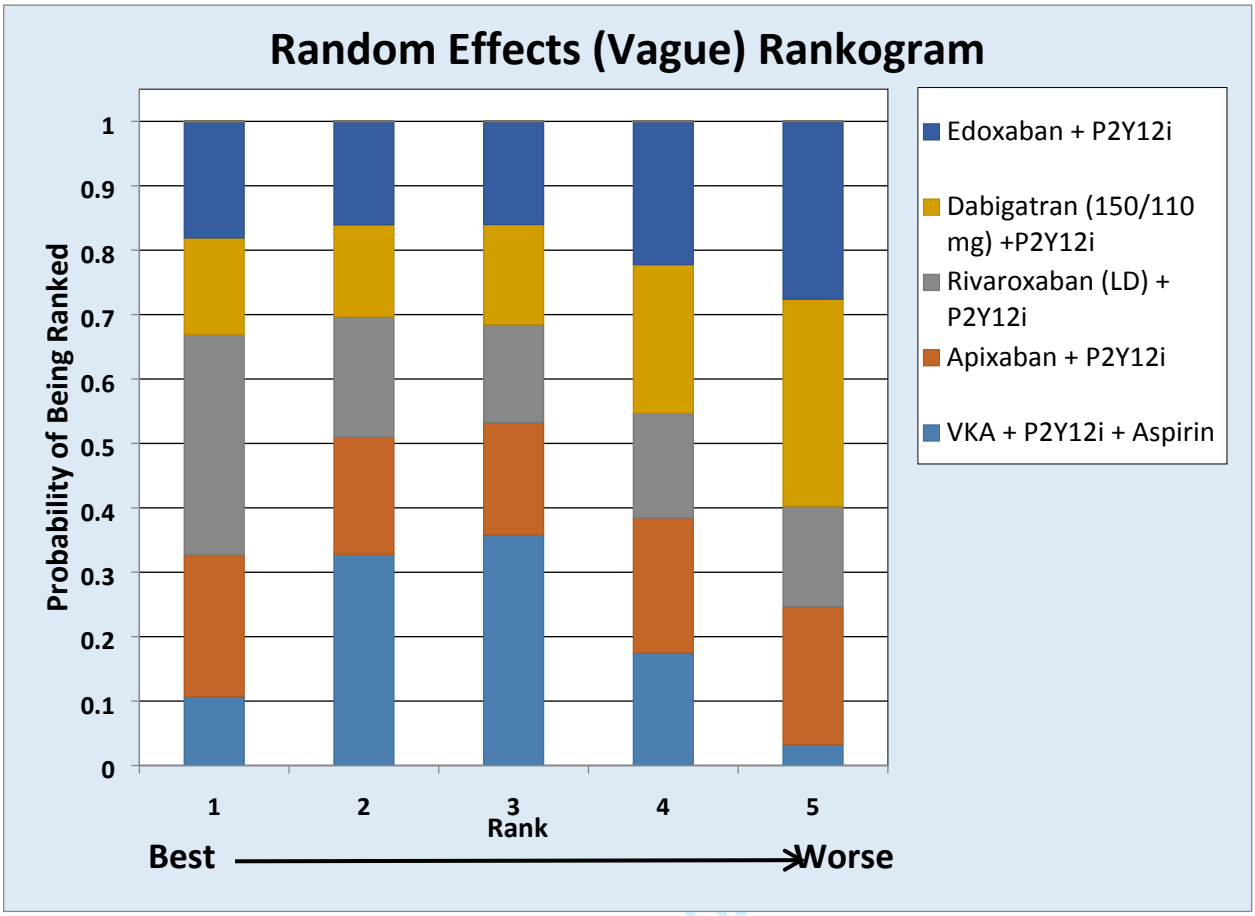

Supplementary Figure 3: The rankogram for different agents in the Myocardial Infarction outcome

VKA: Vitamin K antagonist, P2Y12i: $P2Y_{12}$ inhibitor, LD: Low dose.

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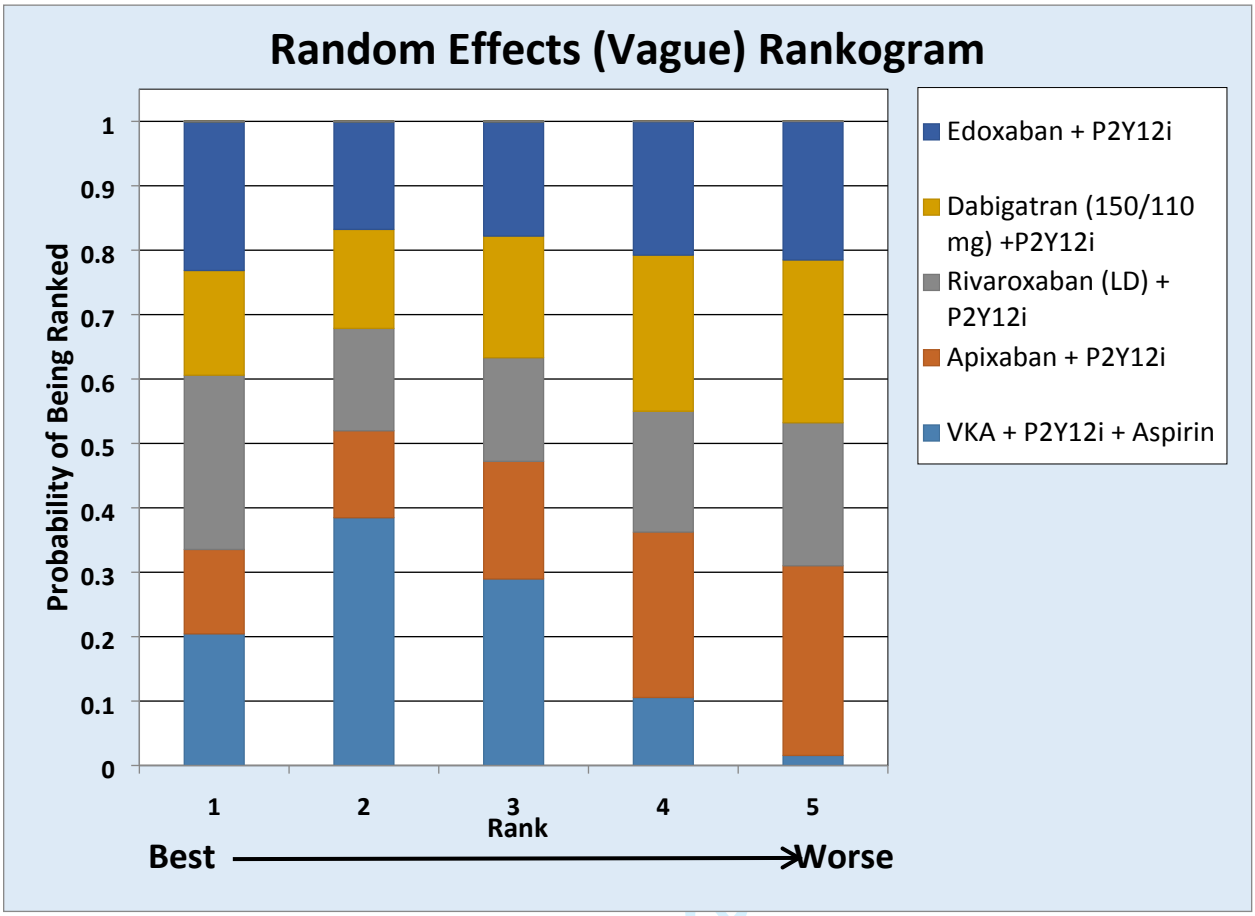

