Real-world versus randomized trial outcomes in similar populations of rivaroxaban-treated patients with non-valvular atrial fibrillation in ROCKET AF and XANTUS

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Abstract

**Aims:** Based on phase III data, non-vitamin K antagonist oral anticoagulants are recommended for stroke prevention in patients with atrial fibrillation. To determine whether trial outcomes translate into similar event rates in unselected patients, this analysis compared outcomes from the real-world XANTUS study with those from the phase III ROCKET AF study.

**Methods:** Individual patient data from 4020 XANTUS patients were re-weighted to match the proportion of selected baseline characteristics in 7061 rivaroxaban-treated patients from ROCKET AF, using the matching-adjusted indirect comparison (MAIC) method. For the primary analysis, CHADS2 scores and gender were selected as relevant variables. Adjusted annualized incidence rates for XANTUS were calculated and compared with incidence rates from ROCKET AF – the ratio of these rates (‘MAIC ratio’) was used as a relative effect estimate.

**Results:** Rates of major bleeding (3.10%/year vs 3.60%/year; MAIC ratio 0.86; 95% confidence interval [CI] 0.67–1.12) and stroke/non-central nervous system systemic embolism (1.54%/year vs 1.70%/year; MAIC ratio 0.91; 95% CI 0.62–1.32) were similar between XANTUS and ROCKET AF. The rate of all-cause death was higher in XANTUS (3.22%/year vs 1.87%/year; MAIC ratio 1.72; 95% CI 1.31–2.27), but the rates of vascular death were similar (1.83%/year vs 1.53%/year; MAIC ratio 1.19; 95% CI 0.84–1.70). Sensitivity analyses weighted by different baseline characteristics supported these results.

**Conclusion:** The low rates of major bleeding and stroke in XANTUS were consistent with results from ROCKET AF. All-cause death, but not vascular death, was higher in XANTUS, as expected in an unselected real-world population.

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**Keywords (maximum of 6):** atrial fibrillation, anticoagulation, real-world evidence, rivaroxaban, ROCKET AF, XANTUS

Condensed abstract

Outcomes between rivaroxaban-treated patients with atrial fibrillation in the real-world XANTUS study and the phase III ROCKET AF study were indirectly compared. Adjusted rates of stroke/systemic embolism and major bleeding were similar between studies, but the adjusted rate of all-cause death was higher in XANTUS than in ROCKET AF.

What’s new

* This is the first analysis to use an indirect comparison method to compare outcomes between a randomized controlled trial setting (ROCKET AF) and a real-word study (XANTUS) in selected and unselected patients with atrial fibrillation receiving rivaroxaban for stroke prevention; the results of this comparison showed consistent efficacy and safety outcomes between the two settings
* After adjusting for differences in baseline characteristics between the high-risk ROCKET AF patient population and the lower-risk XANTUS population, rates of stroke/systemic embolism and major bleeding in rivaroxaban-treated patients were similar between the two studies
* As expected, adjusted rates of all-cause death were higher in the unselected XANTUS population compared with the ROCKET AFpopulation, which excluded patients with concomitant illness associated with a life expectancy of <2 years
* Introduction

Atrial fibrillation (AF) is present in 1–3% of the European population and is associated with a four- to fivefold increase in the risk of stroke.1 Appropriate anticoagulation with vitamin K antagonists (VKAs; e.g., warfarin) or non-VKA oral anticoagulants (NOACs: rivaroxaban, apixaban, dabigatran and edoxaban) has been shown to minimize this risk. The NOACs are recommended as alternatives to VKAs in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines,2 and European Society of Cardiology (ESC) guidelines recommend NOACs in preference to VKAs based on their improved safety profile.3,4

ROCKET AF was a randomized, double-blind phase III clinical trial to evaluate the efficacy and safety of rivaroxaban 20 mg once daily (15 mg once daily in patients with creatinine clearance 30–49 ml/min) versus warfarin for the prevention of stroke/non-central nervous system (CNS) SE in patients with AF.5 XANTUS was an international, prospective, observational study to validate the safety profile of rivaroxaban and assess the incidence of treatment-emergent safety events, such as major bleeding and death, in addition to stroke/non-CNS SE in patients with AF in a real-world setting.6

