Safety and Efficacy of Non-Vitamin K Antagonists in Atrial Fibrillation in the real world: A pooled-analysis and comparison of XANTUS and ETNA-AF-EU studies

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Abstract

Background: This study aims to assess the efficacy and safety of treatment with edoxaban or rivaroxaban for stroke prevention in patients with atrial fibrillation.

Methods: Pooled analysis from two real-world cohorts. Efficacy outcomes were all-cause mortality, cardiovascular mortality and thromboembolic events at 1 year. Safety outcomes were assessed by major or nonmajor bleeding.

Results: A total of 19876 patients were enrolled in both trials. All-cause mortality at 1 year was lower in the rivaroxaban group (118 of 6784 patients [1.7%]) than in the edoxaban group (442 of 13092 patients [3.5%]) (unadjusted odds ratio was 1.97 (95% CI, 1.61 to 2.42; $P < 0.00001$). Cardiovascular mortality was edoxaban (206 of 13092 patients [1.63%]) vs rivaroxaban 49 of 6784 patients [0.72%]) (unadjusted OR, 2.20; 95% CI, 1.61 to 3.00; $p < 0.00001$). Overall, the efficacy outcomes favoured the rivaroxaban cohort (OR 1.97, 95% CI, 1.33 to 2.91; $P = 0.0002$), with no significant difference in ischaemic stroke between the two cohorts (unadjusted OR 1.13, 95% CI, 0.75 to 1.73; $P = 0.56$). Overall, safety outcomes tended to occur more often in the edoxaban cohort (unadjusted OR 0.43, 95% CI, 0.20 to 0.40; $P < 0.00001$).

Conclusion: Rivaroxaban and edoxaban seem to be effective and safe. However, real-world prospective studies evaluating safety and efficacy in certain subgroups are needed.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults and is associated with increased morbidity and mortality [1]. With increasing life expectancy, the burden of comorbidities such as hypertension, diabetes mellitus, heart failure (HF), coronary artery disease (CAD) and chronic kidney disease (CKD), act as potentiators for the development of AF [2, 3].

Thromboembolic phenomena occur due to atrial thrombi in patients with AF, with ischemic stroke being the most common clinical presentation. Vitamin K antagonists for long have been the mainstay of therapy in these patients and have been widely studied in clinical trials with proven efficacy in reducing the risk of stroke [4–6]. The past decade was marked by the introduction of “non-vitamin K antagonist” or “direct” oral anticoagulants (DOACs). Currently available DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) have been validated in phase III trials against warfarin [7–10]. Despite a reduction of clinically significant stroke and a favourable risk profile when compared to warfarin in these trials, the use of DOACs may increase risk of bleeding, including events leading to hospitalization, transfusion, surgery, or involving particularly sensitive anatomic locations [11–12].

Current practice led by the rigorous results from RCTs with a strict protocol-based adherence raises questions about the generalizability of results to routine clinical practice (e.g., the application of strict

exclusion criteria on groups of patients who could otherwise benefit from the treatment). Furthermore, increased costs of RCTs limits follow-up duration and sample size which in turn, may result in decreased ability to detect adverse events.

Real-world data may help to better assess the benefits and risks of DOAC therapy, eventually allowing for more accurate definition of their indications and contraindications [17].

The aim of this study is to compare and assess efficacy and safety of treatment with edoxaban or rivaroxaban for stroke prevention in patients who initiated edoxaban or rivaroxaban treatment for stroke prevention, using a pooled analysis from two real-world prospective cohort studies.

Methods

Both the XANTUS and the ETNA-AF-Europe studies evaluated the safety and efficacy of DOACs in atrial fibrillation, as described in the article by Camm et al. and Groot et al., respectively [13, 14].

Study protocol registered on PROSPERO (CRD42021248187).

Before pooling data, we compared study protocols, in order to identify any recoding needed. We then provided a detailed dataset specification to each investigator (HF and HM) to prepare the data file for pooling. Data was checked for missing or duplicate values and for consistency and plausibility, resolving data queries through direct consultation with each investigator before analysis.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses of RCTs was used for this analysis [18].

