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ORIGINAL INVESTIGATION

All-Cause Mortality and Cardiovascular Outcomes with non-Vitamin K Oral Anticoagulants versus Warfarin in Patients with Heart Failure in the Food and Drug Administration Adverse Event Reporting System (FAERS)

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Short title: Heart failure, anticoagulants and outcomes in FAERS

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ABSTRACT

IMPORTANCE: Many patients with heart failure (HF) are treated with warfarin or non-vitamin K antagonist oral anticoagulants (NOACs). Randomized outcome-driven comparisons of different anticoagulant strategies in HF are lacking. Data from international, government-mandated registries may be useful in understanding the real-life use of various anticoagulants and how they are linked to outcomes.

OBJECTIVE: To assess 2015 annual all-cause mortality, myocardial infarction, and stroke rates co-reported for warfarin and NOACs in subjects with and without HF in the US Food and Drug Administration Adverse Event Reporting System (FAERS) database.

DESIGN, SETTING, PARTICIPANTS: We extracted and examined outcome cases in subjects with HF and on warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban and stratified these according to anticoagulants.

MAIN OUTCOMES AND MEASURES: Annual all-cause mortality, myocardial infarction and stroke in FAERS.

ANALYSIS METHOD: Odds ratio (OR) and Chi-square (χ^2) for oral anticoagulants from FAERS with and without HF among complete primary reports issued in 2015.

RESULTS: FAERS reported 137,026 HF cases, with death co-reported in 42,942 (31.3%). 11,278 (8.2%) HF patients were treated with anticoagulants, with more prescribed warfarin (n=8,260) than all NOACs combined (n=3,018). Very few reports for edoxaban were available. Warfarin consistently displayed a signal for excess adverse events compared to NOACs: OR (95% CI) for the composite of mortality, myocardial infarction and stroke were 1.91 (1.76-2.07) versus apixaban, 1.92 (1.81-2.03) versus dabigatran, 4.09 (3.38-4.37) versus rivaroxaban and 2.64 (2.53-2.76) versus all NOACs combined (all $P < 0.001$). Warfarin, compared to all NOACs combined demonstrated higher rates of all-cause mortality (OR=2.69 (95% CI 2.49-2.90)), myocardial infarction (5.30 (4.17-6.74)), stroke (OR=8.85 (6.61-11.84)), and ischemic stroke (OR=12.73 (8.87-18.27); all $P < 0.001$).

CONCLUSIONS AND RELEVANCE: Annual 2015 FAERS profiles in HF patients reveal that warfarin was numerically dominant. Warfarin was associated with higher risk of death, myocardial infarction and stroke compared to NOACs. These observational data provide real-world insight into a potential safety benefit of NOACs over warfarin in the setting of HF.

Key Words: Warfarin; NOAC; Apixaban; Dabigatran; Edoxaban; Rivaroxaban; Adverse Events; Repository; Safety; Mortality

Clinical Significance

QUESTION How safe are oral anticoagulants in patients with heart failure (HF)?

FINDINGS In this analysis of 137,026 adverse event (AE) reports in subjects with HF, more AE were co-reported with warfarin (n=8,260) than all NOACs combined (n=3,018). Warfarin was more frequently co-reported with all-cause mortality, myocardial infarction and stroke, resulting in significantly higher odds ratios for these outcomes than all NOACs individually and combined.

MEANING In patients with HF and on anticoagulation, analysis of AE reports suggest that NOAC may be safer than warfarin.

INTRODUCTION

Contemporary pharmacotherapy for heart failure (HF) recommended by guidelines bodies does not entail routine use of anticoagulants¹. Yet, a sizable proportion of patients with HF suffers from comorbid conditions, most notably atrial fibrillation^{2,3}. Atrial fibrillation is not only highly prevalent in HF but also worsens prognosis; therefore, warfarin or non-vitamin K oral anticoagulants (NOACs) are important components of medical therapy⁴⁻⁶. Other common indications for oral anticoagulation in HF are thromboembolic events or prosthetic heart valves; the latter requiring warfarin at higher intensity than in atrial fibrillation. As anticoagulation therapy may cause adverse events in real world clinical settings, continued post-marketing clinical surveillance is warranted.