Supplementary Figure 4: The rankogram for different agents in the stent thrombosis outcome

VKA: Vitamin K antagonist, P2Y12i: $P2Y_{12}$ inhibitor, LD: Low dose.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, 7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6, S1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6, 7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7, 8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6, S1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9, 10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Safety and efficacy of dual vs. triple antithrombotic therapy (DAT vs. TAT) in patients with atrial fibrillation following a PCI: a systematic review and network meta-analysis

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Title:

Safety and efficacy of dual vs. triple antithrombotic therapy (DAT vs. TAT) in patients with atrial fibrillation following a PCI: a systematic review and network meta-analysis

Authors:

Renad M Altoukhi [1]

Reema A Alshouimi [1]

Shahad M Al Rammah [1]

Mohammed Y Alzahrani [1]

Abdulaali R Almutairi [2]

Abdulmajeed M Alshehri [1]

Osamah M. Alfayez [3]

Majed S Al Yami [1]

Omar A Almohammed [4]

[1] Department of Pharmacy Practice, College of pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[2] Saudi Food and Drug Authority, Riyadh, Saudi Arabia.

[3] Department of Pharmacy Practice, College of pharmacy, Qassim University, Qassim, Saudi Arabia

[4] Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

Corresponding author contact information:

Omar A Almohammed, B.Pharm, PharmD, PhD
Assistant Professor
Department of Clinical Pharmacy
College of Pharmacy - King Saud University
Mobile: +966555104065
E-mail: oalmohammed@ksu.edu.sa

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Abstract

Objective

Creating an appropriate antithrombotic therapy for patients with atrial fibrillation (AF) who have undergone percutaneous coronary intervention (PCI) remains a dilemma. Several clinical trials compared the use of a dual antithrombotic therapy (DAT) regimen with a direct oral anticoagulants (DOAC) including (apixaban, dabigatran, edoxaban, or rivaroxaban) and a $P2Y_{12}$ inhibitor versus a triple antithrombotic therapy (TAT) that includes a vitamin K antagonist (VKA) plus aspirin and a $P2Y_{12}$ inhibitor in AF patients who have undergone PCI. However, there are no head-to-head trials comparing the DAT regimens to each other. We aimed to compare the efficacy and safety of DAT regimens using a network meta-analysis (NMA) approach.

Design

A systematic review and network meta-analysis of randomized clinical trials

Methods:

We conducted a systematic literature review to identify relevant randomized clinical trials, and performed a Bayesian NMA for International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major (CRNM) bleeding, all-cause mortality, stroke, myocardial infarction (MI), and stent thrombosis outcomes. We used NetMetaXL 1.6.1 and WinBUGS 1.4.3 for the NMA and estimated the probability of ranking the treatments based on the surface under the cumulative ranking curve.

Results:

The comparison between DAT regimens showed no significant difference in the safety or efficacy outcomes. Apixaban regimen was ranked first preferred therapy in-terms of ISTH major or CRNM bleeding and stroke, with a probability of 52% and 54%, respectively. Rivaroxaban regimen was the preferred therapy in-terms of MI and stent thrombosis, with a probability of 34% and 27%, respectively. Dabigatran regimen was ranked first in-terms of all-cause mortality, with a probability of 28%.

Conclusion:

The DAT regimens are as safe and effective as TAT regimens. However, ranking probabilities for the best option in the selected outcomes can be used to guide the selection among these agents based on different patients' conditions.

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Keywords:

DAT, TAT, PCI, Anticoagulants, Atrial Fibrillation, Bleeding

Strengths and limitations of this study:

- The utilized network meta-analysis technique facilitated the comparison of dual antithrombotic therapy regimens versus triple antithrombotic therapy regimen in patients with AF who have undergone PCI.
- Only randomized clinical trials were included in this network meta-analysis
- All the included studies were of high quality with a low risk of bias
- The results were associated with wide confidence intervals, which might affect the precision of the findings.

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INTRODUCTION

Atrial fibrillation (AF) is a common comorbidity in patients with acute coronary syndrome (ACS) due to similar risk factors. The incidence rate of AF in ACS patients ranges from 5% to 23%.[1-5] Appropriate antithrombotic therapy for patients with AF who had ACS or have undergone percutaneous coronary intervention (PCI) is controversial. In patients with AF, oral anticoagulation is recommended for the prevention of cardioembolic stroke,[6] but its efficacy in preventing stent thrombosis for patients with PCI is not well established.

Dual-antiplatelet therapy (DAPT), with aspirin plus a $P2Y_{12}$ inhibitor, is recommended in patients with ACS for secondary prevention of ischemic events and stent thrombosis.[7] Triple therapy, including an oral anticoagulant on top of the DAPT, was recommended by previous guidelines and considered a standard of care for patients with AF who experienced ACS or undergone PCI.[7 8] However, the most recent AHA/ACC/HRS 2019 guidelines suggested the use of dual antithrombotic therapy (DAT: vitamin K antagonist (VKA) or a direct oral anticoagulant (DOAC) plus a $P2Y_{12}$ inhibitor) over the triple antithrombotic therapy (TAT: oral anticoagulant, aspirin and a $P2Y_{12}$ inhibitor),[6] due to the increased risk of bleeding with the triple therapy that was reported in multiple studies.[9-14]

In an attempt to clarify this controversy, six randomized control trials (WOEST, ISAR-TRIPLE, PIONEER-AF-PCI, RE-DUAL-PCI, AUGUSTUS, and ENTRUST-AF-PCI) were conducted to assess the efficacy and safety of the TAT compared to the DAT for patients with AF receiving oral anticoagulation after experiencing ACS or undergoing PCI.[9-14] Although these trials reported a higher incidence of major bleeding in patients receiving the TAT compared to the DAT without significant differences in the risk of ischemic events, it is noteworthy to recognize that these trials were underpowered to detect ischemic events.

Several observational studies found a higher risk of bleeding with the triple therapy that involved vitamin K antagonist, aspirin and a $P2Y_{12}$ inhibitor.[15-17] The objective of this network meta-analysis is to assess the safety and efficacy of a DAT regimen with a DOAC versus a TAT regimen with a VKA in patients with AF who experienced ACS or undergone PCI.

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METHODS

A systemic literature search was conducted on MEDLINE and Embase through October, 2019 to identify randomized clinical trials that evaluated the use of DOACs in patients with AF who experienced ACS or undergone PCI. The search terms included percutaneous coronary intervention, PCI, atrial fibrillation, acute coronary syndrome, ACS, stent, anticoagulants, rivaroxaban, edoxaban, apixaban, dabigatran, DOACs, vitamin K antagonist, VKA, warfarin, aspirin, clopidogrel, triple therapy, double therapy, dual antithrombotic therapy, DAT, triple antithrombotic therapy, and TAT. We also searched for other systematic reviews and meta-analyses and reviewed their references to identify any relevant studies. The search was limited to studies that were published in English within the last ten years.

