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The efficacy and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and coronary artery disease: A meta-analysis of randomized trials

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Abstract

Background: Patients with atrial fibrillation and concomitant coronary artery disease (CAD) are at higher risk for myocardial infarction or cardiovascular death, often require antiplatelet therapy and are therefore exposed to an increased risk of bleeding. This meta-analysis aimed to compare the efficacy and safety profile of non-vitamin K antagonist oral anticoagulants (NOACs) with warfarin in patients with atrial fibrillation and concomitant CAD.

Materials and methods: We performed a trial-level meta-analysis of CAD subgroups from four trials of NOAC versus warfarin in patients with atrial fibrillation, comparing the primary trial endpoints (efficacy: stroke or systemic embolic event; safety: International Society on Thrombosis and Haemostasis major bleeding) in patients with versus those without CAD, and used interaction testing to assess for treatment effect modification.

Results: In total, 58,606 patients with established CAD were included in this meta-analysis. NOACs reduced the risk of stroke/systemic embolic event irrespective of presence of CAD (CAD: 0.76 (0.56–1.04); no CAD: hazard ratio 0.77 (0.56–1.06); *p*-INT 0.93). Similarly, there was no effect modification by presence of CAD for major bleeding (CAD: hazard ratio 0.92 (0.65–1.32), no CAD: 0.83 (0.61–1.12); *p*-INT 0.46) or myocardial infarction (CAD: hazard ratio 0.95 (0.62–1.44); no CAD: hazard ratio 0.95 (0.60–1.50); *p*-INT = 0.98). While NOACs reduced all-cause mortality in patients without CAD compared with warfarin (hazard ratio 0.85 (0.71–1.02)), there was no difference in mortality between NOACs and warfarin in the CAD group (hazard ratio 0.99 (0.82–1.20); *p*-INT 0.01).

Conclusion: The present meta-analysis of four trials supports that NOACs are safe and at least as effective as warfarin in patients with atrial fibrillation and established CAD.

Keywords

Meta-analysis, atrial fibrillation, coronary artery disease, edoxaban, NOAC, warfarin

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Background

Concomitant coronary artery disease (CAD) in patients with atrial fibrillation presents an additional challenge to clinicians as they identify the optimum management that balances the risk of bleeding and protection from ischemic events.[1,2] Patients with CAD are at increased risk of myocardial infarction (MI) or cardiovascular death, often

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require antiplatelet therapy and are therefore exposed to an increased risk of bleeding. Warfarin has been shown to reduce the risk of MI in post-MI patients as well as in patients with atrial fibrillation.[3–5] However, several non-vitamin K antagonist oral anticoagulants (NOACs) are now available and increasingly used for anticoagulation of patients with atrial fibrillation.[6–8] Findings from the ATLAS ACS 2–TIMI 51 trial[9] and the COMPASS trial[10] showed that, compared with placebo, very low-dose rivaroxaban reduced the risk of cardiovascular death, MI, and stroke in patients with CAD but without atrial fibrillation.

This meta-analysis therefore aimed to compare NOACs with warfarin in terms of efficacy and safety and test for effect modification by CAD status.

Materials and methods

Data search and study selection

This meta-analysis was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[11–13] A comprehensive data search of all randomized-controlled phase 3 trials comparing non-vitamin K antagonist oral anticoagulants (NOACs; Factor Xa inhibitors or direct thrombin inhibitors) reporting treatment effects stratified by CAD status was performed using PubMed and included all articles in the English language up to 6 May 2018. We restricted our search to phase 3 controlled trials that included patients with atrial fibrillation who were randomly assigned to receive a NOAC or warfarin, and trials in which both efficacy and safety outcomes were reported. We did not consider trials that included patients with recent (<4 weeks) acute coronary syndrome or revascularization. The search was performed by two independent reviewers (TAZ, RPG) and any discrepancies were resolved by consensus. The search algorithm is presented in detail in the Supplementary Material online. Only aggregated data of previously published publications were extracted. No patients were involved in the conduction of this meta-analysis and thus no informed consent and institutional review board approval was required.