The NOACs with its protagonist agents dabigatran, rivaroxaban, apixaban, and edoxaban have been tested in large-scale randomized clinical trials (RCT) in AF against warfarin, but no large-scale randomized head-to-head comparisons of these NOACs have been performed⁷. In addition, despite their widespread use, post-RCT surveillance safety data on bleeding and other risks of NOACs and warfarin are scarce; in particular, data in the HF population are lacking.

The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is a publicly available database that contains information on adverse event and medication error reports submitted to the FDA⁸. FAERS is a passive surveillance system that relies on voluntary reporting by healthcare professionals and consumers, as well as required mandatory reporting by the pharmaceutical industry. FAERS includes spontaneous reports from US sources; serious and unlabeled spontaneous reports from non-US sources; and serious, unlabeled, and attributable post-marketing clinical trial reports⁹. The past and current use, advantages, challenges and future directions of data mining at the FDA repository have been described in detail¹⁰.

In this paper, we compare all-cause mortality, myocardial infarction and stroke rates from the 2015 FAERS repository, co-reported with HF and associated with the type of oral anticoagulant used. Our hypothesis was that real-world data would show important advantages for NOACs compared to warfarin, as experienced in routine clinical practice.

METHODS

Data source

We performed drug mapping of FAERS cases with an FDA receipt date of 2015, and created a list of synonyms for 5 anticoagulants. All FAERS 2015 records were searched by terms: “warfarin”, “dabigatran”, “rivaroxaban”, “apixaban”, “edoxaban”, “Pradaxa”, “Xarelto”, “Eliquis”,

“Savaysa”, “Lixiana”, “Brumolin”, “Athrombine k”, “Coumadin”, “Coumafen”, “Coumafene”, “Coumaphene”, “Coumarin”, “Coumefene”, “Dethmor”, “Dethnel”, “Dicusate”, “Kumader”, “Kumadu”, “Kumatox”, “Kypfarin”, “Latka 42”, “Maveran”, “Marcoumar”, “Panwarfin”, “Prothromadin”, “Ratorex”, “Rodafarin”, “Rosex”, “Solfarin”, “Vampirinip”, “Warfarat”, “Warfarina”, “Warfarine”, “Warfarinum”, “Zoocoumarin”, “death”, “myocardial infarction”, and “stroke”. Following established search strategies, heart failure was defined if any one of these terms were used as a diagnosis¹¹: “ACUTE PULMONARY OEDEMA”, “CARDIAC ASTHMA”, “CARDIAC CIRRHOSIS”, “CARDIAC FAILURE”, “CARDIAC FAILURE ACUTE”, “CARDIAC FAILURE CHRONIC”, “CARDIAC FAILURE CONGESTIVE”, “CARDIOGENIC SHOCK”, “CARDIORENAL SYNDROME”, “LEFT VENTRICULAR FAILURE”, “LOW CARDIAC OUTPUT SYNDROME”, “PULMONARY CONGESTION”, “PULMONARY OEDEMA”, and “REDUCED LEFT VENTRICULAR EJECTION FRACTION OF LESS THAN 40%”. Duplicate cases were dealt with by combining reports with identical case numbers. We included only reports where oral anticoagulants were clearly indicated as a “primary cause” of the reported event. Cases not reporting an outcome were categorized as negative. To avoid bias, data mining and statistics were performed by independent researchers at FDABLE, LLC (Glastonbury, CT), a for-profit group that specializes in FAERS database analyses.

Patient Involvement

FAERS is a public freely accessible database, where the patient identity is protected by coding. Patients, service users, or providers were not involved in the design of this study. The development of outcome measures was not informed by patients’ priorities, experience, and preferences. No patients were involved in the recruitment to and conduct of the index study.

Outcomes

Primary endpoints for this study were the relative frequencies of all-cause mortality, stroke, and myocardial infarction in FAERS for cases originating in 2015 and co-reported with HF. To circumvent the potential issue of multiple reports for a single event, outcomes were counted by unique case numbers rather than by report numbers. For example, if a single case had multiple separate reports and each report indicated the same event, the qualifying count was a single adverse event and the other update reports were omitted.

