REVIEW ARTICLE

DIRECT ORAL ANTICOAGULANTS UP TO DATE: WHEN, HOW AND WHY. A CRITICAL REVIEW

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Abstract

Over the past 9 years, the pharmacologic approach to stroke prevention in atrial fibrillation (AF) has been revolutionized by the introduction of four direct oral anticoagulants (DOACs) in clinical practice. Their use is supported by the results of phase III randomized controlled trials (RCTs) and by more recent real-world studies, which show that these drugs have at least a comparable efficacy and safety to vitamin K antagonists. Given that there is no RCT ongoing or planned on the direct comparison of different DOACs, the clinician is left with the responsibility to choose among dabigatran, rivaroxaban, apixaban and edoxaban. In this article, we review DOACs' pharmacokinetic and pharmacodynamic properties, focusing on the clinical usefulness of the different dosing regimens and on the once vs. twice a day issue. We also review their use in AF cardioversion, for which only rivaroxaban and edoxaban were evaluated in prospective phase III studies. Furthermore, we discuss the effectiveness and safety of these drugs in the light of real-world studies, with the intention of providing the clinician with practical information that could help in the selection of a specific DOAC for any patient. Finally, the limited evidence supporting the use of reduced doses is discussed.

Keywords: atrial fibrillation, nonvalvular atrial fibrillation, direct oral anticoagulants, warfarin, vitamin K antagonist, dabigatran, rivaroxaban, apixaban, edoxaban, cardioversion, real-world studies.

Abbreviations and Acronyms: AF: atrial fibrillation; BID: twice a day; CI: confidence interval; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; ECV: electrical cardioversion; FXa: factor X activated; HR: hazard ratio; INR: international normalized ratio; PDC: proportion of days covered; QD: once a day; RCT: randomized controlled trial; TEE: transesophageal echocardiogram; VKA: vitamin K antagonist.

1. Introduction and Brief Historical Perspective.

Atrial fibrillation (AF) is the most common sustained arrhythmya, affecting about 2% of the European population.[1] For almost a century, it has been recognized that "auricular" fibrillation, as it was called in the past, carries a high risk of stroke. We know that 20-30% of patients presenting with an ischaemic stroke, receive a diagnosis of AF concomitantly, prior to or after the cerebrovascular event. Furthermore, AF-related strokes usually have a higher risk of mortality and morbidity when compared to strokes from other causes and determine enormous expenditures for health care systems.[2]

It was very early recognized, with the first report published in 1948[3], that anticoagulation with vitamin K antagonists (VKA) can be very effective in reducing stroke risk in AF patients. A large meta-analysis[4] of all published warfarin trials showed that patients on warfarin have a 64% reduction in the risk of stroke and a magnificent 26% reduction in all cause mortality when compared to control or placebo. Furthermore, warfarin proved to be far more effective than antiplatelet agents, with a 37% reduction of stroke risk.

Unfortunately, warfarin therapy has some important limitations: due to its indirect mechanism of action, it has a slow onset and offset of anticoagulant effect, it interacts with food and many drugs and thus has a narrow therapeutic window. Therefore, a continuous monitoring of the INR is warranted to protect patients from stroke and at the same time to avoid exposure to an excessive bleeding risk. In the end, warfarin dosing is both an art and a science, and real world data[5] suggest that the proportion of patients on VKA who are in the therapeutic range for INR (2.0 to 3.0) at any given moment is not more than 60-70%.

2. The New Era of DOACs.

Since 2009, the scientific community has very welcomed the publication of the results of phase III registrative trials on four novel direct oral anti-coagulants (DOACs) for AF and deep venous thrombosis therapy. The study milestones for AF began with the RE-LY[6] trial on dabigatran, then in 2011 with the ROCKET-AF[7] trial on rivaroxaban and with the ARISTOTLE[8] trial on apixaban and in 2013 with the ENGAGE AF-TIMI 48[9] trial on edoxaban (table 1). As shown in a meta-analysis[10] of the results of these studies, the DOACs, as a class, proved noninferior to warfarin with regard to efficacy and safety. Overall, there was a 19% reduction in the combined endpoint of stroke or embolic events, mainly driven by a reduction in haemorragic stroke, a significant 10% reduction in all-cause mortality and an astonishing 52% reduction in intracranial haemorrhages, partially compensated by a 25% increase in gastrointestinal bleeding events.

Currently, an anticoagulant (preferably a DOAC) is recommended for patients who have AF and additional risk factors for stroke among those included in the CHA_2DS_2-VASc risk score (Congestive heart failure, Hypertension, Age 75 or older, Diabetes mellitus, Previous stroke, transient ischaemic attack or thromboembolism, Vascular disease, Age 65-74 years, Sex category). An anticoagulant should be considered for a score of 1 in men or 2 in women and is recommended in men with a score ≥ 2 or in women with a score ≥ 3.[11]

Table 1: DOACs' RCTs main findings.

Study	Number of patients	Stroke or systemic embolism (DOAC vs. W)	Major bleedings (DOAC vs. W)
RE-LY[6]	18113	D150: RR 0.66; 95% CI, 0.53–0.82 D110: RR 0.91; 95% CI, 0.74-1.11	D150: RR 0.94; 95% CI, 0.82–1.07 D110: RR 0.8; 95% CI, 0.69-0.93
ROCKET-AF[7]	14264	HR 0.88; 95% CI, 0.75–1.03	HR 1.04; 95% CI, 0.90–1.2
ARISTOTLE[8]	18201	HR 0.79; 95% CI, 0.66–0.95	HR 0.71; 95% CI, 0.61–0.81
ENGAGE AF-TIMI 48[9]	21105	E60: HR 0.87; 95% CI, 0.73–1.04 E30: HR 1.13; 95% CI, 0.96-1.34	E60: HR 0.80; 95% CI, 0.71–0.91 E30: HR 0.47; 95% CI, 0.41-0.55.

