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Effects of Non–Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: A Systematic Review and Meta-Analysis

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Background—The original non–vitamin K antagonist oral anticoagulant (NOAC) trials in nonvalvular atrial fibrillation (AF) enrolled patients with native valve pathologies. The object of this study was to quantify the benefit–risk profiles of NOACs versus warfarin in AF patients with native valvular heart disease (VHD).

Methods and Results—Trials were identified by exhaustive literature search. Trial data were combined using inverse variance weighting to produce a meta-analytic summary hazard ratio (HR) and 95% confidence interval (CI) of efficacy and safety of NOACs versus warfarin. Our final analysis included 4 randomized controlled trials that enrolled 71 526 participants, including 13 574 with VHD. Pooling results from included trials showed that NOACs versus warfarin reduced stroke or systemic embolism (HR: 0.70; 95% CI, 0.60–0.82) and intracranial hemorrhage (HR: 0.47; 95% CI, 0.24–0.92) in AF patients with VHD. However, risk reduction of major bleeding and intracranial hemorrhage was driven by apixaban, edoxaban, and dabigatran (HR for major bleeding: 0.79 [95% CI, 0.69–0.91]; HR for intracranial hemorrhage: 0.33 [95% CI, 0.25–0.45]) but not rivaroxaban (HR for major bleeding: 1.56 [95% CI, 1.20–2.04]; HR for intracranial hemorrhage: 1.27 [95% CI, 0.77–2.10]).

Conclusions—Among patients with AF and native VHD, NOACs reduce stroke and systemic embolism compared with warfarin. Evidence shows that apixaban, dabigatran, and edoxaban also reduce bleeding in this patient subgroup, whereas major bleeding (but not intracranial hemorrhage or mortality rate) is significantly increased in VHD patients treated with rivaroxaban. NOACs are a reasonable alternative to warfarin in AF patients with VHD. **(*J Am Heart Assoc*. 2017;6:e005835. DOI: 10.1161/JAHA.117.005835.)**

Key Words: anticoagulant • atrial fibrillation • bleeding • stroke • valve

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Patients with atrial fibrillation (AF) have a 4-fold increased risk of ischemic stroke compared with patients with sinus rhythm,[1–3] and the risk of stroke is up to 17-fold higher in AF patients with rheumatic mitral stenosis.[1] Oral anticoagulation with vitamin K antagonists, including warfarin, is indicated for AF patients with mitral stenosis or mechanical heart valve,[4] and these 2 types of valvular heart disease (VHD) were generally excluded from randomized controlled trials (RCTs) that evaluated non–vitamin K antagonist oral anticoagulants (NOACs) versus warfarin in nonvalvular AF patients.[5–8] However, the aforementioned trials actually enrolled patients with other native valve pathologies,[5–8] rendering the term *nonvalvular* AF a misnomer. The term *nonvalvular heart disease*, used in the original NOAC trials, may cause some clinicians to hesitate before prescribing NOACs to AF patients with any form of VHD.

Several post hoc analyses evaluating the effect of NOACs in comparison with warfarin in AF patients with VHD have been published.[9–11] A review of NOACs in AF patients with VHD, based on the aforementioned publications, suggested that little direct evidence exists to support treatment recommendations in clinical practice[12]; however, relevant data[13] from the ENGAGE AF-TIMI 48 (Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial were not included. The objective of this study was to systematically review the totality of the published literature to qualitatively

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Clinical Perspective

What Is New?

- Non–vitamin K antagonist oral anticoagulants, compared with warfarin, reduced stroke or systemic embolism and intracranial hemorrhage in atrial fibrillation patients with or without valvular heart disease.

What Are the Clinical Implications?

- Non–vitamin K antagonist oral anticoagulants are a reasonable alternative to warfarin in atrial fibrillation patients with native valvular heart disease.

and quantitatively evaluate the overall efficacy and safety profiles (ie, stroke or systemic embolism, all-cause mortality, major bleeding, and intracranial hemorrhage) of NOACs, compared with warfarin, in AF patients with and without VHD.

Methods

This study was performed in accordance with the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement.[14] This study was prospectively registered in PROSPERO (CRD42016052243). Regarding the Declaration of Helsinki, because this is a meta-analysis of published articles, it is not necessary to obtain approval from the locally appointed ethics committee or informed consent from patients.

Data Sources and Searches

We searched PubMed (1966 to May 2017), Embase and Medline (1980 to May 2017), the Cochrane Central Register of Controlled Trials (CENTRAL), and presentations at major cardiology conferences within the past year (American Heart Association, American College of Cardiology, European Society of Cardiology) using the terms *novel oral anticoagulants* or *non-vitamin K antagonist oral anticoagulants* or *direct oral anticoagulants* or *dabigatran* or *rivaroxaban* or *apixaban* or *edoxaban* AND *stroke* or *systemic embolism* or *mortality* or *major bleeding* or *intracranial hemorrhage* AND *valvular heart disease* or *mitral regurgitation* or *aortic regurgitation* or *tricuspid regurgitation* or *mitral stenosis* or *aortic stenosis*. There were no language restrictions. We also reviewed the Introduction and Discussion sections of retrieved trials and relevant review articles to identify additional trials.

Study Selection

Criteria for inclusion of a study were as follows: (1) The study design was an RCT; (2) the study included a comparison of a NOAC with warfarin; (3) quantitative estimates of the hazard ratio (HR) and 95% confidence interval (CI) were reported for stroke or systemic embolism with NOACs versus warfarin among AF patients with and without VHD. Studies were excluded if the outcome of stroke or systemic embolism was not either prespecified or adjudicated as a major (primary or secondary) end point. Participants of any age and of either sex were included. One investigator (M.L.) developed selection criteria and conducted literature searches. Another investigator (K.L.P.) assessed these criteria and independently checked the enrolled trials. Discrepancies were resolved by discussion with a third investigator (B.O.) and by referencing the original report.

Data Extraction

All data from eligible studies were extracted by 2 independent investigators according to a standard protocol. Discrepancies were resolved by discussion with a third investigator and by referencing the original report. Recorded data variables were trial name, eligibility criteria, types of VHD, mean age, proportion of women in the study, baseline characteristics, percentage of persistent or permanent AF, baseline $CHADS_2$ scores, history of stroke, history of myocardial infarction, history of heart failure, percentage of prior warfarin use, renal status, and follow-up duration.

