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Safety and Efficacy of Non-Vitamin K Oral Anticoagulant for Atrial Fibrillation Patients Following Percutaneous Coronary Intervention: A Bivariate Analysis of the PIONEER AF-PCI and RE-DUAL PCI Trial

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ABSTRACT

Background: The tradeoff in safety vs. efficacy in substituting a non-vitamin K antagonist oral anticoagulant (NOAC) for a vitamin K antagonist (VKA) in the stented atrial fibrillation (AF) patient has not been quantitatively evaluated. ***Methods:*** Based upon summary data from the PIONEER AF-PCI and RE-DUAL PCI trials, 4 antithrombotic regimens were compared with VKA-based triple therapy: (1) rivaroxaban (riva) 15 mg daily + $P2Y_{12}$ inhibitor; (2) riva 2.5 mg twice daily + $P2Y_{12}$ inhibitor + aspirin; (3) dabigatran (dabi) 110 mg twice daily + $P2Y_{12}$ inhibitor; and (4) dabi 150 mg twice daily + $P2Y_{12}$ inhibitor. A bivariate model with a non-inferiority margin of 1.38 was used to simultaneously assess safety and efficacy. The safety endpoint was major or clinically relevant nonmajor bleeding by International Society on Thrombosis and Haemostasis definitions. The efficacy endpoint was a thromboembolic event (myocardial infarction, stroke, or systemic embolism), death, or urgent revascularization. The bivariate outcome, a measure of risk difference in the net clinical outcome, was compared between antithrombotic regimens. ***Results:*** All 4 NOAC regimens were superior in bleeding and non-inferior in efficacy compared with triple therapy with VKA. Riva 15 mg daily and 2.5 mg twice daily were associated with bivariate combined risk reductions of 5.6% (2.3%–8.8%) and 5.5% (2.1%–8.7%) respectively, and dabi 110 mg twice daily and 150 mg twice daily reduced the bivariate risk by 3.8% (0.5%–7.0%) and 6.3% (2.4%–9.8%) respectively. ***Conclusions:*** A bivariate analysis that simultaneously characterizes both risk and benefit demonstrates that rivaroxaban- and dabigatran-based regimens were both favorable over VKA plus dual antiplatelet therapy among patients with AF undergoing PCI.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01830543 (PIONEER AF-PCI); NCT02164864 (RE-DUAL PCI)

Keywords: thromboembolism; myocardial infarction; stroke; revascularization; mortality; bleeding; anticoagulant

Abbreviations:

AF, atrial fibrillation

ISTH, International Society on Thrombosis and Haemostasis

NCB, net clinical benefit

NOAC, non-vitamin K antagonist oral anticoagulant

PCI, percutaneous coronary intervention

TIMI, Thrombolysis in Myocardial Infarction

VKA, vitamin K antagonist

INTRODUCTION

Approximately 3 to 10% of patients scheduled for percutaneous coronary intervention (PCI) with stent implantation have atrial fibrillation (AF) and both anticoagulant and antiplatelet therapy are indicated to prevent thromboembolic or coronary events.[1, 2] Current practice guidelines recommend anticoagulation with a vitamin K antagonist (VKA) plus dual antiplatelet therapy with a $P2Y_{12}$ inhibitor and aspirin as the standard-of-care in this setting.[3-7] However, VKA-based triple therapy has been associated with a greater risk of major hemorrhage,[8, 9] and this risk of bleeding has prompted efforts to develop new antithrombotic strategies. Until recently, two randomized controlled trials (PIONEER AF-PCI[10] and RE-DUAL PCI[11]) compared the safety and efficacy of non-vitamin K antagonist oral anticoagulant (NOAC) to triple therapy and demonstrated significant bleeding reduction with comparable ischemic outcomes. However, the simultaneous tradeoff between bleeding and ischemic outcomes has not been quantitatively evaluated.

The present study aims to compare the risk-benefit profile of NOAC-based antithrombotic regimens versus VKA-based triple therapy based upon the results of PIONEER AF-PCI trial and RE-DUAL PCI trial. We applied a previously developed bivariate analysis approach[12] to assess the net clinical benefit of therapy that simultaneously weighs thromboembolism, death, and urgent revascularization against bleeding risks.[13]

METHODS

Data Extraction and Study Endpoints

Two randomized controlled trials that compared NOAC-based anticoagulation with VKA in AF patients undergoing coronary stenting were included: PIONEER AF-PCI

(ClinicalTrials.gov: NCT01830543) and RE-DUAL PCI (ClinicalTrials.gov: NCT02164864).[10, 11] In the PIONEER AF-PCI trial, the primary safety endpoint was the occurrence of clinically significant bleeding (a composite of major bleeding, minor bleeding, or bleeding requiring medical attention according to the Thrombolysis in Myocardial Infarction [TIMI] criteria) and the secondary efficacy endpoint was the occurrence of a major adverse cardiovascular event (a composite of death from cardiovascular causes, myocardial infarction, or stroke). In the RE-DUAL PCI trial, the primary safety endpoint was major or clinically relevant nonmajor bleeding event as defined by International Society on Thrombosis and Haemostasis (ISTH) and the secondary efficacy endpoint was a composite of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization. For the purpose of homogeneity in study endpoints, the present study selected ISTH major or clinically relevant nonmajor bleeding as the safety endpoint as used in the RE-DUAL PCI trial, and the composite of thromboembolic event, death, or urgent revascularization as the efficacy endpoint, again as used in the RE-DUAL PCI trial. The frequencies of safety and efficacy events were extracted from secondary analysis of the PIONEER AF-PCI trial and published results of the RE-DUAL trial.[10, 11]

Study Interventions

In the PIONEER AF-PCI trial, 2124 patients were randomly assigned to: 1) rivaroxaban 15 mg once daily + $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel for 12 months); 2) rivaroxaban 2.5 mg twice daily + $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel for 1, 6, or 12 months) + aspirin; and 3) dose-adjusted VKA + $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel for 1, 6, or 12 months) + aspirin. In the RE-DUAL PCI trial, 2725 patients were

randomized to (1) dabigatran 110 mg twice daily + $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor for 12 months); (2) dabigatran 150 mg twice daily + $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor for 12 months); and 3) dose-adjusted VKA + $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor for 12 months) + aspirin (for 1 to 3 months). To compare the safety and efficacy of NOAC-based regimens across the studies, VKA-based triple therapy (VKA plus background dual antiplatelet therapy) was selected as the control group. Similarly, the treatment effect of rivaroxaban-based regimen and dabigatran-based regimen were compared with VKA-based triple therapy. An additional comparison was made between reduced-dose NOAC-based regimen (combination of rivaroxaban 15 mg once daily regimen and dabigatran 110 mg twice daily regimen) and VKA-based triple therapy.

Statistical Analysis

The non-inferiority hypothesis for the efficacy was tested in the PIONEER AF-PCI trial to compare the effect of rivaroxaban dosing strategies with VKA on the composite of thromboembolic events, death, or urgent revascularization (Table 1). The upper boundaries of 95% confidence interval of relative risk for rivaroxaban dosing strategies were less than 1.38 (the non-inferiority margin used in the RE-DUAL PCI trial). Again, to maintain consistency in the bleeding endpoint, the same bleeding definition used in RE-DUAL PCI trial (ISTH major or clinically relevant non-major bleeding) was applied to both studies.

Detailed methodology of the bivariate analysis has been described previously by Kittelson *et al*.[12, 14] In brief, risk differences in safety (RD_S) and efficacy (RD_E) were calculated by subtracting the event rate of the control group from the event rate of the treatment groups. A structured two-dimensional plane was thus defined by RD_S and RD_E, with the lower left quadrant

representing reduction in both safety endpoint (major or clinically relevant nonmajor bleeding) and efficacy endpoint (thromboembolic event, death, or urgent revascularization). The 95% Wald confidence intervals of RD_S and RD_E were reported in Table 2 and summarized as a rectangle on the plane in Figure 1.

