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Practice-derived data on non-vitamin K antagonist oral anticoagulant therapy to complement observations from randomized trials

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Anticoagulation is fundamental in the management of patients with atrial fibrillation (AF). The study aims to provide a comparative review of the major phase III randomized clinical trials (RCTs) and real-world data (RWD) from reliable, high-grade Phase IV studies that assess the efficacy and safety of non-vitamin K antagonist oral anticoagulants (NOACs) vs. vitamin K antagonists (VKAs). Observational studies based on nationwide or health insurance database records on the use of NOACs vs. VKAs in patients with AF were included. We performed a comparison of the efficacy and safety characteristics associated with NOACs vs. VKAs in RCTs and RWD. Although RCTs provide strong support for evidence-based practice, RWD may be used to reflect the broader picture of various clinical settings, provide supplementary insight and fulfil knowledge gaps. Both study types confirmed the safety and efficacy of NOACs in preventing stroke and thromboembolism in patients with AF. In comparison to VKAs, NOACs were associated with reduced risk of ischaemic events and lower rates of adverse events such as major bleeding or intracranial haemorrhage. Administration of NOACs might be associated with increased risk of dose-related gastrointestinal bleeding and myocardial ischaemic events, especially in the early treatment period after switching from VKAs. Special care should be taken in challenging clinical situations like severe renal or hepatic impairment when the treatment regimen needs to be considered individually. Randomized clinical trial and RWD studies are complementary and present comparable findings, affirming that NOACs are safe and effective for anticoagulation of patients with AF in daily clinical practice.

Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia and a major cause of cerebrovascular-related mortality and morbidity.[1,2] Hence, stroke prevention is an important focus in the management of AF.[3] Vitamin K antagonists (VKAs, mainly warfarin), have been the treatment of choice to prevent systemic thromboembolism in AF prior to the discovery of non-vitamin K antagonist oral anticoagulants (NOACs), also known as direct oral anticoagulants.[4–6] Although both groups of drugs are effective at reducing thrombo-embolic risk there is a suggestion that NOACs may be superior with regards to ease of use,

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wider therapeutic range, and less major bleeding.[7–9] As these drugs have been widely used for several years; there is emerging evidence regarding their safety profile from various registers.

In general, randomized control trials (RCTs) are accepted as the gold standard to assess the effectiveness and safety of therapeutic interventions. They often provide robust and high-quality evidence, from which guideline recommendations are derived. Nonetheless, the selection of patients in RCTs are based upon their strict inclusion and exclusion criteria and study setting. As a result, these trials may not be applicable to many patients with similar conditions who are encountered in daily clinical practice. In this regard, real-world data (RWD) provide a more accurate representation of the study population in the clinical setting. As a result, the popularity of real-world studies, as well as their importance in the world of science, have increased significantly over the last decade.[10] Despite this, there are several limitations with RWD. For example, they are reliant on information from various sources such as electronic health records, patient or disease registries, and insurance databases. Therefore, the quality of data may be variable which may result in a disparity between the findings from RCTs and real-world studies.[11,12] Consequently, it is important to integrate and analyse evidence from both sources, as RWD verifies and complements the data obtained from RCTs. When their findings are consistent, the reliability of the information provided increases significantly.[13]

Since the introduction of NOACs, several research studies, either phase III clinical trials or in the real-world setting, have been conducted on their safety and therapeutic effects compared to VKAs. These studies differ considerably in terms of methodology, research group, and results.

The purpose of this study is to perform a comparative review of the data from major phase III clinical trials and real-world evidence from reliable, high-grade Phase IV studies that assess the efficacy and safety of NOACs vs. VKAs.

Methodology

We searched PubMed for observational studies based on nationwide or health insurance database records relating to the implementation of NOACs vs. VKAs in patients with AF. We conducted a comparison of efficacy and safety outcomes associated with the use of NOACs or warfarin from the following phase III, randomized trials of patients with AF: RE-LY,[8] ROCKET-AF,[14] ARISTOTLE,[15] ENGAGE-TIMI 48,[16] and RWD or Phase IV evidence with regard to the risk of stroke or systemic embolism, ischaemic stroke, myocardial infarction, major haemorrhage, intracranial haemorrhage, gastrointestinal haemorrhage, and all-cause death (*Table 1*).

Dabigatran vs. warfarin

In light of the RE-LY study, both efficacy and safety of dabigatran were dose-dependent.[8] Undeniably, administration of high-dose dabigatran (150 mg) compared to warfarin therapy was associated with a significant reduction in the rate of stroke or systemic embolism [relative risk (RR) 0.66, 95% confidence interval (CI) 0.53–0.82; $P < 0.001$), with similar overall rate of bleeding, including major haemorrhage (RR 0.93, 95% CI 0.81–1.07; $P = 0.31$). However, the rate of gastrointestinal bleeding with high-dose dabigatran was higher compared to warfarin therapy (RR 1.50, 95% CI 1.19–1.89; $P < 0.001$) (*Table 1*).[8] In contrast, dabigatran at the dose of 110 mg was non-inferior compared to warfarin therapy in the rate of stroke or systemic embolism (RR 0.91, 95% CI 0.74–1.11; $P = 0.34$), with a significantly lower rate of bleeding, including major haemorrhage (RR 0.80, 95% CI 0.69–0.93; $P = 0.003$) (*Table 2*).[8] Other important findings in the RE-LY study were related to a numerically but non-significant increase in myocardial infarction with high-dose dabigatran, but no statistical difference in all-cause death (*Table 2*).