Study Quality Assessment

All included studies were derived from RCTs. The risk of bias (eg, selection bias, performance bias, detection bias, attrition bias, and reporting bias) of the original included trials was assessed using the Cochrane risk-of-bias algorithm (http://www.cochrane.org/training/cochranehandbook).

Objectives

The objectives of these analyses were (1) to evaluate differences in baseline characteristics among AF patients with and without VHD; (2) to compare the rates of stroke or systemic embolism, all-cause mortality, major bleeding, and intracranial hemorrhage in AF patients with and without VHD; and (3) to assess the efficacy (stroke or systemic embolism, all-cause mortality) and safety (major bleeding, intracranial hemorrhage) of NOACs in comparison to warfarin in AF patients with and without VHD.

Data Synthesis and Analysis

Data on baseline characteristics are reported as median and interquartile range, mean and standard deviation, or

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number and percentage, as appropriate. To explore differences in baseline characteristics among AF patients with and without VHD, we pooled data across trials. Heterogeneity was considered significant when the P value of χ^2 statistics was <0.05 or the I^2 value exceeded 25%. Because the different types of NOACs may have somewhat different treatment effects, a random-effects model was used. We used HRs with 95% CIs to compare the rates of stroke or systemic embolism, all-cause mortality, major bleeding, and intracranial hemorrhage in AF patients with and without VHD and to assess the efficacy and safety of NOACs versus warfarin in AF patients with and without VHD. In each study, we converted these values to their natural logarithms, and we calculated the standard errors from these logarithmic numbers with their corresponding 95% CIs. For the statistical analysis, we combined log HRs and standard errors using the inverse variance approach. If 2 groups of active treatment existed in a trial, we pooled results only from the higher dose NOAC in a trial (eg, dabigatran 150 mg twice daily in the RE-LY trial [Randomized Evaluation of Long-Term Anticoagulant Therapy] and edoxaban 60 mg once daily in the ENGAGE - AF-TIMI 48 trial). The Cochrane Collaboration's Review Manager software package (RevMan 5.3) was used for this meta-analysis.[15]

Results

Basic Characteristics of AF Patients With and Without VHD

The literature review identified 13 articles for detailed assessment, of which 8 were excluded for not reporting relevant data in patients with VHD and 1 was excluded because it was derived from the same study population as another report.[16] Our final analysis included 4 RCTs that enrolled 71 526 patients (Figure 1).[9–11,13] The baseline characteristics of these RCTs based on VHD status are shown in Table 1. Of these patients, 13 574 (19%) had VHD at baseline. The majority of patients with VHD had mitral regurgitation; a smaller proportion had tricuspid regurgitation, aortic stenosis or regurgitation, mild mitral stenosis, or previous valve surgery. The prevalence of female patients, persistent or permanent AF, history of heart failure, history of myocardial infarction or coronary artery disease, and prior warfarin usage was higher in AF patients with than without VHD (Figure 2). AF patients with VHD, compared with no VHD, also had higher rates of moderate renal disease[9,10] and lower creatinine clearance.[10,11,13] Patients in the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, both with

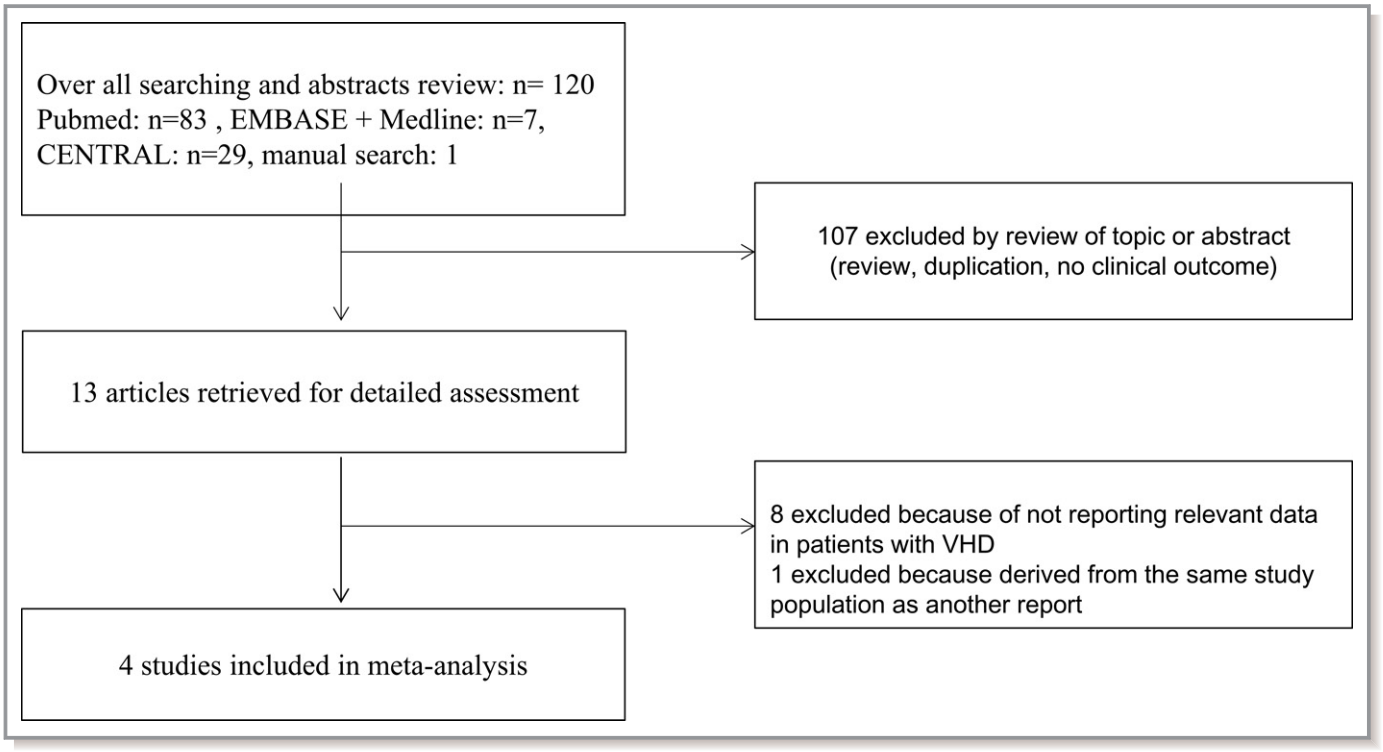

Figure 1. Flow chart of study selection. CENTRAL indicates Cochrane Central Register of Controlled Trials; VHD indicates valvular heart disease.