For each study, episodes of major or clinically relevant non-major (CRNM) bleeding events based on the International Society on Thrombosis and Haemostasis (ISTH) definition,[18] all-cause mortality, stroke, myocardial infarction (MI), stent thrombosis were extracted (Supplementary Table 1). Data were extracted from the published studies and assessed for eligibility by two independent investigators (RMA and RAM) and verified by a third investigator (OAA). The risk of bias assessment was conducted for each study using the Cochrane Collaboration risk of bias assessment tool.[19] A Bayesian network meta-analysis (NMA), a statistical method that can incorporate both direct and indirect comparisons including treatment arms that were not previously compared in head to head trials from a clinical trial, was conducted for the pre-specified outcomes using NetMetaXL 1.6.1 (Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada)[20] and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom). We utilized the random effect binomial model with vague priors and employing Markov chain Monte Carlo simulation for 60000 iterations after discarding 30000 iteration as burn-in simulations initially. Estimates of the outcomes were presented in odds ratio (OR) and 95% credible intervals (95% CrI). Also, we estimated the probability of ranking the treatments based on the surface under the cumulative ranking curve.[21] We reported this NMA according to the preferred reporting items for systematic reviews and meta-analyses for network meta-analyses (PRISMA-NMA).[22]

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Patient and public involvement

Patients and the public were not involved in the design or conduct of the study.

RESULTS

A total of 662 articles were identified in the systematic search. Four studies, PIONEER-AF PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI, met the inclusion criteria, and were included in the current NMA.[11-14] The flowchart in Figure 1 illustrates the process of including and excluding articles for this NMA. The risk of bias assessment of the included trials showed low risk of bias (Supplementary Table 2).

Summary of the included trials

The trials that were included demonstrated favorable results for the pre-specified outcomes towards DOACs when mainly used in a DAT regimen in combination with a $P2Y_{12}$ inhibitor only.[11-14] The PIONEER AF-PCI trial was the first to be conducted to compare the safety and efficacy of using DOACs agent in a DAT regimen to TAT regimen. A DAT regimen including low-dose rivaroxaban (15 mg once daily) in combination with a $P2Y_{12}$ inhibitor (group 1) was compared to a TAT regimen that included $P2Y_{12}$ inhibitor and aspirin in combination with either a very low dose rivaroxaban (2.5 mg twice daily; group 2) or VKA (group 3). The study found the bleeding rates were significantly reduced for groups 1 and 2 compared to group 3 (16.8%, 18.0%, and 26.7%, respectively; hazard ratio [HR] for group 1 vs. 3 =0.59; 95%CI 0.47–0.76; HR for group 2 vs. 3 =0.63; 95%CI 0.50–0.80). However, the rivaroxaban dose that was used in the trial is lower than the recommended daily dose for stroke prevention in atrial fibrillation (20 mg), and the very low dose was not included in the NMA.[11]

The RE-DUAL PCI study was conducted to compare the safety and efficacy of using dabigatran (110 or 150 mg twice daily) in a DAT regimen with a $P2Y_{12}$ inhibitor to a TAT regimen that included $P2Y_{12}$ inhibitor and aspirin in combination with a VKA. The findings of the study demonstrated a significantly lower risk of bleeding for the DAT regimen that included dabigatran to the TAT regimen (HR =0.52; 95%CI 0.42–0.63; P<0.001 for superiority).[12]

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However, it is to be noted that both studies, the PIONEER AF-PCI and RE-DUAL PCI, were not powered to detect any significant disparities in efficacy between the DOACs and VKA.

The AUGUSTUS trial compared the use of apixaban to a VKA along with clopidogrel and aspirin to a placebo using a 2x2 factorial design. The study concluded that a DAT regimen with apixaban and clopidogrel only was both non-inferior and superior to a TAT regimen in-terms of reducing the risk of major or CRNM bleeding (HR =0.69; 95%CI 0.58–0.81; p<0.001 for both non-inferiority and superiority), while there was no difference in the ischemic event outcomes.[13]

The most recent, ENTRUST-AF PCI trial was designed to assess a DAT regimen, that included edoxaban plus a $P2Y_{12}$ inhibitor, to a TAT regimen, that included a VKA plus $P2Y_{12}$ inhibitor and aspirin. Similar to the previous trials, they found a lower rate of bleeding in the DAT regimen in comparison to the TAT regimen (HR =0.83, 95%CI 0.65–1.05; p=0·0010 for non-inferiority). However, unlike other DOACs, the trial found the edoxaban regimen to be non-inferior, but not superior to the TAT regimen.[14]

Network meta-analysis

Demographic characteristics

A total of 7,890 patients were included in the NMA. The mean age for the included patients ranged between 68 and 71 years, and about 22 to 30% of participants were females. The detailed patients' demographics and outcomes from the included studies were presented in Table 1.

ISTH major or CRNM bleeding

There were no significant differences between all DOACs when used in DAT regimens as well as when compared to TAT regimen, using VKA. Among all, DAT regimen containing apixaban was the preferred one, with a probability of 52%, followed by regimens containing dabigatran or rivaroxaban, with a probability of 18% and 17.9%, respectively (Figure 2).

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All-cause mortality

The NMA showed no differences between all DAT regimens containing DOACs as well as between DAT and TAT regimens in regard to all-cause mortality. However, the ranking of DAT regimens showed that dabigatran regimen was the preferred agent, followed by apixaban regimen, and rivaroxaban regimen with a probability of 28%, 21.5%, and 20.8%, respectively (Figure 3 [A], Supplementary Figure 1).

Stroke

Similar to all-cause mortality, the results of the NMA showed no significant difference between the DOACs when used in DAT regimen, and when compared to the TAT regimen, with VKA. Apixaban DAT regimen was ranked first, followed by regimens of edoxaban and rivaroxaban with a probability of 54%, 19.5%, and 12.4%, respectively (Figure 3 [B], Supplementary Figure 2).

Myocardial infarction (MI)

There were no significant differences between all DOACs in the DAT regimens compared to each other or to the TAT regimen, with VKA. Rivaroxaban DAT regimen was the preferred regimen, followed by apixaban regimen and edoxaban regimen, with a probability of 34%, 22%, and 18%, respectively (Figure 4 [A], Supplementary Figure 3).

Stent thrombosis

The odds of stent thrombosis were similar across all DAT regimens with DOACs and TAT regimen, with rivaroxaban DAT regimen being the preferred regimen with a probability of 27% and followed by edoxaban regimen with a probability of 23% (Figure 4 [B], Supplementary figure 4).

