

openheart Clinical consequences of off-label reduced dosing of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis

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ABSTRACT

Objective Postmarketing observational studies report that a substantial percentage of patients with atrial fibrillation (AF) receive a reduced non-vitamin K antagonist oral anticoagulant (NOAC) dose without a clear indication. Recently, increasing evidence has become available to explore the clinical consequences of such off-label reduced dosing (OLRD). This study aims to systematically review and meta-analyse observational studies that report clinical outcomes associated with OLRD of NOACs compared with on-label non-reduced dosing (OLNRD) of NOACs in patients with AF.

Methods and analysis We performed a systematic literature review and meta-analysis of observational studies reporting clinical outcomes in AF patients with OLRD of an NOAC compared with AF patients with OLNRD of an NOAC. Using random effects meta-analyses, we estimated the risk of stroke/thromboembolism, bleeding and all-cause mortality.

Results We included 19 studies with a total of 170 394 NOAC users. In these studies, the percentage of OLRD among patients with an indication for an on-label non-reduced NOAC dose ranged between 9% and 53%. 7 of these 19 studies met the predefined criteria for meta-analysis (n=80 725 patients). The pooled HR associated with OLRD of NOACs was 1.04 (95% CI 0.83 to 1.29; 95% prediction interval (PI) 0.60 to 1.79) for stroke/thromboembolism, 1.10 (95% CI 0.95 to 1.29; 95% PI 0.81 to 1.50) for bleeding and 1.22 (95% CI 0.81 to 1.84; 95% PI 0.55 to 2.70) for all-cause mortality.

Conclusion This meta-analysis shows no statistically significant increased risk of stroke/thromboembolism, nor a decreased bleeding risk, nor a difference in risk of all-cause mortality in patients with OLRD of NOACs. Future research may focus on differences between NOACs.

INTRODUCTION

Oral anticoagulants are of critical value for stroke prevention in atrial fibrillation (AF). Despite the effectiveness of the oldest form of anticoagulation, vitamin K antagonists

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Postmarketing studies reported that many patients with atrial fibrillation receive a reduced dose of non-vitamin K antagonist oral anticoagulants (NOACs) without a clear indication.
- ⇒ To what extent patients experience clinical consequences of such off-label reduced dosing (OLRD) is not yet known.

WHAT THIS STUDY ADDS

- ⇒ While other studies have compared patients with OLRD to patients with on-label dosing (ie, both on-label reduced and on-label non-reduced), we compared OLRD to on-label non-reduced dosing (OLNRD), which is clinically the most relevant comparison.
- ⇒ Our systematic review and meta-analysis showed that there is no statistically significant increased risk of stroke/thromboembolism, nor a decreased bleeding risk, nor a difference in risk of all-cause mortality in patients with OLRD of NOACs compared with OLNRD of NOACs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study summarises all observational studies on the clinical outcomes of OLRD of NOACs, thereby informing clinicians that they, in close discussion with their patients, should decide on the best treatment regimen in the specific situation of each patient.

(VKAs), studies have repeatedly shown that historically patients with AF often do not receive anticoagulants or antiplatelet therapy instead. Such ‘underuse’ of anticoagulants in patients with AF at high risk of stroke was in the order of 50%.¹ With the introduction of non-VKA oral anticoagulants (NOACs) in 2009, underuse of anticoagulants for AF decreased considerably given

that randomised trials showed that NOACs are at least as effective as VKAs, have fewer drug and food interactions, and overall a lower risk of serious bleeding, notably intracranial bleeds.² Moreover, NOACs do not require INR monitoring; a fixed dose can be used.³ Currently, four NOACs have been approved for patients with AF,^{4–8} and these agents rapidly became recommended as first-line agents for most AF patients in clinical guidelines. While this initially alleviated the concerns about ‘underuse’ of anticoagulants, a new pitfall has arisen. For each NOAC, besides a non-reduced dose, a reduced dose is available for specified subgroups of patients. However, accrual of postmarketing evidence showed that many patients (in the order of 20%–30%) receive a reduced NOAC dose without any clear indication, likely to mitigate a presumed high risk of bleeding.^{9–14} This so-called ‘off-label reduced dosing’ (OLRD) may put patients in need of oral anticoagulants at unnecessary risk of thromboembolism, while the anticipated attenuation of bleeding risk may in fact be negligible, or at least does not justify this OLRD.¹⁵

Several systematic reviews have evaluated the clinical consequences of such OLRD.^{14 16–18} However, the included studies in these reviews are highly heterogeneous, suffer from confounding and/or compare patients with OLRD to all patients receiving an on-label dose (ie, both on-label reduced and on-label non-reduced). A more clinically relevant comparison is the comparison of OLRD to on-label non-reduced dosing (OLNRD) only. After all, clinicians wonder what happens if they reduce the dose in patients who are presumed to be at high risk of bleeding (ie, the most common incentive for clinicians to opt for OLRD of NOACs), but who do not formally meet the dose reduction criteria and should, therefore, receive an on-label non-reduced NOAC dose. We; therefore, systematically reviewed all observational studies that report clinical outcomes associated with OLRD of NOACs compared with OLNRD of NOACs in patients with AF and estimated the risk of stroke/thromboembolism, bleeding and all-cause mortality performing meta-analyses only in studies meeting predefined criteria (in order to reduce the impact of confounding).

MATERIALS AND METHODS

Search strategy

We performed a systematic search to identify all observational studies reporting on clinical outcomes associated with OLRD of NOACs for stroke prevention in AF patients from 1 January 2009 to 10 July 2022. We searched PubMed and Embase using search terms for ‘dose reduction’ and ‘NOAC’, including synonyms and MeSH headings where appropriate, and without language restrictions. For the full search syntax, see online supplemental file 1.

Definitions and study selection

We defined OLRD of NOACs as the use of an NOAC dose lower than the recommended on-label non-reduced

NOAC dose in absence of a clear indication for dose reduction as formulated either by the Summary of Product Characteristics (SPC),^{19–22} the Food and Drug Administration (FDA),^{23–26} the European Society of Cardiology (ESC),²⁷ the European Heart Rhythm Association (EHRA),²⁸ the landmark NOAC trials^{5–8} (see [table 1](#)) or other guidelines. Clinical outcomes under consideration were stroke/thromboembolism (defined as (ischaemic) stroke and/or transient ischaemic attack (TIA) and/or thromboembolism), bleeding (defined as (major) bleeding), all-cause hospitalisation, all-cause mortality and major adverse clinical events (MACE) (defined as cardiovascular mortality, and/or myocardial infarction, and/or a composite of cardiovascular diseases, such as stroke/thromboembolism and bleeding).

We selected all original observational studies on stroke prevention in patients with AF without a mechanical heart valve and/or severe mitral valve stenosis, describing the use of any of the registered NOACs (ie, dabigatran, rivaroxaban, apixaban and/or edoxaban), and presenting data on clinical outcomes of treatment with an off-label reduced NOAC dose compared with treatment with the on-label (ie, the recommended) non-reduced NOAC dose. We excluded studies including patients below the age of 18 years or including patients with venous thromboembolism (unless it was possible to analyse AF patients separately), and studies in highly selected patient populations (eg, patients with a highly specific age, only patients with cancer, severe kidney disease, obesity or COVID-19, or those on haemodialysis or after major surgery or arrhythmia surgery). Four reviewers (LJ, RvM, CJvdD and SvD) independently screened the total of selected articles based on title and abstract in duplicate and resolved any uncertainties by discussion. Of all potential studies, three reviewers (LJ, RvM and SvD) independently evaluated the full text for eligibility in duplicate and resolved any disagreements by discussion. Reasons for exclusion were recorded. For each included study, the reference list was evaluated for any additional relevant studies.

