

# Estimated Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants Compared to Optimally Acenocoumarol Anticoagulated 'Real-World' in Patients With Atrial Fibrillation

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## **Estimated Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants Compared to Optimally Acenocoumarol Anticoagulated ‘Real-World’ in Patients With Atrial Fibrillation.**

**Running title: Estimated Effect of NOACs in ‘Real-World’ AF Patients**

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**ABSTRACT**

Non-vitamin K antagonist oral anticoagulants (NOACs) have been proposed as an alternative to vitamin K antagonists in atrial fibrillation (AF) patients but the comparative benefits between NOACs and optimally anticoagulated patients is unknown. We estimated the absolute benefit in clinical outcomes rates of real-world (RW) effect of NOACs in optimally anticoagulated AF patients with acenocoumarol. We included 1,361 patients stable on acenocoumarol with time in therapeutic range of 100% and 6.5 years of follow-up. Estimation of clinical events avoided was calculated applying hazard ratio, absolute and relative risk reduction from the RW meta-analysis. Compared to an optimally anticoagulated population, dabigatran 110mg had the highest estimated stroke reduction (0.97%/year vs 1.47%/year;  $p=0.002$ ), and the benefit was higher than in RE-LY trial. For major bleeding, apixaban showed the highest estimated reduction (1.81%/year vs 2.83%/year;  $p<0.001$ ). For mortality, the largest estimated reduction was with apixaban (2.68%/year). For gastrointestinal bleeding, only apixaban had a significant reduction compared to acenocoumarol (0.69%/year vs 1.10%/year;  $p=0.004$ ), and the reduction was significantly higher than in ARISTOTLE trial. All NOACs showed significantly lower rates for intracranial haemorrhage and had a positive Net Clinical Benefit (NCB) compared to acenocoumarol. Apixaban showed the highest extended estimated NCB 2.64 (95%CI 2.34-2.96). In conclusion, in optimally acenocoumarol anticoagulated AF patients, estimated reductions in all clinical outcomes with various NOACs are evident, with the best effectiveness and safety profile with apixaban. Indeed, the estimated effect with “real world” NOACs would probably be higher than that seen in phase-III clinical trials.

**Key words:** non-vitamin K oral anticoagulants, vitamin K antagonists, atrial fibrillation, real-world

## INTRODUCTION

For many years, vitamin K antagonists (VKAs) have been the only effective oral treatment to reduce thromboembolic events and mortality in Atrial Fibrillation (AF) patients(1). Indeed, it is necessary to achieve high TTR (*i.e.*> 70%) to maximize the efficacy and safety of VKA treatment(2), but this is the main limitation of VKA therapy due to its narrow therapeutic window (3). The non-vitamin K antagonist oral anticoagulants (NOACs) have emerged as an effective and safer alternative to VKAs (4–7). However, the effect of NOACs in clinical trials may not be the same as in ‘real-world’ (RW) practice and the results from RW data studies provide better generalisation of results(8). Currently, there are only four meta-analysis with RW observational data that compare the effect of NOACs and VKAs (9–12).Despite of the effectiveness and safety profile of NOACs even in RW AF patients, VKAs have remained widely used in clinical practice worldwide and many healthcare systems do not implement a first-line strategy with NOACs due to costs. Some studies have even proposed that optimally managed VKA therapy is a valid alternative for AF patients and could be as efficacious as NOACs (13,14), but a comparison between RW effect of NOACs with optimal management of VKA in AF patients is unknown. The main objective of our study is to estimate the absolute benefit of NOACs based on RW data on clinical outcomes in a cohort of optimally anticoagulated AF patients with acenocoumarol.

## METHODS

We included all consecutive outpatients with confirmed diagnosis of AF (paroxysmal, persistent and permanent AF) treated in our anticoagulation clinic in the Southeast Spain from May 2007 to December 2007. The inclusion criteria were patients older than 18 years old with confirmed diagnosis of AF who were stable on

acenocoumarol treatment during at least the 6 previous months. At entry, all patients had time in therapeutic range as measured by the Rosendaal method (15) of 100% to ensure our inclusion of a homogeneous cohort of optimally managed AF patients on acenocoumarol treatment. The exclusion criteria were hospital admission, acute coronary syndrome, surgical interventions or hemodynamic instability during the preceding 6 months. Patients with moderate-severe rheumatic mitral disease or prosthetic heart valve disease were also excluded.

