Novel Oral Anticoagulants – Do Real-world Data Support our Expectations?

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During the last 10 years, four novel oral anticoagulants (NOACs; dabigatran, rivaroxaban, apixaban and edoxaban) were introduced as an alternative to vitamin K antagonists (VKAs; e.g. warfarin), which have been the gold standard for oral anticoagulation for many decades. Atrial fibrillation is one of the most important reasons for an ischaemic stroke. Considering the high lifetime prevalence of atrial fibrillation, a significant proportion of the population will have the indication for oral anticoagulation in order to prevent strokes. Randomised controlled trials comparing NOACs to the gold-standard VKAs have been performed and published with convincing results. Additionally, real-world data from observational and retrospective studies have been released to see whether they meet our expectations of NOACs and which further challenges, concerning individualisation for special patient groups and high-risk collectives, arise.

Atrial fibrillation (AF) is one of the most common cardiac diseases in elderly patients and is associated with increased morbidity and mortality. It is of great importance to treat patients with AF with oral anticoagulants (OACs) to prevent ischaemic strokes, which represents the most relevant complication of AF. For many decades, vitamin K antagonists (VKAs) have been the only available OAC. By increasing use of OACs in patients with AF from the early 90s until the early 2000s, rates of ischaemic stroke have decreased significantly, without a clear rise of haemorrhagic strokes.[1] Nevertheless, the concerns for cerebral bleeding complications are one major reason for the omission of anticoagulation in patients with AF.

During the last decade, four novel non-vitamin-K oral anticoagulants (NOACs), sometimes referred to as direct oral anticoagulants (DOACs), have been introduced and investigated in patients with AF: dabigatran, rivaroxaban, apixaban and edoxaban. Convincing randomised controlled trials (RCTs) comparing NOACs to VKAs have shown at least a similar efficacy with a comparable to reduced bleeding risk.[2–5] Patient adherence was expected to be higher in a drug that does not have to be dose adjusted by regular international normalised ratio (INR) controls and that is not dependent on vitamin K intake. These results have facilitated the hope for reducing ischaemic strokes by increasing the proportion of patients with a regular intake of anticoagulants.

As NOACs have now been available for a couple of years, data from real-world settings and comparisons to the initial RCTs are available. The aim of this review is to address whether these real-world data support our expectations of NOACs.

Randomised controlled trials

RCTs have been conducted to compare NOACs to the gold-standard medication of VKAs; bleeding risk and ischaemic events have been compared for stroke prevention in patients with AF being at risk of stroke represented by the CHADS2 or CHA2DS2-VASc score. Connolly et al. performed an RCT comparing dabigatran (150 mg twice daily [BID] and 110 mg BID) to the VKA warfarin (the RE-LY-trial).[2] ROCKET-AF, an RCT by Patel et al., compared rivaroxaban (20 mg once daily [OD]) to warfarin,[4] and in the ARISTOTLE trial by Granger et al., apixaban (5 mg BID) was compared to warfarin.[3] The fourth NOAC, edoxaban, was compared in two dosages (60 mg and 30 mg) to warfarin in the ENGAGE-TIMI 48 trial by Giugliano et al.[5]

Overview of registries on novel oral anticoagulant use in atrial fibrillation

RCTs represent the highest quality of medical evidence for testing a specific treatment or medication while minimising the risk of a bias by confounders or systematic differences between treatment groups. However, the collected data might not be representative for a real-world setting where multiple concomitant diseases, medications and questionable compliance can all impact the effectiveness of therapy. In the above-mentioned trials, a patient population is present, which

might be distinct from the type of patients encountered in daily clinical routine. A patient with AF might be healthy, but another patient may be elderly with chronic illnesses, multimorbidity and indication for multiple medications. Therefore, real-world observational studies can either endorse the results of the RCT and strengthen their validity remarkably, or question them, cumulating in the need for a repetition of the RCT. The results of real-world data studies are therefore much anticipated.

Graham et al. published real-world data of 67,207 Medicare patients on dabigatran with an intake of either 150 mg or 75 mg BID that were compared to the same number of patients on warfarin.[6] Patients >65 years old with AF and without any other reason for OAC (such as pulmonary embolism or thrombosis), were included. Propensity score matching was used to ensure comparable groups. Interestingly, 16% of patients received a reduced dosage of 75 mg BID, that is not approved in Europe for this indication. Moreover, the trial lacked laboratory data on creatinine clearance, so it remains uncertain whether patients treated with this lower dosage actually had severe renal insufficiency.

Yao et al. performed a retrospective analysis of privately insured and Medicare Advantage patients in the USA and compared 14,307 patients on dabigatran, 7,695 patients on apixaban and 16,175 on rivaroxaban each to the same number of patients on warfarin.[7] Adult patients with non-valvular AF and OAC were included into this analysis. Of note, 10% of patients in the apixaban group and 16% in the dabigatran group had a CHA2DS2-VASc score of 0 and 1, respectively, and therefore no clear indication for OACs. The follow-up of all patients was relatively short with a mean duration of 0.5–0.7 years.

Coleman et al. published the results of the REVISIT-US study in 2016.[8] This was a retrospective study using a USA Market scan database to compare 11,411 rivaroxaban users and 4,083 apixaban users each to the same number of warfarin users by a 1:1 propensity score matching. Patients ≥18 years with non-valvular AF and a CHA2DS2-VASc score ≥2, were included. In this cohort, 17.5% of rivaroxaban and 15.5% of apixaban patients received a reduced dosage (15 mg rivaroxaban OD or 2.5 mg apixaban BID).