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Table 1. Baseline Characteristics by VHD Status in Patients With AF From Included Trials

Characteristic	ARISTOTLE[9]		ENGAGE AF[13]		RE-LY[10]		ROCKET AF[11]	
	VHD (n=4808)	No VHD (n=13 389)	VHD (n=2824)	No VHD (n=18 222)	VHD (n=3950)	No VHD (n=14 162)	VHD (n=1992)	No VHD (n=12 179)
Types of VHD, n (% in VHD category)	MR 3526 (73.3) Mild MS 131 (2.7) AR 887 (18.4) AS 387 (8.0) TR 2124 (44.2) Previous valve surgery 251 (5.2)	…	MR 2250 (79.6) AR 369 (13.0) AS 165 (5.8) Valve surgery 325 (11.5)	…	MR 3101 (78.5) Mild MS 193 (4.9) AR 817 (20.7) AS 471 (11.9) TR 1179 (29.8)	…	MR 1756 (89.6) AR 486 (24.8) AS 215 (11.0) Other 11 (0.6)	…
Age, y, median (25th, 75th) or mean (SD)	71 (64, 77)	69 (62, 76)	71.8 (9.4)	70.4 (9.4)	74 (68, 79)	72 (66, 77)	75 (68, 79)	72 (65, 78)
Female, n (%)	1936 (40.3)	4480 (33.5)	1193 (42.2)	6828 (37.5)	1607 (40.7)	4991 (35.2)	785 (39.3)	4280 (39.6)
Persistent or permanent AF	4212 (87.6)	1198 (83.6)	2269 (80.3)	13 416 (73.6)	1341 (34.0)	4448 (31.4)	1653 (83.0)	9832 (80.7)
$CHADS_2$ score mean (SD) or medium (25th, 75th)	2.2 (1.1)	2.1 (1.1)	2.9 (1.0)	2.8 (1.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.5 (1.0)	3.5 (0.9)
History of stroke, embolism or TIA, n (%)	905 (18.8)	2632 (19.7)	668 (23.7)	5290 (29.0)	875 (22.2)	3078 (21.7)	961 (48.2)	6806 (55.9)
History of heart failure, n (%)	2337 (48.6)	4113 (30.7)	2082 (73.7)	10 011 (54.9)	1570 (39.7)	4223 (29.8)	1402 (70.4)	7449 (61.2)
History of myocardial infarction or CAD	837 (17.4)	1748 (13.1)	1122 (39.8)	5822 (32.3)	1285 (32.5)	3749 (26.5)	482 (24.2)	1964 (16.1)
Hypertension	4102 (85.3)	11 811 (88.2)	2629 (93.1)	17 068 (93.7)	NA	NA	1775 (89.1)	11 049 (90.7)
Diabetes mellitus	1086 (22.6)	3460 (25.8)	908 (32.2)	6696 (36.7)	NA	NA	798 (40.1)	4849 (39.8)
Vitamin K antagonist experienced, n (%)	2918 (62.0)	7418 (55.4)	NA	NA	2673 (67.7)	8562 (60.1)	1444 (72.5)	7409 (60.8)
Renal function, CrCl (mL/min) medium (25th, 75th) or mean (SD)			70.0 (29.6)	77.2 (31.4)	65.8 (51.0, 83.7)	69.0 (54.0, 87.7)	62 (49, 80)	68 (53, 88)
Normal (>80 mL/min), n (%)	1608 (33.6)	5909 (44.3)	NA	NA	NA	NA	NA	NA
Mild impairment (>50–80 mL/min), n (%)	2101 (43.8)	5486 (41.2)	NA	NA	NA	NA	NA	NA
Moderate impairment (>30–50 mL/min), n (%)	980 (20.5)	1766 (13.3)	NA	NA	863 (21.8)	2480 (17.5)	NA	NA
Severe impairment (≤30 mL/min), n (%)	103 (2.1)	167 (1.3)	NA	NA	NA	NA	NA	NA
Median follow-up duration, y	1.8	1.8	2.8	2.8	2.0	2.0	1.9	1.9

AF indicates atrial fibrillation; AR, aortic regurgitation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AS, aortic stenosis; CAD, coronary artery disease; CrCl, creatinine clearance; ENGAGE AF, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; MR, mitral regurgitation; MS, mitral stenosis; NA, not available; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TIA, transient ischemic attack; TR, tricuspid regurgitation; VHD, valvular heart disease.