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Table 1: Patients' demographics and outcomes from the included randomized controlled trials

Name of the Study	PIONEER AF-PCI* [11]		RE-DUAL PCI[12]		AUGUSTUS*[13]		ENTRUST-AF-PCI[14]	
Relevant Groups in the Study	**DAT** Riva+P2Y$_{12}$i	**TAT** VKA+ P2Y$_{12}$i + ASA	**DAT** Dabi+P2Y$_{12}$i	**TAT** VKA+ P2Y$_{12}$i + ASA	**DAT** Apix+P2Y$_{12}$i	**TAT** VKA+ P2Y$_{12}$i + ASA	**DAT** Edox+P2Y$_{12}$i	**TAT** VKA+ P2Y$_{12}$i + ASA
n	696	697	1744	981	1143	1123	751	755
Baseline Characteristics								
Age (years, SD or IQR)	70.4 (9.1)	69.9 (8.7)	70.2 (8.4)	71.7 (8.9)	70.6 (64 - 77)	70.8 (64 - 77)	69 (63 – 77)	70 (64 – 77)
Female (%)	25.5%	26.6%	24.3%	23.5%	27.8%	30.2%	26.0%	25.4%
Risk Factors:								
Diabetes (%)	28.8%	31.3%	35.7%	37.9%	36.2%	36.5%	34.5%	34.2%
Hypertension (%)	73.3%	75.4%	NR	NR	88.5%	88.0%	90.0%	91.0%
Dyslipidemia (%)	42.6%	44.8%	NR	NR	NR	NR	66.2%	64.1%
History of MI (%)	19.8%	22.2%	24.7%	27.3%	NR	NR	25.0%	23.4%
Type of index event (%)								
ACS	51.5%	52.2%	51.6%	48.4%	61.7%	60.7%	51.7%	51.5%
Non-ACS	48.5%	47.8%	48.4%	51.6%	38.3%	39.3%	48.3%	48.5%
Outcomes								
Major or CRNM bleeding (ISTH)	16.8%	25.5%	17%	27%	7.3%	18.7%	17%	20%
Death from any cause	2.3%	1.9%	4.9%	4.9%	3.4%	2.9%	6.1%	4.9%
MI	3.0%	3.5%	4.0%	3.0%	3.3%	2.9%	3.9%	3.0%
Stroke	1.3%	1.2%	1.5%	1.3%	0.4%	1.0%	1.3%	1.6%
Stent thrombosis	0.8%	0.7%	1.3%	0.8%	1.8%	1.0%	1.7%	1.3%

*The patients' baseline characteristics for these studies are based on the overall population in the studies

DAT: Dual antithrombotic therapy, TAT: Triple antithrombotic therapy, Riva: Rivaroxaban, Dabi: Dabigatran, Apex: Apixaban, Edox: Edoxaban, VKA: Vitamin K antagonist, P2Y12i: P2Y12 inhibitors, ASA: Aspirin, MI: Myocardial infarction, CRNM: Clinically relevant non-major, ISTH: International Society on Thrombosis and Haemostasis, NR: Not reported

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DISCUSSION

For patients with atrial fibrillation who experienced ACS or undergone PCI, the selection of a regimen that is both effective in preventing stroke and stent thrombosis while minimizing the risk of bleeding remains a challenge for prescribers. The main focus of this NMA was to estimate the efficacy and safety of different DOACs in DAT regimens compared to each other and to VKA in a TAT regimen for patients with AF who undergone PCI, and to rank the DOACs in terms of difference in the efficacy and safety outcomes. We looked at five main end points, which were ISTH major or CRNM bleeding, all-cause mortality, stroke, MI, and stent thrombosis.

Our results showed no significant difference between a DAT regimen with a DOAC compared to a TAT regimen with a VKA for all the specified outcomes. This demonstrates that the DAT regimen with DOACs is just as safe and effective as the TAT regimen with a VKA. However, apixaban regimen was the preferred option in reducing the risk of major or CRNM bleeding and stroke, dabigatran regimen was ranked as first option in the reduction of all-cause mortality, and rivaroxaban regimen was the preferred in-term of reducing the risk of MI and stent thrombosis. Based on this ranking, VKA was ranked the lowest in comparison to all DOACs' DAT regimens in terms of bleeding, all-cause mortality, and MI. A previous NMA by Lopes et al. presented similar results, but in their NMA, there was a significant difference between the DAT and the TAT regimens with a more favorable outcome in terms of safety for the regimen that includes a DOAC and a $P2Y_{12}$ inhibitor.[23]

The 2016 European Society of Cardiology (ESC) guidelines for the management of AF recommended to initiate the patients' management on the triple therapy that includes an oral anticoagulant (OAC) with aspirin and clopidogrel in the first month of treatment after PCI, or to an extended period of 6 months in case of lower risk of bleeding; then, to continue with a dual therapy (OAC plus aspirin or clopidogrel) for 6 to 12 months, and lifetime therapy on an OAC.[8] Only aspirin and clopidogrel were recommended as antiplatelet therapy as opposed to third generation $P2Y_{12}$ inhibitors due to the increased risk of bleeding and lack of evidence. If

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a DOAC is chosen for anticoagulation, then the lowest effective dose for stroke prevention should be used. However, a regimen of low-dose rivaroxaban plus clopidogrel and aspirin is not recommended for stroke prevention in atrial fibrillation.[8] In the recent AHA/ACC/HRS 2019 guidelines for the management of AF in patients who had undergone PCI, the guidelines favored the DAT over the TAT; for patients with an increased risk of stroke based on their CHA_2DS_2-VASc who should be initiated on triple therapy (OAC plus $P2Y_{12}$ inhibitor plus aspirin), it is recommended to transition them to double therapy at the 4^{th} to 6^{th} week of treatment.[6] However, no recommendations were made in such population regarding the use of apixaban and edoxaban due to the lack of data on these agents at that time.

The results of this NMA align with the findings of previous studies that demonstrates the sufficiency of the DAT regimen for the prevention of stroke in patients with AF who experienced ACS or undergone PCI, with the added benefit of having a reduced risk of bleeding in those patients.[12 9 11 13 10 14] There are some limitations to this NMA. The prominent variation in the design, the length of follow-up period, and sample sizes between the included trials could have possibly contributed to the wide confidence interval and the lack of significance in our analysis. Therefore, the findings should be used with caution until a large direct comparison studies among DOACs are conducted or findings from retrospective studies become available to support this evidence. Perhaps future studies could look more into patient specific outcomes that could be based on differences in terms of sex, age group, presence of other comorbidities, genetic variations, and other $P2Y_{12}$ inhibitors.

Conclusion

The DAT regimens with DOACs are as safe and effective as the TAT regimen with VKA. Moreover, DOACs in DAT regimens had higher ranking probabilities as a best option in the selected outcomes over VKA in a TAT regimen. These ranking probabilities can be used to guide the selection among different DOACs agents based on patients' conditions, until evidence from large and direct comparison studies become available.

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Footnotes:

- **Contributors** MSA, MYA, and ARA designed the study, conducted the analysis, produced the tables and figures, and participated in writing the manuscript. SMA and AMA conducted the literature review, summarized the included trials, and prepared the resulting figure. RMA and RAA extracted the data and contributed to writing the manuscript. OAA and OMA reviewed the extracted data for the analysis and the tables for the results and contributed to writing the manuscript. All authors read and approved the final manuscript.

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- **Competing interests** None declared

- **Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

- **Patient consent for publication** Not required.

- **Provenance and peer review** Not commissioned; externally peer reviewed.