Statistical Analysis

FAERS data were analyzed by “disproportionality” signal and were scored using proportional

reporting ratio and reporting odds ratio¹². For example, in this study, the proportional reporting ratio was used to analyze the relative frequency of a particular outcome category co-reported with one anticoagulant compared to the frequencies co-reported with the remaining agents. A proportional reporting ratio of 1 indicates that an adverse event was co-reported with identical frequency to the comparator drug, whereas a value >2 indicates a frequency two times that of the comparator drug. Chi square contingency analyses—with Yates correction—measured the statistical significance of an observed disproportionality. A higher chi-square value corresponds to a lower probability that the observed disproportionality occurred solely by chance¹².

RESULTS

From 8,288,134 screened total FAERS cases, we omitted 8,151,108 and qualified 137,026 events co-reported with HF. Among these reports, 11,324 were co-reported with both HF and an oral anticoagulant: subjects prescribed warfarin (n=8,260; 72.9%) were numerically dominant compared to subjects prescribed NOACs (n=3,064; 27.1%). With regard to the separate NOACs, 666 cases received apixaban, 1361 dabigatran, 1005 rivaroxaban, and 32 edoxaban (table 1). The odds of FAERS cases co-reporting warfarin and HF were 2.09 versus apixaban, 2.05 versus dabigatran, 4.20 versus rivaroxaban, and 2.21 versus edoxaban. Among warfarin users, a larger proportion was under 75 years of age and a greater proportion co-reported hypertension or diabetes relative to NOACs. Most other demographics including gender were distributed fairly even among warfarin and NOACs cohorts. A very substantial percentage of patients used either concomitant aspirin or other platelet inhibitors.

We identified 3,549 deaths, 956 myocardial infarctions, and 265 strokes of which 209 were reported ischemic and 23 hemorrhagic (table 2). Among the 8,260 total cases with warfarin, 2595 (31.3%) deaths, 850 (10.3%) myocardial infarctions, and 200 (2.4%) strokes were identified, of which 169 (84.5% of all strokes) were ischemic.

The sample size for all-cause mortality comparison against warfarin was sufficient for apixaban ($\chi^2=11.09$), dabigatran ($\chi^2=3.59$), rivaroxaban ($\chi^2=2.53$), and edoxaban ($\chi^2=3.55$). All-cause mortality, myocardial infarction, and stroke for warfarin were higher versus each single NOAC and NOAC combined (table 2). Edoxaban was omitted from individual analysis due to very few available reports but was included in the aggregate NOAC data. There was a consistently higher rate of adverse events for warfarin compared to all NOACs combined with the following odds ratio (OR; confidence interval, 95% CI): for mortality OR 2.69 (2.49-2.90); myocardial infarction OR 4.91 (3.95-6.10); ischemic stroke OR 12.73 (8.87-18.27); and hemorrhagic stroke OR 5.32 (2.07-13.66) (Table 3 and Fig. 1). The risk of any adverse event report with warfarin was also

higher than with each NOAC (Fig. 2).

Discussion

This work in large uniformed international repository data shows that NOACs are associated with more favourable outcomes compared to warfarin in patients with HF. Apixaban, dabigatran, rivaroxaban as well as all NOACs combined (including a limited number of edoxaban reports) were associated with substantially lower numbers of reports and consequently, lower risk for the outcomes all-cause mortality, myocardial infarction, and stroke.

FAERS data originate from spontaneous reports of medication adverse events, medication error reports and product quality complaints submitted by healthcare professionals and the pharmaceutical industry. Given the paucity of comparative randomized trial data on NOACs versus warfarin and their almost complete lack in the HF population, this work provides much needed post-marketing insight real-world clinical practice: First, warfarin was still the numerically dominant anticoagulant in 2015. Second, we targeted only the most definitive clinical outcomes, such as death, myocardial infarction and stroke in our analysis. For each investigated endpoint each NOAC was associated with a more favorable outcome. Third, there appeared to be no major differences between the different NOACS with regards to reported major AE. Lastly, aggregate data for all NOACs combined strongly suggest lower adverse event rates versus warfarin for all examined outcomes.

Strengths of the current data

Our findings provide complementary evidence to data from randomized clinical trials, administrative dataset and registries¹³⁻¹⁷. Following market approval, safety (and efficacy) of novel pharmacological agents must be established in everyday clinical practice such as in this work, with long-term follow up and outside of the rigorously controlled conditions of RCTs. In HF, RCTs usually target highly selected populations, and typically exclude important subgroups (such as those with HF with comorbid kidney dysfunction). Furthermore, even in very recent large HF trials study subjects are often much younger than in real-world clinical practice^{18,19}.

