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Impact of a single non-sex-related stroke risk factor on atrial fibrillation and oral anticoagulant outcomes: a systematic review and meta-analysis

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ABSTRACT

Aims Oral anticoagulants (OACs) are crucial for treating atrial fibrillation (AF) patients at high thromboembolic risk. However, in AF patients at intermediate thromboembolic risk with a single non-sex-related stroke risk factor (CHA_2DS_2-VASc score 1 in men, 2 in women), guidelines advise to consider starting anticoagulation, which may result in OAC non-initiation due to underestimation of the thromboembolic risk of a single stroke risk factor and overestimation of the OAC-related bleeding risk. A critical appraisal of the role of OACs and the benefit–risk profile of non-vitamin K antagonist oral anticoagulants (NOACs) compared with vitamin K antagonists (VKAs) in this patient subgroup are needed.

Methods and results This systematic review provides an overview of literature on the effectiveness and safety of OACs in AF patients with a single non-sex-related stroke risk factor after searching Medline and Embase. Differences between individual stroke risk factors regarding the ischaemic stroke risk in non-anticoagulated AF patients are identified in a meta-analysis, demonstrating the highest increased risk in patients aged 65–74 years old or with diabetes mellitus, followed by heart failure, hypertension and vascular disease. Furthermore, meta-analysis results favour NOACs over VKAs, given their equal effectiveness and superior safety in AF patients at intermediate thromboembolic risk (HR 0.93, 95% CI 0.65 to 1.34 for stroke or systemic embolism; HR 0.60, 95% CI 0.45 to 0.80 for major bleeding; HR 0.48, 95% CI 0.14 to 1.59 for intracranial bleeding; HR 0.58, 95% CI 0.47 to 0.71 for mortality).

Conclusion Our systematic review with meta-analysis favours the use of anticoagulation in AF patients with a single non-sex-related stroke risk factor, especially when age ≥65 years or diabetes mellitus is present, with a preference for NOACs over VKAs.

Key questions

What is already known about this subject?

- Guidelines advise to consider starting oral anticoagulants (OACs) in atrial fibrillation (AF) patients at intermediate thromboembolic risk with a single non-sex-related stroke risk factor (CHA_2DS_2-VASc score 1 in men, 2 in women). Underestimation of the thromboembolic risk and overestimation of the OAC-related bleeding risk may result in OAC non-initiation.

What does this study add?

- In non-anticoagulated AF patients with a single non-sex-related stroke risk factor, not all risk factors were associated with a similar increase in ischaemic stroke risk, as the risk increased most significantly in patients aged between 65 and 74 years old or with diabetes mellitus, followed by congestive heart failure, hypertension or vascular disease.
- Importantly, in line with results in AF patients at high thromboembolic risk, this is the first meta-analysis demonstrating that non-vitamin K antagonist oral anticoagulants (NOACs) may be preferred over vitamin K antagonists in AF patients at intermediate thromboembolic risk, given the similar effectiveness and superior safety.

How might this impact on clinical practice?

- In absence of absolute contra-indications for anticoagulation, every AF patient with a single non-sex-related stroke risk factor appears to benefit from treatment with a NOAC, after careful evaluation of modifiable bleeding risk factors.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide and is associated with a fivefold increased risk of stroke or systemic embolism (stroke/SE).[1] Oral anticoagulants (OACs) are the cornerstone of AF treatment to reduce the thromboembolic risk.[2] Large randomised controlled trials (RCTs) comparing non-vitamin K antagonist oral anticoagulants (NOACs) with vitamin K antagonists (VKAs) in patients with non-valvular AF, have shown that NOACs are efficacious and safe alternatives to VKAs.[3–6] International guidelines[7] have expressed a preference for NOACs over VKAs in AF patients without clear contra-indications for OACs.[7–10] They recommend initiation of an OAC in the presence of ≥2 non-sex-related stroke risk factors (high thromboembolic risk), using the

CHA_2DS_2-VASc score (score of ≥2 in men, ≥3 in women, based on congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, stroke/SE/transient ischaemic attack (TIA) (2 points), vascular disease, age 65–74 years and female sex). In AF patients without a non-sex-related stroke risk factor (low thromboembolic risk: CHA_2DS_2-VASc score of 0 in men, 1 in women), OACs should be omitted. However, in AF patients at intermediate thromboembolic risk with only one non-sex-related stroke risk factor (CHA_2DS_2-VASc score of 1 in men and 2 in women), discrepancies are still present. The European[8 10] and American[9] guidelines recommend that OACs should be considered in AF patients with a single non-sex-related stroke risk factor, whereas the Canadian guidelines[7] recommend OAC initiation in these patients (instead of 'consider an OAC'). Due to the ambiguous advice of guidelines 'to consider anticoagulation', clinicians are left in uncertainty whether or not to start anticoagulation in AF patients with a single non-sex-related stroke risk factor.

In order for the clinician to decide whether anticoagulation is useful or not in patients at intermediate thromboembolic risk, three important aspects should be evaluated. First, does the presence of one stroke risk factor significantly increase the thromboembolic risk in non-anticoagulated AF patients? Second, does the reduction in the thromboembolic risk by starting an OAC in AF patients at intermediate thromboembolic risk outweigh the potential increase in the bleeding risk? Third, if a net clinical benefit for OAC initiation is present, do NOACs provide the same effectiveness and safety as VKAs in these AF patients? This systematic review provides an overview of the literature investigating these research questions. A meta-analysis on the impact of each individual non-sex-related stroke risk factor on the risk of ischaemic stroke in non-anticoagulated AF patients will be performed to identify differences between risk factors, as well as a meta-analysis on the effectiveness and safety of NOACs versus VKAs in AF patients at intermediate thromboembolic risk.

METHODS

Using the Medline and Embase databases, a literature search was performed (see online supplemental etable 1). Longitudinal studies related to (1) the impact of each individual non-sex-related stroke risk factor according to the CHA_2DS_2-VASc score on the risk of ischaemic stroke in non-anticoagulated non-valvular AF patients as compared with AF patients with no stroke risk factors (first meta-analysis), (2) the effectiveness and safety of OACs versus no OACs in AF patients with one stroke risk factor and (3) the effectiveness and safety of NOACs versus VKAs in AF patients with a CHA_2DS_2-VASc score of 1 in men and 2 in women (second meta-analysis) during a mean/median follow-up of at least 6 months were included. If studies only reported results on the effectiveness and safety of NOACs versus VKAs in AF patients with a low $CHADS_2$ score (≤1) but not stratified according to CHA_2DS_2-VASc score, they were excluded for the second meta-analysis, but still included for the qualitative synthesis (systematic review). Studies regarding OAC use for non-AF indications (eg, venous thromboembolism) were excluded. Effectiveness and safety outcomes of interest were thromboembolism (ischaemic stroke or stroke/SE), all-cause mortality, major bleeding, intracranial bleeding and gastrointestinal bleeding. RCTs (post hoc analyses or original trial), longitudinal observational cohort studies and meta-analyses written in English were included for the qualitative synthesis, while cross-sectional studies, reviews, case reports, editorials or conference proceedings were not considered. For both meta-analyses, only (post hoc analyses of) RCTs and longitudinal observational cohort studies were included. No restriction of publication date was used.

Up to 1 November 2020, 6435 articles were identified. Additional articles of interest were selected by screening the reference list of identified studies. After screening title and abstract, 36 articles were selected. After reading the full-text, 13 articles were selected for the qualitative synthesis, 3 for the first meta-analysis (all observational studies) and 3 for the second meta-analysis (1 post hoc analysis of an RCT, 2 observational studies) (figure 1). The study design, patient characteristics and outcome measures of included studies are displayed in tables (online supplemental etable 2-4).

Both meta-analyses were performed using the metafor package in R (R V.3.6.1 with RStudio V.1.2.5001) with a random effects model and inverse-variance weighting, by pooling results based on the logarithm of the adjusted hazard ratios (HRs) and standard error. Data on study characteristics (design, setting and duration), baseline characteristics of included subjects (total number and mean/median age), comparison (eg, NOAC vs VKA) and the effectiveness and safety outcomes of interest (ischaemic stroke for the first meta-analysis; stroke/SE, major bleeding, intracranial bleeding and all-cause mortality for the second meta-analysis) were extracted from the original publications or supplemental materials. Effect sizes were presented as HR with 95% CI) for the outcomes of interest when comparing non-anticoagulated AF patients with one stroke risk factor to no stroke risk factors (first meta-analysis), and NOACs to VKAs in AF patients at intermediate thromboembolic risk (CHA_2DS_2-VASc score 1 in men, 2 in women) (second meta-analysis). A two-sided p value of <0.05 was considered statistically significant. Forest plots were drafted using the forestplot package in R. Heterogeneity was tested using the I^2 statistic, based on a restricted maximum-likelihood estimator.

The risk of bias of each study included in the meta-analyses was assessed using the quality assessment tool 'QUALSYST' from the 'Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields' (online supplemental etable 5,6).[11] Fourteen items of each quantitative study were scored with this tool on the study and outcome levels depending

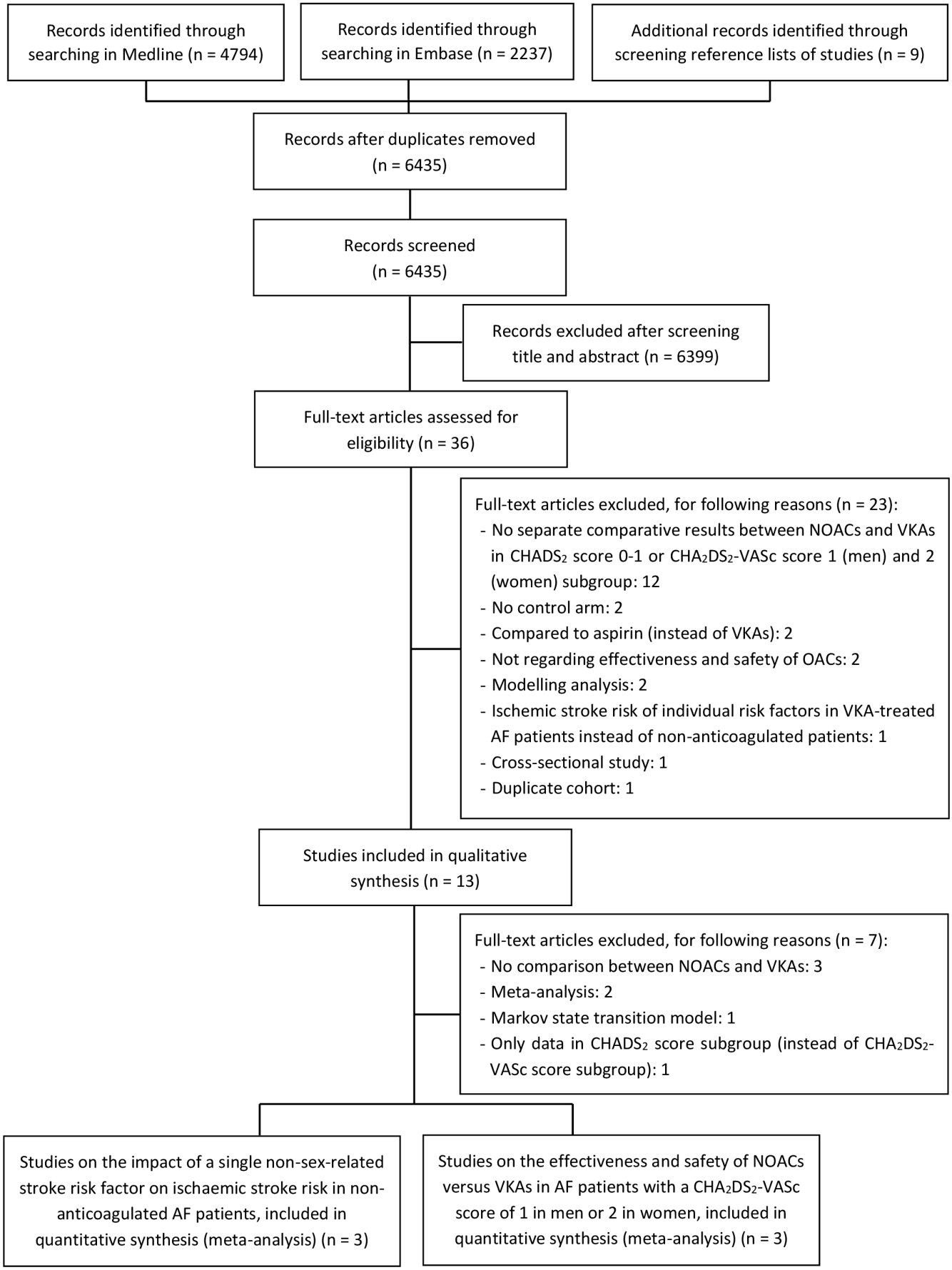

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist.

on the degree to which the specific criteria were met or reported ('yes'=2, 'partial'=1, 'no'=0, 'n/a' if not applicable to a particular study design). A percentage was calculated for each paper by dividing the total sum score obtained across rated items by the total possible score. Studies were included if scoring at least 80% on the quality assessment tool. The risk of publication bias at the outcome level for the studies included in the meta-analyses was assessed through funnel plot asymmetry and Egger's regression test. This work has been performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA checklist included in supplemental materials, online supplemental etable 7).