D110 = dabigatran 110 mg BID; D150 = dabigatran 150 mg BID; E30 = edoxaban 30 mg QD; E60 = edoxaban 60 mg QD; HR = hazard ratio; RR = risk ratio; W = warfarin

3. What is Different between the DOACs and Warfarin?

Warfarin acts indirectly, mainly through the inhibition of the vitamin K dependent activation of coagulation factors II (thrombin), VII, IX and X by γ-carboxilation. Thus, one has to wait for some days to get an anticoagulant effect, with a paradoxical precocious pro-thrombotic risk related to the depletion of protein C and protein S (endogenous vitamin K dependent anticoagulant proteins produced by the liver that have a shorter half life as compared to thrombin). The termination of warfarin effect is also delayed because of an elimination half-life of 40/144 hours and because of the time needed for the liver to synthesize new active proteins.

The DOACs, instead, act by a direct inhibition of coagulation factors. Dabigatran is a competitive and reversible thrombin inhibitor, whereas rivaroxaban, apixaban and edoxaban are factor Xa (FXa) inhibitors. Therefore, they have a very rapid onset and offset of action, with similar half-life of about 12 hours. Also, there is no routinary need to monitor the level of anti-coagulation because of their more predictable dose-effect relationship; in case it is deemed necessary, such as in emergency bleeding/thrombotic situations or when a patient needs to undergo an urgent surgical procedure or in patients with renal/hepatic insufficiency, one can rely on the diluted thrombin time in the case of dabigatran[12,13] and on the antiFXa activity in the case of the three FXa inhibitors.[14]

4. DOACs' Clinical Pharmacokinetics

Besides their different pharmacodynamic profile, the four DOACs show different pharmacokinetic properties that might be useful when selecting the most appropriate drug for a specific patient (see table 2 for details).

Table 2: DOACs' pharmacological aspects.

	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Oral bioavailability	6,5%[15,16]	100% with food, 39% on a empty stomach[17]	50%[18]	62%
Prodrug	Yes	No	No	No
Time to peak concentration	2-3 hours	2,5-4 hours	3-4 hours	1-2 hours
Metabolism/elimination	Renal elimination, 80% unchanged and 20% after hepatic glucuronydation	Hepatic elimination (65%)[19] and renal elimination (35%)[20] via P-glycoprotein	Hepatic elimination (72%)[21] and renal elimination (28%)[22]	Hepatic elimination (50%) and renal elimination (50%)[23]
CYP3A4 mediated metabolism	No	Yes, moderate contribution	Yes, moderate contribution	< 4%
P-glycoprotein substrate	Yes (dabigatran etexilate)[24]	Yes	Yes	Yes
Elimination half-life	12-17 hours	5-9 hours (young), 11-13 hours (elderly)	12 hours	10-14 hours
Usual dose regimen	150 mg BID	20 mg QD	5 mg BID	60 mg QD

Dabigatran etexilate is a pro-drug with no anticoagulant activity, which is converted to the active compound dabigatran by esterases. It is mainly eliminated by the kidneys, thus one has to be particularly careful when prescribing this drug to patients with renal impairment because of the potential risk of accumulation.[25] Dabigatran is given twice daily for stroke prevention in AF, either 150 mg BID or 110 mg BID, a regimen consistent with its half-life. This dosing schedule was chosen after a phase II study[26] on the prevention of deep venous thrombosis (DVT) in orthopaedic surgery, which showed comparable rates of bleeding and DVTs with dabigatran 150 mg BID or dabigatran 300 mg QD. The 150 mg BID regimen was chosen for phase III DVT studies because of a better theoretical safety/efficacy profile based on a logistic regression model.

Rivaroxaban's absorption after an oral administration significantly increases when the drug is taken with food (the area under the curve for plasma concentrations steps up by 39% to an almost 100% bioavailability). Thus, rivaroxaban assumption with food is mandatory. Its elimination half-life is 5-9 hours in the young and 11-13 hours in the elderly. Even though this half-life would suggest a twice-daily dosing of the drug, rivaroxaban is given at a 20 mg dose once daily for stroke prevention in patients with AF.[27] This regimen was chosen after data from DVT prevention studies,[28] which established rivaroxaban 10 mg QD as the standard therapy for DVT prevention after an orthopaedic surgery. The decision to try a QD dosing regimen for rivaroxaban was initially taken on the basis of a similar temporal profile to that of enoxaparin, which is given at a fixed dose once daily for DVT prevention.[29] Subsequently, other studies evaluated the QD vs. BID dosing regimen in the treatment of DVT,[30] and found that the BID regimens were associated with an improved resolution of the DVT but that QD and BID regimens were equal for the prevention of recurrences and were as safe as the comparator of light molecular weight heparin/VKA. These observations explain why the 20 mg QD dosing, a regimen that could theoretically ensure a greater adherence in a population usually taking many drugs at the same time, was chosen for AF. On the contrary, in a dose ranging study on patients with acute coronary syndromes,[31] the most advantageous regimens were the 5 mg BID and the 2.5 mg BID, which were subsequently evaluated in the phase III ATLAS ACS2-TIMI 51 trial,[32] whereas the 20 mg QD regimen carried a nonsignificant higher bleeding risk.