In a meta-analysis by Ntaios et al., all high-quality, retrospective, real-world studies were summarised, including 136,221 patients on rivaroxaban, 606,855 patients of dabigatran and 66,482 patients on apixaban.[9] As endpoint definitions differed between the published studies, a direct comparison of all included patients was difficult.

With respect to edoxaban, published real-world data were sparse until now. The results of the ongoing observational international study ETNA-AF,[10] regarding real-world data on edoxaban, are much awaited. It is hoped that this study will confirm findings of a nationwide Korean observational study by Yu et al., that investigated a limited number of 2,840 patients on high-dose edoxaban (60 mg) and 3,016 patients on low-dose edoxaban (30 mg) and compared them each to a propensity score matched VKA group.[11]

Overview of similarities and differences of randomised controlled trials and real-world data with respect to endpoints

Table 1 summarises the results of the RCTs and compares them to available real-world data. In the following paragraphs, each endpoint is described separately.

Stroke and systemic embolism

In the RE-LY trial, dabigatran 150 mg was shown to reduce the rate of stroke and systemic embolism significantly, while dabigatran 110 mg did not show a significant reduction, when compared to warfarin.[2] In the observational trial by Yao et al. and the meta-analysis by Ntaios et al., dabigatran did not lower the incidence of stroke and systemic embolism significantly.[7, 9] For apixaban, a significant reduction of stroke and systemic embolism was shown, when compared to warfarin in the ARISTOTLE trial.[3] This finding was confirmed in the observational trial by Yao et al. and the meta-analysis by Ntaios et al.[7,9] In the ROCKET-AF trial, non-inferiority for rivaroxaban compared to warfarin was shown concerning stroke or systemic embolism.[4] In the observational trial by Yao et al. and the meta-analysis by Ntaios et al., no significant reduction of stroke and systemic embolism could be shown.[7,9] This specific endpoint was not tested in the ENGAGE-AF-TIMI trial,[5] but in the nationwide Korean study by Yu et al., a significant reduction of stroke and systemic embolism events was observed in edoxaban-treated patients compared to VKA.[11]

Ischaemic stroke

In the RE-LY trial a significant reduction of ischaemic stroke was observed for dabigatran 150 mg; whereas there was no significant reduction in ischaemic stroke for dabigatran 110 mg when compared to warfarin.[2] In the Medicare data analysis by Graham et al., a significant reduction of stroke was shown in the dabigatran group, while in the observational trial by Yao et al. and the meta-analysis by Ntaios et al., no significant difference could be observed.[6,7,9] For apixaban and rivaroxaban, neither in the ARISTOTLE trial (or the ROCKET-AF trial, respectively), nor in the observational trial by Yao et al. and the meta-analysis by Ntaios et al. reported a significant reduction of ischaemic stroke.[3,4,7,9] In the ENGAGE-AF-TIMI trial, ischaemic strokes occurred significantly more often in patients treated with edoxaban 30 mg when compared to warfarin.[5] For the 60 mg dosage group of edoxaban there was no difference.

Haemorrhagic stroke

The incidence of haemorrhagic strokes was significantly reduced in dabigatran (both dosages) when compared to warfarin in the RE-LY trial.[2] This was confirmed in the observational trial by Graham et. al, but not by Yao et al., where no significant reduction could be observed.[6,7] In the ARISTOTLE trial, as well as in the observational trial by Yao et al., haemorrhagic strokes occurred significantly less often in patients treated with apixaban when compared to warfarin.[2,7] Additionally, for rivaroxaban, a significant reduction of haemorrhagic strokes could be shown in the ROCKET-AF trial, which was not confirmed by the observational trial by Yao et al.[4,7] The ENGAGE-AF-TIMI trial showed a significant reduction of haemorrhagic strokes in patients on edoxaban, independent of dosage.[5]

Cerebral bleeding

Cerebral bleeding rates were significantly lower in patients on dabigatran (both dosages) when compared to warfarin in the RE-LY trial.[2] This was confirmed in the real-world observational data by Graham et al. and Yao et al., as well as in the meta-analysis by Ntaios et al.[6,7,9] Likewise, for apixaban, rivaroxaban and edoxaban cerebral bleeding rates were reduced significantly in the ARISTOTLE, ROCKET-AF and ENGAGE-AF-TIMI trials when compared to warfarin,[3–5] which was confirmed in the observational study by Yao et al. and the meta-analysis by Ntaios et al., for apixaban and rivaroxaban, and the nationwide Korean study by Yu et al. for edoxaban.[7,9,11]

Table 1: Outcomes of randomised controlled trials and comparison to real-world data