RESULTS

Impact of single non-sex-related stroke risk factor

Systematic review

Several studies have investigated the impact of each individual non-sex-related stroke risk factor on the risk of ischaemic stroke in non-anticoagulated AF patients (online supplemental etable 2). In a Danish cohort study by Olesen *et al*, an overall thromboembolic rate of 0.78 per 100 person-years (PY) was found in 6369 non-anticoagulated AF patients with no risk factors versus 2.01 per 100 PY in 8203 patients with a single risk factor after 1 year of follow-up.[12] Diabetes mellitus and age 65–74 years old were associated with the highest increase in the thromboembolic risk as compared with subjects without risk factors. Hypertension showed an intermediately increased thromboembolic risk, while vascular disease and congestive heart failure did not significantly increase the risk after 1 year. Similar results were seen after 5 and 10 years of follow-up, although the thromboembolic risk also significantly increased in patients with vascular disease or heart failure, which may indicate that long-term treatment is required until being beneficial.

Similarly, a Taiwanese cohort study by Chao *et al* demonstrated an annual ischaemic stroke rate of 2.75 and 2.55 per 100 PY in 12 935 male and 7900 female non-anticoagulated AF patients, respectively, with a single non-sex-related stroke risk factor after a mean follow-up of 5.2 years.[13] As compared with AF patients without a stroke risk factor, the highest increase in ischaemic stroke risk was observed in patients aged 65–74 years old and patients with diabetes mellitus, followed by congestive heart failure, hypertension and vascular disease.

Moreover, in another Taiwanese cohort study by Hung *et al* stratifying non-anticoagulated AF patients by age, the annual ischaemic stroke rate in 20–49 and 50–64 years old patients without any non-sex-related stroke risk factor (n=3674 and 4301) was 0.63 and 1.96 per 100 PY, respectively, whereas 1.33 and 2.90 per 100 PY in patients with one non-sex-related stroke risk factor aged 20–49 and 50–64 years old, respectively (n=1852 and 4561) and 3.60 per 100 PY in patients 65–74 years old (n=5422).[14] The highest increase in ischaemic stroke risk was observed in younger AF patients (<50 years old) with heart failure or diabetes mellitus as compared with age-matched AF patients without risk factors. Hypertension and vascular disease also significantly increased the risk, but less than heart failure or diabetes mellitus. Likewise, in AF patients aged 50–64 years old, diabetes mellitus was the most important risk factor, followed by congestive heart failure and hypertension, but vascular disease was not associated with a significantly increased ischaemic stroke risk. Finally, age 65–74 years old as a single stroke risk factor also significantly increased the risk of ischaemic stroke as compared with younger AF patients without stroke risk factors.

Meta-analysis

Results of the three above-mentioned longitudinal observational cohort studies[12–14] were pooled in a meta-analysis. All included studies scored >80% on the quality assessment tool 'QUALSYST'[11] (online supplemental etable 5). As compared with non-anticoagulated AF patients without stroke risk factors, the presence of any non-sex-related stroke risk factor (CHA_2DS_2-VASc score 1 in men, 2 in women) was associated with a more than doubled risk of ischaemic stroke (HR 2.03, 95% CI 1.65 to 2.51, I^2 93.3%) (figure 2). The overall pooled ischaemic stroke risk was most significantly increased in AF patients aged 65–74 years old (HR 3.24, 95% CI 2.25 to 4.69, I^2 97.6%) and patients with diabetes mellitus (HR 2.51, 95% CI 2.21 to 2.84, I^2 26.9%) as compared with AF patients without stroke risk factors, followed by congestive heart failure (HR 1.98, 95% CI 1.58 to 2.50, I^2 83.9%) and hypertension (HR 1.74, 95% CI 1.50 to 2.02, I^2 71.9%). Vascular disease was associated with the smallest but still significantly increased ischaemic stroke risk (HR 1.56, 95% CI 1.14 to 2.12, I^2 72.4%).

No publication bias was suspected, although the interpretation may have not been reliable, as less than 10 studies were included in the meta-analysis (online supplemental efigure 3). The overall substantial heterogeneity observed for all risk factors (except for diabetes mellitus) was likely caused by pooling results of the study by Hung *et al*[14] that stratified the cohort by age. In this study, 27.9% and 44.7% of patients were 20–49 and 50–64 years old, respectively. In the study of Olesen *et al*,[12] only 20.5% of patients were <65 years old, while in the study of Chao *et al*,[13] the mean age was 59.1 years±11.3 and 59.1 years±10.2 for male and female AF patients, respectively, which may indicate that these studies included relatively older AF patients than the study of Hung *et al*. As a sensitivity analysis, results of the 20–49 and 50–64 years old patients included in the study of Hung *et al*[14] were first combined (as one group <65 years old), and then subsequently pooled with the results of the other two included studies. Similar trends were observed, though substantial heterogeneity was no longer present (except for hypertension) (online supplemental efigure 1).

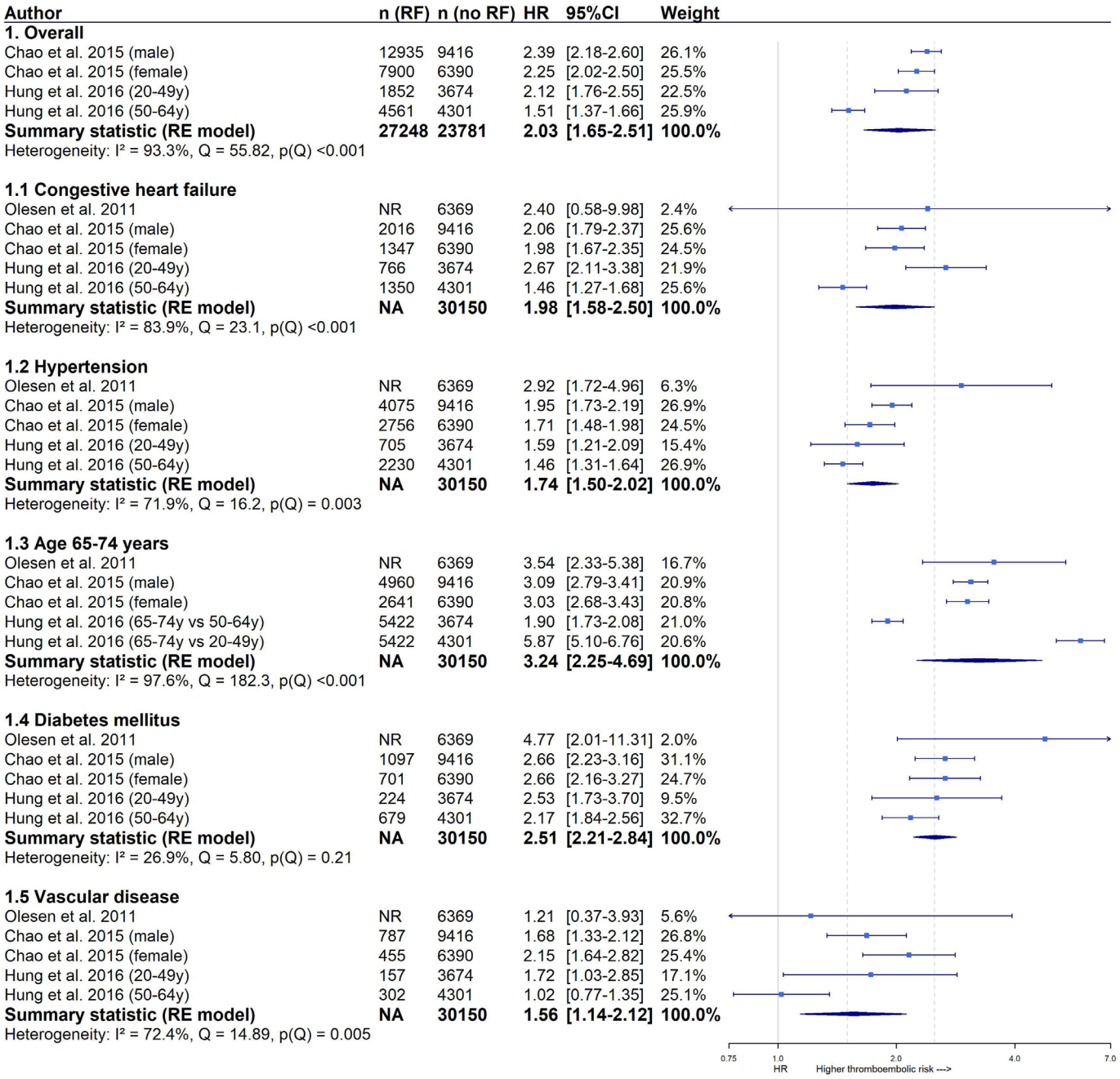

Figure 2 Impact of a single non-sex-related stroke risk factor on ischaemic stroke risk in non-anticoagulated atrial fibrillation patients (CHA_2DS_2-VASc score of 1 in men or 2 in women), represented by HRs compared with AF patients without stroke risk factors (CHA_2DS_2-VASc score 0 in men or 1 in women) (reference group). AF, atrial fibrillation; NA, not applicable; NR, not reported; RE model, random effects model; RF, risk factor; Y, year.

Role for anticoagulation therapy

Observational studies have provided evidence on the benefit of OAC initiation in AF patients at intermediate thromboembolic risk (online supplemental etable 3). In the Danish cohort study by Olesen *et al*, the thromboembolic rate was significantly reduced in VKA-treated AF patients with one stroke risk factor as compared with non-anticoagulated peers, while no reduction in the thromboembolic rate was observed in anticoagulated AF patients without stroke risk factors.[12] Likewise, another Danish cohort study by Lip *et al* also demonstrated a positive net clinical benefit for the use of warfarin in 2262 AF patients with a single stroke risk factor as compared with no OAC use (n=20 103) after both 1 and 5 years of follow-up (based on the risk of stroke, major bleeding and myocardial infarction, weighted for the risk of death following an event).[15] In contrast, a neutral net clinical benefit was observed in 1563 warfarin-treated AF patients without stroke risk factors as compared with no OAC use (n=23 219). Moreover, in the Swedish cohort study by Friberg *et al*, warfarin use was associated with a positive net clinical benefit (based on the avoided ischaemic strokes with

warfarin minus the excess intracranial haemorrhages with warfarin) in AF subjects with a CHA_2DS_2-VASc of 1, but not in subjects with a score of 0.[16] Finally, in the French prospective cohort study by Fauchier *et al*, VKA use (n=600) in AF patients with a single non-sex-related stroke risk factor was associated with a significantly lower risk of stroke/SE/death as compared with no OAC use (n=499), while this was not the case in subjects without stroke risk factors.[17]

Effectiveness and safety of NOACs versus VKAs

Systematic review

Two secondary analyses of RCTs have been performed in AF patients at intermediate thromboembolic risk (online supplemental etable 4). In a post hoc analysis of the RE-LY trial by Oldgren *et al*, the use of dabigatran 150 mg two times per day was associated with significantly lower stroke/SE, major bleeding, intracranial bleeding and all-cause mortality risks as compared with warfarin in AF patients with a $CHADS_2$ score of 0–1 (n=5323). In contrast, dabigatran 110 mg two times per day had similar stroke/SE and all-cause mortality risks, but significantly lower major bleeding and intracranial bleeding risks (no separate data in CHA_2DS_2-VASc score subgroups).[18] Similarly, in a secondary analysis of the ARISTOTLE trial by Lopes *et al*, apixaban was associated with a similar stroke/SE and all-cause mortality risk, but a significantly lower major bleeding and intracranial bleeding risk as compared with warfarin in AF patients with a $CHADS_2$ score of 1 (n=3100 and 3083, respectively).[19] However, in AF patients with a CHA_2DS_2-VASc score of 1 (n=1604), similar risks for all outcomes were observed when comparing apixaban to warfarin, although these results were largely underpowered to detect small differences. After pooling of results in AF patients with a $CHADS_2$ score of 0–1 from the RE-LY and ARISTOTLE trial (n=11 958), the meta-analysis by Lega *et al* illustrated a similar stroke/SE risk, but significantly lower major bleeding risk when comparing NOACs to warfarin.[20]

Besides these limited yet exploratory randomised data, results from observational studies were largely consistent (online supplemental etable 4). A Danish cohort study by Lip *et al*, including AF patients with one non-sex-related stroke risk factor, observed similar stroke/SE risks and significantly lower all-cause mortality risks for each individual standard dose NOAC (3272 dabigatran, 1604 rivaroxaban and 1470 apixaban users) as compared with warfarin (n=7674) after 1 and 2.5 years of follow-up (except for a similar mortality risk for rivaroxaban after 2.5 years of follow-up).[21] Only dabigatran and apixaban were associated with a significantly lower major bleeding risk as compared with warfarin, whereas rivaroxaban with a similar risk. Similarly, in an observational cohort study of Coleman *et al*, the use of rivaroxaban 20 mg once daily in 3319 AF patients with a single non-sex-related stroke risk factor was associated with a significantly lower stroke/SE risk, and similar major bleeding, intracranial bleeding and gastrointestinal bleeding risks as compared with warfarin (n=3319) after 1 and 2 years of follow-up.[22]

Meta-analysis

Results from one randomised study (post hoc analysis of the ARISTOTLE trial)[19] and two observational cohort studies[21 22] were pooled in a meta-analysis (figure 3). Results of the RE-LY trial were not included, as no data were provided in the CHA_2DS_2-VASc score subgroups.[18] All included studies scored >80% on the quality assessment tool 'QUALSYST'[11] (online supplemental etable 6).