Endpoints

As in the NOAC versus warfarin trials in patients with atrial fibrillation, the primary efficacy endpoint was time to the first component of the composite of stroke or systemic embolic event (SEE); the principal safety endpoint was time to major bleeding (as defined by the International Society on Thrombosis and Haemostasis (ISTH)).[14] In addition, data on secondary efficacy and safety endpoints such as all-cause mortality, myocardial infarction, stroke, and intracranial hemorrhage were collected. Only Food and Drug Administration (FDA)-approved dosage regimens were analyzed, resulting in the exclusion of the lower dose edoxaban (30/15 mg) once daily and dabigatran (110 mg) twice daily regimens.

Statistical analysis

A trial-level meta-analysis of both the coronary artery disease (CAD) and no-CAD subgroups was performed using a bivariate random-effects model with the DerSimonian and Laird approach[15] and the Hartung–Knapp adjustment[16] and testing for interaction using R version 3.3.3 (R Core Team, Vienna, Austria) and the R package "meta" (version 4.8-2).[17] Heterogeneity was assessed using Cochrane Q statistic, tau^2, and Higgins' I^2. Statistical significance was assessed at a nominal alpha level of 0.05. All reported p values are two-sided and no adjustments for multiple testing were performed.

Results

Study characteristics

We identified a total of eight manuscripts that were eligible for inclusion, consisting of four subgroup analyses and the four main reports from the four NOAC versus warfarin phase III trials.[6–8,18–22] Figure S1 in the Supplementary Material online shows an overview of the search and the selection process.

As only FDA-approved doses were considered, a total of 58,606 patients were included in the present meta-analysis. While the subgroup analyses of ARISTOTLE, ROCKET-AF, and ENGAGE AF–TIMI 48 stratified patients by presence of CAD,[19,21,22] the subgroup analysis of ROCKET-AF stratified by prior MI.[20] In addition, differences in patient characteristics in the overall trials were observed due to different inclusion criteria (Table 1). In this context, the ROCKET-AF trial had the highest $CHADS_2$ score among all NOAC trials and the lowest median time in the therapeutic range.

Meta-analysis of CAD subgroups from all four NOAC versus warfarin atrial fibrillation trials

In total, 1875 stroke/SEE events (CAD: 583; no CAD: 1292), 3284 major bleeding events (CAD: 1156; no CAD: 2128), and 835 MIs (CAD: 460; no CAD: 375) had occurred in the included trials with the FDA-approved doses.

The present meta-analysis of all published CAD subgroup analyses[19–22] from the NOAC versus warfarin trials showed a significant benefit in favor of NOACs for the endpoint of stroke/SEE (hazard ratio 0.77 (0.66–0.90), $p<0.01$) that did not differ by the presence or absence of CAD (CAD: 0.76 (0.56–1.04); no CAD: hazard ratio 0.77 (0.56-1.06); p-INT 0.93; Figure 1). There was a CAD status independent trend toward a benefit with NOACs for the endpoint of major bleeding (hazard ratio 0.87 (0.73–1.02),

Table 1. Summary of randomized controlled trials and their coronary artery disease subgroup analyses of non-vitamin K antagonist versus warfarin in patients with atrial fibrillation.