Both studies contributed to the clinical evidence for rivaroxaban in the prevention of stroke in patients with AF, but they were conducted in patient populations with a different baseline risk of stroke. By design, ROCKET AF was performed in standardized conditions and in selected patients with AF (N=14,264), each at a moderate-to-high risk of stroke (CHADS2 score ≥2; Figure 1).5 XANTUS enrolled consecutive patients newly initiated on rivaroxaban (N=6784), i.e. a population in whom rivaroxaban was approved for stroke prevention in patients with AF, with no further eligibility criteria for inclusion. The real-world population in XANTUS had a lower baseline risk of stroke; 40.7% (n=2764) of patients in XANTUS had a CHADS2 score of 0 or 1; equivalent patients were excluded from ROCKET AF. The mean (standard deviation) CHADS2 score in XANTUS was 2.0 (1.3)6 compared with 3.5 (0.9) in the rivaroxaban arm of ROCKET AF (Figure 2).5 There were also population differences in the individual components of the CHADS2 score between ROCKET AF and XANTUS (Figure 2).

To compare the outcomes from these two studies realistically, and to assess whether the results obtained in the ROCKET AF phase III clinical trial translate into real-world clinical practice, weighting for these baseline characteristics is necessary. The aim of this analysis was to compare the outcomes of ROCKET AF and XANTUS after adjusting for baseline characteristics.

Methods

The matching-adjusted indirect comparison (MAIC) method, as proposed by Signorovitch and colleagues,7,8 was used to compare individual patient data from XANTUS with the reported results of ROCKET AF. The MAIC method is a recently described statistical method that utilizes individual patient data to allow for more reliable comparisons between treatments in separate studies compared with other indirect comparison methods based only on published aggregate data; this is because the use of individual patient data allows for greater adjustment for observed cross-trial differences, such as resolving differences in key baseline characteristics or outcome definitions.8 Individual patient data from XANTUS were re-weighted to match the proportion of selected baseline characteristics reported for ROCKET AF.By using these ‘balancing weights’, adjusted incidence rates for the outcomes in XANTUS were obtained and compared with the reported outcomes from ROCKET AF. For XANTUS, analyses were based on the safety analysis set, which included patients who had taken at least one dose of rivaroxaban during the observation period, and outcomes were considered treatment-emergent if they occurred from the day of the first dose of rivaroxaban and up to 2 days after the last dose of rivaroxaban in the event of permanent discontinuation. For ROCKET AF, analyses were based on the safety population in the rivaroxaban arm, with outcomes assessed while on treatment (up to 2 days after the last dose). CHADS2 score and gender were selected as relevant variables for adjustment, as these encompass most of the relevant risk factors for stroke whilst also including a large enough number of patients to enable a meaningful analysis. Adjustment based on CHA2DS2-VASc score was not possible because these data were unavailable for the ROCKET AF population. The outcome of vascular death was originally reported in ROCKET AF and defined as death due to cardiovascular causes and/or extra-/intracranial bleeding; these outcomes were reported separately in XANTUS and were therefore combined in the current analysis to determine the equivalent rates of vascular death in XANTUS.

To conduct the analysis, the following steps were performed. Because ROCKET AF excluded individuals with a CHADS2 score of 0 or 1, these patients were also excluded from the XANTUS study population before calculation of the balancing weights. The remaining 4020 patients in XANTUS were re-weighted to adjust for CHADS2 score (categories 2, 3 and 4–6) and gender differences. To judge the impact of this re-weighting on the sample size, an effective sample size was computed.7 The ratio of the adjusted incidence rate in XANTUS (per 100 patient-years) and the observed rate in ROCKET AF (‘MAIC ratio’ or ‘incidence rate ratio’) was used as a relative effect estimate. If the MAIC ratio is close to 1, this supports the assumption that rivaroxaban behaves similarly in both XANTUS and ROCKET AF if population differences are taken into account.

Sensitivity analyses

Sensitivity analyses were carried out in additional models including different baseline characteristics. Several models were assessed and classified as: weighted for the main risk factors for stroke (age [categories <65 years, ≥65–<75 years and ≥75 years]; prior stroke/transient ischaemic attack [TIA]/non-CNS SE [categories: yes and no]; and the combination of these two factors); or weighted for CHADS2 score or for the components of the CHADS2 and CHA2DS2-VASc scores. All baseline characteristics used in the primary model and the sensitivity analyses are shown in Table 1.

