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Estimated absolute effects on efficacy and safety outcomes of using non-vitamin K antagonist oral anticoagulants in ‘real-world’ atrial fibrillation patients: A comparison with optimally acenocoumarol anticoagulated patients.

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ABSTRACT

Background: Non-vitamin K antagonist oral anticoagulants (NOACs) have been proposed as an alternative to vitamin K antagonists (VKA) for atrial fibrillation (AF) patients. Some studies have proposed that well-managed warfarin therapy is still a valid alternative as efficacious as NOACs but the potential impact and absolute effect of NOACs in “real world” optimally management of VKA AF patients is unknown.

Purpose: To estimate the potential absolute benefit in clinical outcome rates if the optimally anticoagulated “real-world” AF patients with acenocoumarol had been treated with NOACs.

Methods: We included 1,361 patients stable on acenocoumarol with a time in therapeutic range of 100% for the previous 6 months and 6.5 years of follow-up. The estimation of clinical events avoided was calculated applying absolute risk reductions, relative risk reductions and hazard ratios from the pivotal clinical trials, relative to acenocoumarol.

Results: Compared to acenocoumarol, the highest estimated event reduction for stroke was seen with dabigatran 150mg, with an estimated reduction of 0.53%/year. For major bleeding, the highest estimated reduction was seen with apixaban (0.88%/year). For mortality, the largest estimated reduction was with dabigatran 150mg (0.75%/year). In net clinical outcome, apixaban had the estimated highest reduction (1.23%/year). All NOACs showed significantly lower rates for intracranial haemorrhage.

Conclusion In optimally acenocoumarol anticoagulated AF patients, estimated reductions in stroke, bleeding and net clinical outcomes with various NOACs are evident. NOACs would potentially show an improvement even amongst optimally VKA AF patients.

Key words: non-vitamin K oral anticoagulants, vitamin K antagonists, atrial fibrillation, mortality, major bleeding, time in therapeutic range

ABBREVIATIONS

AF: Atrial fibrillation

ARR: Absolute risk reduction

eGFR: estimated glomerular filtration rate

ESC: European Society of Cardiology

HR: Hazard ratio

ICH: Intracranial haemorrhage

INR: International normalized ratio

NNT: Number needed to treat

NOAC: Non-vitamin K oral anticoagulant

OAC: Oral anticoagulation

RRR: Relative risk reduction

RW: Real-world

TTR: Time in therapeutic range

VKAs: Vitamin K antagonists

INTRODUCTION

In patients with atrial fibrillation (AF), oral anticoagulation therapy (OAC) with vitamin K antagonists (VKAs) is highly effective for reducing the risk of stroke by 64% and all-cause death by 26%, compared with control(1). The effectiveness and safety of VKA treatment is related to the quality of anticoagulation, assessed by the average percentage of the time in therapeutic range (TTR). Patients who achieve high TTR (>70%) have lower mortality, thromboembolic events and major bleeding than patients with poor anticoagulation control(2,3). Indeed, poor TTR <40% confers a higher risk of stroke than those patients who are left untreated(4). For that reason, clinical guidelines recommended an individual average of TTR of 70% to maximize the efficacy and safety of VKA treatment(5). However, the VKAs show a narrow therapeutic window due to the high inter- and intra-patient variability related to multiple food and drugs-drugs interactions(6); therefore, frequent monitoring and dose adjustment are necessary to achieve an optimal TTR(7).

Non-vitamin K oral anticoagulants (NOACs) have been developed as generally effective and safe alternative to VKAs in AF patients(8). Also, this effectiveness seems consistent across the range of stroke risk assessed by CHADS₂. Nonetheless, many healthcare systems remain unenthusiastic to implement a first-line strategy with NOACs and it is often required to start AF treatment with a VKA and only if they do not have good TTR after 6 months of treatment, only then it is possible to switch to NOACs(9).

Also, the real-world (RW) effectiveness and safety of NOACs in AF patients could be different from the efficacy and safety as shown in the main trials. The NOACs have been compared with warfarin, and in their respective Phase 3 trials, the mean TTR was 64.0% with dabigatran(10), 62.2% with apixaban(11), 55.2% with rivaroxaban(12) and 64.9% with edoxaban(13). Indeed, some studies have proposed that well-managed

warfarin therapy is still a valid alternative for AF patients and could be as efficacious as NOACs (14,15), but the potential impact and absolute effect of NOACs in “real world” optimally management of VKA AF patients is unknown.

The main objective of our study was to estimate the potential absolute benefit in clinical outcome rates if the optimally anticoagulated “real-world” AF patients with acenocoumarol had been treated with NOACs.

METHODS

Between May 2007 and December 2007, we recruited all consecutive outpatients with confirmed diagnosis of paroxysmal, persistent and permanent AF who were stable on acenocoumarol in our single anticoagulation centre in a tertiary hospital in Murcia, Spain. We selected only optimally managed AF patients with stable range of INR (between 2.0-3.0) for at least the previous 6 months and at entry all patients had TTR 100% to ensure baseline homogeneity of the study cohort.

AF patients with rheumatic mitral disease and prosthetic heart valve disease, with hemodynamic instability, hospital admission, acute coronary syndrome or surgical interventions in the preceding 6 months were excluded from the study. All patients provided signed informed consent to participation in the study. The study was conducted according the ethical principles of Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the Ethics Committee from University Hospital Morales Meseguer (Murcia, Spain).