Critical appraisal and risk of bias assessment

Three reviewers (LJ, RvM and SvD) critically appraised all included studies and independently performed a risk of bias assessment in duplicate using the Newcastle-Ottawa quality Scale (NOS) for cohort studies²⁹ supplemented by an item for handling missing data (see online supplemental file 2), and resolved any disagreements by discussion.

Data extraction

From each included study, three reviewers (LJ, RvM and SvD) extracted (1) study and patient characteristics (see online supplemental file 3), (2) the absolute number of patients receiving an off-label reduced NOAC dose and the absolute number of patients receiving the on-label non-reduced NOAC dose and (3) the exact definition of each clinical outcome (stroke/thromboembolism, bleeding, all-cause hospitalisation, all-cause mortality and

Table 1 Indications for dose reduction of NOACs used for stroke prevention in atrial fibrillation patients

	NOAC-trials ⁵⁻⁸	SPC ¹⁹⁻²²	FDA ²³⁻²⁶	ESC guidelines ²⁷	EHRA guidelines ²⁸
Dabigatran	RE-LY: 150 mg b.d. No dose reduction in trial. 110 mg b.d. No dose reduction in trial.	150 mg b.d. → 110 mg b.d. ▶ Age ≥80 years ▶ Verapamil use Consider dose reduction in case of: ▶ Age 75–80 years ▶ CrCl 30–50 mL/min/1.73 m ² ▶ Gastritis/esophagitis/GERD ▶ Other increased bleeding risk	150 mg b.d. → 75 mg b.d. ▶ CrCl 15–30 mL/min/1.73 m ₂ ▶ CrCl 30–50 mL/min/1.73 m ² +dronedaron or systemic ketoconazole	150 mg b.d. → 110 mg b.d. Not reported	150 mg b.d. → 110 mg b.d. ▶ Age ≥80 years ▶ Verapamil use Consider dose reduction in case of: of the following criteria: ▶ Age ≥75 years ▶ CrCl 30–49 mL/min/1.73 m ² ▶ Body weight ≤60 kg ▶ Quinidine, amiodarone, clarithromycin or erythromycin use ▶ Other reasons for increased bleeding risk
Rivaroxaban	ROCKET-AF: 20 mg o.d. → 15 mg o.d. ▶ CrCl 30–49 mL/min/1.73 m ² J-ROCKET-AF: 15 mg o.d. → 10 mg o.d. ▶ CrCl 30–49 mL/min/1.73 m ²	20 mg o.d. → 15 mg o.d. ▶ CrCl 15–49 mL/min/1.73 m ²	20 mg o.d. → 15 mg o.d. ▶ CrCl 15–50 mL/min/1.73 m ²	20 mg o.d. → 15 mg o.d. ▶ CrCl 30–49 mL/min/1.73 m ²	20 mg o.d. → 15 mg o.d. ▶ CrCl 15–49 mL/min/1.73 m ² Consider dose reduction in case of ≥2 of the following criteria: ▶ Age ≥75 years ▶ Body weight ≤60 kg ▶ Dronedaron, quinidine, clarithromycin, erythromycin, fluconazole, ciclosporin, tacrolimus ▶ Amiodarone when CrCl <50 mL/min/1.73 m ² ▶ Other reasons for increased bleeding risk
Apixaban	ARISTOTLE: 5 mg b.d. → 2.5 mg b.d. ▶ ≥2 of the following criteria: – Age ≥80 years – Serum creatinine ≥1.5 mg/dL (133 μmol/L) – Body weight ≤60 kg	5 mg b.d. → 2.5 mg b.d. ▶ CrCl 15–29 mL/min/1.73 m ² ▶ ≥2 of the following criteria: – Age ≥80 years – Serum creatinine ≥1.5 mg/dL (133 μmol/L) – Body weight ≤60 kg	5 mg b.d. → 2.5 mg b.d. ▶ Concomitant dual inhibitors of P-gp and CYP3A4 ▶ ≥2 of the following criteria: – Age ≥80 years – Serum creatinine ≥1.5 mg/dL – Body weight ≤60 kg	5 mg b.d. → 2.5 mg b.d. ▶ ≥2 of the following criteria: – Age ≥80 years – Serum creatinine ≥1.5 mg/dL (133 μmol/L) – Body weight ≤60 kg	5 mg b.d. → 2.5 mg b.d. ▶ CrCl 15–29 mL/min/1.73 m ² ▶ ≥2 of the following criteria: – Age ≥80 years – Serum creatinine ≥1.5 mg/dL – Body weight ≤60 kg Consider dose reduction in case of ≥2 of the following criteria: ▶ Age ≥75 years ▶ Body weight ≤60 kg ▶ Amiodarone, diltiazem, dronedaron, or naproxen use ▶ Other reasons for increased bleeding risk
Edoxaban	ENGAGE AF-TIMI 48: 60 mg o.d. → 30 mg o.d. ▶ CrCl 30–50 mL/min/1.73 m ² ▶ Body weight ≤60 kg ▶ Verapamil, quinidine, dronedaron 30 mg o.d. → 15 mg o.d. ▶ CrCl 30–50 mL/min/1.73 m ² ▶ Body weight ≤60 kg ▶ Verapamil, quinidine, dronedaron	60 mg o.d. → 30 mg o.d. ▶ CrCl 15–50 mL/min/1.73 m ² ▶ Body weight ≤60 kg ▶ Ciclosporin, ketoconazole, dronedaron, erythromycin	60 mg o.d. → 30 mg o.d. ▶ CrCl 15–50 mL/min/1.73 m ²	60 mg o.d. → 30 mg o.d. ▶ CrCl 30–50 mL/min/1.73 m ² ▶ Body weight ≤60 kg ▶ Verapamil, quinidine, dronedaron 30 mg o.d. → 15 mg o.d. ▶ CrCl 30–50 mL/min/1.73 m ² ▶ Body weight ≤60 kg ▶ Verapamil, quinidine, dronedaron	60 mg o.d. → 30 mg o.d. ▶ CrCl 15–49 mL/min/1.73 m ² ▶ Body weight ≤60 kg ▶ Dronedaron, clarithromycin, erythromycin, itraconazole, ketoconazole, posaconazole, voriconazole, cyclosporine, tacrolimus Consider dose reduction in case of ≥2 of the following criteria: ▶ Age ≥75 years ▶ Amiodarone, quinidine, verapamil ▶ Other increased bleeding risk

AF, atrial fibrillation; b.d., two times a day; CrCl, creatinine clearance; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; FDA, Food and Drugs Administration; GERD, gastro-oesophageal reflux disease; NOAC, non-vitamin K antagonist oral anticoagulant; o.d., once daily; SPC, Summary of Product Characteristics.

MACE), its associated relative risk for OLRD compared with OLNRD (stratified by dabigatran, rivaroxaban, apixaban and edoxaban if possible) and the method used to adjust for confounding.

Data analyses

First, we described the results of the systematic search, the main study and patient characteristics, and the results of risk of bias assessment. We calculated the percentage of patients with OLRD of NOACs as the number of patients

with OLRD relative to the total number of patients with an indication for an on-label non-reduced NOAC dose (ie, the sum of patients receiving OLRD and OLNRD).

Finally, where possible, we meta-analysed studies meeting predefined criteria. Foremost, observational studies often suffer from confounding (ie, factors that influence both the use of OLRD and the risk of adverse clinical outcomes) that should always be taken into account in the analyses. Patients who receive a reduced

dose without a clear indication do so for a reason. Therefore, only studies that aimed to reduce the impact of this confounding by indication by applying propensity scoring methods (for at least sex and age) in the analyses of all predefined clinical outcomes in relation to OLRD of NOACs and by reporting an HR were included in the meta-analysis, if in addition the risk of bias was low in the representativeness of the exposed and non-exposed cohort (ie, both awarded with a star according to the NOS) and appropriate guidelines (ie, SPC, FDA, ESC, EHRA or landmark NOAC trial(s)) to determine whether a non-reduced or a reduced NOAC dose is indicated were used. Assuming heterogeneity among studies, we applied random effects meta-analysis of the log transformed HRs using restricted maximum likelihood estimation. We calculated 95% CI by using the Hartung-Knapp-Sidik-Jonkman method.³⁰ Between-study heterogeneity was expressed by the 95% prediction interval (95% PI). This interval indicates the range of occurrence of a specific clinical outcome within patients receiving an off-label reduced NOAC dose that can be expected in future observational studies with similar characteristics as those included in our review.