Overall, NOACs were associated with a similar stroke/SE (HR 0.93, 95% CI 0.65 to 1.34, I^2 29.2%) and intracranial bleeding risk (HR 0.48, 95% CI 0.14 to 1.59, I^2 0.00%), but a significantly lower major bleeding (HR 0.60, 95% CI 0.45 to 0.80, I^2 21.4%) and all-cause mortality risk (HR 0.58, 95% CI 0.47 to 0.71, I^2 0.00%) as compared with warfarin. No substantial heterogeneity nor publication bias (online supplemental efigure 4) was observed. Given the low heterogeneity, an additional fixed effects model was performed, which rendered consistent results (online supplemental efigure 2).

DISCUSSION

The thromboembolic risk associated with AF substantially increases as more stroke risk factors are present in one patient.[18 19 23–25] Indeed, the ischaemic stroke rate in non-anticoagulated AF patients with a CHA_2DS_2-VASc score of 0, 1 and 2 was 0.68, 1.61 and 2.49 per 100 PY, respectively, in a meta-analysis of 10 studies.[25] Intriguingly, in non-anticoagulated AF patients with a single non-sex-related stroke risk factor, not all risk factors were associated with a similar increase in ischaemic stroke risk. In our meta-analysis, the risk of ischaemic stroke in non-anticoagulated AF patients increased 224% and 151% for patients aged between 65 and 74 years old or with diabetes mellitus, respectively, as compared with AF patients without risk factors, followed by a 98%, 74% and 56% significantly increased risk associated with congestive heart failure, hypertension or vascular disease, respectively (figure 2).

Furthermore, this systematic review highlights the beneficial role of OAC initiation over non-initiation in AF patients with a single non-sex-related stroke risk factor. The treatment threshold by which the OAC-induced reduction in ischaemic stroke risk outweighs the increased bleeding risk, was estimated to be an annual ischaemic stroke risk of >1.7%/year for warfarin and >0.9%/year for NOACs in a Markov state transition decision model by Eckman *et al*, given the lower intracranial bleeding risk of NOACs.[26] In AF patients at low thromboembolic risk, the thromboembolic event rate varied from 0.63 per 100 PY[14] in AF patients <50 years old to 0.78 per 100 PY[12] in AF patients <65 years old, which is below the estimated treatment threshold.[12–14] OAC use in these AF patients did not significantly reduce the thromboembolic risk as compared with no OAC use, resulting in a neutral net clinical benefit.[12 15–17] These findings

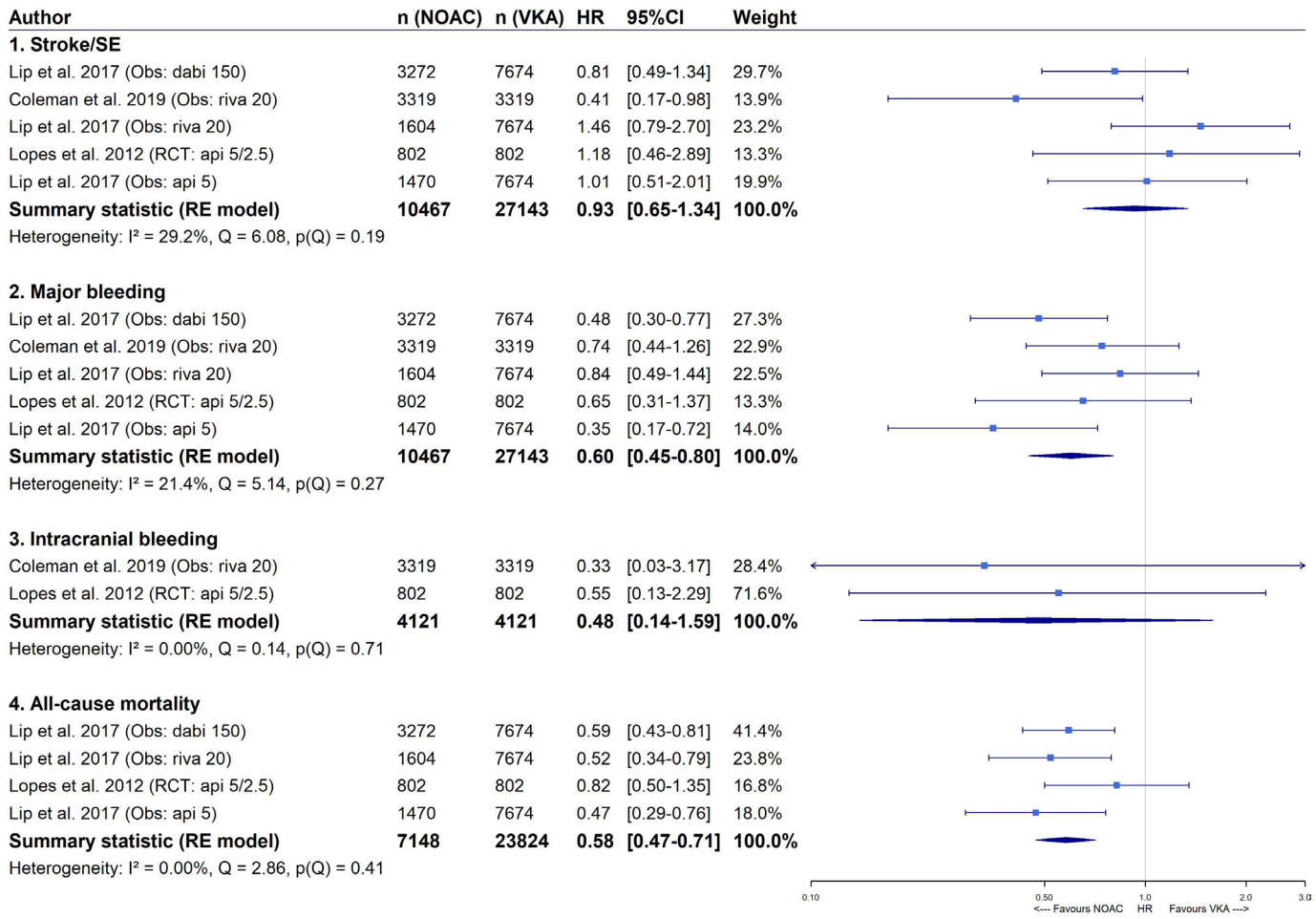

Figure 3 The risk of stroke/systemic embolism, major bleeding, intracranial bleeding and all-cause mortality of NOACs compared with warfarin in atrial fibrillation patients with a single non-sex-related stroke risk factor (CHA_2DS_2-VASc score of 1 in men or in women). Api 5/2.5: apixaban 5 mg (standard dose) or 2.5 mg (reduced dose); Api 5: apixaban 5 mg (standard dose); Dabi 150, dabigatran 150 mg (standard dose); NOAC, non-vitamin K antagonist oral anticoagulant; Obs, longitudinal observational cohort study; RCT, randomised controlled trial (post hoc analysis); RE model: random effects model; Riva 20, rivaroxaban 20 mg (standard dose); stroke/SE: stroke/systemic embolism; VKA, vitamin K antagonist.

confirm the recommendation of guidelines to not anticoagulate AF patients without any stroke risk factors.[7–10] However, in AF patients with a single non-sex-related stroke risk factor, all individual stroke risk factors (except for vascular disease in one study[12]) were associated with ischaemic stroke rates above the treatment threshold for NOACs, with rates varying from 1.00 per 100 PY[14] in AF patients <50 years old with hypertension to 4.12 per 100 PY[14] in AF patients aged 50–64 years with diabetes.[12–14 26] Indeed, OAC use in these AF patients was associated with a positive net clinical benefit compared with no OAC use.[12 15–17]

Our meta-analysis results favour NOACs over VKAs in AF patients at intermediate thromboembolic risk, since these demonstrated similar stroke/SE and intracranial bleeding risks, but significantly lower major bleeding and all-cause mortality risks compared with warfarin (figure 3). However, lack of power limited the interpretability of the risk of intracranial bleeding. To the best of our knowledge, this is the first meta-analysis specifically investigating the effectiveness and safety of NOACs compared with VKAs in AF patients with a single non-sex-related stroke risk factor according to the CHA_2DS_2-VASc score.

Strengths and limitations

The included studies had many strengths, such as the rigorous methodologies and well-defined cohorts of the (post hoc analyses of) RCTs, whereas the observational cohort studies included large groups of patients in a real-world setting with long follow-up durations. However, several limitations should be mentioned. First, data from randomised studies are scarce, since the pivotal phase III RCTs investigating the efficacy and safety of NOACs as compared with VKAs, mostly included AF patients at high thromboembolic risk.[3–6] Indeed, the ROCKET-AF trial[4] for rivaroxaban and the ENGAGE-AF-TIMI 48 trial[6] for edoxaban only included patients at high thromboembolic risk with a $CHADS_2$ score of ≥2 (based on congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/SE/TIA (2 points)), so no randomised data for rivaroxaban or edoxaban in AF patients at

intermediate thromboembolic risk were available.[4 6] Only two phase III RCTs included patients at intermediate thromboembolic risk: the RE-LY trial[3] for dabigatran (inclusion of AF patients with at least one of the following stroke risk factors: prior stroke/TIA; congestive heart failure; age ≥75 years and age 65–74 years old in combination with diabetes mellitus, hypertension or coronary artery disease) and the ARISTOTLE trial[5] for apixaban (inclusion of AF patients with a $CHADS_2$ score of ≥1).[3 5] In other words, AF patients <65 years old with heart failure included in the RE-LY trial and AF patients <65 years old with heart failure, hypertension or diabetes included in the ARISTOTLE trial would be categorised as intermediate thromboembolic risk, resulting in the limited available randomised data from the RE-LY[18] and ARISTOTLE trial.[19] Consequently, RCTs were underpowered for subgroups analyses. In line, as no phase III RCTs investigating the impact of individual non-sex-related stroke risk factors on the ischaemic stroke risk in non-anticoagulated AF patients were identified, we could only include observational studies for this meta-analysis. Second, most observational studies were retrospective in nature and were based on administrative healthcare data, mostly from Denmark or Taiwan, limiting the generalisability to other populations. When appraising the quality of studies using the 'QUALSYST' tool, the included observational studies[12–14 21 22] lacked well-defined outcomes which were robust to measurement bias or were limited in their controlling for important confounders. Third, classification of patients at intermediate thromboembolic risk varied across studies due to the use of the $CHADS_2$ score instead of the CHA_2DS_2-VASc score. This is of major importance, as results in patients with a $CHADS_2$ score of 0 or 1 should not be extrapolated to AF patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women, due to the poor ability of the $CHADS_2$ score to discriminate patients at low and intermediate stroke risk.[8–10 12 19] Theoretically, a patient with a $CHADS_2$ score of 0 can have a CHA_2DS_2-VASc score of up to 3 in case of age 65–74 years old, vascular disease and female sex. Exemplary, in the ARISTOTLE trial, 7052 subjects were 65–74 years old, 4500 subjects had vascular disease and 6416 subjects were women, so these large patient subgroups could have resulted in major differences between the $CHADS_2$ and the CHA_2DS_2-VASc score subgroups.[19] To overcome this limitation, only studies reporting outcome data in patients according to the CHA_2DS_2-VASc score were included in the second meta-analysis. Fourth, in one study,[19] female sex in absence of other stroke risk factors also put patients at intermediate thromboembolic risk (CHA_2DS_2-VASc score 1), while this was not the case for the other studies.[21 22] Fifth, due to the limited number of included studies, results of different (doses of) NOACs were pooled. Finally, in studies investigating the effectiveness and safety of NOACs versus VKAs, AF patients with a single stroke risk factor were pooled, but the proportion of each individual risk factor contributing to this group varied across studies. Most studies[18 19 22] included mainly patients with hypertension (proportion ranging from 58.8%[18] to 77.3%[19]). However, one study[21] especially included patients aged 65–74 years old (59.3% of cases), which may have influenced results, as thromboembolic and bleeding rates may have been higher in study cohorts especially including older AF patients.

