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Non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: A systematic review with meta-analysis and trial sequential analysis

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ABSTRACT

Background: Elderly population is known to be associated with polymedication, comorbidities and altered drug pharmacokinetics. However, the most adequate oral anticoagulant, attending to its relative efficacy and safety, remains unclear.

Methods: We searched for phase III randomized controlled trials (MEDLINE, Cochrane Library, SciELO collection and Web of Science) comparing novel non-vitamin K antagonist oral anticoagulants (NOACs) with Vitamin K antagonists (VKA) in the elderly population (≥75 years-old) in atrial fibrillation (AF). Risk ratios (RR) were calculated using a random effects model. Trial sequential analysis (TSA) was performed in statistically significant results to evaluate whether cumulative sample size was powered.

Results: Four trials rendered data about elderly (≥75 years-old) and younger patients (< 75 years-old) with AF. NOACs demonstrated a 30% significant risk reduction (RR 0.70, 95% CI: 0.61 to 0.80) in elderly patients compared to VKA, without heterogeneity across studies (I^2 = 0%). The TSA showed that cumulative evidence of this subgroup exceeded the minimum information size required for the risk reduction. In younger patients, VKA and NOACs shared a similar risk of stroke and systemic embolism (RR 0.97, 95% CI: 0.79 to 1.18). Regarding major bleeding risk in the elderly, the overall comparative risk of NOACs was not different from VKA (RR 0.91, 95% CI: 0.72 to 1.16; I^2 = 86%).

Conclusions: NOACs reduce significantly the risk of stroke and systemic embolism in elderly patients without increasing major bleeding events. The dimension of stroke risk reduction was significantly higher in the elderly than in younger adults.

1. Introduction

Western countries populations are getting older, with the elderly population representing a significant portion on the population, and even more significantly an important share of patients taking drugs. Elderly patients are very particular as they often have renal (Muhlberg & Platt, 1999) and/or hepatic dysfunction (Le Couteur & McLean, 1998) compared with younger people, which impairs the main excretion pathways of most of the drugs. Therefore, this population is associated with an increased risk of adverse events (McLean & Le Couteur, 2004).

Aged patients frequently have several comorbidities and consequently tend to be polymedicated. In clinical trials, elderly patients are still underrepresented (Schmucker & Vesell, 1999), and extrapolation of risk-benefit ratios from younger adults to geriatric populations is not necessarily valid (McLean & Le Couteur, 2004). Nowadays, guidance exists for inclusion of elder patients in clinical trials with meaningful numbers, as regulatory entities are very keen on ensuring the efficacy and safety of interventions in elderly patients (Agency, 2006).

It is known that age is an independent risk factor for the development of atrial fibrillation (AF) (Bonhorst, Mendes, & Adragao, 2010; Kannel, Wolf, Benjamin, & Levy, 1998), with a markedly increasing

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prevalence with age, affecting about 5% of people over 65 years and 10% of people age ≥ 80 years (Miyasaka, Barnes, & Gersh, 2006). In addition, AF is also related to an increase in both ischemic and hemorrhagic risk (Lip, Nieuwlaat, Pisters, Lane, & Crijns, 2010; Pisters et al., 2010). In the elderly population with AF, these increased thrombotic and hemorrhagic risks must be taken into account. Thus, prescribing anticoagulants may be a double-edged situation, although it is recommended in most of the cases. Recently, the novel oral anticoagulants, also called non-vitamin K antagonist oral anticoagulants (NOACs) such as apixaban, dabigatran, edoxaban, and rivaroxaban have shown to be a good therapeutic option conventional anticoagulants (Caldeira, Barra, Pinto, Ferreira, & Costa, 2015; Caldeira, Barra, & Santos, 2014; Caldeira, Rodrigues, & Barra, 2015; Dentali et al., 2012), but its relative efficacy and safety profiles have not been established in elderly adults. Uncertainty still exists regarding the most adequate oral anticoagulant for elderly patients.

Hereby we aimed to review and quantify through meta-analysis of phase III randomized controlled trials, the relative efficacy and safety of NOACs in the elderly population and compare with their impact in younger patients.

2. Methods

This systematic review was performed using PRISMA statement as a guideline (Liberati, Altman, & Tetzlaff, 2009).