Other potential shortcomings of RCTs may be variations in antecedent warfarin use, different drug discontinuation rates and suboptimal follow-up^{7,20}. For example a FDA-generated analysis found up to double-digit rates of discontinuations and incomplete follow-up rates in RE-LY (21% and 9%), ROCKET-AF (28% and 20%), ARISTOTLE (25% and 15%), and ENGAGE (34% and 10%)²¹.

The study was conducted within a frame of a government-run uniformed international database. Independent specialists focusing on exploring FAERS repository executed all data mining and performed statistics. This neutral approach is important since there has been no studies quantifying adverse events following the four NOACS and warfarin, with no any systematic evidence with regard to associated risks.

The sample sizes for death reports and vascular outcomes were sufficient for each anticoagulant to make reasonable comparisons, since FAERS requires mandatory death, myocardial infarction, and stroke reporting²². Edoxaban as the latest approved NOAC accrued low numbers of FAERS records, therefore exhibiting large confidence intervals.

This work also provides important knowledge on the comparative performance of different anticoagulants. Although each NOAC has been individually trialed against warfarin, multi-NOAC clinical outcome-driven comparisons have not been performed. RCTs aim to advance promising novel compounds by evaluating differences versus standard-of-care but rarely against competitors within the same drug class. Our work includes all anticoagulants and shows similar significant reductions in mortality and other important clinical events with each NOAC relative to warfarin.

Together, this data provides novel and comprehensive insight into the safety of oral anticoagulation therapy in the general public.

Possible weaknesses and limitations

A multitude of factors may limit the validity of our work: this non-randomized observational dataset may be prone to bias by indication for anticoagulation, and exposure to and dose of the anticoagulant; further, by patient factors and medication adherence, and physician preferences and experience.

In HF, there is no indication for anticoagulation unless specific commodities (most commonly, atrial fibrillation) exist. Thus, anticoagulation itself is likely a marker of risk in HF because patients with atrial fibrillation fare worse outcomes than those in sinus rhythm and respond less well to established HF pharmacotherapy³. The indication for and duration, quality and intensity of anticoagulation therapy are unknown and may yield potentially different outcome risks.

First, initial indications for anticoagulants will differ between warfarin and NOACs. For instance, mechanical prosthetic valves require higher-intensity warfarin (INR 2.5 to 3.5) therapy than atrial fibrillation, and none of the NOACS are indicated. Although patients assigned to warfarin at higher intensity spend more time in therapeutic range they may also be more exposed to bleeding events²³. Second, we do not know the relative distribution of specific anticoagulants

among HF patient, making it impossible to distinguish the real causes of event into natural outcome of the disease *per se*, or true drug effect. Third, duration of therapy (patient years) until occurrence of an AE may be different with likely longer exposure with warfarin over NOACs. Fourth, the importance of polypharmacy with drug interactions is unknown, although only FAERS records where oral anticoagulants were indicated as a “primary cause” of the reported event were included.

Besides drug, patient and physician-related factors, reporting bias may also be due to the perception of clinicians which may focus relatively more on AE occurring with novel agents compared to well-established therapies with known risks such as warfarin. Event adjudication is at the reporting physician’s discretion, and source documents are rarely examined. Due to missing feedback between the FDA and filing source many reports suffer from incomplete and/or missing values. Here, age was missing in 24% and gender in 9% of reports. Confusion by indication is also extremely important, but not addressed in the index study. All the records were pooled by HF as a diagnosis, but not AF, valve disease or other anticoagulant indications. True anticoagulants in HF are most likely attributed to AF, but warfarin patients being younger most likely indicative for valve diseases. However, FAERS records can not be adjusted for age or gender, since some data are missing.

We employed advanced mining techniques and statistical algorithms proven to reliably identify sufficiency of sample size and to pick up the “disproportionality signal” to detect the differences among groups. The sample size for reported outcomes for all anticoagulants was sufficient to justify and conduct the index analyses.

