

ORIGINAL INVESTIGATIONS



Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Disease

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ABSTRACT

BACKGROUND Valvular heart disease (VHD) and atrial fibrillation (AF) often coexist. Phase III trials comparing non-vitamin K antagonist oral anticoagulants (NOACs) with warfarin excluded patients with moderate/severe mitral stenosis or mechanical heart valves, but variably included patients with other VHD and valve surgeries.

OBJECTIVES This study aimed to determine relative safety and efficacy of NOACs in patients with VHD.

METHODS We performed a meta-analysis of the 4 phase III AF trials of the currently available NOACs versus warfarin in patients with coexisting VHD to assess pooled estimates of relative risk (RR) and 95% confidence intervals (CIs) for stroke/systemic embolic events (SSEE), major bleeding, intracranial hemorrhage (ICH), and all-cause death.

RESULTS Compared with warfarin, the rate of SSEE in patients treated with higher-dose NOACs was lower and consistent among 13,585 patients with (RR: 0.70; 95% CI: 0.58 to 0.86) or 58,098 without VHD (RR: 0.84; 95% CI: 0.75 to 0.95; interaction $p = 0.13$). Major bleeding in patients on higher-dose NOACs versus warfarin was similar and consistent among patients with (RR: 0.93; 95% CI: 0.68 to 1.27) or without VHD (RR: 0.85; 95% CI: 0.70 to 1.02; interaction $p = 0.63$ for VHD/no-VHD difference). Intracranial hemorrhage was lower with higher-dose NOACs than with warfarin irrespective of VHD (RR: 0.47; 95% CI: 0.24 to 0.93, and 0.49; 95% CI: 0.41 to 0.59, respectively; interaction $p = 0.91$). No protective effect of higher-dose NOACs in preventing all-cause death seemed to be present in patients with VHD versus without VHD (RR: 1.01; 95% CI: 0.90 to 1.14 vs. RR: 0.88; 95% CI: 0.82 to 0.94, respectively; interaction $p = 0.03$).

CONCLUSIONS High-dose NOACs provide overall efficacy and safety similar in AF patients with or without VHD. (J Am Coll Cardiol 2017;69:1363–71) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Valvular heart disease (VHD) and atrial fibrillation (AF) often coexist (1,2). They are independent causes of mortality and morbidity, and both increase the risk of stroke and systemic arterial embolic events (SSEE) (3). The term “valvular AF” has been variously defined in recent trials (4). The presence of moderate/severe mitral stenosis or of a mechanical prosthetic heart valve—conditions known



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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CHADS₂ = congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke

CI = confidence interval

ICH = intracranial hemorrhage

NOAC = non-vitamin K antagonist oral anticoagulant

RCT = randomized clinical trial

RR = risk ratio/relative risk

SSEE = stroke/systemic embolic events

SEM = standard errors of the mean

VHD = valvular heart disease

VKA = vitamin K antagonist

to be at particularly high thromboembolic risk (5)—have been consistently exclusion criteria for the phase III trials comparing the non-vitamin K antagonist oral anticoagulants (NOACs) with warfarin (6–9). One phase II trial testing the direct thrombin inhibitor dabigatran etexilate in patients with mechanical prosthetic valves was prematurely terminated because of excess stroke in the dabigatran arm at doses also associated with excess bleeding (10). In these patients, therefore, vitamin K antagonists (VKAs) are currently the only recommended oral anticoagulants for the prevention of SSEE (11–13), whereas NOAC data on AF and mitral stenosis are lacking.

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However, the RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy) trial with dabigatran (14), 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 with rivaroxaban (15), the ARISTOLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial with apixaban (16), and the ENGAGE AF-TIMI 48 (Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial with edoxaban (17) have included variable proportions of VHD patients, and individually provided no evidence of a differential effect of NOACs over warfarin in patients with and without VHD as to the main efficacy and safety outcomes. However, their individual interpretations are limited by the still relatively limited numbers of patients in each trial with various forms of VHD enrolled, and the variable inclusion criteria. Therefore, we aimed at assessing if there is a differential effect of NOACs versus warfarin in the larger sample size provided by the joint analyses of the 4 pivotal trials, now also including the VHD patient subanalysis of the ENGAGE AF-TIMI 48 trial. If patients with AF and VHD were shown to have a different response to NOACs versus warfarin compared with patients without VHD, this would have a substantial impact on patient care. An aggregate evaluation of the relative performance of the NOACs and warfarin specifically in VHD patients can thus offer valuable information on the efficacy and safety of treating such patients with these drugs.

For this reason we performed a systematic review and meta-analysis of available comparative

trials of NOACs versus VKAs to provide such information.

METHODS

The present meta-analysis was planned, conducted, and reported in accordance with currently available statements for design, analysis, and reporting of meta-analyses of randomized and observational studies (18,19).