Recommendations and implications for clinical practice

Based on the results of our meta-analysis and systematic review, an age of ≥65 years old or diabetes mellitus, and to a lesser extent, congestive heart failure or hypertension, may warrant OAC initiation in AF patients. AF patients <65 years old with vascular disease and to a lesser extent AF patients <50 years old with a single risk factor, represent an 'indecisive area' for OAC initiation, for whom a thorough benefit–risk analysis with shared decision making is crucial.[14]

In these AF patients at intermediate thromboembolic risk, NOACs seem to be preferred over VKAs, given the non-inferior effectiveness and superior safety. Although no direct head-to-head comparisons have been performed, standard dose dabigatran[18] and apixaban[19] may be chosen for stroke prevention, based on preliminary randomised data.[18 19] Observational data on standard dose rivaroxaban were reassuring as well,[21 22] while data on edoxaban are still lacking in this subgroup.

Regarding the implications for clinical practice, our results demonstrate that every AF patient with a single non-sex-related stroke risk factor without absolute contraindications for anticoagulation appears to benefit from NOAC treatment, after careful evaluation of modifiable bleeding risk factors, considering the estimated NOAC treatment threshold[26] and the positive net clinical benefit for OAC initiation.[12 15–17 8 10] Physicians should be aware of the beneficial role of NOACs in this patient subgroup, instead of awaiting anticoagulation initiation until at least two risk factors are present.

Research gaps

Our systematic review identified considerable research gaps. First, more research is required on the effectiveness and safety of NOACs in young AF patients <50 years old at intermediate thromboembolic risk, as this subgroup represents an 'indecisive area' for OAC initiation.[27] However, given the overall low number of identified studies in this systematic review, considerably more (randomised) data on NOACs versus VKAs are needed in this important population with a single non-sex-related stroke risk factor. Second, direct head-to-head comparisons between NOACs are still lacking, so currently no specific NOAC can be recommended for this patient subgroup. Third, the cost-effectiveness of systematically using NOACs in AF patients at intermediate thromboembolic risk should be assessed in future research.

CONCLUSION

In conclusion, our systematic review with meta-analysis favours the use of anticoagulation in AF patients with

a single non-sex-related stroke risk factor. Especially AF patients ≥65 years old or with diabetes mellitus may benefit from anticoagulation, as these risk factors were associated with the highest increase in ischaemic stroke risk in our meta-analysis, followed by congestive heart failure, hypertension and vascular disease. Importantly, in line with results in AF patients at high thromboembolic risk, this is the first meta-analysis demonstrating that NOACs may be preferred over VKAs in AF patients at intermediate thromboembolic risk, given the similar effectiveness and superior safety.

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Correction: *Impact of a single non-sex-related stroke risk factor on atrial fibrillation and oral anticoagulant outcomes: a systematic review and meta-analysis*

Grymonprez M, Steurbaut S, De Sutter A, *et al*. Impact of a single non-sex-related stroke risk factor on atrial fibrillation and oral anticoagulant outcomes: a systematic review and meta-analysis. *Open Heart* 2020;7:e001465. doi: 10.1136/openhrt-2020-001465.

This article has been corrected since it was first published. The provenance and peer review statement has been included.

Open Heart 2021;**8**:e001465corr1. doi:10.1136/openhrt-2020-001465corr1

Supplemental materials

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Supplemental tables

eTable 1: Search strategy

The following search terms were used in Medline:

Patient	“Atrial Fibrillation"[Mesh] OR "Atrial Fibrillation"[TIAB]
Intervention and **C**ontrol	“Apixaban"[TIAB] OR "Apixaban"[Supplementary Concept] OR "Rivaroxaban"[Mesh] OR "Rivaroxaban"[TIAB] OR "Edoxaban"[TIAB] OR “Edoxaban"[Supplementary Concept] OR "Dabigatran"[Mesh] OR "Dabigatran"[TIAB] OR "Antithrombins"[Mesh] OR "Factor Xa Inhibitors"[Mesh] OR "New oral anticoagulants"[TIAB] OR "NOAC"[TIAB] OR "Direct oral anticoagulants"[TIAB] OR "DOAC"[TIAB] OR "Non-vitamin K antagonist oral anticoagulants"[TIAB]
Outcome	"Thromboembolism"[Mesh] OR "Thromboembolism"[TIAB] OR "Thrombosis"[TIAB] OR "Stroke"[TIAB] OR "Hemorrhage"[TIAB] OR "Hemorrhage"[Mesh] OR "Bleeding"[TIAB]
Filter	English

The following search terms were used in Embase:

Patient	('atrial fibrillation':ab,ti OR 'atrial fibrillation'/exp) AND ('cha2ds2-vasc score':ab,ti OR 'cha2ds2-vasc score'/exp OR 'stroke risk factor':ab,ti OR 'chads2 score':ab,ti OR 'chads2 score'/exp)
Intervention and **C**ontrol	apixaban:ab,ti OR 'apixaban'/exp OR rivaroxaban:ab,ti OR 'rivaroxaban'/exp OR edoxaban:ab,ti OR 'edoxaban'/exp OR dabigatran:ab,ti OR 'dabigatran'/exp OR 'new oral anticoagulant':ab,ti OR 'new oral anticoagulant'/exp OR NOAC:ab,ti OR DOAC:ab,ti OR 'direct oral anticoagulant':ab,ti OR 'direct oral anticoagulant'/exp OR 'non vitamin k antagonist oral anticoagulant':ab,ti OR 'non-vitamin k antagonist oral anticoagulant':ab,ti OR 'non vitamin k antagonist oral anticoagulant'/exp OR 'non vitamin k oral anticoagulant':ab,ti OR 'non-vitamin k oral anticoagulant':ab,ti
Outcome	thromboembolism:ab,ti OR 'thromboembolism'/exp OR thrombosis:ab,ti OR 'thrombosis'/exp OR stroke:ab,ti OR 'stroke'/exp OR hemorrhage:ab,ti OR haemorrhage:ab,ti OR bleeding:ab,ti OR 'bleeding'/exp

eTable 1: Search strategy.

eTable 2: Impact of a single non-sex-related stroke risk factor

Author	Study design	Study cohort	n	Mean/median age (years +/- SD; [IQR])	Mean/median follow-up (+/- SD; [IQR])	Thromboembolism (Event rate [95% CI] and/or HR [95% CI])		
Olesen et al. 2011[1]	Observational retrospective nationwide study (Denmark)	Hospital-discharged non-anticoagulated AF patients in Denmark (1997-2006), using the national patient registry. Impact of individual CHA_2DS_2-VASc score risk factors on the risk of thromboembolism (stroke/SE and/or pulmonary embolism; in supplemental materials risk estimates on stroke/SE risk).	73 538 overall, 6369 with CHA_2DS_2-VASc score 0, 8203 with CHA_2DS_2-VASc score 1	**<65 years old:** 15 130 (20.5%) **65-74 years old:** 14 544 (19.8%) **≥75 years old:** 43 864 (59.7%) (mean/median age NR)	Up to 10 years of follow-up (maximum duration, no mean/median follow-up reported)	**After 1y follow-up:** ***Stroke/SE/pulmonary embolism:*** **CHA_2DS_2-VASc score 0:** Event rate: 0.78 per 100 PY [0.58-1.04] **CHA_2DS_2-VASc score 1:** *Overall:* 2.01 per 100 PY [1.70-2.36] *Heart failure:* 1.50 per 100 PY [0.37-5.98] *Hypertension:* 2.14 per 100 PY [1.46-3.15] *Diabetes:* 3.47 per 100 PY [1.65-7.27] *Vascular disease:* 0.75 per 100 PY [0.24-2.33] *Age 65-74y:* 2.88 per 100 PY [2.29-3.62] *Female sex:* 1.24 per 100 PY [0.89-1.73] ***Stroke/SE (supplemental materials):*** **CHA_2DS_2-VASc score 0:** HR 1.00 (reference) **CHA_2DS_2-VASc score 1:** *Heart failure:* HR 2.40 [0.58-9.98] *Hypertension: HR 2.92 [1.72-4.96]* *Age 65-74 years: HR 3.54 [2.33-5.38]* *Diabetes mellitus: HR 4.77 [2.01-11.31]* *Vascular disease:* HR 1.21 [0.37-3.93] *Female sex:* HR 1.47 [0.88-2.44]	**After 5y follow-up:** ***Stroke/SE/pulmonary embolism:*** **CHA_2DS_2-VASc score 0:** Event rate: 0.69 per 100 PY [0.59-0.81] **CHA_2DS_2-VASc score 1:** *Overall:* 1.51 per 100 PY [1.37-1.67] ***Stroke/SE:*** **CHA_2DS_2-VASc score 0:** HR 1.00 (reference) **CHA_2DS_2-VASc score 1:** *Heart failure: HR 3.52 [1.85-6.69]* *Hypertension: HR 2.33 [1.73-3.15]* *Age 65-74 years: HR 2.95 [2.34-3.72]* *Diabetes mellitus: HR 3.54 [2.11-5.94]* *Vascular disease: HR 2.10 [1.30-3.40]* *Female sex:* HR 1.18 [0.88-1.57]	**After 10y follow-up:** ***Stroke/SE/pulmonary embolism:*** **CHA_2DS_2-VASc score 0:** Event rate: 0.66 per 100 PY [0.57-0.76] **CHA_2DS_2-VASc score 1:** *Overall:* 1.45 per 100 PY [1.32-1.58] ***Stroke/SE:*** **CHA_2DS_2-VASc score 0:** HR 1.00 (reference) **CHA_2DS_2-VASc score 1:** *Heart failure: HR 2.75 [1.45-5.20]* *Hypertension: HR 2.17 [1.65-2.85]* *Age 65-74 years: HR 3.02 [2.46-3.71]* *Diabetes mellitus: HR 3.04 [1.85-5.01]* *Vascular disease: HR 2.21 [1.45-3.37]* *Female sex:* HR 1.16 [0.90-1.50]
Chao et al. 2015[2]	Observational retrospective nationwide study (Taiwan)	Non-anticoagulated AF patients with a single non-sex-related stroke risk factor, using the National Health Insurance Research Database in Taiwan from 1996-2011. Male AF patients with one risk factor: 38.3% age 65-74y, 31.5% hypertension, 15.6%	**AF males with CHA_2DS_2-VASc score 1:** 12 935; **AF females with score 2:** 7900	**AF males with CHA_2DS_2-VASc score 1:** 59.1y +/- 11.3 **AF females with score 2:** 59.1y +/- 10.2	5.2 years +/- 4.3	***Ischemic stroke:*** **AF males:** **CHA_2DS_2-VASc score 0:** HR 1.00 (reference) **CHA_2DS_2-VASc score 1:** *Overall*: Event rate 2.75 per 100 PY [2.62-2.87]; *HR 2.39 [2.18-2.60]* *Heart failure:* Event rate 2.37 per 100 PY [2.10-2.67]; *HR 2.06 [1.79-2.37]* *Hypertension:* Event rate 2.18 per 100 PY [1.99-2.38]; *HR 1.95 [1.73-2.19]* *Age 65-74 years:* Event rate 3.50 per 100 PY [3.27-3.74]; *HR 3.09 [2.79-3.41]* *Diabetes mellitus:* Event rate 2.96 per 100 PY [2.52-3.47]; *HR 2.66 [2.23-3.16]* *Vascular disease:* Event rate 1.96 per 100 PY [1.56-2.42]; *HR 1.68 [1.33-2.12]*		