Data collection

At baseline, clinical and demographic data were collected from all AF patients and included in a complete medical history. We included demographic information, data on cardiovascular risk factors and comorbidities. We also calculated the TTR after 6 months of entry. Stroke risk was calculated using the CHADS₂ (Congestive heart failure, Hypertension, Age \geq 75 years, Diabetes mellitus, Stroke or transient ischemic attack) and CHA₂DS₂-VASc [Congestive heart failure, Hypertension, Age \geq 75 years, Diabetes mellitus, Stroke or transient ischemic attack, Vascular disease, Age 65-74 years and Sex category (female)] scores. Renal function was assessed at baseline visit.

Follow-up and clinical outcomes

Follow-up was performed through visits to the anticoagulation clinic and started the day of the inclusion for 6.5 years. No patient was lost to follow-up. Adverse thromboembolic events (stroke/transient ischaemic attack) and myocardial infarction were collected. Death was classified as a fatal cardiovascular event (acute coronary syndrome, heart failure, lethal arrhythmia or sudden death, artery aneurysm rupture or stroke) or another nonvascular death fatal event. Major bleeding events were defined according to the 2005 International Society of Thrombosis and Haemostasis criteria(16) fatal bleeding or symptomatic bleeding in a critical anatomical site (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial or intramuscular with compartment syndrome) and/or bleeding causing a fall in Hb ≥ 20 g/L, or transfusion of ≥ 2 units of whole blood or red blood cells. Net clinical outcome was defined as the composite of stroke, major bleeding and all mortality.

Statistical analyses

Quantitative variables were described using the mean \pm standard deviation or median [interquartile range]. Categorical variables are expressed as percentages. Normal distribution of continuous variables was tested with the Kolmogorov-Smirnov method.

Estimation of potential real-world effect of NOACs

All adverse outcomes rates were calculated for optimally anticoagulated patients with acenocoumarol. The estimated rates (ie. the estimated rates if the patients had been treated with NOACs instead of acenocoumarol) of stroke, myocardial infarction, major

bleeding, gastrointestinal bleeding, intracranial haemorrhage, all-cause mortality, cardiovascular mortality and net clinical outcomes were calculated by multiplying the hazard ratios from the four pivotal trials (RE-LY(10), ARISTOTLE(11), ROCKET-AF(12) and ENGAGE-AF(13) trials) by the reference rates of our optimally anticoagulated AF patients. Estimated rates according CHADS₂ score (used in the respective trials) were also analyzed. We calculated the relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT) of each adverse event with the reference event rates for patients exposed to warfarin and NOACs in each pivotal clinical trial. The ARRs, *i.e.* the absolute numbers of clinical events that theoretically might be avoided by using dabigatran, apixaban, rivaroxaban or edoxaban instead of acenocoumarol in optimally anticoagulated patients were calculated by multiplying RRRs from pivotal trials by the reference event rates for anticoagulated patients of our populations as Amin *et al* previously described(17). After that, the resulting absolute reduction numbers were employed to calculate NNT for each event.

Comparisons between two event rates (real and estimated rates) with T-Test were performed and p-values with 95% confidence intervals were calculated.

In all analyses, statistical significance was defined as $p < 0.05$. Statistical analyses were performed with SPSS version 22.0 (SPSS Inc, Chicago, IL, USA) and MedCalc v. 16.4.3 (MedCalc Software bvba, Ostend, Belgium) statistical packages for Windows.

RESULTS

Baseline characteristics of optimally anticoagulated AF population and all pivotal clinical trials are shown in **Table 1**.

Overall, data on 1,361 AF patients on acenocoumarol were analyzed (48.7% males, median age: 76 [IQR 71-81] years). The median TTR at 6 months after entry (median follow-up 214 days [IQR 213-2014]) was 80% (IQR 66-100). After 6.5 [IQR 4.3-7.9] years of follow-up, 130 patients had stroke (1.47%/year), 250 patients had major bleeding events (2.83%/year) and 551 patients died (6.23%/year). The distribution of bleeding events was as follow: 97 patients had gastrointestinal bleeding (1.10%/year) and 78 patients had intracranial haemorrhage (0.88%/year). During the follow up, 136 patients (10% of the optimally managed AF population) discontinued oral anticoagulation therapy.

The estimated effect of NOACs and the estimated reduction compared to acenocoumarol treatment are summarized in **Table 2** and **Figure 1**.

Thromboembolic events

Stroke

We estimated that the rates of stroke would be 0.94%/year (95%CI 0.76-1.15%/year) for dabigatran 150 mg, 1.35%/year (95% CI 1.13-1.59 %/year) for dabigatran 110 mg, 1.16%/year (95%CI 0.97-1.40%/year) for apixaban, 1.25%/year (95%CI 1.05-1.50%/year) for rivaroxaban and 1.29%/year (95%CI 1.08-1.53%/year) for edoxaban. Compared to the optimally anticoagulated AF patients on acenocoumarol, only dabigatran 150 mg showed an estimated significant reduction with 0.53 stroke events per

100 patient-years (*i.e.* 47 strokes avoided over total sample) that would be avoided, giving NNT of 189 for stroke using dabigatran 150 mg instead of acenocoumarol.

Myocardial infarction

We observed a significant higher estimated rate of MI with dabigatran 150 mg (0.86%/year vs 1.19%/year; $p=0.031$) and dabigatran 110 mg (0.86%/year vs 1.10%/year; $p=0.043$) in comparison with the optimally management of acenocoumarol treatment.