SEARCH STRATEGY AND SELECTION CRITERIA. We searched PubMed, the U.S. National Institutes of Health Clinical Trials Registry (Clinicaltrials.gov), the Cochrane Library, Web of Science, as well as abstracts from major cardiology societies' meetings. Search terms used were “dabigatran” OR “rivaroxaban” OR “apixaban” “OR “edoxaban” AND “warfarin” AND “atrial fibrillation” AND “valvular heart disease”. We also searched websites, including theheart.org, escardio.org, and ResearchGate, for relevant materials. References of the articles identified in this manner were also searched to locate additional references that, although not identified by the search strategy, might be useful for this meta-analysis.

Two of the authors (G.R. and F.R.) performed the screening of titles and abstracts, reviewed full-text articles, and determined their eligibility. The search was performed for the period between January 2007 and August 2016, and was limited to the English language literature. Reviewers were not blinded to study authors or outcomes. Divergences were resolved by consensus. We included only phase III randomized clinical trials (RCTs) comparing the available NOACs with warfarin in patients with AF. We excluded the 2 phase III trials comparing ximelagatran with warfarin in patients with AF (20,21), because ximelagatran was withdrawn from the market in 2006.

DATA EXTRACTION AND QUALITY ASSESSMENT.

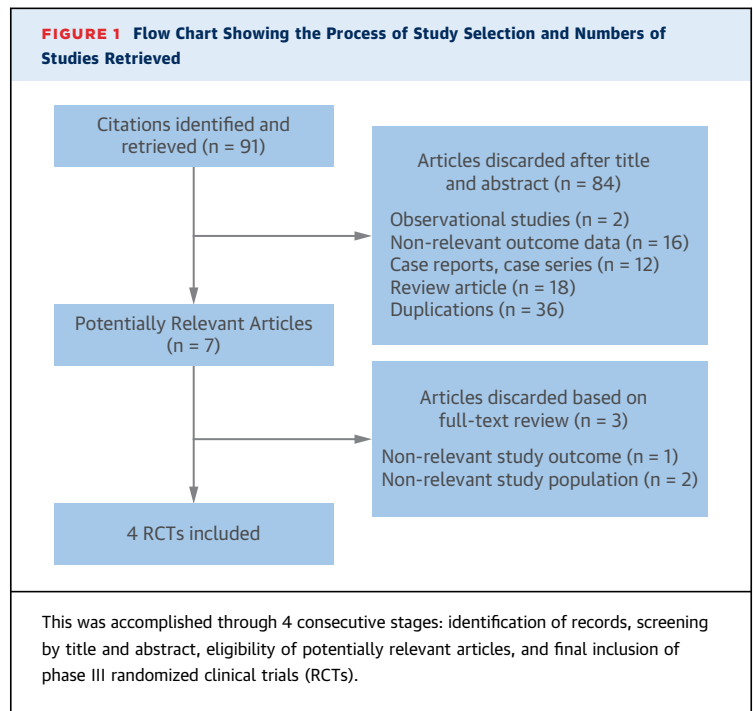
We performed a first pre-specified, trial-based analysis aimed at comparing primary efficacy and safety outcomes as stratified by VHD status and randomized treatment in the 4 phase III RCTs comparing efficacy and safety of NOACs with warfarin for stroke prevention in patients with AF (6–9). Data were collected from the 3 published post hoc analyses of RE-LY (14), ROCKET AF (15), and ARISTOTLE (16), through personal communication, and through a joint work with the principal investigator (R.P.G.) of ENGAGE AF-TIMI 48 (17), who is a co-author of this paper.

Outcomes of interest for the current meta-analysis were stroke or SSEE, major bleeding, intracranial hemorrhage (ICH), and all-cause death. Ischemic stroke alone was considered in patients from the

ARISTOTLE and ENGAGE AF-TIMI 48 trials because data were not available from the other 2 trials. Endpoint definitions across the original trials are reported in the main trial papers and/or in their supplemental appendices (6-9).

STATISTICAL ANALYSIS. The main meta-analysis included subgroups of patients randomized to the higher dose of dabigatran (150 mg twice daily) enrolled in RE-LY (14), and to the higher dose of edoxaban (60 mg or reduced dose 30 mg daily for patients with ≥ 1 of the following criteria: creatinine clearance [CrCl] 30 to 50 ml/min, weight ≤ 60 kg, or concomitant therapy with strong P-glycoprotein inhibitors) enrolled in ENGAGE AF-TIMI 48 (17), combined with the single dose of rivaroxaban (20 mg daily reduced to 15 mg daily for patients with CrCl 30 to 49 ml/min) tested in the ROCKET AF (15), and with the single dose of apixaban (5 mg twice daily reduced to 2.5 twice daily in patients with ≥ 2 of the following: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 133 $\mu\text{mol/l}$ or 1.5 mg/dl) enrolled in the ARISTOTLE (16) trials. We selected this strategy to avoid merging different benefits and risks of various NOAC doses versus warfarin, and to provide an unequivocal interpretation of the results, in agreement with the strategy adopted in the overall NOAC effect meta-analysis by Ruff et al. (22). In a secondary analysis, we combined all doses of all NOACs (both higher and lower doses of dabigatran and edoxaban, together with rivaroxaban and apixaban).