The follow-up period was one year for both studies, but ETNA-AF-Europe is expected per protocol to have a follow-up period of four years.

The outcomes evaluated were all-cause mortality, cardiovascular mortality, thromboembolic events (including stroke, myocardial infarction, systemic embolism, transient ischaemic attack), bleeding (including major bleeding [defined using International Society on Thrombosis and Haemostasis criteria] and non-major bleeding [defined as any bleeding event not meeting the criteria for major bleeding]).

Prespecified subgroups according to baseline patient characteristics were age, sex, weight, body mass index, kidney function (glomerular filtration rate), coexisting conditions (hypertension, diabetes, congestive heart failure, myocardial infarction; previous stroke/systemic embolism or transient ischaemic attack). AF type at the time of enrolment, CHADS2 and CHA2DS2-VASc score were also noted [19, 20].

Both XANTUS and ETNA-AF-Europe investigators had no role in the design or conduction of the study, including the collection, analysis, or interpretation of the data, or in the writing of the manuscript or decision to submit it for publication.

Statistical analysis

All comparisons were estimated on an intention-to-treat basis. Categorical variables were described as percentages and estimated by odds ratio (OR) with a 95% confidence interval (CI). Continuous variables were described as mean $\pm$ standard deviation and analysed by weighted mean difference (WMD).

Statistic value I^2 assessed by Q test was used to quantify the degree of interstudy heterogeneity.

Considering the intrinsic variation in study design, we calculated the OR and WMD estimates using random-effects model for all comparisons. All P values were two-tailed, and the statistical significance was set at 0.05. Statistical analyses were performed using the Revman software package (Review Manager, Version 5.4. Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration).

Results

Study population

From June 2012 to December 2013, the XANTUS study enrolled 6784 patients across Europe, Israel, and Canada; the ETNA-AF-EU study enrolled 13,092 patients between November 2016 and February 2018 across 10 European countries (Austria, Belgium, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland and UK). Patients were routinely assigned to receive rivaroxaban or edoxaban, respectively. After the exclusion of patients who withdrew consent, or were lost to follow-up, a total of 19,876 patients were followed for 12 months. Baseline characteristics are as shown (Table 1). Patients in the XANTUS were significantly younger (71.5% vs 73.6%, $p = 0.0009$), when compared to the ETNA-AF-EU cohort. When comparing by age group, the XANTUS cohort had a higher proportion of patients < 65 years old (21.8% vs 15.2%, $p = 0.00001$); and patients between 65–74 years (41% vs 34%, $p = < 0.00001$). ETNA-AF-EU had a higher proportion of patients with 75 years or more (50.7% vs 37.2%, $p = < 0.00001$). Of note, ETNA-AF-EU had 89% and 10% of patients respectively less than 85 years old and more than 85 years old. The XANTUS cohort did not include patients in this age range.

Table 1
Patients Baseline Characteristics

	XANTUS n = 6,784	ETNA-AF- Europe n = 13,092	P-value Comparison among studies
Male, n (%)	4,016 (59.2%)	7,430 (56.8%)	0.0009
Age (years), mean ± SD	71.5 ± 10.0	73.6 ± 9.46	< 0.00001
By age sub-groups, n (%)			
< 65 years	1,478 (21.8%)	1,994 (15.2%)	< 0.00001
65–74 years	2,782 (41.0%)	4,456 (34.0%)	< 0.00001
≥75 years	2,524 (37.2%)	6,640 (50.7%)	< 0.00001
< 85 years	NA	11,718 (89.5%)	-
≥85 years	NA	1,372 (10.5%)	-
Body weight (kg), mean ± SD	83.0 ± 17.3	81.0 ± 17.29	< 0.00001
BMI (kg/m ²), mean ± SD	28.3 ± 5.0	28.1 ± 5.11	0.008
CrCl (mL/min), mean ± SD	NA	74.3 ± 30.42	-
Co-morbidities, n (%)			
Hypertension	5065 (74.7%)	10088 (77.1%)	0.0002
Diabetes mellitus	1333 (19.6%)	2879 (22.0%)	0.0001
Congestive HF	1265 (18.6%)	777 (5.9%)	< 0.00001
Myocardial Infarction	688 (10.1%)	560 (4.3%)	< 0.00001
Previous history of stroke and ICH, n (%)			
Ischaemic stroke	1291 (19.0%)	778 (5.9%)	< 0.00001