		heart failure, 8.5% diabetes, 6.1% vascular disease; female AF patients with one risk factor: 34.9% hypertension, 33.4% age 65-74y, 17.0% heart failure, 8.9% diabetes, 5.8% vascular disease.				**AF females:** **CHA_2DS_2-VASc score 1:** HR 1.00 (reference) **CHA_2DS_2-VASc score 2:** *Overall*: Event rate 2.55 per 100 PY [2.41-2.70]; *HR 2.25 [2.02-2.50]* *Heart failure:* Event rate 2.22 per 100 PY [1.91-2.57]; *HR 1.98 [1.67-2.35]* *Hypertension:* Event rate 1.91 per 100 PY [1.70-2.14]; *HR 1.71 [1.48-1.98]* *Age 65-74 years:* Event rate 3.34 per 100 PY [3.06-3.64]; *HR 3.03 [2.68-3.43]* *Diabetes mellitus:* Event rate 2.88 per 100 PY [2.37-3.47]; *HR 2.66 [2.16-3.27]* *Vascular disease:* Event rate 2.25 per 100 PY [1.72-2.91]; *HR 2.15 [1.64-2.82]*
Hung et al. 2016[3]	Observational retrospective nationwide study (Taiwan)	Non-anticoagulated AF patients with a single non-sex-related stroke risk factor, using the National Health Insurance Research Database in Taiwan from 1996-2003, stratified into 3 age groups: 20-49, 50-64 and 65-74 years old.	**Age 20-49y:** 3674 no risk factors, 1852 one risk factor (766 heart failure, 705 hypertension, 224 diabetes, 157 vascular disease) **Age 50-64y:** 4301 no risk factors, 4561 one risk factor (1350 heart failure, 2230 hypertension, 679 diabetes, 302 vascular disease) **Age 65-74y:** 5422 one risk factor (age)	NR	**Age 20-49y:** 36 942.2 PY in patients with no risk factors, 15 838.9 PY in patients with one risk factor **Age 50-64y:** 37 265.0 PY in patients with no risk factors, 9535.9 PY in patients with one risk factor **Age 65-74y:** 33 727.0 PY	***Ischemic stroke:*** **20-49 years:** **CHA_2DS_2-VASc score 0 (male) or 1 (female):** Event rate 0.63 per 100 PY; HR 1.00 (reference) **CHA_2DS_2-VASc score 1 (male) or 2 (female):** *Overall*: Event rate 1.33 per 100 PY; *HR 2.12 [1.76-2.55]* *Heart failure:* Event rate 1.69 per 100 PY; *HR 2.67 [2.11-3.38]* *Hypertension:* Event rate 1.00 per 100 PY; *HR 1.59 [1.21-2.09]* *Diabetes mellitus:* Event rate 1.59 per 100 PY; *HR 2.53 [1.73-3.70]* *Vascular disease:* Event rate 1.07 per 100 PY; *HR 1.72 [1.03-2.85]* **50-64 years:** **CHA_2DS_2-VASc score 0 (male) or 1 (female):** Event rate 1.96 per 100 PY; HR 1.00 (reference) **CHA_2DS_2-VASc score 1 (male) or 2 (female):** *Overall*: Event rate 2.90 per 100 PY, *HR 1.51 [1.37-1.66]* *Heart failure:* Event rate 2.81 per 100 PY; *HR 1.46 [1.27-1.68]* *Hypertension:* Event rate 2.81 per 100 PY; *HR 1.46 [1.31-1.64]* *Diabetes mellitus:* Event rate 4.12 per 100 PY; *HR 2.17 [1.84-2.56]* *Vascular disease:* Event rate 1.94 per 100 PY; HR 1.02 [0.77-1.35] **65-74 years:** **CHA_2DS_2-VASc score 1 (male) or 2 (female):** *Age 65-74 years:* Event rate 3.60 per 100 PY; *HR 1.90 [1.73-2.08]* compared to age 50-64y; *HR 5.87 [5.10-6.76]* compared to age 20-49y
Joundi et al. 2016[4]	Meta-analysis	Meta-analysis of 10 studies, reporting the risk of ischemic stroke for non-anticoagulated AF patients with a CHA_2DS_2-VASc score or 0, 1 or 2.	**CHA_2DS_2-VASc score 0:** 109 197 PY; **Score 1:** 166 017 PY; **Score 2:** 133 298 PY	NR	**Score 0:** 109 197 PY; **Score 1:** 166 017 PY; **Score 2:** 133 298 PY	***Ischemic stroke:*** **CHA_2DS_2-VASc score 0:** Event rate 0.68 per 100 PY [0.12-1.23] **CHA_2DS_2-VASc score 1:** Event rate 1.61 per 100 PY [0.00-3.23] **CHA_2DS_2-VASc score 2:** Event rate 2.49 per 100 PY [1.16-3.83]

eTable 2: Overview of included studies investigating the impact of a single non-sex-related stroke risk factor on thromboembolic outcomes in atrial fibrillation.

Italic: significantly higher risk.

AF: atrial fibrillation; CI: confidence interval; HR hazard ratio; IQR: interquartile range; NR: not reported; PY: person-years; SD: standard deviation; Stroke/SE: stroke/systemic embolism; y: year.

eTable 3: Role of anticoagulation therapy versus no anticoagulation in case of a single non-sex-related stroke risk factor

Author	Study design	Study cohort	n	Mean/median age (years +/- SD; [IQR])	Mean/median follow-up (+/- SD; [IQR])	Thromboembolism (Event rate [95% CI] and/or HR [95% CI])	Major bleeding (Event rate)	Intracranial bleeding (Event rate)	All-cause mortality (Event rate)	Other
Olesen et al. 2011[1]	Observational retrospective nationwide study (Denmark)	Hospital-discharged AF patients in Denmark (1997-2006), using the national patient registry. Risk of thromboembolism using VKAs versus no OAC in patients with CHA2DS2-VASc score of 0 or 1.	73 538 overall, 6369 with CHA_2DS_2-VASc score 0, 8203 with CHA_2DS_2-VASc score 1	**<65 years old:** 15 130 (20.5%); **65-74 years old:** 14 544 (19.8%); **≥75 years old:** 43 864 (59.7%) (mean/median age NR)	Up to 10 years of follow-up (maximum duration, no mean/median follow-up reported)	***Stroke/SE/pulmonary embolism:*** **CHA_2DS_2-VASc score 0:** *No OAC:* 0.78 per 100 PY [0.58-1.04] *VKA:* 0.81 per 100 PY [0.56-1.17] **CHA_2DS_2-VASc score 1:** *No OAC:* 2.01 per 100 PY [1.70-2.36] *VKA:* **1.23 per 100 PY [0.98-1.56]** (event rates, risk estimates NR)	NR	NR	NR	NR
Lip et al. 2015[5]	Observational retrospective nationwide study (Denmark)	AF patients with no or one non-sex-related stroke risk factor using the national patient registry, net clinical benefit (based on stroke, major extracranial bleeding, intracranial bleeding and myocardial infarction, weighted for the risk of death following an event) of VKA versus no OAC.	**No risk factor:** 23 219 no OAC, 1563 warf; **Single risk factor:** 20 103 no OAC, 2262 warf	60y [52-66] no OAC, 62y [57-68] warf	5.77y +/- 4.47 no OAC, 4.72y +/- 4.51 warf	***Ischemic stroke:*** **No stroke risk factors:** ***After 1y of follow-up:*** *No OAC:* 0.75 per 100 PY *Warf:* 0.53 per 100 PY ***After 5y of follow-up:*** *No OAC:* 0.55 per 100 PY *Warf:* 0.54 per 100 PY **One non-sex-related stroke risk factor:** ***After 1y of follow-up:*** *No OAC:* 1.78 per 100 PY *Warf:* 1.15 per 100 PY ***After 5y of follow-up:*** *No OAC:* 1.34 per 100 PY *Warf:* 0.96 per 100 PY (event rates, risk estimates NR)	***Extracranial bleeding:*** **No risk factors:** ***After 1y:*** *No OAC:* 1.22 per 100 PY *Warf:* 1.41 per 100 PY ***After 5y:*** *No OAC:* 1.02 per 100 PY *Warf:* 1.05 per 100 PY **One risk factor:** ***After 1y:*** *No OAC:* 2.51 per 100 PY *Warf:* 1.91 per 100 PY ***After 5y:*** *No OAC:* 1.92 per 100 PY *Warf:* 1.90 per 100 PY	**No risk factors:** ***After 1y:*** *No OAC:* 0.27 per 100 PY *Warf:* 0.09 per 100 PY ***After 5y:*** *No OAC:* 0.15 per 100 PY *Warf:* 0.19 per 100 PY **One risk factor:** ***After 1y:*** *No OAC:* 0.48 per 100 PY *Warf:* 0.57 per 100 PY ***After 5y:*** *No OAC:* 0.35 per 100 PY *Warf:* 0.40 per 100 PY	**No risk factors:** ***After 1y:*** *No OAC:* 4.21 per 100 PY *Warf:* 1.93 per 100 PY ***After 5y:*** *No OAC:* 2.18 per 100 PY *Warf:* 1.26 per 100 PY **One risk factor:** ***After 1y:*** *No OAC:* 9.67 per 100 PY *Warf:* 4.40 per 100 PY ***After 5y:*** *No OAC:* 5.76 per 100 PY *Warf:* 3.15 per 100 PY	***Net clinical benefit*:*** **No risk factors:** ***After 1y:*** Warf vs no OAC: 0.59 [-0.19; 1.38] ***After 5y:*** Warf vs no OAC: -0.11 [-0.54; 0.32] **One risk factor:** ***After 1y:*** Warf vs no OAC: **1.68 [0.63; 2.74]** ***After 5y:*** Warf vs no OAC: **0.59 [0.11; 1.08]**

Friberg et al. 2012[6]	Observational retrospective nationwide study (Sweden)	AF patients (53% male) included from the Swedish Hospital Discharge Register, stratified according to the CHA_2DS_2-VASc score. Net clinical benefit (based on ischemic stroke versus intracranial bleeding) and adjusted composite risk of ischemic stroke, intracranial bleeding and death, of warfarin versus no OAC.	**Overall:** 68 306 warf, 90 706 no OAC (NR for no versus single stroke risk factor)	**Overall:** 78.4y +/- 12.6 no OAC; 73.8y +/- 10.2 warf (NR for no versus single stroke risk factor)	1.5 y +/- 1.1 (260 000 PY)	***Ischemic stroke/intracranial bleeding/death:*** **CHA_2DS_2-VASc score 0:** Warf vs no OAC: **HR 0.74 [0.58-0.93]** **CHA_2DS_2-VASc score 1:** Warf vs no OAC: **HR 0.50 [0.43-0.57]**	NR	NR	NR	***Net clinical benefit**:*** **CHA_2DS_2-VASc score 0:** Warf vs no OAC: 0.0 [-0.1, 0.1] **CHA_2DS_2-VASc score 1:** Warf vs no OAC: **0.3 [0.1-0.4]**
Fauchier et al. 2016[7]	Observational prospective cohort study (France)	AF patients (30% female) with no or one non-sex-related stroke risk factor included in the Loire Valley AF Project. Risk of stroke/SE/death using VKAs versus no OAC, adjusted for age and sex.	**No risk factor:** 1078 (453 VKA use (42%)) **Single risk factor:** 1099 (600 VKA use (55%))	55y +/- 14 overall; 50y +/- 15 no OAC; 58y +/- 11 VKA (NR for no versus single stroke risk factor)	979 days +/- 1158	***Stroke/SE/death:*** **No stroke risk factors:** VKA vs no OAC: HR 0.68 [0.35-1.31] **One non-sex-related stroke risk factor:** VKA vs no OAC: **HR 0.59 [0.40-0.86]**	NR	NR	NR	NR
Eckman et al. 2011[8]	Markov state transition decision model	Ischemic stroke rates derived from the ATRIA cohort and RE-LY trial (dabi)	NR	NR	NR	NR	NR	NR	NR	***Treatment threshold:*** *Warf:* Ischemic stroke rate >1.7%/y *NOAC:* ischemic stroke rate >0.9%/y

eTable 3: Overview of included studies investigating the role of anticoagulation versus no anticoagulation in case of a single non-sex-related stroke risk factor.

Bold: significantly lower risk.

* Net clinical benefit (NCB)[5]: Calculated as the weighted sum of differences in outcome rates between non-anticoagulated AF patients and VKA-treated AF patients. Outcomes of interest were ischemic stroke, major extracranial bleeding, intracranial bleeding and myocardial infarction. Weights were estimated based on the adjusted risk for death after occurrence of these outcomes during five years of follow-up. A positive NCB represents an advantage for treatment.

** Net clinical benefit (NCB)[6]: The risk for ischemic stroke without warfarin use minus the risk of intracranial bleeding with warfarin use.