In support of the results above, the available RWD found dabigatran to have similar efficacy compared to warfarin but with a better safety profile.[13] Dabigatran use compared to warfarin was associated with lower risk of intracranial haemorrhage [hazard ratio (HR) 0.42, 95% CI 0.37–0.49; $P < 0.001$],[17–28] and all-cause death (HR 0.63, 95% CI 0.52–0.76; $P < 0.001$).[19,20,22,25,29,30] There was no suggestion of a higher risk of myocardial infarction with dabigatran use in five studies utilizing real-world databases.[18,19,25,31,32] Both RCTs and RWD were broadly consistent with comparable effects of dabigatran and warfarin in reducing the risk of stroke and systemic embolism[24,31,33–36] and increased risk of gastrointestinal bleeding with high-dose dabigatran (*Table 2*).[8,13,17–22,25–28]

The inconsistencies observed between the RCT and RWD are likely multifactorial.

Most of the RCTs are multicentre studies which were conducted with a predominantly international western European or American population. There was often minor participation from those in other regions. Although RWD studies are also frequently performed on large populations, they usually based on nationwide cohorts, which may or may not be ethnically diverse, and might reflect the discrepancies resulting from the specific population characteristics.

Therefore, genetic and environmental factors may account for some of the differences seen. For instance, a real-world study in an Asian cohort showed no significant disparity in the risk of gastrointestinal bleeding or myocardial infarction between those on dabigatran and warfarin.[19] Another reason for the inconsistencies may be related to inappropriate use of dosing regimens. It was previously reported that there was a frequent prescription of low-dose dabigatran among Asian patients in the real world, due to false assumptions associated with lower body size in this population.

Real-world data studies also shed light on the possibility of increased risk of gastrointestinal bleeding and myocardial infarction in patients receiving dabigatran vs. warfarin, while identifying that a switch to NOACs from VKA was associated with an initial high-risk period. This may partly be explained by the need for drug saturation and weaker attenuation of thrombin generation early on with the use of dabigatran.[18,25,27]

Table 1. Real-world data evidence on NOACs safety and efficiency

Author, year Country	Number of patients	Study design	Study groups	Findings for NOAC vs. warfarin
Larsen, 2014 Denmark	33 855 Naïve: Dabigatran: 7063 Warfarin: 14 126 Experienced: Dabigatran 4252 Warfarin 8504	Nationwide registry	Dabigatran vs. Warfarin	Highest bleeding rate in warfarin-naïve comparing to experienced users and naïve dabigatran.
Larsen, 2014, Denmark	66 198 Naïve: Dabigatran: 4818 Warfarin 8133 Experienced: Dabigatran: 3379 Warfarin: 49 868	Nationwide cohort	Patients who switched from warfarin to dabigatran vs. those who maintained on warfarin.	Switching from warfarin to dabigatran was associated with increased risk of myocardial infarction during the initial period (110 mg HR 3.01, 95% CI 1.48–6.10; 150 mg HR 2.97, 95% CI 1.31–6.73)
Sarrazin, 2014, USA	85 334 Dabigatran: 1394 Warfarin: 83 950	Nationwide observational study	Patients who switched from warfarin to dabigatran vs. those who maintained on warfarin	Increased risk of gastrointestinal bleeding in switchers from warfarin to dabigatran (HR 1.54, 95% CI 1.20–1.97)
Avgil-Tsadok, 2015, Canada	63 110 Dabigatran: 15 918 Warfarin: 47 192	Population-based	Dabigatran vs. warfarin	No difference in stroke risk (HR 1.05, 95% CI 0.93–1.19) Lower rate of intracranial bleeding (HR 0.60, 95% CI 0.50–0.76) Higher rate of gastrointestinal bleeding (HR 1.30, 95% CI 1.14–1.50)
Bouillon, 2015 France	17 410 Switchers: 6705 VKA: 10 705	Matched cohort	Patients who switched from VKAs to NOAC vs. those who maintained on VKAs	Patients who switched from VKAs to NOACs are not associated with increased risk of bleeding compared to those who maintained VKAs.
Graham, 2015 USA	134 414 Dabigatran: 67 207 Warfarin: 67 207	Retrospective cohort	Dabigatran vs. warfarin	Lower stroke risk (HR 0.80, 95% CI 0.67–0.96), lower intracranial bleeding risk (HR 0.34, 95% CI 0.26–0.46) and death (HR 0.86, 95%CI 0.77–0.96). Increased gastrointestinal bleeding risk (HR 1.28, 95% CI 1.14–1.44)
Lauffenburger, 2015 USA	64 935 Dabigatran: 21 104 Warfarin: 43 831	Retrospective cohort	Dabigatran vs. warfarin	Lower risk of ischaemic stroke or systemic embolism (HR 0.86, 95% CI 0.79–0.93), haemorrhagic stroke (HR 0.51, 95% CI 0.40–0.65) and acute myocardial infarction (HR 0.94, 95% CI 0.77–0.99) and higher risk of gastrointestinal bleeding (HR 1.11, 95% CI 1.02–1.22).
Maura, 2015 France	32 807 Dabigatran: 8443 Rivaroxaban: 4651 Warfarin: 19 713	Nationwide registry	Dabigatran vs. warfarin Rivaroxaban vs. warfarin	No significant differences between dabigatran/rivaroxaban and warfarin in bleeding or thromboembolism risk.