Results

Primary analysis: adjustment for CHADS2 score and gender differences

The adjusted annualized incidence rates for XANTUS were compared with the incidence rates for ROCKET AF (Table 2). The effective sample size for the primary model after re-weighting was 2492. The adjusted incidence rate of treatment-emergent adjudicated major bleeding in XANTUS was similar to the incidence rate in ROCKET AF (3.10%/year vs 3.60%/year; MAIC rate ratio 0.86; 95% confidence interval [CI] 0.67–1.12). For the outcome of stroke/non-CNS SE, the adjusted incidence rate in XANTUS was also similar to the incidence rate in ROCKET AF (1.54%/year vs 1.70%/year; MAIC rate ratio 0.91; 95% CI 0.62–1.32). The adjusted incidence rate of myocardial infarction (MI) in XANTUS was similar to the incidence rate in ROCKET AF (0.75%/year vs 0.91%/year; MAIC rate ratio 0.82; 95% CI 0.49–1.39).

The adjusted incidence rate of all-cause death in XANTUS was higher than the incidence rate in ROCKET AF (3.22%/year vs 1.87%/year; MAIC rate ratio 1.72; 95% CI 1.31–2.27). The adjusted incidence rate of vascular death in XANTUS was similar to the incidence rate in ROCKET AF (1.83%/year vs 1.53%/year; MAIC rate ratio 1.19; 95% CI 0.84–1.70).

Sensitivity analyses

Sensitivity analyses were carried out, adjusting for different baseline characteristics (Table 3). The impact of re-weighting on sample size could be observed in the estimated effective sample size, with matching for a multitude of clinical components providing small numbers. These models supported the results obtained from the primary model (Table 2).

The adjusted annualized incidence rates of major bleeding were slightly lower in XANTUS than the incidence rates in ROCKET AF in models weighted for age, prior stroke/TIA/non-CNS SE, age plus prior stroke/TIA/non-CNS SE and for CHA2DS2-VASc components. Similar rates were observed in models weighted for CHADS2 score and for the components of the CHADS2 score. The adjusted annualized incidence rates of stroke/non-CNS SE were slightly lower in XANTUS than the incidence rates in ROCKET AF in models weighted for age, prior stroke/TIA/non-CNS SE, and age plus prior stroke/TIA/non-CNS SE. Similar rates were observed in models weighted for CHADS2 score and for the components of the CHADS2 and CHA2DS2-VASc scores.

For the outcome of all-cause death, the annualized adjusted incidence rates in XANTUS were higher than the incidence rates in ROCKET AF in all analyses but, as for the primary model, the annualized adjusted incidence rates in XANTUS and incidence rates in ROCKET AF were similar for the outcome of vascular death in all models.

Discussion

Comparisons of phase III data with data from routine clinical practice are important to confirm that the safety and efficacy performance of a drug translates into safety and effectiveness in a broad patient population. There is now a growing body of prospective evidence from real-world studies such as XANTUS,6 XALIA9 and XAMOS10 for rivaroxaban, as well as registry studies providing evidence for all NOACs such as GARFIELD-AF,11 PREFER in AF12 and the Danish Registry,13 which have generally confirmed the safety and efficacy of NOACs in clinical practice. Findings from a retrospective analysis of patients enrolled in Medicare showed a reduction in the risk of stroke and intracranial haemorrhage associated with a twice-daily dabigatran (150 mg) regimen versus warfarin in patients with AF.14 Although these real-world findings are based on a retrospective database analysis, they are highly consistent with results of the RE-LY phase III trial.15

Indirect comparisons between studies require appropriate methods to adjust for differences in study design as well as patient characteristics and risk factors for adverse outcomes at baseline. The current analysis compared rivaroxaban for stroke prevention in patients with AF from the ROCKET AF phase III study with data from the real-world XANTUS study – two studies that included different patient populations, with patients in the real-life XANTUS study having a lower baseline stroke risk than those in ROCKET AF. Rates of major bleeding and stroke/non-CNS SE in the international, prospective, observational XANTUS study6 were lower than those seen in the rivaroxaban group in ROCKET AF.5 In addition, the incidence rates of all-cause death based on the safety populations were similar in XANTUS and ROCKET AF (1.9%/year).