Clinically important risk difference was set at 15% to approximate the maximum effect size among the four NOAC-based regimens (Table 2). The non-inferiority margin was set at 1.38 in accordance with the methods recommended by the Food and Drug Administration for the evaluation of NOAC in stroke prevention.[15] Consequently, in the present analysis, the acceptable threshold for excessive risk difference (NI_S and NI_E) was set at 5.7% (i.e., the rate of safety or efficacy outcome in the treatment group cannot exceed that in the control group by more than 5.7% when the maximum effect size is reached). Derivation of the NCB curve is provided in the Supplementary Material.[12, 14]

The NCB curve divided the risk-benefit plane into two regions: lack-of-benefit region vs. benefit region (Figure 1). The lack-of-benefit region was defined as the partition above the curve. The risk-benefit profile was deemed favorable against the control group if the 95% CI rectangle did not contain the lack-of-benefit region. Furthermore, bivariate outcomes were quantitatively assessed by the minimum distance from the NCB curve to three reference points: 1) center of the rectangle, representing the point estimate of the bivariate outcome; 2) southwest corner of the rectangle, representing the lower boundary of the bivariate outcome; and 3) northeast corner of the rectangle, representing the upper boundary of the bivariate outcome. Accordingly, the collective treatment effect on safety and efficacy was presented as a point estimate along with a range of of bivariate risk difference. Although their technical statistical properties are different, these metrics are analogous to reporting the point estimate with 95% confidence interval; that is,

positive values indicate increased risk and negative values indicate decreased risk. Finally, a sensitivity analysis was performed to test a spectrum of non-inferiority margins, ranging from a more stringent margin of 1.14 (used in the ENCHANTED trial for evaluating the impact of thrombolysis on death or disability[16]) to a less stringent margin of 1.35.

The work was supported by research grants from Janssen Scientific Affairs and Bayer, the sponsors of the study. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

RESULTS

Summary of Trial Results

Non-inferiority in efficacy and superiority in bleeding were first assessed separately (Table 1 and Table 2). The rivaroxaban-based regimens and the dabigatran 150 mg twice daily regimen were non-inferior to VKA triple therapy with respect to the RE-DUAL efficacy endpoint (Table 1). The superiority of rivaroxaban-based or dabigatran-based therapy over VKA with respect to bleeding has been demonstrated previously (Table 2).[10, 11]

Qualitative Assessment of the Bivariate Outcome

While the above analyses evaluate safety and efficacy separately, a bivariate analysis was performed to assess safety and efficacy simultaneously. Results of four antithrombotic regimens were expressed as a rectangle defined by the 95% confidence interval of risk difference in safety and efficacy on the risk-benefit plane (Figure 2). The 0.00% vertical line and 0.00% horizontal line represented the superiority boundary for safety and efficacy, respectively. The rectangles for all four NOAC-based regimens were on the left to the vertical line, indicating that these

regimens achieved superiority in bleeding compared with VKA. The four rectangles crossed the horizontal line, indicating that superiority in efficacy was not achieved. Similarly, rivaroxaban-based regimen, dabigatran-based regimen, and reduced dosing strategy were superior in safety when compared with VKA-based triple therapy (Figure 3 and Figure 4).

The NCB curve was derived using a non-inferiority margin of 1.38 (corresponding to an acceptable threshold for excessive risk difference of 5.7%) and divided the plane into two regions. The rectangles of the four NOAC-based regimens did not contain the partition above the curve (lack-of-benefit region), indicating that these regimens were favorable over VKA (Figure 2). Similar risk-benefit profiles were observed in rivaroxaban- or dabigatran-based regimen as well as reduced-dose regimen (Figure 3 and Figure 4). Analysis of the pooled data suggested that NOAC-based regimen was superior in safety and non-inferior in efficacy (Figure 5).

Quantitative Assessment of the Bivariate Outcome

Quantitatively, bivariate outcomes were assessed by the minimum distance from the NCB curve to the center (point estimate) and opposing corners of the rectangle (upper and lower boundaries). The effect size in terms of bivariate outcome was then summarized in the forest plot (Figure 6). Rivaroxaban 15 mg once daily and 2.5 mg twice daily were associated with a bivariate risk reduction of 5.6% (2.3%–8.8%) and 5.5% (2.1%–8.8%) respectively, and dabigatran 110 mg twice daily and 150 mg twice daily reduced the risk by 3.8% (0.5%–7.0%) and 6.3% (2.4%–9.8%) respectively. Both the combined 2.5 mg and 15 mg rivaroxaban-based and the combined 110 mg and 150 mg dabigatran-based regimens were favorable over VKA, with a bivariate risk reduction of 5.6% (3.2%–7.8%) and 4.9% (2.5%–7.3%), respectively. The

reduced-dose regimens of 15 mg Rivaroxaban and 110 mg Dabigatran and all 4 NOAC-based regimens combined demonstrated comparable bivariate risk reductions over VKA of 4.5% (2.2%–6.8%) and 5.5% (3.4%–7.5%), respectively (Figure 6).

Sensitivity Analysis of the Non-Inferiority Margin

In the sensitivity analysis, a spectrum of non-inferiority margin (i.e., 1.14, 1.20, 1.25, 1.30, and 1.35) was used to test the robustness of treatment effects of NOAC-based regimens (Figure S1 to Figure S5). Rivaroxaban 15 mg daily and rivaroxaban 2.5 mg twice daily maintain an advantage over VKA when the non-inferiority margin is set at 1.25. Dabigatran 110 mg twice daily and dabigatran 150 mg twice daily maintained an advantage over VKA when the margin was set at 1.35 and 1.20, respectively. When all 4 regimens were taken together, the NOAC-based regimens showed a favorable profile at the non-inferiority bound of 1.14. In other words, if a 2.1% threshold of risk difference is clinically acceptable, NOAC would be preferred over VKA in the bivariate model that weighs thromboembolism, death, and urgent revascularization against bleeding risks.

DISCUSSION

Clinicians must consider bleeding and ischemic outcomes simultaneously when making a decision regarding antithrombotic management in AF patients undergoing stent placement. The superiority of rivaroxaban-based or dabigatran-based therapy over VKA based strategies with respect to bleeding has been demonstrated previously.[10, 11] If a regimen is safer, then with respect to efficacy, non-inferiority instead of superiority is a reasonable goal. The advantage of a bivariate analysis is that it potentially allows one to evaluate if whether a regimen is superior in

safety and simultaneously non-inferior in efficacy yielding an overall net clinical benefit.[13, 14] The efficacy endpoint in RE-DUAL was used for the non-inferiority analysis as it was broader and yielded more events than the narrower endpoint used in the PIONEER study (i.e., myocardial infarction, stroke, and cardiovascular death). When weighed against the same scale of bleeding risk, both rivaroxaban-based and dabigatran-based regimens were favorable over a VKA-based regimen. Using the efficacy endpoint from the RE-DUAL trial, the rivaroxaban regimens also achieve non-inferiority when analyzed as the sole endpoint independent of safety using traditional statistical methods. Results from the PIONEER AF-PCI trial and RE-DUAL PCI trial both demonstrate that NOAC-based anticoagulation plus background antiplatelet therapy can be a desirable alternative to VKA-based triple therapy.