AF: atrial fibrillation; Api: apixaban; CI: confidence interval; Dabi: dabigatran; HR hazard ratio; IQR: interquartile range; NCB: net clinical benefit; NOAC: non-vitamin K antagonist oral anticoagulant; NR: not reported; OAC: oral anticoagulant; PY: person-years; RCT: randomized controlled trial; Riva: rivaroxaban; SD: standard deviation; Stroke/SE: stroke/systemic embolism; VKA: vitamin K antagonist; Warf: warfarin; y: year.

eTable 4: Effectiveness and safety of NOACs as compared to VKAs in case of a single non-sex-related stroke risk factor

Author	Study design	Study cohort	n	Mean/median age (years +/- SD; [IQR])	Mean/median follow-up (+/- SD; [IQR])	Stroke/SE (HR [95% CI])	Major bleeding (HR [95% CI])	Intracranial bleeding (HR [95% CI])	All-cause mortality (HR [95% CI])
Oldgren et al. 2011[9]	Phase III RCT (worldwide)	AF patients included in the RE-LY trial (dabi vs warf), categorized according to **$CHADS_2$ score 0-1**, 2 and 3-6. $CHADS_2$ score 0-1 driven by hypertension in 58.8%, age ≥75 years in 18.1%, heart failure in 12.5% and diabetes mellitus in 2.8%. Industry-sponsored.	**$CHADS_2$ 0:** 452; **$CHADS_2$ 1:** 5323;	**$CHADS_2$ 0-1:** 69.5y +/- 7.4;	2 years (overall, NR for $CHADS_2$ 0-1 group)	**$CHADS_2$ 0-1:** Dabi 150 vs warf: **0.61 [0.37-0.99]** Dabi 110 vs warf: 0.98 [0.63-1.51]	**$CHADS_2$ 0-1:** Dabi 150 vs warf: **0.74 [0.56-0.99]** Dabi 110 vs warf: **0.65 [0.49-0.88]**	**$CHADS_2$ 0-1:** Dabi 150 vs warf: **0.37 [0.16-0.84]** Dabi 110 vs warf: **0.37 [0.16-0.83]**	**$CHADS_2$ 0-1:** Dabi 150 vs warf: **0.73 [0.54-0.98]** Dabi 110 vs warf: 0.88 [0.66-1.16]
Lopes et al. 2012[10]	Phase III RCT (worldwide)	AF patients included in the ARISTOTLE trial (api vs warf), categorized according to **$CHADS_2$ or CHA_2DS_2-VASc score 1**, 2 or ≥3. $CHADS_2$ score 1 driven by hypertension in 77.3%, heart failure in 16.1%, age ≥75 years in 9.3% and diabetes in 3.2%. CHA_2DS_2-VASc score 1 also included female sex as single stroke risk factor. Industry-sponsored.	**$CHADS_2$ 1**: 6183 overall (3100 api, 3083 warf); **CHA_2DS_2-VASc 1**: 1604 overall	**$CHADS_2$ 1**: 67.0y [60-71] (overall, no separate results in CHA_2DS_2-VASc or HAS-BLED score groups)	1.8 years [1.4-2.3] (overall, no separate results in $CHADS_2$ score groups)	**$CHADS_2$ 1**: Api vs warf: 0.85 [0.57-1.27] **CHA_2DS_2-VASc score 1:** Api vs warf: 1.18 [0.46-2.89]	**$CHADS_2$ 1**: Api vs warf: **0.59 [0.44-0.78]** **CHA_2DS_2-VASc score 1**: Api vs warf: 0.65 [0.31-1.37]	**$CHADS_2$ 1**: Api vs warf: **0.45 [0.24-0.82]** **CHA_2DS_2-VASc score 1**: Api vs warf: 0.55 [0.13-2.29]	**$CHADS_2$ 1**: Api vs warf: 0.96 [0.76-1.22] **CHA_2DS_2-VASc score 1**: Api vs warf: 0.82 [0.50-1.35]
Lega et al. 2014[11]	Meta-analysis	Pooling of results in AF patients with a $CHADS_2$ score of 0-1 from the RE-LY and ARISTOTLE trial. NOAC (dabi 150, dabi 110, api) vs warfarin.	**$CHADS_2$ 0-1:** 11 958 overall	NR	NR	**$CHADS_2$ 0-1:** NOAC vs warf: RR 0.83 [0.64, 1.07]	**$CHADS_2$ 0-1:** NOAC vs warf: **RR 0.67 [0.57-0.79]**	NR	NR
Coleman et al. 2019[12]	Observational retrospective nationwide study (U.S.A.)	AF patients with a single non-sex-related stroke risk factor from administrative claims database, OAC-naïve patients initiating rivaroxaban 20 mg or warfarin (1:1 PSM). Hypertension in 68.3% of patients, age 65-74 years in 19.1%, diabetes in 6.1% and heart failure in 5.1%. Industry-sponsored.	**CHA_2DS_2-VASc score 1 (men) or 2 (women):** 3319 riva, 3319 warf (1:1 PSM)	**CHA_2DS_2-VASc score 1 (men) or 2 (women):** 60y [55-64] riva, 60y [56-64] warf	1.6 years [0.7-2.0]	**CHA_2DS_2-VASc score 1 (men) or 2 (women):** ***After 1y of follow-up:*** Riva vs warf: **0.41 [0.17-0.98]** ***After 2y:*** Riva vs warf: **0.46 [0.23-0.92]**	**Score 1 (men) or 2 (women):** ***After 1y:*** Riva vs warf: 0.74 [0.44-1.26] ***After 2y:*** Riva vs warf: 0.65 [0.42-1.02]	**Score 1 (men) or 2 (women):** ***After 1y:*** Riva vs warf: 0.33 [0.03-3.17] ***After 2y:*** Riva vs warf: 0.14 [0.02-1.11]	NR
Lip et al. 2017[13]	Observational retrospective nationwide study	AF patients with a single non-sex-related stroke risk factor using the national patient registry, OAC-naïve, standard dose NOACs	**CHA_2DS_2-VASc score 1 (men) or 2 (women):**	**CHA_2DS_2-VASc score 1 (men) or 2 (women):**	2.6 years +/- 1.6 overall,	**CHA_2DS_2-VASc score 1 (men) or 2 (women):** ***After 1y follow-up:*** Dabi 150 vs warf:	**Score 1 (men) or 2 (women):** ***After 1y:*** Dabi 150 vs warf:	NR	**Score 1 (men) or 2 (women):** ***After 1y:*** Dabi 150 vs warf:

	(Denmark)	(dabi 150 mg, riva 20 mg and api 5 mg) vs warf. Age 65-74 years in 59.3% of patients, hypertension in 31.7%, diabetes in 3.2%, vascular disease in 3.1% and heart failure in 2.6%.	14 020 overall: 3272 dabi, 1604 riva, 1470 api, 7674 warf	66.2y [61.3-69.8] dabi, 67.2y [62.4-70.7] riva, 67.4y [62.5-70.9] api, 66.2y [60.5-70.4] warf	1.1 years +/- 0.7 api, otherwise NR	0.81 [0.49-1.34] Riva 20 vs warf: 1.46 [0.79-2.70] Api 5 vs warf: 1.01 [0.51-2.01] ***After 2.5y:*** Dabi 150 vs warf: 0.84 [0.58-1.21] Riva 20 vs warf: 1.08 [0.63-1.87] Api 5 vs warf: 1.09 [0.60-1.99]	**0.48 [0.30-0.77]** Riva 20 vs warf: 0.84 [0.49-1.44] Api 5 vs warf: **0.35 [0.17-0.72]** ***After 2.5y:*** Dabi 150 vs warf: **0.49 [0.35-0.69]** Riva 20 vs warf: 0.75 [0.47-1.20] Api 5 vs warf: **0.37 [0.20-0.69]**		**0.59 [0.43-0.81]** Riva vs warf: **0.52 [0.34-0.79]** Api vs warf: **0.47 [0.29-0.76]** ***After 2.5y:*** Dabi 150 vs warf: **0.60 [0.47-0.76]** Riva vs warf: 0.80 [0.58-1.10] Api vs warf: **0.45 [0.29-0.70]**

eTable 4: Overview of included studies investigating the effectiveness and safety of NOACs as compared to VKAs in case of a single non-sex-related stroke risk factor

Bold: significantly lower risk.

AF: atrial fibrillation; Api: apixaban; Api 5: apixaban 5 mg (standard dose); CI: confidence interval; Dabi: dabigatran; Dabi 110: dabigatran 110 mg (reduced dose); Dabi 150: dabigatran 150 mg (standard dose); HR hazard ratio; IQR: interquartile range; NOAC: non-vitamin K antagonist oral anticoagulant; NR: not reported; OAC: oral anticoagulant; PSM: propensity score matching; RCT: randomized controlled trial; Riva: rivaroxaban; Riva 20: rivaroxaban 20 mg (standard dose); SD: standard deviation; Stroke/SE: stroke/systemic embolism; U.S.A.: United States of America; VKA: vitamin K antagonist; Warf: warfarin; y: year.

eTable 5: Assessment of bias within studies on the impact of a single stroke risk factor

A)

Reference: Olesen et al. 2011[1]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?		1 (prospective observational study with baseline characteristics reported for included non-anticoagulated AF cohort, but not specifically compared in subgroup with CHA_2DS_2-VASc score 0, 1 or 2)		
5	If interventional and random allocation was possible, was it reported?				N/A
6	If interventional and blinding of investigators was possible, was it reported?				N/A
7	If interventional and blinding of subjects was possible, was it reported?				N/A
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (outcome measures retrospectively assessed in administrative healthcare claims database using ICD-codes, which are prone to misclassification bias)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?		1 (only adjusted for antiplatelet use; due to retrospective use of administrative healthcare claims database, unmeasured confounders and biases (such as confounding by indication) may still be present)		
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 19/22 (86.4%)					

B)

Reference: Chao et al. 2015[2]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?		1 (only description of mean age, sex and baseline prevalence of CHA_2DS_2-VASc risk factor components in male and female non-anticoagulated AF cohort)		
5	If interventional and random allocation was possible, was it reported?				N/A
6	If interventional and blinding of investigators was possible, was it reported?				N/A
7	If interventional and blinding of subjects was possible, was it reported?				N/A
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (outcome measures retrospectively assessed in administrative healthcare claims database using ICD-codes, which are prone to misclassification bias)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?		1 (only adjusted for sex; due to retrospective use of administrative healthcare claims database, unmeasured confounders and biases (such as confounding by indication) may still be present)		
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 19/22 (86.4%)					

C)

Reference: Hung et al. 2016[3]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?		1 (only description of baseline prevalence of CHA_2DS_2-VASc risk factor components in non-anticoagulated AF cohort, stratified according to age 20-49, 50-64 and 65-74 years old)		
5	If interventional and random allocation was possible, was it reported?				N/A
6	If interventional and blinding of investigators was possible, was it reported?				N/A
7	If interventional and blinding of subjects was possible, was it reported?				N/A
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (outcome measures retrospectively assessed in administrative healthcare claims database using ICD-codes, which are prone to misclassification bias)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?		1 (only stratified according to age; due to retrospective use of administrative healthcare claims database, unmeasured confounders and biases (such as confounding by indication) may still be present)		
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 19/22 (86.4%)					

eTable 5: Assessment of bias within studies included in the first meta-analysis regarding the impact of a single non-sex-related stroke risk factor on ischemic stroke risk in non-anticoagulated atrial fibrillation patients (**A-C:** 3 longitudinal observational cohort studies), using the quality assessment tool 'QUALSYST' from the "Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields" was used.[14] With this tool, 14 items of each quantitative study, were scored on the study and outcome levels depending on the degree to which the specific criteria were met or reported ("yes" = 2, "partial" = 1, "no" = 0). Items not applicable to a particular study design were marked "n/a" and were excluded from the calculation of the summary score. A percentage was calculated for each paper by dividing the total sum score obtained across rated items by the total possible score.

