# Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) versus Warfarin in Patients with Atrial Fibrillation and (Morbid) Obesity or Low Body Weight: A Systematic Review and Meta-Analysis

**Maxim Grymonprez, MD[1*]; Tine L. De Backer, MD, PhD[2]; Stephane Steurbaut, PhD[3]; Koen Boussery, PhD[1]; Lies Lahousse, PhD[1,4]**

[1] Department of Bioanalysis, Pharmaceutical Care Unit, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, 9000, Ghent, Belgium.

[2] Department of Cardiology, Ghent University Hospital, C. Heymanslaan 10, 9000, Ghent, Belgium.

[3] Centre for Pharmaceutical Research, Research group of Clinical Pharmacology and Clinical Pharmacy, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090, Jette, Belgium.

[4] Department of Epidemiology, Erasmus Medical Center, Doctor Molewaterplein 40, 3015, Rotterdam, The Netherlands.

*** Corresponding author:**
Grymonprez Maxim
Maxim.grymonprez@ugent.be
ORCID iD: 0000-0002-0145-6486

## Abstract

**Purpose:** Oral anticoagulants are crucial for preventing systemic thromboembolism in atrial fibrillation (AF), with guidelines preferring non-vitamin K antagonist oral anticoagulants (NOACs) over vitamin K antagonists (VKAs) in the general AF population. However, as NOACs are administered in fixed doses, concerns of unintentional underdosing in morbidly obese patients and unintentional overdosing in underweight patients have emerged. Therefore, a critical appraisal of the benefit-risk profile of NOACs in AF patients across the body weight spectrum is needed.

**Methods and results:** After searching Medline, this systematic review discusses the impact of body weight on the risk-benefit profile of NOACs versus VKAs. The meta-analysis demonstrated that NOAC use in obese and class III obese AF patients (body mass index (BMI) ≥30 and ≥40 kg/m², respectively) was associated with significantly lower stroke/systemic embolism (stroke/SE) risks (RR 0.82, 95%CI [0.71-0.96] and RR 0.75, 95%CI [0.64-0.87], respectively), similar to lower major bleeding risks (RR 0.83, 95%CI [0.69-1.00] and RR 0.74, 95%CI [0.57-0.95], respectively) and similar mortality risks (RR 0.92, 95%CI [0.73-1.15] and RR 1.17, 95%CI [0.83-1.64], respectively) as compared to VKAs. In AF patients ≤60 kg, significantly lower stroke/SE (RR 0.63, 95%CI [0.56-0.71]) and major bleeding risks (RR 0.71, 95%CI [0.62-0.80]), but similar mortality risks (RR 0.68, 95%CI [0.42-1.10]) were observed for NOAC- versus VKA-treated patients.

**Conclusion:** The benefit-risk profile of NOACs seems preserved in (morbidly) obese AF patients and patients with low body weight. However, more data are needed on underweight AF patients (BMI <18.5 kg/m²) and on differences between NOACs in these patients.

**Keywords:** Atrial fibrillation, oral anticoagulant, NOAC, VKA, obesity, low body weight

## 1. Introduction

Since atrial fibrillation (AF) is associated with a substantially increased risk of thromboembolism, oral anticoagulants (OACs) are crucial in its treatment.[1,2] For many years, vitamin K antagonists (VKAs) were the first choice antithrombotic treatment. Since their emergence more than a decade ago, non-vitamin K antagonist oral anticoagulants (NOACs) are effective and safe alternatives for stroke prevention in non-valvular AF (hereby referenced as AF), based on results from 4 large phase III randomized controlled trials (RCTs) (RE-LY trial for dabigatran[3], ROCKET AF trial for rivaroxaban[4], ARISTOTLE trial for apixaban[5] and ENGAGE AF-TIMI 48 trial for edoxaban[6]).[1,3-6] However, as NOACs are administered in fixed doses regardless of body weight (except for dose reduction of apixaban (in presence of another risk factor) and edoxaban if ≤60 kg)[7-10], concerns have risen whether the effectiveness and safety of NOACs can be guaranteed in AF patients with a low body weight (≤60 kg), being underweight (body mass index (BMI) <18.5 kg/m² as defined by the World Health Organisation, WHO)[11] or being morbidly obese (BMI ≥40 kg/m²)[11]. Indeed, modest effects of the extremes of body weight on the pharmacokinetic and –dynamic profile of NOACs have been demonstrated, although the clinical relevance of these findings is questioned.[12-16] Nevertheless, this leads to the perception that in morbidly obese patients, a fixed NOAC dose may be insufficient for adequate thromboprophylaxis due to higher distribution volumes and therefore lower plasma concentrations (unintentional underdosing), whereas in underweight patients, a fixed dose may lead to excessive bleeding risks due to lower distribution volumes and higher plasma concentrations (unintentional overdosing).[17] The 2018 European Heart Rhythm Association (EHRA) guidelines still recommend the use of VKAs in morbidly obese patients (BMI ≥40 kg/m², body weight >120 kg) due to lack of data for NOACs in these patients.[1] These guidelines also appraise a weight of ≤60 kg as a criterion to consider a dose reduction of dabigatran and rivaroxaban if at least one other risk factor (e.g. age ≥75 years, history of gastrointestinal bleeding, concomitant antiplatelet or NSAID use...) is present.[1]

Aiming to help guide clinicians in daily clinical practice, this systematic review provides an overview of the literature regarding the impact of body weight on the effectiveness and safety of NOACs versus VKAs. Two meta-analyses investigate the effectiveness and safety of NOACs versus VKAs in (morbidly) obese AF patients and in AF patients with a low body weight of ≤60 kg, respectively.