2.1. Eligibility criteria

We considered for this systematic review published randomized clinical trials (RCTs) evaluating patients with non-valvular AF treated with NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) or Vitamin K Antagonists (VKA) (Caldeira, David, Costa, Ferreira, & Pinto, 2017). Studies had to report detailed data about clinical outcomes (stroke or systemic embolism, or major bleeding) in elderly patients (≥75 years old).

Only phase III RCTs were included in this study in order to obtain robust data without the bias associated to statistical effects of small size underpowered studies on meta-analysis results (Lane, 2013; Turner, Bird, & Higgins, 2013; Kjaergard, Villumsen, & Gluud, 2001; Zhang, Xu, & Ni, 2013). Furthermore, we were interested in determining the risk associated with approved NOACs and their commonly used doses in AF (Apixaban 5 mg, and 2.5 mg with dose reduction criteria; Dabigatran 110 mg and 150 mg; Edoxaban 60 mg, and 30 mg with dose reduction criteria; Rivaroxaban 20 mg, and 15 mg with dose reduction criteria).

There were no restrictions regarding drug treatment duration or follow-up.

2.2. Data sources

MEDLINE, Cochrane Library (CENTRAL), SciELO collection, and Web of Science databases (inception to January 2017) were searched to retrieve RCTs evaluating NOACs *vs*. VKA. Search strategy is outlined in the Supplementary Online.

Reference lists of systematic reviews, as well as the reference list of each included study were comprehensively searched. We also sought the data available at the public reports of these drugs in the web sites of regulatory entities (U.S. Food and Drug Administration, European Medicines Agency and Australian Therapeutic Goods Administration), irrespective of the initial search.

2.3. Study selection

After study deduplication, the references obtained in the electronic search were screened independently by two authors through title and abstract for full-text assessment eligibility.

Study characteristics and results were extracted into a standardized form. The data from different NOACs doses were merged into a single arm. Whenever available the data from younger patients were also retrieved for a comparative analysis. Included studies were appraised for methodological bias risk with Cochrane Collaboration's Risk of Bias Tool (Higgins & Green, 2011). Studies were not excluded *a priori* based on quality reporting assessment.

2.4. Outcomes

The primary efficacy outcome was stroke and systemic embolism and the primary safety outcome was major bleeding as determined by the International Society of Thrombosis and Haemostasis (Schulman & Kearon, 2005).

2.5. Data analysis

We used RevMan 5.3.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for statistical analysis and to derive forest plot showing the results of individual studies and pooled analysis.

Meta-analysis was performed using a random effects model to estimate pooled risk ratio (RR) and 95% confidence intervals (95% CIs). The effect measurement estimate chosen was RR since relative measures are more similar across studies with different designs, populations and lengths of follow-up compared to absolute measures, such as risk difference (Deeks, 2002). When significant differences were found, it was also determined the number needed to treat (NNT) and 95% CI taking into account the control baseline risk.

Heterogeneity is considered the percentage of total variation between studies and it was assessed through the I^2 test (Higgins & Thompson, 2002). The results of elderly patients were compared with those from younger patients using.

Trial Sequential Analyses (TSA) were performed for primary outcomes using TSA version 0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark, 2011) to explore whether cumulative data were adequately powered to evaluate the outcomes in the subgroups (Brok, Thorlund, Gluud, & Wetterslev, 2008; Caldeira, Rodrigues, Pinto, Ferreira, & Costa, 2017; Rodrigues et al., 2016). The required information size and the O'Brien-Fleming adjacent trial sequential alpha spending monitoring boundaries were calculated based on a two-sided 5% risk of a type I error, 10% risk of a type II error (power of 90%), risk reduction based on pooled analysis (or an arbitrary 10% risk reduction in the case of lower pooled risk reduction estimates), the weighted incidence of events in the control group, and heterogeneity (Caldeira, Rodrigues et al., 2017; Rodrigues et al., 2016). Power of the outcomes was interpreted if significance was reached with either a minimum sample size, or crossing trial sequential alpha spending monitoring boundary.

3. Results

Four trials rendered data about elderly and younger patients with AF randomized to NOACs or VKA (Connolly, Ezekowitz, & Yusuf, 2009; Giugliano, Ruff, & Braunwald, 2013; Granger, Alexander, & McMurray, 2011; Patel, Mahaffey, & Garg, 2011) (Supplementary Fig. 1 and Table 1). There were 24,709 with 75 years-old or higher, and 39,800 patients with less than 75 years-old. The risk of bias of the studies is detailed in Supplementary Fig. 2.