At entry, complete medical history of each patient was collected with clinical and demographic characteristics. Blood samples were also collected at inclusion visit. Thromboembolic risk was calculated with CHA<sub>2</sub>DS<sub>2</sub>-VASc score (16) and bleeding risk was calculated with HAS-BLED score (17). All patients received anticoagulation therapy with acenocoumarol (the commonest VKA used in Spain) and all patients at entry had all their INR in therapeutic range (between 2.0 and 3.0) during the previous 6 months.

Follow-up was conducted through personal visits to the anticoagulation clinic and started the day of the inclusion, with no patients lost of follow-up. Adverse thromboembolic events (stroke/transitory ischaemic attack), cardiovascular mortality, all-cause mortality, major bleeding, intracranial bleeding and gastrointestinal bleeding were collected. Major bleeding events were defined according to the 2005 International Society of Thrombosis and Haemostasis criteria(18).

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).

All statistical analyses were performed retrospectively, although our dataset was collected prospectively. Continuous variables were tested for normality with Kolmogorov-Smirnov test and presented as mean  $\pm$  standard deviation or median [interquartile range, IQR]. Categorical variables are expressed as percentages. The Chi-square test was used to compare proportions.

#### *Estimation of potential real-world effect of NOACs*

We calculated the estimated rates for stroke, major bleeding, gastrointestinal bleeding, intracranial haemorrhage and all-cause mortality using NOACs instead of acenocoumarol by multiplying the pooled Hazard Ratios (HR) obtained for each clinical adverse event from the three meta-analyses providing the estimated effect seen in RW of dabigatran(10), rivaroxaban(11) and apixaban(12) against the RW rates seen amongst our optimally anticoagulated patients with acenocoumarol after follow-up. We personally contacted with the main investigators of each meta-analyses to know the selection strategy of the studies included in the meta-analyses to calculate the different HR for each clinical event. We also compared differences between our reference real rates to the estimated RW effect and with the estimated effect in clinical trials using the Hazard Ratios (HRs) from RE-LY(4), ROCKET(6) and ARISTOTLE(5) clinical trials. We also calculated the absolute risk reduction (ARRs), relative risk reduction (RRRs) and number needed to treat (NNTs). We calculated the estimated absolute numbers of all adverse clinical events that theoretically might be avoided by using dabigatran, rivaroxaban and apixaban instead of acenocoumarol by multiplying the RRRs from RW meta-analysis by the event rates of our anticoagulated population. The resulting ARR were used to calculate the NNTs to prevent one adverse event as Amin *et al.* previously performed(19).

We evaluated the weighed net clinical benefit of the estimated use of each NOAC compared to acenocoumarol. We evaluated the crude incidence rate (IR) per 100 patient-years of each weighted event for patients for patients receiving acenocoumarol and the estimated crude incidence rate for each NOAC.

We calculated both, using the standardized weights proposed by Singer *et al.*(20) (1.5 for ICH) and using our own weights associated with major bleeding, ICH and gastrointestinal bleeding using stroke as a reference(21). (Appendix 1 and **Supplementary Table 2**).

Statistical significance was defined as  $p < 0.05$  and 95% confidence intervals were calculated for all the analyses. 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 AF population are summarized in **Supplementary Table 1**. We enrolled 1,361 AF patients [median age 76, IQR (71-81) years; 663 (48.7%) males]. 1,116 (82.0%) patients had hypertension, 267 (15.9%) had previous stroke and 113 (8.3%) previous bleeding. After 6.5 [IQR 4.3-7.9] years of follow-up, 130 (1.47%/year) patients had stroke/transitory ischaemic attack, 78 (0.88%/year) patients had ICH, 97 (1.10%/year) had gastrointestinal bleeding and 250 (2.83%/year) had major bleeding events. Also, 551 (6.23%/year) patients died during the follow-up.

The estimated effect of each NOAC in RW, in phase III clinical trials and the estimated reduction compared acenocoumarol, RW NOACs and phase III clinical trials are shown in **Table 1** for dabigatran, **Table 2** for rivaroxaban and **Table 3** for apixaban; and **Figure 1** and **Figure 2**.



We estimated that the rates for stroke using RW NOACs would be 1.34%/year for dabigatran 150 mg, 0.97%/year for dabigatran 110mg, 1.26%/year for rivaroxaban and 1.23%/year for apixaban. In phase III clinical trials, Dabigatran 150 mg had the highest estimated reduction for stroke (0.94% vs 1.47%;  $p=0.001$ ).