Consistent with **apixaban**'s 12 hours half-life, the appropriate dosing regimen of this drug is 5 mg BID, a regimen that was not directly evaluated in AF but was initially chosen based on the results of studies on DVT prevention in orthopaedic surgery,[33] which showed a similar number of bleedings but a tendency for a better efficacy for twice daily dosing. In the context of acute coronary syndromes, apixaban was evaluated in a dose ranging phase II study, in which both the 20 mg QD and the 10 mg BID regimens were discontinued due to excessive bleeding rates, a finding more directly attributable to an over-dosing of the drug[34] than to the dosing schedule.

Edoxaban is the only anticoagulant prescribed for stroke prevention in AF for which the dosing regimen of 60 mg QD was directly evaluated in AF patients in a phase II study.[35] When compared to a 60 mg QD regimen, a 30 mg BID regimen unexpectedly resulted in a higher risk of bleeding, which the authors attributed to the higher steady state trough levels. However, it's also possible that the BID regimen, with two concentration peaks per day, produces a longer period of time for which the drug concentration is over a certain threshold that critically increases the risk of bleeding, and definitive conclusions can't be drawn due to a limited number of patients included in this phase II study.

As mentioned above, all the DOACs are substrates for P-glycoprotein secretion, a factor that must be taken into account when prescribing strong P-glycoprotein inhibitors (e.g., verapamil, dronedarone, amiodarone, quinidine) together with a DOAC by using a reduced dose regimen (e.g., dabigatran 110 mg BID, rivaroxaban 15 mg QD, apixaban 2,5 mg BID or edoxaban 30 mg QD) or, as in the case of dabigatran and dronedarone, by avoiding co-administration because of the risk of DOAC accumulation. Also, all the DOACs are at least partially renally eliminated, thus dabigatran use is contraindicated in Europe in case of an eGFR < 30 ml/min, whereas the three FXa inhibitors are contraindicated when the eGFR < 15 ml/min.

5. Once a day or twice a day?

As already pointed out, giving once a day a drug that has a 12 hours half-life may appear as a distortion form a pharmacokinetic perspective, but may have valid explanations.

A meta-analysis[36] of data from the four DOACs RCT showed a significant benefit with the BID regimens. In this meta-analysis, common estimates (CE) were generated for the results of the two trials which studied a BID regimen (RE-LY and ARISTOTLE) and for the results of the two trials which studied a QD regimen (ROCKET-AF and ENGAGE AF-TIMI 48). When the efficacy endpoint of stroke or systemic embolism was taken into account, it resulted significantly lower for dabigatran-150 than for the CE of the QD regimens, with an HR = 0.75 (95% CI 0.58–0.96) and it resulted nonsignificantly lower for apixaban than for the CE of the QD regimens, with an HR = 0.91 (95% CI 0.73–1.13). For the only endpoint of stroke, there was a trend towards a greater efficacy for the CE of the BID regimens than for the CE of the QD regimens, with an HR = 0.85 (95% CI 0.69–1.05). Finally, with regards to the safety endpoint of intracranial hemorrhage, there was a large and significant advantage for the CE of the BID regimens when compared to rivaroxaban, with HR = 0.57 (95% CI 0.37–0.88), whereas there was a nonsignificant trend towards improvement with the CE of the BID regimens when compared to edoxaban, with HR = 0.81 (95% CI 0.54–1.22).

These results could suggest that a BID administration of drugs that have a 12 hours half-life, by producing a more stable concentration of these drugs in the plasma and thus reducing the peak to trough concentration ratio, may prevent thrombosis and bleeding more effectively. Nonetheless, it must be pointed out that patients included in the different registrative studies were different, with a higher $CHADS_2$ score in the ROCKET-AF study of rivaroxaban, potentially confounding these results; furthermore, a BID regimen, by producing higher steady state trough levels, might be disadvantageous, as demonstrated in the phase II study of edoxaban for AF, thus leaving the question of BID or QD still open.

5.1. Patient Adherence

One more factor to weigh when choosing between a BID and a QD regimen is the higher theoretical compliance and adherence to the latter. For example, in a study reporting data from a large claims database of patients with AF,[37] among various classes of drugs, those with a QD regimen appeared to have a higher adherence and persistence than those with a BID regimen.

But, first of all, what's the difference among compliance, adherence and persistence?

The term **adherence** may be defined as the extent to which medical recommendations are followed as suggested and it is clear, as pointed out in a statement by the American Heart Association in 1997, that it is influenced by the behaviour of the individual but also by the social and healthcare system.[38] Nowadays the term **compliance** has almost completely been substituted by the term **adherence** that implies that the patient is at the same level of the healthcare provider, actively collaborating to reach the common goal of health promotion and not just passively following instructions. Adherence is made up by three components, initiation of a treatment, implementation of the dosing regimen and discontinuation, with the interval between initiation and discontinuation defined as "**persistence**".[39] More practically, adherence can be defined as the percentage of patients with a proportion of days covered (PDC) (e.g. numbers of days on which a medication was taken as prescribed) ≥80 %.[40]

Some data from real world observational studies show us that rivaroxaban, with its QD regimen, has a better adherence than the other DOACs,[41] even though in some studies rivaroxaban's PDC resulted similar to that of apixaban[42] or dabigatran.[43] Of course, adherence to therapy is maximal at the beginning, then following a time-dependent decline.