- **Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

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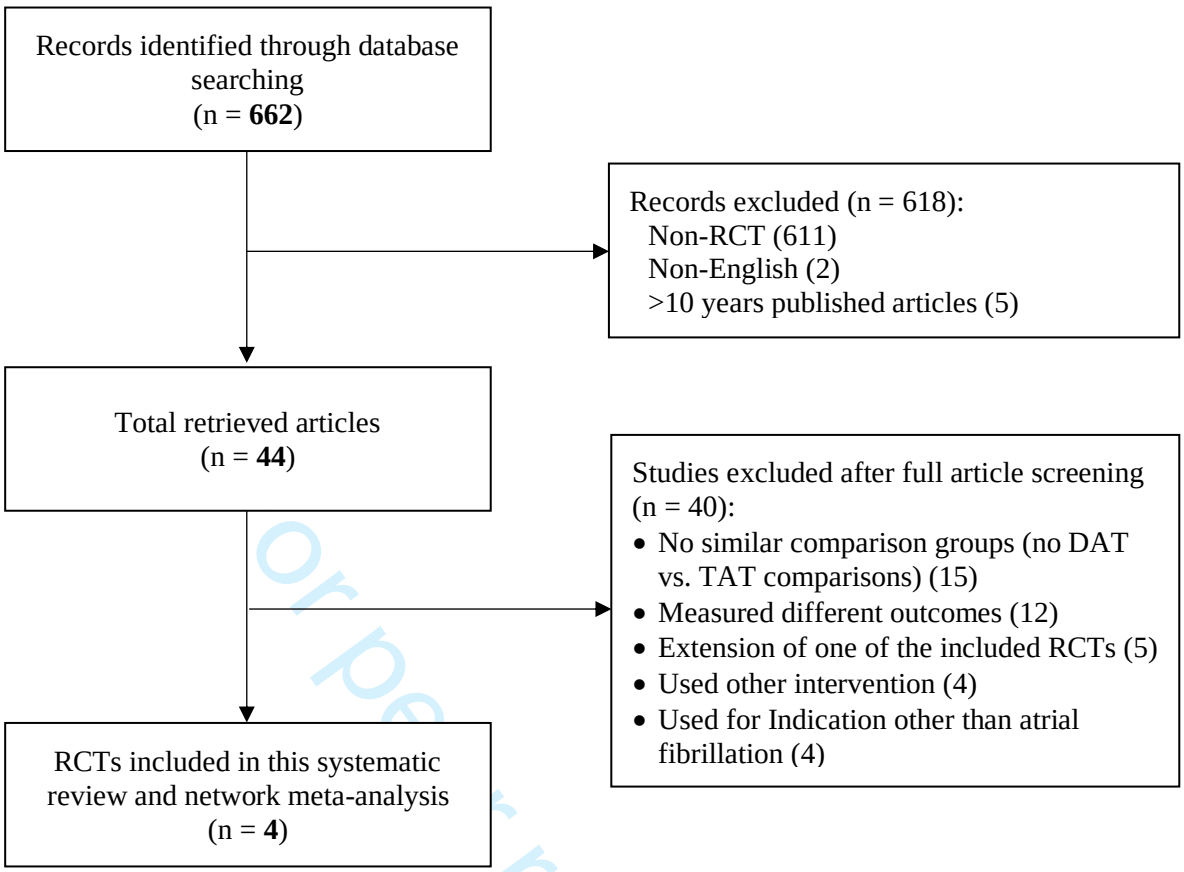

Figure 1: Flow diagram for studies included in the network meta-analysis

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Apixaban + P2Y$_{12}$i				
0.59 (0.02 – 20.88)	**Dabigatran (110/150 mg) + P2Y$_{12}$i**			
0.58 (0.02 – 20.55)	0.98 (0.03 – 34.48)	**Rivaroxaban (LD) + P2Y$_{12}$i**		
0.42 (0.01 – 14.90)	0.71 (0.02 – 25.50)	0.73 (0.02 – 25.58)	**Edoxaban + P2Y$_{12}$i**	
0.34 (0.03 – 4.34)	0.58 (0.05 – 7.13)	0.59 (0.05 – 7.46)	0.81 (0.07 – 10.28)	**VKA + P2Y$_{12}$i + Aspirin**

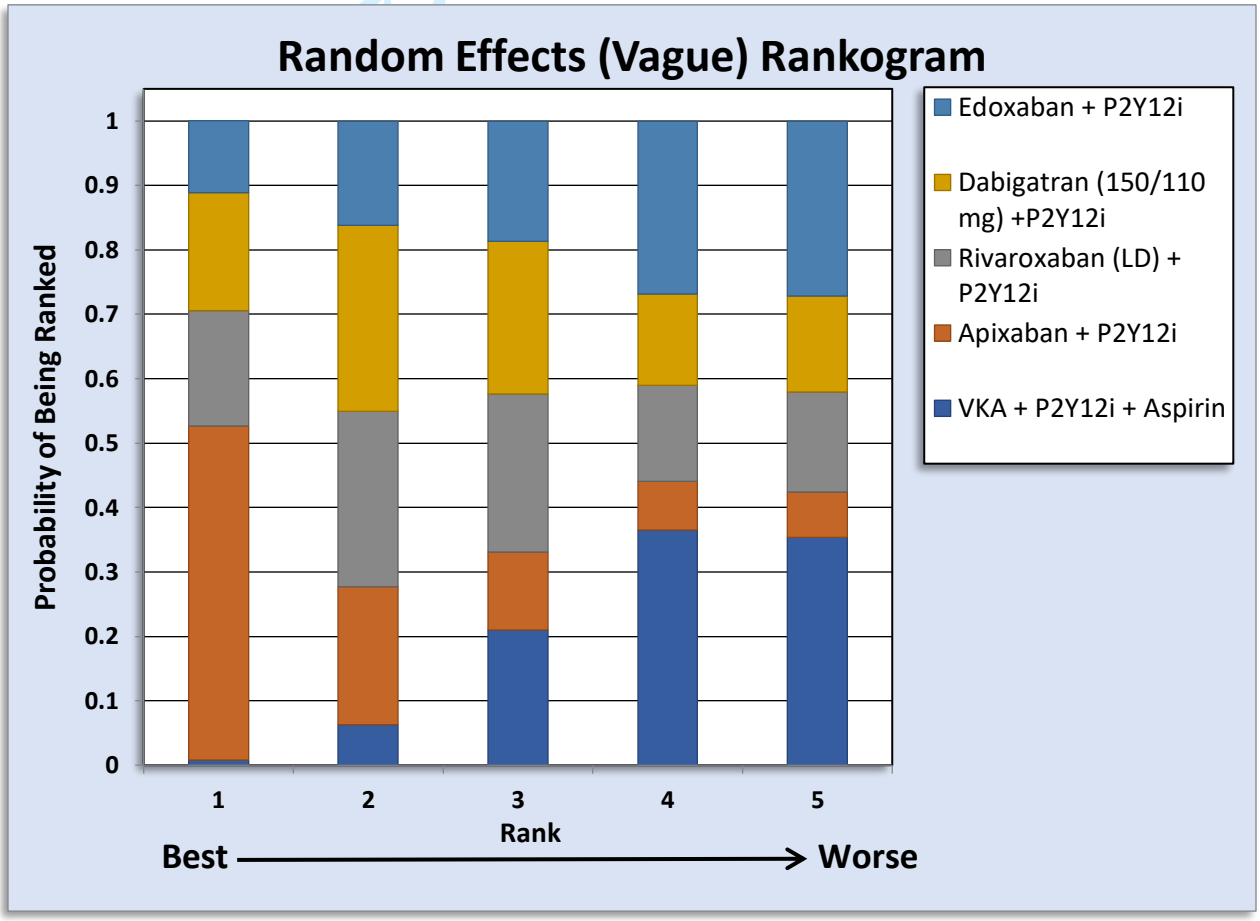

Figure 2: The network meta-analysis and the rankogram results for the International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major (CRNM) bleeding.