3.1. Stroke and systemic embolism

Concerning the risk of stroke and systemic embolism, NOACs demonstrated a 26% significant risk reduction (RR 0.70, 95% CI: 0.61 to 0.80; NNT 83, 95% CI: 64–124) in elderly patients compared to VKA, without heterogeneity across studies (I^2 = 0%) (Fig. 1). The TSA showed that cumulative evidence of this subgroup doubled (258%) the minimum information size required (9587 patients) adjusted for the

Table 1
Main characteristics of included studies.

Study	Design	Mean/Median Age	Comparison	Elderly patients (% of the RCT)	Follow-up
ARISTOTLE	Double-blinded RCT	70	Apixaban 5 mg BID *vs.* VKA, Target INR 2.0-3.0	5678 (31.2%)	1.8 years
RE-LY	Open-label RCT	71	Dabigatran 110 mg/150 mg BID *vs.* VKA, Target INR 2.0-3.0	7238 (40.0%)	2 years
ENGAGE-AF	Double-blinded RCT	72	Edoxaban 60 mg/30 mg OD *vs.* VKA, Target INR 2.0-3.0	8432 (40.1%)	2.8 years
ROCKET-AF	Double-blinded RCT	73	Rivaroxaban 20 mg OD *vs.* VKA, Target INR 2.0-3.0	6150 (43.4%)	1.9 years

BID: Twice daily; INR: International Normalized Ratio; NOAC: Non-vitamin K Antagonist Oral Anticoagulant; NVAF: Non-valvular atrial fibrillation; OD: Once daily; RCT: Randomized controlled trial; VKA: Vitamin K Antagonist.

obtained risk reduction (Fig. 2).

In younger patients, VKA and NOACs shared a similar risk of stroke and systemic embolism (RR 0.97, 95% CI: 0.79–1.18) (Fig. 1). This analysis was remarkable for moderate statistical heterogeneity (I^2 = 52%). NOACs showed to have an increased efficacy in elderly patients compared to younger ones (p = 0.01 for subgroup differences). The TSA showed that the sample size required for 10% risk reduction (adjusted for the statistical heterogeneity) was greater than the evaluated population (9.6% of the minimum information size; Supplementary Fig. 3).

3.2. Major bleeding

Regarding major bleeding risk in the elderly, the overall comparative risk of NOACs was not different from VKA (RR 0.91, 95% CI: 0.72–1.16). However, important heterogeneity was noticed (I^2 = 86%) (Fig. 3). This was mainly driven by the neutral results of dabigatran and rivaroxaban in RE-LY and ROCKET AF, respectively. Edoxaban and apixaban showed significant improvements in elderly patients' major bleeding risk. TSA showed that the current heterogeneity-adjusted information size is low (8.5% of the minimum adjusted information size required) (Supplementary Fig. 4).

In younger patients, NOACs decreased significantly the rate of major bleedings (RR 0.77, 95% CI: 0.67 to 0.89, I^2 = 56%; NNT 88, 95% CI: 62–185) (Fig. 3). The minimum information size adjusted for the heterogeneity for major bleeding risk reduction in the subgroup of patients with < 75 years old was achieved (128% of the minimum information size) (Fig. 4).

Both in younger and elderly subgroups, the bleeding risk assessment was remarkable for substantial heterogeneity, which may be attributed to the individual differences of NOACs. Apixaban and edoxaban showed a consistent risk reduction in major bleeding in either elderly or younger subgroups. In this latter subgroup, dabigatran was also associated to significant risk reduction.

3.3. The clinical impact of different regimens in elderly patients

Fig. 5 show the impact of different doses of NOACs in efficacy and safety among the subpopulation of elderly patients (≥75 years). All NOACs regimens except dabigatran 110 mg twice daily reduced significantly the risk of stroke or systemic embolism in the elderly. Regarding major bleeding, dabigatran increased significantly the risk of major bleeding in a dose-dependent manner (the risk was numerically higher with 150 mg twice daily, compared with the estimate of 110 mg twice daily). Apixaban and edoxaban reduced significantly the risk of major bleeding among elderly patients with AF compared with VKA. The major bleeding risk of rivaroxaban was similar to the VKA risk in this subpopulation

4. Discussion

The proportion of elderly patients in the population is increasing, therefore it is of the utmost importance to consider their specificities when treating them. Elderly patients are more likely to have more comorbidities and concomitant drugs to interact. Furthermore, age is an independent risk factor for both bleeding and thromboembolic events (Lip et al., 2010; Pisters et al., 2010). This dual increase in bleeding and thrombotic risk in the elderly may lead to uncertainty in the prescription of anticoagulants. The best anticoagulant for this population needs to stay in line with the ethical principle of no harm, *primum non nocere*.