Table 3: representative adherence studies for DOACs

Study	N of patients	PDC for warfarin	PDC for dabigatran	PDC for rivaroxaban	PDC for apixaban
McHorney et al[41]	Rivaroxaban: 13645; Apixaban: 6304; Dabigatran: 3360; Warfarin: 13366	At 6 months: PDC ≥80 % = 64.5%	At 6 months: PDC ≥80 % = 69.2%	At 6months: PDC ≥80 % = 80.1%	At 6 months: PDC ≥80 % = 75.8%
Brown et al[42]	Rivaroxaban: 9817; Dabigatran: 2751 Apixaban: 2773	NA	At 3 months: PDC = 76 ± 29% At 9 months: PDC = 57 ± 35%	At 3 months: PDC = 83 ± 26% At 9 months: PDC = 66 ± 34%	At 3 months: PDC = 82 ± 26% At 9 months: 66 ± 33%
Borne et al[44]	Dabigatran: 2095; Rivaroxaban: 571; Apixaban 216	NA	At 12 months: PDC = 84 ± 20%	At 12 months: PDC = 86 ± 18%	At 12 months: PDC = 89 ± 14%
Manzoor et al[43]	Dabigatran: 49210; Rivaroxaban: 15807; Apixaban: 1073	NA	At 6 months: PDC = 78.6 ± 27.7% At 12 months: PDC = 73.4 ± 31.6%	At 6 months: PDC = 76.5 ± 30.7% At 12 months: PDC = 69.7 ± 34.8%	At 6 months: PDC = 80.9 ± 24.9% At 12 months: not available

NA = not available; PDC = proportion of days covered.

Interestingly, some data[44] suggest a significant association between a lower adherence and mortality or stroke for patients on dabigatran, with a tendency towards a similar result for patients on rivaroxaban, thus providing an insight on nonadherence clinical consequence.

In addition, anticoagulant experienced patients seem to have a greater adherence than anticoagulant naive patients. This finding might be explained by the negative impact that using warfarin usually has on a patient's life.[45] Therefore, warfarin experienced patients are well

motivated to be successful on a DOAC. Moreover, patients previously involved in structured anticoagulation clinics usually have a better education with regard to adherence.

One last important aspect to consider is the consequence of missing a dose, which is not well captured by parameters like the PDC. A pharmacokinetic simulation[46] reported that missing a dose translates in 2 hours of risk of thromboembolic complications for a BID regimen as opposed to 10 hours with a QD regimen. Thus, whereas a once a day regimen may appear easier to comply with, at the same time adherence needs to be near-perfect to get a clinical advantage. On the contrary, a twice a day regimen may be more flexible and forgiving in case of imperfect adherence. Clearly, these aspects need to be studied in greater depth before a definitive conclusion can be drawn and are of the utmost importance for the proper management of anticoagulation of AF patients.[47]

6. DOACs and AF Cardioversion

Historically, AF cardioversion, that is, to deliver an electrical shock or to administer a drug in order to bring the heart back to sinus rhythm, has been considered a procedure associated with a significant thrombo-embolic risk.[48] To illustrate, old data report a 5-7% risk of stroke or systemic embolism.

From the 1960s, it was recognized that a prophylactic period of anticoagulation with a VKA could reduce this risk to 0-0.8%.[49] When a cardioversion is considered for a haemodinamically stable patient with an AF episode, the first step is to evaluate for how long this episode lasted. If the arrhythmia has been present for less than 48 hours, a cardioversion can be attempted giving an anticoagulant acutely with consequent low risk of thromboembolic complications. This recommendation, however, was never evaluated in a randomized controlled trial but proved to be safe in a Finnish retrospective observational study,[50] in which the rate of thromboembolic complications was 0.7%, with a time dependent increase from 0.3% when cardioversion was performed within 12 hours from the beginning of the AF episode to 1.1% when it was performed after the first 12 hours.

Conversely, if the AF episode was longer than 48 hours, there are two options: to give an anticoagulant for at least 3 weeks and then to perform the cardioversion with a 0.3-0.8% risk of thromboembolic complications,[51] or alternatively to perform a trans-esophageal echocardiogram (TEE) that will exclude auricular thromboses,[52] allowing an equally safe cardioversion.

The use of DOACs in the context of cardioversion may have the advantage of avoiding any delays potentially produced by the necessity to ensure therapeutic INR levels for three weeks before the cardioversion in case a VKA is prescribed. The evidence supporting the use of the various DOACs is variable; only rivaroxaban and edoxaban were evaluated in prospective studies (see table 4).

Table 4: DOACs in AF Cardioversion

Study	Intervention and population	Design	% ECV	Stroke or systemic embolism	Major bleedings	Atrial thrombus	Early cardioversion
Nagarakanti et al.[53]	D vs. W, 1983 cardioversions	Retrospective post-hoc analysis of the RE-LY trial	83.5%	0.77% (D110) vs. 0.3% (D150) vs. 0.6% (W)	1.7% (D110) vs. 0.6% (D150) vs. 0.6% (W)	1.8% (D110) vs. 1.2% (D150) vs. 1.1% (W)	No
Piccini et al.[54]	R vs. W, 375 cardioversions and 85 ablations	Retrospective post-hoc analysis of the ROCKET-AF trial	48.2%	1.88% (R) vs. 1.86% (W)	18.8% (R) vs. 13% (W)	Not reported	No
X-VeRT, Cappato et al.[55]	R vs. VKA, 1504 patients	Randomized, open label, prospective	97.6%	0.2% (R) vs. 0.6% (VKA)	0.6% (R) vs. 0.8% (VKA).	2% (R) vs. 1.99% (VKA)	Yes, 58% of cardioversions
Flaker et al.[56]	A vs. W, 743 cardioversions	Retrospective post-hoc analysis of the ARISTOTLE trial	Not reported	0 (A) vs. 0 (W)	0.3% (A) vs. 0.2% (W)	0 (A) vs. 0 (W)	No
Plitt et al.[58]	E vs. W, 632 cardioversions	Retrospective post-hoc analysis of the ENGAGE AF TIMI 48 trial	100%	1.8% (E30) vs. 0 (E60) vs. 0 (W)	0 (E) vs. 0 (W)	Not reported	No
ENSURE-AF, Goette et al[59]	E vs. H-W, 2199 patients	Randomized, open label, prospective	100%	0,2% (E) vs. 0,3% (H-W)	0,2% (E) vs. 0,4% (H-W)	8% (E) vs. 7,1% (H-W)	Yes, 53,7% with a TEE-guided strategy

A = apixaban; D = dabigatran; E = edoxaban; ECV = electrical cardioversion; H-W = heparin-warfarin; R = rivaroxaban; VKA = vitamin K antagonists; W = warfarin.