Bleeding events

Major bleeding

We estimated that the rates of major bleeding would be 2.63%/year (95% CI 2.34-2.96%/year) for dabigatran 150 mg, 2.26%/year (95% CI 1.99-2.57%/year) for dabigatran 110 mg, 1.95%/year (95% CI 1.69-2.23%/year) for apixaban, 2.94%/year (95% CI 2.63-3.27%/year) for rivaroxaban and 2.26%/year (95% CI 1.99-2.57%/year) for edoxaban. Compared to the optimally anticoagulated AF patients on acenocoumarol, the highest significant event estimated reduction was observed with apixaban with 0.88 bleeding events per 100 patient-years (78 bleeding events avoided over total sample) that would be avoided giving NNT of 114 for bleeding using apixaban instead of acenocoumarol.

Intracranial Haemorrhage

All NOACs showed an estimated significant intracranial haemorrhage rate reduction in comparison with the optimally anticoagulation therapy with acenocoumarol. The estimated highest event reduction was observed with dabigatran 110 mg and 0.61 intracranial bleeding events per 100 patient-years (*i.e.* 54 bleeding events avoided over total sample) would be avoided using dabigatran 110 mg instead of acenocoumarol.

Gastrointestinal bleeding

None of the NOACs showed an estimated significant reduction in gastrointestinal bleeding in comparison with optimally management of acenocoumarol treatment. However, dabigatran 150 mg (1.10%/year vs 1.65%/year; $p=0.002$) and rivaroxaban (1.10%/year vs 1.60%/year; $p=0.004$) demonstrated higher gastrointestinal bleeding events compared to acenocoumarol.

Mortality

We estimated that the rates of all-cause mortality would be 5.48%/year (95%CI 5.10-5.88%/year) for dabigatran 150 mg, 5.67%/year (95%CI 5.29-6.07%/year) for dabigatran 110 mg, 5.54%/year (95%CI 5.15-5.94%/year) for apixaban and 5.73% (95%CI 5.34-6.13%/year) for rivaroxaban and edoxaban. Compared to the optimally anticoagulated AF patients on acenocoumarol, only dabigatran 150 mg showed an estimated significant reduction in mortality and 0.75 deaths per 100 patient-years (*i.e.* 66 deaths avoided over total sample) would be avoided giving NNT of 133 for mortality using dabigatran 150 mg instead of acenocoumarol. Any NOAC showed an estimated significant reduction for cardiovascular mortality compared to acenocoumarol.

Net clinical outcomes

Apixaban and edoxaban had significantly lower estimated rates of net clinical outcomes in comparison with the optimally management of acenocoumarol treatment. The estimated highest event reduction was observed with apixaban with 1.23 net clinical events per 100 patient-years (*i.e.* 109 composite adverse events avoided over total sample)

would be avoided, resulting in a NNT of 81 patients for the composite event using apixaban instead of acenocoumarol.

Estimated effect of NOACs in high risk subgroup according to CHADS₂ score

In the high-risk subgroup (CHADS₂ ≥ 3), apixaban showed the best composite reduction profile with an estimated significant reduction for stroke (1.97%/year vs 1.38%/year; $p=0.042$), major bleeding (3.34% vs 2.53%; $p=0.039$) and intracranial haemorrhage (1.01%/year vs 0.29%/year; $p<0.001$). Dabigatran 150 mg, dabigatran 110 mg and apixaban showed estimated significant risk reductions for intracranial haemorrhage through the different CHADS₂ scores in comparison with acenocoumarol treatment (**Figure 2, Supplementary Table 1**).

DISCUSSION

In an optimally anticoagulated acenocoumarol AF patients, potential estimated reductions in stroke, bleeding and net clinical outcomes with various NOACs are evident. All NOACs showed an expected significant reduction for intracranial haemorrhage. Thus, NOACs showed an improvement in both effectiveness and safety profile even in optimally VKA anticoagulated AF patients.

Clinical trials are not always representative of RW settings because the randomized trials enrol highly selected patients with few elderly patients and closely monitored anticoagulation therapy and other comorbidities but their results are used to change the daily clinical practice (18). We observed differences in our baseline characteristics of AF population with older patients and higher comorbidities in comparison with pivotal trials except for ROCKET trial. Gaps in translation from trials to clinical practice inevitably occur and the effects of NOACs in RW could be very different (19). We observed higher rates of events in our population than in clinical trials. For example, in our optimally controlled AF population, we observed higher rates of ICH (0.88%/year) than in clinical trials (0.4-0.7%/year) but our rates were similar to other real-world studies (0.7-1.3%/year) (20,21). Despite our patients have good TTR at the beginning of the registry, there were real-world patients with comorbidities and treated according usual clinical practice guidelines without additional care to be included in a registry. Clinical trials populations are really selected and with more additional visits and extra-care than daily clinical practice. This may reflect inherently different risk profiles between “real-world” and clinical trial cohorts.