Dabigatran 110 mg versus warfarin, RE-LY RCT[2]			
Outcome	Relative risk (95% CI)	p-value	
Stroke rate			
Stroke or SE	0.91 (0.74–1.11)	0.34	
Ischaemic	1.11 (0.89–1.40)	0.35	
Haemorrhagic	0.31 (0.17–0.56)	<0.001	
Bleeding rate			
Cerebral bleeding	0.31 (0.20–0.47)	<0.001	
Major bleeding	0.80 (0.69–0.93)	0.003	
GI bleeding	1.10 (0.86–1.41)	0.43	
Mortality			
Cardiovascular death	0.90 (0.77–1.06)	0.2	
All-cause death	0.91 (0.80–1.03)	0.13	
Dabigatran 150 mg versus warfarin, RE-LY RCT[2]			
Outcome	Relative risk (95% CI)	p-value	
Stroke rate			
Stroke or SE	0.66 (0.53–0.82)	0.001	
Ischaemic	0.76 (0.60–0.98)	0.03	
Haemorrhagic	0.26 (0.14–0.49)	<0.001	
Bleeding rate			
Cerebral bleeding	0.40 (0.27–0.60)	<0.001	
Major bleeding	0.93 (0.81–1.07)	0.31	
GI bleeding	1.50 (1.19–1.89)	<0.001	
Mortality			
Cardiovascular death	0.85 (0.72–0.99)	0.04	
All-cause death	0.88 (0.77–1.00)	0.051	
Dabigatran versus warfarin, real-world data[6,7,9]			
Outcome	Relative risk (95% CI)	p-value	Corresponds to RCT?
Stroke rate			
Stroke or SE			
Graham et al.[6]	NR	NR	
Yao et al.[7]	0.98 (0.76–1.26)	0.88	Yes, for 110 mg in RCT
Ntaios et al.[9]	0.93 (0.77–1.14)	0.50	Yes, for 110 mg in RCT
Ischaemic			
Graham et al.[6]	0.80 (0.67–0.96)	0.02	Yes, for 150 mg in RCT
Yao et al.[7]	1.06 (0.79–1.42)	0.70	Yes, for 110 mg in RCT
Ntaios et al.[9]	0.96 (0.80–1.16)	0.69	Yes, for 110 mg in RCT
Haemorrhagic			
Graham et al.[6]	0.33 (0.24–0.47)	<0.001	Yes, for both doses
Yao et al.[7]	0.56 (0.30–1.04)	0.07	Significance in RCT
Ntaios et al.[9]	NR		
Bleeding rate			
Cerebral bleeding			
Graham et al.[6]	0.34 (0.26–0.46)	<0.001	Yes, for both doses
Yao et al.[7]	0.36 (0.23–0.56)	<0.001	Yes, for both doses
Ntaios et al.[9]	0.42 (0.37–0.49)	<0.00001	Yes, for both doses
Major bleeding			
Graham et al.[6]	0.97 (0.88–1.07)	0.50	Yes, for 150 mg in RCT
Yao et al.[7]	0.79 (0.67–0.94)	<0.01	Yes, for 110 mg in RCT
Ntaios et al.[9]	0.83 (0.65–1.05)	0.12	Yes, for 150 mg in RCT

Table 1: Cont.

GI bleeding			
Graham et al.[6]	1.28 (1.14–1.44)	<0.001	Yes, for 150 mg in RCT
Yao et al.[7]	1.03 (0.84–1.26)	0.78	Yes, for 110 mg in RCT
Ntaios et al.[9]	1.20 (1.06–1.36)	0.003	Yes, for 150 mg in RCT
Mortality			
Cardiovascular death			
Graham et al.[6]	0.86 (0.77–0.96)	0.006	No significance in RCT, but same trend
Yao et al.[7]	NR	NR	
Ntaios et al.[9]	NR	NR	
All-cause death			
Graham et al.[6]	NR	NR	
Yao et al.[7]	NR	NR	
Ntaios et al.[9]	0.63 (0.52–0.76)	<0.00001	No significance in RCT, but same trend
Apixaban versus warfarin, ARISTOTLE RCT[3]			
Outcome	Relative risk (95% CI)	p-value	
Stroke rate			
Stroke or SE	0.79 (0.66–0.95)	0.01	
Ischaemic	0.92 (0.74–1.13)	0.42	
Haemorrhagic	0.51 (0.35–0.75)	<0.001	
Bleeding rate			
Cerebral bleeding	0.42 (0.30–0.58)	<0.001	
Major bleeding	0.69 (0.60–0.80)	<0.001	
GI bleeding	0.89 (0.70–1.15)	0.037	
Mortality			
Cardiovascular death	NR	NR	
All-cause death	0.89 (0.80–0.998)	0.047	
Apixaban versus warfarin, real-world data[7,9]			
Outcome	Relative risk (95% CI)	p-value	Corresponds to RCT?
Stroke rate			
Stroke or SE			
Yao et al.[7]	0.67 (0.46–0.98)	0.04	Yes
Ntaios et al.[9]	NR	NR	
Ischaemic			
Yao et al.[7]	0.83 (0.53–1.29)	0.40	Yes
Ntaios et al.[9]	0.95 (0.75–1.19)	0.65	Yes
Haemorrhagic			
Yao et al.[7]	0.35 (0.14–0.88)	0.03	Yes
Ntaios et al.[9]	NR	NR	
Bleeding rate			
Cerebral bleeding			
Yao et al.[7]	0.24 (0.12–0.50)	<0.001	Yes
Ntaios et al.[9]	0.45 (0.31–0.63)	<0.00001	Yes
Major bleeding			
Yao et al.[7]	0.45 (0.34–0.59)	<0.001	Yes
Ntaios et al.[9]	0.55 (0.48–0.63)	<0.00001	Yes
GI bleeding			
Yao et al.[7]	0.51 (0.37–0.70)	<0.001	Yes
Ntaios et al.[9]	0.63 (0.42–0.95)	0.03	Yes
Mortality			
Cardiovascular death			
Yao et al.[7]	NR	NR	
Ntaios et al.[9]	NR	NR	

Table 1: Cont.