## 2. Methods

Using the Medline database, an extensive literature search was performed (see supplemental materials, eTable 1). Longitudinal studies on the effectiveness and safety of NOACs (dabigatran, rivaroxaban, apixaban and/or edoxaban) versus VKAs (warfarin, acenocoumarol and/or phenprocoumon) during a mean/median follow-up of at least 6 months in adult non-valvular AF patients with low body weight (≤50-60 kg), underweight (BMI <18.5 kg/m²)[11], overweight (BMI 25-<30 kg/m²)[11], obesity (BMI ≥30 kg/m²)[11] and class II-III obesity (BMI 35-<40 and ≥40 kg/m², respectively)[11] were included. Studies were excluded if OACs were used for non-AF indications such as venous thromboembolism (VTE). Effectiveness and safety outcomes of interest were stroke or systemic embolism (stroke/SE), major bleeding (overall, intracranial and/or gastrointestinal) and all-cause mortality. RCTs (original trial or secondary analyses), longitudinal observational cohort studies and meta-analyses written in English were included for the systematic review, while case reports, editorials, cross-sectional studies or reviews were not considered. For the meta-analyses, only results from phase III RCTs (original trial or secondary analyses) and longitudinal observational cohort studies regarding the effectiveness (stroke/SE, mortality) and safety (major bleeding, intracranial bleeding, gastrointestinal bleeding) of NOACs versus VKAs in overweight or (morbidly) obese AF patients (as defined by the WHO BMI classification)[11], and in low body weight AF patients ≤60 kg were included, respectively. No restriction of publication date was used.

On August 1, 2020, 4593 articles were identified. Additional articles of interest were selected by screening the reference list of studies. After screening title and abstract, 40 articles were selected. After reading the full-text, 20 articles were selected for the systematic review, of which 7 were used for the meta-analysis on the effectiveness and safety of NOACs in (morbidly) obese AF patients (4 phase III RCTs, 3 observational studies) and 6 for the meta-analysis on the effectiveness and safety of NOACs in low body weight AF patients (4 phase III RCTs, 2 observational studies) (Fig. 1). An overview of the included studies with study design, patient characteristics, assessed OACs (including proportion of reduced dose NOAC use, off-label NOAC dosing and mean time in therapeutic range (TTR) in VKA users) and outcome measures is displayed in eTable 2.

The meta-analyses were performed using a random effects model with the Mantel-Haenszel method. Data of the study methodology (setting, design and duration), patient characteristics (total number and age), comparison (NOAC vs VKA) and the aforementioned effectiveness and safety outcomes of interest were extracted from the original publications, supplemental materials or documents from regulatory submissions for drug approval to the FDA (the U.S. Food and Drug Administration; for data of phase III RCTs in specific BMI subgroups). If the number of events were missing, they were calculated based on the event rate, patient-years and/or risk estimate. The effect measures of each included study were calculated and reported as the relative risk (RR) with 95% confidence interval (CI), visually presented in forest plots. A two-sided p-value of <0.05 was considered statistically significant. Heterogeneity was tested using the $I^2$-statistic. The risk of bias of studies 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" (eTable 3-4).[18] Fourteen items of each study were scored on the study quality and outcome levels depending on the degree to which the specific criteria were met or reported ("yes" = 2, "partial" = 1, "no" = 0, "n/a" if not applicable). For each study, a percentage was calculated by dividing the total score obtained across rated items by the total possible score. Studies were included if scoring at least 80% on the quality assessment tool. Furthermore, the risk of publication bias at the outcome level was evaluated through funnel plot asymmetry. All analyses were performed with Review

Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014). 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, eTable 5).