	RE-LY [6]		ROCKET-AF[8]		ARISTOTLE[7]		ENGAGE AF– TIMI 48[18]	
Drug	Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
Mechanism of action	Direct thrombin inhibitor		Factor Xa inhibitor		Factor Xa inhibitor		Factor Xa inhibitor	
Trial characteristics:								
Blinding	Open label		Double blind, double dummy		Double blind, double dummy		Double blind, double dummy	
Doses analyzed	150 mg b.i.d.		20 mg[a] q.d.		5 mg[a] b.i.d		60 mg[a] q.d.	
Median follow-up time, years	2.0		1.9		1.8		2.8	
Mean $CHADS_2$ score (SD)	2.1 (1.1)		3.5 (0.9)		2.1 (1.1)		2.8 (1.0)	
Median time in the therapeutic range, warfarin arm	67%		58%		66%		68%	
Trial participants, *n*	18,113		14,264		18,201		21,105	
Qualifying risk factor:								
Age ⩾75 years, %	40.1		43.7[23]		31.2		40.2	
Prior stroke/TIA, %	19.9		54.7		19.5		28.3	
Congestive heart failure, %	32.0		62.5		35.5		57.4	
Diabetes mellitus, %	23.4		40.0		25.0		36.1	
Hypertension, %	78.9		90.6		87.5		93.6	
Prior myocardial infarction, %	16.6		17.3		14.2		11.5	
Aspirin use, %	40.0		36.5		30.9		29.3	
P2Y12 inhibitor use, %	5.6		2.5		1.9		2.3	
CAD subgroup analyses	Hohnloser et al.[19]		Mahaffey et al.[20]		Bahit et al.[21]		Zelniker et al.[22]	
Definition of CAD	History of known CAD or prior myocardial infarction (not described in more detail)		Prior myocardial infarction		History of CAD, MI, and/or coronary revascularization		Prior myocardial infarction, coronary revascularization, or known medically treated coronary stenosis	
Proportion of patients with CAD as defined per subgroup analysis	31		17.3		36.5		21.4	
Presence of CAD/MI:	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Median age, years	N/A	N/A	73 (67–79)	73 (65–78)	70 (63–76)	70 (62–76)	73 (66–79)	72 (64–77)
Female sex, %	N/A	N/A	25.4	42.7	29.8	38.4	33.3	33.3
Prior stroke/TIA, %	N/A	N/A	45.8	53.7	21.4	18.3	25.8	29.0
Congestive heart failure, %	N/A	N/A	77.8	59.2	47.7	28.4	63.1	55.9
Diabetes mellitus, %	N/A	N/A	46.6	38.5	29.2	22.5	44.4	33.9
Hypertension, %	N/A	N/A	93.8	89.8	90.2	85.9	94.8	93.3
Aspirin, %	N/A	N/A	47.4	33.9	42.2	24.5	45.1	25.0

[a]Dose reduced in selected patients described in the protocols.
CAD: coronary artery disease; MI: myocardial infarction; NA: not available TIA: transient ischemic attack.