We performed analyses in R V.1.3.1093,³¹ with the package ‘metaphor’ V.3.4-0.³²

RESULTS

Systematic search

The results of the systematic search are shown in figure 1. The initial search in PubMed and Embase yielded 10 780 records of which we removed 2337 duplicates. Title and abstract screening of the remaining 8443 records resulted in the selection of 132 records. After assessment of the full text, eligibility criteria were met in 19 articles.

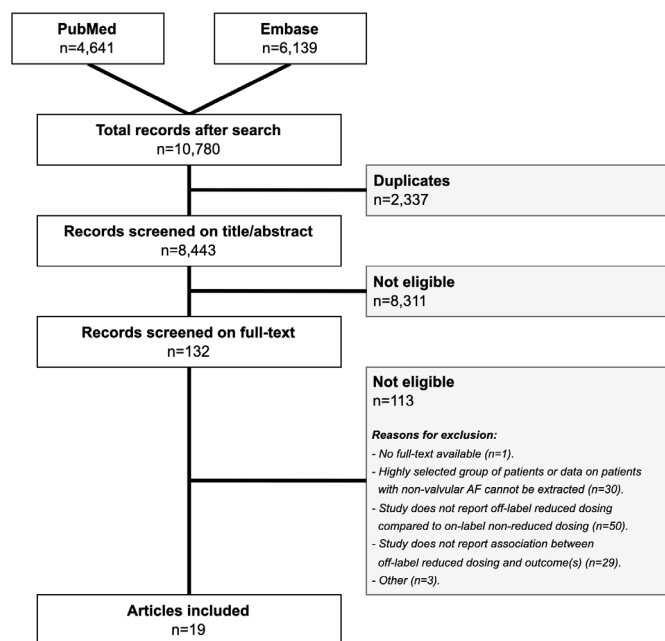


Figure 1 Flow chart with the results of the systematic search. AF, atrial fibrillation.

For an overview of the excluded studies based on full-text screening, including reason for exclusion, see online supplemental file 4. No additional relevant studies were found. Eventually, 19 studies were included in the current systematic review.³³⁻⁵¹

Study and patient characteristics of all included studies

The 19 included original observational studies, involving 170 394 NOAC-users, showed data from October 2010 to December 2017. The majority of the studies were carried out in Asian countries (most notable in Japan (n=8) and Korea (n=4)) and in the USA (n=4), and showed data on rivaroxaban (n=7), apixaban (n=7), dabigatran (n=4) and edoxaban (n=1). Duration of follow-up ranged from a median of 4.0 months to a median of 39.3 months.

The percentage of male sex ranged from 47.4% to 78.0%; the mean age of study populations ranged from 67.2 to 78.7 years. Overall, hypertension was the most common reported comorbidity, ranging from 54.0% to 95.4%. The percentage of patients with a history of (ischaemic) stroke (and TIA and/or thromboembolism) ranged from 5.9% to 49.8%. The percentage of OLRD ranged from 8.9% to 53.0%. A detailed overview of all extracted study and patient characteristics can be found in online supplemental file 5.

Risk of bias assessment

An overview of the risk of bias assessment can be found in online supplemental file 6. In general, all studies scored well on the selection, comparability and outcome category of the NOS, except for demonstrating that the outcome of interest was not present at the start of the study and adequacy of follow-up of the cohorts.⁴² Three out of 19 studies reported on the handling of missing data, all using multiple imputation.

Meta-analysis of clinical outcomes associated with OLRD of NOACs

Seven studies met the predefined criteria for meta-analysis (n=80 725) (see online supplemental file 7).^{34 35 37 43 46 47 50} The percentage of OLRD in these studies ranged from 9.6% to 53.0%. The pooled HR associated with OLRD of NOACs in AF patients was 1.04 (95% CI 0.83 to 1.29; 95% PI 0.60 to 1.79) for stroke/thromboembolism, 1.10 (95% CI 0.95 to 1.29; 95% PI 0.81 to 1.50) for bleeding and 1.22 (95% CI 0.81 to 1.84; 95% PI 0.55 to 2.70) for all-cause mortality (figure 2). Of studies meeting our criteria for meta-analysis no study reported on all-cause hospitalisation, and only two studies reported on MACE, (HR of 1.2 (95% CI 1.05 to 1.37) and 1.4 (0.94 to 2.1)).^{43 47}

When also including studies that used multivariate regression to adjust for confounding, we could meta-analyse one additional study that did not change our results (data not shown).³³

DISCUSSION

In this systematic review and meta-analysis of observational studies, we found no statistically significant increased risk