One simple approach to assess net clinical benefit (NCB) is to subtract the event rate of safety outcome from the rate of efficacy outcome. The linear function of this conventional approaches treats the tradeoff as symmetrical and unlimited. Thus, a substantial increase in bleeding would be inappropriately deemed acceptable given a corresponding reduction in thromboembolism. A more sophisticated approach, however, is to calculate NCB in a bivariate model which is a novel statistical method devised to characterize the non-linear nature of tradeoffs in a two-dimensional outcome.[13, 14] The bivariate model is a weighted aggregate of risk difference determined by the relative impact of treatment on safety versus efficacy.[17] The output includes a qualitative display on the safety-efficacy plane and a quantitative comparison of the risk difference as the bivariate outcome. The bivariate approach has been utilized to compare the risk-benefit profile of anticoagulation and antihypertensive strategies and to devise the stopping criteria for the interim analysis.[14, 18-20] Furthermore, in the Kids-DOTT trial (ClinicalTrials.gov Identifier: NCT00687882), the bivariate endpoint was utilized as the primary outcome measure

to gauge the tradeoff between the risks of recurrent venous thromboembolism and bleeding associated with shortened-duration vs. conventional-duration anticoagulation. This approach could be a valuable addition to the conventional tools to evaluate the risk-benefit balance of treatment.

As in the interpretation of unidimensional outcome, inference derived from the bivariate model may be affected by the choice of non-inferiority margin. There are no historical data to guide the determination of non-inferiority margin for the endpoint of bleeding and thromboembolic events in the population of AF with stent placement. This study adopts the non-inferiority margin of 1.38, as recommended by the regulatory agency for NOAC trials in the assessment of stroke prevention,[15] which has been considered as the most clinically relevant available reference.[21] Thus far there is no consensus on the best practice for simultaneously analyzing multiple disparate endpoints to appraise the net clinical benefit of antithrombotic regimens.[22, 23] Nevertheless, results from the present analysis inform future trials regarding the extent of excessive thromboembolic risks that may be considered acceptable provided the substantial benefits in bleeding reduction with NOAC-based regimens.

LIMITATIONS

The present analysis evaluates the tradeoff between the primary safety endpoint (clinical significant bleeding) and the primary efficacy endpoint (thromboembolism, death, and urgent revascularization) which presumably have comparable clinical impact. Patient values and preferences were not considered when assessing the risk-benefit of antithrombotic regimens. The tradeoff between the components of the safety and efficacy composite endpoints (for instance, TIMI major bleeding versus myocardial infarction) was not assessed although it may

also be of clinical interest. It is also noteworthy that the present analysis did not account for multiple or recurrent events. In addition, study-level data instead of individual-level data were analyzed in the bivariate model without accounting for potential between-study variance in treatment effects. Furthermore, both included trials were powered for the bleeding endpoint rather than the quantified bivariate outcome in this analysis. Finally, only 12% and 9% of the PIONEER and RE-DUAL study participants presented with STEMI and had primary PCI as the index event. More data are required to confirm the net clinical benefit of NOAC-based regimen in this subset.

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CONCLUSIONS

In the management of AF patients who received coronary stenting, both rivaroxaban-based and dabigatran-based regimens were favorable over VKA plus dual antiplatelet therapy in a bivariate analysis that weighs thromboembolism, death, and urgent revascularization against bleeding risks.

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Legends of Figures

Figure 1. Interpretation of the bivariate analysis. Qualitatively, a favorable net clinical benefit is established if the rectangle defined by 95% confidence interval of risk difference does not include the lack-of-benefit region. Quantitatively, the bivariate outcome is measured by the minimum distance from the curve to the center (point estimate), southwest corner (lower bound), and northeast corner (upper bound) of the rectangle.

Figure 2. Bivariate analysis of four antithrombotic regimens.

Figure 3. Bivariate analysis of rivaroxaban-based and dabigatran-based regimens

Figure 4. Bivariate analysis of reduced-dose (rivaroxaban 15 mg daily or dabigatran 110 mg twice daily) regimen

Figure 5. Bivariate analysis of all NOAC-based regimens

Figure 6. Comparison of bivariate outcome among antithrombotic regimens

Table 1. The composite efficacy endpoint of thromboembolic event, death, and urgent revascularization in the PIONEER AF-PCI and RE-DUAL PCI trial *

Antithrombotic Regimen	Treatment n/N (%)	VKA n/N (%)	Relative Risk (95% CI)	P-value for Non-Inferiorit
PIONEER AF-PCI				
Rivaroxaban 15 mg once daily + $P2Y_{12}$ inhibitor	63/694 (9.08)	64/695 (9.21)	0.99 (0.71 to	0.0234
Rivaroxaban 2.5 mg twice daily + $P2Y_{12}$ inhibitor +	64/704 (9.09)	64/695 (9.21)	0.99 (0.71 to	0.0234
Rivaroxaban (combined)	127/1398 (9.08)	64/695 (9.21)	0.99 (0.74 to	0.0108
RE-DUAL PCI				
Dabigatran 110 mg twice daily + $P2Y_{12}$ inhibitor	149/981 (15.19)	131/981	1.14 (0.92 to	0.0407
Dabigatran 150 mg twice daily + $P2Y_{12}$ inhibitor	90/763 (11.80)	98/764 (12.83)	0.92 (0.70 to	0.0015
Dabigatran (combined)	239/1744	131/981	1.03 (0.84 to	0.0017

* P-value for non-inferiority was calculated at the one-sided alpha level of 0.025 with upper confidence limit of 1.38.

Table 2. Safety and efficacy of antithrombotic regimens in the PIONEER AF-PCI and RE-DUAL PCI trial *

Antithrombotic Regimen	Treatment n/N (%)	Control n/N (%)	Risk Difference % (95% CI)	P-value for Superiority
Safety endpoint: ISTH major or clinically relevant nonmajor bleeding				
PIONEER AF-PCI				
Rivaroxaban 15 mg once daily + $P2Y_{12}$ inhibitor	110/696	170/697	-8.59 (-12.77 to -	<0.0001
Rivaroxaban 2.5 mg twice daily + $P2Y_{12}$ inhibitor +	119/706	170/697	-7.53 (-11.75 to -	0.0005
Rivaroxaban-based regimen (Regimen 1 + 2)	229/1402	170/697	-8.06 (-11.79 to -	<0.0001
RE-DUAL PCI				
Dabigatran 110 mg twice daily + $P2Y_{12}$ inhibitor	151/981	264/981	-11.52 (-15.10 to -	<0.0001
Dabigatran 150 mg twice daily + $P2Y_{12}$ inhibitor	154/763	196/764	-5.47 (-9.68 to -	0.0110
Dabigatran-based regimen (Regimen 3 + 4)	305/1744	264/981	-9.42 (-12.72 to -	<0.0001
Reduced-dose NOAC-based regimen (Regimen 1 + 3)	261/1677	434/1678	-10.30 (-13.02 to -	<0.0001
NOAC-based regimen (Regimen 1 + 2 + 3 + 4)	534/3146	434/1678	-8.89 (-11.36 to -	<0.0001
Efficacy endpoint: thromboembolic event, death, or urgent revascularization				
PIONEER AF-PCI				
Rivaroxaban 15 mg once daily + $P2Y_{12}$ inhibitor	63/694 (9.08)	64/695 (9.21)	-0.13 (-3.16 to	0.93
Rivaroxaban 2.5 mg twice daily + $P2Y_{12}$ inhibitor +	64/704 (9.09)	64/695 (9.21)	-0.12 (-3.14 to	0.94
Rivaroxaban-based regimen (Regimen 1 + 2)	127/1398	64/695 (9.21)	-0.12 (-2.75 to	0.93
RE-DUAL PCI				
Dabigatran 110 mg twice daily + $P2Y_{12}$ inhibitor	149/981	131/981	1.83 (-1.26 to	0.25
Dabigatran 150 mg twice daily + $P2Y_{12}$ inhibitor	90/763	98/764	-1.03 (-4.33 to	0.54
Dabigatran-based regimen (Regimen 3 + 4)	239/1744	131/981	0.35 (-2.32 to	0.80
Reduced-dose NOAC-based regimen (Regimen 1 + 3)	212/1675	195/1676	1.02 (-1.19 to	0.37
NOAC-based regimen (Regimen 1 + 2 + 3 + 4)	366/3142	195/1676	0.01 (-1.89 to	0.99

* All 95% confidence intervals of the risk differences exclude the non-inferiority margin of +5.7%