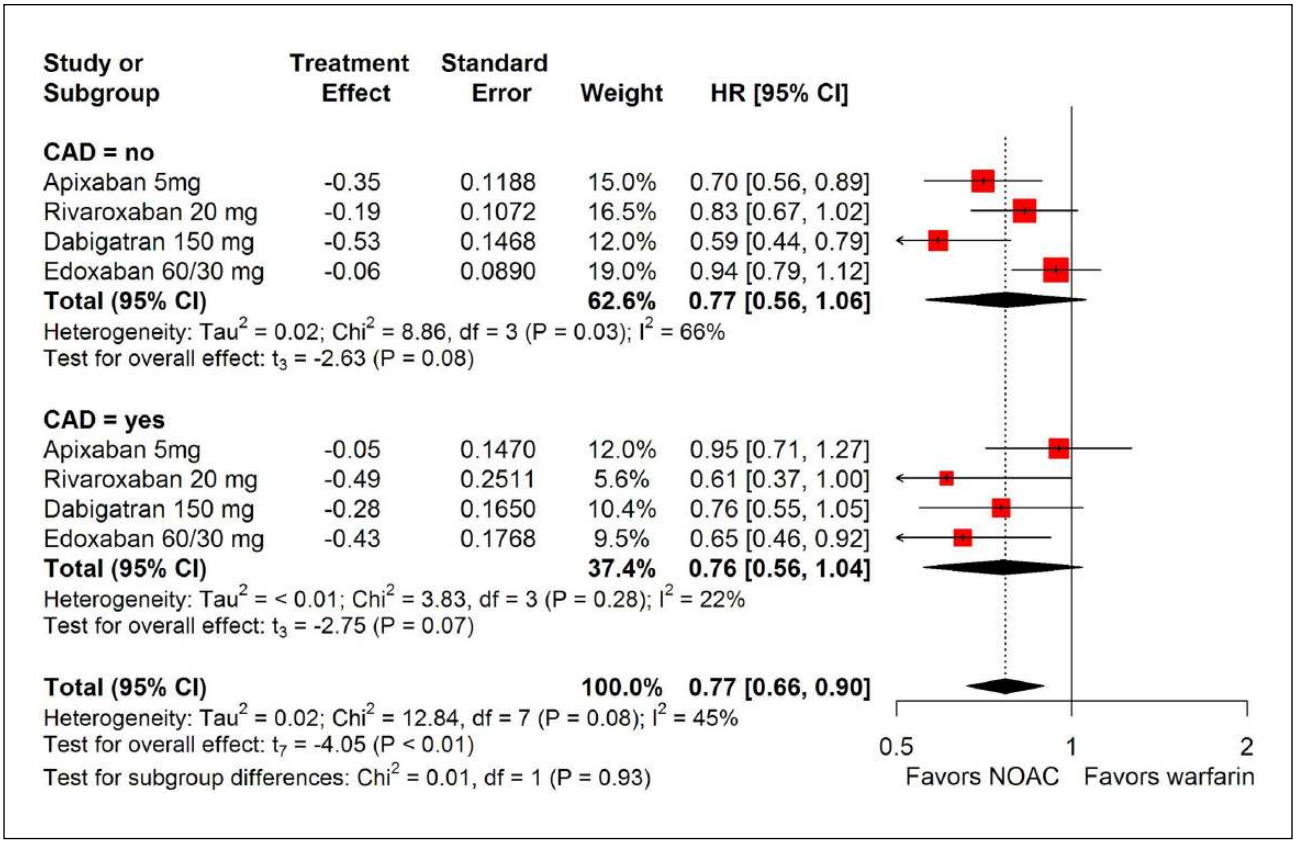

Figure 1. Meta-analysis of non-vitamin K studies on stroke/systemic embolic event stratified by the presence of coronary artery disease. Forest plot for risk of the composite of stroke or systemic embolic event according to presence or absence of established coronary artery disease. Random effects including corresponding *p*-values (*z*-score or *t*-score) are presented per subgroup and for both groups combined. Random effects models were estimated using Hartung–Knapp adjustment. DerSimonian–Laird estimator (tau), Cochrane's Q statistic (chi), and Higgins' and Thompson's I^2 are measurements of heterogeneity estimating the between-study variance. Tests for subgroup difference is represented by the interaction *p*-value.
CAD: coronary artery disease; CI: confidence interval; df: degrees of freedom; HR: hazard ratio; NOAC: non-vitamin K antagonist oral anticoagulant; TE: standardized treatment effect; SE: standard error of the standardized treatment effect; t: test statistic using t score.

$p = 0.08$; CAD: hazard ratio 0.92 (0.65–1.32), no CAD: 0.83 (0.61–1.12); *p*-INT 0.46; Figure 2). There was substantial heterogeneity in both the CAD (I^2 62%) and no-CAD group (I^2 79%). In the CAD cohort, the ROCKET-AF trial had less favorable results with rivaroxaban in these patients, meanwhile in the no-CAD group the ARISTOTLE trial demonstrated a more favorable effect of apixaban (Figure 2).

No difference between NOACs and warfarin was found for prevention of MI regardless of CAD status (CAD: hazard ratio 0.95 (0.62–1.44); no CAD: hazard ratio 0.95 (0.60–1.50); *p*-INT = 0.98; Figure 3).

Meta-analyzing only three trials (due to the absence of available mortality data from RE-LY), a significant interaction by CAD status was found for all-cause mortality (*p*-INT 0.01; Figure 4). While NOACs tended to reduce all-cause mortality in patients without CAD compared with warfarin (hazard ratio 0.85 (0.71–1.02)), there was no difference in mortality between NOACs and warfarin in the CAD group (hazard ratio 0.99 (0.82–1.20)). This interaction remained statistically significant (*p*-INT <0.01) even after removing the ROCKET-AF trial, which included only patients with prior MI in the CAD group. There was also a significant benefit of NOACs for both stroke (CAD: 0.80 (0.50–1.29), no CAD: 0.84 (0.581.22), *p*-INT 0.70; Supplementary Figure S2) and intracranial hemorrhage (CAD: 0.40 (0.16–1.03), no CAD: 0.52 (0.35–0.77); *p*-INT 0.27; Supplementary Figure S3) that was independent of CAD status.