## 3. Results

### Systematic review

In (morbidly) obese AF patients, discrepant results on the comparative effectiveness and safety of NOACs versus VKAs were identified between randomized and observational real-world studies (eTable 2). In the 4 phase III RCTs, the efficacy and safety of NOACs as compared to VKAs were at least preserved in both obese and morbidly obese AF patients. Indeed, in obese AF patients, NOACs were associated with similar (for standard or reduced dose dabigatran[19], rivaroxaban[20] and apixaban[21]) to lower (for edoxaban[14]) stroke/SE, similar major bleeding (for all NOACs), and similar (for edoxaban[14]) to lower (for apixaban[21]) mortality risks as compared to warfarin in the respective RCTs.[14,19-21] Likewise, in class II and III obese AF patients, similar stroke/SE, major bleeding and mortality risks were observed for NOACs (most data on apixaban and edoxaban) versus warfarin.[14,19,21] In line, equal efficacy and safety outcomes were observed in apixaban-treated AF patients >120 kg[17] and standard or reduced dose dabigatran-treated patients ≥100 kg[3,19,22] as compared to warfarin. Only for apixaban, results in AF patients >140 kg have been provided, though considerably limited by small sample sizes, documenting similar stroke/SE and mortality risks compared to warfarin, whereas major bleeding risks could not be estimated due to a lack of events.[17] After pooling randomized data from 3 phase III RCTs, the meta-analysis by Proietti et al. observed similar odds for stroke/SE and major bleeding in NOAC- versus warfarin-treated obese AF patients.[23] However, the recent meta-analysis by Malik et al., including data from 4 phase III RCTs, demonstrated significantly lower odds for stroke/SE and major bleeding, but similar odds for all-cause mortality in overweight and obese AF patients treated with NOACs compared to warfarin.[24] Furthermore, several observational studies have highlighted comparable to superior effectiveness and safety results of NOACs versus VKAs in (morbidly) obese AF patients, however most studies were performed in the U.S., retrospective in design and industry-sponsored.[25-29] Indeed, depending on the investigated NOAC, in obese AF patients, similar[26,29] to lower[25,26] stroke/SE, similar[26,29] to lower[25,26] major bleeding, similar[26] to lower[25,26] intracranial bleeding, and similar[26], lower[25,26] to higher[26] gastrointestinal bleeding risks were observed as compared to warfarin.[25,26] In head-to-head comparisons between NOACs in obese AF patients performed by an industry-sponsored study, apixaban was associated with a superior safety profile over dabigatran and rivaroxaban, and even a superior effectiveness profile over rivaroxaban.[26] However, the superior safety over dabigatran and superior effectiveness over rivaroxaban were attenuated in a subgroup analysis specifically comparing standard dose NOACs.[26] Furthermore, in morbidly obese AF patients, similar thromboembolic[25-28] and similar[27,28] to lower[25,26] major bleeding risks were observed for NOACs as compared to VKAs.[25-28] After pooling data from 1 phase III RCT (ARISTOTLE trial[17]) and 4 retrospective cohort studies, the meta-analysis of Kido et al. observed that NOAC use was associated with a similar odds for stroke/SE but significantly lower odds for major bleeding as compared to warfarin in morbidly obese AF patients (defined as BMI >40 kg/m² or body weight >120 kg).[30]

In underweight AF patients, the amount of randomized data is scarce, since only 131, 194 and 177 patients had a BMI of <18.5 kg/m² in the ROCKET-AF[20], ARISTOTLE[21] and ENGAGE AF-TIMI 48 trial[14], respectively (not reported in the RE-LY trial[3]). Moreover, to the best of our knowledge, no observational studies comparing NOACs to VKAs have been performed in this BMI subgroup so far. Consequently, no adequately powered studies have specifically investigated the effectiveness and safety of NOACs versus VKAs in underweight AF patients. However, preliminary randomized and observational data are available in AF patients with a low body weight of

<50-60 kg, illustrating the at least preserved effectiveness and safety of NOACs (eTable 2). Indeed, in the RE-LY trial, similar stroke/SE and major bleeding rates were observed in AF patients <50 kg using standard or reduced dose dabigatran[3,19,22] as compared to warfarin, whereas in AF patients ≤60 kg, significantly lower stroke/SE and similar major bleeding risks were associated with standard dose dabigatran[31] versus warfarin use.[3,19,22,31] Likewise, in AF patients ≤60 kg, as compared to warfarin, similar stroke/SE and major bleeding risks for rivaroxaban and reduced dose edoxaban were demonstrated in the ROCKET AF[32] and ENGAGE AF-TIMI 48 trial[33], respectively.[32,33] In the ARISTOTLE trial, apixaban use in AF patients ≤60 kg was associated with significantly lower stroke/SE, major bleeding and intracranial bleeding risks, but similar gastrointestinal bleeding and mortality risks as compared to warfarin.[17] Moreover, 2 observational studies investigated the effectiveness and safety of OACs in low body weight AF patients, also observing the at least preserved benefit-risk profile of NOACs compared to VKAs. Indeed, in a Korean retrospective cohort study, NOAC-treated AF patients ≤60 kg had significantly less ischemic stroke, major bleeding, intracranial bleeding, gastro-intestinal bleeding and all-cause mortality as compared to warfarin, although off-label NOAC under- and overdosing were noted in 31% and 4% of patients, respectively.[34] Results remained consistent in patients <50 kg and stratified according to standard or reduced dose NOACs versus warfarin, except for a similar gastrointestinal bleeding risk. In an Italian prospective cohort study including AF patients ≥80 years weighing ≤60 kg, NOAC use was associated with similar stroke/SE and major bleeding risks, but significantly lower all-cause mortality risks as compared to VKAs, although inappropriate NOAC under- and overdosing was observed in 5.3% and 13.5% of subjects, respectively.[35]

## Meta-analysis in (morbidly) obese AF patients

To assess the effectiveness and safety of NOACs in (morbidly) obese AF patients, results from 4 phase III RCTs[14,19-21] and 3 longitudinal observational cohort studies[25-27] were pooled in a meta-analysis. As only one study[25] provided data on the intracranial and gastrointestinal bleeding risk in morbidly obese patients, while none in overweight or class II obese patients, these outcomes could not be included in the meta-analysis in the respective BMI subgroups.

