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Review

Clinical effects of off-label reduced doses of Direct Oral Anticoagulants: A systematic review and meta-analysis

Mariana Q. Pereira [a], Cláudio David [b,c,d], Ana G. Almeida [c,d], Dulce Brito [c,d], Fausto J. Pinto [c,d], Daniel Caldeira [b,c,d,*]

[a] Faculdade de Medicina, Universidade de Lisboa, Portugal
[b] Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina, Universidade de Lisboa, Portugal
[c] Serviço de Cardiologia, Hospital Universitário de Santa Maria (CHLN), CAML, Lisboa, Portugal
[d] Cardiovascular da Universidade de Lisboa - CCUL (CCUL@RISE), Faculdade de Medicina, Universidade de Lisboa, Portugal

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ABSTRACT

Backgound: Atrial Fibrillation (AF) is the most prevalent cardiac arrhythmia among older patients, associated with thromboembolic events. Direct Oral Anticoagulants (DOAC) are the treatment of choice for most patients, but its use may have risks on standard dose. However, it is still unclear the effects related with the use of a lower dose off labelled DOAC.

Objectives: We conducted a systematic review and meta-analysis to assess the effects of off-label underdose use of DOAC in patients with AF.

Methods: MEDLINE, Cochrane Central Register of Controlled Trials, PsycINFO databases and EMBASE were searched for observational longitudinal studies evaluating the outcomes on off label underdosed patients compared with standard dosed patients with AF. We performed a random-effects meta-analysis to estimate the pooled Hazard Ratios (HR) with 95% Cis.

Results: Eighteen cohort studies evaluating 237,533 patients with AF were included. Off-label underdose DOAC use is associated with higher risk of all-cause mortality [HR = 1.27 (95%CI 1.09–1.48)] and cardiovascular composite outcomes [HR = 1.32 (95%CI 1.08–1.62)], when compared with standard dose DOAC use. The effects in thromboembolic events [HR = 1.14 (95%CI 1.00–1.31)], major bleeding [HR = 1.02 (95%CI 0.91–1.15)], and composite of ischemic and bleeding events [HR = 1.22 (95%CI 0.79–1.88)] were not statistically significant. The certainty in the evidence was low or very low.

Conclusions: Off label underdose DOAC use is associated with higher risk of all-cause mortality and cardiovascular composite outcomes, compared with standard dose.

1. Introduction

Atrial fibrillation (AF) is a cardiac arrythmia associated with an increased risk of stroke and death. In patients who are newly diagnosed with AF, the mortality risk is especially high during the first four months [1].

Direct Oral Anticoagulants (DOAC) are nowadays recommended as the treatment of choice for most patients with AF [2]. DOAC specific characteristics are the rapid onset of action, a short half-life, a predictable anticoagulant effect in standard conditions, not requiring prothrombin time monitoring, and a low level of food–drug interactions [3–5]. Due to their pharmacological profiles, this class of drugs is administered at a defined dose taking into account clinical indications, individual characteristics and renal function, without current indications for dose adjustment based on laboratory testing.

The use of DOACs on an off-label dose is becoming a common clinical practice [6], although data associated with its clinical consequences is still limited and clinical efficacy may be compromised. This can be explained by the fact that the fixed-dosing strategy is possibly at risk of confusion due to multiple dose regimens depending on indications and physiological and clinical parameters (age, body weight, renal insufficiency), and interacting drugs [7].

* Corresponding author at: Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina da Universidade de Lisboa, Av. Prof. Egas Moniz, Lisboa 1649-028, Portugal.
E-mail address: dgcaldeira@hotmail.com (D. Caldeira).

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During the current days, the challenge faced by clinicians remains on selecting the optimal choice and dose of DOAC to maintain the delicate equilibrium between thrombosis and bleeding risk of patients, especially those with multiple medical co-morbidities or multiple co-medication [8–10]. The use of DOACs on standard dose may have risks, but the effects related with the use of a lower dose off labelled DOAC are still unclear [10].

Notably, there is a gap in knowledge about the efficacy and safety of reduced dose DOAC despite the disproportionately high usage of reduced dose DOAC, which is a cause of concern. Therefore, studies examining the effectiveness and safety of standard dose or reduced dose DOAC in direct comparisons are warranted [11,12].