These differences may, in part, be explained by different stroke risk and baseline characteristics between patient populations in XANTUS and ROCKET AF. This is reflected in the differences in the individual components of the CHADS2 score between the two studies; a much higher proportion of patients had relevant CHADS2 co-morbidities at baseline in ROCKET AF (Figure 2; Table 1). In particular, a larger proportion of patients with prior stroke/TIA/non-CNS SE were included in ROCKET AF compared with XANTUS, and the proportion of patients with heart failure, hypertension or diabetes mellitus at inclusion in the study was higher in ROCKET AF than in XANTUS.

CHADS2 score and gender were selected for the primary analysis, because these baseline characteristics were deemed relevant to compare outcomes in these two studies. Gender differences in outcomes have previously been observed in patients with AF. In ROCKET AF, women were shown to have a higher risk of stroke but a lower risk of vascular death and bleeding events compared with men.16 Additionally, among patients with AF, men were more likely to have had a prior MI than women.17

Adjusting for baseline characteristics using the MAIC method revealed a high degree of similarity between the XANTUS and ROCKET AF populations with respect to rates of major bleeding, stroke or non-CNS SE, and MI. The adjusted incidence rates of all-cause death were higher in XANTUS than the incidence rates in ROCKET AF. This might be expected in a real-life study that included patients with a range of co-morbidities that would result in exclusion from clinical trials. Patients enrolled in clinical trials might receive better overall care than those in real-life practice, which may account for this difference between the two studies. Additionally, it is generally difficult to compare phase III mortality data with real-life data because patients with potentially fatal conditions unrelated to the disease being studied are often excluded from phase III trials. In ROCKET AF, patients with a serious concomitant illness associated with a life expectancy of <2 years were excluded,5 whereas XANTUS had no exclusion criteria, so patients could be enrolled irrespective of life expectancy.6 XANTUS also included patients with potentially fatal non-cardiovascular co-morbidities – for example, 105 patients (1.5%) were identified as having active cancer at baseline. In ROCKET AF, 81.7% (170/208) of deaths in the rivaroxaban treatment group had a vascular cause,5 whereas in XANTUS, cardiovascular death and death due to bleeding only constituted 41.5% (49/118) and 10.2% (12/118) of adjudicated causes of death, respectively.6 However, the incidence rates of vascular death (death due to cardiovascular causes and extra/intracranial bleeding) were similar in XANTUS and ROCKET AF after adjusting for CHADS2 score and gender. Other main causes of treatment-emergent death in XANTUS included cancer and infectious disease (in 19.5% [23/118] and 8.5% [10/118] of deaths, respectively).6 Data on cause-specific treatment-emergent death in the ROCKET AF safety population are not available; however, in the intention-to-treat population, 10.8% (63/582) of deaths in patients randomized to rivaroxaban were due to cancer.18

The sensitivity analyses confirmed the results of the primary analysis. Large differences in populations led to smaller sample sizes and greater weights for certain groups of patients in some of the analyses, which might have made the results of these analyses less reliable.

Limitations

A thorough statistical methodology was used to perform comparisons between XANTUS and ROCKET AF. However, the results are based on a model, and all the limitations attached to such a methodology apply here. Notably, although the use of individual patient data from XANTUS and MAIC allowed adjustment for differences between the XANTUS and ROCKET AF populations, unobserved differences may have resulted in residual confounding. Using individual patient data from ROCKET AF would have been preferable, but such data were not available for this analysis.

Re-weighting the individual patient data for XANTUS with an increased number of baseline characteristics in some of the sensitivity analyses, particularly the CHA2DS2-VASc components model, resulted in a low effective sample size (N<1000); results in smaller populations should be interpreted with caution.

Finally, differences in rivaroxaban dose between XANTUS and ROCKET AF were not considered in this analysis. In XANTUS, some patients received dosing that was different from the label recommendation (15% of patients with a documented creatinine clearance ≥50 ml/min initially received rivaroxaban 15 mg once daily, and 36% of patients with a documented creatinine clearance <50 ml/min initially received rivaroxaban 20 mg once daily),6 – inappropriately dosed patients were not excluded from this analysis.