Estimates are presented in odds ratio (OR) and 95% credible intervals (95% CrI). VKA: Vitamin K antagonist, P2Y$_{12}$i: P2Y$_{12}$ inhibitor, LD: Low dose

VKA + P2Y$_{12}$i + Aspirin				
1.00 (0.08 – 12.33)	**Dabigatran (110/150 mg) + P2Y$_{12}$i**			
0.87 (0.07 – 11.19)	0.87 (0.02 – 31.42)	**Apixaban + P2Y$_{12}$i**		
0.80 (0.06 – 11.00)	0.80 (0.02 – 30.36)	0.93 (0.03 – 35.56)	**Rivaroxaban (LD) + P2Y$_{12}$i**	
0.79 (0.06 – 10.21)	0.79 (0.02 – 29.03)	0.91 (0.02 – 33.73)	0.99 (0.03 – 37.82)	**Edoxaban + P2Y$_{12}$i**

(A) All-cause mortality

Apixaban + P2Y$_{12}$i				
0.48 (0.01 – 19.86)	**Edoxaban + P2Y$_{12}$i**			
0.40 (0.03 – 5.70)	0.83 (0.06 – 11.41)	**VKA + P2Y$_{12}$i + Aspirin**		
0.34 (0.01 – 14.68)	0.71 (0.02 – 30.36)	0.86 (0.06 – 12.35)	**Rivaroxaban (LD) + P2Y$_{12}$i**	
0.34 (0.01 – 13.86)	0.72 (0.02 – 28.15)	0.88 (0.07 – 11.33)	1.02 (0.02 – 40.06)	**Dabigatran (110/150 mg) + P2Y$_{12}$i**

(B) Stroke

Figure 3: The network meta-analysis results for (A) all-cause mortality, and (B) stroke.

Estimates are presented in odds ratio (OR) and 95% credible intervals (95% CrI). VKA: Vitamin K antagonist, P2Y$_{12}$i: P2Y$_{12}$ inhibitor, LD: Low dose.

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VKA + P2Y$_{12}$i + Aspirin				
0.77 (0.05 – 12.50)	**Rivaroxaban (LD) + P2Y$_{12}$i**			
0.73 (0.05 – 10.81)	0.95 (0.02 – 48.03)	**Edoxaban + P2Y$_{12}$i**		
0.62 (0.05 – 8.52)	0.81 (0.02 – 36.90)	0.85 (0.02 – 36.67)	**Dabigatran (110/150 mg) + P2Y$_{12}$i**	
0.56 (0.04 – 7.52)	0.72 (0.02 – 32.96)	0.76 (0.02 – 32.03)	0.90 (0.02 – 35.85)	**Apixaban + P2Y$_{12}$i**

A) Myocardial infarction

Rivaroxaban (LD) + P2Y$_{12}$i				
0.90 (0.07 – 11.95)	**VKA + P2Y$_{12}$i + Aspirin**			
0.80 (0.02 – 29.72)	0.89 (0.07 – 11.55)	**Apixaban + P2Y$_{12}$i**		
0.71 (0.02 – 26.93)	0.79 (0.06 – 10.33)	0.89 (0.02 – 33.59)	**Edoxaban + P2Y$_{12}$i**	
0.65 (0.02 – 25.35)	0.72 (0.06 – 9.49)	0.81 (0.02 – 30.88)	0.92 (0.02 – 35.80)	**Dabigatran (110/150 mg) + P2Y$_{12}$i**

B) Stent thrombosis

Figure 4: The network meta-analysis results for (A) myocardial infarction, and (B) stent thrombosis.

Estimates are presented in odds ratio (OR) and 95% credible intervals (95% CrI). VKA: Vitamin K antagonist, P2Y$_{12}$i: P2Y$_{12}$ inhibitor, LD: Low dose.

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Supplementary Table 1: Inclusion/exclusion criteria and outcomes of the network meta-analysis

Inclusion and exclusion criteria
Studies included if: • Randomized Clinical trials • Published in English • Published in the last 10 years (from date of literature search) **Studies excluded if:** • Non-randomized controlled trails • Published in language other than English • Published before more than 10 years (from date of literature search)
Outcomes
• Major bleeding • Clinically relevant non-major (CRNM) bleeding • All-cause mortality • Stroke • Myocardial infarction (MI) • Stent thrombosis

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Supplementary Table 2: Risk of bias for the included randomized controlled trials

	PIONEER AF-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST AF-PCI
Random sequence generation *(Selection bias)*	⊕	⊕	⊕	⊕
Allocation concealment *(Selection bias)*	⊕	⊕	⊕	⊕
Blinding of participants and personnel *(Performance bias)*	⊕	⊕	⊕	⊕
Incomplete outcome data *(Attrition bias)*	⊕	⊕	⊕	⊕
Selective reporting *(Reporting bias)*	⊕	⊕	⊕	⊕
Other sources of bias	⊕	⊕	⊕	⊕

(+) denotes low risk of bias, blank denotes unclear risk of bias, and (−) denotes high risk of bias.