Discussion

A meta-analysis of all four NOAC versus warfarin trials in patients with atrial fibrillation stratified by CAD status showed that the presence of CAD did not modulate the therapeutic effect on the primary outcomes of prevention of

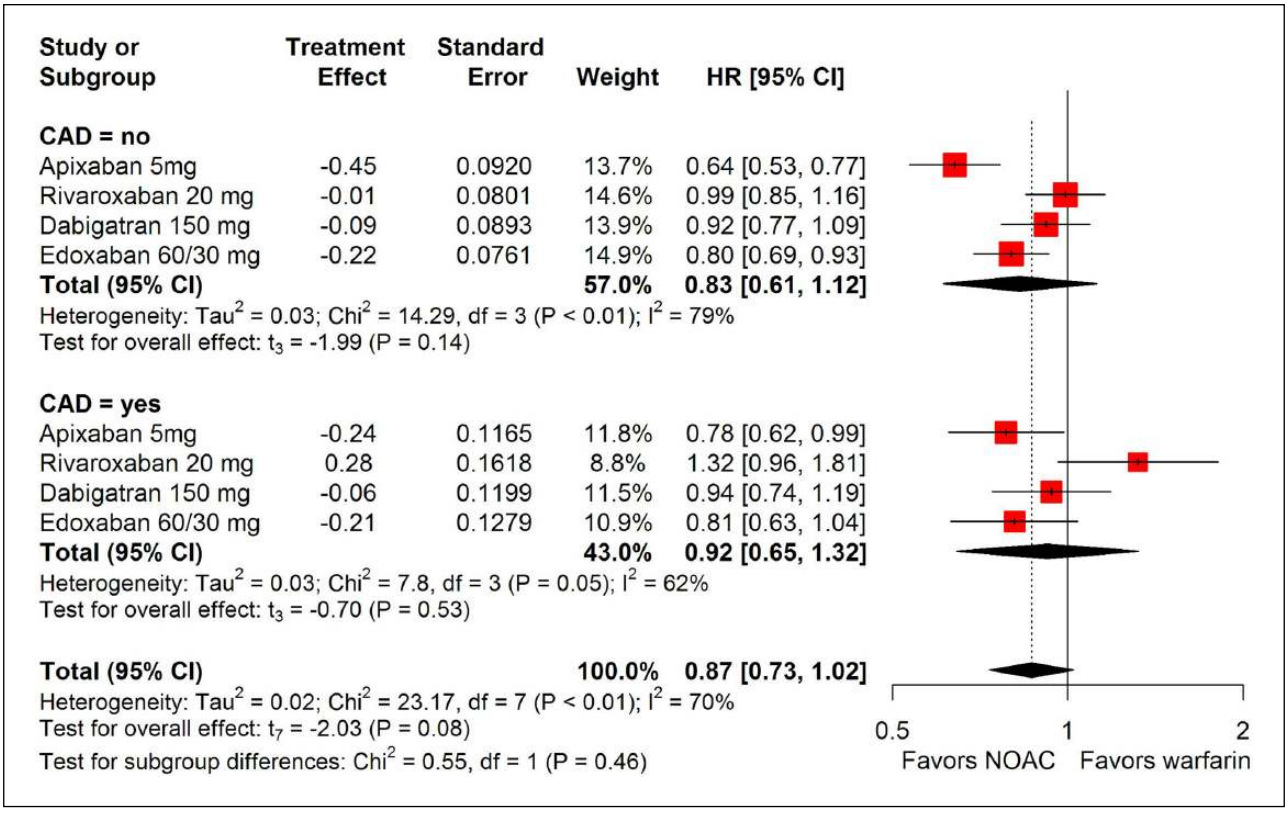

Figure 2. Meta-analysis of non-vitamin K studies on major bleeding stratified by the presence of coronary artery disease. Forest plot for risk of major bleeding according to presence or absence of established coronary artery disease.
CAD: coronary artery disease; CI: confidence interval; df: degrees of freedom; HR: hazard ratio; NOAC: non-vitamin K antagonist oral anticoagulant; t: test statistic using t score.