AF, atrial fibrillation; † In XANTUS group includes both (paroxysmal and non-paroxysmal). NA, Not Applicable; BMI, Body Mass Index; CHADS, congestive heart failure, hypertension, age > 75 years, diabetes; previous stroke, CHADSVASC, congestive heart failure, hypertension, age > 75 years, diabetes; previous stroke; Vascular disease; crnm, clinically relevant non-major, HF, heart failure, CrCl, Creatinine clearance, SD, standard Deviation.

	XANTUS n = 6,784	ETNA-AF- Europe n = 13,092	P-value Comparison among studies
Intracranial haemorrhage	NA	62 (0.5%)	-
Previous history of bleeding, n (%)			
Major	NA	129 (1.0%)	-
Major or CRNM	NA	270 (2.1%)	-
AF type, n (%)			
First diagnosed	1,253 (18.5%)	NA	-
Paroxysmal	2,757 (40.6%)	7,039 (53.9%)	< 0.00001
Persistent	923 (13.6%)	3,159 (24.2%)	< 0.00001
Permanent [†]	1,835 (27.0%)	2,864 (21.9%)	< 0.00001
CHADS2, mean ± SD	2.0 ± 1.3	1.7 ± 1.07	< 0.00001
CHA2DS2-VASc, mean ± SD	2.0 ± 1.3	3.1 ± 1.40	< 0.00001
AF, atrial fibrillation; † In XANTUS group includes both (paroxysmal and non-paroxysmal). NA, Not Applicable; BMI, Body Mass Index; CHADS, congestive heart failure, hypertension, age > 75 years, diabetes; previous stroke, CHADSVASC, congestive heart failure, hypertension, age > 75 years, diabetes; previous stroke; Vascular disease; crnm, clinically relevant non-major, HF, heart failure, CrCl, Creatinine clearance, SD, standard Deviation.			

Patients in the XANTUS cohort had a significantly higher body weight and body mass index, $p = < 0.00001$ and $p = 0.008$, respectively.

Known history of hypertension and diabetes mellitus were significantly lower in the XANTUS cohort when comparing with ETNA-AF-EU cohort, (74% vs 77.1%, $p = 0.0002$) and (19.6% vs 22%, $p = 0.0001$), respectively. Known congestive heart failure and myocardial infarction were higher in the XANTUS cohort (18.6% vs 5.9%, $p = < 0.00001$, and 10.1% vs 4.3%, $p = < 0.00001$, respectively).

Previous ischemic stroke was significantly more frequent in the XANTUS cohort (19% vs 5.9%, $p = < 0.00001$).

Regarding AF type at baseline, paroxysmal and persistent types were significantly lower in the XANTUS cohort (40.6% vs 53.9%, $p = < 0.00001$, and 13.6% vs 24.2%, $p = < 0.00001$, respectively). Permanent AF was more prevalent in the XANTUS cohort (27% vs 21.9%, $p = < 0.00001$). CHA2DS2-VASc was significantly lower in the XANTUS cohort ($p = < 0.00001$).

Efficacy outcomes

All-cause mortality at 1 year was significantly lower in the XANTUS cohort. Death occurred in 442 of 13092 patients (3.5%) in the ETNA-AF-EU vs 118 of 6784 (1.7%) in the XANTUS cohort ($p = < 0.00001$, Table 2). The overall all-cause mortality odds ratio was 1.97 (95% confidence interval [CI], 1.61 to 2.42; $p = < 0.00001$). The same trend was noted for cardiovascular mortality, 206 of 13092 (1.63%) vs 49 of 6784 (0.72%) patients (OR, 2.20; 95% CI, 1.61 to 3.00; $p = < 0.00001$) for ETNA-AF-EU vs XANTUS, respectively.