(continued)

Table 1. Continued

Author, year Country	Number of patients	Study design	Study groups	Findings for NOAC vs. warfarin
Seeger, 2015 USA	38 378 Dabigatran: 19 189 Warfarin: 19 189	Nationwide registry	Dabigatran vs. warfarin	No significant difference in stroke prevention Lower bleeding risk (HR 0.75, 95% CI 0.65–0.87).
Villines, 2015 USA	25 586 Dabigatran: 12 793 Warfarin: 12 793	Retrospective cohort	Dabigatran vs. warfarin	Lower stroke (HR 0.73, 95% CI 0.55–0.97), major intracranial (HR 0.49, 95% CI 0.30–0.79), urogenital (HR 0.36, 95% CI 0.18–0.74) bleeding, MI (HR 0.65, 95% CI 0.45–0.95), and death risk (HR 0.64, 95% CI 0.55–0.74).
Chan, 2016 Taiwan	19 853 Dabigatran: 9940 Warfarin: 9913	Nationwide registry	Dabigatran vs. warfarin	Lower stroke risk (HR 0.62, 95% CI 0.52–0.73) Lower rate of intracranial bleeding (HR 0.44, 95% CI 0.32–0.60) Lower rate of all-cause mortality (HR 0.45, 95% CI 0.38–0.53)
Chan, 2016 Taiwan	15 088 Dabigatran: 5921 Rivaroxaban: 3916 Warfarin: 5251	Nationwide cohort	Dabigatran vs. warfarin Rivaroxaban vs. warfarin Dabigatran vs. rivaroxaban	Lower risk of ischaemic stroke and systemic embolism (HR 0.64, 95% CI 0.49–0.83; HR 0.51, 95% CI 0.35–0.74, respectively), intracranial bleeding (HR 0.44 95% CI 0.28–0.70; HR 0.30, 95% CI 0.15–0.60, respectively) and all-cause mortality (HR 0.47, 95% CI 0.33–0.67; HR 0.40, 95% CI 0.30–0.52, respectively). No difference between dabigatran and rivaroxaban.
Coleman, 2016 USA	30 988 Rivaroxaban: 11 411 Apixaban: 4083 Warfarin: 15 494	Retrospective cohort	Rivaroxaban vs. warfarin Apixaban vs. warfarin	Lower risk of combined endpoint of ischaemic stroke or intracranial haemorrhage on rivaroxaban compared to warfarin (HR 0.61, 95% CI 0.45–0.82) Lower risk of intracranial haemorrhage on apixaban (HR 0.38, 95% CI 0.17–0.88)
Larsen, 2016 Denmark	61 678 Dabigatran: 12 701 Rivaroxaban: 7192 Apixaban: 6349 Warfarin: 35 436	Nationwide cohort	Dabigatran vs. warfarin Rivaroxaban vs. warfarin Apixaban vs. warfarin	No difference in stroke risk. Lower annual rates of ischaemic stroke or systemic embolism (3.0% vs. 3.3%) on rivaroxaban. Lower annual risk of death on apixaban (5.2%) and dabigatran (2.7%). Lower composite outcome risk on apixaban and dabigatran (3.3% vs. 2.4% vs. 5.0%, respectively).
Laliberte, 2016 Canada	18 270 Rivaroxaban: 3654 Warfarin: 14 616	Retrospective cohort	Rivaroxaban vs. warfarin	No significant differences in bleeding, systemic embolism, and composite outcomes risk.
Lip, 2016 UK	45 361 Dabigatran: 4661 Rivaroxaban: 17 801 Apixaban: 7438 Warfarin: 15 461	Retrospective cohort	Dabigatran vs. warfarin Rivaroxaban vs. warfarin Dabigatran vs. rivaroxaban	Lower bleeding risk on apixaban (HR 0.53, 95% CI 0.39–0.71) and dabigatran (HR 0.69, 95% CI 0.50–0.96). No difference between rivaroxaban and warfarin. Higher risk of major bleeding on rivaroxaban than on apixaban (HR 1.82, 95% CI 1.36–2.43)
Nishtala, 2016 New Zealand	9920 Dabigatran: 4835 Warfarin: 4835	International observational study	Dabigatran vs. warfarin	Lower any haemorrhage risk regardless of dabigatran dose (110 mg HR 0.40, 95% CI 0.31–0.52; 150 mg HR 0.29, 95% CI 0.19–0.41)