The purpose of the study is to conduct a systematic review and meta-analysis on the impact, effects, and outcomes of the use of off-label dose-reduced direct anticoagulants in the referred population, patients with AF.

2. Methods

This systematic review follows the reporting principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13].

2.1. Protocol and guidance

The study protocol was reported following PRIMA-P guidelines [13,14] and was registered at PROSPERO [15].

2.2. Eligibility criteria

2.2.1. Study design and participants of interest

We considered eligible all observational longitudinal studies (whether prospective or retrospective) in patients with AF, evaluating the effects of off label dose reduced DOAC, compared with standard DOAC use.

Case series (including self-controlled case series), clinical controlled trials, case reports, cross-sectional studies, reviews and commentaries were not included.

2.3. Information sources and searching method

MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO databases and EMBASE (April 2021) were searched for observational longitudinal studies evaluating the outcomes of patients with atrial fibrillation treated with off label low-dose DOACs compared with standard doses.

Reference lists of systematic reviews, as well as the reference list of include studies were comprehensively searched. The search strategy, including terms use for the database search, are available in supplementary material

2.4. Study selection and outcome measurements

After excluding duplicate records obtained in the electronic search, studies were included if they (1) were observational studies; (2) included AF patients; (3) compared off label reduced dose DOAC and standard dose DOAC. The outcomes of interest were: thromboembolic events, major bleeding, cardiovascular composite outcome (including mortality, stroke, myocardial infarction and/or coronary revascularization), composite of ischaemic and bleeding events, all cause mortality (net clinical benefit). We assessed the relation between specific DOACs – rivaroxaban, dabigatran and apixaban – and its outcomes as well.

2.5. Study records and data extraction

The record retrieved through electronic databases search were screened independently by two authors (MQP and DC). Suitable studies were evaluated for the inclusion in the review through full-text assessment. Study selection and data extraction were performed independently. If different data were available for the same trial, the most recent report was considered.

Two reviewers (MQP and DC) independently extracted data from included observational studies using a standardized electronic from. Disagreements were solved with consensus. Study characteristics and results were extracted independently into a standardized form. These data included: authors and year of publication, study design, follow-up, local, population details (age, gender, thromboembolic and haemorrhagic scores/risk factors, baseline comorbidities), outcomes.

2.6. Risk of bias in individual studies

The risk of bias was evaluated by the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool [16] which uses an hypothetical randomized controlled trial (RCT) for each outcome included to evaluate the risk of bias. The seven predefined specific domains of analysis were: confounding, selection of participants into the study, classification of interventions, derivations from intended interventions, missing data, measurements of outcomes and selection of the reported result. Two independent review authors (MQP and DC) performed critical assessments for each domain of the risk of bias tool. Disagreements throughout this process were solved by consensus.

2.7. Data synthesis

The outcome was treated as a dichotomous data. We used the reported estimates when the studies reported Hazard Ratio (HR). When studies did not reported HR, Risk Ratio (RR) and 95% confidence interval (95% CI) were used to estimate pooled results from studies.

The data from the outcomes of interest were pooled using RevMan version 5.4 (The Nordic Cochrane Centre, Copenhagen; The Cochrane Collaboration, 2014) and meta-analysis were performed using the inverse variance method and random effects model. Statistical heterogeneity was assessed through I^2 variability (measures the percentage of total variation between studies attributed to interstudy heterogeneity rather than random). We considered statistical heterogeneity as low if $I^2 < 25\%$; moderate if I^2 25–75%; and high if $I^2 > 75\%$. The I^2 statistic publication bias assessment was performed through funnel plot examination and Egger test if more than 10 studies were included [17].

2.8. Confidence in pooled data

We used the Grading of Recommendations, Assessment and Evaluation (GRADE) framework to report the overall quality of evidence for each outcome. The certainty in the evidence for each outcome was graded as “high”, “moderate”, “low”, or “very low” [18–20].

The GRADE approach was independently assessed by two investigators (MQP and DC) and discrepancies were solved by consensus.