In obese AF patients (BMI ≥30 kg/m²), NOACs (n = 95777 for stroke/SE) were associated with significantly lower stroke/SE (RR 0.82, 95%CI [0.71-0.96], $I^2$ 70%) and intracranial bleeding risks (RR 0.47, 95%CI [0.38-0.57], $I^2$ 11%), but similar major bleeding (RR 0.83, 95%CI [0.69-1.00], p-value 0.05, $I^2$ 92%), gastrointestinal bleeding (RR 0.82, 95%CI [0.56-1.20], $I^2$ 97%) and mortality risks (RR 0.92, 95%CI [0.73-1.15], $I^2$ 70%) as compared to warfarin (n = 95576) (Fig. 2). In class III obese AF patients (BMI ≥40 kg/m²), NOAC use (n = 30297 for stroke/SE) was associated with significantly lower stroke/SE (RR 0.75, 95%CI [0.64-0.87], $I^2$ 0%) and major bleeding risks (RR 0.74, 95%CI [0.57-0.95], $I^2$ 86%), but a similar mortality risk (RR 1.17, 95%CI [0.83-1.64], $I^2$ 0%) as compared to warfarin (n = 30343) (Fig. 3). However, thromboembolic and bleeding risks in this BMI subgroup were primarily driven by the 3 large observational studies[25-27], as only 2 RCTs[14,21] provided limited data. Noteworthy, randomized studies illustrated a similar pooled efficacy and safety of NOACs compared to VKAs in obese and class III obese patients, whereas observational studies demonstrated a non-inferior to superior benefit-risk profile after pooling of the results (Fig. 2-3). Furthermore, similar trends were seen in overweight AF patients (BMI 25-<30 kg/m²), documenting significantly lower stroke/SE (RR 0.87, 95%CI [0.77-0.99], $I^2$ 0%) and major bleeding risks (RR 0.83, 95%CI [0.72-0.96], $I^2$ 53%), but a similar mortality risk (RR 0.90, 95%CI [0.80-1.02], $I^2$

5%) for NOACs (n = 13471 for stroke/SE) as compared to warfarin (n = 13459), though only based on results from four randomized studies (eFig. 1 in supplemental materials). However, in class II obese patients (BMI 35-<40 kg/m²), reduced but non-significant risk estimates for all outcomes were observed when comparing NOACs (n = 12483 for stroke/SE) to VKAs (n = 12526) (RR 0.72, 95%CI [0.50-1.02], $I^2$ 51% for stroke/SE; RR 0.83, 95%CI [0.65-1.06], $I^2$ 63% for major bleeding; RR 0.95, 95%CI [0.74-1.23], $I^2$ 0% for mortality), based on data from only 1 observational study[25] next to the 3 RCTs (eFig. 2). The reduced number of individuals in long-term outcomes (especially mortality follow-up, 1580 NOAC and 1573 warfarin users), the reduced number of events (e.g. 176 and 247 stroke/SE events in NOAC and warfarin users, respectively) and heterogeneity among studies may have resulted in the lack of power to demonstrate significantly reduced risks in this BMI subgroup.

No publication bias was suspected based on visual inspection of the funnel plots, although the interpretability was limited due to inclusion of less than 10 studies (eFig. 6). All included studies scored >80% on the quality assessment tool 'QUALSYST'[18] (eTable 3). For stroke/SE and mortality, no substantial heterogeneity was detected in class III obese AF patients, while substantial heterogeneity was present for both outcomes in obese patients. In a sensitivity analysis, after separately excluding results of each observational study, significantly lower stroke/SE risks for NOACs versus VKAs in obese patients were still observed with lower residual heterogeneity present, except for a similar risk after excluding results of apixaban versus warfarin from the study by Deitelzweig et al.[26] (eFig. 3). For major bleeding and gastrointestinal bleeding, substantial heterogeneity was also present in (class III) obese patients, probably as a result of differential safety profiles of the individual NOACs documented in the observational study by Deitelzweig et al.[26] Lastly, for intracranial bleeding in obese patients, heterogeneity was low.

## Meta-analysis in low body weight AF patients

Due to the lack of sufficient randomized and observational data in underweight AF patients (BMI <18.5 kg/m²), a meta-analysis was performed in AF patients with a low body weight of ≤60 kg, by pooling results from 4 phase III RCTs[17,31-33] and 2 longitudinal observational cohort studies[34,35]. As only 2 studies[17,34] provided data on the intracranial and gastrointestinal bleeding risk, these outcomes were not included in the meta-analysis.