Table 2
Outcomes in XANTUS and ETNA-AF

	XANTUS n = 6,784	ETNA-AF-Europe n = 13,092	P-value Between studies
All-cause mortality, n (%)	118 (1.7%)	442 (3.5%)	< 0.00001
Cardiovascular mortality, n (%)	49 (0.72%)	206 (1.63%)	< 0.00001
Thromboembolic events, n (%)			
Stroke ischaemic, n (%)	32 (0.5%)	70 (0.56%)	0.56
Transient ischaemic attack, n (%)	32 (0.5%)	NA	-
Systemic embolism, n (%)	8 (0.1%)	103 (0.82%)	< 0.00001
Myocardial infarction, n (%)	27 (0.4)	66 (0.52%)	0.30
CNS Bleeding			
Haemorrhagic stroke, n (%)	11 (0.2%)	14 (0.11%)	0.30
Intracranial haemorrhage, n (%)	26(0.4%)	30 (0.24%)	0.05
Major bleeding, n (%)	128 (1.9%)	132 (1.05%)	< 0.00001
CRNM bleeding, n (%)	878 (12.9%)	293 (2.35%)	< 0.00001
Major GI bleeding, n (%)	52 (0.8%)	51 (0.40%)	0.00006
TIA, transient ischaemic attack; SE, systemic embolism; MI, myocardial infarction; CNS, Central Nervous System; CRNM, Clinically Relevant Non-major bleeding (GI, gastrointestinal; ICH, intracranial haemorrhage). a. XANTUS includes combined results of both stroke/SE + SE			

Myocardial infarction, Ischemic stroke and systemic embolism were more common in the ETNA-AF-EU cohort when compared to the XANTUS cohort (Table 2)., but only systemic embolism was significantly

higher in the ETNA-AF-EU cohort (OR, 6.72; 95% CI, 3.27 to 13.80; $p < 0.00001$) (Fig. 3). The overall efficacy outcome favours the XANTUS cohort ($p = 0.0002$; $I^2 = 82\%$).

Safety outcomes

There were no differences between haemorrhagic stroke between the two cohorts, 14 (0.11%) vs 11 (0.2%, $p = 0.30$) patients. However intracranial haemorrhage was significantly higher in the ETNA-AF-EU 30 (0.24%) vs 26 (0.4%) patients (OR 0.60; 95% CI, 0.35 to 1.01; $p = 0.05$). Major bleeding was significantly higher in the ETNA-AF-EU cohort (OR 0.53; 95% CI 0.41 to 0.68; $p < 0.00001$). Clinically relevant non-major bleeding (CRNM bleeding) and major GI bleeding were also higher in the ETNA-AF-EU cohort, 293 of 13092 (2.35%; OR 0.15; 95% CI 0.13 to 0.18; $p < 0.00001$) and 878 of 6784 (12.9%; OR, 0.51; 95% CI, 0.34 to 0.75; $p = 0.0006$) patients, respectively. Overall safety outcome favours the ETNA-AF-EU cohort ($p < 0.00001$; $I^2 = 96\%$)(Fig. 4).

Discussion

The results of this prospective cohort-level pooled-analysis provide a robust in-depth insight into the overall effectiveness of DOACs in patients presenting nonvalvular atrial fibrillation than the results of the individual phase 4 trials. We found evidence that treatment with DOAC resulted in lower mortality, a finding that is consistent with the results of previous trial-level meta-analysis [15–16]. Nonetheless, results from meta-analysis of phase III trials should be interpreted with caution as different methods may be applied in the conduction of these trials. Although the two cohorts included in this analysis occurred in geographically distinct health care systems, there was no evidence of any cohort-specific effect.