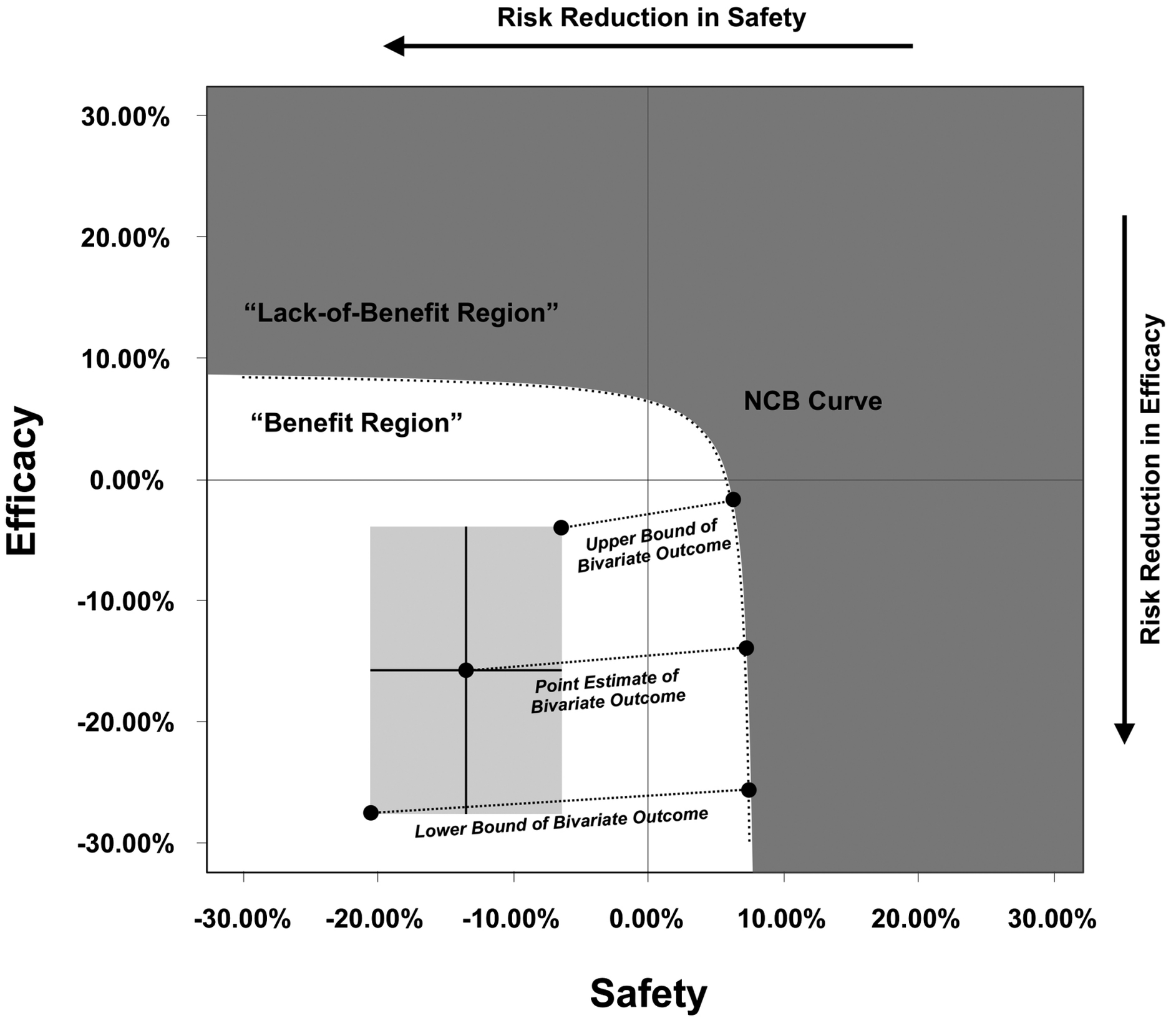
Risk Reduction in Safety
30.00%
20.00%
10.00%
0.00%
-10.00%
-20.00%
-30.00%
"Lack-of-Benefit Region"
"Benefit Region"
NCB Curve
Upper Bound of Bivariate Outcome
Point Estimate of Bivariate Outcome
Lower Bound of Bivariate Outcome
Efficacy
Risk Reduction in Efficacy
-30.00%
-20.00%
-10.00%
0.00%
10.00%
20.00%
30.00%
Safety

Figure 1

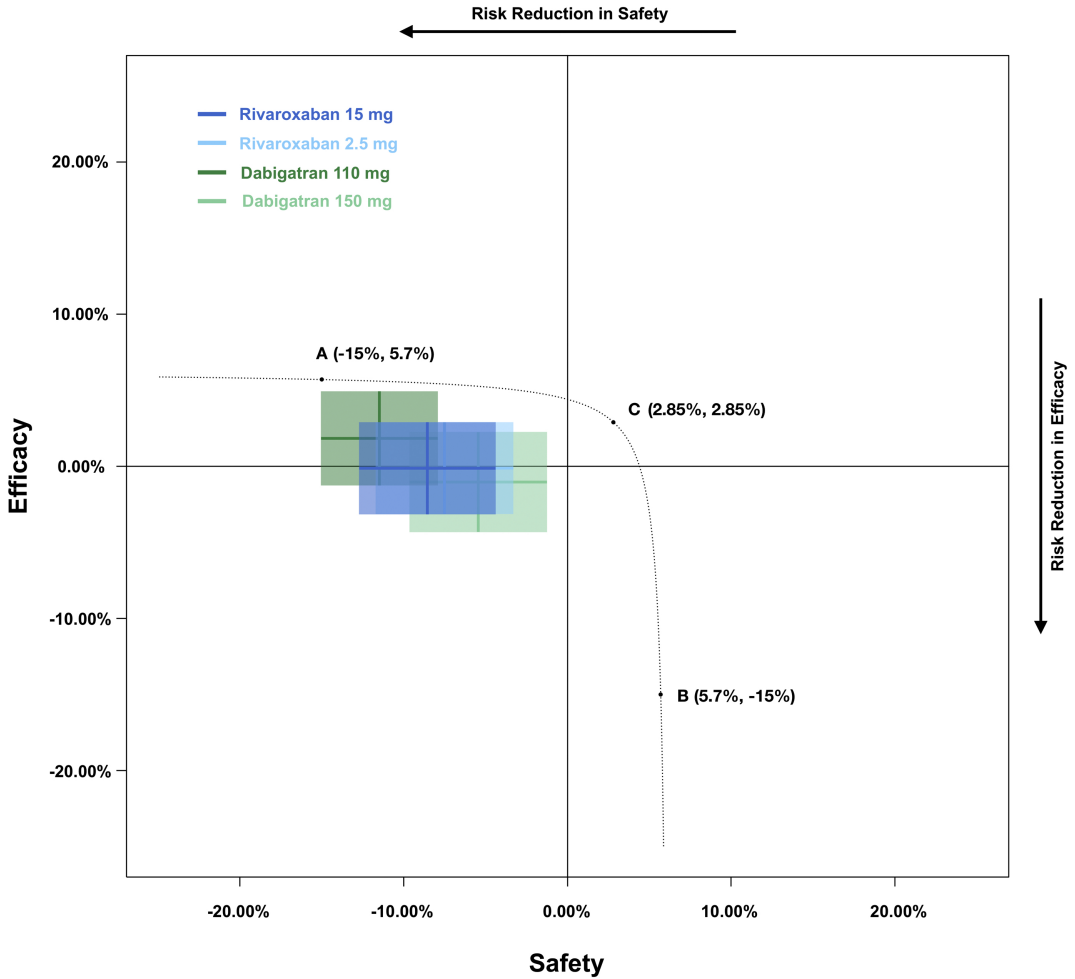
Risk Reduction in Safety
Rivaroxaban 15 mg
Rivaroxaban 2.5 mg
Dabigatran 110 mg
Dabigatran 150 mg
20.00%
10.00%
0.00%
-10.00%
-20.00%
Efficacy
A (-15%, 5.7%)
C (2.85%, 2.85%)
B (5.7%, -15%)
-20.00%
-10.00%
0.00%
10.00%
20.00%
Safety
Risk Reduction in Efficacy