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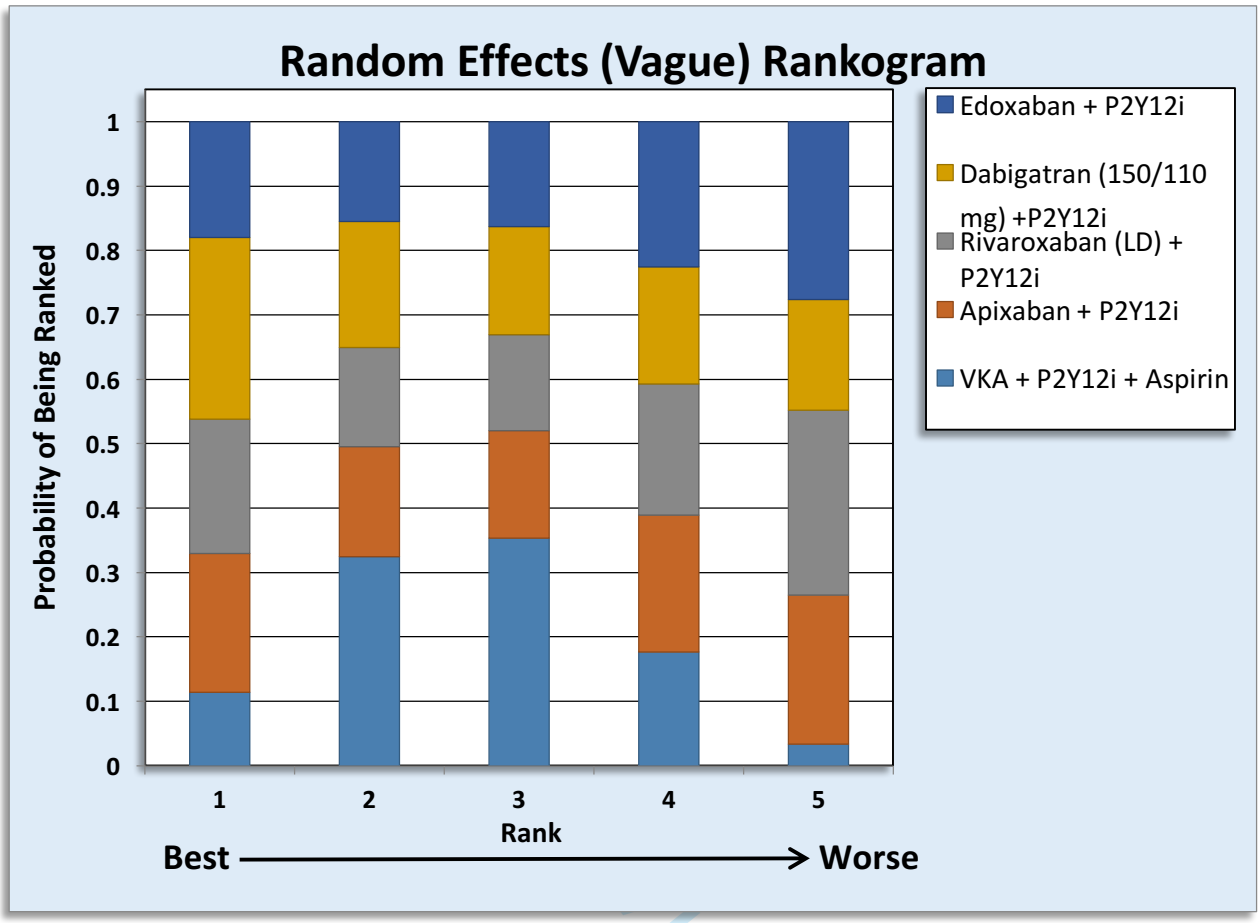

Supplementary Figure 1: The rankogram for different agents in the all-cause mortality outcome

VKA: Vitamin K antagonist, P2Y12i: $P2Y_{12}$ inhibitor, LD: Low dose.

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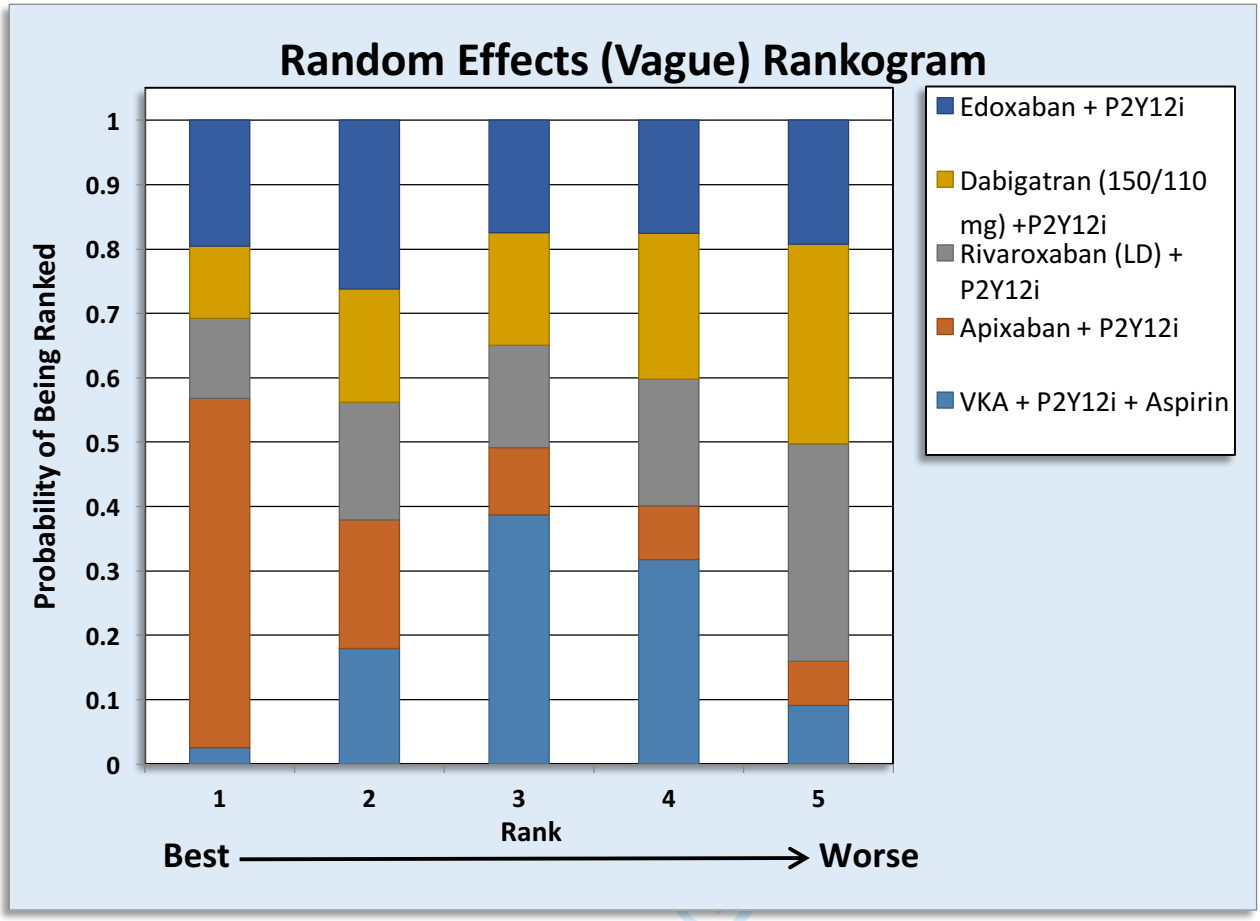

Supplementary Figure 2: The rankogram for different agents in the stroke outcome

VKA: Vitamin K antagonist, P2Y12i: $P2Y_{12}$ inhibitor, LD: Low dose.