In low body weight AF patients ≤60 kg, NOAC use (n = 17342 for stroke/SE) was associated with significantly lower stroke/SE (RR 0.63, 95%CI [0.56-0.71], $I^2$ 0%) and major bleeding risks (RR 0.71, 95%CI [0.62-0.80], $I^2$ 0%), but similar mortality risks (RR 0.68, 95%CI [0.42-1.10], $I^2$ 91%) as compared to warfarin (n = 10868) (Fig. 4). Overall, results between randomized and observational studies were consistent. However, as the included observational studies[34,35] reported considerable off-label NOAC dosing, a sensitivity analysis was performed only including appropriately dosed NOACs (n = 12420) compared to warfarin (n = 10868) in low body weight AF patients ≤60 kg, which rendered consistent results (RR 0.63, 95%CI [0.54-0.73], $I^2$ 7% for stroke/SE; RR 0.70, 95%CI [0.61-0.80], $I^2$ 0% for major bleeding; RR 0.71, 95%CI [0.45-1.11], $I^2$ 90% for mortality) (eFig. 4).

No publication bias was suspected based on visual inspection of the funnel plots (though interpretability was limited) (eFig. 7). All included studies scored >80% on the quality assessment tool 'QUALSYST'[18] (eTable 4). No substantial heterogeneity was detected for the thromboembolic and bleeding outcomes. However, due to heterogeneous results in the 3 pooled studies[17,34,35], considerable heterogeneity ($I^2$ 91%) was present for the mortality risk, even after separately excluding results of each observational study in a sensitivity analysis (eFig. 5).

## 4. Discussion

Our meta-analysis based on 4 randomized[14,19-21] and 3 observational[25-27] studies investigating the effectiveness and safety of NOACs versus VKAs in (morbidly) obese AF patients, has highlighted the at least preserved benefit-risk profile of NOACs, in line with results of the meta-analysis of Proietti et al.[23], Malik et al.[24] and Kido et al.[30]. Indeed, NOAC use was associated with significantly lower thromboembolic, similar to lower major bleeding and similar mortality risks in obese and class III obese AF patients as compared to VKAs (Fig. 2-3, eFig. 1-2). However, as these superior results of NOACs were primarily driven by observational studies[25-27], while the benefit-risk profile of NOACs in (morbidly) obese AF patients was largely similar to VKAs in randomized studies[14,19-21], our superior results should be interpreted with caution. Nevertheless, concerns of unintentional NOAC underdosing with excessive thromboembolic risks in morbidly obese AF patients appear to be unfounded. Moreover, as we have demonstrated a superior effectiveness and safety of NOACs as compared to VKAs in class III obese AF patients with a BMI of ≥40 kg/m², NOAC use seems warranted in morbidly obese AF patients, bearing in mind that the 2018 EHRA guidelines[1] still recommend VKA use in this patient subgroup.

Furthermore, our second meta-analysis based on 4 randomized[17,31-33] and 2 observational[34,35] studies has illustrated that also in AF patients with a low body weight of ≤60 kg, NOACs were associated with a superior effectiveness and safety, but similar mortality risk as compared to VKAs (Fig. 4). Therefore, concerns of unintentional overdosing resulting in excessive bleeding risks in AF patients with a low body weight were not observed, justifying the use of NOACs in lean patients in an appropriate dosage in accordance with the manufacturer drug labelling[7-10]. However, our findings should not be extrapolated to underweight AF patients (BMI <18.5 kg/m²), for whom sufficient randomized and observational data are currently lacking, due to the fact that a low body weight of ≤60 kg does not automatically correspond with underweight. Exemplary, in the ENGAGE AF-TIMI 48 trial, 175, 1648, 241, 7 and 1 patients with a weight of ≤60 kg were classified as underweight, normal weight, overweight, class I obese and class II obese, respectively.[14] Moreover, although we demonstrated a superior effectiveness and safety of NOACs in AF patients with a low body weight, the potential influence of ethnic differences should be mentioned. Low body weight AF patients tend to be more Asian than normal weight or obese patients. Exemplary, in the ARISTOTLE trial, 46.6%, 12.9% and 3.2% of patients weighing ≤60, 60-120 and >120 kg respectively were Asian, while 17.1%, 44.0% and 31.2% of patients respectively were European.[17] As Asian AF patients tend to have more VKA-related major bleeding events (especially intracranial bleeding), higher stroke rates (especially haemorrhagic stroke) and a lower mean time in therapeutic range (TTR) among VKA users than Caucasian AF patients, the superior effectiveness and safety profile of NOACs over VKAs in low body weight AF patients may have been influenced by these underlying ethnic differences.[36-39]

### Strengths and limitations

Our systematic review and meta-analysis has several strengths, such as the inclusion of both phase III RCTs, characterised by meticulous methodologies and well-defined cohorts, and longitudinal observational cohort studies, which include large real-world patient subgroups with long follow-up. By pooling results, we have included large numbers of patients for each outcome, even in the subgroup of patients with class III obesity or low body weight, who were underrepresented in randomized studies. Furthermore, for patients with (morbid) obesity, we only