RW observational studies and meta-analysis found NOACs are overall safe and effective alternatives to warfarin treatment(22–24). Data from the Danish nationwide

databases reflected all NOACs seem to be safe and effective alternatives to warfarin without significant differences for ischaemic stroke and the risk of death and major bleeding were significant lower with apixaban(25). For example, Carmo *et al.*(26) performed a meta-analysis of 20 observational RW studies with more than 700,000 AF patients and showed that dabigatran was associated with a lower risk of ischaemic stroke. In our analysis, we observed dabigatran 150 mg was the drug that would have the highest estimated reduction of ischaemic stroke. In RELY clinical trial(10), the absolute difference between dabigatran150 mg and warfarin was 0.56%/year whereas in our data, we observed an estimated reduction of 0.53%/year in our optimally anticoagulated AF population. We observed in RW population similar potential estimated effect of dabigatran than in clinical trial. Recently, Korenstra *et al.*(27) showed that dabigatran in RW appears to be as effective as but significantly safer than acenocoumarol. Indeed, Lip *et al.*(28) conducted a RW comparison of major bleeding risk on NOACs and concluded that in newly anticoagulated AF patients, apixaban and dabigatran initiation was associated with significantly lower risk of major bleeding compared to warfarin. In our study, apixaban had the highest estimated reduction in major bleeding, even in the high-risk AF patients ($CHADS_2 \geq 3$).

The use of VKA therapy has many limitations due to drug-food and drug-drug interactions and its variable dose requirement with narrow therapeutic window(29). Indeed, in initiation period of VKA treatment, the TTR is lower than TTR measured after the warfarin inception period (30).Patients initiating VKAs had two-fold increased risk of ischaemic stroke in the first 30 days of use(3). NOACs have demonstrated rapid onset-offset due to their predictable pharmacodynamic and pharmacokinetic action so NOACs could avoid this increase in thromboembolic events at the onset of OAC therapy. In our study, we have shown that NOACs could reduce adverse clinical outcomes even in

optimally management AF patients with TTR 100%. Indeed, Björck *et al.* (14,15) analyzed Swedish AF patients and compared the rates of clinical outcomes between well-managed patients with TTR >70% or below and observed low risk of complications in well-managed group. They proposed VKA treatment with high TTR could be as effective as NOACs in preventing adverse outcomes. Contrary to the Swedish results, we observed that, even in patients with optimal anticoagulation management of VKA therapy (TTR 100%), NOACs demonstrated a superior effect in efficacy and safety.

The debate whether or not to switch stable warfarin patients to a NOACs will continue because this question cannot be answered until a clinical trial is performed comparing NOACs with TTR >70% (31), which is unlikely to happen. We observed in our optimally anticoagulated AF population lower stroke and bleeding rates than in pivotal clinical trials and despite this, NOACs still presented an estimated reduction effect for all clinical outcomes.

Indeed, apixaban may offer the highest estimated favourable balance of efficacy and safety with the highest estimated reduction in net clinical outcomes. This effect was also estimated for high baseline risk assessed by CHADS₂ ≥ 3 in comparison with acenocoumarol. Banerjee *et al.* (32) analyzed the net clinical benefit of NOACs using data from the Danish National Patient Registry and concluded that when the risk of bleeding and stroke are both high, NOACs appear to have a greater net clinical benefit compared to warfarin.

The use of NOACs has been increasing since their introduction but the adoption into clinical practice has been slower than expected due to several factors. The ORBIT-AF(33)and GARFIELD(34) registries showed that NOAC use ranged from 9 to 32% in

new-onset AF and 8 to 66% in patients with established AF, with considerable variation between countries(35).

Several potential limitations are associated with NOAC prescription: health costs, adherence (and persistence) to NOAC treatment, monitoring requirements for renal function and a lower frequency of outpatient follow-up visits (which may be disadvantageous to some patients with multiple comorbidities). Many healthcare systems are currently unenthusiastic to implement a first-line strategy with NOACs due to the higher costs(9). Instead several cost-effective studies have shown additional health benefits in terms of quality-adjusted life-years of NOACs treatment compared with warfarin(36–38), many restrictions for use were observed in developed health systems and the authorization process of the prescription can be delayed (39). Low levels of adherence to NOAC are associated with bleeding and thromboembolic events, and cessation of oral anticoagulation is an important risk factor for stroke and mortality in AF patients(40,41). We also observed high rates of discontinuation therapy in the pivotal clinical trials, especially with edoxaban with 34% in both edoxaban and warfarin groups. In our cohort, we observed a rate of VKA discontinuation of 10%.

Limitations

This study is limited by its single center design and by a Caucasian based population. All statistical analyses were performed retrospectively although our dataset was collected prospectively. Although in pivotal clinical trials NOACs were compared with warfarin, we have used acenocoumarol because is the most common VKA used in Spain. The differences observed in anticoagulation control dependent on the type of VKA may result from a shorter half-life of acenocoumarol compared to warfarin (10 vs 36h). Warfarin

provides more stable anticoagulation with warfarin, but without significant differences on the time on therapeutic range in optimally managed AF patients. Patients are representative of a Spanish population and results might not be extrapolated to other countries. Moreover, the rate of stroke for CHADS₂ score was not reported in the pivotal clinical trials but the rate of a combined endpoint of stroke and systemic embolism was published. We have infrequent rate of systemic embolism so we applied the combined rate for an estimation of the absolute number of stroke events avoided across CHADS₂ risk categories. ROCKET-AF clinical trial population had higher rate of comorbidities, risk factors, CHADS₂ and HAS-BLED score in both, rivaroxaban and warfarin group. Although we did not perform a direct comparison between NOACs, some care should be taken when the clinical trials results were generalizing. We cannot perform a direct comparison using propensity score to homogenize the baseline characteristics then we assumed this limitation of our study. We did not compare differences between NOACs but we compared the differences between NOACs and optimal management of VKA therapy. Indeed, in ROCKET – AF clinical trials, the authors did not provide the hazard ratios or incidence rate of net clinical benefit for warfarin or rivaroxaban group, neither per protocol or intention to treat. In order to avoid the accumulation of errors by secondary analyses, we did not perform the comparison of net clinical benefit with rivaroxaban. For the adverse event comparison, we used the annual rate and assumed a constant and invariable adverse event rate and this may not be constant due the elderly and high comorbidities of real-world acenocoumarol population”.