All-cause death			
Yao et al.[7]	NR	NR	
Ntaios et al.[9]	0.65 (0.56–0.75)	<0.00001	Yes
Rivaroxaban versus warfarin, ROCKET-AF RCT[4]			
Outcome	Relative risk (95% CI)	p-value	
Stroke rate			
Stroke or SE	0.79 (0.66–0.96)	<0.001 for non-inferiority	
Ischaemic	0.94 (0.75–1.17)	0.581	
Haemorrhagic	0.59 (0.37–0.93)	0.024	
Bleeding rate			
Cerebral bleeding	0.67 (0.47–0.93)	0.02	
Major bleeding	1.04 (0.90–1.20)	0.58	
GI bleeding	NR (3.2% of patients on rivaroxaban versus 2.2% patients on warfarin)	<0.001	
Mortality			
Cardiovascular death	0.89 (0.73–1.10)	0.289	
All-cause death	0.85 (0.70–1.02)	0.073	
Rivaroxaban versus warfarin real-world data[7–9]			
Outcome	Relative risk (95% CI)	p-value	Corresponds to RCT?
Stroke rate			
Stroke or SE			
Yao et al.[7]	0.93 (0.72–1.19)	0.56	RCT tested non-inferiority
REVIST-US[8]	NR	NR	
Ntaios et al.[9]	0.87 (0.71–1.07)	0.18	RCT tested non-inferiority
Ischaemic			
Yao et al.[7]	1.01 (0.75–1.36)	0.95	Yes
REVIST-US[8]	0.71 (0.47–1.07)	NR	
Ntaios et al.[9]	0.89 (0.76–1.04)	0.13	Yes
Haemorrhagic			
Yao et al.[7]	0.61 (0.35–1.07)	0.08	Significance in RCT
REVIST-US[8]	NR	NR	
Ntaios et al.[9]	NR	NR	
Bleeding rate			
Cerebral bleeding			
Yao et al.[7]	0.51 (0.35–0.75)	<0.001	Yes
REVIST-US[8]	0.53 (0.35–0.80)	NR	Yes
Ntaios et al.[9]	0.64 (0.47–0.86)	0.004	
Major bleeding			
Yao et al.[7]	1.04 (0.90–1.20)	0.60	Yes
REVIST-US[8]	NR	NR	
Ntaios et al.[9]	1.0 (0.92–1.08)	0.92	Yes
GI bleeding			
Yao et al.[7]	1.21 (1.02–1.43)	0.03	Yes
REVIST-US[8]	NR	NR	
Ntaios et al.[9]	1.24 (1.08–1.41)	0.002	Yes
Mortality			
Cardiovascular death			
Yao et al.[7]	NR	NR	
REVIST-US[8]	NR	NR	
Ntaios et al.[9]	NR	NR	
All-cause death			
Yao et al.[7]	NR	NR	
REVIST-US[8]	NR	NR	
Ntaios et al.[9]	0.67 (0.35–1.30)	0.24	Yes

Table 1: Cont.

Edoxaban 60 mg versus warfarin, ENGAGE-AF-TIMI 48 RCT[5]			
Outcome	Relative risk (95% CI)	p-value	
Stroke rate			
Stroke or SE	NR	NR	
Ischaemic	1.00 (0.83–1.19)	0.97	
Haemorrhagic	0.54 (0.38–0.77)	<0.001	
Bleeding rate			
Cerebral bleeding	0.47 (0.34–0.63)	<0.001	
Major bleeding	0.80 (0.71–0.91)	<0.001	
GI bleeding	1.23 (1.02–1.50)	0.03	
Mortality			
Cardiovascular death	0.86 (0.77–0.97)	0.013	
All-cause death	0.92 (0.83–1.01)	0.08	
Edoxaban 30 mg versus warfarin, ENGAGE-AF-TIMI 48 RCT[5]			
Outcome	Relative risk (95% CI)	p-value	
Stroke rate			
Stroke or SE	NR	NR	
Ischaemic	1.41 (1.19–1.67)	<0.001	
Haemorrhagic	0.33 (0.22–0.50)	<0.001	
Bleeding rate			
Cerebral bleeding	0.30 (0.21–0.43)	<0.001	
Major bleeding	0.47 (0.41–0.55)	<0.001	
GI bleeding	0.67 (0.53–0.83)	<0.001	
Mortality			
Cardiovascular death	0.85 (0.76–0.96)	0.008	
All-cause death	0.87 (0.79–0.96)	0.006	
Edoxaban 60 mg versus warfarin, real-world data; Yu et al.[11]			
Outcome	Relative risk (95% CI)	p-value	Corresponds to RCT?
Stroke rate			
Stroke or SE	0.44 (0.31–0.64)	<0.001	No comparable endpoint
Ischaemic	NR		
Haemorrhagic	NR		
Bleeding rate			
Cerebral bleeding	0.35 (0.15–0.83)	NR	Yes
Major bleeding	0.40 (0.26–0.61)	<0.001	Yes
GI bleeding	0.42 (0.26–0.69)	NR	No
Mortality			
Cardiovascular death	NR	NR	
All-cause death	0.34 (0.22–0.53)	<0.001	Yes
Edoxaban 30 mg versus warfarin, real-world data; Yu et al.[11]			
Outcome	Relative risk (95% CI)	p-value	Corresponds to RCT?
Stroke rate			
Stroke or SE	0.57 (0.42–0.78)	0.009	No comparable endpoint
Ischaemic	NR	NR	
Haemorrhagic	NR	NR	
Bleeding rate			
Cerebral bleeding	0.44 (0.24–0.82)	NR	Yes
Major bleeding	0.61 (0.43–0.85)	0.003	Yes
GI bleeding	0.59 (0.40–0.88)	NR	Yes
Mortality			
Cardiovascular death	NR		
All-cause death	0.55 (0.41–0.73)	<0.001	Yes

CI = confidence interval; GI = gastrointestinal; NR = not reported; RCT = randomised controlled trial; SE = systemic embolism.