The categorical variables are reported as percentages, and continuous variables as mean and standard deviation or median and interquartile range, as appropriate. Outcome data were extracted as hazard ratios (HRs) and 95% confidence intervals (CIs) for NOACs versus warfarin among patients with or without VHD. The HRs were considered as risk ratios (RRs), as previously described (23). We reported unadjusted RRs, since adjusted HRs were obtained with different adjustment models across the 4 trials. RRs and corresponding standard errors of the mean (SEMs), which were derived from 95% CIs or p values, were logarithmically transformed to stabilize variance and normalize the distributions. RRs were pooled in a random-effect, generic inverse variance meta-analysis to compute summary effect sizes of safety and efficacy of NOACs versus VKAs in patients with or without VHD. Each study estimate of the relative treatment was given a weight that was equal to the inverse of the variance of the effect estimate, i.e., 1 divided by the squared SEM. To test for subgroup interactions and to compare the effect size between VHD and no-VHD subgroups, a Cochran's



Q test was performed to assess the dispersion of the summary effects around the combined effect, as described by Borenstein et al. (24); we considered evidence of heterogeneity to exist if the p value was < 0.10 . We also performed statistical tests allowing to describe the percentage of total variation across studies that is due to heterogeneity rather than to chance. This describes the percentage of the variability in effect estimated from the different subgroups that is due to genuine subgroup interactions rather than sampling error. A value of $I^2 > 50\%$ was taken as indicating significant heterogeneity. The CIs of the summary estimates of different subgroups were also evaluated, with nonoverlap of the confidence intervals indicating statistical significance.

Jackknife sensitivity analyses were also performed for each endpoint of interest and combining all doses of all drugs (both higher and lower doses of dabigatran and of edoxaban together with the single-dose regimens tested for rivaroxaban and apixaban) to verify the robustness of the results and the impact of each single study on the summary estimate of the effect. Pooled estimates were recalculated multiple times using a random-effects model, each time with removal of a single study from the baseline group (25).

The Cochrane Collaboration Tool was used to assess risk bias and to evaluate reporting quality through the following items: random sequence generation method, allocation concealment, blinding of

TABLE 1 Main Characteristics for Studies Included and VHD Subgroup Analyses

Original Trial	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI 48				
Publication	Connolly et al. (6), 2009	Patel et al. (7), 2011	Granger et al. (8), 2011	Giugliano et al. (9), 2013				
Sample size, n	18,113	14,264	18,201	21,105				
Study drug	Dabigatran 110 mg twice daily, or dabigatran 150 mg twice daily, or warfarin (target INR 2.5)	Rivaroxaban 20 mg once daily (or 15 mg once daily with CrCl 30-49 ml/min), or warfarin (target INR 2.5)	Apixaban 5 mg twice daily (2.5 mg twice daily with ≥ 2 of the following criteria: age ≥ 80 yrs, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl, 133 μ mol/l), or warfarin (target INR 2.5)	Edoxaban 60 mg once daily (30 mg once daily with ≥ 1 of the following criteria: CrCl 30-50 ml/min, weight ≤ 60 kg, or concomitant therapy with strong P-gp inhibitors (verapamil or chinidine), or edoxaban 30 mg once daily (15 mg once daily with ≥ 1 of the previous criteria), or warfarin (target INR 2.5))				
Mean CHADS ₂ score	2.1	3.5	2.1	2.8				
Median TTR, % (IQR)	67 (54-78)	58 (43-71)	66 (52-77)	68 (57-77)				
Exclusion criteria regarding VHD	History of heart valve disorder (i.e., prosthetic valve or hemodynamically relevant valve disease)	Hemodynamically significant mitral valve stenosis or prosthetic heart valve	Valvular disease requiring surgery, prosthetic mechanical heart valve, moderate or severe mitral stenosis	Moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve				
VHD Subgroup Analysis	Ezekowitz, et al. (14)	Breithardt, et al. (15)	Avezum, et al. (16)	De Caterina, et al. (17)				
Study design	Post hoc analysis of an open-label RCT	Post hoc analysis of a double-blinded RCT	Post hoc analysis of a double-blinded RCT	Post hoc analysis of a double-blinded RCT				
Year of publication of VHD data	2014	2014	2015	2016				
Type of outcome analysis	Intention-to-treat	Efficacy intention-to-treat safety on-treatment	Efficacy intention-to-treat safety modified intention-to-treat	Efficacy intention-to-treat safety modified intention-to-treat				
Patients with VHD, n (%)	3,950 (22)	2,003 (14)	4,808 (26)	2,824 (13)				
Baseline Characteristics Grouped by VHD Status	VHD	No VHD	VHD	No VHD	VHD	No VHD	VHD	No VHD
Median age, yrs	74*	72	75*	72	71*	69	73*	72
Heart failure, %	40*	30	70*	61	49*†	31	74*	55
Diabetes mellitus, %	24‡	23	NA	NA	23	26*	32	37*
Previous stroke, TIA or SE, %	22	22	48	56*	19	20	24	29*§
Hypertension, %	77‡	79	89	91*	85	88	93	94
CAD, %	33*	26	24*	16	17*	13	40*	32
Sustained AF, %	NA	NA	83*	81	88*	84	80*	74
Mean CHADS ₂ score	2.3	2.1	3.5	3.5	2.2*	2.1	2.9*	2.8
Mean HAS-BLED score	NA	NA	2.8	2.8	NA	NA	2.6*	2.5