3. Results

3.1. Study selection

The electronic database search yielded 444 references. After screening of title and abstract and evaluation for full-text eligibility, 18 studies remained for inclusion in the qualitative synthesis, and 18 studies in the meta-analysis (Supplementary Fig. 1) [21–38].

3.2. Study characteristics

All 18 studies included in the meta-analysis were cohort studies (thirteen retrospective and five prospective). There were no randomized clinical trials (RCTs) included.

The main characteristics of the included studies are depicted in Table 1.

The mean age of the patients in the studies ranged between 63 years and 82 years.

The number of participants ranged from 327 to 53,649. In the study, the CHA2DS2-VASC score ranged from 1,3 to 5 points. The duration of follow-up varied between 3,6 to 40 months, on average.

3.3. Pooled analysis

We performed the meta-analysis for all-cause mortality using data from eighteen studies, which included a total of 237,533 patients with AF (Supplementary Fig. 1).

Fifteen studies reported thromboembolic events (stroke/systemic embolism), fourteen reported major bleeding, nine reported mortality, four reported cardiovascular composite outcome, and three reported a composite of ischemic and bleeding events.

The pooled analysis showed that off label low dose DOAC was associated with a significant higher risk of all-cause mortality with HR = 1.27 (95% CI 1.09 to 1.48), with I^2 = 71%, when compared with standard dose of DOAC (Fig. 1).

Similarly, the pooled analysis on cardiovascular composite outcomes showed that off label low dose DOAC was associated with a significant higher risk with HR = 1.32 (95% CI 1.08 to 1.62), with I^2 = 66%, in comparison with standard dose of DOAC (Fig. 1).

Regarding other outcomes, we analysed thromboembolic events (stroke/systemic embolism), major bleeding and composite of ischemic and bleeding events. In these outcomes, there were no statistically significant differences: HR = 1.14 (95% CI 1.00 to 1.31), with I^2 = 62%; HR = 1.02 (95% CI 0.91 to 1.15), with I^2 = 44%; and HR = 1.22 (95% CI 0.79 to 1.88), with I^2 = 49%, respectively (Fig. 1 and Supplementary Fig. 2).

Table 1
Studies Characteristics.