Major bleeding

Concerning major bleeding, a significant reduction could be shown for dabigatran 110 mg but not for dabigatran 150 mg when compared to warfarin (RE-LY trial).[2] A trend towards fewer events in the dabigatran group was also shown in the observational study by Yao et al., but not in the Medicare data by Graham et al. or in the meta-analysis by Ntaios et al.[6,7,9] A significant reduction of major bleeding was observed in patients on apixaban, when compared to warfarin, in the ARISTOTLE trial,[3] which was confirmed in the observational trial by Yao et al. and the meta-analysis by Ntaios et al.[7,9] For rivaroxaban, no significant reduction could be shown whether in the ROCKET-AF-trial, nor in the observational study by Yao et al. or the meta-analysis by Ntaios et al.[3,4,7,9] In the ENGAGE-AF-TIMI trial, a significant reduction of major bleeding was shown, which was confirmed in the nationwide Korean observational trial.[5,11]

Gastrointestinal bleeding

Rates of gastrointestinal (GI) bleeding were significantly elevated in patients on dabigatran 150 mg, but not in the 110 mg dosage group, when compared to warfarin in the RE-LY trial.[2] This significant increase in GI bleeding rates could also be seen in the observational study by Graham et al. and the meta-analysis by Ntaios et al.[6,9] However, the observational study by Yao et al. did not show a significant difference in GI bleeding rates for dabigatran in comparison to VKA.[7] In the ARISTOTLE trial, a significant reduction in GI bleeding was shown for apixaban,[3] which was in line with the results of the observational study by Yao et al. and the meta-analysis by Ntaios et al.[7,9] For rivaroxaban, significantly higher GI bleeding rates were observed in the ROCKET-AF trial and confirmed in the observational trial by Yao et al. and the meta-analysis by Ntaios et al.[3,4,7,9] In the ENGAGE-AF-TIMI trial, significantly higher GI bleeding rates were observed for edoxaban 60 mg, whereas significantly lower GI bleeding rates were shown for edoxaban 30 mg.[5] In contrast, in the nationwide Korean observational study, GI bleedings occurred less often in both dosage groups.[11]

Cardiovascular death

For dabigatran 110 mg no significant reduction of cardiovascular death was shown, whereas for dabigatran 150 mg, a significant reduction of cardiovascular death was observed in the RE-LY trial.[2] In the observational data by Graham et al., a clear and significant reduction of cardiovascular death in patients on dabigatran could be detected.[6] This endpoint was not investigated in the ARISTOTLE trial, but a significant reduction of cardiovascular death was shown in the meta-analysis by Ntaios et al.[2,3,9] For rivaroxaban, no significant reduction of cardiovascular death was shown in the ROCKET-AF trial, while this endpoint was not addressed for rivaroxaban in the observational studies.[4] In the ENGAGE-AF-TIMI trial, a significant reduction of cardiovascular death was observed for both edoxaban dosages.[5]

All-cause death

For dabigatran, no significant reduction in all-cause death was observed in the RE-LY trial.[2] However, in the meta-analysis by Ntaios et al., a significant reduction could be shown.[9] For apixaban, in the ARISTOTLE trial, a significant reduction in all-cause death was shown.[2,3] In line with this finding, the meta-analysis by Ntaios et al. also showed a significant reduction in all-cause death for patients treated with apixaban versus VKA.[9] In the ROCKET-AF trial as well as the meta-analysis by Ntaios et al., no significant reduction of all-cause death was observed for patients treated with rivaroxaban.[4,9] In contrast, for edoxaban 30 mg, a significant reduction of all-cause death was shown in the ENGAGE-AF-TIMI trial and confirmed in the nationwide

Korean observational trial, in which a significant reduction of this endpoint was observed for both dosages.[5,11]

Myocardial infarction

For dabigatran, rates of myocardial infarction were investigated in the RE-LY trial.[2] They were significantly higher in dabigatran 150 mg in comparison to warfarin. However, in the huge meta-analysis by Ntaios et al. analysing 66,090 patients on dabigatran, the dabigatran patients had a similar rate of myocardial infarctions compared to patients on VKAs without signs of a pro-ischaemic risk.[9]

Problems with novel oral anticoagulant use in daily life
Severe renal insufficiency

One of the reasons why patients with AF still receive VKA therapy is kidney failure. Apixaban, edoxaban and rivaroxaban have been approved for patients with renal insufficiency and a creatinine clearance of over 15 mg/dl, and dabigatran has been approved for a creatinine clearance of over 30 mg/dl. A retrospective analysis by Siontis et al., investigated patients with severe renal insufficiency and apixaban intake. Only patients on dialysis at the time of OAC prescription were included. The analysis compared 2,351 patients on apixaban to 7,053 patients on warfarin. No statistical difference in event rates of stroke/systemic embolism and all-cause death could be shown; however, patients on apixaban suffered significantly fewer major bleeding events ($p<0.001$). Of note, patients on high-dose apixaban (5 mg BID) had significantly fewer event rates of stroke/systemic embolism and all cause death, as well as major bleeding, when compared to patients on warfarin.[12] Chan et al. retrospectively investigated 281 patients on dabigatran and 244 patients on rivaroxaban with dialysis in 2015. There was no significant difference in hospitalisations or death from bleeding between the two groups. The authors, however, described that one of limitations of this study was that the numbers of included patients and occurred events were too low to detect meaningful differences.[13]