(continued)

Table 1. Continued

Author, year Country	Number of patients	Study design	Study groups	Findings for NOAC vs. warfarin
Yao, 2016 USA	152 708 Dabigatran: 28 614 Rivaroxaban: 32 350 Apixaban: 15 390 Warfarin: 76 354	Retrospective cohort	Dabigatran vs. warfarin Rivaroxaban vs. warfarin Apixaban vs. warfarin	Lower stroke risk on apixaban (HR 0.67, 95% CI 0.46–0.98). No difference on dabigatran and rivaroxaban. Lower bleeding risk on apixaban and dabigatran (HR 0.45, 95% CI 0.34–0.59 and HR 0.79, 95% CI 0.67–0.94, respectively).
Bengtson, 2017 Japan	145 666 Dabigatran: 32 918 Rivaroxaban: 3301 Warfarin: 109 447	Retrospective cohort	Dabigatran vs. warfarin and Rivaroxaban vs. warfarin in those switching from VKA and naïve patients	Lower stroke risk in dabigatran naïve vs. warfarin (HR 0.65, 95% CI 0.52–0.82) Similar risk in switchers from VKA to dabigatran (HR 1.20, 95% CI 0.95–1.51) No difference in stroke and bleeding risk between rivaroxaban and warfarin (HR 1.10, 95% CI 0.58–2.10, HR 0.40, 95% CI 0.05–3.59)
Halvorsen, 2017 Norway	32 675 Dabigatran: 7925 Rivaroxaban: 6817 Apixaban: 6506 Warfarin: 11 427	Nationwide registry	Dabigatran vs. warfarin Rivaroxaban vs. warfarin Apixaban vs. warfarin	Lower major bleeding risk in apixaban (HR 0.70, 95% CI 0.61–0.80) and dabigatran (HR 0.74, 95% CI 0.66–0.84).
Staerk, 2017 Denmark	43 299 Dabigatran: 12 613 Rivaroxaban: 5693 Apixaban: 6899 Warfarin: 18 094	Nationwide registry	Dabigatran vs. warfarin Rivaroxaban vs. warfarin Apixaban vs. warfarin	No difference in anticoagulant-naïve patients in stroke/systemic thromboembolism risk Lower intracranial bleeding risk on dabigatran (−0.34%, 95% CI −0.47 to −0.21%) and apixaban (−0.20, 95% CI −0.38 to −0.01%).
Yu, 2018 Korea	11 172 Edoxaban: 5856 Warfarin: 5856	Nationwide registry	Edoxaban vs. warfarin	Lower risk of stroke or systemic embolism with low- or high-dose edoxaban (HR 0.57, 95% CI 0.42–0.78; HR 0.44, 95% CI 0.31–0.64, respectively) Lower rate of major bleeding with low- or high-dose edoxaban (HR 0.61, 95% CI 0.43–0.85; HR 0.40, 95% CI 0.26–0.61, respectively) Lower rate of mortality with low- or high-dose edoxaban (HR 0.55, 95% CI 0.41–0.73; HR 0.43, 95% CI 0.22–0.53, respectively)
Lee, 2018 Korea	35 765 Edoxaban: 4061 Warfarin: 12 183	Nationwide registry	Edoxaban vs. warfarin	Lower risk of ischaemic stroke (HR 0.69, 95% CI 0.49–0.96), intracranial haemorrhage (HR 0.41, 95% CI 0.18–0.79), hospitalization for gastrointestinal bleeding (HR 0.60, 95% CI 0.36–0.93), hospitalization for major bleeding (HR 0.53, 95% CI 0.35–0.78), and all-cause mortality (HR 0.72, 95% CI 0.55–0.92).
Datar, 2019 USA	21 493 NOAC: 11 649 Warfarin: 9844	Retrospective observational study	NOACs vs. warfarin	Lower risk of ischaemic (HR 0.88, 95% CI 0.79–0.98) and haemorrhagic stroke (HR 0.65, 95% CI 0.46–0.92), systemic embolism (HR 0.53, 95% CI 0.43–0.65) and composite outcome (HR 0.78, 95% CI 0.71–0.86) No difference in bleeding risk.

(continued)

Table 1. Continued

Author, year Country	Number of patients	Study design	Study groups	Findings for NOAC vs. warfarin
Hohnloser, 2019	51 606 Dabigatran: 3973 Rivaroxaban: 17 333 Apixaban: 8832 Warfarin: 21 468	Retrospective observational study	Patients who discontinued NOACs treatment Switched from VKAs to NOACs Switched from NOACs to VKAs Switched from one NOAC to another	No difference in overall discontinuation rates between VKAs and NOACs and in majority were caused by occurrence of stroke, myocardial infarction, and gastrointestinal bleeding episodes.