Based on the RW effect, Dabigatran 110 mg was the only NOAC that showed significantly lower stroke rate compared with optimally management of AF with acenocoumarol (0.97%/year vs 1.47%/year;  $p=0.002$ ) and this effect in RW was higher than that expected in the RE-LY clinical trial (0.97%/year vs 1.35%/year;  $p=0.017$ ). Using dabigatran 110 mg instead of acenocoumarol, 0.50 stroke events per 100 patient-years (*i.e.* 45 strokes avoided over the total sample) would be avoided, resulting in a NNT of 204 for avoiding 1 stroke. The use of dabigatran 110 mg in RW showed an estimated benefit effect on stroke prevention of 135% (95%CI 127%-143%) compared with the full effect of acenocoumarol.

We estimated that the rates of all-cause mortality using RW NOACs would be 4.36%/year for dabigatran 150mg, 4.92%/year for dabigatran 110mg, 6.48%/year for rivaroxaban and 3.55%/year for apixaban. We observed significantly lower mortality rates with dabigatran 150mg, dabigatran 110 mg and apixaban than with optimally management with acenocoumarol. Indeed, the effect observed in RW NOACs was significantly higher than in phase III clinical trials for these NOACs. For rivaroxaban, there was a trend to higher mortality in RW use.

Compared to the optimally anticoagulated AF patients on acenocoumarol, apixaban showed the highest significant reduction in mortality with 2.68 deaths per 100 patient-years (237 deaths avoided over the total sample, *i.e.* 43% deaths less) would be avoided using apixaban instead of acenocoumarol with optimally management, resulting in a NNT of 37 to avoid 1 death. The use of apixaban in RW showed an

estimated benefit effect on mortality prevention of 143% (95%CI 139-147) compared with the full effect of acenocoumarol.

We estimated that the rates of major bleeding would be 2.29%/year for dabigatran 150 mg, 2.12%/year for dabigatran 110 mg, 2.80%/year for rivaroxaban and 1.81%/year with apixaban. We observed a significant reduction in major bleeding using dabigatran 150 mg, dabigatran 110 mg and apixaban instead of optimally management with acenocoumarol. The significantly highest reduction was observed with apixaban with 1.02 major bleeding per 100 patient-years (*i.e.* 90 bleeding events avoided over total sample) that would be avoided resulting in a NNT of 101 to avoid 1 major bleeding using apixaban instead of acenocoumarol. The use of apixaban in RW showed an estimated benefit effect on major bleeding prevention of 136% (95%CI 130-142) compared with the full effect of acenocoumarol.

We observed that all NOACs showed significantly lower ICH rates in comparison with the optimally management VKA therapy with acenocoumarol and the effect in RW was similar than the observed in clinical trials. The estimated highest event reduction was observed with dabigatran 150 mg and 0.50 intracranial bleeding events per 100 patient-years (*i.e.* 44 bleeding events avoided over total sample) would be avoided using dabigatran 150 mg instead of acenocoumarol resulting in a NNT of 182 to avoid 1 ICH using dabigatran instead of acenocoumarol. The use of dabigatran 150 mg in RW showed an estimated benefit effect on ICH prevention of 156% (95%CI 145-167) compared with the full effect of acenocoumarol.

The estimated rates of RW NOAC for gastrointestinal bleeding were 1.30%/year for dabigatran 150 mg, 1.06%/year for dabigatran 110 mg, 1.32%/year for rivaroxaban and 0.69%/year for apixaban. Apixaban was the only NOAC that showed significantly estimated reduction effect for gastrointestinal bleeding in comparison with

acenocoumarol (1.10%/year vs 0.69%/year;  $p=0.004$ ) and the effect was significantly higher than it would be expected in the clinical trial. Therefore 0.41 gastrointestinal bleeding events per 100 patient-years (*i.e.* 36 bleeding events avoided over total sample) would be avoided using apixaban instead of acenocoumarol resulting in a NNT of 263 to avoid 1 gastrointestinal bleeding using apixaban. The use of apixaban in RW showed an estimated benefit effect on gastrointestinal bleeding prevention of 137% (95%CI 128-147) compared with the full effect of acenocoumarol.