Figure 2

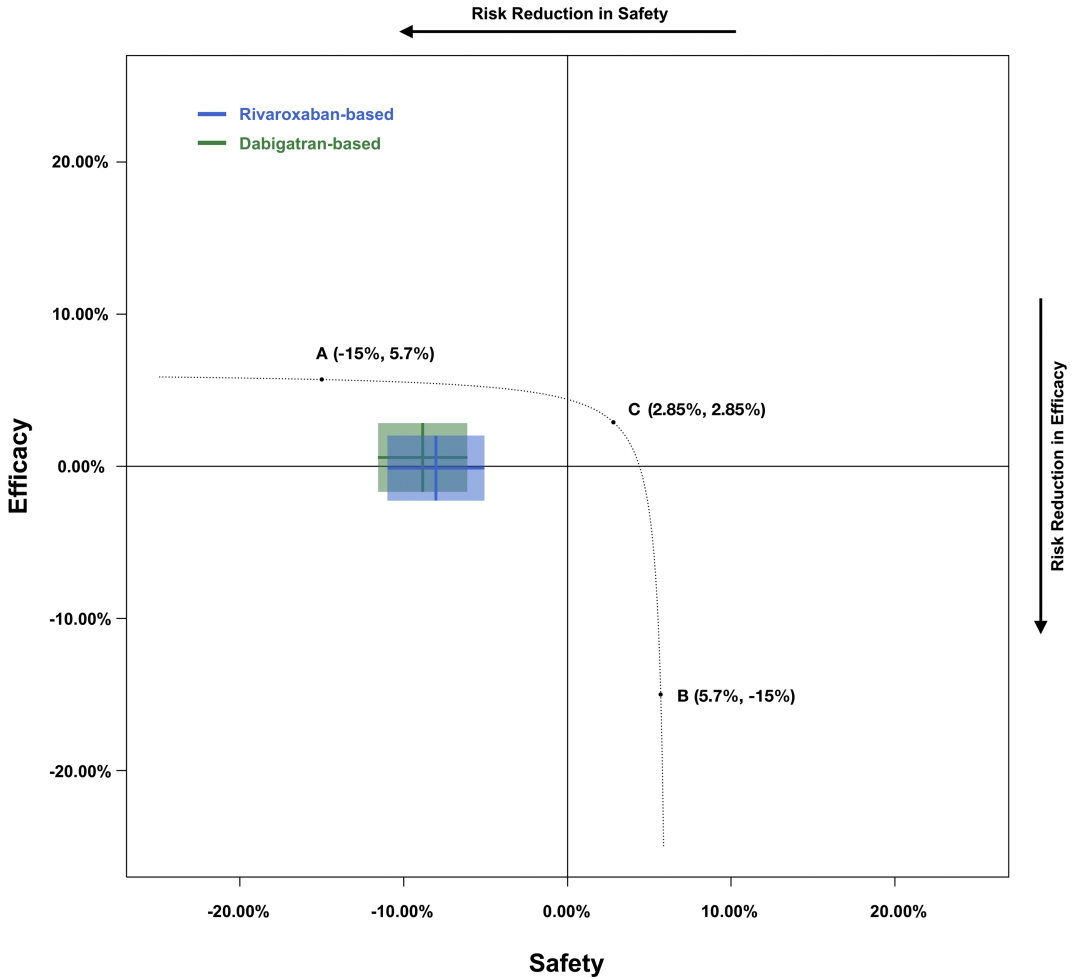
Risk Reduction in Safety
Rivaroxaban-based
Dabigatran-based
20.00%
10.00%
0.00%
-10.00%
-20.00%
Efficacy
A (-15%, 5.7%)
C (2.85%, 2.85%)
B (5.7%, -15%)
-20.00%
-10.00%
0.00%
10.00%
20.00%
Safety
Risk Reduction in Efficacy

Figure 3

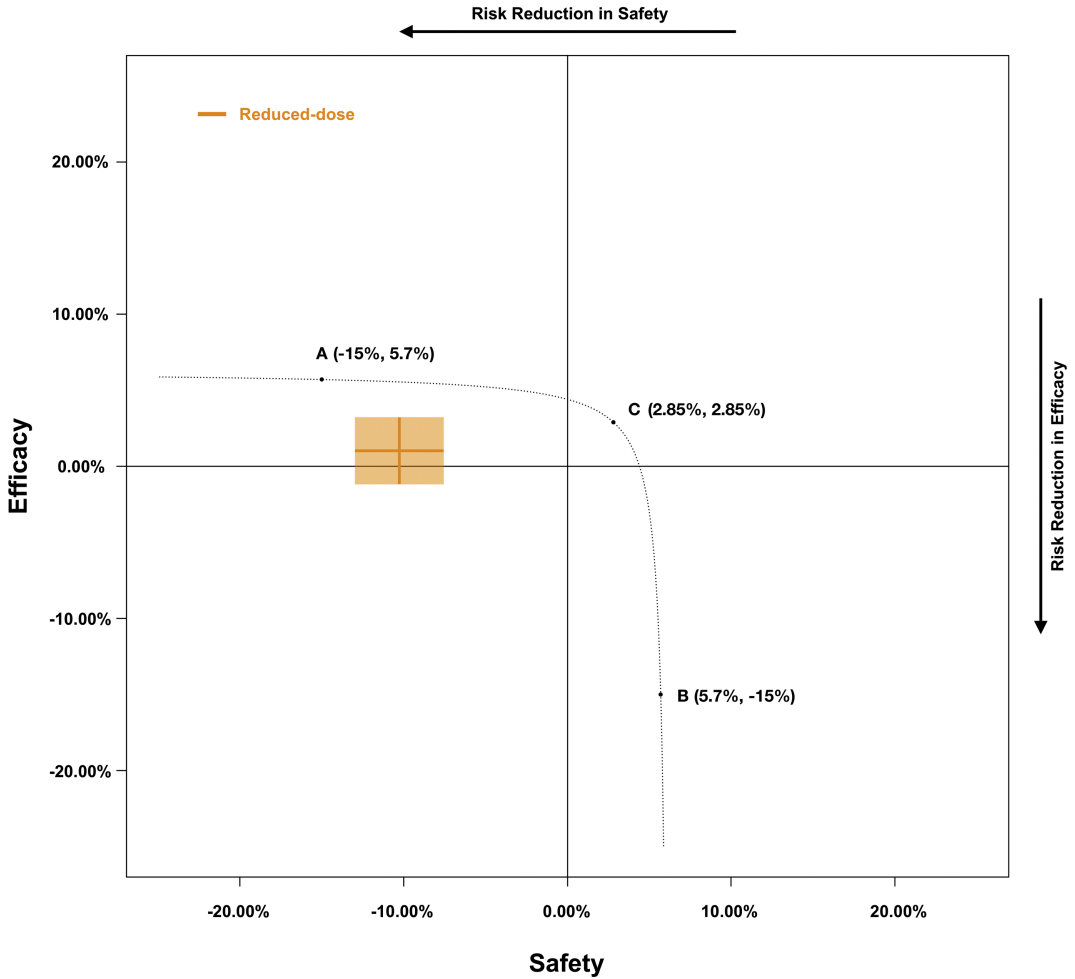
Risk Reduction in Safety
Reduced-dose
20.00%
10.00%
0.00%
-10.00%
-20.00%
Efficacy
A (-15%, 5.7%)
C (2.85%, 2.85%)
B (5.7%, -15%)
-20.00%
-10.00%
0.00%
10.00%
20.00%
Safety
Risk Reduction in Efficacy