*p < 0.05 vs. other group. †For the ARISTOTLE, we report heart failure or reduced LVEF. ‡p value vs. other group not available. §For the ENGAGE AF, we report stroke or TIA (without systemic embolic event). ¶Bleeding events were analyzed in the safety population (for all patients who took at least 1 dose of study drug).

AF = atrial fibrillation; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CAD = coronary artery disease; CHADS₂ = congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke; CrCl = creatinine clearance; ENGAGE AF-TIMI = Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction; INR = international normalized ratio; IQR = interquartile range; LVEF = left ventricular ejection fraction; NA = not applicable; P-gp = P-glycoprotein; RCT = randomized clinical trial; RE-LY = Randomized Evaluation of Long Term Anticoagulation Therapy; ROCKET = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SE = systemic embolism; TIA = transient ischemic attack; TTR = time in therapeutic range; VHD = valvular heart disease.

participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, description of withdrawals, and any other risk of bias features (26).

The statistical analysis and graphs were performed using the Review Manager (RevMan) software package version 5.3 for OSX (The Nordic Cochrane Centre, The Cochrane Collaboration, 2008, Copenhagen, Denmark) and STATA 11.0 version (STATA, College Station, Texas).

RESULTS

We identified 4 studies with the predefined selection criteria, with an overall population of 13,585 patients

with VHD from a total population of 71,683 patients (Figure 1).

Table 1 reports the main characteristics of studies included and related post hoc analyses, and baseline characteristics of patients grouped by VHD status. Compared with patients without VHD, patients with VHD were on average at higher risk because they were older, had more sustained forms of AF, had higher rate of heart failure history and of coronary artery disease, and higher congestive heart failure, hypertension (CHADS₂) scores (with the exception of patients from ROCKET AF). Table 2 reports the frequency of VHD subtypes in patients randomized in the 4 trials.

In a total of 13,585 patients with VHD included in this main analysis, we found a similar rate of SSEE

(RR: 1.13; 95% CI: 0.99 to 1.28), and significantly higher rates of major bleeding (RR: 1.30; 95% CI: 1.13 to 1.49) and all-cause death (RR: 1.34; 95% CI: 1.13 to 1.59), compared with the 58,098 patients classified as without VHD (Online Figures 1A to 1C).

The rate of SSEE in patients treated with higher-dose NOACs compared with warfarin was lower and consistent among patients with either VHD (RR: 0.70; 95% CI: 0.58 to 0.86), or without VHD (RR: 0.84; 95% CI: 0.75 to 0.95; test for subgroup interaction $p = 0.13$; $I^2 = 57%$) (Central Illustration). There was no significant statistical heterogeneity among the studies ($p = 0.31$; $I^2 = 16%$). We observed a trend towards a better protection of NOACs versus warfarin in VHD patients considering ischemic stroke alone in patients from ARISTOTLE and ENGAGE AF-TIMI 48 trials. This is in contrast to patients without VHD in whom apixaban and higher-dose edoxaban did not reduce the risk of incident ischemic stroke compared with warfarin (VHD RR: 0.75; 95% CI: 0.56 to 1.02; no-VHD RR: 1.04; 95% CI: 0.89 to 1.22; test for subgroup interaction $p = 0.06$; $I^2 = 71%$) (Online Figure 2).

The rate of major bleeding for patients treated with higher-dose NOACs compared with warfarin was similar and consistent in patients with either VHD (RR: 0.93; 95% CI: 0.68 to 1.27), or without VHD (RR: 0.85; 95% CI: 0.70 to 1.02) (test for subgroup interaction $p = 0.63$; $I^2 = 0%$); however, in this case there was a significant statistical heterogeneity across studies (Cochran's $Q p < 0.0001$; $I^2 = 78%$) (Central Illustration).

Notably, higher-dose NOACs reduced ICH compared with warfarin to a similar degree among AF patients with and without VHD (RR: 0.47; 95% CI: 0.24 to 0.93, and RR: 0.49; 95% CI: 0.41 to 0.59, respectively; test for subgroup interaction $p = 0.91$; $I^2 = 0%$) (Figure 2). There was also an apparent better protection from all cause-death in patients without VHD treated with higher-dose NOACs versus warfarin compared with patients with VHD (RR: 0.88; 95% CI: 0.82 to 0.94, and RR: 1.01; 95% CI: 0.90 to 1.14, respectively; test for subgroup interaction $p = 0.03$, $I^2 = 78%$) (Figure 3). For these outcomes, we found no significant statistical heterogeneity among studies.