**Table 4** shows the net clinical benefit (NCB) of acenocoumarol versus each NOAC by stroke and ICH, and by stroke and all significant bleeding events. All NOACs were predicted to have a positive NCB balancing stroke against ICH and a positive NCB balancing stroke against all significant bleeding events. Dabigatran 110 mg had the highest positive NCB balancing stroke against ICH while Apixaban was the NOAC with the highest positive NCB balancing stroke against all significant bleeding events.

## DISCUSSION

In an optimally acenocoumarol anticoagulated AF patients, estimated reductions in all clinical outcomes with various NOACs are evident. In RW, dabigatran 110 mg showed the highest reduction in stroke rates and apixaban showed the highest effect on mortality, major bleeding and gastrointestinal bleeding in comparison with acenocoumarol, with also the highest positive NCB. Thus, the effect of “real-world” NOACs showed an improvement in both effectiveness and safety profile even in optimally VKA anticoagulated AF patients, higher than in phase III clinical trials.

In our analyses, we performed an estimated rate of events (ie the estimated rates if the patients had been treated with NOACs instead of acenocoumarol) because in clinical

practice is unlikely to make a real comparison between optimally anticoagulated patients with VKA and NOACs to assess the different adverse events with long follow-up (6.5 years).

Ischemic stroke risk reduction was only observed with Dabigatran 150 mg compared with warfarin in the RE-LY(4) clinical trial whereas dabigatran 110 mg was non-inferior to warfarin for stroke. In the ARISTOTLE trial, apixaban was superior to warfarin in preventing stroke/SE whereas rivaroxaban was noninferior to warfarin for the prevention of stroke/SE. Korenstra *et al.*(22) compared dabigatran with acenocoumarol and they did not find significant differences between both treatments where VKA patients were well managed, with a mean TTR of 78%. In our study, comparing with the full effect of acenocoumarol, the use of dabigatran 110 mg in RW showed an estimated benefit effect on stroke prevention of 135% and the estimated effect was higher in RW than that expected from the clinical trial. All NOACs in their phase III clinical trials and in the RW data showed lower rates of ICH in comparison with warfarin and we also observed a significant estimated reduction of ICH with all NOACs. For major bleeding events, different safety profiles have been observed between the NOACs(23). Lip *et al.*(24) conducted a RW comparison of major bleeding between NOACs and showed that apixaban and dabigatran initiation was associated with lower risk of major bleeding and rivaroxaban had higher risk compared to warfarin. We observed that the use of apixaban in RW showed an estimated benefit effect on major bleeding prevention of 136% compared with the full effect of acenocoumarol. When focused on gastrointestinal bleeding, apixaban had the highest estimated reduction and the effect was higher than the expected in its clinical trial, with an estimated benefit of apixaban treatment of 137%.

We also noted significantly lower expected rates for mortality with dabigatran and apixaban. Indeed, apixaban had the highest estimated reduction in mortality. These findings are consistent with the results of previous observational studies in which the benefits of dabigatran and apixaban in mortality were greater over VKAs(25,26). Although our patients had higher TTR than other RW data or clinical trials, we had higher rates of mortality due to the long-time of follow-up (6.5 years), the comorbidities and because our patients were treated according to daily clinical practice without additional care to be included in a registry. Nonetheless, our data show a greater effect regarding to mortality than to major bleeding. Indeed, the effect in RW on mortality is greater than in phase 3 clinical trials although RW patients tended to be more elderly, with more comorbidities and thus, a higher risk of death. Banerjee *et al.* (27) showed that when thromboembolic and bleeding risk are both high, NOACs appear to have a great NCB compared to warfarin. In our analysis, we estimated positive NCB for all NOACs with the greatest effect for the combined outcomes of stroke and any significant bleeding seen with apixaban.

Nonetheless, many healthcare systems do not implement a first-line strategy with NOACs due to costs 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 (28,29). Data from Swedish national quality registries (13) reported less rates of adverse clinical outcomes in well-managed AF patients with TTR higher than 70%. Indeed, recent studies(14) proposed that VKA treatment with high TTR could be as efficacious as NOACs given that the main benefits of NOACs compared with warfarin may be only marginal in those patients with high TTR. Carmo *et al.*(30) conducted a meta-analysis of the effect of NOACs compared with warfarin at different levels of TTR and showed that the superiority of NOACs in stroke prevention was lost

with TTR>70% but the risk of major bleeding was significantly lower with NOACs. We observed that even in the full effect of VKA treatment, NOACs reported significantly higher effect in all adverse events reduction.