Figure 4

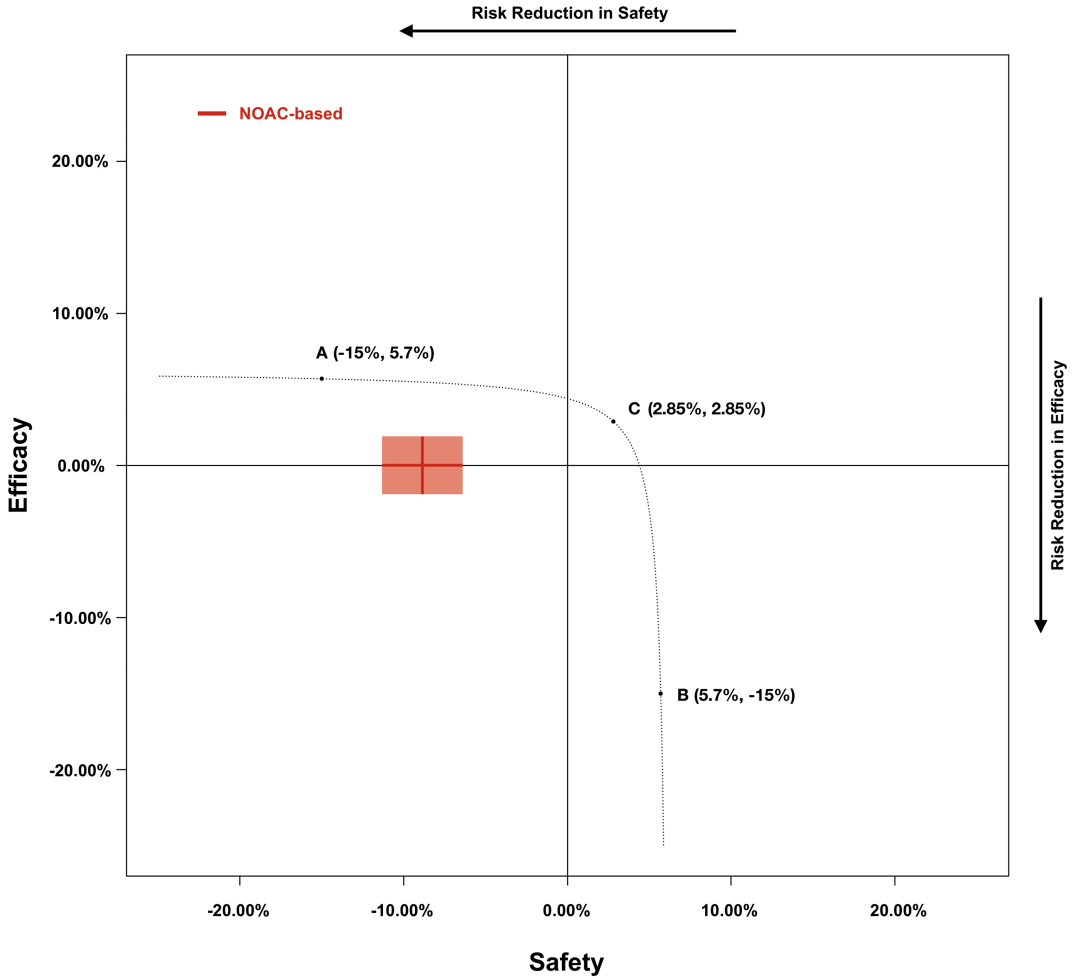
Risk Reduction in Safety
NOAC-based
20.00%
10.00%
0.00%
-10.00%
-20.00%
Efficacy
A (-15%, 5.7%)
C (2.85%, 2.85%)
B (5.7%, -15%)
Risk Reduction in Efficacy
-20.00%
-10.00%
0.00%
10.00%
20.00%
Safety

Figure 5

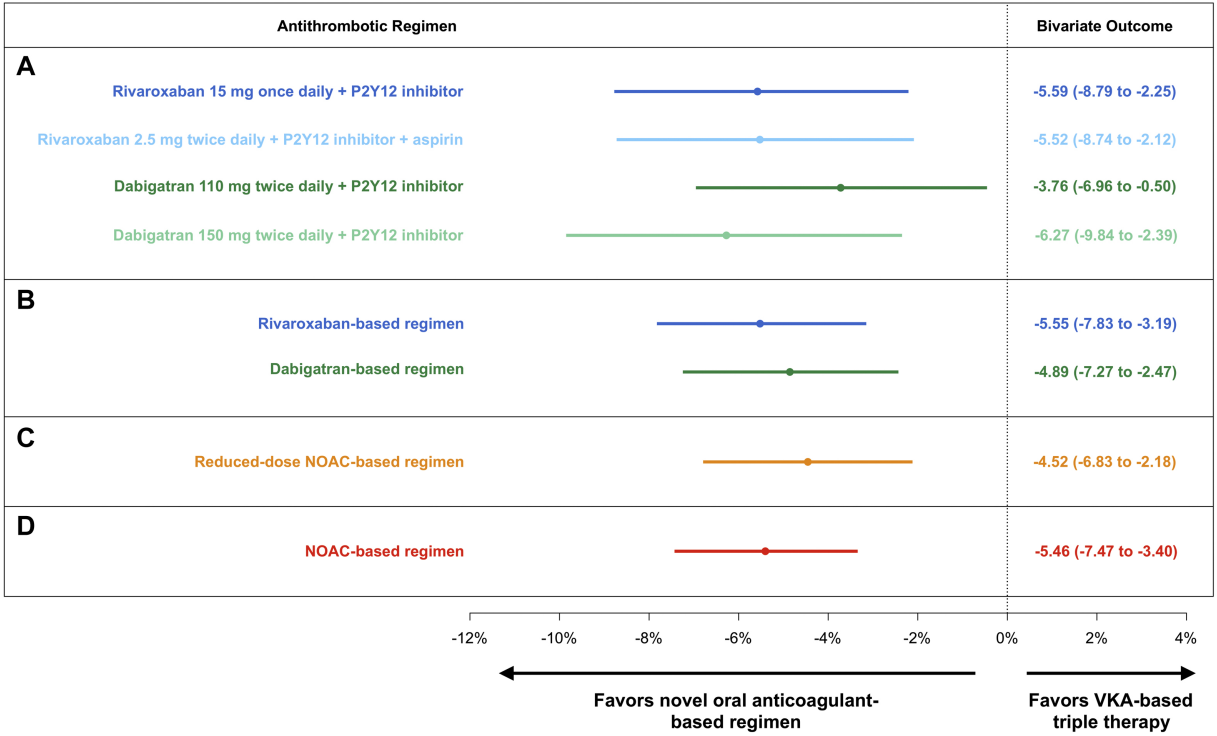
Antithrombotic Regimen
Bivariate Outcome
A
Rivaroxaban 15 mg once daily + P2Y12 inhibitor
-5.59 (-8.79 to -2.25)
Rivaroxaban 2.5 mg twice daily + P2Y12 inhibitor + aspirin
-5.52 (-8.74 to -2.12)
Dabigatran 110 mg twice daily + P2Y12 inhibitor
-3.76 (-6.96 to -0.50)
Dabigatran 150 mg twice daily + P2Y12 inhibitor
-6.27 (-9.84 to -2.39)
B
Rivaroxaban-based regimen
-5.55 (-7.83 to -3.19)
Dabigatran-based regimen
-4.89 (-7.27 to -2.47)
C
Reduced-dose NOAC-based regimen
-4.52 (-6.83 to -2.18)
D
NOAC-based regimen
-5.46 (-7.47 to -3.40)
-12%
-10%
-8%
-6%
-4%
-2%
0%
2%
4%
Favors novel oral anticoagulant-based regimen
Favors VKA-based triple therapy