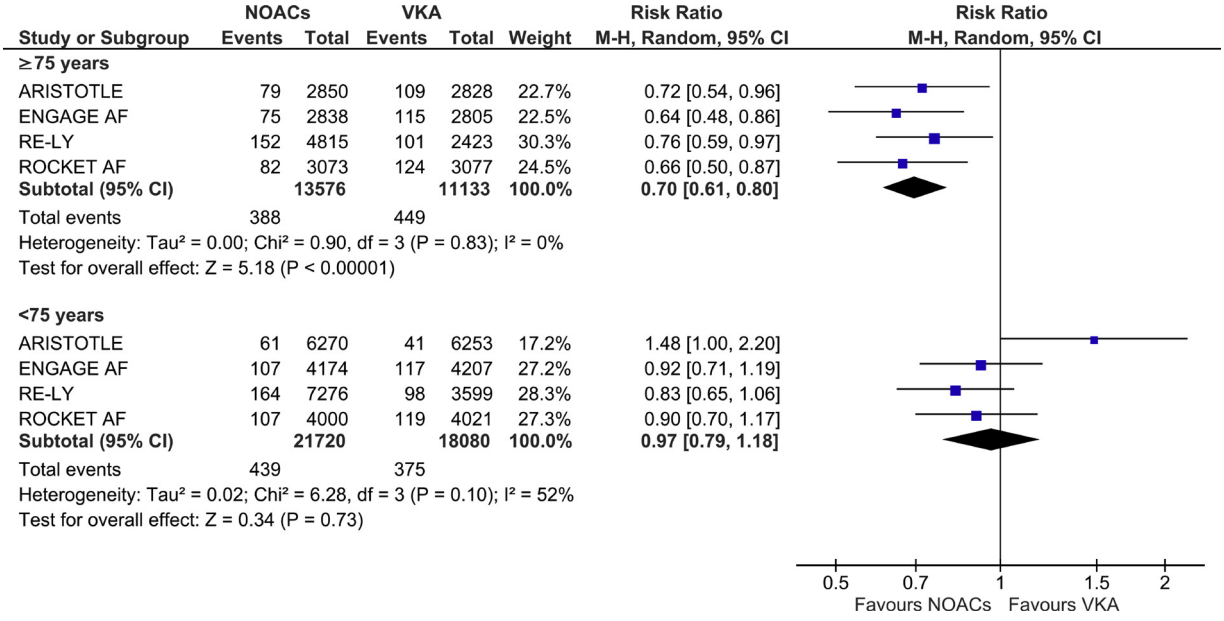

Fig. 1. Forest plot of meta-analysis evaluating stroke and systemic embolism in elderly (≥75 years) and younger patients (< 75 years).