6.1. Dabigatran

In a post-hoc analysis of the RE-LY trial[53] focusing on 1270 patients undergoing 1983 cardioversions (prevalently electrical) during the study, stroke or systemic embolism occurred rarely and with similar rates in patients receiving warfarin, dabigatran-110 mg and dabigatran-150 mg; these treatments were safe with regard to major bleedings.

6.2. Rivaroxaban

A post-hoc analysis of the ROCKET-AF study,[54] including both patients undergoing cardioversions and patients undergoing ablations, established the efficacy and safety of rivaroxaban in this context. There were only 3 thromboembolic events in patients taking rivaroxaban and 3 events in patients taking warfarin and similar safety with regard to major bleedings; however, given that composite data for patients undergoing ablation and patients undergoing cardioversion were given, further evidence was needed.

Thus, the prospective phase IIIb X-VeRT (eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with non-valvular aTrial fibrillation scheduled for cardioversion) study[55] was conducted on 1504 patients undergoing elective cardioversion. These patients were randomly assigned to rivaroxaban 20 mg QD (or 15 mg QD in case of an eGFR between 30 and 49 ml/min) or a VKA with a target INR of 2 to 3 in a 2:1 ratio. Investigators could choose between two strategies: a delayed cardioversion (42% of the study population), in which patients had to take the anticoagulant for at least 3 weeks before the cardioversion, or an early cardioversion (58% of the study population), in which the anticoagulant had to be taken for 1-5 days before the cardioversion. A far higher proportion of patients in the latter group underwent a transesophageal echocardiogram (TEE) to exclude an auricular thrombosis prior to cardioversion (64.7% vs. 10.1%). Rivaroxaban resulted as effective as warfarin for the composite efficacy endpoint (stroke, non-central nervous system embolism, transient ischaemic attack, myocardial infarction, and all-cause mortality), both as a whole and irrespectively of the timing chosen for cardioversion. In addition, there was no difference in safety outcomes. Even more interestingly, in the delayed group, rivaroxaban users underwent cardioversion earlier than warfarin users (mean values, 25 days vs. 34 days), because of the anticipated difficulty in achieving an adequate period of anticoagulation with warfarin in three weeks. Thus, even though the X-VeRT study was underpowered to provide statistically rigorous results, rivaroxaban use in patients undergoing cardioversion is supported by good quality data, which show that rivaroxaban has a similar efficacy and safety to warfarin. Furthermore, rivaroxaban allows a prompter cardioversion and seems safe even in an early cardioversion strategy.

6.3. Apixaban

The use of apixaban in cardioversion is supported by a post-hoc analysis of patients cardioverted while enrolled in the ARISTOTLE trial.[56] Out of the 743 cardioversions attempted in the 540 patients considered in this analysis, the number of clinically meaningful efficacy and safety outcomes was similar among patients treated with apixaban and those treated with warfarin. There were no strokes or systemic embolisms occurring in either group and just one major bleeding event per group.

To further validate and extend these findings, the prospective open-label real world Eliquis evaluated in acute cardioversion coMpared to usuAl treatmeNts for AnTicoagulation in subjects with NVAF (EMANATE)[57] study has been conducted and will support the use of apixaban in patients undergoing cardioversion.

6.4. Edoxaban

During the course of the ENGAGE AF-TIMI 48 trial, there were 832 attempted cardioversions. A post hoc analysis[58] excluded 200 cardioversions which were performed on patients who last took an anticoagulant more than 3 days prior to the cardioversion. This analysis showed a similar efficacy for edoxaban and warfarin, with just two strokes or systemic embolisms in the edoxaban-30 mg group and no events in the edoxaban 60-mg group or in the warfarin group. It also showed a very good safety profile, with no major bleedings reported.

To confirm and validate these observations, the prospective phase IIIb Edoxaban vs. Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation (ENSURE-AF) study[59] was conducted on 2199 patients undergoing a planned electrical cardioversion. These patients were randomized in a 1:1 fashion to receive either edoxaban (60 mg or 30 mg in case of a body weight < 60kg, an eGFR of 15-50 ml/min or the concurrent use of a P-gp inhibitor other than amiodarone) or heparin-warfarin. According to the local investigator, patients could undergo a TEE-guided cardioversion, in which both the TEE and the cardioversion had to be performed within 3 days of randomization (with edoxaban started at least 2 hours before the cardioversion), or a non TEE-guided cardioversion, in which patients had to receive at least 3 weeks of anticoagulation prior to cardioversion. The combined primary efficacy endpoint (stroke, systemic embolic event, myocardial infarction and cardiovascular mortality) occurred in a similar small number of patients receiving edoxaban and heparin-warfarin and the same was true for the combined primary safety endpoint (major and clinically relevant non-major bleeding events), irrespectively of TEE use. There was no difference in the delay between randomization and cardioversion in both treatment groups, likely because of a strict heparin protocol in the heparin-warfarin group. Thus, even though ENSURE-AF was exploratory due to underpowerment to show differences in efficacy and safety outcomes, it supports the use of edoxaban in patients undergoing a cardioversion both in an “acute” setting, that is as soon as 2 hours after the first dose of the drug in a TEE-guided approach, and in a delayed setting, after 3 weeks of anticoagulation, without a TEE.

