

Review Article

Direct Oral Anticoagulants and Warfarin in Patients with Non-Valvular Atrial Fibrillation: Which Choice in Everyday Clinical Practice?

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Summary

The introduction of direct oral anticoagulants (DOACs) represents an epochal advance for stroke and arterial systemic embolism prevention in patients with non-valvular atrial fibrillation (NVAF), nevertheless their employment is no longer so easy to be applied to the general population. Even though advantages of DOACs in terms of efficacy and safety compared with traditional vitamin K antagonists (VKAs) has been shown in clinical trials, some mental reservations prevent a larger diffusion in routine practice. In addition the access to DOACs may pose an issue for many patients under healthcare systems not assuring these drugs. Indeed many physicians continue to prescribe VKAs in patients with NVAF just in those particular conditions which should require use of DOACs. Clinicians may be educated on the management of these new oral anticoagulants in order to choose the drug appropriately and to prevent as well as to treat bleeding complications. This paper aims to review the effectiveness and safety of three DOACs commercially available in comparison with warfarin as evaluated in those studies that report mainly information from international databases and post marketing surveillance studies (PMSS) and to consider their implication in real-life. The studies reported in this review show that among all DOACs commercially available in comparison to warfarin, apixaban is associated with lower risks either of stroke and systemic arterial thromboembolism or major bleeding (MB). Dabigatran demonstrates similar risk of stroke but lower risk of MB while rivaroxaban is associated with similar risks of both stroke and MB. A higher risk for major gastrointestinal bleeding (GIB) occurs in patients on dabigatran 150 mg and rivaroxaban 20 mg. Same results approximately has been obtained when DOACs were compared with each other.

ABBREVIATIONS

NVAF: Non-Valvular Atrial Fibrillation; DOACs: Direct Oral Anticoagulants; VKAs: Vitamin K Antagonists; GIB: Gastrointestinal Bleeding; ICH: Intracranial Haemorrhage; MI: Myocardial Infarction; PMSS: Post Marketing Surveillance Studies; MB: Major Bleeding; PSM: Propensity Score-Matched

INTRODUCTION

NVAF represents a high lifetime risk after age of 40 years and is associated with an increased risk of stroke and arterial systemic embolism [1]. Oral anticoagulation with VKAs has been the “gold standard” therapy for the last 50 years and can reduce the risk of stroke by more than 60% [2]. However VKAs have many limitations: the need of laboratory control by international normalized ratio of prothrombin time and dose adjustment, numerous food and drug interactions, different compliance between adult and elderly people, increased risk of MB with the age including ICH. The DOACs, as new oral anticoagulant strategy, because of their pharmacological properties may be given in fixed-dose, they reduce likelihood of drug–drug and drug–food interactions, and do not need coagulation monitoring, as compared to VKAs (Table 1) [3]. DOACs proved to be effective

and safe in clinical trials of large cohorts of patients with NVAF [4-7].

Nowadays commercially available DOACs are dabigatran (direct thrombin inhibitor), rivaroxaban, apixaban and edoxaban (factor Xa inhibitors). Dabigatran has been the first to be approved in US and in Italy for prevention stroke and systemic embolism in patients suffered from NVAF, while rivaroxaban, apixaban and edoxaban subsequently were approved.

Recently many PMSS are published which report outcomes of DOACs in clinical practice, as population-based health databases with particular attention to bleeding and adverse events [8-10].

AIMS OF THIS PAPER

This article aims to report the most relevant information from PMSS and databases of medical insurances regarding efficacy and safety of DOACs compared to VKAs and to each other for preventing NVAF in everyday clinical practice.

METHODS

Literature research has been performed by PubMed. The Medical Subject Headings and keywords used were “new oral anticoagulants”, “direct oral anticoagulants”, “apixaban”,

Table 1: Main characteristics of direct oral anticoagulants and warfarin.

agent	mechanism of action	half-life (hours)	renal clearance (%)	liver clearance (%)	dose (mg)	interactions	laboratory control
dabigatran	anti-factorIIa	6-10	80	20	110-150 twicedaily	protonpumpinhibitors	no
rivaroxaban	anti-factorXa	10-15	65	35	15-20 once daily	CYP3A4 inhib.	no
apixaban	anti-factorXa	12-14	30	70	2.5-5 twicedaily	CYP3A4 inhib.	no
edoxaban	anti-factorXa	10-14	35	65	30-60 twicedaily	CYP3A4 inhib.	no
warfarin	vitamin K antagonist	36-48	20	80	adjusted by INR	drugs and food	yes

Table 2: Risk of stroke/systemic embolism and of major bleeding of matched DOACs using Cox proportional hazards regression analysis.