Rivaroxaban vs. warfarin

Results from the ROCKET-AF study and RWD[18,26,33,37] were comparable with regards to the influence on the risk of stroke or systemic embolism, ROCKET-AF reported a lower risk of stroke or systemic embolism with rivaroxaban compared to warfarin using an on-treatment analysis (HR 0.79, 95% CI 0.65–0.95; $P = 0.01$ for superiority) (*Table 2*). However, the risk of stroke or systemic embolism was non-significant with a conventional intention-to-treat analysis.[14] Based on a systematic review and meta-analysis of 28 real-world studies, no significant difference was found between rivaroxaban and warfarin in terms of ischaemic stroke or systemic embolism risk (HR 0.73, 95% CI 0.52–1.04; $P = 0.13$).[13] Despite the lack of statistical difference between rivaroxaban and warfarin for the outcome of major haemorrhage[21,26,29,31,33,35,37,38] either in the RCT (HR 1.04, 95% CI 0.90–1.20; $P = 0.58$) or RWD (HR 1.00, 95% CI 0.92–1.08; $P = 0.92$), both the RCT and RWD concur that rivaroxaban had a significant advantage over warfarin in lowering the risk of intracranial haemorrhage (RCT: HR 0.67, 95% CI 0.47–0.93; $P = 0.02$).[13,14,18,21,24,26,33,37,39] Both types of studies consistently found no significant difference between rivaroxaban and warfarin therapy in the risk of myocardial infarction[18,31] and all-cause death[29,33] (*Table 2*). Moreover, the use of rivaroxaban was associated with a higher risk of gastrointestinal haemorrhage compared to warfarin[18,26,33,37] (*Table 3*).

Apixaban vs. warfarin

Most studies on apixaban were positive with a favourable risk–benefit ratio.[13,24,26], Moreover, in the RWD, the analysed outcomes (stroke, all-cause mortality, major haemorrhage, intracranial, and gastrointestinal bleeding rates), were even more beneficial than in the RCT.[13,15] In the ARISTOTLE study, compared to warfarin, apixaban significantly reduced the risk of stroke or systemic embolism (HR 0.79, 95% CI 0.66–0.95; $P = 0.01$) and also decreased the risk of bleeding, including major and intracranial haemorrhage (HR 0.69, 95% CI 0.60–0.80; $P < 0.001$; HR 0.42, 95% CI 0.30–0.58; $P < 0.001$, respectively) (*Table 3*). There was no difference between apixaban and warfarin in the risk of gastrointestinal bleeding in the ARISTOTLE trial (HR 0.89, 95% CI 0.70–1.15; $P = 0.37$), while the risk of GI bleeding was significantly lower with apixaban in the RWD (HR 0.63, 95% CI 0.42–0.95; $P = 0.03$).[21,29] Similar findings that were reported in the RCT for other parameters were observed in the RWD, which supports and confirms the superiority of apixaban over warfarin (*Table 4*).[21,24,26,29,38,39] Another important finding in the RCT, which was consistent in real-world studies was the significant reduction in all-cause death with apixaban compared to warfarin (RCT: HR 0.89, 95% CI 0.80–0.998; $P = 0.047$; RWD: HR 0.65, 95% CI 0.56–0.75; $P < 0.00001$).[15,29] Additionally, apixaban therapy in ARISTOTLE was associated with a lower rate of discontinuation compared to warfarin (25.3% vs.

Table 2. Dabigatran in comparison to VKA

Event \ Dose (mg)	Real-world data studies[13]	RE-LY trial[8]	
	Dabigatran dose adjusted	Dabigatran 110 mg	Dabigatran 150 mg
Stroke or systemic embolism	No statistical difference (HR 0.93, 95% CI 0.77-1.14; $P = 0.21$)	No statistical difference (RR 0.91,95% CI 0.74-1.11 $P = 0.34$)	Lower rate (RR 0.66, 95% CI 0.53-0.82; $P < 0.001$
Ischaemic stroke	No statistical difference (HR 0.96, 95% CI 0.80-1.16; $P = 0.69$)	No statistical difference (RR 1.11, 95% CI 0.89-1.40; $P = 0.35$)	Lower rate (RR 0.76, 95% CI 0.60-0.98; $P = 0.03$)
Myocardial infarction	No statistical difference (HR 0.96, 95% CI 0.77-1.21; $P = 0.74$)	Higher rate (RR 1.35, 95% CI 0.98-1.87; $P = 0.07$)	Higher rate (RR 1.38, 95% CI 1.00-1.91; $P = 0.048$)
All-cause mortality	Lower risk (HR 0.63, 95% CI 0.52-0.76; $P < 0.001$)	No statistical difference (RR 0.91, 95% CI 0.80-1.03; $P = 0.13$)	No statistical difference (RR 0.88, 95% CI 0.77-1.00; $P = 0.051$)
Major haemorrhage	No statistical difference (HR 0.83, 95% CI 0.65-1.05; $P = 0.12$)	Lower rate (RR 0.80, 95% CI 0.69-0.93; $P = 0.003$)	No statistical difference (RR 0.93, 95% C; 0.81-1.07; $P = 0.31$)
Intracranial haemorrhage	Lower risk (HR 0.42, 95% CI 0.37-0.49; $P < 0.001$)	Lower rate (RR 0.31, 95% CI 0.20-0.47; $P < 0.001$)	Lower rate (RR 0.40, 95% CI 0.27-0.60; $P < 0.001$)
Gastrointestinal haemorrhage	Higher risk (HR 1.20, 95% CI 1.06-1.36; $P = 0.003$)	No statistical difference (RR 1.10, 95% CI 0.86-1.41; $P = 0.43$)	Higher rate (RR 1.50, 95% CI 1.19-1.89; $P < 0.001$)