CONCLUSIONS

In an optimally anticoagulated acenocoumarol AF patients, potential estimated reductions in stroke, bleeding and net clinical outcomes with various NOACs are evident. All NOACs showed an expected significant reduction for intracranial haemorrhage. Thus, NOACs showed an improvement in both effectiveness and safety profile even in optimally VKA anticoagulated AF patients.

REFERENCES

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007 Jun 19;146(12):857–67.
2. Sjögren V, Grzymala-Lubanski B, Renlund H, Friberg L, Lip GYH, Svensson PJ, et al. Safety and efficacy of well managed warfarin. A report from the Swedish quality register Auricula. *Thromb Haemost.* 2015 Jun;113(6):1370–7.
3. Hylek EM. Vitamin K antagonists and time in the therapeutic range: implications, challenges, and strategies for improvement. *J Thromb Thrombolysis.* 2013 Apr;35(3):333–5.
4. Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa T-P. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost.* 2011 Nov;106(5):968–77.
5. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016 Oct 7;37(38):2893–962.
6. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. *Thromb Haemost.* 2013 Dec;110(6):1087–107.
7. Van Den Ham HA, Klungel OH, Leufkens HGM, Van Staa TP. The patterns of anticoagulation control and the risk of stroke, bleeding and mortality in patients with non-valvular atrial fibrillation. *J Thromb Haemost JTH.* 2013 Jan;11(1):107–15.
8. Blann AD, Skjøth F, Rasmussen LH, Larsen TB, Lip GYH. Edoxaban versus placebo, aspirin, or aspirin plus clopidogrel for stroke prevention in atrial fibrillation. *Thromb Haemost.* 2015;114(2):403–9.
9. Lip GY. Atrial fibrillation and stroke prevention: brief observations on the last decade. *Expert Rev Cardiovasc Ther.* 2014 Apr;12(4):403–6.
10. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009 Sep 17;361(12):1139–51.
11. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al.

- Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011 Sep 15;365(11):981–92.
12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011 Sep 8;365(10):883–91.
 13. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013 Nov 28;369(22):2093–104.
 14. Björck F, Renlund H, Lip GYH, Wester P, Svensson PJ, Själander A. Outcomes in a Warfarin-Treated Population With Atrial Fibrillation. *JAMA Cardiol*. 2016 May 1;1(2):172–80.
 15. Björck F, Sandén P, Renlund H, Svensson PJ, Själander A. Warfarin treatment quality is consistently high in both anticoagulation clinics and primary care setting in Sweden. *Thromb Res*. 2015 Aug;136(2):216–20.
 16. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost JTH*. 2005 Apr;3(4):692–4.
 17. Amin A, Stokes M, Wu N, Gatt E, Makenbaeva D, Wiederkehr D, et al. Application of randomized clinical trial data to actual practice: apixaban therapy for reduction of stroke risk in non-valvular atrial fibrillation patients. *Curr Med Res Opin*. 2013 Oct;29(10):1253–61.
 18. Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. 2003 Nov 26;290(20):2685–92.
 19. Freedman B, Lip GYH. “Unreal world” or “real world” data in oral anticoagulant treatment of atrial fibrillation. *Thromb Haemost*. 2016 Sep 27;116(4):587–9.
 20. Martinez C, Katholing A, Wallenhorst C, Freedman SB. Therapy persistence in newly diagnosed non-valvular atrial fibrillation treated with warfarin or NOAC. A cohort study. *Thromb Haemost*. 2016 Jan;115(1):31–9.
 21. Wilson MR, Parakramawansa R, Quinn TJ, Tait RC. Quality and predictors of anticoagulant control with vitamin K antagonist for stroke prevention in atrial fibrillation. *Thromb Haemost*. 2016 Aug 30;116(3):578–80.
 22. Lip GYH, Mitchell SA, Liu X, Liu LZ, Phatak H, Kachroo S, et al. Relative efficacy and

safety of non-Vitamin K oral anticoagulants for non-valvular atrial fibrillation: Network meta-analysis comparing apixaban, dabigatran, rivaroxaban and edoxaban in three patient subgroups. *Int J Cardiol.* 2016 Feb 1;204:88–94.

23. Villines TC, Schnee J, Fraeman K, Siu K, Reynolds MW, Collins J, et al. A comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrillation patients in a large healthcare system. *Thromb Haemost.* 2015 Nov 25;114(6):1290–8.

24. Beyer-Westendorf J, Camm AJ, Coleman CI, Tamayo S. Rivaroxaban real-world evidence: Validating safety and effectiveness in clinical practice. *Thromb Haemost.* 2016 Sep 28;116(Suppl. 2):S13–23.

25. Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GYH. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ.* 2016 Jun 16;353:i3189.

26. Carmo J, Moscoso Costa F, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation. Meta-analysis of observational comparison studies with vitamin K antagonists. *Thromb Haemost.* 2016 Sep 27;116(4):754–63.