DOAC	Risk of stroke/SE	Risk of major bleeding
dabigatran	[HR] 0.98, 95% CI 0.76–1.26, P= 0.98	[HR] 0.79, 95% CI 0.67–0.94, P<0.01
rivaroxaban	[HR] 0.93, 95% CI 0.72–1.19, P= 0.56	[HR] 1.04, 95% CI 0.90–1.20, P=0.60
apixaban	[HR] 0.67, 95% CI 0.46–0.98, P=0.04)	[HR] 0.45, 95% CI 0.34–0.59, P<0.001

All DOACs proved to have a lower risk of ICH.

Table 3: Risk of stroke, other thromboembolic events, major bleeding and death between different dosage of dabigatran and rivaroxaban using Cox proportional hazards regression analysis.

DOAC	Risk of stroke
dabigatran 150 mg bid vs rivaroxaban 20 mg od	[HR] 1.05; 95 % CI 0.97–1.13
dabigatran 75 mg bid vs rivaroxaban 15 mg od	[HR] 1.05; 95 % CI 0.94–1.18
	Risk of other thromboembolic events
dabigatran 150 mg bid vs rivaroxaban 20 mg od	[HR] 1.28; 95 % CI 1.14–1.44
dabigatran 75 mg bid vs rivaroxaban 15 mg od	[HR] 1.37; 95 % CI 1.15–1.62
	Risk of major bleeding
dabigatran 150 mg bid vs rivaroxaban 20 mg od	[HR] 1.32; 95 % CI 1.17–1.50
dabigatran 75 mg bid vs rivaroxaban 15 mg od	[HR] 1.51; 95 % CI 1.25–1.82
	Risk of death
dabigatran 150 mg bid vs rivaroxaban 20 mg od	[HR] 1.36; 95 % CI 1.19–1.56
dabigatran 75 mg bid vs rivaroxaban 15 mg od	[HR] 1.21; 95 % CI 1.04–1.41

“dabigatran”, “edoxaban”, “rivaroxaban”, “vitamin K antagonists”, “non-valvular atrial fibrillation”, “stroke”, “systemic arterial embolism”, and “prevention”.

Data from real-life studies

Since 2015 the risk of bleeding in patients treated with dabigatran vs VKAs was focused in many observational studies.

The results of these studies are broadly consistent with those of RE-LY trial. Several information has been reported in Danish studies of national databases about the use of DOACs in real-life. In a study, aimed to assess the efficacy and safety in an “everyday clinical practice” large population of anticoagulant-naïve patients with NVAf treated with dabigatran compared with warfarin, stroke and systemic embolism were not significantly different between patients on warfarin as well as those on dabigatran. Adjusted mortality was significantly lower with both dabigatran doses (110 mg b.i.d., propensity score-matched (PSM) group stratified hazard ratio [HR]: 0.79, 95% confidence interval [CI]: 0.65 to 0.95; 150 mg b.i.d., HR: 0.57, 95% CI: 0.40 to 0.80). Less ICH was observed with both dabigatran doses (110 mg b.i.d., HR: 0.24, 95% CI: 0.08 to 0.56; 150 mg b.i.d., HR: 0.08, 95% CI: 0.01 to 0.40). The incidence of myocardial infarction (MI) was lower with both dabigatran doses (110 mg b.i.d., HR: 0.30, 95% CI: 0.18 to 0.49; 150 mg b.i.d., a HR: 0.40, 95% CI: 0.21 to 0.70). GIB was lower with dabigatran 110 mg b.i.d. (HR: 0.60, 95% CI: 0.37 to 0.93) compared with warfarin but not with dabigatran 150 mg b.i.d [11]. Nevertheless in another observational study of nationwide Danish registries a cohort of VKA-naïve “new starters” on dabigatran (110 mg bid and 150 mg bid dose regimes) or warfarin, and a cohort of prior VKA-experienced “switchers” to dabigatran or “continuers” on warfarin followed for an average of 16 months, was found that switching from warfarin to dabigatran increased the risk of MI compared with continued warfarin usage in the early period after switching [12].