7. Efficacy and Safety in Real-World

Real world data represent a fundamental tool in the hands of the clinician in that they complement and extend the information accrued through clinical trials. Given that Edoxaban has only recently received regulatory agencies' approval, we do not have enough real world information on this drug and we are waiting for data from the ETNA-AF (Edoxaban Treatment in routiNe clinical prActice in patients with non-valvular Atrial Fibrillation) registry.

Over the past few years, hundreds of real-world studies have been published. They provide us with a huge amount of data, which generally confirm the results of randomized clinical trials. In the following section, findings from the most interesting studies and meta-analyses will be discussed (see tables 5 and 6 for a summary of these studies). However, when it comes to

comparisons among different drugs in real-world studies, some limitations must be recognized, such as selective prescribing and the presence of unmeasured factors, which may confound the observations reported.

Table 5: Meta-analyses of real world studies.

Author	N of studies	N of patients	Comparison	Any stroke or systemic embolism (SSE)	Major bleedings (MB)
Ntaios et al[60]	28	66992(SSE); 348896(MB)	Dabigatran vs. VKA	HR, 0.93; 95% CI, 0.77–1.14	HR, 0,83; 95% CI, 0,65-1,05
		50620(SSE); 167532(MB)	Rivaroxaban vs. VKA	HR, 0.87; 95% CI, 0.71–1.07	HR, 1,00; 95% CI, 0,92-1,08
		15390(SSE); 89036(MB)	Apixaban vs. VKA	HR, 0.67; 95% CI, 0.46–0.98	HR, 0,55; 95% CI, 0,48-0,63
Romanelli et al[61]	7	348750		Stroke:	ICH:
			Dabigatran-150 mg vs. warfarin	HR, 0,92; 95% CI, 0,84-1,01	HR, 0,44; 95% CI, 0,34-0,59
			Dabigatran-110 mg vs. warfarin	HR, 0.92; 95% CI, 0.72–1.18	HR, 0.49; 95% CI, 0.34–0.72
Weeda et al[63]	9	51533	Rivaroxaban vs. VKA	NA	3.32 events/100 patients-years; 95% CI, 2.28-4.25
Bai et al[64]	17	NA	Rivaroxaban vs. warfarin	HR, 0.75; 95% CI, 0.64–0.85	HR, 0.99; 95% CI, 0.91–1.07
			Rivaroxaban vs. dabigatran	HR, 1.02; 95% CI, 0.91–1.13	HR, 1.38; 95% CI, 1.27–1.49

CI: confidence interval; HR: hazard ratio; NA: not available; VKA: vitamin K antagonist

7.1. DOACs vs. VKA

A very recently published meta-analysis[60] of 28 real world studies regarding the comparison of the three DOACs with VKA has shown that the three DOACs carry a significantly lower risk of intracranial hemorrhage (ICH) when compared to VKA and similar rates of ischemic stroke and ischemic stroke or systemic embolism. It also showed that the number of gastrointestinal hemorrhages was lower in patients treated with apixaban than in patients on VKA. In addition,

the number of myocardial infarctions was similar in patients treated with dabigatran and rivaroxaban and in patients treated with VKA. Finally, both apixaban and dabigatran use was associated with a significant reduction in mortality in that meta-analysis.

7.2. Dabigatran vs. Warfarin

Another earlier meta-analysis[61] regarding the comparison between dabigatran and warfarin was based on data from seven real world cohort retrospective studies, which included a total of 348750 patients (an approximately twenty-fold larger population than the RE-LY trial) observed for a mean of 2.2 years. It showed quite unexpectedly that dabigatran-150 mg was not superior to warfarin in preventing stroke, but had a significantly lower hazard of intracranial hemorrhage, with a 56% and a 51% relative hazard reduction with dabigatran-150 mg and dabigatran-110 mg, respectively. These results are concordant with the RE-LY trial, in which dabigatran 150 mg and dabigatran 110 mg had, respectively, a 60% and a 69% reduction in the hazard of intracranial hemorrhage. Furthermore, dabigatran-150 mg carried a significantly greater hazard of gastrointestinal bleeding than warfarin (1.23; 1.01–1.50; P =0.041), which was more evident in studies of older versus younger populations.

7.3. The XANTUS Study

Rivaroxaban has been evaluated in the prospective observational phase IV XArelto on preveNtion of sTroke and non-central nervoUS system systemic embolism in patients with non-valvular atrial fibrillation (XANTUS)[62] study, which included 6784 patients, followed for a mean of 329 days. Patients had a lower CHADS2 score than in the ROCKET-AF trial (a median of 2 vs. 3.5) and fewer patients had had a previous stroke/systemic embolism or TIA (19% vs. 55%); thus, this study included a population at a lower risk of stroke than the phase III trial, that is, a population closer to that studied in the other DOACs trials (in the RE-LY, the median CHADS2 score was 2.1-2.2 and 20% of patients had had a previous stroke/TIA; in the ARISTOTLE trial, the mean CHADS2 score was 2.1 and 19% had had a previous stroke/TIA; in the ENGAGE AF-TIMI 48 the mean CHADS2 score was 2.8 and 28% of the study population had experienced a previous stroke/TIA). Not unexpectedly, the number of major bleedings was lower in the XANTUS than in the ROCKET-AF (2.1/100 patient years vs. 3.6/100 patient years) as it was the number of strokes (0.7/100 patient years vs. 1.7/100 patient years).