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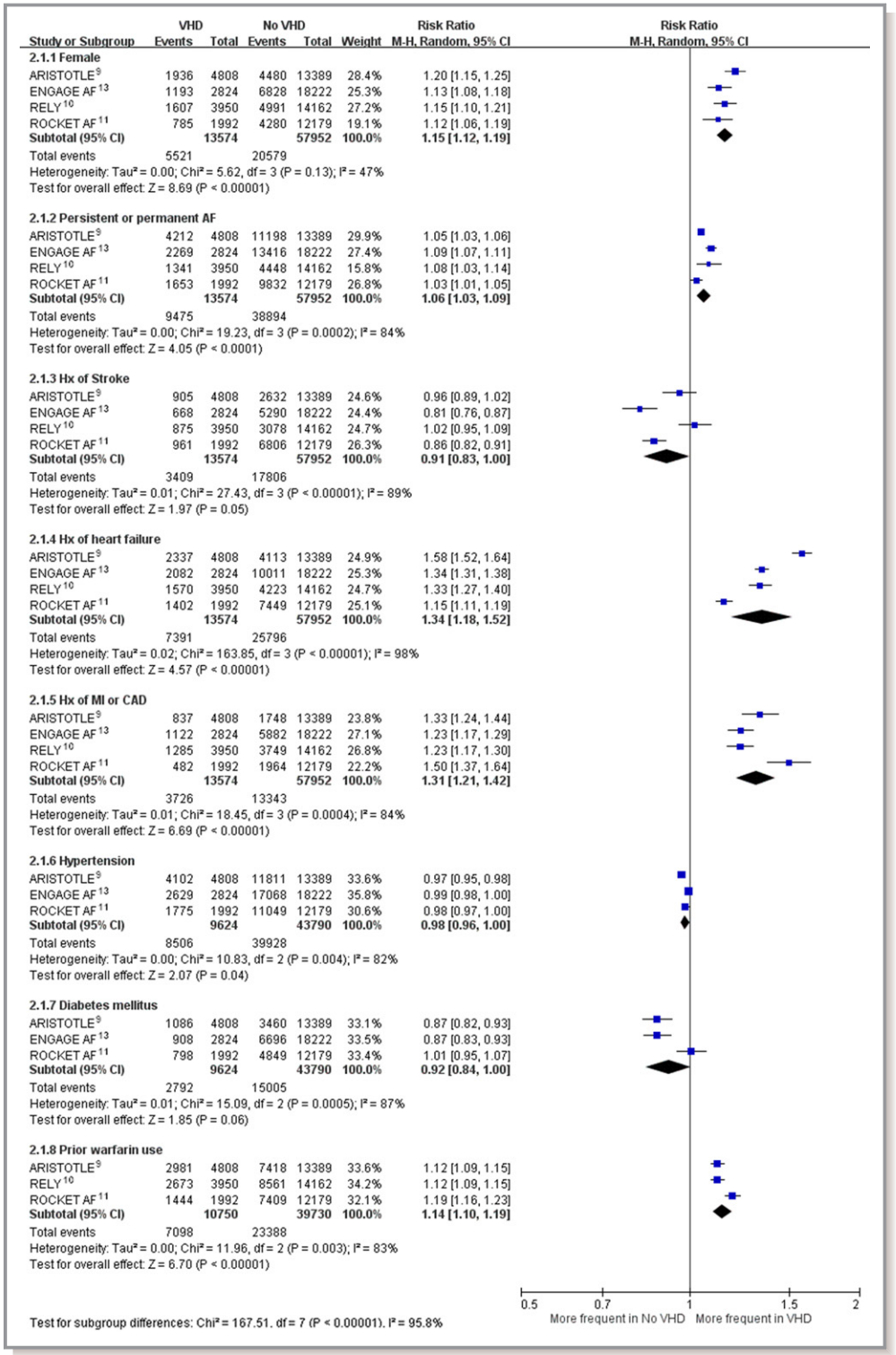

Figure 2. Prevalence of baseline characteristics of AF patients with and without valvular heart disease. AF indicates atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CAD, coronary artery disease; CI, confidence interval; ENGAGE AF, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; Hx, history; M-H, Mantel–Haenszel; MI, myocardial infarction; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VHD, valvular heart disease.

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Table 2. Risk-of-Bias Assessment of Original Randomized Controlled Trials

Trial	ARISTOTLE[7]	ENGAGE AF[8]	RE-LY[5]	ROCKET AF[6]
Random sequence generation (selection bias)	Low risk Quote: "Each subject will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio by the Interactive Voice Response System (IVRS)." Comment: probably done	Low risk Quote: "Patients were randomly assigned, in a 1:1:1 ratio. Randomization was performed with the use of a central, 24-hour, interactive, computerized response system." Comment: probably done	Low risk Quote: "The patients were randomized by a central randomization service, through an interactive voice response system (IVRS)." Comment: probably done	Low risk Quote: "Treatment allocation is randomized using a blinded, central telephonic Interactive Voice Response System." Comment: probably done
Allocation concealment (selection bias)	Low risk Quote: "Randomization schedules will be generated and kept by Bristol-Myers Squibb (BMS)" Comment: probably done	Low risk Quote: "Randomization was performed with the use of a central, 24-hour, interactive, computerized response system" Comment: probably done	Low risk Quote: "Randomization service located at the Coordinating Centre at Population Health Research Institute (PHRI) in Hamilton, Canada" Comment: probably done	Low risk To effect concealment of randomization, treatment allocation is randomized using a blinded, central telephonic Interactive Voice Response System Comment: probably done
Blinding of participants and personnel (performance bias)	Low risk Quote: "double-blind, double-dummy, parallel-arm study" Comment: probably done	Low risk Quote: "double-blind, double-dummy trial" Comment: probably done	High risk Quote: "open-label, randomized trial with blinded evaluation of all outcomes" Comment: probably done	Low risk Quote: "double-blind, double-dummy, randomized trial" Comment: probably done
Blinding of outcome assessment (detection bias)	Low risk Quote: "double blind" Comment: probably done	Low risk Quote: "double-blind, double-dummy trial" Comment: probably done	Low risk Quote: "open-label, randomized trial with blinded evaluation of all outcomes" Comment: probably done	Low risk Quote: "double-blind, double-dummy, randomized trial" Comment: probably done
Incomplete outcome data (attrition bias)	Low risk Comment: <1% patients lost follow-up	Low risk Comment: 0.5% incomplete information on the primary end point	Low risk Comment: 0.11% lost to follow-up	Low risk Comment: 0.22% lost to follow-up
Selective reporting (reporting bias)	Low risk Comment: study protocol is available, and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study protocol is available, and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified
Other potential bias	Low risk Comment: study seems to be free of other sources of bias	Low risk Comment: study seems to be free of other sources of bias	Low risk Comment: study seems to be free of other sources of bias	Low risk Comment: study seems to be free of other sources of bias

ARISTOTLE indicates Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

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and without VHD, had substantially higher $CHADS_2$ stroke risk scores. The median follow-up duration ranged from 1.8 years[9] to 2.8 years.[13] The assessment of risk of bias in the original RCTs[5–8] is shown in Table 2, and all 4 relevant trials were of good quality with low risk of bias.