27. Korenstra J, Wijtvliet EPJ, Veeger NJGM, Geluk CA, Bartels GL, Posma JL, et al. Effectiveness and safety of dabigatran versus acenocoumarol in “real-world” patients with atrial fibrillation. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol.* 2016 Sep;18(9):1319–27.

28. Lip GYH, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. *Thromb Haemost.* 2016 Oct 28;116(5):975–86.

29. Roldán V, Marín F. The importance of excellence in the quality of anticoagulation control whilst taking vitamin K antagonists. *Thromb Haemost.* 2015 Apr;113(4):671–3.

30. Garcia DA, Lopes RD, Hylek EM. New-onset atrial fibrillation and warfarin initiation: high risk periods and implications for new antithrombotic drugs. *Thromb Haemost.* 2010 Dec;104(6):1099–105.

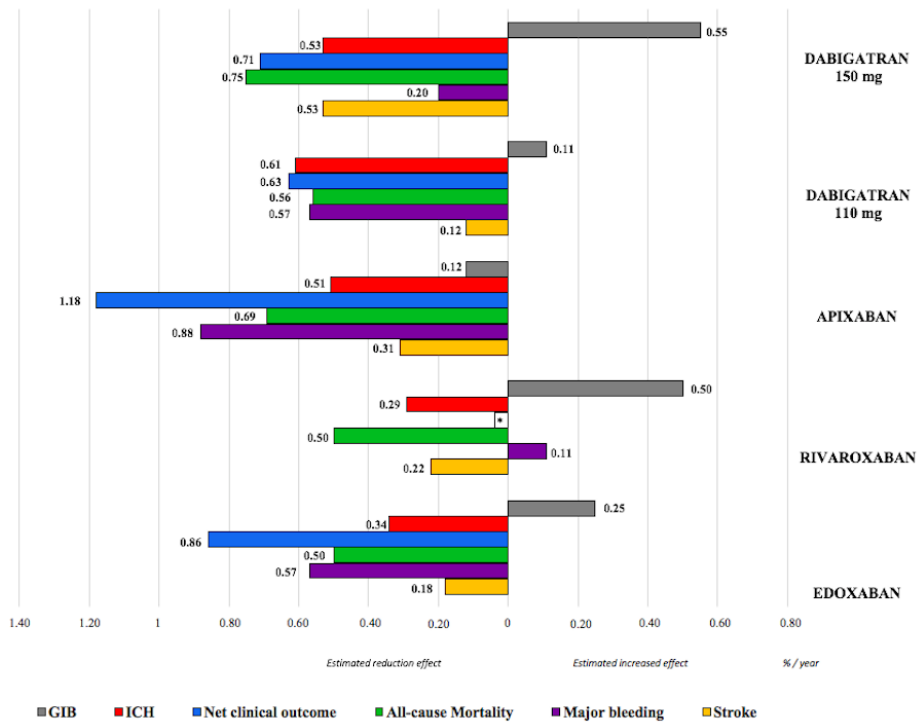
31. Hylek EM, Ko D, Cove CL. Gaps in translation from trials to practice: non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation. *Thromb Haemost.* 2014 May 5;111(5):783–8.

32. Banerjee A, Lane DA, Torp-Pedersen C, Lip GYH. Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a “real world” atrial fibrillation population: a modelling analysis based on a nationwide cohort study. *Thromb Haemost.* 2012 Mar;107(3):584–9.
33. Steinberg BA, Blanco RG, Ollis D, Kim S, Holmes DN, Kowey PR, et al. Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II: rationale and design of the ORBIT-AF II registry. *Am Heart J.* 2014 Aug;168(2):160–7.
34. Goto S, Oh S, Cools F, Koretsune Y, Angchaisuksiri P, Rushton-Smith SK, et al. Regional differences in use of antithrombotic therapy for stroke prevention in atrial fibrillation and associated outcomes: European and Asian insights. *Eur Heart J* [Internet]. 2013 Aug 1 [cited 2017 Jun 4];34(suppl_1). Available from: https://academic.oup.com/eurheartj/article/34/suppl_1/P4277/2862413/Regional-differences-in-use-of-antithrombotic
35. Akao M, Beyer-Westendorf J, Goto S, Peterson E. Stroke prevention in atrial fibrillation: evidence from real-life studies. *Eur Heart J Suppl.* 2015 Jul 1;17(suppl_D):D42–52.
36. Wisløff T, Hagen G, Klemp M. Economic evaluation of warfarin, dabigatran, rivaroxaban, and apixaban for stroke prevention in atrial fibrillation. *Pharmacoeconomics.* 2014 Jun;32(6):601–12.
37. Hernandez I, Smith KJ, Zhang Y. Cost-effectiveness of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation at high risk of bleeding and normal kidney function. *Thromb Res.* 2017 Feb;150:123–30.
38. Krejczy M, Harenberg J, Wehling M, Obermann K, Lip GYH. Cost-effectiveness of anticoagulation in patients with nonvalvular atrial fibrillation with edoxaban compared to warfarin in Germany. *BioMed Res Int.* 2015;2015:876923.
39. Roldán I, Marín F, Cardiovascular Thrombosis Group of the Spanish Society of Cardiology and the proposal development Committee, Spanish Society of Cardiology (SEC), Spanish Thrombosis and Hemostasis Society (SETH), Spanish Society of Neurology (SEN), et al. On the Way to a Better Use of Anticoagulants in Nonvalvular Atrial Fibrillation. Proposed Amendment to the Therapeutic Positioning Report UT/V4/23122013. *Rev Espanola Cardiol Engl Ed.* 2016 Jun;69(6):551–3.
40. Gallego P, Roldan V, Marín F, Romera M, Valdés M, Vicente V, et al. Cessation of oral anticoagulation in relation to mortality and the risk of thrombotic events in patients with atrial fibrillation. *Thromb Haemost.* 2013 Dec;110(6):1189–98.