stroke/SEE or major bleeding favoring NOACs over warfarin. While NOACs demonstrated similar effects on most outcomes tested in both subgroups, we observed a statistically significant interaction effect on all-cause mortality indicating a similar effect between warfarin and NOACs in the CAD group, but a numerically greater benefit of NOACs in patients without CAD. This was largely driven by the ROCKET-AF trial, which tended to have better outcomes with rivaroxaban (as compared with warfarin) in patients without prior MI compared with patients with prior MI. The underlying causes of the observed interaction are unknown. Of note, we did not find any other significant differences in treatment efficacy and safety based on CAD status, thus we cannot exclude a type I error. Important differences between the ROCKET-AF trial and the other three trials may have contributed to the significant interaction. The ROCKET-AF trial included patients with the highest mean $CHADS_2$ score of all NOAC trials and its secondary subgroup analysis stratified patients by history of MI instead of prior CAD. Whether differences in the above factors or NOAC characteristics, or the play of chance, were responsible for the observed interaction cannot be definitely established without trials that directly compare NOACs head-to-head.

NOACs have become an attractive alternative to warfarin in patients with atrial fibrillation, as they do not have to be routinely monitored, possess a rapid onset of action, lack significant food interactions, and have fewer potential for drug interactions.[24–27] In addition, a meta-analysis published from our group[28] showed a significant 19% reduction in stroke/SEE, a 52% reduction of intracranial hemorrhage, and a significant 10% reduction of all-cause mortality with NOACs as compared with warfarin.

There is also growing interest in NOACs for prevention of non-stroke cardiovascular ischemic events in patients with CAD given the promising results of the ATLAS ACS 2–TIMI 51 trial[9] and the COMPASS trial.[10] However, contrary to the studies included in this meta-analysis, these trials tested lower doses of NOACs in patients who did not have atrial fibrillation, and the comparator was placebo and not warfarin (which itself possesses cardiovascular protective effects[3–5]).

It is also important to consider that the use of additional antiplatelet therapy increases the risk of bleeding