Outcomes According to VHD Status

Pooling results from included trials, AF patients with versus without VHD had similar rates of stroke (ischemic or hemorrhagic) or systemic embolism (HR: 1.10; 95% CI, 0.95–1.28; P=0.04 for heterogeneity, I^2=63%) and intracranial hemorrhage (HR: 1.15; 95% CI, 0.95–1.40; P=0.35 for heterogeneity, I^2=4%). AF patients with VHD had higher rates of all-cause mortality (HR: 1.26; 95% CI, 1.07–1.47; P<0.0001 for heterogeneity; I^2=86%) and major bleeding (HR: 1.24; 95% CI, 1.14–1.34; P=0.25 for heterogeneity; I^2=26%) than AF patients without VHD (Figure 3).

Efficacy and Safety of NOACs and Warfarin in Patients With and Without VHD

Pooling results from the 4 included trials showed that the benefits of NOACs in comparison with warfarin in reducing stroke or systemic embolism were consistent in AF patients with VHD (HR: 0.70; 95% CI, 0.60–0.82; P=0.60 for heterogeneity; I^2=0%) and without VHD (HR: 0.84; 95% CI, 0.74–0.94; P=0.13 for heterogeneity; I^2=46%; Figure 4A).

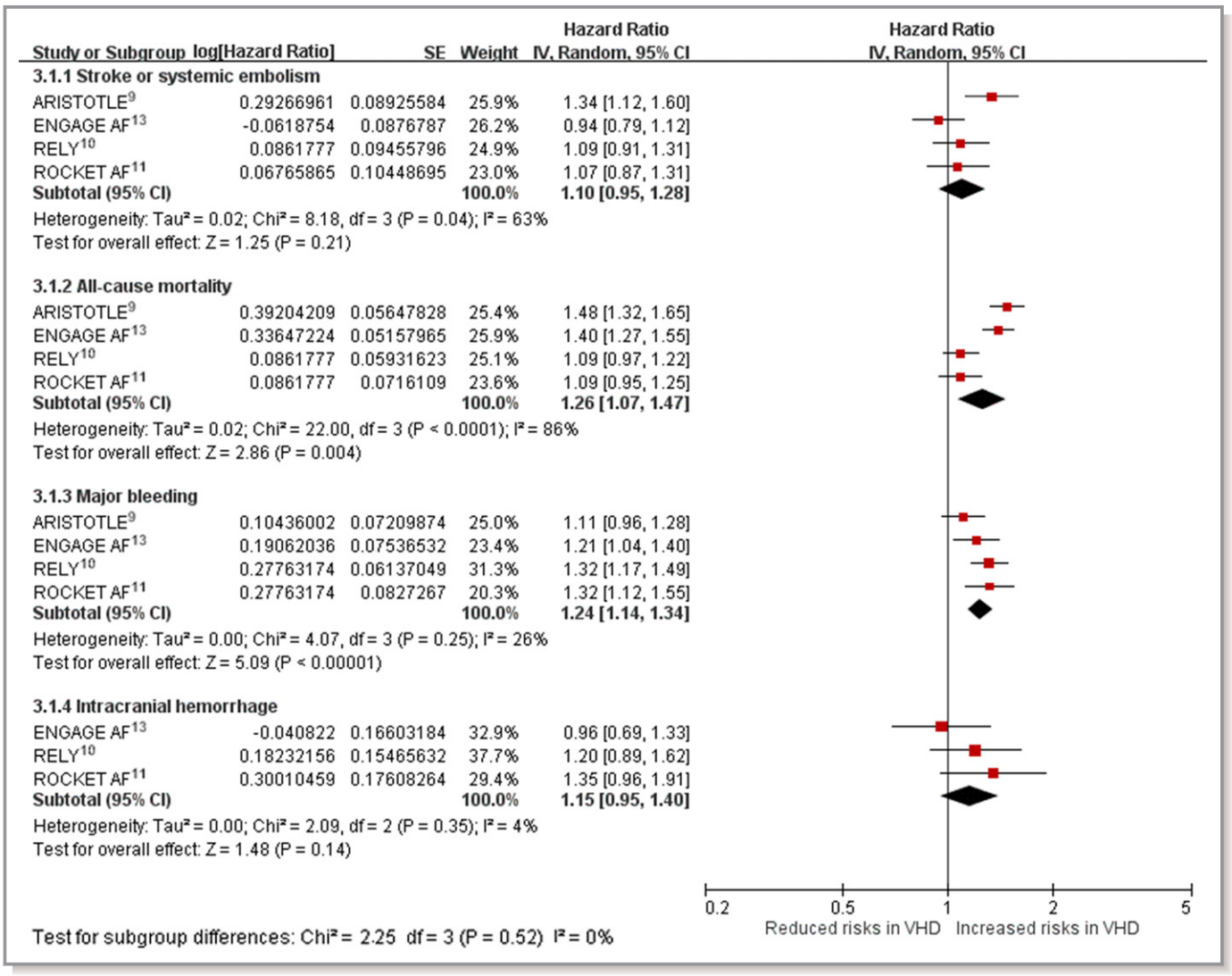

Figure 3. Hazard ratio with 95% confidence interval of outcomes, using overall patients enrolled in included trials, based on valvular status (VHD vs non-VHD). ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; ENGAGE AF, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; IV, instrumental variable; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VHD indicates valvular heart disease.