Summary and conclusions

Our data provides real-world insight into a possible benefit of NOACs over warfarin in patients with HF using oral anticoagulation. Annual 2015 FAERS profiles in HF patients reveal that warfarin was overrepresented among adverse event reports. Compared to NOACs, the use of warfarin was associated with significantly increased all-cause mortality and major cardiovascular events. The observed favorable risk-benefit profile is in agreement with the magnitude of such effect reported in a pooled trial meta-analysis⁷.

Yet, there may be substantial differences in the risk profile of the patients who use NOACs compared with warfarin, and interpretation of this analysis should be done with utmost caution.

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Contributors

SA, DA, IH, DK, RJM and VS conceived the study and planned the analytic approach. TvL, JJ, IH, DK, RJM and VS interpreted the results. TvL, IH, DA, RJM and VS drafted the paper. JJ, IH, DK, RJM and SA commented on and edited further drafts. VS and DA produced the final manuscript. All authors approved the final version.

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Disclosures / conflicts-of-interest

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Table 1. Demographics and clinical characteristics in 11,324 subjects with HF co-reported with NOACs or warfarin in FAERS.

Variable	Warfarin n=8260 (%)	All NOACs n=3064 (%)	Apixaban n=666 (%)	Dabigatran n=1361 (%)	Rivaroxaban n=1005 (%)	Edoxaban n=32 (%)
Age (> 75 y.o.)	2627* (31.8%)	1424 (46.5%)	325 (48.8%)	646 (47.5%)	446 (44.4%)	7 (21.9%)
Female gender	3741 (50.4%)	1448 (47.3%)	314 (49.1%)	622 (47.5%)	503 (51.5%)	9 (56.3%)
Diabetes	414 (5.0%)	37 (1.2%)	4 (0.6%)	18 (1.3%)	15 (1.5%)	0 (0.0%)
Hypertension	1243 (15.0%)	170 (5.6%)	41 (6.2%)	56 (4.1%)	72 (7.2%)	1 (3.1%)
Renal failure	35 (0.4%)	22 (0.7%)	7 (1.1%)	5 (0.4%)	9 (0.9%)	1 (3.1%)
Aspirin use	2095 (25.4%)	598 (19.5%)	121 (18.2%)	246 (18.1%)	228 (22.7%)	3 (9.4%)
Other antiplatelet use	635 (7.7%)	177 (5.8%)	33 (5.0%)	83 (6.1%)	61 (6.1%)	0 (0.0%)

Percentages relate to the total number of the respective anticoagulant co-reported with HF (in top row).

Table 2. Numerical overview of reports on mortality and cardiovascular outcomes in subjects with HF co-reported with NOACs or warfarin.

Outcome	Warfarin (%)	All NOACs (%)	Apixaban (%)	Dabigatran (%)	Rivaroxaban (%)	Edoxaban (%)
All-cause mortality	2595 (31.4)	939 (31.1)	175 (26.3)	475 (34.9)	301 (30.0)	3 (0.0)
Myocardial infarction	718	87	17	41	29	0
Stroke	200	65	12	28	25	0
Ischemic stroke	169	40	5	18	17	0
Hemorrhagic stroke	16	7	2	1	4	0
Total Events	8260 (72.9)	3064	666 (5.9)	1361 (12.0)	1005 (8.9)	32 (0.3)

Percentages relate to the total number of the respective anticoagulant co-reported with HF.

Table 3. Risk of adverse outcomes co-reported with warfarin compared to NOACs in HF patients

OR (95% CI)	Warfarin vs all NOACs	Warfarin vs Apixaban	Warfarin vs Dabigatran	Warfarin vs Rivaroxaban
All-Cause mortality	2.69 (2.49-2.90)***	2.15 (1.83-2.52)***	2.19 (1.98-2.42)***	3.71 (3.28-4.19)***
Myocardial infarction	4.91 (3.95-6.10)***	2.57 (1.62-4.08)***	4.81 (3.60-6.45)***	5.74 (4.01-8.23)***
Stroke	8.85 (6.61-11.84)***	3.83 (2.12-6.91)***	8.46 (5.67-12.62)***	10.4 (6.83-15.82)***
Hemorrhagic stroke	5.32 (2.07-13.66)***	1.08 (0.24-4.76)	8.43 (1.11-63.85)*	5.43 (1.81-16.33)***
Ischemic stroke	12.73 (8.87-18.27)***	8.47 (3.45-20.79)***	12.91 (7.90-21.10)***	11.69 (7.06-19.36)***
Total Events	2.64 (2.53-2.76)***	1.91 (1.76-2.07)***	1.92 (1.81-2.03)***	4.09 (3.38-4.37)***

***p<0.001, **p<0.01, *p<0.05 versus warfarin. Individual edoxaban data is not displayed due to few reports but are entered into NOAC aggregate.