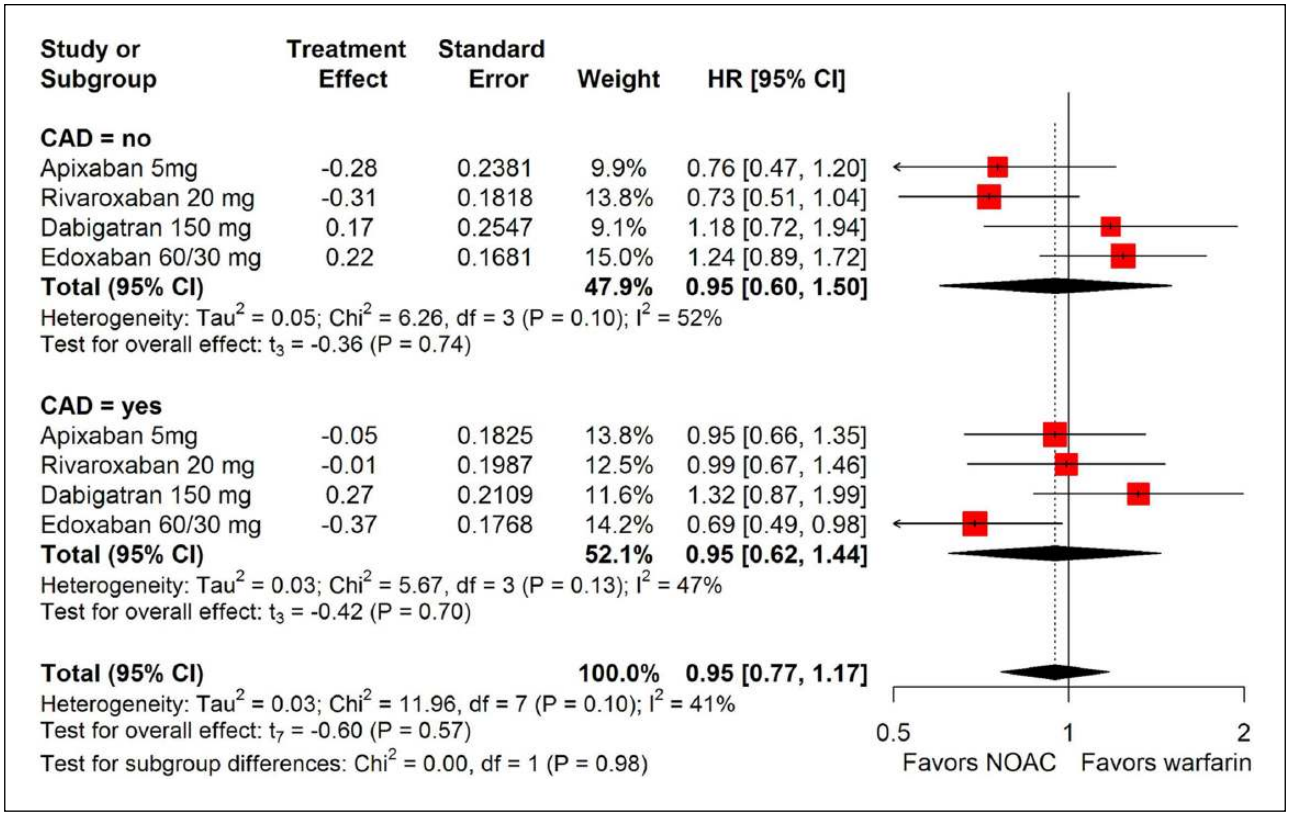

Figure 3. Meta-analysis of non-vitamin K studies on myocardial infarction stratified by the presence of coronary artery disease. Forest plot for risk of myocardial infarction according to presence or absence of established coronary artery disease.
CAD: coronary artery disease; CI: confidence interval; df: degrees of freedom; HR: hazard ratio; NOAC: non-vitamin K antagonist oral anticoagulant; t: test statistic using t score

in patients on anticoagulation.[29] In this context, a meta-analysis comparing NOACs with warfarin in patients with atrial fibrillation on concomitant aspirin found that NOACs were more effective than warfarin in reducing stroke and SEE, while the bleeding risk was similar with NOACs compared with warfarin on a background of aspirin.[30]

Limitations

We acknowledge several limitations. First, this meta-analysis used aggregated study-level data rather than individual participant data. Despite the large number of patients included, the limited number of available NOAC trials including their different patient characteristics and inclusion criteria might have reduced the precision of the estimated treatment effect of the subgroups in the presented meta-analyses. In addition, for some endpoints (stroke, intracranial hemorrhage, and all-cause mortality) no data from the RE-LY trial was available. Presence of CAD was investigator-reported and the definitions of CAD varied between the included trials (ROCKET-AF provided data for only prior MI). The median age in the NOAC versus warfarin trials was 72 years and patients had several risk factors for atherosclerosis. Therefore, the presence of subclinical CAD in some patients classified as no CAD is highly probable. As patients with recent acute coronary syndrome and revascularization were excluded from the primary trials, the generalizability is limited to patients with atrial fibrillation and stable CAD.

Furthermore, we observed a substantial amount of heterogeneity for several outcomes, for which random effects models were used. However, it remains unclear whether the observed heterogeneity was due to the different drugs, doses, definitions of CAD, or the study cohorts. It is important to consider that although we included only FDA-approved doses, they were not necessarily functionally the same across the tested NOACs. Furthermore, different definitions of the primary safety endpoint were used across the primary NOAC trials. However, as ISTH major bleeding was consistently reported in the CAD subgroup analyses from the randomized trials, we used it for our analysis.