Concomitant dual antiplatelet therapy

There have been a couple of RCTs in recent years investigating the use of NOACs in a triple-therapy collective (e.g. patients with AF and stenting, who are therefore in need of a combination of OACs and anti-platelet therapy). Mainly, these trials have tested the use of dabigatran,[14] rivaroxaban,[15] and apixaban[16] instead of VKAs in a dual-treatment strategy with a P2Y12 inhibitor against a standard triple therapy with a VKA, a P2Y12 inhibitor and aspirin. The extremely high risk of bleeding of up to 44% annually[17] was reduced in all triple-therapy trials with omitting aspirin and only treating patients with a dual-therapy concept with a NOAC (instead of VKA) and a P2Y12 inhibitor.[14–16] The ongoing ENTRUST-AF percutaneous coronary intervention trial will answer the question of a dual therapy with edoxaban and a P2Y12 inhibitor in the context of AF and stenting, instead of triple therapy.[18] It is of great importance that none of those already released trials were powered for a potentially higher risk of thromboembolic events (e.g. stent thrombosis), when omitting aspirin. Also, results of RCTs investigating patients with a sole acute coronary syndrome collective are missing, just as real-world data, confirming those results (see *Table 2* for ongoing trials on NOACs).

Elderly patients

A great proportion of daily-treated patients belong to a high-risk collective, for example because of high age and increased tendency to fall, advanced renal insufficiency and multiple comorbidities and co-medications.[19] These patients have always

Table 2: Ongoing interventional trials on novel oral anticoagulants and stroke prevention in patients with atrial fibrillation

Title (ClinicalTrials.gov identifier)	Trial description
Dabigatran	
DECISIVE: Dabigatran Versus Conventional Treatment for Prevention of Silent Cerebral Infarct in Atrial Fibrillation Associated With Valvular Disease (NCT02982850)	**Inclusion**: 120 patients with AF and at least moderate aortic valvular stenosis/regurgitation, mitral valvular stenosis/regurgitation **Randomisation**: dabigatran versus VKA/aspirin **Primary endpoint**: composite of clinical cerebral infarct or new cerebral MRI lesions
RE-LATED AF: Resolution of Left Atrial-Appendage Thrombus - Effects of Dabigatran in Patients With AF (NCT02256683)	**Inclusion**: 110 patients with non-valvular AF and newly diagnosed LAA thrombus **Randomisation**: dabigatran versus VKA **Primary endpoint**: time to complete LAA thrombus resolution
Apixaban	
ATTICUS: Apixaban for Treatment of Embolic Stroke of Undetermined Source (NCT02427126)	**Inclusion**: 500 patients with ESUS and at least one non-major risk-factor for cardiac embolism **Randomisation**: apixaban versus aspirin **Primary endpoint**: imaging endpoint – occurrence of at least one new ischaemic lesion at 12 months after study drug initiation when compared to baseline MRI before study drug initiation
ARCADIA: AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (NCT03192215)	**Inclusion**: 1,100 patients ≥45 years old with ESUS and atrial cardiopathy **Randomisation**: apixaban versus aspirin **Primary endpoint**: incidence of recurrent stroke
ARTESiA: Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (NCT01938248)	**Inclusion**: 4,000 patients ≥50 years old with subclinical AF between 6 minutes and 24 hours, detected by implanted pacemaker, defibrillator or cardiac monitor and risk factor for stroke **Randomisation**: apixaban versus aspirin **Primary endpoints**: 1. composite of ischaemic stroke and systemic embolism, 2. major bleed
APPROACH-ACS-AF: APixaban vs. PhenpRocoumon in Patients With ACS and AF (NCT02789917)	**Inclusion**: 400 patients with non-valvular AF and ACS **Randomisation**: dual therapy (apixaban + clopidogrel) versus triple-therapy (VKA + clopidogrel + aspirin) **Primary endpoint**: BARC grade ≥2 bleeding events
Rivaroxaban	
RIWAMP: Rivaroxaban vs Warfarin in Patients With Metallic Prosthesis (NCT03566303)	**Inclusion**: 100 patients with mechanical prosthetic valve replacement after at least 3 months postoperative **Randomisation**: rivaroxaban versus VKA **Primary endpoint**: thromboembolic events
BRAIN-AF: Blinded Randomized Trial of Anticoagulation to Prevent Ischaemic Stroke and Neurocognitive Impairment in AF (NCT02387229)	**Inclusion**: 3,250 patients 32–65 years old with non-valvular AF and low stroke risk **Randomisation**: rivaroxaban 15 mg versus standard of care **Primary endpoint**: composite endpoint of stroke, TIA and neurocognitive decline
A Trial of Rivaroxaban Versus Warfarin in Dissolving Left Atrial Appendage Thrombus in Patients With Atrial Fibrillation (NCT03792152)	**Inclusion**: 90 patients with non-valvular AF and newly diagnosed LA thrombus **Randomisation**: rivaroxaban versus VKA **Primary endpoint**: number of patients whose thrombus in the LA or LAA was completely dissolved within 3–6 weeks
Edoxaban	
ENRICH-AF: EdoxabaN foR IntraCranial Haemorrhage Survivors With Atrial Fibrillation (NCT03950076)	**Inclusion**: 1,200 patients ≥45 years with AF and recent intracranial haemorrhage **Randomisation**: edoxaban versus no OAC/singe antithrombotic therapy **Primary endpoints**: 1. stoke, 2. major haemorrhage
ENVISAGE-TAVI AF: Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation (NCT02943785)	**Inclusion**: 1,400 patients with AF and transfemoral TAVR **Randomisation**: edoxaban versus VKA **Primary endpoints**: 1. net adverse clinical events (the composite of all-cause death, myocardial infarction, ischaemic stroke, systemic thromboembolism, valve thrombosis, and major bleeding events), 2. major bleeding
ENTRUST-AF-PCI: Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (NCT02866175)	**Inclusion**: 1,500 patients with AF and PCI with stenting **Randomisation**: dual therapy with edoxaban + P2Y12 antagonist versus VKA + P2Y12 antagonist + aspirin **Primary endpoint**: primary safety end point is the incidence of major or clinically relevant non-major bleeding
NOAH-AFNET 6: Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NCT02618577)	**Inclusion**: 2,686 patients with atrial high rate episodes (≥6 minutes, <24 hours) detected in pacemaker or defibrillator device ≥65 years and a CHA2DS2-VASc score ≥2 **Randomisation**: edoxaban versus aspirin/placebo (depending on CV risk) **Primary endpoint**: time to the first occurrence of stroke, systemic embolism, or CV death
All NOACs	
ELAN: Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation: an international, multicentre, randomised-controlled, two-arm, assessor-blinded trial (NCT03148457)	**Inclusion**: 2,000 patients with ischaemic stroke **Randomisation**: early versus late (standard) initiation of NOAC **Primary endpoint**: composite of major bleeding, recurrent ischaemic stroke, systemic embolism and/or vascular death