Conclusions

The low rates of major bleeding, stroke and vascular death in the rivaroxaban-treated XANTUS population were generally consistent with the results from ROCKET AF, and comparing the outcomes of the appropriately adjusted XANTUS population with those from the phase III ROCKET AF confirmed the validity of the XANTUS real-world experience.

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Conflict of interest

AJC has received institutional research grants and personal fees as an advisor or speaker for Bayer, Boehringer Ingelheim, Daiichi Sankyo and Pfizer/Bristol-Myers Squibb. PA has served as a consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo, Edwards, FibroGen, GSK, Kowa Pharmaceutical, Lundbeck, Medtronic, Merck, Pfizer, Sanofi and ShingPoon. SHa has served as a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer and Sanofi. SHe, SK, and MB are employees of Bayer AG. PK has received research support from the British Heart Foundation, the Leducq Foundation, the German Centre for Heart Research and from several drug and device companies active in atrial fibrillation; he has also received honoraria from several such companies, including Bayer, Boehringer Ingelheim, Daiichi Sankyo and Pfizer/Bristol-Myers Squibb. He is listed as inventor on two pending patents held by the University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). ML is an employee of Chrestos Concept, which received funding for this analysis from Bayer AG. AGGT has been a consultant for Astellas, Bayer, Janssen Pharmaceutical Research & Development, Portola and Takeda.

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Tables

**Table 1.** Baseline characteristics in XANTUS and ROCKET AF

|  |  |  |  |
| --- | --- | --- | --- |
| **Baseline characteristic** | **XANTUS: overall(N=6784)** | **XANTUS: after exclusion of patients with CHADS2 score of 0 or 1 (N=4020)** | **ROCKET AF (rivaroxaban arm): safety population (N=7061)a** |
| Aged <65 years | 21.8 | 14.0 | 23.3 |
| Aged ≥65 to <75 years  | 36.8 | 25.5 | 33.2 |
| Aged ≥75 years  | 41.4 | 60.5 | 43.5 |
| Hypertension  | 74.7 | 89.4 | 90.2 |
| Congestive heart failure  | 18.6 | 28.6 | 62.7 |
| Diabetes  | 19.6 | 31.4 | 40.2 |
| Prior stroke/TIA/non-CNS SE | 19.0 | 32.1 | 55.0 |
| CHADS2 score 2  | 30.0 | 50.6 | 13.1 |
| CHADS2 score 3  | 16.4 | 27.6 | 42.8 |
| CHADS2 score ≥4  | 12.9 | 21.8 | 44.1 |
| Female  | 40.8 | 43.7 | 39.5 |
| Vascular diseaseb  | 24.8 | 31.9 | 5.6c |

Incidence rates shown as %.

aExcluding site 042012.

bDefined as ischaemic heart disease, peripheral artery disease or cerebrovascular disease in XANTUS, and defined as peripheral vascular disease in ROCKET AF.

cIntention-to-treat population.

CNS, central nervous system; SE, systemic embolism; TIA, transient ischaemic attack.

**Table 2** Incidence rates of treatment-emergent adjudicated outcomes and MAIC rate ratios after weighting for CHADS2 score and gender

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcome | XANTUS pre-matching (N=6784) | XANTUS (excluding CHADS2 0 and 1) pre-matching(N=4020) | XANTUS post-matchinga(N=2492) | ROCKET AFb(N=7061) | MAIC rate ratio |
| Major bleeding | 2.10 (1.75–2.50) | 2.89 (2.36–3.50) | 3.10 (2.44–3.94) | 3.60 (3.26–3.97)c | 0.86 (0.67–1.12) |
| Stroke/non-CNS SE | 0.83 (0.62–1.10) | 1.13 (0.81–1.54) | 1.54 (1.09–2.19) | 1.70 (1.47–1.96) | 0.91 (0.62–1.32) |
| MI | 0.44 (0.29–0.64) | 0.52 (0.32–0.82) | 0.75 (0.46–1.22) | 0.91 (0.75–1.11) | 0.82 (0.49–1.39) |
| Death | 1.93 (1.60–2.31) | 2.62 (2.12–3.20) | 3.22 (2.53–4.09) | 1.87 (1.63–2.14) | 1.72 (1.31–2.27) |
| Vascular deathd | 1.00 (0.76–1.28) | 1.43 (1.07–1.88) | 1.83 (1.33–2.51) | 1.53 (1.32–1.78) | 1.19 (0.84–1.70) |

Incidence rates shown as: %/year (95% CI); MAIC rate ratio shown as: ratio (95% CI).

aEffective sample size.

bRivaroxaban arm.

cMajor bleeding safety population (n=7111).

dDefined as death due to cardiovascular causes or intracranial/extracranial bleeding.