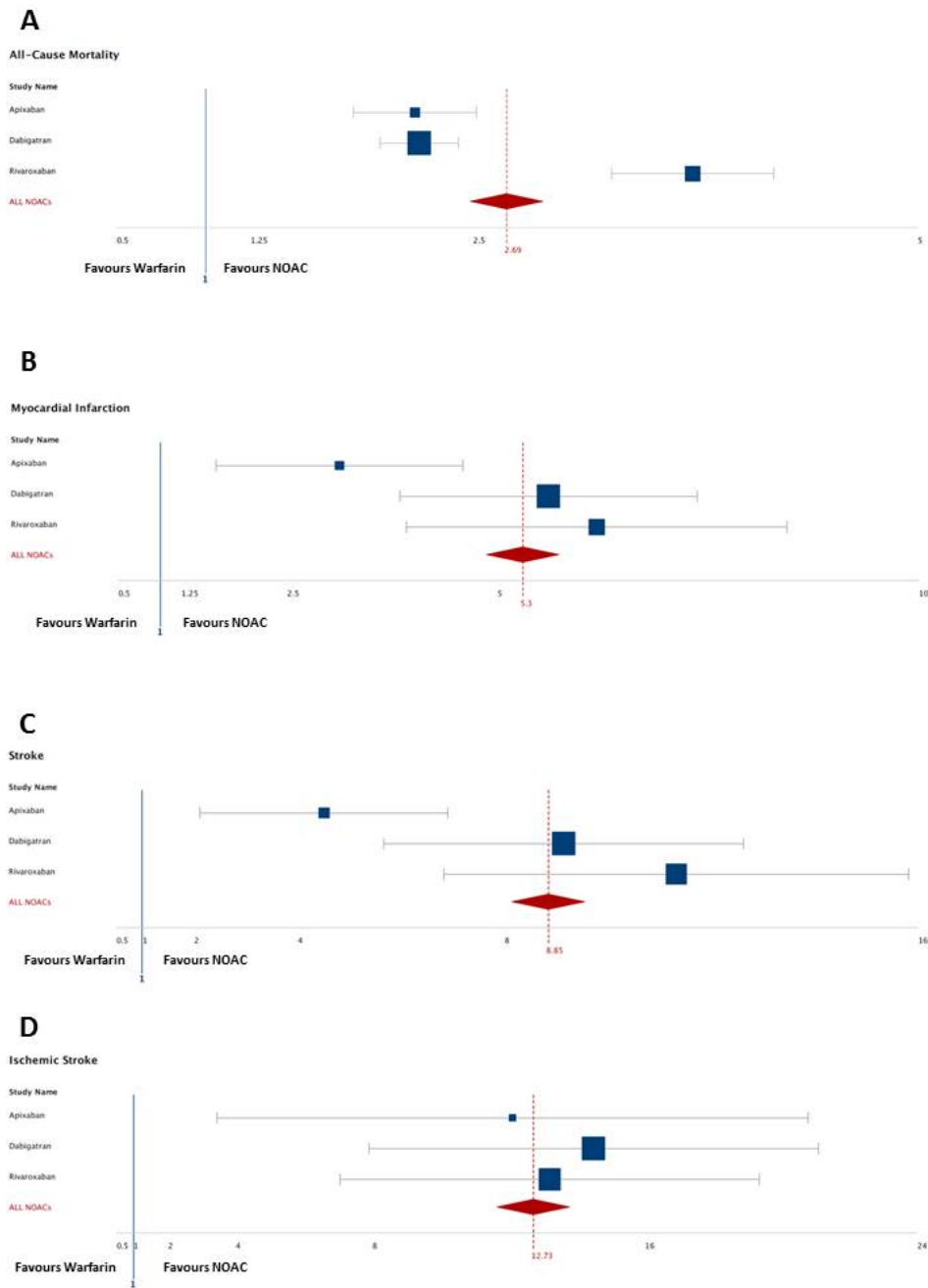


Figure 1: Adverse event profile in HF subjects co-reported with warfarin or NOAC use in FAERS in 2015.