This study has several limitations that should be noted. Our data represent the observations of oral anticoagulation treatment with acenocoumarol without direct comparison between VKAs and NOACs, and thus, would be subject to limitations inherent to the methodology. All out patients were treated with acenocoumarol, which has a shorter half-life than warfarin (10 vs 36 h), so the estimation effect of NOACs in warfarin population may not be equivalent. Patients are representative of a Spanish population (mainly Caucasian) and thus, the results might not be extrapolated to other regions. Indeed, all statistical analyses were performed retrospectively although our dataset was collected prospectively. No observational RW studies have been performed with edoxaban yet, thus we did not compare it with acenocoumarol. Although we did not perform a direct comparison between NOACs, some care should be taken when the clinical results of the meta-analyses were generalized. 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. To calculate the estimated rates for clinical events, we used the hazard ratio from clinical trials and from the three meta-analyses. Although the study quality of the manuscripts included to perform all these three meta-analyses was assessed according to the Newcastle-Ottawa scale, potential biases were linked to the inherent methodology of the meta-analyses (inclusion and exclusion criteria of each study, events available, heterogeneity...).

In conclusion, in optimally acenocoumarol anticoagulated AF patients, estimated reductions in all clinical outcomes with various NOACs are evident from our analysis. In RW, Dabigatran 110 mg showed the highest reduction in stroke rates and apixaban showed the highest effect on mortality, major bleeding and gastrointestinal bleeding in comparison with acenocoumarol, with also the highest positive net clinical benefit. Indeed, the effect in “real-world” NOACs was higher than in phase 3 clinical trials. Thus, the effect of “real-world” NOACs showed an improvement in both effectiveness and safety profile even in optimally anticoagulated AF patients on VKA.

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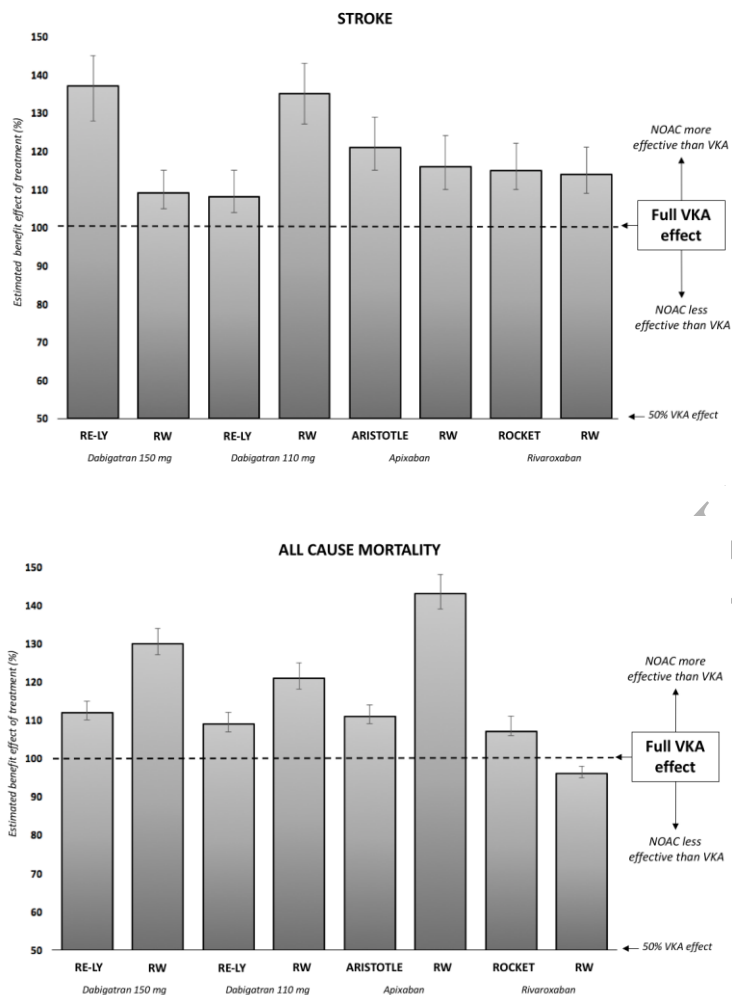
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ACCEPTED MANUSCRIPT