CI, confidence interval; CNS, central nervous system; MAIC, matching-adjusted indirect comparison; MI, myocardial infarction; SE, systemic embolism.

**Table 3** Sensitivity analyses: adjusted incidence rates and MAIC rate ratios after adjusting for different baseline characteristics in XANTUS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model** | **Major bleeding** | **Stroke/non-CNS SE** | **Death** | **Vascular deatha** |
| **IRb (95% CI)** | **MAIC RRc(95% CI)** | **IRb(95% CI)** | **MAIC RRc(95% CI)** | **IRb(95% CI)** | **MAIC RRc(95% CI)** | **IRb(95% CI)** | **MAIC RRc(95% CI)** |
| Aged (n=3552)e | 2.64 (2.15–3.23) | 0.73 (0.58–0.92) | 1.11 (0.80–1.54) | 0.65 (0.46–0.93) | 2.51 (2.02–3.11) | 1.34 (1.04–1.73) | 1.43(1.07–1.91) | 0.93(0.67–1.29) |
| Prior stroke/TIA/non-CNS SE (n=3241)e | 2.73 (2.21–3.39) | 0.76 (0.60–0.96) | 1.26 (0.90–1.77) | 0.74 (0.52–1.07) | 2.70 (2.16–3.38) | 1.44 (1.11–1.88) | 1.46(1.08–1.98) | 0.95(0.68–1.34) |
| Age,d prior stroke/TIA/non-CNS SE (n=2981)e | 2.53 (2.03–3.16) | 0.70 (0.55–0.90) | 1.17 (0.83–1.63) | 0.69 (0.48–0.99) | 2.53 (2.02–3.18) | 1.35 (1.04–1.76) | 1.44(1.05–1.97) | 0.94(0.66–1.33) |
| CHADS2 score (n=2526)e | 3.09(2.43–3.92) | 0.86(0.66–1.11) | 1.57(1.11–2.23) | 0.93(0.64–1.35) | 3.20(2.52–4.06) | 1.71(1.30–2.25) | 1.79(1.30–2.45) | 1.17(0.82–1.66) |
| CHADS2 components (n=1623)e | 3.39(2.48–4.63) | 0.94(0.68–1.31) | 1.56(1.04–2.33) | 0.92(0.60–1.41) | 3.79(2.78–5.17) | 2.03(1.45–2.84) | 2.16(1.46–3.21) | 1.41(0.93–2.16) |
| CHA2DS2-VASc components (n=937)e | 2.25(1.49–3.39) | 0.62(0.41–0.95) | 1.71(0.97–3.01) | 1.00(0.56–1.80) | 3.42(2.27–5.15) | 1.83(1.19–2.81) | 1.64(0.96–2.80) | 1.07(0.62–1.87) |

Incidence rates shown as: %/year (95% CI); MAIC rate ratio shown as: ratio (95% CI).

**a**Defined as death due to cardiovascular causes or intracranial/extracranial bleeding.

bIncidence rates after adjustment.

 cFor XANTUS versus ROCKET AF.

dAge categories: <65 years, ≥65 to <75 years and ≥75 years.

eXANTUS effective sample size (n).

CI, confidence interval; CNS, central nervous system; IR, incidence rate; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SE, systemic embolism; TIA, transient ischaemic attack.

Figure legends

**Figure 1.** Baseline CHADS2 score in (A) ROCKET AF5 and (B) XANTUS.6

**a**Safety population excluding site 042012.

bValue at two decimal places: 0.01.

**Figure 2.** Differences in key baseline characteristics between ROCKET AF5 and XANTUS.6 CNS, central nervous system; MI, myocardial infarction; SD, standard deviation; SE, systemic embolism; TIA, transient ischaemic attack.

Figures

 

**Figure 1.**



**Figure 2.**