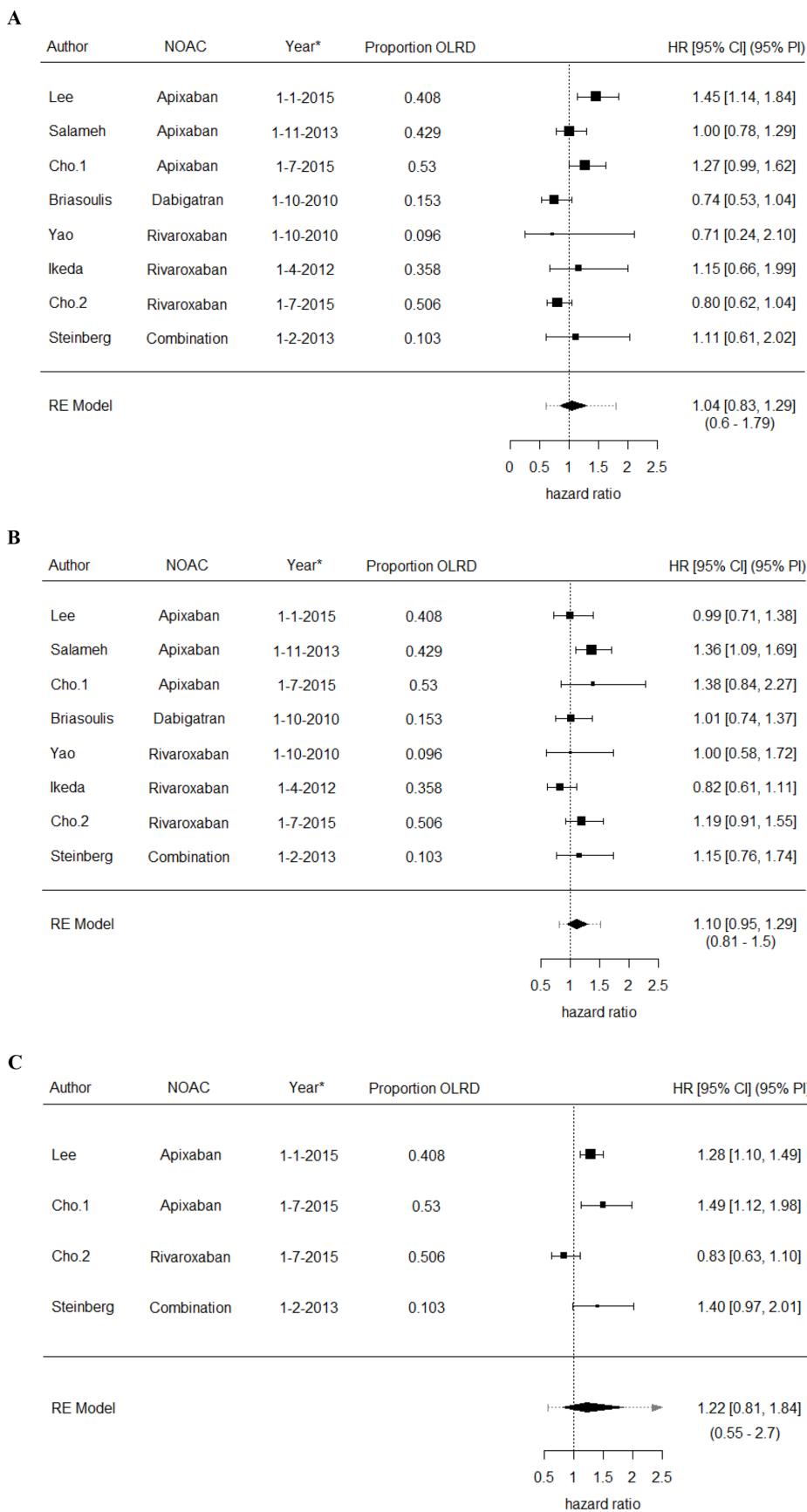


Figure 2 Meta-analyses in atrial fibrillation patients with off-label reduced dosing of an NOAC versus on-label non-reduced dosing of an NOAC. (A) With outcome (ischaemic) stroke (and TIA and/or thromboembolism). (B) With outcome bleeding. (C) With outcome mortality. *Year=starting date of inclusion of patients. NOAC, non-vitamin K antagonist oral anticoagulant; OLRD, off-label reduced dosing; PI, prediction interval; TIA, transient ischaemic attack.

of stroke/thromboembolism, nor a decreased bleeding risk, nor a difference in risk of all-cause mortality in patients with OLRD compared with OLNRD of NOACs.

The effect of OLRD of NOACs

Although all point estimates in our meta-analysis lie above 1, indicating a possible harmful effect, it cannot be concluded from our meta-analysis that OLRD of NOACs overall in fact is harmful, not to mention beneficial. However, it should be realised that NOACs differ. First, plasma levels may be more stable for some NOACs than for others due to once daily (rivaroxaban and edoxaban) versus two times daily (dabigatran and apixaban) dosing. Second, NOACs vary in the percentage by which the dose should be reduced (50% for apixaban and edoxaban; 25%–33% for dabigatran and rivaroxaban). Finally, some NOACs have more extensive dose reduction criteria than others, which might suggest that OLNRD of NOACs with more extensive dose reduction criteria is more tailored to the individual patient and that OLRD of these NOACs might cause more harm. This may explain why data in our study suggest a harmful effect of OLRD specifically for apixaban (of the apixaban studies, almost all HRs for stroke/thromboembolism, bleeding and all-cause mortality are above 1). However, we cannot confirm this, because there were not sufficient studies meeting our inclusion criteria for meta-analysis stratified by the four different NOACs.

Comparison with existing literature

In a recent meta-analysis, Caso *et al* compared OLRD to on-label dosing (ie, both on-label reduced and on-label non-reduced). This showed that OLRD increased the risk of all-cause mortality (HR 1.28 (95% CI 1.10 to 1.49)) with a null effect on major bleeding (HR 1.04 (95% CI 0.90 to 1.19)).¹⁸

In another previous meta-analysis, the authors also compared OLRD to, again, on-label dosing and used less stringent inclusion criteria, which allowed them to include more studies and examine each NOAC separately. This showed that OLRD of rivaroxaban may increase the risk of stroke/thromboembolism (HR 1.31 (95% CI 1.05 to 1.63)) compared with on-label dosing of rivaroxaban, whereas OLRD of apixaban may increase the incidence of all-cause mortality (HR 1.21 (95% CI 1.05 to 1.40)) compared with on-label dosing of apixaban. They reported no differences in outcomes when comparing OLRD versus on-label dosing of dabigatran and edoxaban.¹⁶

A third meta-analysis combined the four NOACs in their analyses and showed higher risk of stroke/systemic embolism (risk ratio (RR) 1.24 (95% CI 1.14 to 1.35)) without a reduction in bleeding risk (RR 1.18 (95% CI 0.91 to 1.53)) and a higher risk of all-cause mortality (RR 1.58 (95% CI 1.25 to 1.99)) in patients with OLRD compared with on-label dosing. However, this meta-analysis largely lacked measures to prevent confounding. Moreover, it also compared OLRD to on-label dosing (ie,

both on-label reduced and on-label non-reduced) instead of comparing OLRD to OLNRD as we did.¹⁷

In contrast to these previous studies, we did not find an increased risk for all-cause mortality in patients with OLRD. The most obvious explanation could be the comparison we choose. Unlike previous meta-analyses, we restricted our included studies to those comparing OLRD to OLNRD. This is the most clinically relevant comparison, as it represents the patient groups—those without an indication for dose reduction—in whom clinicians face a dosing dilemma most often.

Strengths and limitations

This selection of studies comparing OLRD only with OLNRD is the major strength of our study. Second, we tried to minimise the influence of confounding by indication as best as possible by including only studies meeting predefined criteria, including applying propensity scoring methods. Finally, we conducted a very comprehensive and thorough search which resulted in a large sample size.

Limitations of our study are: (1) the inclusion of a predominantly Asian population who has shown to have different pharmacokinetics, meaning that our results cannot be generalised on a one-to-one basis to, for example, the Western population; (2) the fact that we could not include enough studies to stratify by NOAC in the meta-analysis; (3) risks of misclassification within studies (eg, when an NOAC dose has been changed by a cardiologist but is not yet recorded in the general practitioner's file, while the latter has been requested by the study) and significant heterogeneity between studies (eg, in the duration of follow-up (with a median ranging from 4 to 24 months in our meta-analyses)) which is both inherent to using data from observational studies and (4) conducting our research at study level rather than at patient level (as we did not have data on individual patient level).

Clinical implications and areas for future research

Choosing an NOAC dose is all about balancing stroke risk against bleeding risk. Our results indicate that the risk of stroke may not be increased while the risk of bleeding may not be decreased in patients that are prescribed OLRD of NOACs compared with patients with OLNRD of NOACs. This may be considered as an argument to adhere to prescription guidelines in most, if not all, patients. However, our results may also indicate that OLRD of NOACs may not be harmful in specific cases. Physicians, in close discussion with their patients, may use our findings to decide on the treatment regimen in the specific situation of each patient. Future research may focus on these situations and, and perhaps more importantly, on differences between NOACs.

In conclusion, this systematic review and meta-analysis shows that there is no statistically increased risk of stroke/thromboembolism, nor a decreased bleeding risk, nor a difference in risk of all-cause mortality in patients with

OLRD of NOACs compared with patients with OLNRD of NOACs. Future research may focus on differences between NOACs.

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Contributors LJ, RvM, CJvdD, G-JG and SvD conceived and designed this study. LJ, RvM, CJvdD and SvD screened and selected the articles for inclusion. LJ, RvM and SvD performed the data extraction and risk of bias assessment. SvD performed statistical analyses. All authors contributed to the interpretation of the results. LJ, RvM and SvD wrote the first manuscript draft and subsequent revisions. All authors critically revised the manuscript and gave final approval. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPLEMENT

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Supplement 1: Search syntax

Search from January 1st 2009 until July 10th 2022, PubMed:

(dose*[Title/Abstract] OR dosa*[Title/Abstract] OR dosi*[Title/Abstract]) AND

(low[Title/Abstract] OR lower*[Title/Abstract] OR adjust*[Title/Abstract] OR adapt*[Title/Abstract] OR alter*[Title/Abstract] OR modif*[Title/Abstract] OR regulat*[Title/Abstract] OR tailor*[Title/Abstract] OR reduc*[Title/Abstract] OR underdos*[Title/Abstract] OR *recommend*[Title/Abstract] OR inappropria*[Title/Abstract] OR appropria*[Title/Abstract] OR incorrect*[Title/Abstract] OR correct*[Title/Abstract] OR incongrue*[Title/Abstract] OR congrue*[Title/Abstract] OR discord*[Title/Abstract] OR concord*[Title/Abstract] OR offlabel[Title/Abstract] OR off-label[Title/Abstract] OR (off[Title/Abstract] AND label[Title/Abstract]) OR “Off-Label Use”[Mesh]) AND