41. Rivera-Caravaca JM, Roldán V, Esteve-Pastor MA, Valdés M, Vicente V, Lip GYH, et al. Cessation of oral anticoagulation is an important risk factor for stroke and mortality in atrial fibrillation patients. *Thromb Haemost.* 2017 Mar 23;

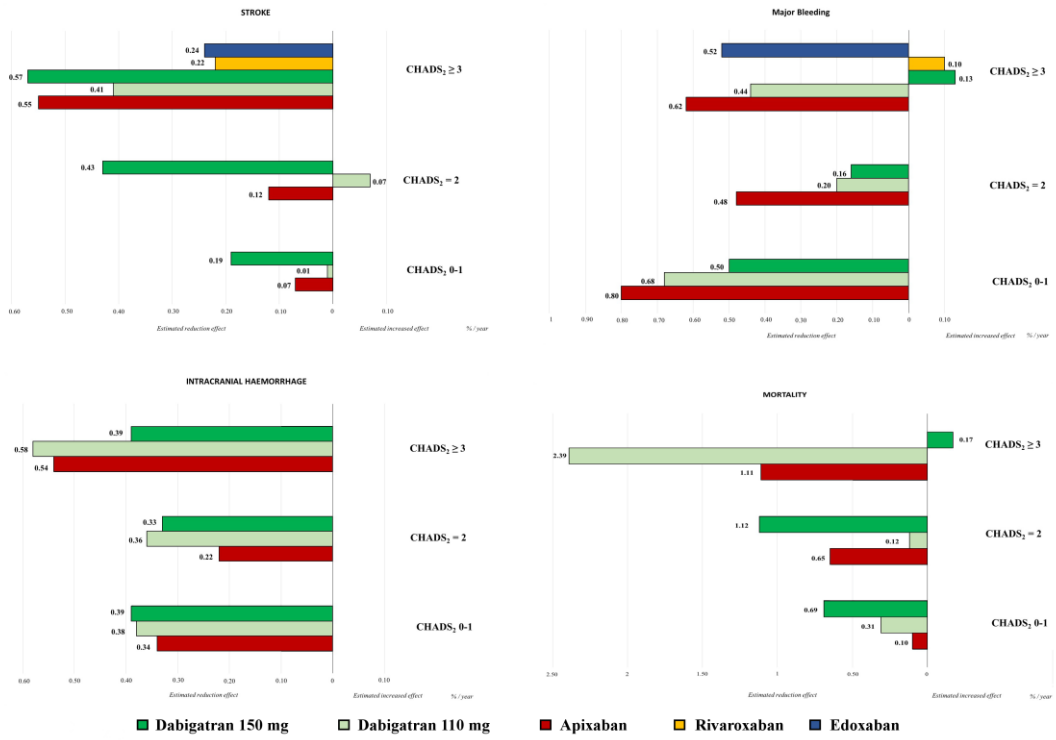
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Figure 1



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Figure 2



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Table 1. Baseline clinical characteristics.

	RE-LY ¹¹		ARISTOTLE ¹²		ROCKET ¹³		ENGAGE ¹⁴		Optimally Managemen
	Dabig atran	Warf arin	Apixa ban	Warf arin	Rivaro xaban	Warfa rin	Edoxa ban	Warf arin	Acenoco umarol
	n=60 75	n=60 22	n=912 0	n=908 1	n=713 1	n=7133	n=703 5	n=703 6	n=1361
Demographic									
Male sex	3840 (63.2)	3809 (63.3)	3234 (35.5)	3182 (35.0)	2831 (39.7)	2832 (39.7)	2669 (37.9)	2641 (37.5)	663 (48.7)
Age (years)	71.5± 8.8	71.6± 8.6	70 (63- 76)	70 (63- 76)	73 (65- 78)	73 (65- 78)	72 (64- 78)	72 (64- 78)	76 (71- 81)
Comorbidities									
Hypertension	4795 (78.9)	4750 (78.9)	7962 (87.3)	7954 (87.6)	6436 (90.3)	6474 (90.8)	6591 (93.7)	6588 (93.6)	1116 (82.0)
Diabetes mellitus	1402 (23.1)	1410 (23.4)	2284 (25.0)	2263 (24.9)	2878 (40.4)	2817 (39.5)	2559 (36.4)	2521 (35.8)	363 (26.7)
Heart failure	1934 (31.8)	1922 (31.9)	3235 (35.5)	3216 (35.4)	4467 (62.6)	4441 (62.3)	4097 (58.2)	4048 (57.5)	429 (31.5)
Previous stroke	1233 (20.3)	1195 (19.8)	1748 (19.2)	1790 (19.7)	3916 (54.9)	3895 (54.6)	1976 (28.1)	1991 (28.3)	267 (19.6)
Renal disease									