7.4. Rivaroxaban vs. Warfarin

A meta-analysis[63] focused on the comparison between rivaroxaban and VKA regarding safety issues. This work gathered data from nine observational studies on 51533 patients and showed that rivaroxaban use in a real-world setting has a safety comparable to that observed in the phase III trial ROCKET-AF, with mean pooled rates of any major bleeding with rivaroxaban of 3.32 events/110 patient-years, higher than in the XANTUS study. This finding can be interpreted considering that the population studied was at a higher risk than that in the XANTUS study, and was thus similar to that in the ROCKET-AF.

7.5. Rivaroxaban vs. Dabigatran vs. Warfarin

One more meta-analysis[64] dealt with the comparison among rivaroxaban, dabigatran and

warfarin. It included 17 real-world studies, with 3 studies evaluating rivaroxaban vs. dabigatran, 11 rivaroxaban vs. warfarin and 3 doing both the comparisons. In the rivaroxaban vs. warfarin analysis, the rate of stroke/thromboembolism was lower for rivaroxaban than for warfarin. The pooled rate of major bleeding was similar for rivaroxaban and warfarin, but there was a net reduction in intracranial hemorrhages, "compensated" by an increase in gastrointestinal hemorrhages with the former. The mortality rates did not differ between the two treatment groups. In the rivaroxaban vs. dabigatran analysis, there was not any significant difference in the stroke/thromboembolism rate, whereas the major bleeding rate was significantly higher for rivaroxaban. Furthermore, rivaroxaban was associated with increased risk in all-cause mortality, any bleeding and gastro-intestinal bleeding, but similar risk of acute myocardial infarction and ICH, when compared with dabigatran. Hence, even though these results are limited by several factors such as heterogeneity and differences in the inclusion/exclusion criteria of the various studies in this meta-analysis, one should be particularly careful when prescribing rivaroxaban in individuals at high gastrointestinal bleeding risk.

Table 6: the Dresden Registry

Study	Drug	Patients	Stroke/TIA/systemic embolism	Major bleedings
Beyer-Westendorf et al[66]	Dabigatran	341	2.93/100 patient-years; 95% CI, 1.6-4.9	2.3/100 patient-years
Hecker J et al[67]	Rivaroxaban	1204	2.03/100 patient-years; 95% CI, 1.5-2.7	3.0/100 patient-years
Helmert et al[68]	Apixaban	514	2.4/100 patient-years; 95% CI, 1.5-3.5	2.8/100 patient-years
Michalski et al[69]	VKA	427	1.3/100 patient-years	4.15/100 patient-years; 95% CI, 2.6-6.29

7.6. The Dresden Registry

Registries are among the most interesting real world studies, in that they capture information on unselected patients prospectively.[65] The Dresden DOAC Registry provides us with information on the safety and effectiveness of the various DOACs (see Table 5 for details). This registry has shown that, in a real world setting, dabigatran,[66] rivaroxaban[67] and apixaban[68] perform substantially similarly with regard to both efficacy and safety. Also, the number of thromboembolic events in patients on dabigatran and apixaban was higher in this registry than in the registrative studies and similar to that observed with rivaroxaban in the ROCKET-AF trial. This finding points out once again that patients enrolled in the ROCKET-AF trial were a higher risk population as compared to those in the RE-LY or in the ARISTOTLE trials. All the DOACs users in the Dresden registry showed lower major bleeding rates when compared to very well managed (time in therapeutic range = 75%) and carefully selected VKA users in the same registry, whose rate of major bleedings was 4.2/100 patient-years.[69]

7.7. Danish Nationwide Databases

An interesting prospective cohort study[70] conducted in Denmark on a nationwide cohort of 61678 patients prescribed an oral anticoagulant for the first time reported on the comparative effectiveness and safety of DOACs vs. warfarin. 57% of patients received warfarin, 21% dabigatran, 12% rivaroxaban and 10% apixaban; all DOACs were prescribed in full dose. There were some differences among the groups prescribed the different anticoagulants: patients receiving dabigatran were younger and with a lower CHA2DS2-VASc score (2.2) than patients receiving the other drugs (CHA2DS2-VASc = 2.8). Patients on apixaban had a higher prevalence of previous ischaemic stroke, systemic embolism, or transient ischaemic attack (21%), whereas previous vascular disease was most prevalent among patients started on warfarin. This study showed no difference in the weighted rate of stroke/systemic embolism among the single DOACs (2.9-3.9/100 person-years) and warfarin (3.3/100 person years). The weighted rates of major bleeding and all bleedings were similar between rivaroxaban and warfarin; dabigatran and apixaban, instead, had lower rates of these endpoints. The risk of death was similar for rivaroxaban and warfarin, and it was higher than for dabigatran or apixaban. However, as already pointed out, patients baseline characteristics were different for each drug, potentially confounding these findings.

7.8. A Systematic Review of Safety

A very recent systematic review[71] compared the various oral anti coagulants with regard to safety and is very informative since it took into consideration 26 studies, mainly administrative claims related or registry based. In the dabigatran vs. VKA analysis, findings were quite variable, with nine out of sixteen studies reporting a lower major bleeding rate when compared with warfarin and the other seven reporting no difference. In the rivaroxaban vs. VKA analysis, seven studies were taken into consideration, without any difference in major bleeding rates between the two treatment groups in any of the studies. The apixaban vs. VKA analysis, based on findings from eight studies, was consistent showing a lower major bleeding rate in patients taking apixaban.