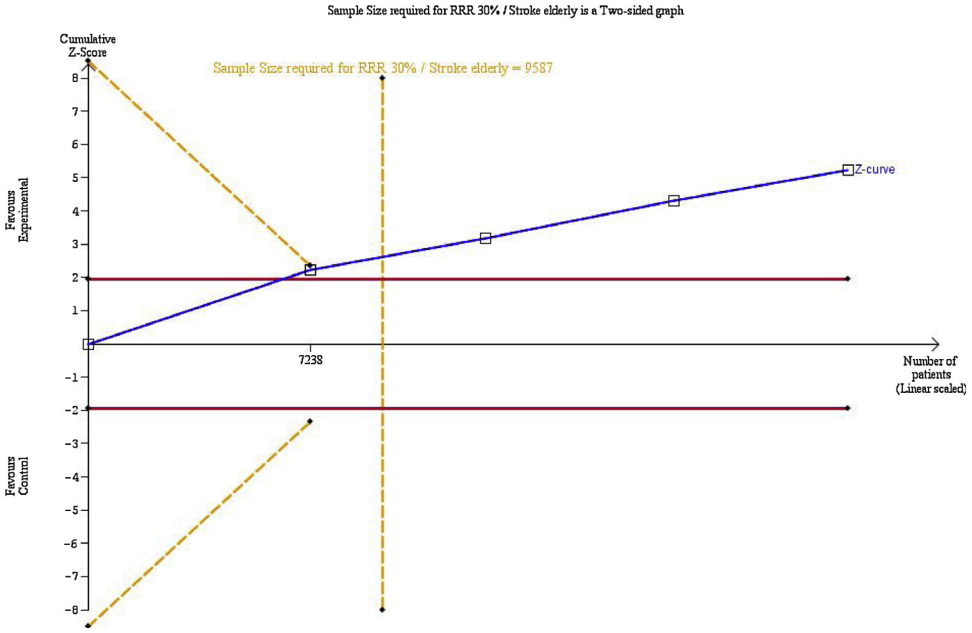

Fig. 2. Plot of the trial sequential analysis (TSA) for stroke and systemic embolism in the elderly. The blue line corresponds to the cumulative Z-score line. Unfilled diamonds correspond to clinical trial. The solid horizontal red line corresponds to the conventional test boundaries of two-sided 5%. Statistical significance is achieved when the blue line (z-score line) crosses the red line. Orange dotted lines corresponds to the Alpha-spending O'Brien-Fleming boundaries.

NOACs have demonstrated some advantages over VKA in adults but the logical leap of risk-benefit ratios from younger adults to geriatric populations may not be entirely valid (McLean & Le Couteur, 2004). Little has been published about the safety and efficacy profiles of NOACs in the elderly adults, and thus this article helps filling this grey area of knowledge. The few articles already published compared the outcomes in the elderly population as a subgroup of the total population (Sharma, Cornelius, Patel, Davies, & Molokhia, 2015). In this article, we compared the elderly adults (≥75 years old) directly with younger adults (< 75 years old) in order to emphasise any differences in the safety and efficacy profiles of drugs. Furthermore, the trial sequential analyses provided further information regarding the robustness of these subgroups' data.

This systematic review and meta-analysis investigating the use of NOACs in AF elderly patients has demonstrated that NOACs were more effective than VKA in the elderly ≥75 years old patients. There was a significant 30% risk reduction of stroke and systemic embolism in elderly patients with NOACs compared to VKA. In fact, each NOAC individually showed significant stroke risk reduction in the elderly, without heterogeneity across studies. The dimension of stroke risk reduction was significantly higher in the elderly, whereas in younger adults NOACs proved as effective as VKA. Low body mass index in frail and elderly adults, altered body composition of muscle and fatty tissue, polypharmacy, the high frequency of renal impairment, and an altered pharmacokinetic profile of drugs, may be some of the factors influencing these results. However, further investigations are needed to shed some light on this area.

In addition to the benefits of the pooled NOACs in elderly adults, there was a non-significant 9% risk reduction of major bleedings when compared to VKA. This non-significant risk reduction seems to be due to the neutral results of dabigatran and rivaroxaban. Only apixaban and edoxaban with VKA showed a significant risk reduction of major bleedings.