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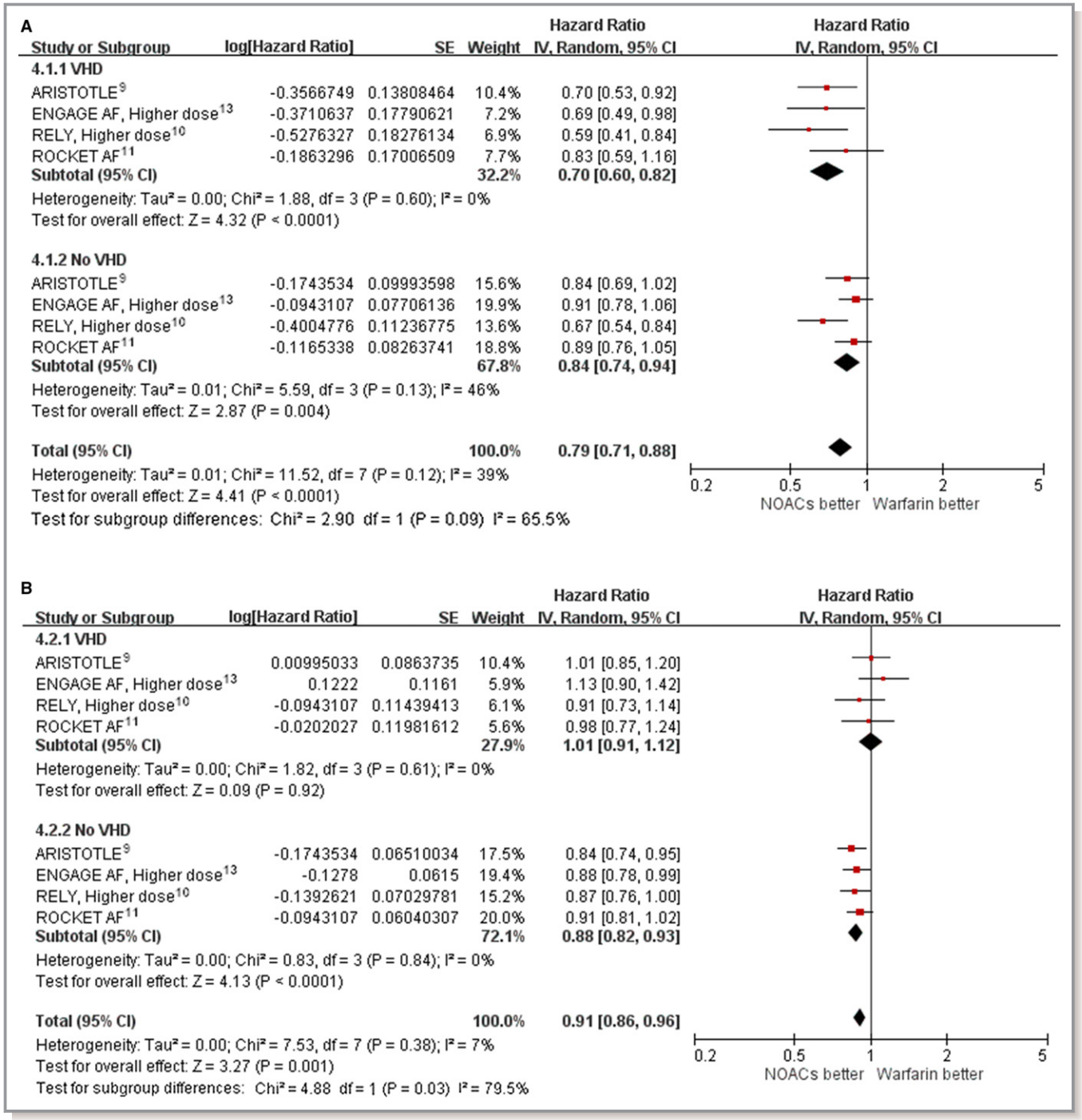

Figure 4. Hazard ratio with 95% confidence interval of efficacy outcomes (NOACs vs warfarin) in patients with and without VHD. A, Stroke or systemic embolism. B, Death. In ARISTOTLE, patients received apixaban 5 mg twice daily. ENGAGE AF used a higher dose, and patients received edoxaban 60 mg once daily. RE-LY was higher dose, and patients received dabigatran 150 mg twice daily. In ROCKET AF, patients received rivaroxaban 20 or 15 mg once daily. ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; ENGAGE AF, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; IV, instrumental variable; NOAC, non–vitamin K antagonist oral anticoagulant; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VHD indicates valvular heart disease.

Pooling results from the 4 included trials showed that the NOACs in comparison with warfarin did not reduce the overall mortality rate in AF patients with VHD (HR: 1.01; 95% CI, 0.91–1.12; P=0.61 for heterogeneity; I^2=0%) but reduced mortality in AF patients without VHD (HR: 0.88; 95% CI, 0.82–0.93; P=0.84 for heterogeneity; I^2=0%). These

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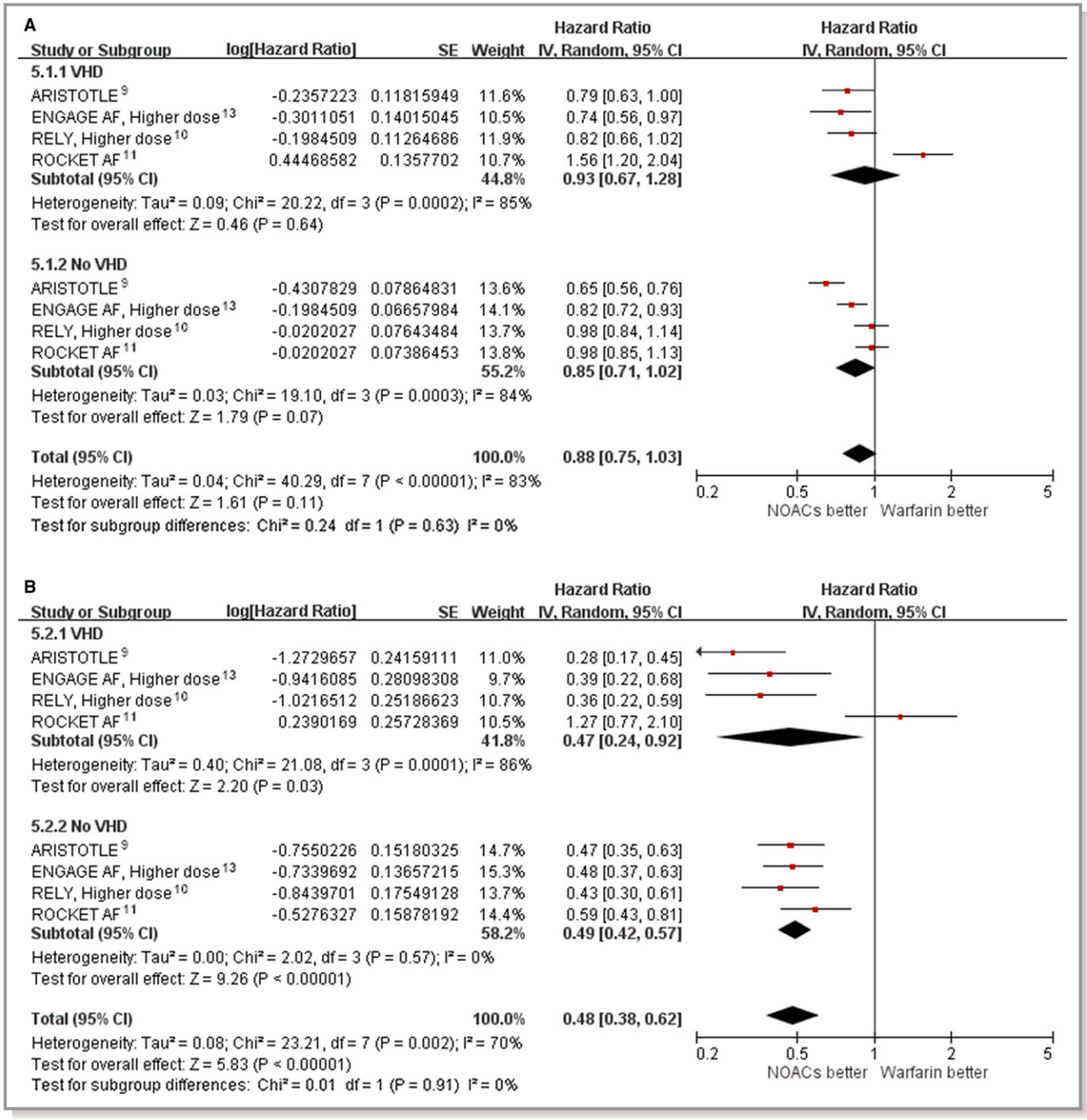