included patients based on an increased BMI instead of high body weight, as a body weight of >120 kg does not necessarily correspond with class III obesity (e.g. any person larger than 1.73 metres with a body weight of 120 kg would have a BMI of <40 kg/m²). However, several limitations should be mentioned complicating the comparability of studies. First, NOAC dosages varied between studies, as dabigatran 75 mg twice daily is the approved reduced dosage in the U.S.[31] (as opposed to 110 mg twice daily in Europe)[1,9]. Similarly, off-label NOAC dosing may have influenced results, especially in observational studies, although only two studies[34,35] did mention the proportion of inappropriate NOAC dosing. However, our results were consistent in a sensitivity analysis only including on-label NOAC dosing versus VKAs in low body weight AF patients (eFig. 4). Moreover, we have pooled the results of different NOACs and NOAC dosages to assess the class effect of NOACs, due to a lack of sufficient data for the individual NOACs and frequent non-reporting of outcomes according to the NOAC dosage. As the use of reduced dose NOACs did vary across studies (e.g. 4% in class III obese AF patients in the ENGAGE AF-TIMI 48 trial[14] to 25% in rivaroxaban-treated obese patients in the study by Deitelzweig et al.[26]), this may have impacted our results. Second, classification of patients according to BMI or body weight differed between studies, as one study[29] categorized patients according to the BMI quartiles instead of the WHO BMI classification[11], and another study[3,22] defined low body weight as <50 kg instead of ≤60 kg. Third, BMI and body weight were usually measured at baseline, not adjusting for weight changes during follow-up. However, in the ARISTOTLE trial, only very small changes in weight in each weight category were noted during follow-up.[17] Fourth, effectiveness endpoints differed from our outcomes of interest and complicated the comparability of results, as some studies[28,29] examined the risk of stroke/VTE. Fifth, as results on the effectiveness and safety of NOACs versus VKAs in class III obese AF patients were primarily driven by observational studies performed in the U.S.[25-28], while most low body weight AF patients had an Asian ethnicity[17,34], these results should not be automatically extrapolated to other populations due to potential underlying ethnic differences. Sixth, several observational studies[25-27,34] were retrospective in design and used data from administrative healthcare claims databases, which are prone to coding errors. Indeed, when using the 'QUALSYST' tool to assess the quality of studies, some included observational studies lacked well defined outcomes which were robust to measurement bias or were limited by unmeasured confounding. Seventh, as RCTs are usually underpowered for subgroups analyses, run too short for (long-term) safety outcomes, and differ in study design and patient population, pooled results from randomized studies should be interpreted with caution. Lastly, due to a general lack of data, we could not account for differences in potential confounders between studies, such as baseline comedication use (e.g. antiplatelets), comorbidities (e.g. chronic kidney disease, CKD) or mean TTR in VKA users. However, the baseline prevalence of several covariates in included studies, if reported, was largely comparable in obese patients, such as hypertension (87-97%)[14,20,21,27], CKD (10-15%)[14,25,27] and antiplatelet use (30-37%)[14,20,21] (see eTable 2). On the contrary, the baseline prevalence of other covariates tended to differ, such as diabetes (33-54%)[14,20,21,25,27], prior stroke/SE (16-48%)[14,20,21] and mean TTR (56-66%)[14,20]. In line, selection bias due to differences in baseline characteristics of the included study population may in part explain the observed heterogeneity in some analyses. For example, the heterogeneity in the mortality risk of NOAC- versus VKA-treated obese AF patients may have resulted from the inclusion of older obese AF patients in the ENGAGE AF-TIMI 48 trial[14] (median age 71 years [65-78]) than in the ARISTOTLE trial[21] (mean age 67 years +/- 9), potentially diminishing the favourable effects of NOACs on mortality risks as age increases. Likewise, the detected substantial heterogeneity for thromboembolic and bleeding outcomes in low body weight AF patients may have

resulted from differences in age (e.g. median age of 74 years [66-79] in ARISTOTLE trial[17], whereas mean age of 84 years +/- 5 in the study by Russo et al.[35]) and study population (Korean healthcare claims database in the study by Lee et al.[34], whereas Italian multicentre study among octogenarians in the study by Russo et al.[35]).

## Recommendations for clinical practice

Based on the results of our meta-analysis, the use of appropriately dosed NOACs seems warranted in both (morbidly) obese AF patients and patients with a low body weight. Although one retrospective study[26] specifically compared NOACs among obese AF patients, no specific NOAC can yet be recommended in any patient subgroup across the weight spectrum until more data become available.

## Research gaps

Despite the abundance of data in obese AF patients and the recently emerging data in morbidly obese patients, sufficient data is still lacking in underweight AF patients. Future research on the effectiveness and safety of NOACs as compared to VKAs in AF patients with a BMI of <18.5 kg/m² is urgently needed, preferably in other than Asian populations, in order to confirm the reassuring findings observed in low body weight AF patients. Likewise, more data are needed in AF patients with other extreme forms of body weight, such as a body weight of >150 kg or BMI ≥50 kg/m², as our reassuring findings in class III obese patients (BMI ≥40 kg/m²) may not be generalizable to patients with even higher body weights. Moreover, as sufficient data on the intracranial and gastrointestinal bleeding risk of NOACs versus VKAs is lacking in morbidly obese and low body weight AF patients, it would be of interest to assess these outcomes in future research, in order to investigate whether the observed superior safety profile of NOACs in these subgroups is also primarily driven by a lower intracranial and/or gastrointestinal bleeding risk. Lastly, no specific NOAC can yet be recommended in (morbidly) obese or low body weight AF patients due to the lack of sufficient direct head-to-head comparisons between NOACs.