Finally, we performed an analysis including all NOAC dose arms studied against warfarin. Also, in this case, we considered SSEE major bleeding, ICH, and all-cause death. The results are substantially similar to those restricted to the higher dose NOACs. Inclusion of the lower doses of dabigatran and edoxaban decreased the magnitude of the risk reduction for SSEE with NOACs versus warfarin and resulted in less major bleeding than warfarin both in patients with and without VHD (Online Figures 3A and 3B), as

TABLE 2 Frequency of Valvular Heart Disease Subtypes in Patients Randomized in RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 Trials

VHD Subtype	RE-LY (n = 3,950)	ROCKET-AF (n = 2,003)	ARISTOTLE (n = 4,808)	ENGAGE AF-TIMI 48 (n = 2,824)
Moderate/severe mitral regurgitation	3,101 (78.5)	1,756 (87.7)	3,526 (73.3)	2,250 (79.6)
Mild mitral stenosis*	193 (4.9)	NR	131 (2.7)	254 (9.0)
Moderate/severe aortic regurgitation	817 (20.7)	486 (24.3)	887 (18.4)	369 (13.0)
Moderate/severe aortic stenosis	471 (11.9)	215 (10.7)	384 (8.0)	165 (5.8)
Moderate/severe tricuspid regurgitation	1,179 (29.8)	NR	2,124 (44.0)	NR
Valve surgery (other than mechanical prosthetic heart valve)	NR	106 (5.3)†	251 (5.2)	516 (18.2)

Values are n (%). *These patients were analyzed with the No-VHD group because the VHD definition adopted always included at least "moderate" VHD. †Biologic prosthetic valves also excluded.
NR = not reported; other abbreviations as in Table 1.

consistently shown by the jackknife sensitivity analysis omitting higher or lower doses of dabigatran and edoxaban together (Online Table 1). Similarly to major bleeding, the risk reduction of ICH by NOACs versus warfarin was slightly amplified after the inclusion of the lower doses in the analysis, but ICH was reduced consistently both in VHD and no-VHD patients (Online Figure 4A). Conversely, the inclusion of lower doses did not modify the relative risk of all-cause death (Online Figure 4B).

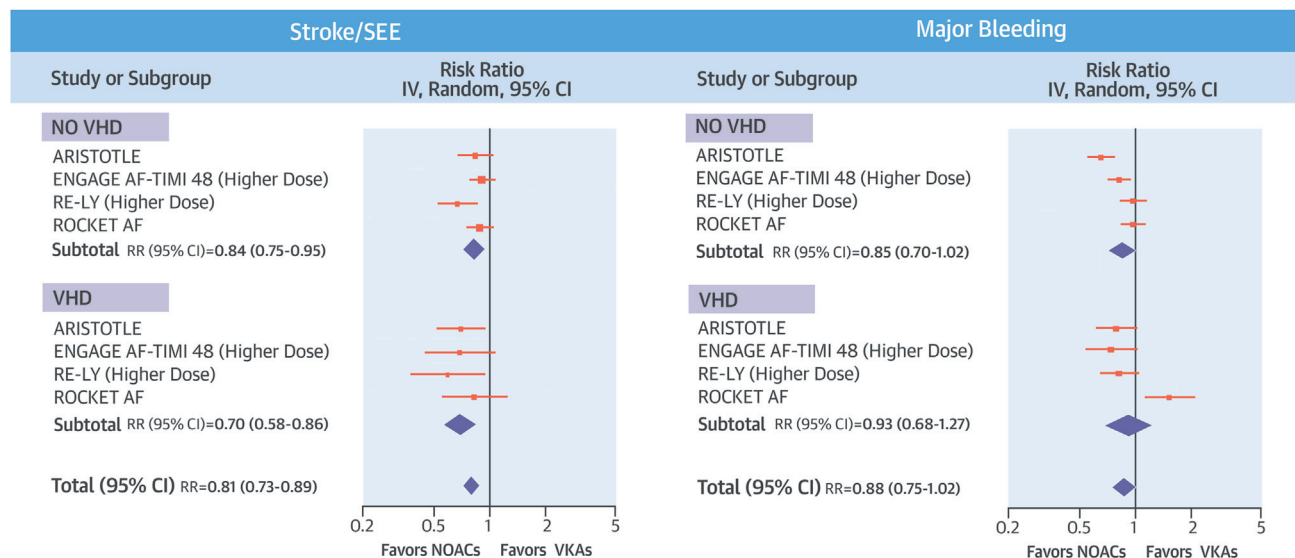
Sensitivity analyses showed that some studies significantly affected the pooled RRs for SSEE and major bleeding (Online Table 2). Particularly, compared with the overall analysis, exclusion of the lower-dose edoxaban arm improved the risk reduction of SSEE by the remaining NOACs versus warfarin in patients without VHD; the exclusion of rivaroxaban improved the risk reduction of major bleeding by the remaining NOACs versus warfarin in patients with VHD, whereas the exclusion of apixaban diminished this risk reduction (Online Table 2).