Villines TC et al., also compared the safety and effectiveness of dabigatran and warfarin in clinical practice with a PSM cohort study (12,793 patients per group; mean age 74) comparing treatment with dabigatran or warfarin in the US Department of Defense database. Primary outcomes were stroke and MB. Secondary outcomes included ischaemic and hemorrhagic stroke, major GIB, urogenital or other bleeding, MI and death. Time-to-event was investigated using Kaplan-Meier survival analyses. Outcomes comparisons were made utilising Cox-proportional hazards models of PSM groups. Dabigatran users experienced fewer strokes (adjusted HR [95 % CI] 0.73 [0.55-0.97]), major ICH (0.49 [0.30-0.79]), urogenital (0.36 [0.18-0.74]) and other (0.38 [0.22-0.66]) bleeding, MI (0.65 [0.45-0.95]) and deaths (0.64 [0.55-0.74]) than the warfarin group. MB (0.87 [0.74-1.03]) and major GIB (1.13 [0.94-1.37]) were similar between groups but major lower GIB were more frequent (1.30 [1.04-1.62]) with

dabigatran. In conclusion, compared with warfarin, dabigatran treatment was associated with a lower risk of stroke and most outcomes measured, but increased incidence of major lower GIB [13].

Similar findings were obtained in 2016 by Graham et al., Authors evaluated in the U.S. Medicare study the largest cohort of patients taking dabigatran as compared with warfarin [14]. Bleeding risk was compared in a PSM population of patients with NVAF who were naïve to anticoagulation and assumed either warfarin or dabigatran (67,207 patients in each group). It has been showed that the risk for MB with dabigatran was similar to warfarin (adjusted HR0.97; 95% CI, 0.88-1.07). Risk for ICH was significantly reduced with dabigatran (HR0.34; 95%CI, 0.26-0.46), but risk for major GIB was increased (HR 1.28; 95% CI, 1.14-1.44). Moreover the risk of GIB was highest in women aged 75-84 years (HR 1.50; 95%CI, 1.20-1.88) as well as in men and women 85 years (HR 1.55; 95% CI, 1.04-2.32) and (HR 2.18; 95%CI, 1.61-2.97) respectively. No difference in the rate of acute MI in both the groups was found (HR 0.92; 95% CI, 0.78-1.08).

US Department of Defense electronic health care records were consulted to describe MB rates in 27,467 patients receiving rivaroxaban [15]. This study showed that 496 MB events occurred in 478 patients, an incidence of 2.86 per 100 person-years (95% CI: 2.61-3.13). The patients with MB were older, mean age of 78.4 (SD 7.7) vs 75.7 (SD 9.7) years, compared to patients with no MB. Patients with MB had higher rates of concomitant diseases: hypertension (95.6% vs 75.8%), coronary artery disease (64.2% vs 36.7%), heart failure (48.5% vs 23.7%), and renal disease (38.7% vs 16.7%). Patients with MB took different doses of rivaroxaban: 63.2% 20 mg, 32.2% 15 mg, and 4.6% 10 mg respectively. The most frequent MB were GIB (88.5%) or ICH (7.5%). Of patients with MB 46.7% received a transfusion, while none received any type of clotting factor. Fourteen persons with MB died during their hospitalization (mean age 82.4 years), yielding a fatal bleeding incidence rate of 0.08 per 100 person-years (95% CI: 0.05-0.14).