Study (1st author) /year	Design	Region	Study Population (DOAC of the study)	Mean age/% male	Outcomes	Baseline CHA2DS2VASC sccore
Wen-Han Cheng, 2019 [21]	Observational retrospective single-center study	Taiwan	2214 patients (rivaroxaban)	75,7/64%	S, ICH, ACSS	2.9
Benjamin A. Steinberg, 2018 [22]	Retrospective cohort study	USA	7925 patients (apixaban, dabigatran, edoxaban, rivaroxaban)	71/58,7%	ACSS, MB [ISTH], ACM, MI	Score 0: 264 (3.3%) Score 1: 749 (9.5%) Score ≥ 2: 6992 (87.2%)
Pierre Amarenco, 2019 [23]	Prospective, observational study	Europe, Canada, and Israel	6784 patients (rivaroxaban)	70,5/69,7%	ACSS, MB [ISTH], ACM	3.3
Ronen Arbel, 2019 [24]	Retrospective cohort study	Israel	8425 patients (apixaban, dabigatran, rivaroxaban)	72–81/ 45–50%	ACSS, ACM, MI	4.4–5.1
Alexandros Briasoulis 2020 [25]	Retrospective cohort study	USA	8035 and 19,712 (27,747) (dabigatran, rivaroxaban)	−−/ 42,9-52,1%	S, MB [ISTH], GIB, ICH	–
Nobuhiro Murata 2019 [26]	Prospective, observational study	Japan	3268 patients (apixaban, dabigatran, edoxaban, rivaroxaban)	71,7/71,5%	ACSS, TIA, SE, MB [ISTH], ICH, ACM, C	2.9 ± 1.5
Takanori Ikeda 2019 [27]	Prospective, single-arm, observational study	Japan	6521 patients (rivaroxaban)	68–74,8/ 60–88,4%	ACB, MB [ISTH], A, BT, S, ICH, ACSS, MI, CHF	3.0 ± 2.8
Alan John Camm 2020 [28]	Prospective observational study	USA	A total of 34,926 patients; 10,426 patients received a DOAC (apixaban, dabigatran, edoxaban, rivaroxaban)	70–77/49,2-58,2%	ACSS, ACM, MB [ISTH]	3.0–4.0
Maram Salameh 2020 [29]	Retrospective cohort study	Israel	27,765 patients (apixaban)	78,7/−−-	MB [ISTH], GIB, ICH, ACSS	4.8 ± 1.6
José Paulo de Almeida 2020 [30]	Retrospective cohort study	Portugal	327 patients (apixaban, dabigatran, rivaroxaban)	82/38,5%	ACSS, MB [ISTH], ACM	5.0 ± 1.5
Xiaoxi Yao 2017 [31]	Retrospective cohort study	EUA	14,865 patients (apixaban, dabigatran, rivaroxaban)	57,3%	ACSS, MB [ISTH], ACM	4.0
Hee Tae Yu 2020 [32]	Retrospective cohort study	Republic of Korea	53,649 patients (apixaban, dabigatran, edoxaban, rivaroxaban)	60,3%	ACSS, MB [ISTH], ICH, GIB, MI, ACM	4.6 ± 1.8
Kwang-No Lee 2020 [33]	Retrospective observational study	Republic of Korea	6392 patients: 2659 warfin; 3733 DOAC: in which 1554 reduced dose; 2179 standard dose (apixaban, dabigatran, edoxaban, rivaroxaban)	62,4%	ACSS, MB [ISTH]	3.0
Min Soo Cho 2020 [34]	Retrospective observational study	Republic of Korea	16,568 patients (apixaban, rivaroxaban)	55,9–68,2%	ACSS, SE, MB [ISTH], ACM	3.1–3.6
Tomoaki Kobayashi 2020 [35]	Prospective observational study	Japan	2216 patients (apixaban, dabigatran, edoxaban, rivaroxaban)	61,7–76,4%	ACSS, MI, ACM	–
Yi-Hsin Chan 2020 [36]	Retrospective observational study	Taiwan	2068, 5135, 2589, 1483, and 2342 AF patients (taking dabigatran, rivaroxaban, apixaban, edoxaban, and warfarin, respectively)	58%	ACSS, MB [ISTH]	3.5 ± 1.6
Phannita Wattanaruengchai 2021 [37]	Retrospective observational study	Thailand	1200 patients (apixaban, dabigatran, rivaroxaban)	48,9%	ACSS, MB [ISTH]	4.1 ± 1.7
Hasan Ashraf 2021 [38]	Retrospective observational study	USA	8125 patients (apixaban, dabigatran, edoxaban, rivaroxaban)	56,4%	ACSS, MB [ISTH], ACM	3.7 ± 1.3

ACB - All cause bleeding, ACM - All cause mortality, ACSS - All cause stroke and systemic embolism, BT - Blood Transfusion, C - Composite (major bleeding, stroke/systemic embolism, and death), CHF – Congestive Heart Failure, GIB - Gastrointestinal Bleeding, ICH - Intracranial haemorrhage, MB - Major Bleeding, MI - Myocardial Infarction, S – Stroke, SE - Systemic Embolism, TE – Thromboembolism, TIA - Transient ischemic attack.
[ISTH] – major bleeding defined using the International Society on Thrombosis and Haemostasis.