(dabigatran[Title/Abstract] OR “dabigatran”[Mesh] OR pradaxa[Title/Abstract] OR rivaroxaban[Title/Abstract] OR “rivaroxaban”[Mesh] OR xarelto[Title/Abstract] OR apixaban[Title/Abstract] OR eliquis[Title/Abstract] OR edoxaban[Title/Abstract] OR lixiana[Title/Abstract] OR NOAC*[Title/Abstract] OR DOAC*[Title/Abstract] OR ((anticoagul*[Title/Abstract] OR anti-coagul*[Title/Abstract] OR “Anticoagulants”[Mesh]) AND (novel[Title/Abstract] OR new[Title/Abstract] OR direct[Title/Abstract])) OR (non[Title/Abstract] AND ((*vitamin*[Title/Abstract] AND *antagonist*[Title/Abstract]) OR VKA[Title/Abstract])))

Search from January 1st 2009 until July 10th 2022, EMBASE:

(dose*:ti,ab OR dosa*:ti,ab OR dosi*:ti,ab) AND

(low:ti,ab OR lower*:ti,ab OR adjust*:ti,ab OR adapt*:ti,ab OR alter*:ti,ab OR modif*:ti,ab
OR regulat*:ti,ab OR tailor*:ti,ab OR reduc*:ti,ab OR underdos*:ti,ab OR recommend*:ti,ab
OR non-recommend*ti,ab OR nonrecommend*ti:ab OR inappropria*:ti,ab OR
appropria*:ti,ab OR incorrect*:ti,ab OR correct*:ti,ab OR incongrue*:ti,ab OR congrue*:ti,ab
OR discord*:ti,ab OR concord*:ti,ab OR offlabel:ti,ab OR 'off-label':ti,ab OR 'off label':ti,ab
OR 'off label drug use'/exp) AND

(dabigatran:ti,ab OR 'dabigatran'/exp OR 'dabigatran etexilate'/exp OR pradaxa:ti,ab OR
rivaroxaban:ti,ab OR 'rivaroxaban'/exp OR xarelto:ti,ab OR apixaban:ti,ab OR 'apixaban'/exp
OR eliquis:ti,ab OR edoxaban:ti,ab OR 'edoxaban'/exp OR lixiana:ti,ab OR noac*:ti,ab OR
DOAC*:ti,ab OR

((anticoagul*:ti,ab OR 'anti-coagul*':ti,ab OR 'anticoagulant agent'/exp) AND (novel:ti,ab OR
new:ti,ab OR direct:ti,ab) OR (non*:ti,ab AND ((vitamin*:ti,ab AND antagonist*:ti,ab) OR
(VKA*:ti,ab)))) AND

'article'/it AND [embase]/lim AND [1-1-2009]/sd NOT [10-07-2022]/sd

Supplement 2: Risk of bias assessment items based on the Newcastle-Ottawa quality assessment Scale for cohort studies (NOS)

Note: A study can be awarded a maximum of one star (i.e. *) for each numbered item within the Selection, Outcome and Missing data categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort

- a. truly representative of the average AF patient without a mechanical heart valve and/or severe mitral valve stenosis who is treated with a NOAC for stroke prevention in the community *
- b. somewhat representative of the average AF patient without a mechanical heart valve and/or severe mitral valve stenosis who is treated with a NOAC for stroke prevention in the community *
- c. selected group of users eg nurses, volunteers
- d. no description of the derivation of the cohort

2) Selection of the non exposed cohort

- a. drawn from the same community as the exposed cohort *
- b. drawn from a different source
- c. no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

- a. secure record (eg surgical records) *
- b. structured interview *
- c. written self report
- d. no description

- 4) Demonstration that outcome of interest was not present at start of study
 - a. yes *
 - b. no

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis
 - a. study controls for sex and age *
 - b. study controls for any additional factor *

Outcome

- 1) Assessment of outcome
 - a. independent blind assessment *
 - b. record linkage *
 - c. self report
 - d. no description
- 2) Was follow-up long enough for outcomes to occur
 - a. yes (i.e. >90 days) *
 - b. no
 - c. no follow-up period was reported
- 3) Adequacy of follow-up of cohorts
 - a. complete follow up – all subjects accounted for *
 - b. subjects lost to follow up unlikely to introduce bias – small number lost -
>90% follow up, or description provided of those lost *
 - c. follow up rate <90% and no description of those lost
 - d. no statement

Missing data

- 1) Handling missing data
 - a. multiple imputation *
 - b. no multiple imputation
 - c. not reported

Supplement 3: Extracted study and patient characteristics

Study characteristics	Data source (i.e. electronic health record, prospective registry)
	Country
	Setting (i.e. general care, specialist care, both)
	Time frame (i.e. inclusion period)
	NOAC (i.e. dabigatran, rivaroxaban, apixaban, edoxaban)
	Guideline used to determine whether a non-reduced or a reduced NOAC dose was indicated (i.e. SPC, FDA, ESC, EHRA, landmark NOAC trial(s), other guideline, not reported)
	Number of included patients with AF who use a NOAC
	Duration of follow-up in months
Patient characteristics	Male sex in percentage
	Age in years in mean (or median)
	Weight in kilograms in mean (or median)
	Body mass index in mean (or median)
	eGFR (or CrCl) in mean (or median)
	Patients with an eGFR below 50 in percentage
	Patients with hypertension in percentage
	Patients with a history of (ischemic) stroke (and TIA and/or thromboembolism) in percentage (including definition)
	Patients with a history of hemorrhagic stroke in percentage
	Patients with (a history of) coronary heart disease in percentage (including definition)
	Patients with (a history of) (peripheral) vascular disease in percentage
	Patients with heart failure in percentage
	Patients with (a history of) other cardiovascular disease in percentage (including definition)
	Patients with diabetes mellitus in percentage
	Patients with chronic kidney disease in percentage (including definition)
	Patients using concomitant drugs that interact with NOACs in percentage (including the type of drug)

AF = atrial fibrillation; CrCl = creatinine clearance; eGFR = estimated Glomerular Filtration Rate; EHRA = European Heart Rhythm Association; ESC = European Society of Cardiology; FDA = Food and Drugs Administration; NOAC = non-vitamin K antagonist oral anticoagulant; SPC = Summary of Product Characteristics; VKA = vitamin K antagonist.

Supplement 4: Overview of the excluded studies based on full-text screening, including reason for exclusion*

Author	Year	Reference	Reason for exclusion
Lafon	2018	(1)	No full-text available
Aguilar	2021	(2)	Highly selected group of patients or data on patients with non-valvular atrial fibrillation cannot be extracted
Alcusky	2018	(3)	
Alghadeer	2017	(4)	
Alnsasra	2018	(5)	
Altay	2017	(6)	
Asahina	2020	(7)	
Chaudhry	2021	(8)	
de Almeida	2020	(9)	
Eschler	2021	(10)	
Frol	2020	(11)	
George	2019	(12)	
Gurevitz	2021	(13)	
Haque	2021	(14)	
Inohara	2020	(15)	
Jackevicius	2021	(16)	
Khan	2016	(17)	
Kim	2019	(18)	
Kwon	2016	(19)	
Lafon	2017	(20)	
Mitrovic	2017	(21)	
Nahornyj	2020	(22)	
Paciaroni	2019	(23)	
Rutherford	2021	(24)	
Shinoda	2018	(25)	
Shinohara	2019	(26)	
Shinohara	2019	(27)	
Szeto	2021	(28)	