Figure 6

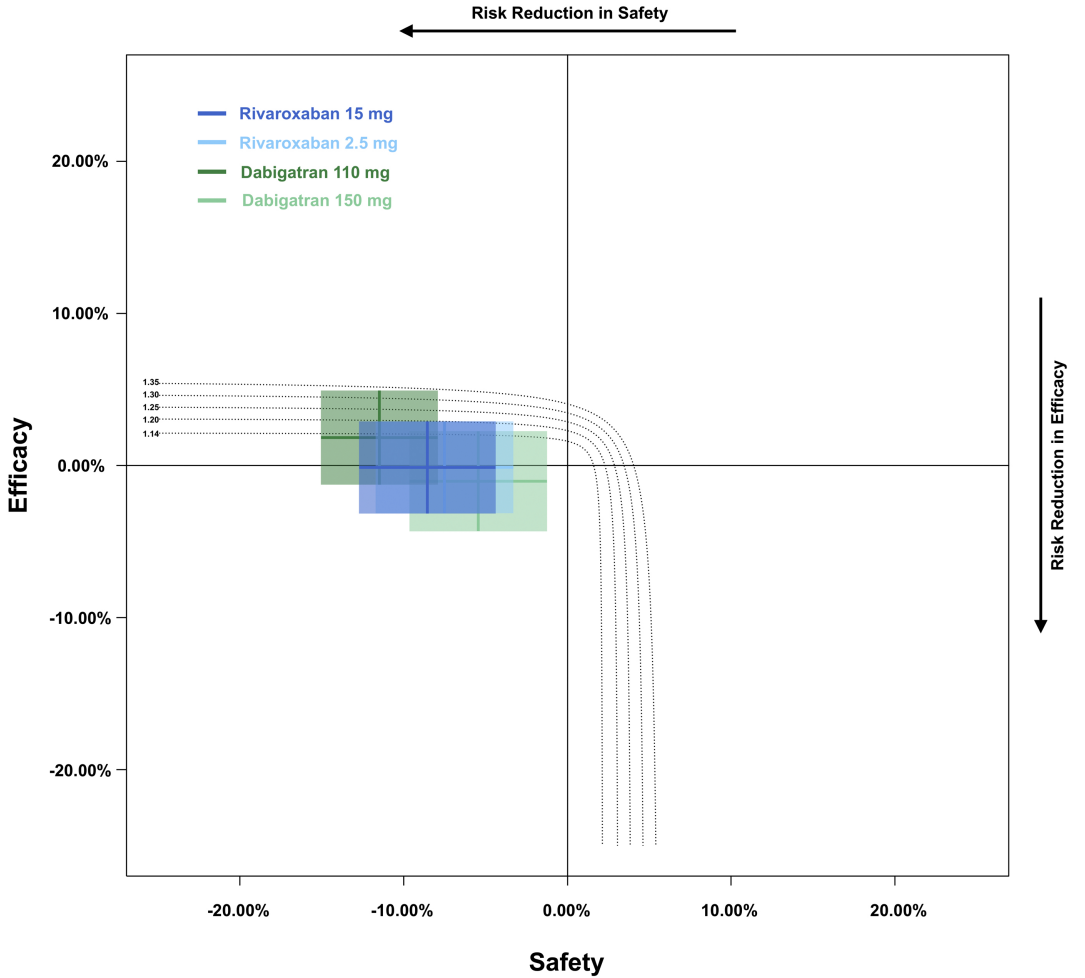
Risk Reduction in Safety
Rivaroxaban 15 mg
Rivaroxaban 2.5 mg
Dabigatran 110 mg
Dabigatran 150 mg
20.00%
10.00%
0.00%
-10.00%
-20.00%
Efficacy
1.35
1.30
1.25
1.20
1.14
-20.00%
-10.00%
0.00%
10.00%
20.00%
Safety
Risk Reduction in Efficacy

Figure 7

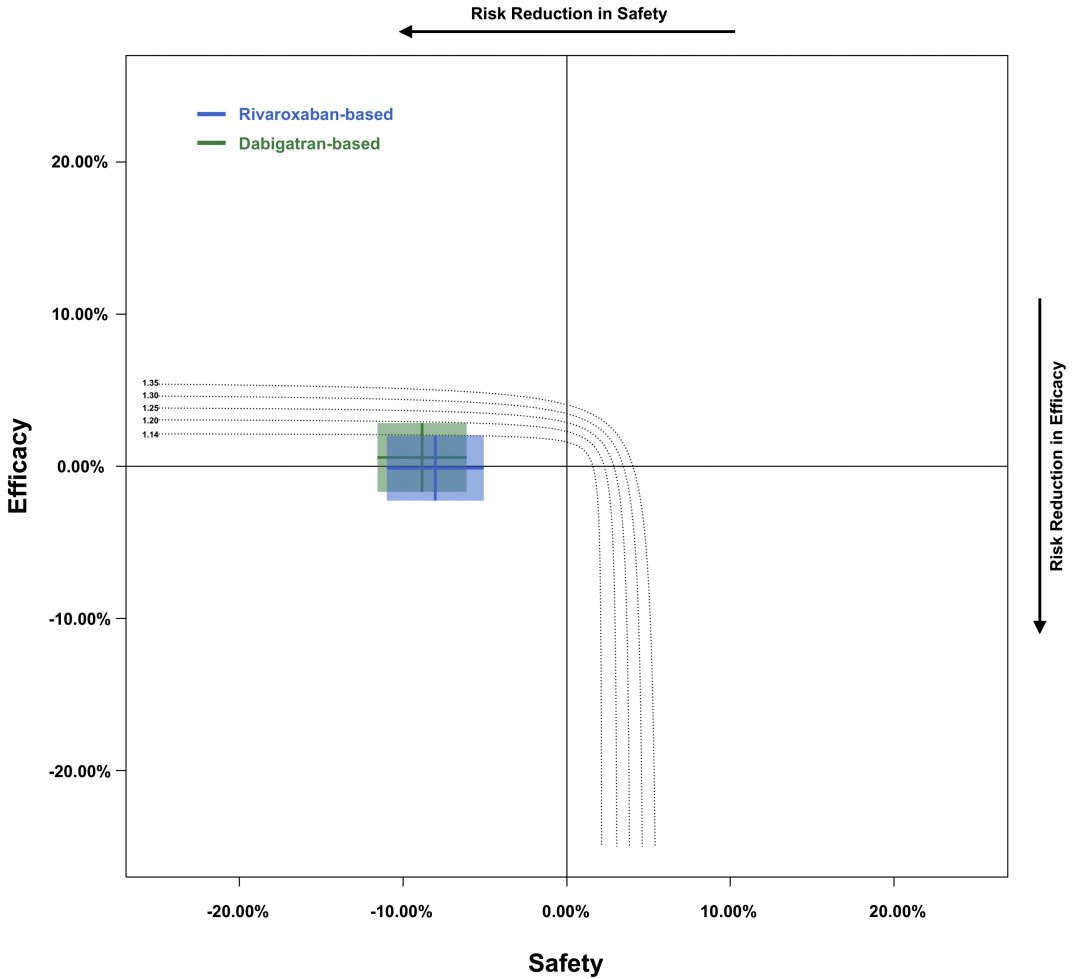
Risk Reduction in Safety
Rivaroxaban-based
Dabigatran-based
20.00%
10.00%
0.00%
-10.00%
-20.00%
Efficacy
1.35
1.30
1.25
1.20
1.14
-20.00%
-10.00%
0.00%
10.00%
20.00%
Safety
Risk Reduction in Efficacy