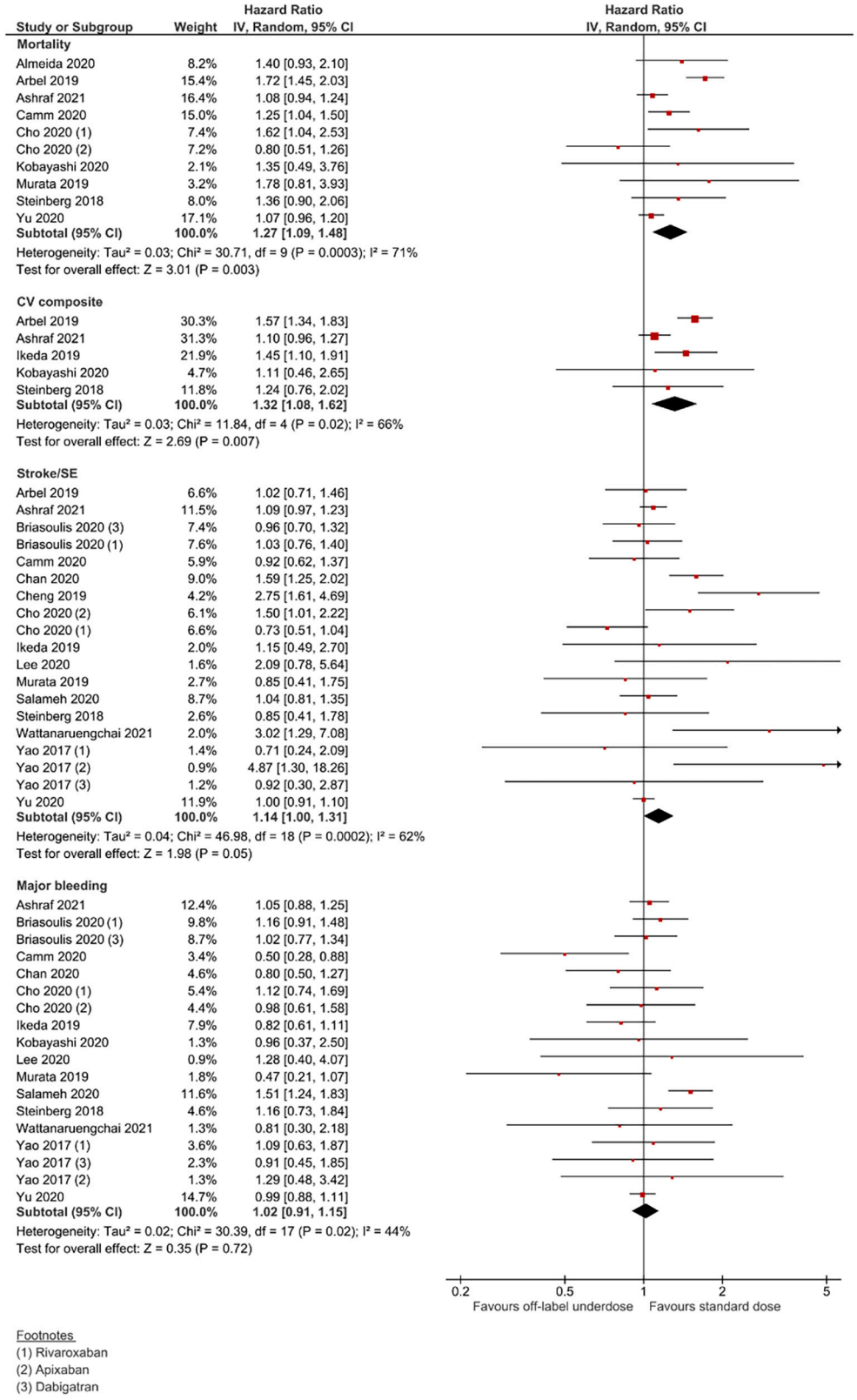

Fig. 1. Forest plot of the pooled analysis evaluating the effect of off label under dose DOAC compared with standard dose DOAC on Mortality, Cardiovascular (CV) Composite Events, Thromboembolic events [Stroke/Systemic Embolism (SE)], Major Bleeding.

Furthermore, by evaluating the outcomes on specific DOAC, the results showed that rivaroxaban on an off label low dose was associated with a significant higher risk of cardiovascular composite outcomes: HR = 1.38 (95% CI 1.14 to 1.67), with I^2 = 0% (Supplementary Fig. 3); dabigatran showed no statistically significant differences in the outcomes (Supplementary Fig. 4); and apixaban on an off label low dose was associated with a significant higher risk of thromboembolic events (stroke/systemic embolism): HR = 1.30 (95% CI 1.01 to 1.67), with I^2 =

60% (Supplementary Fig. 5).

3.4. Risk of bias within studies and publication bias

According to the ROBINS-I tool (Supplementary Table 2), ten studies had a moderate risk of bias and the eight other studies had a serious risk of bias. Funnel plots were evaluated (Fig. 1) and the assessment of publication bias did not retrieve any significant results in the Egger test (Supplementary Table 3).