Ting	2020	(29)	Study does not report off-label reduced dosing compared to on-label non-reduced dosing.
Tran	2017	(30)	
Whitworth	2017	(31)	
Akagi	2019	(32)	
Akao	2014	(33)	
Amarenco	2018	(34)	
Anouassi	2021	(35)	
Armbruster	2014	(36)	
Ashraf	2021	(37)	
Blin	2019	(38)	
Bouget	2020	(39)	
Camm	2020	(40)	
Chan	2020	(41)	
Chen	2021	(42)	
Cheng	2019	(43)	
Cho	2019	(44)	
De Caterina	2021	(45)	
Ebrahimi	2017	(46)	
Feng	2021	(47)	
Fernandez	2021	(48)	
Forslund	2018	(49)	
Gabitova	2019	(50)	
Godino	2020	(51)	
Hecker	2016	(52)	
Helmert	2017	(53)	
Hussain	2012	(54)	
Inoue	2019	(55)	
Isaacs	2013	(56)	
Isaacs	2016	(57)	
Jang	2019	(58)	
Jansson	2019	(59)	
Kohsaka	2020	(60)	

Kotalczyk	2021	(61)
Larsen	2013	(62)
Lee	2015	(63)
Li	2017	(64)
Marzona	2021	(65)
Muniz Lobato	2018	(66)
Navarro-Almenzar	2019	(67)
Nielsen	2017	(68)
Ogawa	2014	(69)
Perreault	2020	(70)
Qian	2021	(71)
Racciah	2021	(72)
Rahme	2021	(73)
Ruiz-Ortiz	2020	(74)
Russo	2015	(75)
Sato	2018	(76)
Shrestha	2018	(77)
Staerk	2018	(78)
Sugrue	2021	(79)
Wattananuengchai	2020	(80)
Yu	2020	(81)
Bando	2018	(82)
Bang	2020	(83)
Barra	2016	(84)
Bastida	2017	(85)
Brook	2020	(86)
Chao	2021	(87)
Eschler	2020	(88)
Gustafson	2019	(89)
Ionin	2021	(90)
Kartas	2019	(91)
Kilickiran Avci	2016	(92)

Kimmons	2014	(93)	Study does not report association between off-label reduced dosing and outcome(s).
Larock	2014	(94)	
Lee	2020	(95)	
Lodzinski	2020	(96)	
Masunaga	2018	(97)	
Miyazaki	2022	(98)	
Pisters	2017	(99)	
Sato	2018	(100)	
Sato	2020	(101)	
Suwa	2019	(102)	
Tedders	2013	(103)	
Tellor	2015	(104)	
Tran	2014	(105)	
Umei	2017	(106)	
Vinding	2019	(107)	
Xing	2019	(108)	
Yiginer	2017	(109)	
Zeymer	2020	(110)	Other
Abe	2021	(111)	
Steinberg	2016	(112)	
Ueda	2020	(113)	

* In case there were several reasons to exclude a study, the reason mentioned first in the table above is reported.

Supplement 5: Detailed overview of all extracted study and patient characteristics

Last date of inclusion	First date of inclusion	Setting (i.e. general care, specialist care, both)	Country	Data source	Year	Study characteristics	Author*
31-12-2017	01-01-2011	Both	Israel	EHR	2019		Arbel (114)
30-06-2016	01-11-2012	Both	Japan	PR	2021		Atarashi (115)
31-12-2016	01-10-2010	Both	USA	EHR	2020		Briasoulis – dabigatran/rivaroxaban (116)
31-12-2016	01-10-2010	Both	USA	EHR	2020		Briasoulis – dabigatran (116)
31-12-2016	01-10-2010	Both	USA	EHR	2020		Briasoulis – rivaroxaban (116)
31-12-2016	01-07-2015	SC	Korea	EHR	2020		Cho – rivaroxaban/apixaban (117)
31-12-2016	01-07-2015	SC	Korea	EHR	2020		Cho – rivaroxaban (117)
31-12-2016	01-07-2015	SC	Korea	EHR	2020		Cho – apixaban (117)
n.r.	01-08-2015	Both	Multi-national ¹	PR	2020		de Groot (118)
30-06-2014	01-04-2012	Both	Japan	PR	2019		Ikeda (119)
30-11-2013	12-12-2011	Both	Japan	PR	2019		Inoue – 2019 (120)
31-08-2014	01-09-2013	Both	Japan	PR	2020		Inoue – 2020 (121)
30-11-2017	01-06-2011	SC	Japan	PR	2020		Kobayashi (122)
31-12-2013	01-01-2012	SC	Korea	EHR	2017		Lee – 2017 (123)
31-12-2016	01-01-2014	Both	Korea	EHR	2019		Lee – 2019 (124)
31-12-2017	01-01-2015	Both	Korea	EHR	2021		Lee – 2021 (125)
31-12-2015	01-09-2013	Both	Japan	PR	2019		Murata (126)
30-11-2017	01-06-2011	Both	Japan	PR	2020		Ohno (127)
31-12-2017	01-11-2013	Both	Israel	EHR	2020		Salameh (128)
31-07-2016	01-02-2013	Both	USA	PR	2018		Steinberg (129)
30-06-2016	01-01-2013	SC	USA	EHR	2017		Tellor (130)
31-07-2017	01-05-2012	SC	Japan	PR	2019		Yagi (131)
30-09-2015	01-10-2010	Both	USA	EHR	2017		Yao – dabigatran (132)
30-09-2015	01-10-2010	Both	USA	EHR	2017		Yao – rivaroxaban (132)
30-09-2015	01-10-2010	Both	USA	EHR	2017		Yao – apixaban (132)

Supplemental material

Open Heart

Joosten LPT, et al. *Open Heart* 2023; 10:e002197. doi: 10.1136/openhrt-2022-002197

eGFR <50 (%)	eGFR (mean)	Body mass index (mean)	Weight in kg (mean)	Age in years (mean)	Male sex (%)	Patient characteristics	Duration of follow-up (months)	NOAC-users (n)	Guideline used	NOAC
n.r.	71.5	30.2	n.r.	75.5	48.0			23	8,425	SPC
n.r.	n.r.	n.r.	62.7	71.6	67.7		n.r.	6,806	J-ROCKET-AF	R
48.8 ¹¹	n.r.	n.r.	n.r.	n.r.	n.r.		12.5	27,747	D: FDA R: other ²	D/R
53.0 ¹¹	n.r.	n.r.	n.r.	n.r.	50.6		14.8	8,035	FDA	D
47.0 ¹¹	n.r.	n.r.	n.r.	n.r.	50.2		11.6	19,712	Other ²	R
n.r.	69.6 ^o	25.3	n.r.	70.3	54.4		15.0 [‡]	16,568	R: ROCKET-AF A: ARISTOTLE	R/A
n.r.	72.7 ^o	25.5	n.r.	69.8	59.4		15.0 [‡]	9,639	ROCKET-AF	R
n.r.	65.4 ^o	25.0	n.r.	71.0	47.4		15.0 [‡]	6,929	ARISTOTLE	A
n.r.	74.3 ^o	28.1	81.0	73.6	56.8		11.6 [‡]	13,092	SPC	E
0	77.7 ^o	24.7	64.9	70.4	68.3		±12	6,521 ¹⁰	J-ROCKET-AF	R
18	72.9 ^o	24.0	62.7	70.9	66.9		15.1 [‡]	6,443	Other ³	D
31.4	62.2 ^o	n.r.	59.5	74.5	58.9		17.4	6,294	ARISTOTLE	A
n.r.	80.3 ^o	n.r.	65.8	67.2	73.6		13.4	1,245	ARISTOTLE + other ⁴	D/R/A/E
n.r.	66.1 ^o ‡	n.r.	n.r.	74.0	62.2		±12	844	Other ⁵	D
n.r.	82.5 ^o	24.8	64.9	69.8 [‡]	57.4		16.8 [‡]	13,594	ROCKET-AF	R
7.6	77.1	24.6	63.6	72.6	56		24 [‡]	8,512	ESC	A
n.r.	70.5 ^o	24.1	63.8	71.7	71.5		39.3 [‡]	1,658	ARISTOTLE + other ⁶	D/R/A/E
n.r.	65.4	23.7	60.9	71.6	63.6		13.4	2,195	ARISTOTLE + SPC + other ⁷	D/R/A/E
n.r.	63.8	n.r.	78.1	78.7	48.3		15.3	27,765	SPC	A
n.r.	81.7 ^o ‡	n.r.	n.r.	71 [‡]	58.7		12.0 [‡]	7,925	FDA	D/R/A/E
n.r.	42 ^o	n.r.	86.9	75.1	48.7		16.3	707	FDA	A
15.7	64.1	n.r.	67.1	69.1	78		10.8 [‡]	661	J-ROCKET-AF	R
13.6	71.6	n.r.	n.r.	68.3	61.7		4.0 [‡]	4,653	Other ⁸	D
0	76.4	n.r.	n.r.	69.6	59.9		4.0 [‡]	5,399	FDA	R
12.6	71.1	n.r.	n.r.	72.4	50.6		4.0 [‡]	3,340	Other ⁹	A