Camm AJ et al., are investigators of Xantus study, an international, prospective, observational trial to describe the use of rivaroxaban in a broad NVAF patient population [16]. Consecutive patients with NVAF newly started on rivaroxaban were followed up at ~3-month intervals for 1 year, or for at least 30 days after permanent discontinuation. All adverse events (AEs) were recorded as AEs or serious AEs; major outcomes (including MB, symptomatic thromboembolic events [stroke, systemic embolism, transient ischaemic attack, and MI], and all-cause death) were centrally adjudicated. There were 6784 patients treated with rivaroxaban at 311 centers in Europe, Israel, and Canada. Mean patient age was 71.5 years (range 19-99), 41% were female, and 9.4% had documented severe or moderate renal impairment (creatinine clearance < 50 mL/min). The mean CHADS2 and CHA2DS2-VASc scores were 2.0 and 3.4, respectively; 859 (12.7%) patients had a CHA2DS2-VASc score of 0 or 1. The mean treatment duration was 329 days. Treatment-emergent MB occurred in 128 patients (2.1 events per 100 patient-years), 118 (1.9 events per 100 patient-years) died, and 43 (0.7 events per 100 patient-years) suffered a stroke. 598 patients (8.8%) had at least one interruption of rivaroxaban

therapy, which was most commonly because of a need for surgery, or because of bleeding or other AEs. Authors concluded that rates of stroke and MB were low in patients receiving rivaroxaban in routine clinical practice. These findings show that "real-world" routine clinical care is consistent with the safety profile observed in the trial Rocket AF. Apixaban given to patients with NVAF showed a lower rate of bleeding in comparison with warfarin (information from a Humedica medical record database concerning 2038 patients on apixaban and 24,872 on warfarin) (HR 1.34; 95% CI, 1.13-1.58) [17].

Patients hospitalized for MB while on treatment with VKAs or DOACs were included in a multicenter study to compare clinical presentation, management and outcome of bleeding [18]. The primary study outcome was death at 30days. The study included 806 patients, 76% on VKAs and 24% on DOACs. MB was ICH in 51% and 21% patients on VKAs or DOACs respectively (Odds Ratio [OR] 3.79; 95% CI 2.59-5.54) a GIB in 46% and 25% patients on DOACs and VKAs respectively (OR 2.62; 95% CI 1.87-3.68). Death at 30days occurred in 130 patients (16%), 18% and 9% of VKA and DOAC patients (HR 1.95; 95% CI 1.19-3.22, $p=0.008$). The rate of death at 30 days was similar in VKA and DOAC patients with ICH, 26% and 24% respectively (HR 1.05, 95% CI 0.54-2.02) and GIB, 11% and 7% respectively, (HR 1.46, 95% CI 0.57-3.74) but higher in VKA than DOAC patients with other MB, 10% and 3% respectively (HR 3.42, 95% CI 0.78-15.03). Admission for ICH is less frequent for DOAC patients compared with VKA patients. Admission for major GIB is more frequent for DOAC as compared to VKA patients. Mortality seems lower in patients with MB on DOACs rather than on VKAs but this finding varies across different types of MB.

Information was gotten about patients with NVAF taking apixaban, dabigatran, rivaroxaban, and warfarin using an US insurance database over a period of 5 years. Investigators created 3 matched cohorts using 1:1 propensity score: apixaban versus warfarin ($n=15,390$), dabigatran versus warfarin ($n=28,614$), and rivaroxaban versus warfarin ($n=32,350$). Apixaban was associated to a lower risk of stroke and systemic arterial embolism by Cox proportional hazards regression (HR 0.67, 95% CI 0.46-0.98, $P=0.04$), while dabigatran and rivaroxaban showed a similar risk (dabigatran: HR 0.98, 95% CI 0.76-1.26, $P=0.98$; rivaroxaban: HR 0.93, 95% CI 0.72-1.19, $P=0.56$). Apixaban and dabigatran were associated with lower risk for MB (apixaban: HR 0.45, 95% CI 0.34-0.59, $P < 0.001$; dabigatran: HR 0.79, 95% CI 0.67-0.94, $P < 0.01$), rivaroxaban was associated with a similar risk (HR 1.04, 95% CI 0.90-1.20, $P=0.60$). All DOACs proved to have a lower risk of ICH (Table 2) [19].