RE-LY, The Randomized Evaluation of Long-Term Anticoagulation Therapy.

Table 3. Rivaroxaban in comparison to VKA

Event \ Dose (mg)	Real-world data studies[13]	ROCKET AF trial[14]
	Rivaroxaban dose adjusted	Rivaroxaban 20 mg
Stroke or systemic embolism	No statistical difference (HR 0.87, 95% CI 0.71-1.07; $P = 0.08$)	Lower rate (HR 0.79, 95% CI 0.65-0.95; $P = 0.02$ for superiority)
Ischaemic stroke	No statistical difference (HR 0.89, 95% CI 0.76-1.04; $P = 0.13$)	No statistical difference (HR 0.94, 95% CI 0.75-1.17; $P = 0.581$)
Myocardial infarction	No statistical difference (HR 1.02, 95% CI 0.54-1.89; $P = 0.96$)	No statistical difference (HR 0.81, 95% CI 0.63-1.06; $P = 0.121$)
Death	No statistical difference (HR 0.67, 95% CI 0.35-1.30; $P = 0.24$)	No statistical difference (HR 0.85, 95% CI 0.70-1.02; $P = 0.073$)
Major haemorrhage	No statistical difference (HR 1.00, 95% CI 0.92-1.08; $P = 0.92$)	No statistical difference (HR 1.04, 95% CI 0.90-1.20; $P = 0.58$)
Intracranial haemorrhage	Lower rate (HR 0.64, 95% CI 0.47-0.86; $P = 0.004$)	Lower rate (HR 0.67, 95% CI; 0.47-0.93; $P = 0.02$)
Gastrointestinal haemorrhage	Higher rate (HR 1.24, 95% CI 1.08-1.41; $P = 0.002$)	Higher rate (HR 1.47, $P < 0.001$)

ROCKET AF, The Rivaroxaban Once Daily Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

27.5%, $P < 0.001$, respectively).[15] Unlike RCTs, discontinuation rates are rarely analysed in the RWD. From the limited data available, a study on 51 000 patients with AF showed no relevant differences in discontinuation rates between the use of apixaban and warfarin.[40] However, a separate real-world study demonstrated higher adherence to apixaban compared to warfarin in the long-term.[41]

Edoxaban vs. warfarin

There are more real-world or Phase IV evidence on the effects of edoxaban compared to other NOACs. There are two approved edoxaban dose regimens, based on patients individual characteristic: high-dose edoxaban regimen (60 mg) and reduced to 30 mg (low-dose edoxaban regimen) used in patients when estimated creatinine clearance

Table 4. Apixaban in comparison to VKA

Event \ Dose (mg)	Real-world data studies[13]	ARISTOTLE trial[15]
	Apixaban dose adjusted	Apixaban 5 mg
Stroke or systemic embolism	Lower rate (HR 0.67, 95% CI 0.46-0.98; $P = 0.04$)	Lower rate (HR 0.79, 95% CI 0.66-0.95; $P = 0.01$)
Ischaemic stroke	No statistical difference (HR 0.95, 95% CI 0.75-1.19; $P = 0.65$)	Lower rate (HR 0.92, 95% CI 0.74-1.13; $P = 0.42$)
Myocardial infarction	Not available	No statistical difference (HR 0.88, 95% CI 0.66-1.17; $P = 0.37$)
Death	Lower rate (HR 0.65, 95% CI 0.56-0.75; $P < 0.00001$)	Lower rate (HR 0.89, 95% CI 0.80-0.998; $P = 0.047$)
Major haemorrhage	Lower rate (HR 0.55, 95% CI 0.48-0.63; $P < 0.00001$)	Lower rate (HR 0.69, 95% CI 0.60-0.80; $P < 0.001$)
Intracranial haemorrhage	Lower rate (HR 0.45, 95% CI 0.31-0.63; $P < 0.00001$)	Lower rate (HR 0.42, 95% CI 0.30-0.58; $P < 0.001$)
Gastrointestinal haemorrhage	Lower rate (HR 0.63, 95% CI 0.42-0.95; $P = 0.03$)	No statistical difference (HR 0.89, 95% CI 0.70-1.15; $P = 0.37$)

ARISTOTLE, Apixaban for reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation.