Figure 8

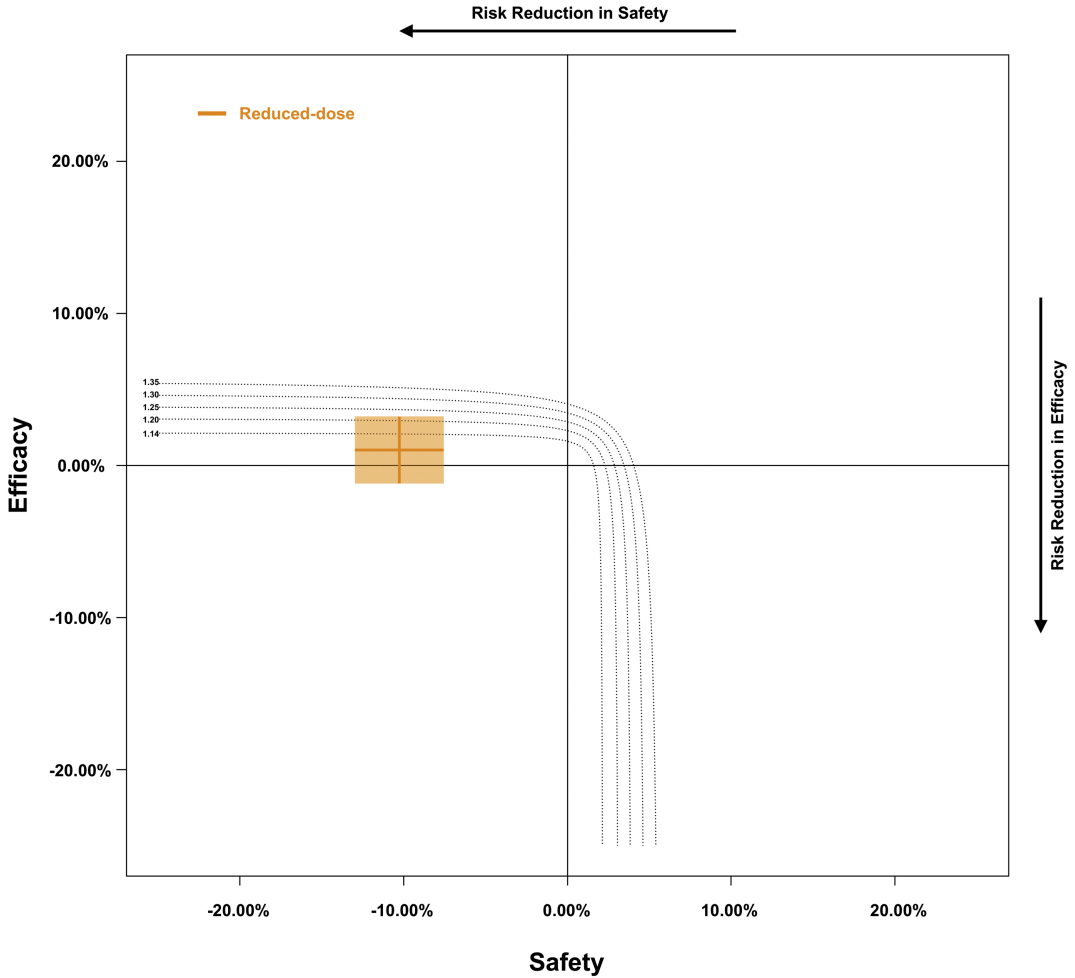
Risk Reduction in Safety
Reduced-dose
20.00%
10.00%
0.00%
-10.00%
-20.00%
Efficacy
1.35
1.30
1.25
1.20
1.14
-20.00%
-10.00%
0.00%
10.00%
20.00%
Safety
Risk Reduction in Efficacy

Figure 9

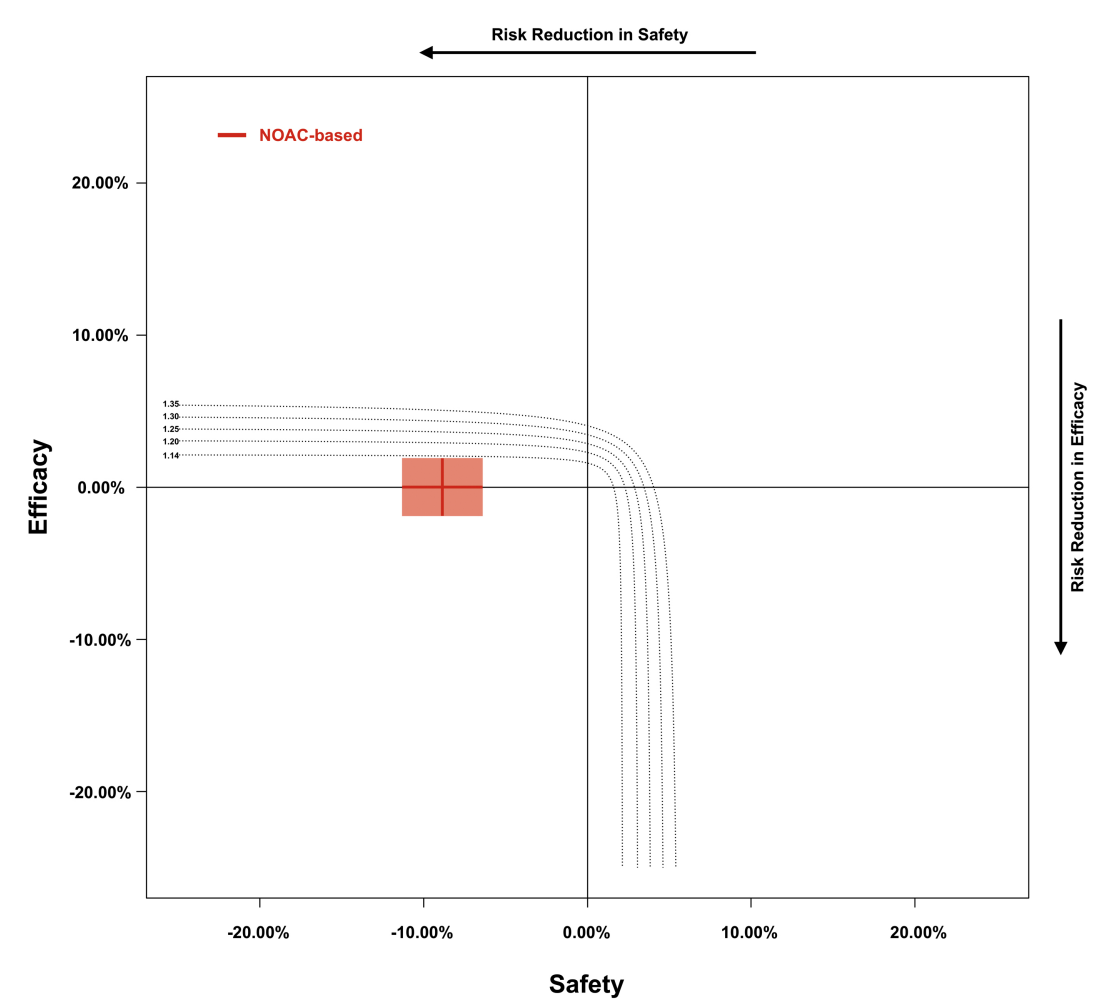
Risk Reduction in Safety
NOAC-based
20.00%
10.00%
0.00%
-10.00%
-20.00%
Efficacy
1.35
1.30
1.25
1.20
1.14
-20.00%
-10.00%
0.00%
10.00%
20.00%
Safety
Risk Reduction in Efficacy

Figure 10

Antithrombotic Regimen	Non-Inferiority Margin				
	1.14	1.20	1.25	1.30	1.35
Rivaroxaban 15 mg once daily + P2Y12 inhibitor			●	●	●
Rivaroxaban 2.5 mg twice daily + P2Y12 inhibitor + aspirin			●	●	●
Dabigatran 110 mg twice daily + P2Y12 inhibitor					●
Dabigatran 150 mg twice daily + P2Y12 inhibitor		●	●	●	●
Rivaroxaban-based regimen		●	●	●	●
Dabigatran-based regimen		●	●	●	●
Reduced-dose NOAC-based regimen			●	●	●
NOAC-based regimen	●	●	●	●	●

● = Favors over VKA-based triple therapy

Figure 11