Oral anticoagulation (OAC) for stroke prevention is one of the mainstays of management of AF, and warfarin has been used for a long time. Vitamin K antagonists (VKA) are associated with approximately 64% risk reduction of stroke when compared to placebo [21, 22]. In terms of efficacy, DOACs have proven to be noninferior to VKAs in stroke prevention. However, DOACs presented a safer profile with regards to serious bleeding when compared to VKAs [23–25]. In our analysis there were no significant differences in ischaemic stroke and myocardial infarction rates among patients treated with two different DOACs. This finding is in line with a previous meta-analysis by Gargiulo et.al [26]. However, systemic embolism was found to be significantly lower in the XANTUS cohort. Almutairi et.al, has reported inconsistencies in the effect of rivaroxaban (in terms of stroke/SE, major bleeding in VTE) between RCTs and observational retrospective studies [27]. Currently there are no similar prospective studies comparing safety and efficacy in this manner, so we have no other term of comparison. Furthermore, we do not know the proportion of patients on combination therapy (antiplatelet and DOAC), and whether or not that played a role in the efficacy outcomes.

Prevention of thromboembolic events may come at a cost of increased bleeding risk. However current guidelines state that a high bleeding risk score should not be a motive to withhold OAC [28]. A study by Kim et.al., found overall major bleeding and intracranial bleeding to be significantly lower when compared

to warfarin, (RR 0.80, 95%CI 0.67–0.94, $p = 0.008$, $I^2 = 84\%$ and $RR < 0.50$, $p < 0.01$), respectively. Furthermore, intracranial bleeding was lower irrespective of age or dose [29]. The present analysis found significantly lower overall safety outcomes, although the comparison is between DOACs. Nonetheless, differences were noted among the two prospective cohorts, where the overall bleeding events were found to be higher in the ETNA-AF-EU cohort. Our results were unadjusted, and with a high degree of heterogeneity, which may indicate a degree of bias. The fact that the ETNA-AF-EU cohort had an older population, may be a plausible justification for this finding. Another important factor may be dose-related (standard vs low dose). A subanalysis of a study performed by Xue and Zhang, found that standard-dose DOAC users had lower risks of stroke and systemic embolism, all-cause death, major bleeding, intracranial bleeding, and gastrointestinal bleeding, whereas low-dose DOAC users showed reduced risks of major bleeding and intracranial bleeding but had comparable risks of efficacy outcomes [30].

To the best of our knowledge this is the first analysis assessing safety and efficacy of DOACs in atrial fibrillation using prospective cohort's data, and unlike the results of observational studies, this real-world prospective data relies exclusively on random assignment, avoiding biases related to confounding by indication, regression to the mean, or preconceptions of trends in cardiovascular-related mortality. This calls for collaboration among groups to address key methodologic aspects of independently conducted research, that should be harmonized in advance, to enable generation of stronger evidence-based data. Furthermore, this suggests that by aligning key measurements and using a prespecified plan to perform a prospective meta-analysis of real-world patient data to answer questions beyond the scope of each individual trial, advantages for all parts involved in the research, investigators, patients and funding agencies could be achieved.

Study Limitations

This is an aggregate data pooled-analysis, individual patient data are not publicly available at the time, therefore, subgroup analyses exploring specific subsets of patients or the role of different variables across the cohorts was not done but is highly desirable. The analysis is also limited by the underlying internal and external validity of the two studies. Neither was blinded, which may introduce bias. Patients were enrolled in several regions of the world, and groups may not be representative especially those in low-income and middle-income countries.

Conclusion

Despite the limitations, our analysis showed that use of DOACs is effective and safe; there are still questions to be addressed regarding the safety and efficacy profiles in given subgroups, and thus more real-world prospective studies evaluating the effectiveness and safety of this agents is needed.

Declarations

Author contribution

HF, HM method design, JA reviewing method and resolving query disputes. Writing the manuscript HF. ARF, FM critically reviewing the manuscript. JM and CM equally participated as senior authors and further revision of the manuscript.

Conflict of interest

The authors declare no conflicts of interest in association with the present study.

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Figures

Figure 1

Forrest-plot Showing Efficacy Outcomes. Odds ratio were adjusted. The size of the square corresponds to the number of patients in each subgroup.

Figure 2

Forrest-plot Showing Safety Outcomes. Odds ratio were adjusted. The size of the square corresponds to the number of patients in each subgroup.

Figure 3

Funnel plot showing uneven distribution of outcomes, indicating high risk of bias