Figure 5. Hazard ratio with 95% confidence interval of safety outcomes (NOACs vs warfarin) in patients with and without VHD. A, Major bleeding. B, Intracranial hemorrhage. In ARISTOTLE, patients received apixaban 5 mg twice daily. ENGAGE AF used a higher dose, and patients received edoxaban 60 mg once daily. RE-LY was higher dose, and patients received dabigatran 150 mg twice daily. In ROCKET AF, patients received rivaroxaban 20 or 15 mg once daily. ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; ENGAGE AF, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; IV, instrumental variable; NOAC, non–vitamin K antagonist oral anticoagulant; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VHD indicates valvular heart disease.

differences in the HRs for the mortality rates (NOACs/warfarin) between the VHD and no-VHD groups achieved statistical significance (P=0.03 for subgroup differences in HR; Figure 4B).

Pooling results from the 4 included trials showed that the NOACs in comparison with warfarin did not significantly reduce major bleeding in AF patients with VHD (HR: 0.93; 95% CI, 0.67–1.28; P=0.0002 for heterogeneity; I^2=85%) or

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without VHD (HR: 0.85; 95% CI, 0.71–1.02; *P*=0.0003 for heterogeneity; I^2=84%; Figure 5A). Pooling results from 4 included trials showed that the benefits of NOACs in comparison with warfarin in reducing intracranial hemorrhage were consistent in patients with VHD (HR: 0.47; 95% CI, 0.24–0.92; *P*=0.0001 for heterogeneity; I^2=86%) and without VHD (HR: 0.49; 95% CI, 0.42–0.57; *P*=0.57 for heterogeneity; I^2=0%; Figure 5B).

We conducted further analyses to explore substantial heterogeneity in major bleeding and intracranial hemorrhage end points among AF patients with VHD. Apixaban, edoxaban, and dabigatran versus warfarin reduced major bleeding (HR: 0.79; 95% CI, 0.69–0.91; *P*=0.85 for heterogeneity; I^2=0%) among patients with VHD, whereas rivaroxaban versus warfarin increased major bleeding (HR: 1.56; 95% CI, 1.20–2.04; Figure 6A). In patients with VHD, apixaban, edoxaban,