## FIGURE LEGENDS

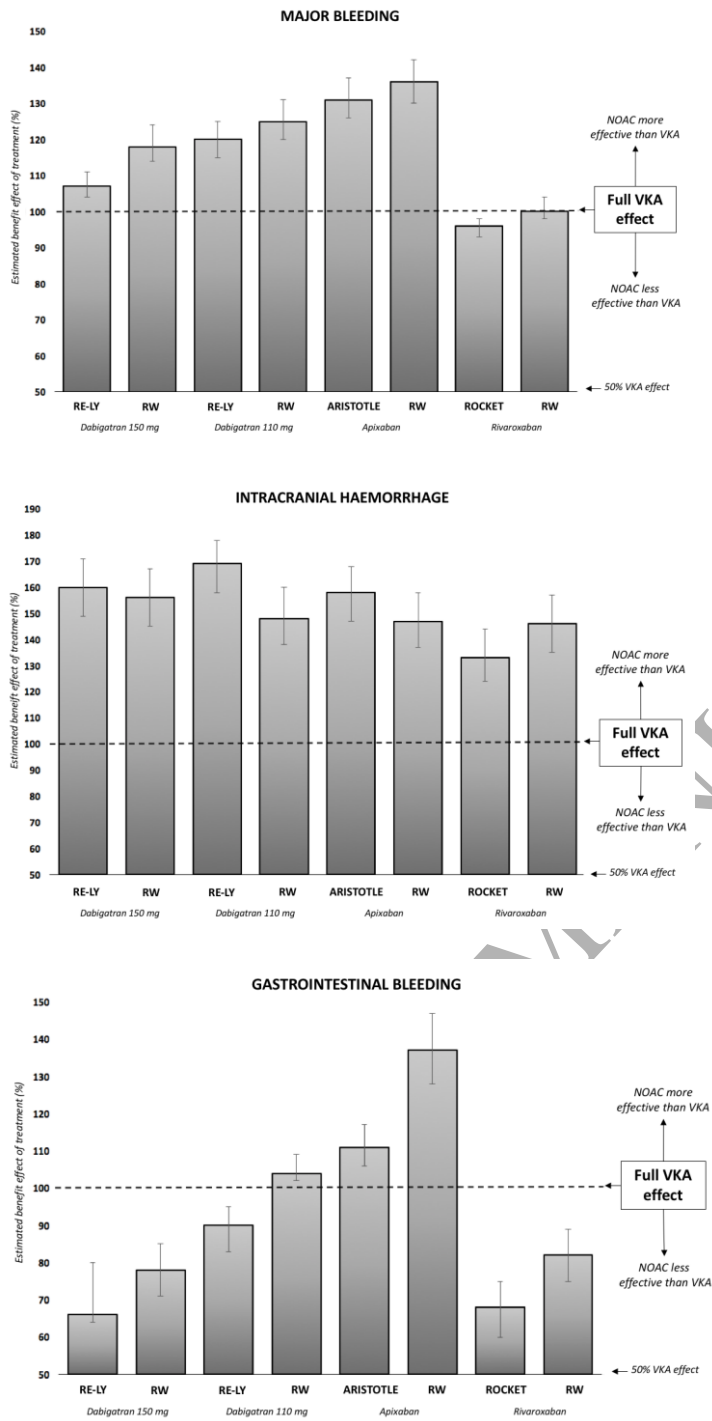


**Figure 1: Estimated effect of VKA and NOACs on the effectiveness outcomes.**

**a) Stroke**

**b) All-cause mortality**

RW: "Real-World". VKA: Vitamin K Antagonists. NOAC: non-vitamin k oral antagonist oral anticoagulants.



**Figure 2: Estimated effect of VKA and NOACs on the safety outcomes.**

**a) Major bleeding**

**b) Intracranial Haemorrhage**

**c) Gastrointestinal Bleeding**

*RW: "Real-World". VKA: Vitamin K Antagonists. NOAC: non-vitamin k oral antagonist oral anticoagulants.*