Table 2: Cont.

PRESTIGE-AF: PREvention of STroke in Intracerebral haemorrhaGE Survivors With Atrial Fibrillation (NCT03996772)	**Inclusion:** 654 patients with recent history on non-traumatic intracranial haemorrhage, atrial fibrillation and indication for OAC **Randomisation:** NOAC versus no OAC/aspirin **Primary endpoint:** 1. time to the first incident ischaemic stroke event, 2. time to the first recurrent intracerebral haemorrhage event
DANNOAC-AF: The Danish Non-vitamin K Antagonist Oral Anticoagulation Study in Patients With Atrial Fibrillation (NCT03129490)	**Inclusion:** 11,000 patients with newly diagnosed non-valvular AF **Randomisation:** dabigatran versus apixaban versus rivaroxaban versus edoxaban **Primary endpoint:** A composite endpoint of stroke, myocardial infarction, thromboembolic event or all-cause death

ACS = acute coronary syndrome; AF = atrial fibrillation; BARC = Bleeding Academic Research Consortium; CV = cardiovascular; ESUS = embolic stroke of undetermined source; LA = left atrium; LAA = left atrial appendage; MRI = magnetic resonance imaging; NOAC = new oral anticoagulant; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; TAVR = transcatheter aortic valve replacement; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

been, and still are, underrepresented in RCTs, as the mean age of patients in RCTs comparing NOACs to VKA is between 70–73 years and the CHADS2 score, indicating the stroke risk, is low to moderate in those trials (from 2.0 in the ARISTOTLE trial, up to 3.5 in the 'ROCKET-AF' trial).[2–5] This makes it complex to find the best possible treatment option for elderly and high-risk patients. Therefore, it is important to focus on these high-risk patients, that we treat in our daily clinical routine, in future trials.

Mechanical valves

Real-world data of observational and retrospective studies that were released in recent years mostly confirm the findings of the initial RCTs and strengthen them further.[2–9,11] Still, VKAs are the hallmark of anticoagulation for selected patients with contraindication for NOACs, as well as for stroke and thrombosis prophylaxis in patients with mechanical heart valves. In this context of mechanical heart valves, a sole clinical trial with NOACs was performed and stopped prematurely due to exaggerated stroke and bleeding risks.[20] For this indication, VKAs, therefore, remain the gold standard.

Dosing problem in real-world patients

One of the problems that appears in real-world data trials is inadequate dosing. In RCTs, patients are treated with the intended dosage of their study drug (see *Table 3* for NOAC dosing for different indications). In a real-world setting, a not-irrelevant number of patients is treated with an inadequately low drug dosage for multiple reasons. This makes it harder to compare real-world data to the initial pivotal trials. In the RE-LY trial, dabigatran was tested in two fixed dosages (150 mg BID and 110 mg BID), in the real-world trial 16% of dabigatran users received a reduced dosage (75 mg BID) despite the fact that only 33% of those patients had the diagnosis of a chronic kidney disease, and only 20% of those, a severe kidney disease (and therefore the indication for dose reduction).[6] Data from the ORBIT-AF II trial concerning dose reduction were investigated and presented by Steinberg et al. In this analysis, 6,636 (84%) out of 7,925 patients on NOACs received the full dosage, which was an adequate dosing in 96% of the cases. The remaining 1,289 patients (16%) received a reduced dosage of their NOAC.[21] Interestingly, in only 43% of those cases, the dose reduction was consistent with US Food and Drug Administration labelling and recommendations. Patients on rivaroxaban received an appropriately reduced dosage in 52%; whereas, patients on apixaban had an appropriate dose reduction in only 37% of the cases. Thus 63% of apixaban-treated patients received a reduced dosage without indication. Patients in those groups with inappropriate dose reduction for rivaroxaban or apixaban did not show a higher rate

of thromboembolic events and all-cause mortality.[21] Regarding edoxaban, an analysis of baseline characteristics and dose adherence was already published prior to the end of the awaited ETNA-AF trial.[10,22] In 13,474 European patients, dose reduction was performed in 23.3%,[22] which is in line with the patients with dose reduction in the ENGAGE-AF-TIMI 48 trial.[5] But if all globally investigated patients (24,431) are taken into account, a dose reduction was performed in 43.1%, which is a much higher number than reported in the RCT.[22]