In younger adults, pooled NOACs decreased significantly the rate of

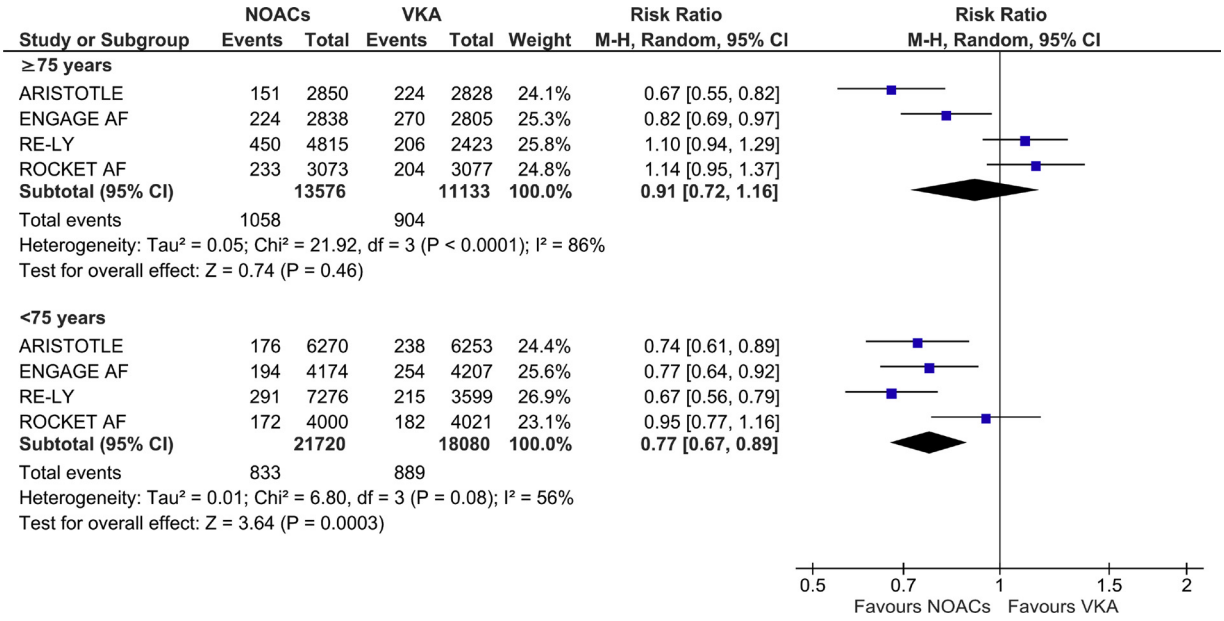

Fig. 3. Forest plot of meta-analysis evaluating major bleeding risk in elderly (≥75 years) and younger patients (< 75 years).

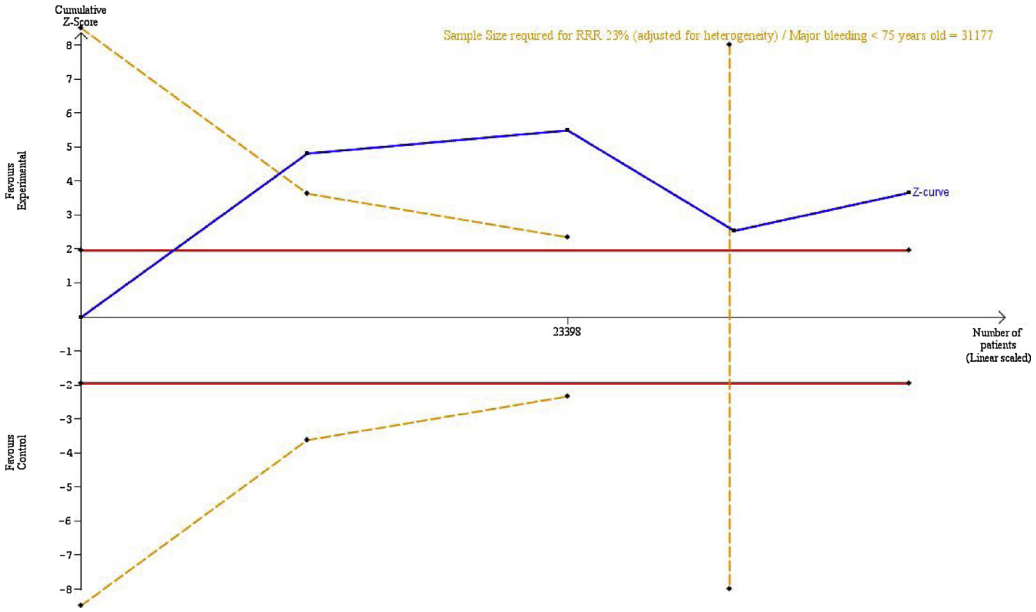

Fig. 4. Plot of the trial sequential analysis (TSA) for major bleeding in patients with < 75 years old. The blue line corresponds to the cumulative Z-score line. Unfilled diamonds correspond to clinical trial. The solid horizontal red line corresponds to the conventional test boundaries of two-sided 5%. Statistical significance is achieved when the blue line (z-score line) crosses the red line. Orange dotted lines corresponds to the Alpha-spending O'Brien-Fleming boundaries.