As for the comparisons among the three DOACs, in the dabigatran vs. rivaroxaban analysis, three out of four studies showed a better safety profile for dabigatran with the remaining study showing no difference. Seven studies compared apixaban and rivaroxaban, and showed a very large and significant reduction in major bleeding rate with apixaban (HR: 0.39–0.74; range of 95% CIs: 0.28–0.85). The comparison between apixaban and dabigatran was examined in seven studies: six showed a non-significant reduction in major bleeding rates with apixaban, whereas the remaining one showed no difference. Once again, these data need to be interpreted with great caution because of their heterogeneity, and readers must remember that not all real-world studies are created equal because of great differences in the populations studied (age, CHA_2DS_2-VASc scores, HASBLED scores, concomitant antiplatelet drugs) and in methodological issues.

8. Evidence Base for Low Doses

The evidence base supporting the use of reduced doses (that is, dabigatran 110 mg BID, rivaroxaban 15 mg QD, apixaban 2,5 mg BID, edoxaban 30 mg QD) is variable.

Dabigatran and edoxaban are the only DOACs for which the same patient population was

exposed to two different intensities of anticoagulation in the respective phase III trials.

In the RE-LY trial,[6] 6015 patients out of the 18113 enrolled were randomized to Dabigatran 110 mg. Dabigatran 110 mg BID proved noninferior to warfarin for stroke or systemic embolism prevention and safer for major bleedings. A subgroup analysis showed that advanced age is a risk factor for bleeding.[72] Therefore, Dabigatran 110 mg BID is recommended for those aged 80 years or above and for those taking verapamil concurrently, whereas it should be considered for those between 75 and 80 years, for an eGFR between 30 and 49 ml/min and for patients with a high bleeding risk. In the US, dabigatran 75 mg BID can be prescribed in case of an eGFR of 15-29 ml/min based on in vitro pharmacokinetics of the drug, whereas the 110 mg BID dose was not approved by the FDA.[73]

In the ENGAGE AF-TIMI 48 trial,[9] 7034 patients out of the 21105 included received edoxaban 30 mg QD. This dosage proved noninferior to warfarin for stroke or systemic embolism and safer for major bleedings. When compared to edoxaban 60 mg QD, the low dose (30 mg QD) proved safer with regard to major bleedings but less effective for stroke or systemic embolism prevention. Edoxaban 30 mg QD is recommended for patients with a low body weight (≤ 60 kg), in case of an eGFR between 15 and 49 or with concurrent administration of strong P-gp inhibitors.

As for rivaroxaban and apixaban, two different populations were exposed to a similar intensity of anticoagulation in phase III trials.

In the ARISTOTLE trial,[8] only 428 patients out of a total of 18201 received Apixaban 2.5 mg BID. The criteria for dose reduction were at least two of age ≥80, body weight ≤ 60 kg and serum creatinine ≥1.5 mg/dl and they have been kept in the label. A post hoc analysis[74] conducted on 790 patients aged 75 years or more compared apixaban 2.5 mg BID to warfarin. Apixaban proved more effective than warfarin in this analysis (HR 0.52, 95% confidence interval 0.25 to 1.08) and safer, with less major bleedings. Unfortunately, we do not have information regarding the indications for dose reduction in this subgroup.

In the ROCKET AF trial, the protocol mandated a dose reduction to rivaroxaban 15 mg QD in case of an eGFR between 30 and 49 ml/min. In the end, 1474 patients out of 14264 received Rivaroxaban 15 mg QD. In this group, efficacy and safety were similar to warfarin, thus reproducing the results observed in the whole cohort studied. Therefore, rivaroxaban should be given at a 15 mg QD dose when the eGFR is between 30 and 49 ml/min and it should be used with caution when the eGFR is between 15 and 29 ml/min.

Even though real-world data regarding the use of reduced dose DOACs are limited, this is an interesting topic since we estimate that approximately one third of patients are treated with these regimens. A recent real-world Danish study[75] evaluated dabigatran 110 mg BID, rivaroxaban 15 mg QD, apixaban 2.5 mg BID and warfarin in an anticoagulant naive population of 55644 atrial fibrillation patients. In this cohort, apixaban had a higher one year ischaemic stroke or systemic embolism rate (apixaban 4.8%; Dabigatran 110 BID 3.3%; rivaroxaban 15 mg QD 3.5%; warfarin 3.7%). In the DOAC vs. warfarin analysis, both dabigatran 110 mg BID and rivaroxaban 15 mg QD had a trend towards lower rates of ischaemic stroke or systemic embolism, whereas the reverse was true for apixaban 2.5 mg BID. For the principal safety outcome of any bleeding events, dabigatran had a significantly lower rate than warfarin, whereas there was no significant difference among apixaban, rivaroxaban and warfarin. However, these results need to be taken

with caution, since confoundings related to selective prescribing cannot completely be ruled out.

9. Conclusions

Over the past 9 years, the pharmacological approach to anticoagulation of patients with AF at risk of thromboembolic events has been revolutionized by the introduction of DOACs in clinical practice. These drugs show at least a comparable efficacy and safety profile to VKAs and, as a class, carry a far lower risk of intracranial hemorrhage. Furthermore, by means of their more predictable pharmacokinetic profile, they ensure a stable level of anticoagulation without needing any INR monitoring. However, given that these drugs are all at least partially renally eliminated, renal function needs to be monitored to avoid potentially dangerous drug accumulation. Their metabolism determines a certain risk of interactions with other drugs, which must be taken into account. Even though real-world studies provide us with a huge amount of information, which generally confirms that derived from registrative studies, their results must be interpreted with great caution because of the heterogeneity of the studied patients and of the methodologies. Nonetheless, we have so far a lot of data that with a well educated criticism may help to select the most appropriate anticoagulant treatment, always considering that a RCT comparing treatment with different DOACs will never be done.

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