Patients undergoing atrial fibrillation ablation

Patients undergoing ablation for AF are typically on OAC treatment. The major complications in ablation procedures comprise stroke and transient ischaemic attacks. For the reduction of those, systemic anticoagulation before, during and after ablation is necessary. During the ablation procedure, heparin can be administered; maintaining the activated clotting time >300 seconds, before and after ablation OAC is recommended for at least 8 weeks.[23] In the COMPARE trial, uninterrupted VKA therapy was shown to be superior to bridging with heparin concerning stroke and minor bleeding rates.[24] For the four NOACs, four RCTs were performed evaluating the risk for bleeding and stroke in uninterrupted NOAC use versus uninterrupted intake of VKA. Cappato et al. showed in the VENTURE AF trial that uninterrupted intake of rivaroxaban and VKA do not result in significantly different bleeding or stroke rates.[25] For dabigatran, Calkins et al. reported a significant reduction of major bleedings with continuous dabigatran versus continuous VKA intake in patients undergoing AF ablation in the RE-CIRCUIT trial. The stroke rate was very low and no statistically significant difference between the treatment groups could be observed.[26] Kirchhof et al. showed in the AXAFA AFNET 5 trial that continuous apixaban intake compared to VKA intake is safe and effective in patients undergoing AF ablation with respect to stroke and bleeding.[27] Consistently, the same was shown for edoxaban; Hohnloser et al. investigated continuous edoxaban intake versus continuous VKA intake in patients undergoing AF ablation in the ELIMINATE AF trial. Similar event rates with regard to bleeding and stroke events could be observed for either treatment strategy.[28]

Do real-world data support our expectations?

Evidence-based guidelines recommend OAC for patients with AF and risk factors for stroke.[29,30] Nevertheless, this effective way of preventing strokes is still underused.[31] The main reasons for not prescribing OACs are a history of bleeding or the tendency to fall – both resulting in the fear of major bleedings.[32] After the RCTs and real-world data trials, discussed above, NOACs were expected to reduce the number of

Table 3: Indication and dosing of novel oral anticoagulants

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Stroke prophylaxis in non-valvular AF	150 mg BID 110 mg BID in patients ≥80 years, verapamil intake, or elevated bleeding risk Consider 110 mg BID in patients with CrCL (30–50 mL/min)	5 mg BID 2.5 mg BID in patients with at least two of the three following: ≥80 years; body weight ≤60 kg, creatinine ≥1.5 mg/dl; CrCl 15–30 mL/min	20 mg OD 15 mg OD in patients with CrCl 15–49 mL/min	60 mg OD 30 mg OD in patients ≤60 kg, CrCl 15–50 mL/min or intake of dronedarone, cyclosporin, erythromycin or ketoconazol
Treatment of PE or DVT	150 mg BID after at least 5 days of parenteral anticoagulation	10 mg BID for 7 days, followed by 5 mg BID Prophylaxis after 6-month treatment: 2.5 mg BID	15 mg BID for 21 days, followed by 20 mg OD (15 mg OD in patients with CrCl 15–49 mL/min) Prophylaxis after 6-month treatment: 10 mg OD In patients with malignome or recurrent PE: 20 mg OD	60 mg OD after at least 5 days of parenteral anticoagulation
Prophylaxis of thrombosis in patients after hip or knee replacement surgery		2.5 mg BID	10 mg OD	
Chronic kidney injury	Contraindicated in patients with CrCl <30 mL/min	Contraindicated in patients with CrCl <15 mL/min	Contraindicated in patients with CrCl <15 mL/min	Contraindicated in patients with CrCl <15 mL/min
Prophylayxis of atherothrombotic events in patients with CAD or PAD			2.5 mg BID (in addition to aspirin)	
Antidote	Idarucizumab	Andexanet alfa	Andexanet alfa	

AF = atrial fibrillation; BID = twice daily; CAD = coronary artery disease; CrCl = creatinine clearance; DVT = deep vein thrombosis; OD = once daily; PAD = peripheral arterial disease; PE = pulmonary embolism.

patients with AF suffering a stroke or a severe adverse reaction like a major bleeding event under OACs. Probably based on these results, the use of NOACs increased worldwide in recent years from 4.2% (from March 2010 to June 2012) to 37% (from June 2014 to June 2015), with a consecutive fall of VKA-use, but a rise of total anticoagulation from 57.4% (from March 2010 to June 2012) to 71.1% (from June 2014 to June 2015), as described in the GARFIELD-AF registry.[33] Notably, the number of patients with OAC rose in all levels of risk (stratified by CHA2DS2-VASc score), including those patients with a score of 0, probably indicating overtreatment. Further analysis showed a rise of NOAC prescription, particularly in elderly patients or patients with dementia, which might previously not have received an adequate treatment.[33]

Conclusion

After the introduction of the four NOACs: dabigatran, rivaroxaban, apixaban and edoxaban, RCTs were performed to ensure their efficacy and safety when compared to the gold-standard VKAs. The results of the RCTs had a huge impact and already significantly changed daily clinical practice. Subsequently, real-world data from different patient groups are available now. These data sets show that the results of RCTs are also largely reflected in a real-world setting. Due to these convincing results, the guidelines on anticoagulation in patients with newly diagnosed AF were changed and a NOAC treatment should now be preferred over a VKA treatment. This underlines the importance and the great value of NOACs in our daily clinical practice. ❑

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