Qualitatively, the overall risk of reporting bias was low according to the Cochrane Collaboration Tool classification (26) (Online Figure 5).

DISCUSSION

The present meta-analysis suggests that, compared with patients with AF without VHD, patients with AF and VHD: 1) were on average at higher risk (they were older, had more frequently sustained AF, had a higher prevalence of heart failure and coronary artery disease, and a higher CHADS₂ score); and 2) had higher rates of major bleeding and all-cause death. The present meta-analysis also however indicates that 3) the efficacy and safety of NOACs versus

CENTRAL ILLUSTRATION SSEE and Major Bleeding in Patients Without and With VHD, Treated With Higher-Dose NOACs or Warfarin



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Forest plot with individual and summary estimates of the relative risk (RR) and 95% confidence interval (CI) of stroke/SEE and major bleeding for higher-dose NOACs versus warfarin among patients without and with VHD, separately and overall. A random-effect model was applied to estimate RR and 95% CI. Squares and diamond sizes are proportional to study weight. Inter-study heterogeneity, separately reported for no-VHD and VHD groups, and for the overall population, was tested using Cochran's Q test (see text for details). The figure shows that the relative efficacy and safety of NOACs versus warfarin as to the main efficacy (stroke/SEE) and safety (major bleeding) endpoints are similar in no-VHD and VHD patients. CI = confidence interval; IV = inverse variance; NOAC = non-vitamin K antagonist oral anticoagulant; RR = relative risk; SEE = systemic embolic events; VHD = valvular heart disease.

warfarin is consistent in AF patients with and without VHD included in phase III trials. Indeed, for all primary efficacy and safety outcomes in all 4 RCTs comparing NOACs with warfarin in patients with AF, we found that coexisting VHD did not affect the overall relative protection of NOACs in terms of prevention of SSEE and major bleeding.

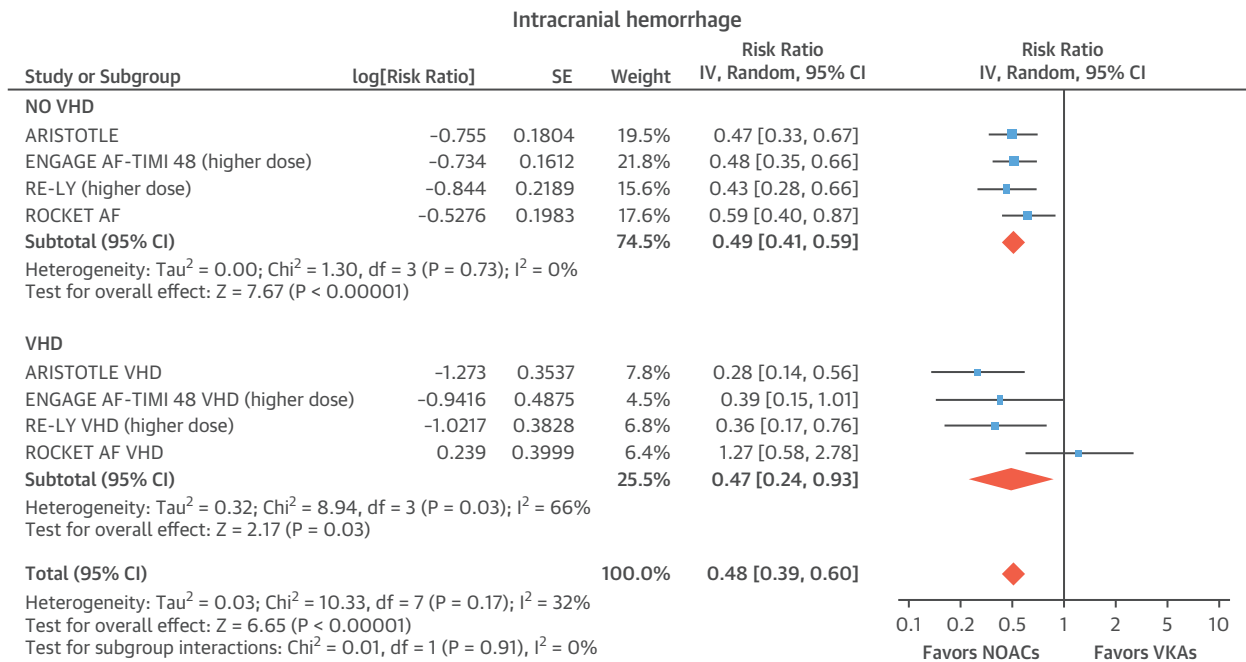
As shown in **Table 1**, there were different definitions of VHD in the 4 phase III trials and patients had variable types of VHD. Therefore, VHD patients allowed in the various trials, despite substantially overlapping, also differed in several aspects, making the overall interpretation of findings potentially difficult. Our results, however, show similar or better outcomes with NOACs versus warfarin in VHD patients, and provide reassurance in treating AF patients with the types of VHD here studied.