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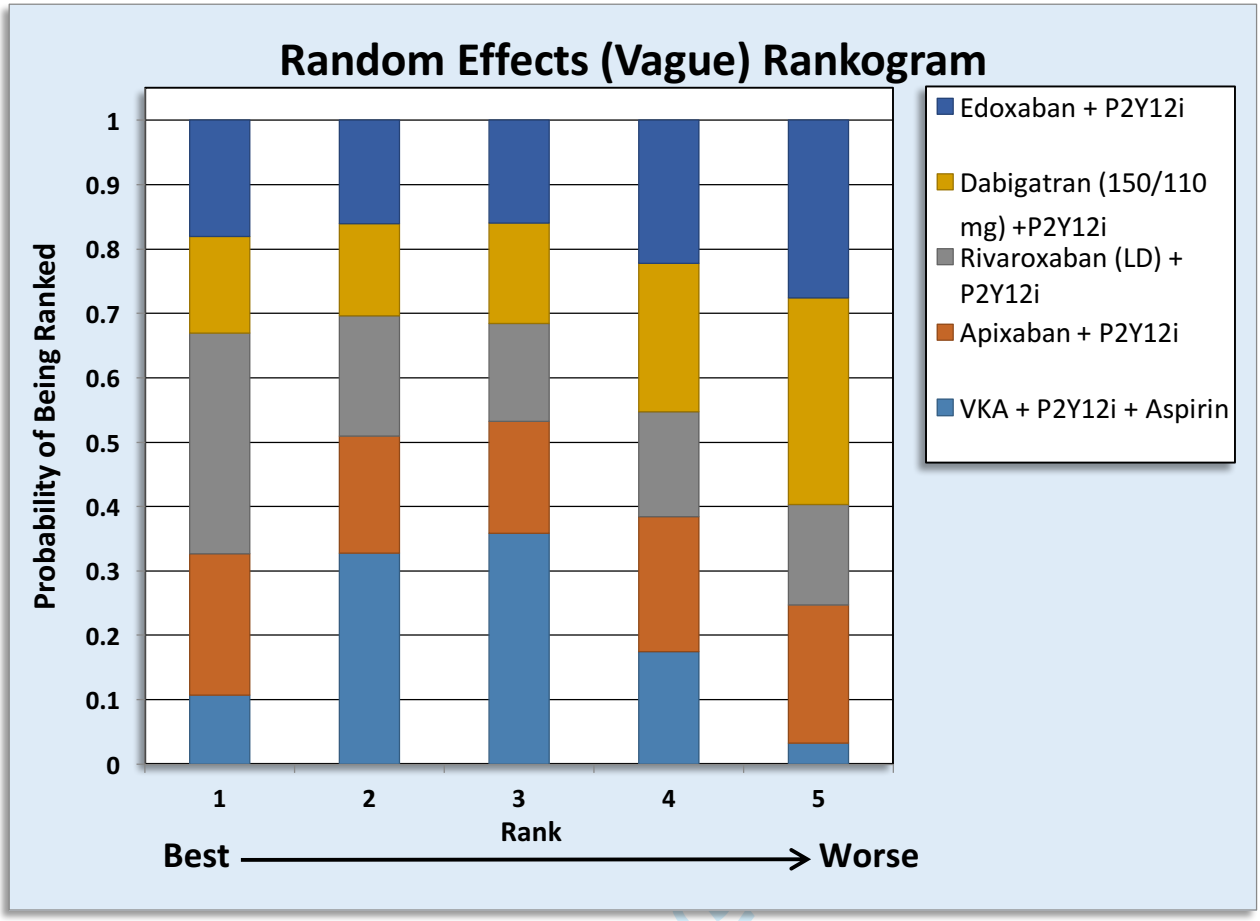

Supplementary Figure 3: The rankogram for different agents in the Myocardial Infarction outcome

VKA: Vitamin K antagonist, P2Y12i: $P2Y_{12}$ inhibitor, LD: Low dose.

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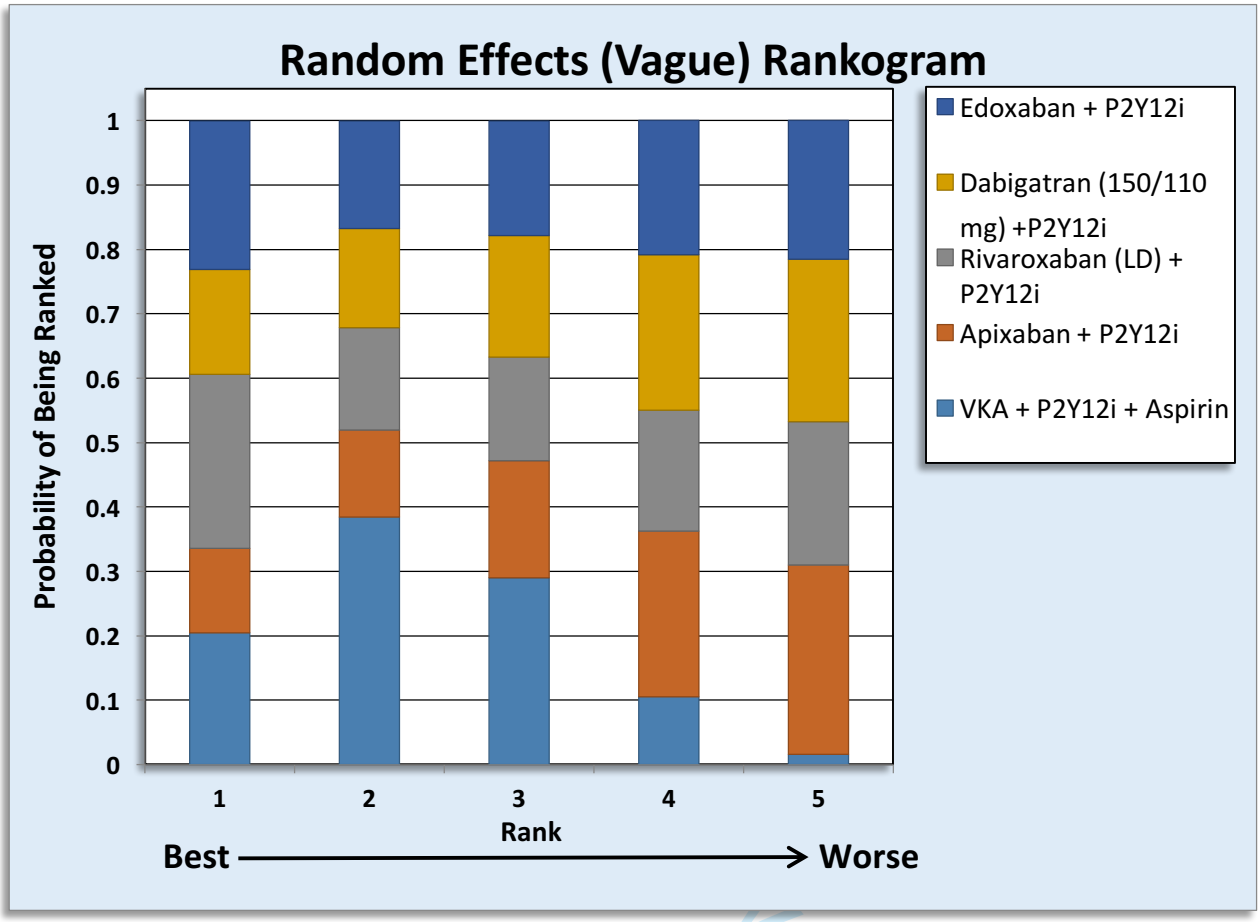

Supplementary Figure 4: The rankogram for different agents in the stent thrombosis outcome

VKA: Vitamin K antagonist, P2Y12i: $P2Y_{12}$ inhibitor, LD: Low dose.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, and Table S1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I_2) for each meta-analysis.	5

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6 - 9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6, and Table S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6, 7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7, 8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6, and Table S2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10, 11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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