AF: atrial fibrillation; ICD: International Classification of Diseases.

eTable 6: Assessment of bias within studies on the effectiveness and safety of NOACs versus VKAs in patients with a single stroke risk factor

A)

Reference: Lopes et al. 2012[10]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?		1 (randomized study with description of baseline characteristics for NOAC- and VKA-treated cohort according to $CHADS_2$ score 1, 2 or ≥3, but not specifically compared between NOAC and VKA, nor according to CHA_2DS_2-VASc score 0, 1 or 2)		
5	If interventional and random allocation was possible, was it reported?	2			
6	If interventional and blinding of investigators was possible, was it reported?	2			
7	If interventional and blinding of subjects was possible, was it reported?	2			
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	2			
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?	2			
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 27/28 (96.4%)					

B)

Reference: Coleman et al. 2019[12]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?	2			
5	If interventional and random allocation was possible, was it reported?				N/A
6	If interventional and blinding of investigators was possible, was it reported?				N/A
7	If interventional and blinding of subjects was possible, was it reported?				N/A
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (outcome measures retrospectively assessed in administrative healthcare claims database using ICD-codes, which are prone to misclassification bias)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?		1 (adequately adjusted for predefined set of covariates using propensity score matching, but due to retrospective use of administrative healthcare claims database, unmeasured confounders and biases (such as confounding by indication) may still be present)		
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 20/22 (90.9%)					

C)

Reference: Lip et al. 2017[13]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?	2			
5	If interventional and random allocation was possible, was it reported?				N/A
6	If interventional and blinding of investigators was possible, was it reported?				N/A
7	If interventional and blinding of subjects was possible, was it reported?				N/A
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (outcome measures retrospectively assessed in administrative healthcare claims database using ICD-codes, which are prone to misclassification bias)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?		1 (adequately adjusted for predefined set of covariates using inverse probability of treatment weighted analysis, but due to retrospective use of administrative healthcare claims database, unmeasured confounders and biases (such as confounding by indication) may still be present)		
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 20/22 (90.9%)					

eTable 6: Assessment of bias within studies included in the second meta-analysis regarding the effectiveness and safety of NOACs versus VKAs in atrial fibrillation patients with a single stroke risk factor (**A:** 1 post hoc analysis of randomized controlled trial; **B-C:** 2 longitudinal observational cohort studies), using the quality assessment tool 'QUALSYST' from the "Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields" was used.[14]

AF: atrial fibrillation; ICD: International Classification of Diseases.

eTable 7: PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eTable 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

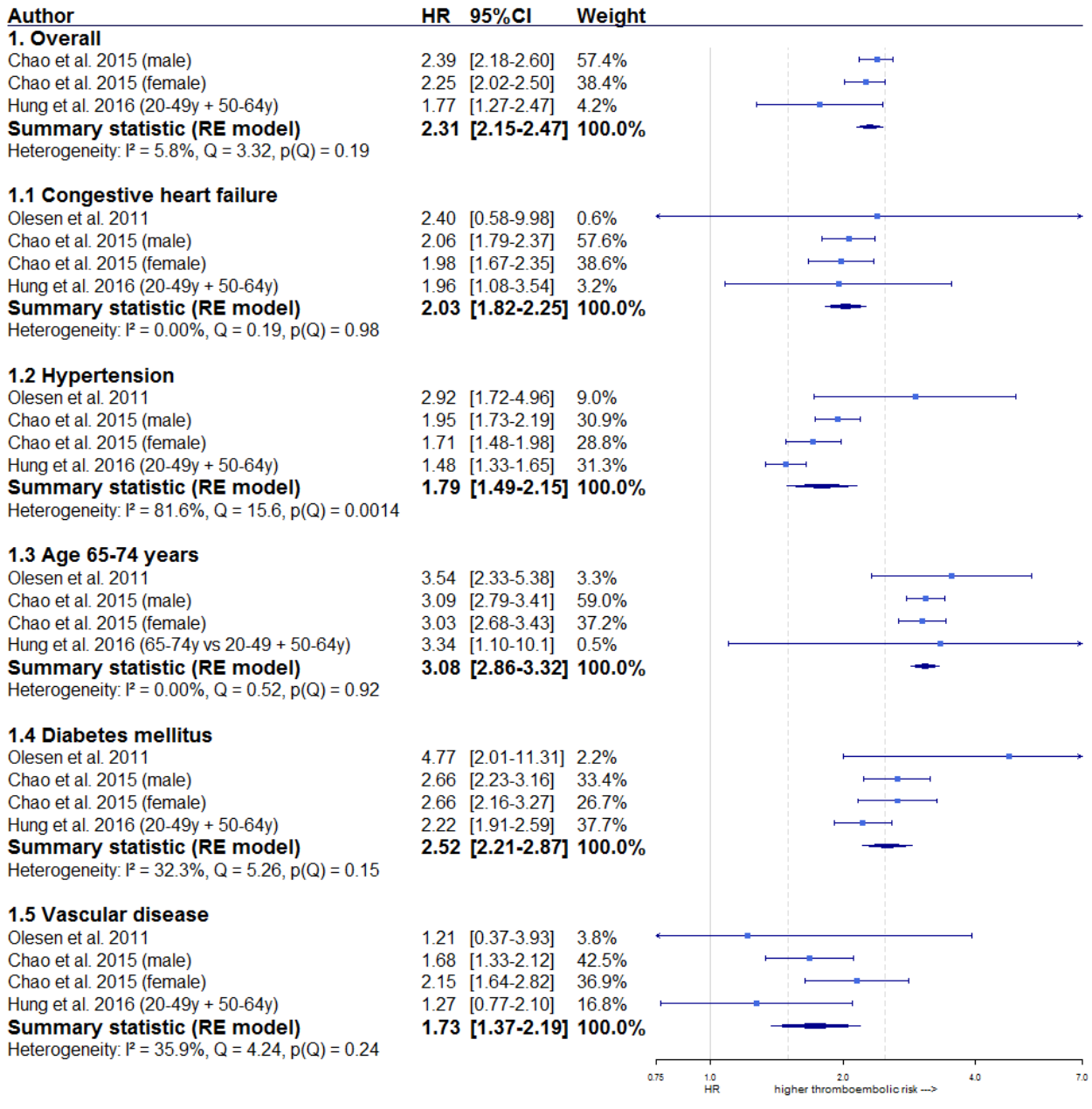
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5 + Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	eTable 2-4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	eTable 5-6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	eTable 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8, 10 + Figure 2-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, 10 + eFigure 3-4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8 + eFigure 1
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplemental figures

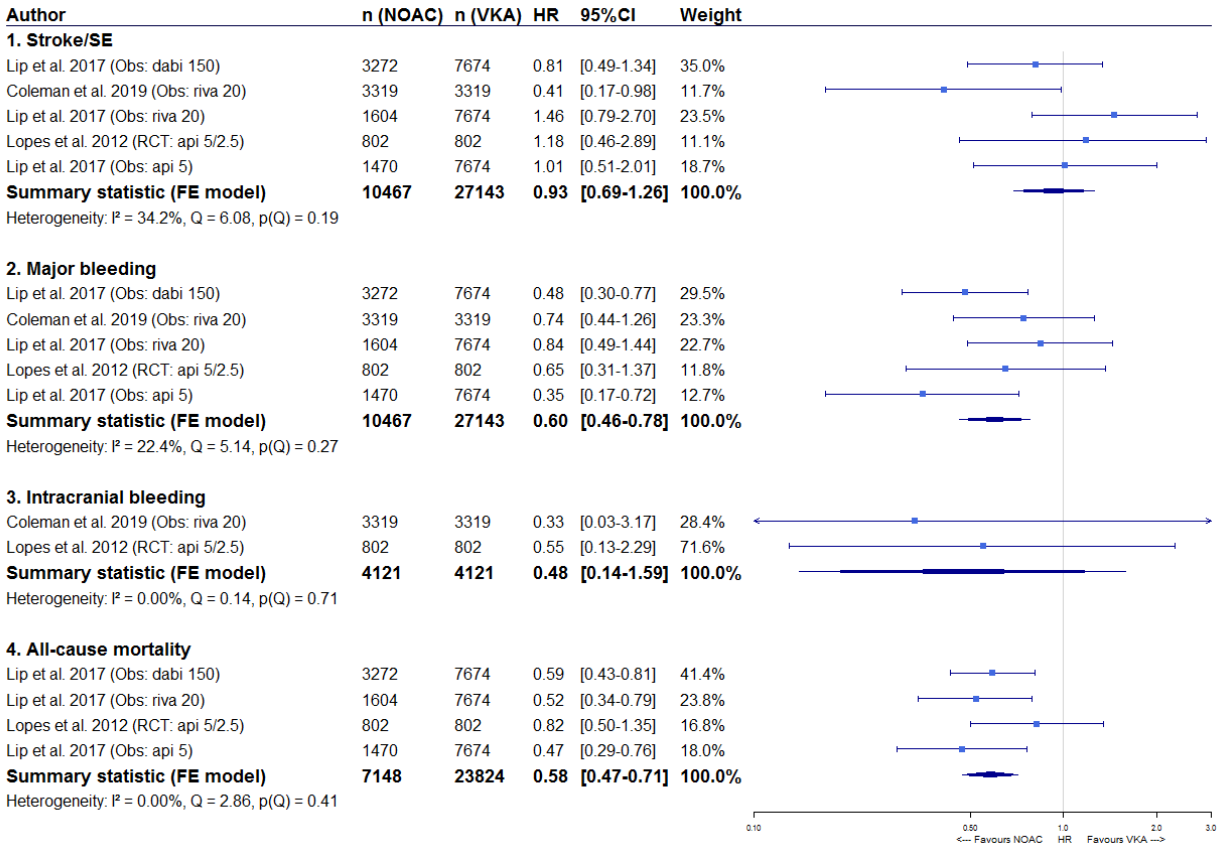
eFigure 1: Sensitivity analysis on the impact of a single non-sex-related stroke risk factor after first pooling the results of the study by Hung et al.



eFigure 1: Sensitivity analysis on the impact of a single non-sex-related stroke risk factor on the ischemic stroke risk in non-anticoagulated atrial fibrillation patients (CHA_2DS_2-VASc score of 1 in men or 2 in women), represented by hazard ratios as compared to AF patients without stroke risk factors (CHA_2DS_2-VASc score 0 in men or 1 in women) (reference group), after first pooling the risk estimates of 20-49 and 50-64 year old patients included in the study of Hung et al., and then subsequently pooling with the results of the other two included studies.

AF: atrial fibrillation; CI: confidence interval; HR: hazard ratio; RE model: random effects model; y: year.

eFigure 2: The effectiveness and safety of NOACs versus warfarin in AF patients with a single stroke risk factor, using a fixed effects model

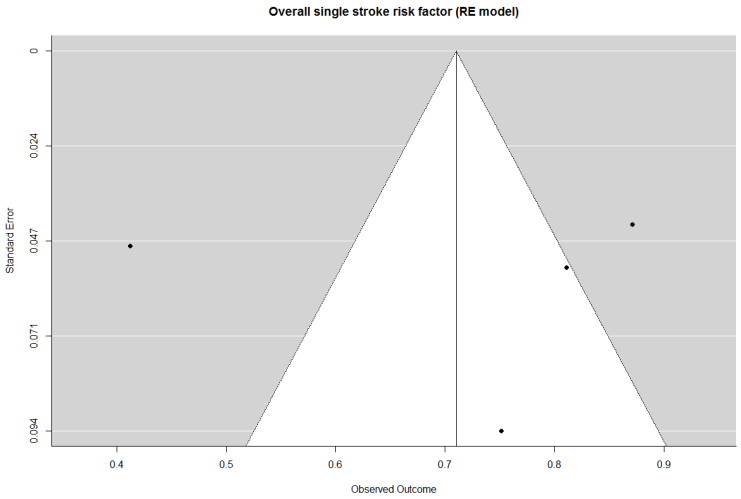


eFigure 2: The risk of stroke/systemic embolism, major bleeding, intracranial bleeding and all-cause mortality of NOACs as compared to warfarin in atrial fibrillation patients with a single stroke risk factor (CHA_2DS_2-VASc score of 1 in men or 2 in women), using a fixed effects model (instead of random effects model)

Api 5/2.5: apixaban 5 mg (standard dose) or 2.5 mg (reduced dose); Api 5: apixaban 5 mg (standard dose); CI: confidence interval; Dabi 150: dabigatran 150 mg (standard dose); FE model: fixed effects model; HR: hazard ratio; NOAC: non-vitamin K antagonist oral anticoagulant; Obs: longitudinal observational cohort study; RCT: randomized controlled trial (post hoc analysis); Riva 20: rivaroxaban 20 mg (standard dose); Stroke/SE: stroke/systemic embolism

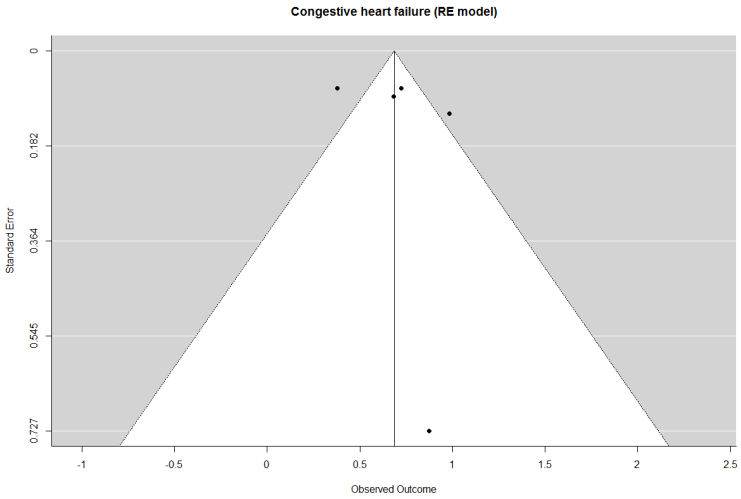
eFigure 3: Assessment of publication bias in studies on the impact of a single stroke risk factor

A)