(CrCl) of 30–50 mL/min, a body weight of 60 kg, or the concomitant use of specific PgP inhibitors.

In general, the RWD are consistent with the ENGAGE AF-TIMI 48 study, supporting the better safety profile of edoxaban compared to warfarin. In the RCT, both edoxaban treatment regimens (low- or high-dose) were non-inferior in comparison to warfarin for stroke prevention, but the study placed a greater emphasis on the higher efficiency in stroke prevention with use of the higher, recommended dose. Moreover, both doses of edoxaban were associated with reduced adverse events including major bleeding, cardiovascular death, and composite outcome (defined as stroke/systemic embolism or cardiovascular death) compared to warfarin.[42] The aforementioned results were broadly consistent with those from RWD studies but also indicated the efficacy of the lower edoxaban dose in stroke and systemic embolism prevention and safety in terms of reducing bleeding adverse events (*Table 5*). Edoxaban was reported to be superior compared to warfarin in terms of efficacy and safety in real-world studies conducted in an Asian population.[43,44] In comparison to warfarin, the rate of ischaemic stroke in isolation in the RCT was higher with low-dose edoxaban (HR 1.41, 95% CI 1.19-1.67; $P < 0.001$) but similar with high-dose edoxaban (HR 1.00, 95% CI 0.83-1.19; $P = 0.97$).[42] The reduced efficacy of low-dose edoxaban was not observed in real-world studies.[43,44] There were further discrepancies shown between the results from the RCT and RWD for edoxaban. For example, the rate of myocardial infarction was lower for both low- and high-dose edoxaban compared to warfarin in the RWD (HR 0.58, 95% CI 0.35–0.98 and HR 0.34, 95% CI 0.15–0.81, respectively). Meanwhile, the RCT reports no benefit of edoxaban in this regard (*Table 4*).[42-44] Furthermore, the risk of gastrointestinal haemorrhage was increased with high-dose edoxaban compared to warfarin in the RCT (HR 1.23, 95% CI 1.02-1.50; $P = 0.03$), whilst this risk was found to be lower with both low- and high-dose edoxaban in the RWD.[43,44] In terms of the risk of major bleeding, intracranial haemorrhage, and death, both RCT and RWD appear broadly similar with reduced risk in edoxaban compared to warfarin therapy (*Table 5*).[42-44]

Non-vitamin K antagonist oral anticoagulants as a group

When considering the individual NOACs as a group, despite minor differences in the effects of each drug, mainly in terms of gastrointestinal haemorrhage and major bleeding, they are all as effective as warfarin in preventing stroke or systemic embolism but with a lower risk of intracranial bleeding. This was a consistent finding observed throughout all the major studies, in both the RCTs and RWD. Overall, NOACs were characterized by a favourable risk-benefit ratio due to a better safety profile compared to warfarin. An additional advantage of NOACs over warfarin based on comprehensive comparisons of real-world outcomes in patients with AF was the substantial reduction in healthcare costs.[45] Moreover, expenditure for all-cause hospitalization and outpatient medical care were lower for NOACs compared with warfarin.[46] In terms of practicality and patient satisfaction, a further advantage of NOACs was related to better patients adherence due to ease of use with no need for frequent laboratory monitoring or dose adjustments. Furthermore, NOACs were proven to have fewer interactions with food and other medications compared to warfarin.[47]

Several analyses have assessed whether the superiority of NOACs over warfarin was dependent on anticoagulation control with warfarin therapy (i.e. time-in-therapeutic range).[48,49] Nonetheless, well-managed warfarin therapy was proven to be efficient and associated with low risk of adverse events,[48] NOAC medication seems to have better adherence, and therefore, in general, are associated with better outcomes.[49] Hence, it appears that NOACs may be a better option for patients with difficulties in maintaining adequate anticoagulation control with warfarin.[50-52] Also