Post hoc analyses of the individual phase III trials of NOACs versus warfarin have indicated that VHD patients have higher rates of several efficacy and safety outcomes compared with patients without VHD. Indeed, compared with no-VHD, VHD patients

from the RE-LY trial had similar risk of SSEE and death and higher risk of major bleeding (14); VHD patients from the ENGAGE AF-TIMI 48 (17) trial had similar risk of SSEE and higher risks of death and major bleeding; VHD patients from ARISTOTLE (16) had higher risk of SSEE, death, and a trend towards higher risk of major bleeding; and VHD patients from ROCKET AF (15) had higher risks of systemic embolism events alone and major bleeding. Our analysis confirmed that VHD patients overall have a trend to higher risk of SSEE, and significantly higher risk of major bleeding and all-cause death.

We found that the better protection of NOACs versus warfarin in terms of prevention of SSEE was consistent among patients with or without VHD. Furthermore, our subanalysis of the ARISTOTLE and ENGAGE AF-TIMI 48 trials, reporting ischemic stroke or systemic embolism events in isolation in the VHD/no-VHD groups, whereby the test for interaction was of borderline statistical significance, favored apixaban and higher-dose edoxaban in patients with VHD ($p = 0.06$) (Online Figure 2). Conversely, the

FIGURE 2 Intracranial Hemorrhage in Patients Without and With VHD, Treated With Higher-Dose NOACs or Warfarin in the Selected Trials



Forest plot with individual and summary estimates of the RR and 95% CI of intracranial hemorrhage for higher dose NOACs versus warfarin among patients without and with VHD, separately and overall. A random-effect model was applied to estimate RR and 95% CI. Square and diamond sizes are proportional to study weight. Inter-study heterogeneity, separately reported for no-VHD and VHD groups, and for the overall population, was tested using Cochran's Q test (see text for details). CI = confidence interval; IV = inverse variance; NOAC = non-vitamin K antagonist oral anticoagulant; RR = relative risk; SEE = systemic embolic events; VHD = valvular heart disease.

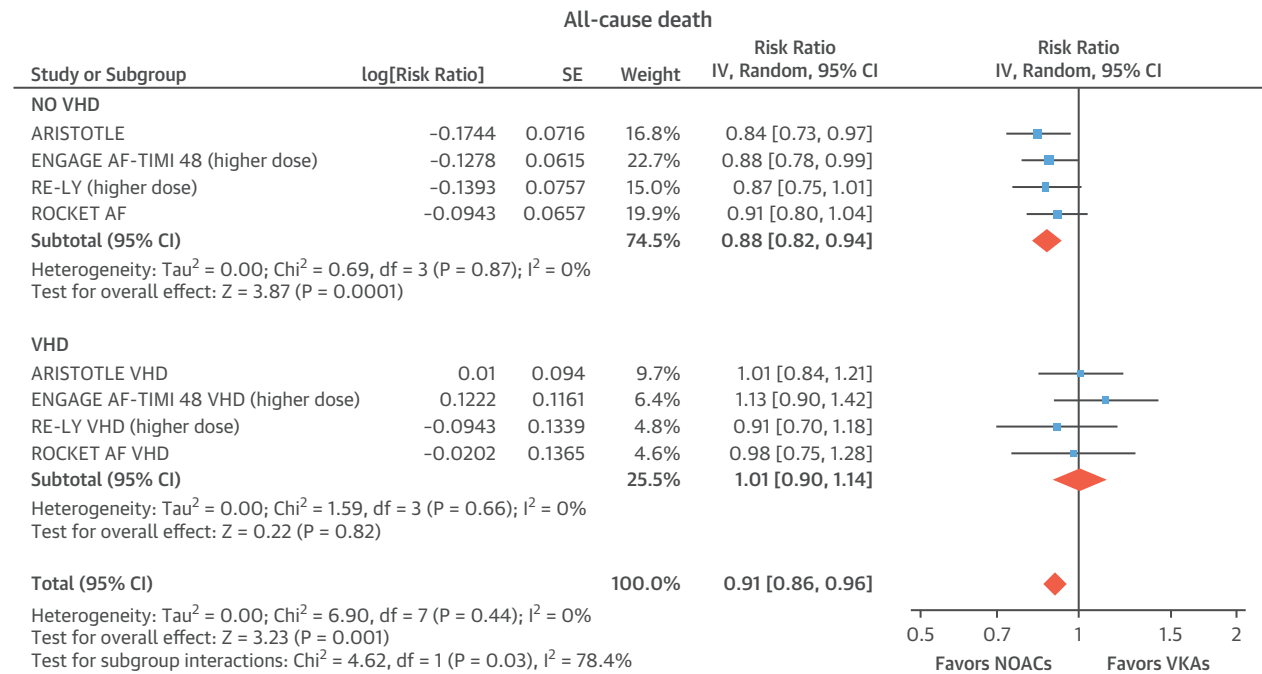
protective effect of higher-dose NOACs in terms of prevention of all-cause death seemed not to be present in patients with VHD. The reasons for this, especially with regard to the latter finding, are unclear. The finding of an apparent lesser protection from death by NOACs in the VHD versus the no-VHD group may be spurious, or alternatively related to a different sensitivity of some components of death to the effect of NOACs versus warfarin in VHD patients (2). However, the small number of death events may also have caused a Type I error. In any case, for all-cause death the overall HR in VHD patients was here found to be exactly 1.00, suggesting, also in this case, no overall harm for NOACs versus warfarin in VHD patients.