eGFR > 80 ml/min	1945 (32.2)	1941 (32.5)	3761 (41.2)	3757 (41.4)	2285 (32.1)	2222 (31.2)	2612 (37.1)	2595 (36.9)	954 (70.1)
eGFR 80-50 ml/min	2852 (47.3)	2898 (48.5)	3817 (41.9)	3770 (41.5)	3298 (46.2)	3400 (47.6)	2985 (42.4)	3030 (43.1)	282 (20.7)
eGFR < 50 ml/min	1232 (20.4)	1126 (18.8)	1502 (16.5)	1515 (16.7)	1490 (20.8)	1459(2 0.4)	1287 (18.2)	1297 (18.4)	61 (4.6)
CHADS₂	2.2±1. 2	2.1±1 .1	2.1±1. 1	2.1±1. 1	3.48±0 .94	3.46±0. 95	2.8±1. 0	2.8±1. 0	2.4±2.3
Discontinuation rate	21.2 %	16.6 %	25.3%	27.5%	23.7%	22.2%	34.4%	34.5%	10.0%
Follow-up	2 years		1.8 years		1.9 years		2.8 years		6.5 years

eGFR: estimated glomerular filtration rate. VKA: Vitamin K antagonists. CHADS₂ = Congestive heart failure or left ventricular dysfunction (1); Hypertension (1), Age ≥75 (1), Diabetes mellitus (1) and prior Stroke/TIA or systemic embolism (2). Numeric values are means ± standard deviation, median and interquartile range or number (percentage).

Table 2: Estimated effect of NOACs.

	Acenocoumarol 150mg <i>n</i> <i>n</i> (%/year, <i>r</i>)	Dabigatran 150mg <i>n</i> <i>n</i> (%/year, <i>r</i>)	Acenocoumarol vs Dabigatran 150 mg <i>p</i> value	NNT	Dabigatran 110 mg <i>n</i> <i>n</i> (%/year, <i>r</i>)	Acenocoumarol vs Dabigatran 110 mg <i>p</i> value	NNT	Apixaban <i>n</i> <i>n</i> (%/year, <i>r</i>)	Acenocoumarol vs Apixaban <i>n</i> <i>p</i> value	N
Stroke	130 (1.47)	83 (0.94)	0.001	18	119 (1.35)	0.486	909	103 (1.16)	0.076	3 2 3
Myocardial Infarction	76 (0.86)	105 (1.19)	0.031	30	103 (1.16)	0.043	323	67 (0.76)	0.452	9 0 9
All-cause mortality	551 (6.23)	485 (5.48)	0.041	13	502 (5.67)	0.131	179	490 (5.54)	0.057	1 4 5
Cardiovascular mortality	75 (0.85)	64 (0.72)	0.351	76	68 (0.77)	0.588	117	67 (0.76)	0.502	1 1 1
Major bleeding	250 (2.83)	233 (2.63)	0.439	50	200 (2.26)	0.018	185	172 (1.95)	0.001	1 1 4

Gastrointestina	97									8
		146	0.002	18	107		101	87		3
I bleeding	(1.10)	(1.65)		8	(1.21)	0.483	0	(0.98)	0.461	3
Intracranial	78									1
		31	<0.001	19	24			33		9
haemorrhage	(0.88)	(0.35)		2	(0.27)	<0.001	164	(0.37)	<0.001	6
Net clinical	693	630		14	637			588		8
outcome	(7.83)	(7.12)	0.083	3	(7.20)	0.125	181	(6.65)	0.033	5

NNT: Number needed to treat. Net clinical outcome was defined as the composite of stroke, major bleeding and all mortality.

Table 2: Estimated effect of NOACs (Continue).

	Acenocoumarol n (%/year)	Rivaroxaban n (%/year)	Acenocoumarol vs Rivaroxaban p value	NNT	Edoxaban n (%/year)	Acenocoumarol vs Edoxaban 60 mg p value	NNT
Stroke	130 (1.47)	111 (1.25)	0.221	423	114 (1.29)	0.306	555
Myocardial Infarction	76 (0.86)	61 (0.69)	0.200	625	71 (0.80)	0.680	200
All-cause mortality	551 (6.23)	507 (5.73)	0.176	200	507 (5.73)	0.176	200
Cardiovascular mortality	75 (0.85)	67 (0.76)	0.502	1111	65 (0.73)	0.398	833
Major bleeding	250 (2.83)	260 (2.94)	0.657	588	200 (2.26)	0.018	185
Gastrointestinal bleeding	97 (1.10)	142 (1.60)	0.004	202	119 (1.35)	0.134	400
Intracranial haemorrhage	78 (0.88)	52 (0.59)	0.022	384	36 (0.41)	0.001	213

Net clinical	693			617		
outcome	(7.83)	-	-	(6.97)	0.036	128

NNT: Number needed to treat. Net clinical outcome was defined as the composite of stroke, major bleeding and all mortality. Data to calculated was no reported in ROCKET trial for rivaroxaban.

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What is known about this topic

- Therapy with vitamin K antagonists (VKAs) is highly effective for reducing risk of stroke and mortality but VKAs have a narrow therapeutic window.
- Non-Vitamin K oral anticoagulants (NOACs) have been developed as generally effective and safe alternative to VKAs in AF patients
- The potential impact and absolute effect of NOACs in “real world” optimally management of VKA AF patients is unknown.

What does this paper add?

- In an optimally acenocoumarol anticoagulated AF patients, estimated reductions in stroke, bleeding and net clinical outcomes with NOACs are evident.
- The greatest efficacy for stroke and mortality estimated reduction was seen with dabigatran 150mg, and best expected safety with apixaban.
- All NOACs showed an estimated significant reduction for intracranial haemorrhage.