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Open Heart

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Concomitant PI (%)	Chronic kidney disease (%) – definition	Diabetes mellitus (%)	(History of) other cardiovascular disease (%) – definition	Heart failure (%)	(History of) (peripheral) vascular disease (%)	(History of) coronary heart disease (%) – definition	History of hemorrhagic stroke (%)	History of (ischemic) stroke (and TIA and/or thromboembolism) (%) – definition	Hypertension (%)
42.3	18.0 – ²¹	59.8	n.r.	26.9	16.6	n.r. – n.a.	n.r.	31.4 – ¹²	95.4
9.4	n.r. – n.a.	24.7	n.r.	26.5	n.r.	4.2 – MI	1.9	20.2 – ¹³	71.2
26.6	24.9 – ²²	48.9	n.r.	29.9	n.r.	6.5 – MI	0.9	24.5 – ¹²	93.2
27.5	23.3 – ²²	49.2	n.r.	34.4	n.r.	5.7 – MI	0.7	24.8 – ¹²	93.9
26.2	25.6 – ²²	48.8	n.r.	28.0	n.r.	6.8 – MI	1.0	24.3 – ¹²	92.9
9.1 ²⁹	2.7 – ²³	46.6	n.r.	19.1	11.4	n.r. – n.a.	1.1	19.9 – ¹⁴	87.6
8.9 ²⁹	1.8 – ²³	47.0	n.r.	18.7	11.0	n.r. – n.a.	0.9	18.6 – ¹⁴	88.4
9.5 ²⁹	3.9 – ²³	46.1	n.r.	19.6	11.8	n.r. – n.a.	1.5	21.8 – ¹⁴	86.4
n.r.	n.r. – n.a.	22.0	n.r.	5.9	3.3 ¹⁸	4.3 – MI	0.5	5.9 – ¹³	77.1
13.7	0 – ²⁴	23.3	3.2 – ¹⁹	21.0	n.r.	n.r. – n.a.	n.r.	20.5 – ¹⁵	74.5
13.8	n.r. – n.a.	20.4	n.r.	18.2	n.r.	n.r. – n.a.	n.r.	20.2 – ¹²	66.7
18.8	41.5 – ²⁵	55	n.r.	30.4	n.r.	n.r. – n.a.	n.r.	17.5 – ¹⁵	61.2
21.9 ³⁰	n.r. – n.a.	28.4	n.r.	17.4	n.r.	18.5 – CAD	n.r.	16.9 – ¹²	71.2
n.r.	n.r. – n.a.	22.2	n.r.	9.1	n.r.	5.8 – MI	n.r.	49.8 – ¹⁶	65.2
n.r.	n.r. – n.a.	22.4	n.r.	30.4	17.7 ¹⁸	2.8 – MI	n.r.	n.r. – n.a.	72.2
34.3	n.r. – n.a.	27.8	n.r.	46.1	26.8 ¹⁸	6.1 – MI	n.r.	29.2 – ¹²	85.5
12.7	n.r. – n.a.	21.6	n.r.	19.1	11.7	n.r. – n.a.	n.r.	10.1 – ¹⁶	69.4
21.5	39.2 – ²⁶	26.1	n.r.	32.5	7.2	19.9 – CAD	n.r.	20.3 – ¹²	73.3
48.9	2.8 – ²⁷	46.4	n.r.	32.6	12.5	31.9 – MI	n.r.	24.9 – ¹²	90.1
25.7 ³⁰	n.r. – n.a.	n.r.	n.r.	n.r.	n.r.	n.r. – n.a.	n.r.	11.1 – ¹⁶	n.r.
53.3	5 – ²⁸	n.r.	n.r.	n.r.	n.r.	n.r. – n.a.	n.r.	n.r. – n.a.	n.r.
11.0	n.r. – n.a.	16	5.0 – ²⁰	17.0	n.r.	n.r. – n.a.	n.r.	6.0 – ¹⁵	54
6.4	n.r. – n.a.	41.8	n.r.	27.9	25.2	n.r. – n.a.	1.0	14.0 – ¹⁷	88.7
7.4	n.r. – n.a.	39.3	n.r.	26.5	26.7	n.r. – n.a.	0.8	13.1 – ¹⁷	88.1
7.5	n.r. – n.a.	39.7	n.r.	31.8	29.1	n.r. – n.a.	1.6	14.7 – ¹⁷	90.8

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Open Heart

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OLRD of patients with an indication for an on-label non-reduced NOAC dose (%)	On-label non-reduced dose (n)	Off-label reduced dose (n)	Off-label reduced and on-label non-reduced NOAC dose	Other concomitant drug that interacts with NOACs (%) – type of drug	Concomitant P-gp inhibitor (%)	Concomitant NSAID (%)
39.0	5,140	3,285		n.r. – n.a.	n.r.	43.3
30.2	3,717	1,609		n.r. – n.a.	n.r.	n.r.
19.2	14,962	3,564		18.2 – warfarin	19.6	51.0
15.3	5,621	1,013		24.4 – warfarin	22.5	50.9
21.5	9,341	2,551		15.7 – warfarin	18.4	51.0
51.6	8,019	8,549		4.9 – ADP-2 inhibitor	n.r.	n.r.
50.6	4,760	4,879		4.5 – ADP-2 inhibitor	n.r.	n.r.
53.0	3,259	3,670		5.6 – ADP-2 inhibitor	n.r.	n.r.
11.2	8,872	1,114		n.r. – n.a.	n.r.	n.r.
35.8	4,185	2,336		n.r. – n.a.	n.r.	n.r.
49.7	1,196	1,181		n.r. – n.a.	3.3	n.r.
22.5	3,241	941		n.r. – n.a.	n.r.	n.r.
27.1	907	338		n.r. – n.a.	n.r.	n.r.
38.4	294	183		n.r. – n.a.	n.r.	n.r.
42.6	7,798	5,796		n.r. – n.a.	n.r.	n.r.
40.8	4,194	2,890		n.r. – n.a.	n.r.	n.r.
33.1	746	369		n.r. – n.a.	n.r.	2.0
27.1	907	338		n.r. – n.a.	n.r.	n.r.
42.9	13,141	9,885		n.r. – n.a.	n.r.	n.r.
10.3	6,376	734		n.r. – n.a.	n.r.	n.r.
17.0	477	98		n.r. – n.a.	n.r.	n.r.
23.1	409	123		n.r. – n.a.	n.r.	n.r.
8.9	4,241	412		n.r. – n.a.	n.r.	4.8
9.6	4,881	518		n.r. – n.a.	n.r.	4.8
16.5	2,790	550		n.r. – n.a.	n.r.	5.0

A = apixaban; ADP = adenosine diphosphate; AF = atrial fibrillation; b.i.d. = bis in die (= twice a day); CAD = coronary artery disease; CrCl = creatinine clearance; D = dabigatran; E = edoxaban; eGFR = estimated Glomerular Filtration Rate; EHR = electronic health record; ESC = European Society of Cardiology; FDA = Food and Drugs Administration; GI = gastrointestinal; ICD = International Classification of Diseases and Related Health Problems; i.e. = id est (= that is); kg = kilogram; MI = myocardial infarction; n.a. = not applicable; NOAC = non-vitamin K antagonist oral anticoagulant; n.r. = not reported; NSAID = non-steroidal anti-inflammatory drug; o.d. = omnie die (= once a day); OLRD = off-label reduced dosing; P-gp = P-glycoprotein; PI = platelet inhibitor; PR = prospective registry; R = rivaroxaban; SC = specialist care; SPC = Summary of Product Characteristics; TIA = transient ischemic attack; USA = United States of America; VKA = vitamin K antagonist.