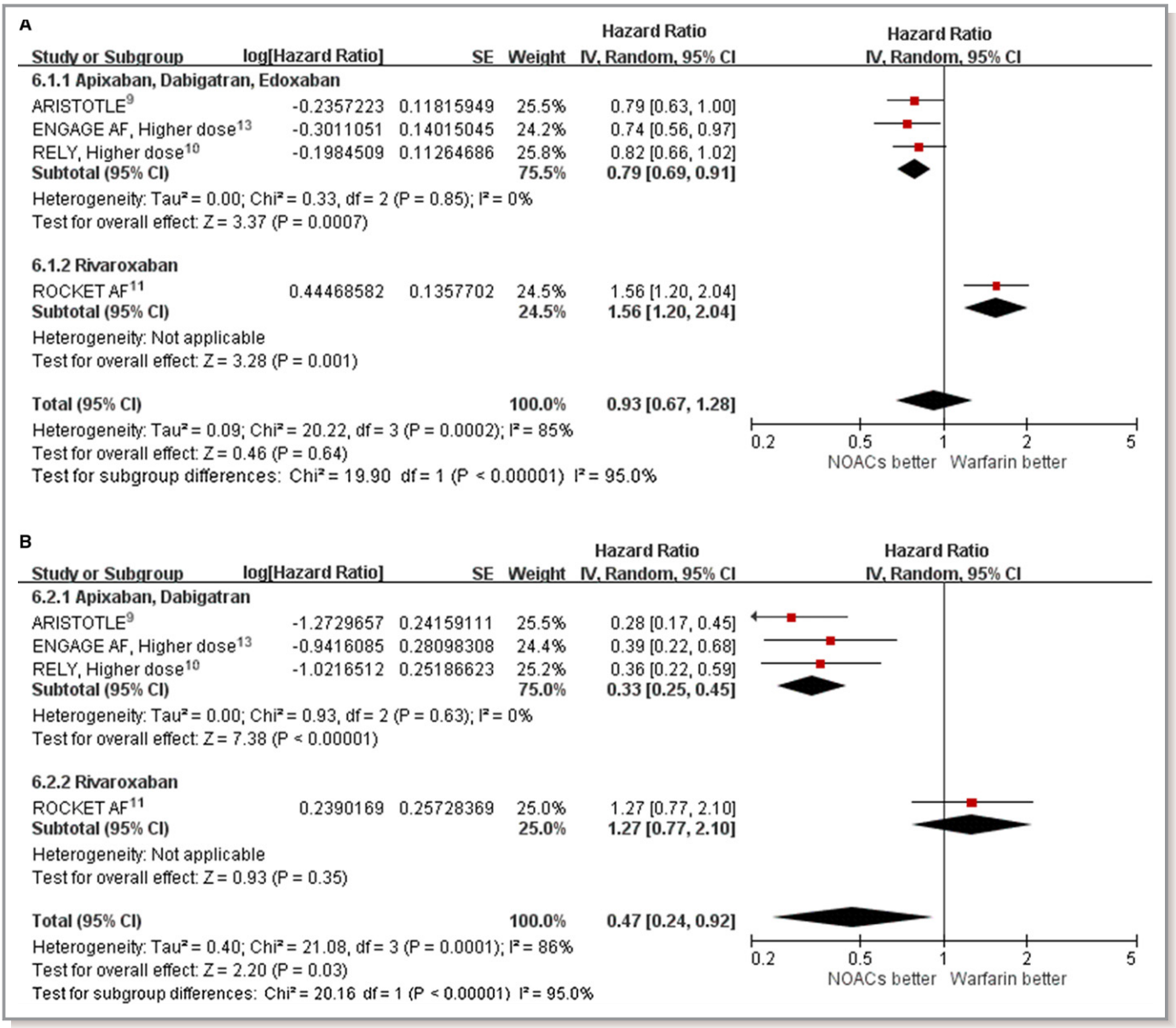

Figure 6. Effect of different non–vitamin K antagonist oral anticoagulants (dabigatran and apixaban vs rivaroxaban) in atrial fibrillation patients with valvular heart disease for safety end points. A, Major bleeding. B, Intracranial hemorrhage. In ARISTOTLE, patients received apixaban 5 mg twice daily. ENGAGE AF used a higher dose, and patients received edoxaban 60 mg once daily. RE-LY was higher dose, and patients received dabigatran 150 mg twice daily. In ROCKET AF, patients received rivaroxaban 20 or 15 mg once daily. ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; ENGAGE AF, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; IV, instrumental variable; NOAC, non–vitamin K antagonist oral anticoagulant; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

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and dabigatran versus warfarin reduced intracranial hemorrhage (HR: 0.33; 95% CI, 0.25–0.45; P=0.63 for heterogeneity; I^2=0%), whereas rivaroxaban versus warfarin did not show a difference in intracranial hemorrhage (HR: 1.27; 95% CI, 0.77–2.10; Figure 6B).

Discussion

In this meta-analysis of 4 RCTs comparing NOACs and warfarin in >70 000 AF patients, we found that one-fifth of patients with "nonvalvular" AF had moderate or severe VHD. AF patients with VHD were at modestly higher risk of all-cause mortality and major bleeding than those without VHD. Importantly, the benefits of NOACs in comparison with warfarin in reducing stroke or systemic embolism were consistent in AF patients with or without VHD.

Prevention of ischemic stroke in patients with AF cannot be overemphasized. Traditionally, the vitamin K antagonists, notably warfarin, have been the cornerstone for stroke prevention in patients with AF[17]; however, warfarin has a narrow window of therapeutic benefit, marked variation in its effect in different patients, a need for a long-term coagulation monitor, and increased risks of major bleeding, especially devastating intracranial hemorrhage.[18] Although the original individual NOAC trials were designed as noninferiority trials and not superiority, this meta-analysis of the pooled trials shows the NOACs, in aggregate, to be superior to warfarin for patients both with and without VHD. We observed substantial heterogeneity in major bleeding and intracranial hemorrhage end points among AF patients with VHD for which dabigatran, edoxaban, and apixaban reduced major bleeding and intracranial hemorrhage versus warfarin, whereas rivaroxaban appeared to increase major bleeding and did not reduce intracranial hemorrhage. Although rivaroxaban significantly reduced intracranial hemorrhage overall in the ROCKET trial, this effect was not seen in patients with VHD.[16] Still, there was no increase in mortality risk in VHD patients treated with rivaroxaban versus warfarin. We noted that several recent observational analyses of real-world outcomes with NOACs have been reported recently. Those results have been mixed regarding extracranial bleeding risk with rivaroxaban.

A meta-analysis comprising the overall patient population of 4 large clinical trials showed that NOACs, compared with warfarin, further decreased the risk of stroke or systemic embolism, death, and intracranial hemorrhage in nonvalvular AF patients.[19] Although experts may well understand that the term *nonvalvular* actually denotes that these trial patients do not have significant mitral valve stenosis or prosthetic heart valves, others may be hesitant to apply NOACs to AF patients with other types of VHD. The current study makes it clear that NOACs have similar benefits in terms of reducing stroke or systemic embolism as well as intracranial hemorrhage in AF patients both with and without VHD.

No dedicated clinical trial to date has compared NOACs with warfarin in AF patients with moderate or severe mitral valve stenosis, and so warfarin use in these patients is suggested.[4] The use of a NOAC, dabigatran, in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications compared with warfarin and thus is not justified for these patients.[20]

This study has limitations. First, a meta-analysis is a retrospective approach, and subgroup analysis in patients with and without VHD was not prespecified in the original clinical trials. Second, AF patients with and without VHD had different baseline characteristics, as did patients enrolled in the 4 trials. Substantial bias might remain despite statistical adjustment. Third, the RE-LY and ENGAGE AF trials used both higher and lower dose NOACs as active treatment agents, and their comparisons with warfarin were reported separately. Because this was a study-level meta-analysis, we were unable to combine groups of NOAC in a trial to create a single pairwise comparison. Consequently, only data from the higher dose NOACs versus warfarin were used in this meta-analysis.

In conclusion, this meta-analysis showed that AF patients with native VHD had a higher risk of all-cause mortality and major bleeding. NOACs, compared with warfarin, reduced stroke or systemic embolism as well as intracranial hemorrhage in AF patients with or without VHD. Although evidence supported increased extracranial bleeding risk among VHD patients treated with rivaroxaban versus warfarin, there was no increase in mortality risk. Our results further establish that for AF patients with native VHD, NOACs are an attractive alternative to warfarin for stroke preventive therapy.

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Disclosures

None.

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Effects of Non–Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: A Systematic Review and Meta–Analysis

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