Table 5. Edoxaban in comparison to VKA

Event \ Dose (mg)	Real-world data studies[43]		ENGAGE AF-TIMI 48 trial[42]
	Edoxaban 60 mg	Edoxaban 30 mg	Edoxaban 60/30 mg
Stroke or systemic embolism	Lower rate (HR 0.44, 95% CI 0.31-0.64; $P < 0.05$)	Lower rate (HR 0.57, 95% CI 0.42-0.78; $P < 0.05$)	No statistical difference (HR 1.13, 95% CI 0.97-1.31; $P = 0.12$)
Ischaemic stroke	No statistical difference[44] (HR 0.67, 95% CI 0.36-1.15; $P = 0.18$)	No statistical difference[44] (HR 0.73, 95% CI 0.48-1.08; $P = 0.13$)	No statistical difference (HR 1.00, 95% CI 0.83-1.19; $P = 0.97$)
Myocardial infarction	Lower rate (HR 0.34, 95% CI 0.15-0.81; $P < 0.05$)	Lower rate (HR 0.58, 95% CI 0.35-0.98; $P < 0.05$)	No statistical difference (HR 0.94, 95% CI 0.74-1.19; $P = 0.60$)
Death	Lower rate (HR 0.34, 95% CI 0.15-0.81; $P < 0.05$)	Lower rate (HR 0.55, 95% CI 0.41-0.73; $P < 0.05$)	Lower rate (HR 0.92, 95% CI 0.83-1.01; $P = 0.08$)
Major haemorrhage	Lower rate (HR 0.40, 95% CI 0.26-0.61; $P < 0.05$)	Lower rate (HR 0.61, 95% CI 0.43-0.85; $P < 0.05$)	Lower rate (HR 0.80, 95% CI 0.71-0.91; $P < 0.001$)
Intracranial haemorrhage	Lower rate (HR 0.35, 95% CI 0.15-0.83; $P < 0.05$)	Lower rate (HR 0.44, 95% CI 0.24-0.82; $P < 0.05$)	Lower rate (HR 0.47, 95% CI 0.34-0.63; $P < 0.001$)
Gastrointestinal haemorrhage	Lower rate (HR 0.42, 95% CI 0.26-0.69; $P < 0.05$)	Lower rate (HR 0.59, 95% CI 0.40-0.88; $P < 0.05$)	Higher rate (HR 1.23, 95% CI 1.02-1.50; $P = 0.03$)

ENGAGE AF-TIMI 48, The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48.

some of NOACs such as Apixaban appear to be safer in terms of gastrointestinal bleeding risk. Nonetheless, there are some considerations with the use of NOACs. Importantly, there is limited evidence to support their use in patients with a severe reduction in kidney function. In fact, this group of patients were systematically excluded from RCTs studying the effects of NOACs in comparison to warfarin. Therefore, the efficacy and safety profile of these drugs in patients with severe kidney impairment remains uncertain. A large meta-analysis of cohort studies showed that among patients with AF and concomitant severe kidney impairment, the use of apixaban was associated with a lower risk of major bleeding and similar risk of thromboembolism comparing to warfarin.[53] Interestingly, however, the benefits of warfarin in reducing stroke risk among these patients have not been established.[54,55] Therefore, the comparable thrombo-embolic risk in those receiving apixaban and warfarin in the previous trial may be due to the lack of effectiveness of both these drugs.

Another issue is the possibility of use NOACs as an alternative to VKAs in patients with valvular heart disease and prosthetic valve replacement, namely those with biological and mechanical prosthetic valves (MPV). Mechanical prosthetic valves are considered as more thrombogenic than biological prosthetic valves (BPV), hence the standard therapeutic option is long-term anticoagulation with VKAs as NOACs are currently not recommended in patients with MPV.[56]

In many analysis, NOACs are considered as alternatives to VKAs in patients with BPV.[56-58] No significant differences were found between NOACs and VKAs in terms of primary outcomes including stroke or systemic embolism, all-cause stroke, ischaemic stroke, myocardial infarction, all-cause death, and cardiovascular death as well as its safety regarding occurrence of bleeding (major bleeding, intracranial haemorrhage, and gastrointestinal haemorrhage).[59] That indicates that NOACs, mainly edoxaban and apixaban are safe and effective also in patients with AF and prior BPV replacement or valve repair.[60,61]

Overall, further studies are needed to understand the mechanism contributing to thrombo-embolic risk in AF and kidney impairment.

Conclusions

Randomized controlled trials are the cornerstone for determining the safety and efficacy of novel treatments while RWD evaluates the results from the implementation of this treatment in a broader range of clinical environments. Both study types are complementary to one another and

should be used to provide a better understanding of the management of complex conditions such as AF. By comparing the RCTs and RWD on NOACs, we revealed a significant agreement between the results that demonstrate the efficacy and safety profile with this group of medications. Given the broad range of treatment options available for patients with AF, it is important that as clinicians, we are able to offer individualized treatment options.

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Erratum

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Erratum to: Practice-derived data on Non-vitamin K antagonist Oral Anticoagulant (NOAC) therapy to complement observations from randomized trials [*European Heart Journal Supplements* 2020;22:I1–I12, doi:10.1093/eurheartj/suaa100]

In the originally published version of this manuscript, several errors were noted and listed in this erratum.

Upon the original publication, there was an error under the "Edoxaban vs. warfarin" heading. The text in the first paragraph should read: "body weight of 60 kg, or the concomitant use of specific PgP inhibitors." instead of "body weight of 60 kg, or the concomitant use of verapamil or quinidine.".

Upon the original publication, there were two errors in Table 5, Edoxaban in comparison to VKA. The errors are as follows:

The first column heading under "ENGAGE AF-TIMI 48 trial[42]" should read: "Edoxaban 60/30 mg" instead of "Edoxaban 60 mg".
Table 5, included column Edoxaban 30mg" under the heading: "ENGAGE AF-TIMI 48 trial[42]". This has been deleted.

These have now been corrected online. The publisher apologises for the errors.