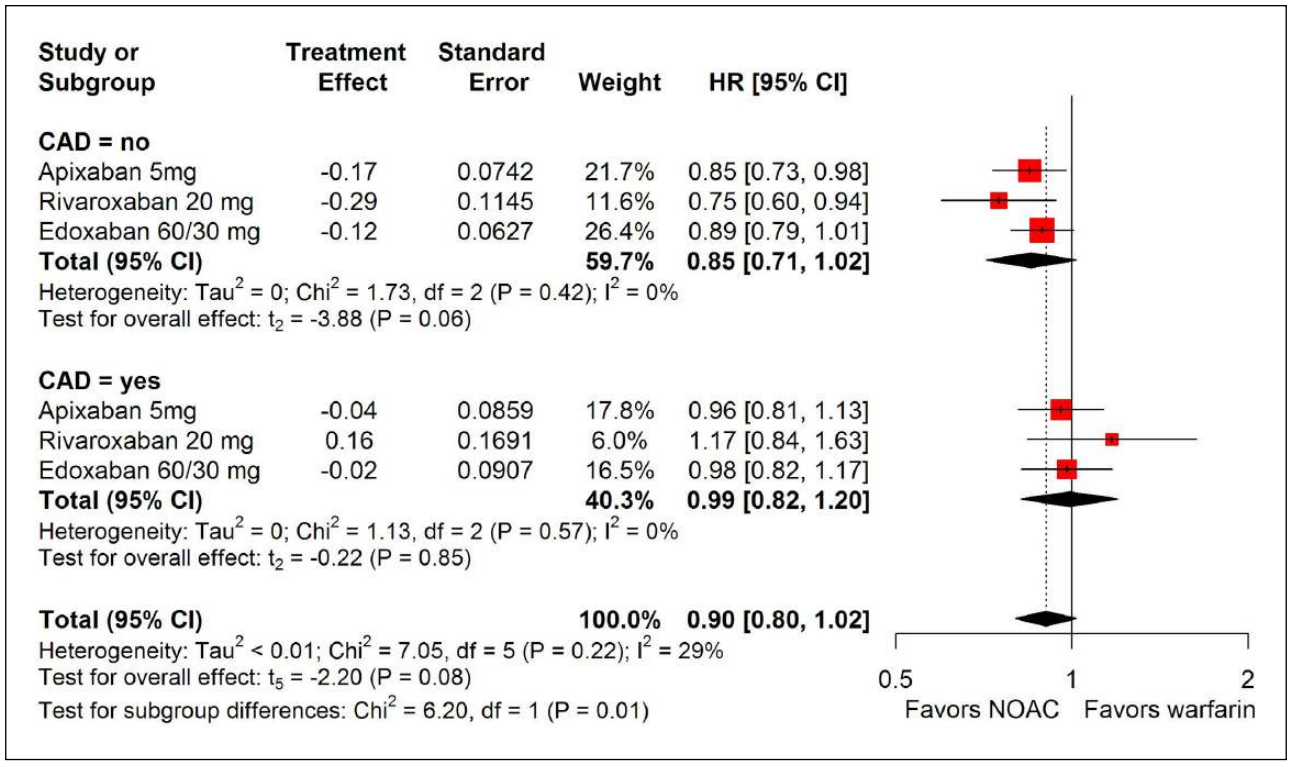

Figure 4. Meta-analysis of non-vitamin K studies on all-cause mortality stratified by the presence of coronary artery disease. Forest plot for risk of all-cause mortality according to presence or absence of established coronary artery disease.
CAD: coronary artery disease; CI: confidence interval; df: degrees of freedom; HR: hazard ratio; NOAC: non-vitamin K antagonist oral anticoagulant; t: test statistic using t score

Conclusion

A meta-analysis of the NOAC versus warfarin trials in patients with atrial fibrillation showed a significant benefit in favor of NOACs for the endpoints of stroke/SEE, any stroke, and intracranial hemorrhage regardless of presence or absence of CAD. The totality of the evidence to date supports the use of NOACs in patients with atrial fibrillation, regardless of the presence or absence of concomitant CAD.

Acknowledgements

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Conflict of interest

TAZ reports grants from German Research Foundation (Deutsche Forschungsgemeinschaft; grant number: ZE 1109/1-1), and grant support from Daiichi-Sankyo to his institution. CTR reports grant support from Daiichi-Sankyo to his institution; grants and personal fees from Daiichi-Sankyo, personal fees from Bayer, Portola, and Janssen outside the submitted work. EMA reports grant support from Daiichi-Sankyo to his institution and grants from Daiichi-Sankyo outside the submitted work. RPG reports grants support from Daiichi-Sankyo to his institution, grants, and personal fees from Amgen, personal fees from Daiichi-Sankyo, personal fees from Merck, Boehringer-Ingelheim, Bristol-Myers-Squibb, CVS Caremark, GlaxoSmithKline, Lexicon, Portola, and Pfizer outside the submitted work.

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