**Table 1:** Estimated effect of Dabigatran 150 mg and dabigatran 110 mg.

	Acenocoumarol	Dabigatran 150mg RE-LY	Dabigatran 150 mg RW	Acenocoumarol vs Dabigatran 150 mg RE-LY <i>p value</i>	Acenocoumarol vs Dabigatran 150 mg RW <i>p value</i>	RW vs RE-LY	NNT
<b>Stroke (n)</b>	130	83	118				
<i>% year (95%CI %/year)</i>	1.47% (1.25%-1.73%)	0.94% (0.76%-1.15%)	1.34% (1.12%-1.58%)	<b>0.001</b>	0.446	<b>0.014</b>	213
<b>All-cause mortality (n)</b>	551	485	386				
<i>% year (95%CI %/year)</i>	6.23% (5.83%-6.63%)	5.48% (5.10%-5.88%)	4.36% (4.0%-4.74%)	<b>0.041</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	56
<b>Major bleeding (n)</b>	250	233	203				
<i>% year (95%CI %/year)</i>	2.83% (2.52%-3.16%)	2.63% (2.34%-2.96%)	2.29% (2.02%-2.60%)	0.439	<b>0.027</b>	0.150	175
<b>Gastrointestinal bleeding (n)</b>	97	146	115				
<i>% year (95%CI %/year)</i>	1.10% (0.90%-1.33%)	1.65% (1.41%-1.92%)	1.30% (1.09%-1.55%)	<b>0.002</b>	0.216	0.055	-400
<b>Intracranial haemorrhage (n)</b>	78	31	34				
				<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.709	182

*% year (95%CI %/year)*    0.88% (0.71%-1.09%)    0.35% (0.25%-0.49%)    0.38% (0.28%-0.53%)

*RW: "Real-World". NNT: Number needed to treat (comparing Acenocoumarol vs Dabigatran 150 mg RW). 95% CI: 95% Confidence Interval (%/year)*

**Table 1 (continued)**

	Acenocoumarol	Dabigatran 110mg RE-LY	Dabigatran 110 mg RW	Acenocoumarol vs Dabigatran 110 mg		RW vs RE-LY	NNT
				RE-LY <i>p value</i>	Dabigatran 110 mg RW <i>p value</i>		
<b>Stroke (n)</b>	130	119	85				
<i>% year (95%CI %/year)</i>	1.47% (1.25%-1.73%)	1.35% (1.13%-1.59%)	0.97% (0.78%-1.18%)	0.486	<b>0.002</b>	<b>0.017</b>	204
<b>All-cause mortality (n)</b>	551	502	435				
<i>% year (95%CI %/year)</i>	6.23% (5.83%-6.63%)	5.67% (5.29%-6.07%)	4.92% (4.54%-6.31%)	0.131	<b>0.002</b>	<b>0.028</b>	70
<b>Major bleeding (n)</b>	250	200	188				
<i>% year (95%CI %/year)</i>	2.83% (2.52%-3.16%)	2.26% (1.99%-2.57%)	2.12% (1.86%-2.42%)	<b>0.018</b>	<b>0.003</b>	0.542	154



<b>Gastrointestinal bleeding (n)</b>	97	107	94				
<i>% year (95%CI %/year)</i>	1.10% (0.90%-1.33%)	1.21% (1.01%-1.45%)	1.06% (0.87%-1.29%)	0.483	0.828	0.359	189
<b>Intracranial haemorrhage (n)</b>	78	24	40				
<i>% year (95%CI %/year)</i>	0.88% (0.71%-1.09%)	0.27% (0.18%-0.40%)	0.45% (0.33%-0.61%)	<0.001	<0.001	0.045	161

*RW: "Real-World". NNT: Number needed to treat (comparing Acenocoumarol vs Dabigatran 110 mg RW). 95% CI: 95% Confidence Interval (%/year)*

Table 2: Estimated effect of Rivaroxaban

	Acenocoumarol	Rivaroxaban ROCKET-AF	Rivaroxaban RW	Acenocoumarol vs Rivaroxaban ROCKET <i>p value</i>	Acenocoumarol vs Rivaroxaban RW <i>p value</i>	ROCKET vs RW	NNT
<b>Stroke (n)</b>	130	111	112				
<i>% year (95%CI %/year)</i>	1.47% (1.25%-1.73%)	1.25% (1.05%-1.50%)	1.26% (1.06%-1.51%)	0.221	0.247	0.946	526
<b>All-cause mortality (n)</b>	551	507	573				
<i>% year (95%CI %/year)</i>	6.23% (5.83%-6.63%)	5.73% (5.34%-6.13%)	6.48% (6.08%-6.88%)	0.176	0.517	<b>0.046</b>	- 95
<b>Major bleeding (n)</b>	250	260	248				
<i>% year (95%CI %/year)</i>	2.83% (2.52%-3.16%)	2.94% (2.63%-3.27%)	2.80% (2.50%-3.13%)	0.657	0.928	0.594	5000
<b>Gastrointestinal bleeding (n)</b>	97	142	117				
<i>% year (95%CI %/year)</i>	1.10% (0.90%-1.33%)	1.61% (1.37%-1.87%)	1.32% (1.11%-1.57%)	<b>0.004</b>	0.171	0.120	- 363