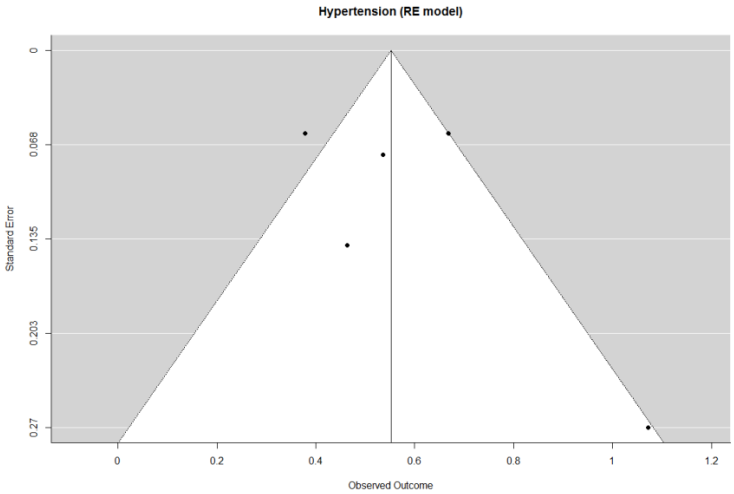
Egger's test: test for funnel plot asymmetry: z = 0.14, p = 0.89

B)



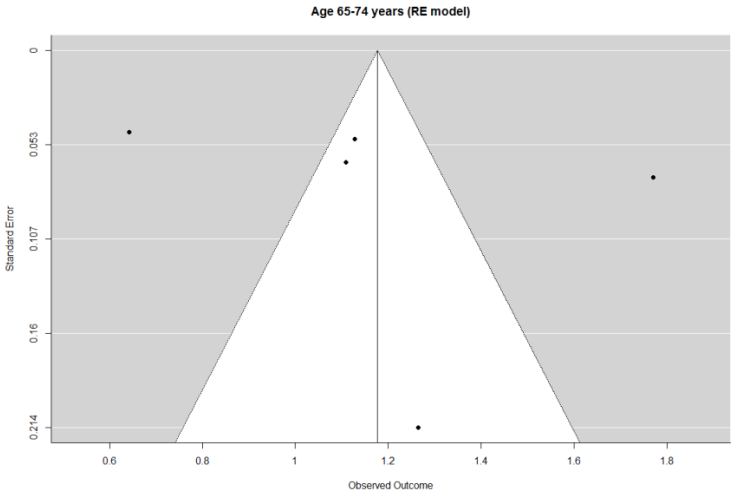
Egger's test: test for funnel plot asymmetry: z = 0.54, p = 0.59

C)



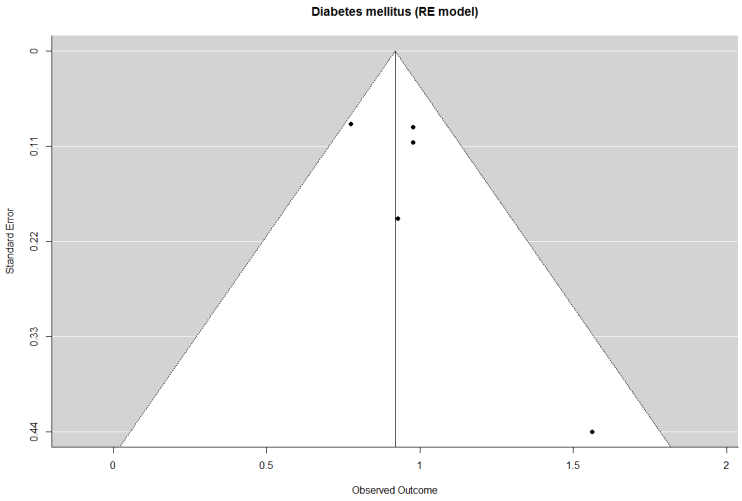
Egger's test: test for funnel plot asymmetry: z = 1.39, p = 0.17

D)



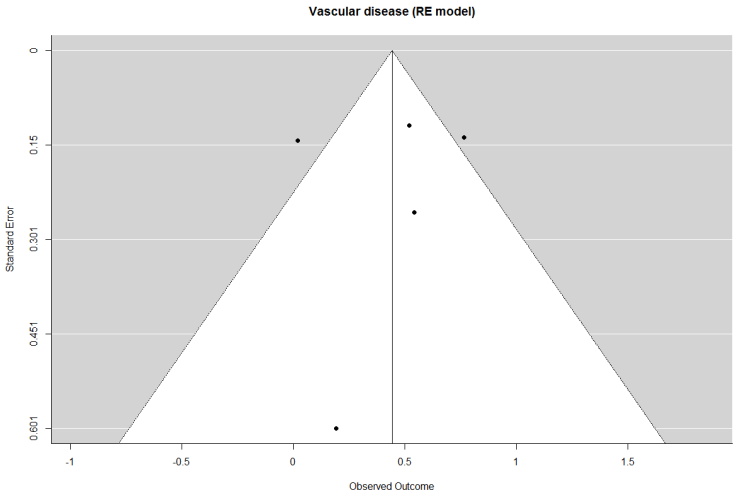
Egger's test: test for funnel plot asymmetry: z = 0.44, p = 0.66

E)



Egger's test: test for funnel plot asymmetry: z = 1.43, p = 0.15

F)

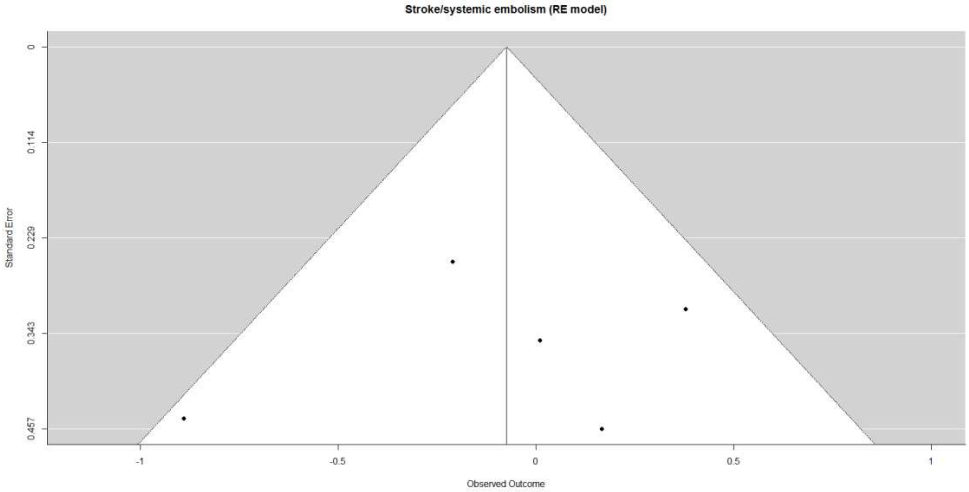


Egger's test: test for funnel plot asymmetry: z = -0.30, p = 0.76

eFigure 3: Funnel plot and Egger's test for assessment of potential publication bias for studies on the impact of **A)** any single non-sex-related stroke risk factor, **B)** congestive heart failure, **C)** hypertension, **D)** age 65-74 years old, **E)** diabetes mellitus, and **F)** vascular disease, in non-anticoagulated atrial fibrillation patients as compared to atrial fibrillation patients without stroke risk factors (CHA_2DS_2-VASc score 0 in men, 1 in women).
RE model: random effects model.

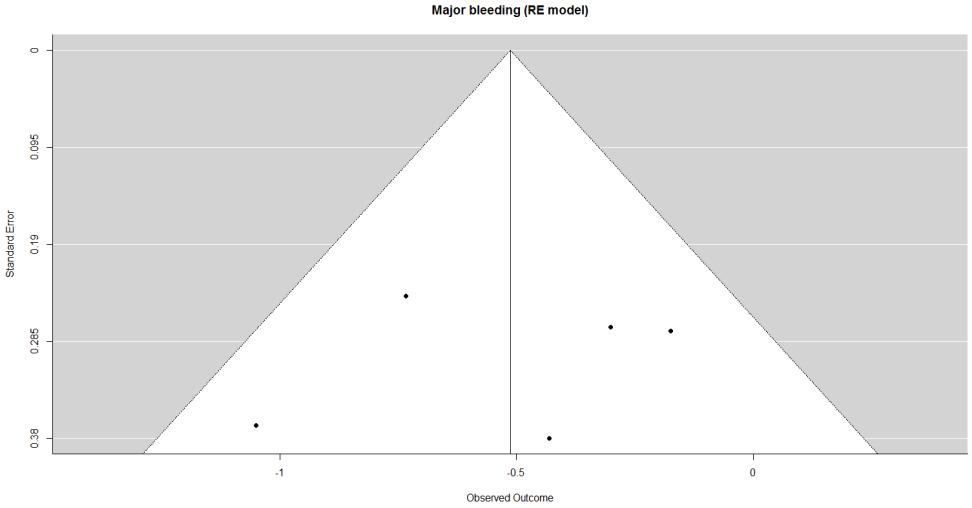
eFigure 4: Assessment of publication bias in studies on the effectiveness and safety of NOACs versus VKAs in patients with a single stroke risk factor

A)



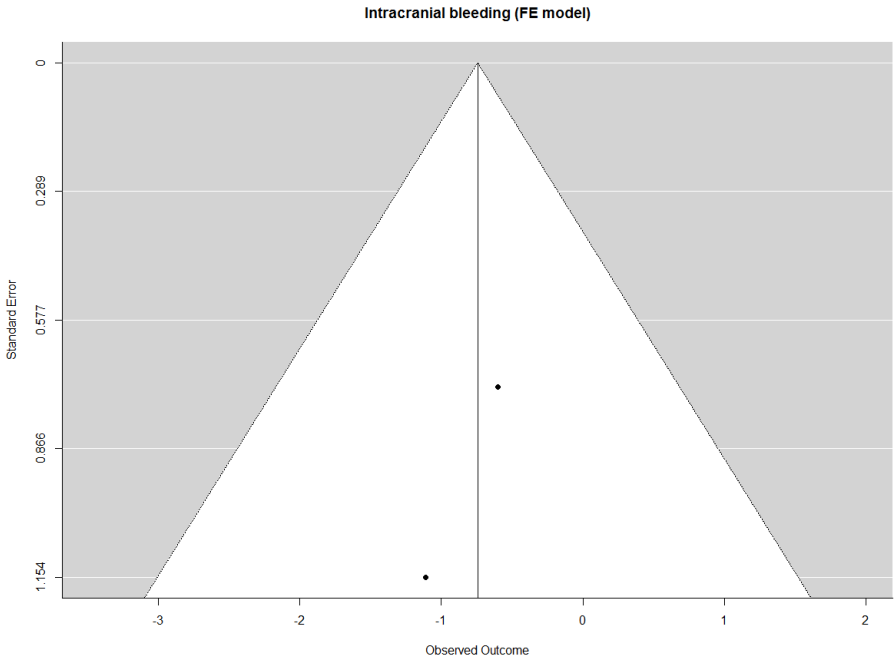
Egger's test: test for funnel plot asymmetry: z = -0.51, p = 0.61

B)



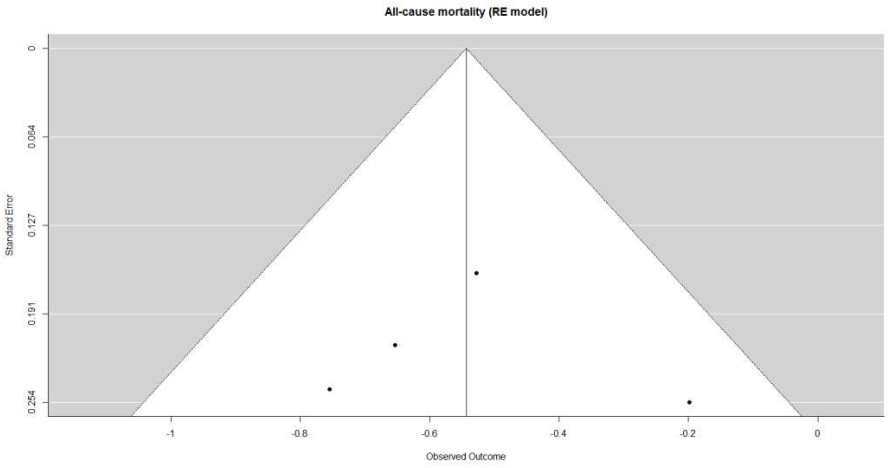
Egger's test: test for funnel plot asymmetry: z = -0.50, p = 0.62

C)



Egger's test: test for funnel plot asymmetry (fixed effects model): z = -0.37, p = 0.71

D)



Egger's test: test for funnel plot asymmetry: z = 0.22, p = 0.83

eFigure 4: Funnel plot and Egger's test for assessment of potential publication bias for studies on the risk of **A)** stroke/systemic embolism, **B)** major bleeding, **C)** intracranial bleeding, and **D)** all-cause mortality of NOACs as compared to warfarin in atrial fibrillation patients with a single stroke risk factor, based on a CHA_2DS_2-VASc score of 1 in men or 2 in women.

FE model: fixed effects model; RE model: random effects model.

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