Conversely, pooled results of other safety endpoints, such as major bleeding and ICH, were consistent with the main results from the original trials, which showed a tendency toward fewer major bleeding and a 50% reduction in ICH (22). Hence, the information from the 4 phase III trials is complementary, and the overall message of this

meta-analysis is that, despite their higher thromboembolic and hemorrhagic risk, VHD patients are protected with NOACs at least as well as patients without VHD.

We could not analyze data according to subtypes of native valve disease or valve procedures/surgeries because of the lack of homogeneous data. However, in a subanalysis by location of valve disease performed in VHD patients from ARISTOTLE (16) and ENGAGE AF-TIMI 48 (17), it has been shown that both the subgroup of patients with mitral valve disease and those with aortic valve disease had consistent benefits of apixaban and edoxaban versus warfarin for prevention of SSEE and major bleeding. Similar benefits of apixaban in comparison with warfarin were also reported as seen in patients with tricuspid valve disease and in patients with previous valve surgery (data not shown) and without a distinction between different types of surgery (16). In a retrospective analysis of ROCKET AF (27), patients with aortic stenosis had the highest rates of efficacy and safety outcomes, but there were no significant

FIGURE 3 All-Cause Death in Patients Without and With VHD, Treated With Higher-Dose NOACs or Warfarin in the Selected Trials



Forest plot with individual and summary estimates of the RR and 95% CI of all-cause death for higher dose NOACs versus warfarin among patients without and with VHD, separately and overall. A random-effect model was applied to estimate RR and 95% CI. Squares and diamond sizes are proportional to study weight. Inter-study heterogeneity, separately reported for no-VHD and VHD groups, and for the overall population, was tested using Cochran's Q test (see text for details). Abbreviations as in Figure 2.

interactions among patients randomized to rivaroxaban and warfarin across the 3 subgroups of mitral regurgitation + aortic regurgitation, aortic stenosis, and no-VHD patients, for all efficacy endpoints, including SSEE. However, patients with mitral regurgitation or aortic regurgitation had an elevated risk of major bleeding with rivaroxaban compared with warfarin. Finally, in a post hoc analysis of the RE-LY trial (14), outcomes were not different between patients with mild rheumatic mitral stenosis and patients without VHD; also, in patients with exclusive right-sided valve lesions, outcomes were similar as in patients without VHD.

STUDY LIMITATIONS. First, our analysis was based on aggregate data abstracted from original publications, but not on individual patient-level data. This prevented us from conducting in-depth subgroup analyses or meta-regressions.

Second, original RCTs had different designs: one of these, RE-LY, was open-label, whereas the others were double-blinded. Moreover, inclusion/exclusion criteria were different, and the definition and subtypes

of VHD were not consistent across the studies. Furthermore, classification of valvular lesions and severity relied largely on clinical data collected in the case report forms, and only in a small proportion of patient (from ARISTOTLE and ENGAGE AF-TIMI 48) on detailed echocardiographic information on VHD. This heterogeneity may be a further limitation to conclusions.

Third, the significant statistical between-trials heterogeneity observed in the analysis of major bleeding and the high degree of uncertainty of sensitivity analyses for the endpoints of interest may affect the robustness of the results. This reflects the heterogeneity of results from the 4 main RCTs in terms of efficacy and safety outcomes.

CONCLUSIONS

In patients with AF and VHD (other than moderate/severe mitral stenosis or mechanical heart valves) NOACs are attractive alternatives to VKAs because the coexistence of VHD does not affect the overall relative efficacy or safety of NOACs in terms of

prevention of SSEE and major bleeding. Current definitions of “valvular” and “nonvalvular” AF are misleading, and the use of NOACs should be permitted in most patients with VHD. The recently proposed term “MARM-AF,” standing for “Mechanical And Rheumatic Mitral valvular AF” (4), could be useful to identify the true high risk AF patients for whom VKAs are the anticoagulants of choice.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In the phase III trials comparing NOACs with warfarin in patients with AF, the relative efficacy and safety of NOACs were similar in patients with or without mitral insufficiency, aortic stenosis, aortic insufficiency, bioprosthetic valves, or valve repair surgery, suggesting that NOACs can be safely used in patients without moderate-to-severe mitral stenosis or mechanical valves.

TRANSLATIONAL OUTLOOK: Future trials should specifically address patients with bioprosthetic heart valves and valve repair surgery who were relatively underrepresented in trials performed to date.

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APPENDIX For supplemental figures and tables, please see the online version of this article.