3.5. Assessment of the quality of the evidence

The GRADE framework assessment of the quality of the evidence can be seen in Table 2 and is further detailed in the supplemental material. We considered the quality of the evidence for all outcomes to be low and very low.

4. Discussion

The main finding of this meta-analysis is that the best available evidence, based on low quality cumulative data, shows that the use of off label underdose DOAC on AF patients is associated with a significantly higher risk of all-cause mortality and cardiovascular composite outcomes, when compared with standard dose DOAC use. The effect in thromboembolic events (stroke/systemic embolism), major bleeding, and composite of ischemic and bleeding events was not statistically significant. However, it is important to mention that this value, in thromboembolic events, is just narrowly insignificant, as this meta-analysis shows.

An observational study is usually considered insufficient evidence of cause-effect relationship, and such evidence should rely in more controlled and longer studies, such as randomized clinical trials (RCT). Some RCT (ENGAGE AF-TIMI 48 trial) [39] proved a different conclusion than our meta-analysis, in which both doses of DOAC were associated with very similar incidence of cardiovascular composite outcome, mostly myocardial infarction related events.

On the other hand, in our study, the effect of lower dose on major bleeding was not statistically significant, but in RCT (RCT ENGAGE AF-TIMI 48 trial and RE-LY) [39,40] a lower dose of DOAC was associated with lower gastrointestinal bleeding and with a trend towards a reduced risk of major bleeding (although not significant).

Although the effect of off label low dose in thromboembolic events (stroke/systemic embolism) is not statistically significant in this meta-analysis, in specific observational studies (Ikeda 2019) [27] and RCT [39,40] it was greater, with higher rates of events described.

In most of the studies included, by analysing the outcomes before adjustment, patients receiving lower doses of NOACs were observed to have a notably increased risk of adverse events, including thromboembolic events, bleeding events, and death. However, when accounted the differences in patients' characteristics with adjustment, these increased rates were not significant. Nevertheless, we caution that most studies included in our analysis had limited power to detect significant differences [10]. Therefore, we should not forget that biologic plausibility suggests that lower doses could lead to worse thromboembolic outcomes (including death).

That being said, it becomes relevant to understand that patients' comorbidities have an impact on their clinical outcome, particularly on the outcomes here mentioned. In the making of this meta-analysis, there was few or absent data regarding the severity or management of the included patient's comorbidities, both of which are relevant factors for the confounding control. Moreover, the very low to low quality of evidence can also contribute to this confounding bias, due to comorbidities.

Nonetheless, although pooled analysis of these trials yielded statistically significant and clinically relevant effects, statistically significant heterogeneity was found among the results of the studies. This heterogeneity was driven by differences such as the use of different DOACs [21], comorbidities, body weight, co-medications [22], and others [9,22].

All things considered, it is meaningful to consider that other residual confounding risk factors might be associated with more bleeding events, on top of: coexisting morbidities, previous bleeding, concomitant medications, frailty, tendency for falls, and severity of underlying diseases. Additionally, although the uptake of DOACs for the prevention of stroke in patients with AF at risk is rapidly growing worldwide, there are large variations depending on the socioeconomic status of the countries under consideration as well [24]. The nationwide coverage of health benefits by public health insurance is extremely relevant (as seen in Japan [7], for example), as the universal coverage would increase the availability

Table 2
GRADE framework assessment of the quality evidence.

Certainty assessment								Summary of findings		
Outcome	Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)
								With Standard Dose DOAC	With Off Label Underdose DOAC	
Thrombombolic Events (stroke/ systemic embolism)	404172 (15 obsrvational studies)	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low	116201/ 202086 (57.5%)	54579/ 202086 (27.0%)	HR 1.14 (1.00 to 1.31)
Major Bleeding	387346 (14 observational studies)	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low	109643/ 193673 (56.6%)	50922/ 193673 (26.3%)	HR 1.02 (0.91 to 1.15)
Mortality	218638 (9 observational studies)	Serious[a]	Serious[b]	Not serious	Not serious	None	⊕⊕◯◯ Low	67057/ 109319 (61.3%)	34220/ 109319 (31.3%)	HR 1.27 (1.09 to 1.48)
Cardiovascular Composite	50174 (4 observational studies)	Serious[a]	Not serious	Not serious	Not serious	None	⊕⊕◯◯ Low	15913/ 25087 (63.4%)	6567/25087 (26.2%)	HR 1.51 (1.32 to 1.71)
Composite of Ischemic and Bleeding Events	17538 (3 observational studies)	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low	4514/ 8769 (51.5%)	1074/8769 (12.2%)	HR 1.22 (0.79 to 1.88)