Fig 1. Forest plots depicting OR for all cause mortality (A), myocardial infarction (B), ischemic stroke (C) and hemorrhagic stroke in warfarin users relative to NOAC. For all outcomes, NOACs compared to warfarin exhibit a favourable risk profile.

OR for any AE with warfarin versus

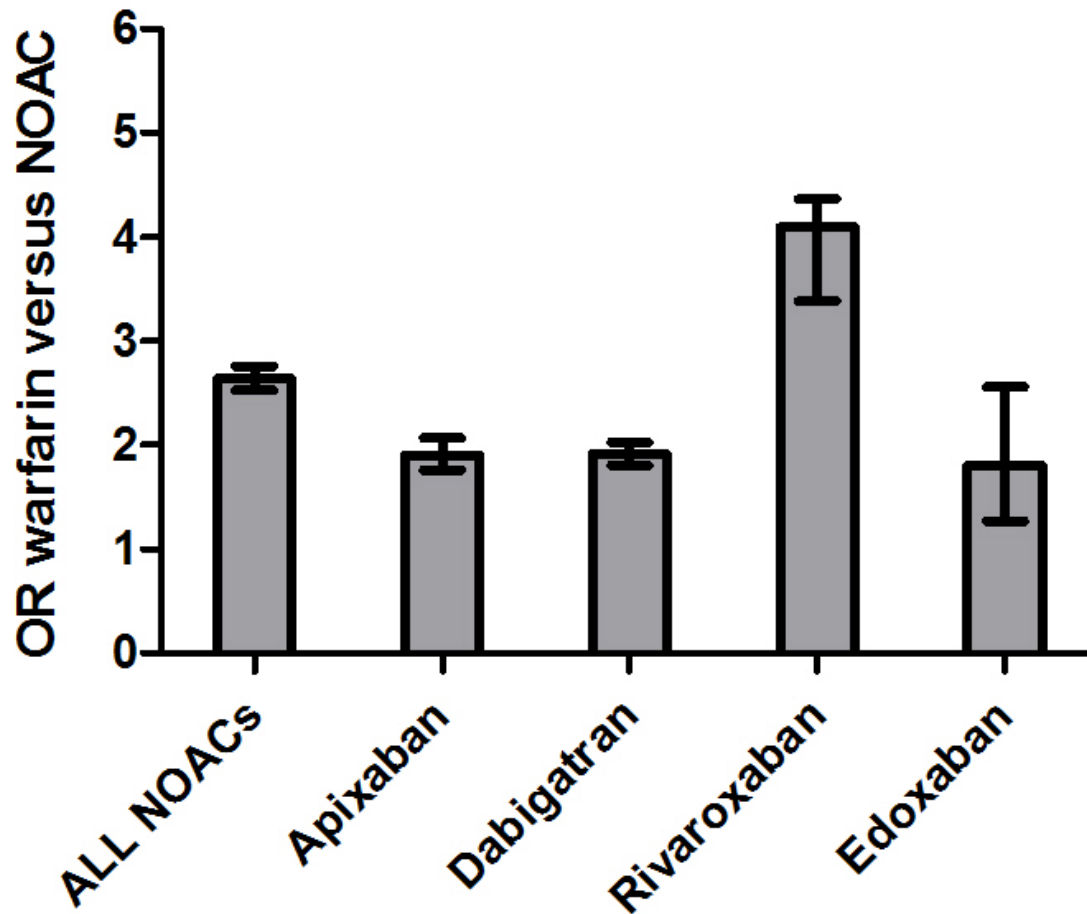


Figure 2: Total adverse events in HF subjects co-reported with warfarin or NOAC use in FAERS in 2015.

Column bars showing the OR with 95% confidence intervals for any adverse event report in HF subjects using warfarin versus NOAC. For any adverse outcome, NOACs individually and combined exhibit a favourable risk profile versus warfarin.

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