Effectiveness and safety of dabigatran versus rivaroxaban were compared by Hernandez and Zhang using US Medicare data in patients with NVAF [20]. Dabigatran 150/75 mg bid or rivaroxaban 20/15 mg od were considered. Overall 7322 patients received dabigatran 150 mg and 5799 rivaroxaban 20 mg, while 1818 received dabigatran 75 mg and 2568 rivaroxaban 15 mg respectively. Patients were followed until stroke, other thromboembolic events, bleeding, discontinuation or switch of an anticoagulant, death, or the end of study occurred. Cox proportional hazard models with propensity score weighting to compare clinical outcomes between groups were performed. No

difference was found for the risk of stroke between dabigatran 150 mg and rivaroxaban 20 mg (HR1.05; 95 % CI0.97-1.13) or between dabigatran 75 mg and rivaroxaban 15 mg (HR 1.05; 95 % CI 0.94-1.18). Rivaroxaban 20 mg compared with dabigatran 150 mg, showed a higher risk of other thromboembolic events (HR1.28; 95 % CI 1.14-1.44), MB (HR 1.32; 95 % CI 1.17-1.50), and death (HR 1.36; 95 % CI 1.19-1.56). The risk of thromboembolic events other than stroke (HR 1.37; 95 % CI 1.15-1.62), MB (HR 1.51; 95 % CI 1.25-1.82), and death (HR 1.21; 95 % CI 1.04-1.41) was also higher for rivaroxaban 15 mg than for dabigatran 75 mg. Authors concluded that there was no difference in stroke prevention between rivaroxaban and dabigatran, however rivaroxaban was associated with a higher risk of thromboembolic events other than stroke, death, and MB (Table 3).

To date no real-life studies on edoxaban in patients with NVAf were found.

DISCUSSION

Anticoagulation therapy is mandatory to prevent stroke and arterial systemic embolization in patients with NVAf. Nowadays 4 DOACs are commercially available worldwide: dabigatran, rivaroxaban, apixaban and edoxaban which have shown similar or superior efficacy and safety if compared to warfarin. This review from observational studies and PMSS reports information on dabigatran, rivaroxaban and apixaban. Database from real-life studies of these drugs regarding their increasing use in everyday clinical routine are available. They give much more information than randomized clinical trials. The pharmacological profile of DOACs overcomes many disadvantages of VKAs, such as dosage adjustments, periodic laboratory control, and drug-food interactions. Moreover the DOACs have been shown to cause significantly less ICH, even though more GIB have been observed. The majority of results from database concerning dabigatran are consistent with those of RE-LY study. A higher risk for major GIB occurs in patients on dabigatran 150 mg and rivaroxaban 20 mg. Additional studies have clarified bleeding risks for rivaroxaban and apixaban. These studies confirmed that the most considerable major bleeding occurring with rivaroxaban was GIB rather than ICH. Apixaban is associated with lower risk either of stroke and systemic arterial thromboembolism or MB, while dabigatran demonstrates similar risk of stroke but lower risk of MB. Rivaroxaban is associated with similar risks of both stroke and MB. Same results approximately have been obtained when DOACs were compared with each other. Nevertheless unlike with warfarin, which has reversal protocols with known antidotes easily available, clinicians are not yet well aware on the reversal strategies in DOACs.

CONCLUSION

Observational studies and PMSS reported in this paper use a large cohort of patients treated with dabigatran, rivaroxaban and apixaban or warfarin with the aim of preventing in NVAf in everyday clinical practice. They show a reduced risk of MB among all DOACs considered in comparison with VKAs with lower incidence of ICH, even though a higher incidence of GIB with rivaroxaban and dabigatran was observed. Moreover similar efficacy to that of VKAs have been reported on DOACs concerning prevention of stroke and arterial systemic embolism.

Real-life studies have their objectified weaknesses due to non-controlled and heterogeneous patient population as well as to influence of different variables such as the individual compliance, other co-morbidities and drug-drug/drug-food interactions. However, they provide a lot of information on how DOACs may be applied to the real world. In addition these findings may help to facilitate the choice of oral anticoagulant treatment in clinical practice. DOACs are proving to be effective and safe, however warfarin still plays an important role, so that the choice of the most appropriate therapy depends on individual risk factors and habits of patients.

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