CI: confidence interval; HR: hazard ratio.
[a] Several studies marked serious risk in ROBINS risk of bias assessment.
[b] There was a significant heterogeneity in the studies that may change conclusions.
[c] The Confidence Interval overlaps no effect (RR includes 1.0).

(and use) of hypertensive and/or lipid-lowering drugs, which may have an impact on the results of this meta-analysis related with thromboembolic events.

Therefore, despite the high prevalence of patients whose fixed-dosing strategy is possibly at risk of confusion due to multiple dose regimens depending on indications and physiological and clinical parameters, the use of off label DOACs on an off label reduced dose is associated with relevant clinical consequences, as verified in the results of this meta-analysis. The understanding of factors that influence decisions to prescribe different doses than those in regulatory recommendations is necessary to improve practice [41,42]. Notably, it is relevant to follow these recommendations in order to avoid the adverse outcomes observed in patients taking off label low dose DOAC.

4.1. Strengths and limitations

The main strength of this meta-analysis relies on the fact that it addresses an issue that is very relevant nowadays, which is the off label use of inappropriate lower doses of DOAC in patients with AF, a practice that has become common in Medicine [41].

This meta-analysis has, however, limitations inherent to the included studies. Studies that evaluate the impact of off label reduced dose DOAC in patients with AF are observational which makes it advisable to be cautious when interpreting results, since they are prone to bias, more particularly, selection or residual confounding bias. On the other hand, this meta-analysis has revealed moderate to high heterogeneity ($I^2 >$ 50%) in some of the reports, especially for mortality. Thirdly, it is notable that not all studies have reported mortality, although the majority of them have reported stroke/systemic embolism, which is therefore a limitation as this "selective" endpoints reporting from the studies may have exaggerated the mortality benefit in the present meta-analysis.

To counterbalance this limitation, it is important to mention that observational studies give a more accurate representation of the real word when compared with RCT, which include only a quite selected sample of the general population.

Moreover, given the nature of this subject, there are no better studies that analyse the effects of off label reduced dose DOAC as the observational studies do, and which could not be reproduced in controlled studies such as randomized clinical.

On a brief note, it should be noted that although we present results regarding specific DOAC and their associated outcomes, this meta-analysis has value for the overall analysis, considering the studies that were included. Therefore, it would be a limitation to discuss the conclusions of these results.

5. Conclusion

Our data supports the hypothesis that off label underdose DOAC use is associated with higher risk of all-cause mortality and cardiovascular composite outcome, when compared with standard dose DOAC use. We found no significant effect in thromboembolic events (stroke/systemic embolism), major bleeding and composite of ischemic and bleeding events.

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CRediT authorship contribution statement

Mariana Q. Pereira: Investigation, Data curation, Writing – original draft, Writing – review & editing. **Cláudio David:** Methodology, Writing – review & editing, Visualization. **Ana G. Almeida:** Writing – review & editing, Visualization. **Dulce Brito:** Writing – review & editing, Visualization. **Fausto J. Pinto:** Writing – review & editing, Visualization. **Daniel Caldeira:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – review & editing, Visualization, Supervision.

Declaration of Competing Interest

DC has participated in educational meetings and/or attended a conferences or symposia (including travel, accommodation and/or hospitality) with Bial, Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Merck Serono, Ferrer, Pfizer, Novartis and Roche. FJP had consultant and speaker fees with Astra Zeneca, Bayer, BMS, Boehringer Ingelheim and Daiichi Sankyo. DB has received consultancy and/or lecture fees from Genzyme-Sanofi, Novartis, Orion, Pfizer, Roche, Servier, St. Jude, Servier, Vifor, and attended meetings sponsored by Shire Human Genetic Therapies.

The remaining authors have nothing to declare.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Appendix A. Supplementary data

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