¹ Austria, Belgium, Germany, Ireland, Italy, Portugal, Spain, Switzerland, The Netherlands, United Kingdom; ² FDA or concomitant use of a dual P-gp-Cyp3A4 inhibitor (including ketoconazole, fluconazole, itraconazole, cobicistat, conivaptan, indinavir, voriconazole, posaconazole, nefzadone HCL, ritonavir, saquinavir, telithromycin); ³ age ≥ 70 years, CrCl of 30-50mL/min, prior GI-bleeding, or concomitant use of oral P-gp inhibitors; ⁴ D: elderly >70 years, CrCl 30-50mL/min, concomitant use of P-gp inhibitors, history of GI-bleeding, R: CrCl 15-49mL/min, A: ARISTOTLE, E: body weight ≤ 60 kg, CrCl 15-50mL/min, concomitant use of P-gp inhibitors; ⁵ old age (≥ 75 years old), renal dysfunction (glomerular filtration rate <50 mL/min), or low body weight (<50 kg); ⁶ D 110mg b.i.d.: CrCl 30-50mL/min, age ≥ 70 years and a prior history of bleeding, R 10mg

o.d.: CrCl 15-50mL/min, A 2.5mg b.i.d.: ARISTOTLE, E 30mg o.d.: CrCl 15-50mL/min or body weight <60kg; ⁷ D: age ≥70 years, CrCl 30-50mL/min, concomitant P-gp inhibitors, or history of GI-bleeding, R: SPC, A: ARISTOTLE, E: SPC; ⁸ eGFR<30mL/min/1.73m²; ⁹ serum creatinine level ≥1.5mg/dl; ¹⁰ only patients with CrCl ≥50ml/min; ¹¹ eGFR <60 instead of eGFR <50; ¹² stroke; ¹³ ischemic stroke; ¹⁴ stroke, TIA or thromboembolism; ¹⁵ ischemic stroke or TIA; ¹⁶ stroke or TIA; ¹⁷ thromboembolism (arterial); ¹⁸ peripheral artery disease; ¹⁹ MI and/or peripheral artery disease and/or aortic plaque; ²⁰ MI or arteriosclerosis obliterans; ²¹ chronic renal failure; ²² renal disease (ICD-9 and ICD-10 codes): moderate (stage III) or severe (stage IV, V); ²³ chronic kidney disease (i.e. presence of ICD-10 codes for chronic kidney disease); ²⁴ CrCl <50mL/min; ²⁵ renal disorder; ²⁶ insufficient kidney function; ²⁷ chronic dialysis, renal transplantation or serum creatinine >200mmol/L; ²⁸ hemodialysis; ²⁹ i.e. aspirin; ³⁰ i.e. aspirin, cilostazol, clopidogrel, ticlopidine.

* In case articles concern the same author, a note is added after the author to indicate what makes the articles distinct. Substudies are indented and greyed out. Studies included in the meta-analysis are underlined and presented against a white background; † median instead of mean; ° CrCl instead of eGFR.

Supplement 6: Results of risk of bias assessment

Author	Year	Reference	Selection				Comparability	Outcome			Missing data
			Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Arbel	2019	(114)	*	*	*		**	*	*		
Atarashi	2021	(115)	*	*	*		**	*	*		
Briasoulis	2020	(116)	*		*		**	*	*		
Cho	2020	(117)	*		*		**	*	*		
de Groot	2020	(118)	*	*	*			*	*		
Ikeda	2019	(119)	*	*	*		**	*	*		
Inoue	2019	(120)	*	*	*		*	*	*	*	
Inoue	2020	(121)	*	*	*		*	*	*		
Kobayashi	2020	(122)	*	*	*		**	*	*		*
Lee	2017	(123)	*	*	*		**	*	*		
Lee	2019	(124)		*	*	*	**	*	*		
Lee	2021	(125)	*	*	*		**	*	*		
Murata	2019	(126)	*	*	*		**	*	*	*	
Ohno	2020	(127)	*	*	*		**	*	*		*
Salameh	2020	(128)	*	*	*		**	*	*		
Steinberg	2018	(129)	*	*	*		**	*	*	*	*
Tellor	2017	(130)	*		*			*	*		
Yagi	2019	(131)	*	*	*			*	*		
Yao	2017	(132)	*	*	*		**	*	*		

Supplement 7: Results of defining the most homogeneous and best quality studies for meta-analyses

Author*	Year	Reference	Low risk of bias in the representativeness of the exposed and non-exposed cohort (i.e. both awarded with a star according to the NOS)	Uses appropriate guidelines (i.e. SPC, FDA, ESC, EHRA, landmark NOAC trial(s))	Uses a form of propensity adjustment in the analysis of clinical outcomes associated with OLRD and reports a hazard ratio	Belongs to the most homogeneous and best quality studies
Arbel	2019	(114)	Yes	Yes	No	No
Atarashi	2021	(115)	Yes	Yes	No	No
Briasoulis dabigatran/ rivaroxaban	2020	(116)	Yes	No	Yes	No
Briasoulis dabigatran	2020	(116)	Yes	Yes	Yes	Yes
Briasoulis rivaroxaban	2020	(116)	Yes	No	Yes	No
Cho rivaroxaban/ apixaban	2020	(117)	Yes	Yes	No	No
Cho rivaroxaban	2020	(117)	Yes	Yes	Yes	Yes
Cho apixaban	2020	(117)	Yes	Yes	Yes	Yes
de Groot	2020	(118)	Yes	Yes	No	No
Ikeda	2019	(119)	Yes	Yes	Yes	Yes
Inoue	2019	(120)	Yes	No	No	No
Inoue	2020	(121)	Yes	Yes	No	No
Kobayashi	2020	(122)	Yes	No	Yes	No
Lee	2017	(123)	Yes	No	Yes	No
Lee	2019	(124)	No	Yes	Yes	No
Lee	2021	(125)	Yes	Yes	Yes	Yes
Murata	2019	(126)	Yes	No	Yes	No
Ohno	2020	(127)	Yes	No	No	No
Salameh	2020	(128)	Yes	Yes	Yes	Yes

Steinberg	2018	(129)	Yes	Yes	Yes	Yes
Tellor	2017	(130)	Yes	Yes	No	No
Yagi	2019	(131)	Yes	Yes	No	No
Yao dabigatran	2017	(132)	Yes	No	Yes	No
Yao rivaroxaban	2017	(132)	Yes	Yes	Yes	Yes
Yao apixaban	2017	(132)	Yes	No	Yes	No

EHRA = European Heart Rhythm Association; ESC= European Society of Cardiology; FDA = Food and Drugs Administration; i.e. = id est (= that is); NOS = Newcastle-Ottawa quality assessment Scale for cohort studies; NOAC = non-vitamin K antagonist oral anticoagulant; OLRD = off-label reduced dosing; SPC = Summary of Product Characteristics.

* In case articles concern the same author and year, a note is added after the author to indicate what makes the articles distinct.

Supplement 8: Supplemental references

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