## 5. Conclusion

In conclusion, despite modest effects of body weight on the pharmacokinetics and -dynamics of NOACs, the use of appropriately dosed NOACs seems justified in patients at the extremes of body weight, as this meta-analysis has highlighted the at least preserved effectiveness and safety profile of NOACs compared to VKAs in (morbidly) obese AF patients and in AF patients with low body weight. However, research gaps on the benefit-risk profile of NOACs in underweight AF patients and on which NOAC to prefer in these patient subgroups, were identified, necessitating more research.

## Declarations

**Funding:** This research was supported by grants from the Fund for Scientific Research Flanders (FWO) [grant number 11C0820N to Maxim Grymonprez].

**Conflicts of interests:** The authors have no conflicts of interest to declare that are relevant to the content of this article.

**Ethics approval:** Not applicable.

**Consent to participate:** Not applicable.

**Consent for publication:** Not applicable.

**Availability of data and material**: The data underlying this article are available in the article and in its online supplemental materials.

**Code availability:** Not applicable.

**Authors' contributions:** Maxim Grymonprez and Lies Lahousse contributed to the concept and design of the systematic review. Maxim Grymonprez performed the literature search, data analysis, interpretation and writing. The first draft of the manuscript was written by Maxim Grymonprez. Tine De Backer, Stephane Steurbaut, Koen Boussery and Lies Lahousse revised the manuscript critically. All authors read and approved the final manuscript.

**Acknowledgments:** None.

# References


1. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39(16):1330-93.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-8.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51.
4. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-91.
5. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92.
6. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093-104.
7. Eliquis. Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf. Accessed 10 July 2020.
8. Lixiana. Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/lixiana-epar-product-information_en.pdf. Accessed 10 July 2020.
9. Pradaxa. Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf. Accessed 10 July 2020.
10. Xarelto. Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf. Accessed 10 July 2020.
11. World Health Organization (WHO) Body mass index (BMI) classification. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi. Accessed 10 July 2020.
12. Upreti VV, Wang J, Barrett YC, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. Br J Clin Pharmacol. 2013;76(6):908-16.
13. Yamashita T, Koretsune Y, Yasaka M, et al. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. Circulation journal : official journal of the Japanese Circulation Society. 2012;76(8):1840-7.
14. Boriani G, Ruff CT, Kuder JF, et al. Relationship between body mass index and outcomes in patients with atrial fibrillation treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. Eur Heart J. 2019;40(19):1541-50.
15. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). Journal of the American College of Cardiology. 2014;63(4):321-8.
16. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. Journal of clinical pharmacology. 2007;47(2):218-26.
17. Hohnloser SH, Fudim M, Alexander JH, et al. Efficacy and Safety of Apixaban Versus Warfarin in Patients With Atrial Fibrillation and Extremes in Body Weight. Circulation. 2019;139(20):2292-300.
18. Kmet L, Lee R, Cook L. The quality assessment tool 'QUALSYST' from the "Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields". https://www.ihe.ca/advanced-search/standard-quality-assessment-criteria-for-evaluating-primary-research-papers-from-a-variety-of-fields. Accessed 1 August 2020. 2004.
19. Boehringer Ingelheim Pharmaceuticals. FDA Briefing Information, Dabigatran Etexilate Mesylate Capsules, for the September 20, 2010 Meeting of the Cardiovascular and Renal Drugs Advisory Committee. https://wayback.archive-it.org/7993/20170405212218/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM247244.pdf. Accessed 10 July 2020.
20. Balla SR, Cyr DD, Lokhnygina Y, et al. Relation of Risk of Stroke in Patients With Atrial Fibrillation to Body Mass Index (from Patients Treated With Rivaroxaban and Warfarin in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation Trial). The American journal of cardiology. 2017;119(12):1989-96.
21. Sandhu RK, Ezekowitz J, Andersson U, et al. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. Eur Heart J. 2016;37(38):2869-78.

22. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation. 2011;123(21):2363-72.
23. Proietti M, Guiducci E, Cheli P, Lip GY. Is There an Obesity Paradox for Outcomes in Atrial Fibrillation? A Systematic Review and Meta-Analysis of Non-Vitamin K Antagonist Oral Anticoagulant Trials. Stroke. 2017;48(4):857-66.
24. Malik AH, Yandrapalli S, Shetty S, et al. Impact of weight on the efficacy and safety of direct-acting oral anticoagulants in patients with non-valvular atrial fibrillation: a meta-analysis. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2020;22(3):361-7.
25. Costa OS, Beyer-Westendorf J, Ashton V, et al. Effectiveness and safety of rivaroxaban versus warfarin in obese nonvalvular atrial fibrillation patients: analysis of electronic health record data. Current medical research and opinion. 2020;36(7):1081-8.
26. Deitelzweig S, Keshishian A, Kang A, et al. Effectiveness and Safety of Oral Anticoagulants among NVAF Patients with Obesity: Insights from the ARISTOPHANES Study. Journal of clinical medicine. 2020;9(6).
27. Peterson ED, Ashton V, Chen YW, Wu B, Spyropoulos AC. Comparative effectiveness, safety, and costs of rivaroxaban and warfarin among morbidly obese patients with atrial fibrillation. Am Heart J. 2019;212:113-9.
28. Patil T, Lebrecht M. A single center retrospective cohort study evaluating use of direct oral anticoagulants (DOACs) in morbidly obese veteran population. Thromb Res. 2020;192:124-30.
29. Patti G, Pecen L, Manu MC, et al. Thromboembolic and bleeding risk in obese patients with atrial fibrillation according to different anticoagulation strategies. Int J Cardiol. 2020;318:67-73.
30. Kido K, Shimizu M, Shiga T, Hashiguchi M. Meta-Analysis Comparing Direct Oral Anticoagulants Versus Warfarin in Morbidly Obese Patients With Atrial Fibrillation. The American journal of cardiology. 2020;126:23-8.
31. Boehringer Ingelheim. Pradaxa (dabigatran), U.S. Food and Drug Administration Highlights of Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022512s027lbl.pdf. Accessed 10 July 2020.
32. Xarelto (rivaroxaban). U.S. Food and Drug Administration Highlights of Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022406s028lbl.pdf. Accessed 10 July 2020.
33. Savaysa (edoxaban). U.S. Food and Drug Administration Highlights of Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf. Accessed 10 July 2020.
34. Lee SR, Choi EK, Park CS, et al. Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation and Low Body Weight. Journal of the American College of Cardiology. 2019;73(8):919-31.
35. Russo V, Attena E, Di Maio M, et al. Non-vitamin K vs vitamin K oral anticoagulants in patients aged > 80 year with atrial fibrillation and low body weight. European journal of clinical investigation. 2020:e13335.
36. Hori M, Connolly SJ, Zhu J, et al. Dabigatran versus warfarin: effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. Stroke. 2013;44(7):1891-6.
37. Chiang C-E, Wang K-L, Lip GYH. Stroke prevention in atrial fibrillation: an Asian perspective. Thrombosis and haemostasis. 2014;111(5):789-97.
38. Chao TF, Chen SA, Ruff CT, et al. Clinical outcomes, edoxaban concentration, and anti-factor Xa activity of Asian patients with atrial fibrillation compared with non-Asians in the ENGAGE AF-TIMI 48 trial. Eur Heart J. 2019;40(19):1518-27.
39. Piccini JP, Hellkamp AS, Lokhnygina Y, et al. Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: results from the ROCKET AF trial. J Am Heart Assoc. 2014;3(2):e000521.

## Figure captions

**Fig. 1** PRISMA flow diagram

AF: atrial fibrillation; BMI: body mass index; NOAC: non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; VTE: venous thromboembolism; WHO: World Health Organisation

**Fig. 2** The risk of **a)** stroke or systemic embolism, **b)** major bleeding, **c)** all-cause mortality, **d)** intracranial bleeding, and **e)** gastrointestinal bleeding for NOACs versus VKAs in obese AF patients (BMI ≥30 kg/m²)

AF: atrial fibrillation; Api 5/2.5: apixaban 5 mg (standard dose) and 2.5 mg (reduced dose); ARISTOTLE: the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; BMI: body mass index; CI: confidence interval; Dabi 150/110: dabigatran 150 mg (standard dose) and 110 mg (reduced dose); ENGAGE AF-TIMI 48: the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 trial; M-H: Mantel-Haenszel (statistical method); NOAC: non-vitamin K antagonist oral anticoagulant; RCT: randomized controlled trial; RE-LY: the Randomized Evaluation of Long-Term Anticoagulation Therapy; Riva 20/15: rivaroxaban 20 mg (standard dose) and 15 mg (reduced dose); ROCKET AF: the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VKAs: vitamin K antagonists

**Fig. 3** The risk of **a)** stroke or systemic embolism, **b)** major bleeding, and **c)** all-cause mortality for NOACs versus VKAs in class III obese AF patients (BMI ≥40 kg/m²)

AF: atrial fibrillation; Api 5/2.5: apixaban 5 mg (standard dose) and 2.5 mg (reduced dose); ARISTOTLE: the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; BMI: body mass index; CI: confidence interval; Dabi 150/110: dabigatran 150 mg (standard dose) and 110 mg (reduced dose); ENGAGE AF-TIMI 48: the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 trial; M-H: Mantel-Haenszel (statistical method); NOAC: non-vitamin K antagonist oral anticoagulant; RCT: randomized controlled trial; Riva 20/15: rivaroxaban 20 mg (standard dose) and 15 mg (reduced dose); VKAs: vitamin K antagonists

**Fig. 4** The risk of **a)** stroke or systemic embolism, **b)** major bleeding, and **c)** all-cause mortality for NOACs versus VKAs in AF patients with a low body weight (≤60 kg)

AF: atrial fibrillation; ARISTOTLE: the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; CI: confidence interval; Dabi 150: dabigatran 150 mg (standard dose); ENGAGE AF-TIMI 48: the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 trial; M-H: Mantel-Haenszel (statistical method); NOAC: non-vitamin K antagonist oral anticoagulant; RCT: randomized controlled trial; RE-LY: the Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF: the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VKAs: vitamin K antagonists