<b>Intracranial haemorrhage (n)</b>	78	52	42				
<b>% year (95%CI %/year)</b>	0.88% (0.71%-1.09%)	0.59% (0.45%-0.77%)	0.48% (0.35%-0.64%)	<b>0.022</b>	<b>&lt;0.001</b>	0.302	384

*RW: "Real-World". NNT: Number needed to treat (comparing Acenocoumarol vs Rivaroxaban RW). 95% CI: 95% Confidence Interval (%/year).*

Table 3: Estimated effect of Apixaban

	Acenocoumarol	Apixaban ARISTOTLE	Apixaban RW	Acenocoumarol vs Apixaban ARISTOTLE <i>p value</i>	Acenocoumarol vs Apixaban RW <i>p value</i>	ARISTOTLE vs RW	NNT
<b>Stroke (n)</b>	130	103	109				
<i>% year (95%CI %/year)</i>	1.47% (1.25%-1.73%)	1.16% (0.97%-1.40%)	1.23% (1.03%-1.47%)	0.076	0.174	0.680	417
<b>All-cause mortality (n)</b>	551	490	314				
<i>% year (95%CI %/year)</i>	6.23% (5.83%-6.63%)	5.54% (5.15%-5.94%)	3.55% (3.22%-3.91%)	0.057	<0.001	<0.001	37
<b>Major bleeding (n)</b>	250	172	160				
<i>% year (95%CI %/year)</i>	2.83% (2.52%-3.16%)	1.95% (1.69%-2.23%)	1.81% (1.56%-2.09%)	0.001	<0.001	0.510	101
<b>Gastrointestinal bleeding (n)</b>	97	87	61				
<i>% year (95%CI %/year)</i>	1.10% (0.90%-1.33%)	0.98% (0.80%-1.20%)	0.69% (0.54%-0.88%)	0.461	0.004	0.033	263

<b>Intracranial haemorrhage (n)</b>	78	33	41				
<b>% year (95%CI %/year)</b>	0.88% (0.71%-1.09%)	0.37% (0.27%-0.52%)	0.46% (0.34%-0.62%)	<b>&lt;0.001</b>	<b>0.007</b>	0.352	169

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*RW: "Real-World". NNT: Number needed to treat. (comparing Acenocoumarol vs Apixaban. 95% CI: 95% Confidence Interval (%/year).*

**Table 4:** Net clinical benefit (95% confidence interval) of NOACs versus acenocoumarol.

	Dabigatran 150 mg	Dabigatran 110 mg	Rivaroxaban	Apixaban
	NCB (95%CI)	NCB (95%CI)	NCB (95%CI)	NCB (95%CI)
<b>Net Clinical benefit simplified (Singer et al.)</b>	0.88 (0.71-1.09)	1.15 (0.96-1.39)	0.87 (0.70-1.08)	0.81 (0.65-1.02)
<b>Net Clinical Benefit simplified</b>	0.82 (0.65-1.02)	1.09 (0.89-1.31)	0.76 (0.60-0.95)	0.82 (0.65-1.02)
<b>Net clinical benefit extended</b>	1.31 (1.10-1.56)	2.08 (1.82-2.38)	0.55 (0.42-0.73)	2.64 (2.34-2.96)

NBC: Net clinical benefit prevented per 100 person-years (95% confidence interval).

NCB simplified (Singer et al) was calculated as: (ischaemic stroke rate on acenocoumarol + 1.50 intracranial haemorrhage rate on acenocoumarol) - (ischaemic stroke rate on each NOAC + 1.50 intracranial haemorrhage rate on each NOAC).

NCB simplified was calculated as: (ischaemic stroke rate on acenocoumarol + 1.38 intracranial haemorrhage rate on acenocoumarol) - (ischaemic stroke rate on each NOAC + 1.38 intracranial haemorrhage rate on each NOAC).

NCB extended was calculated as: (ischaemic stroke rate on acenocoumarol + 1.38 intracranial haemorrhage rate on acenocoumarol + 1. Major bleeding rate + gastrointestinal bleeding on acenocoumarol) - (ischaemic stroke rate on each NOAC + 1.5 intracranial haemorrhage rate on each NOAC)