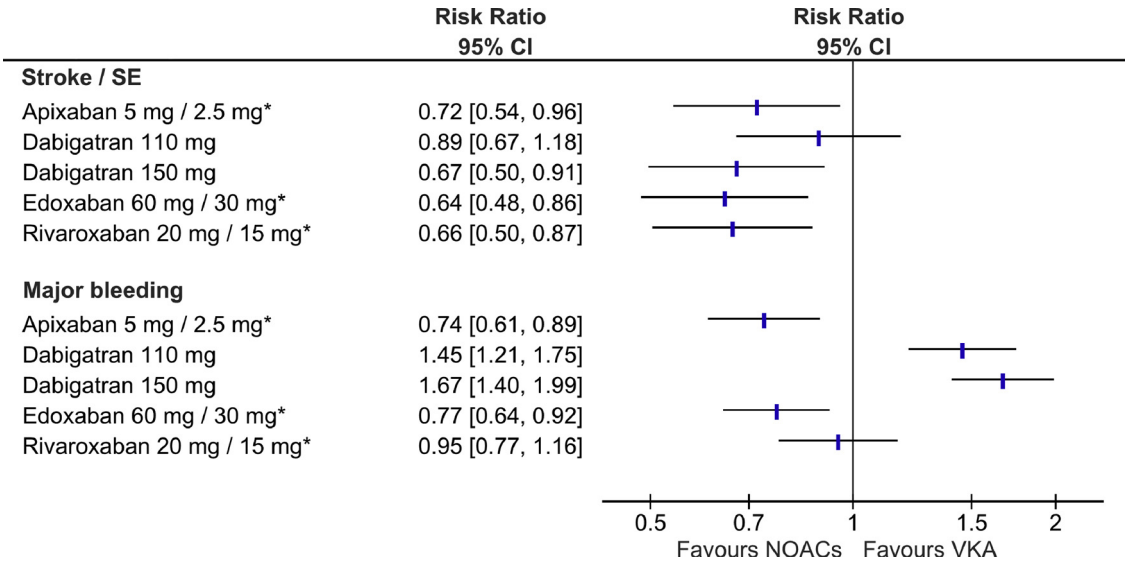

Fig. 5. Results of efficacy and safety of the different approved regimens for AF in elderly patients. *Reduced doses used according to the criteria of each trial.

major bleedings. Also of relevance, the thrombin inhibitor dabigatran showed a significant risk reduction of major bleedings in younger adults when compared to VKA, whereas rivaroxaban showed a similar risk.

Despite the increase in the prescription of anticoagulants, these drugs are still underused in the elderly (Gage, Boechler, & Doggette, 2000). The results here obtained are reassuring for NOACs use in elderly patients. There was a significant risk reduction of stroke compared to VKA, while major bleeding risk was not increased. Furthermore, the dimension of stroke risk reduction was significantly higher in elderly patients compared to younger ones.

This is particularly important for physicians that do not prescribe oral anticoagulants to elderly patients, namely VKA, due to the supposed high bleeding risk or due to the perceived difficulties of elderly patients in handling with all VKA needs (Caldeira, Cruz, & Morgado, 2014; Pereira-Da-Silva, Souto Moura, & Azevedo, 2013). The BAFTA trial demonstrated that warfarin reduced stroke risk in the elderly without increasing the risk of major hemorrhage, compared with acetylsalicylic acid, an antiplatelet drug considered to be an antithrombotic option for some physicians (Mant, Hobbs, & Fletcher, 2007). More recently, the AVERROES trial that included patients unsuitable for VKA, apixaban showed a significant 67% stroke risk reduction in elderly compared to acetylsalicylic acid, without increasing the risk of major bleeding (Connolly, Eikelboom, & Joyner, 2011). Therefore, NOACs look suitable, efficacious and safe for elderly patients with non-valvular AF.

Our results are limited by methodological issues associated to the individual studies and meta-analysis. The results of our meta-analysis are based on study-level data and not on individual patients' data. Furthermore, the meta-analysis is majorly composed by specific subgroups (≥75 years and < 75 years) derived from secondary analyses of RCTs which downgrades the robustness of the data.

We pooled together the different NOACs under the assumption of a class effect of these drugs, which may be assumed for efficacy purposes in elderly patients, but not for safety purposes due to substantial heterogeneity between the trials as shown in Fig. 5. The trial sequential analysis (TSA) was performed and this step represents an addition to previously published reviews (Sharma et al., 2015). TSA analysed the strength of each subgroup analyses and we concluded that the efficacy data of NOACs in elderly patients are robust.

5. Conclusions

These results have demonstrated that NOACs are at least as effective as VKA in the elderly population ≥75 years old. NOACs reduced significantly the risk of stroke and systemic embolism in elderly patients without increasing major bleeding events and the results are robust for this subgroup. In younger adults, NOACs demonstrated to be as effective as VKA reducing the risk of stroke, but superior to VKA reducing major bleeding events.

Conflict of interests

JJF had speaker and consultant fees with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme; FJP had consultant and speaker fees with Astra Zeneca, Bayer and Boehringer Ingelheim; the remaining authors do not have any competing interests to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.archger.2018.12.013.

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