This publication discusses findings from the XANTUS study, the first large, international, prospective study to collect real-world safety and efficacy data on rivaroxaban use in the non-valvular atrial fibrillation (NVAF) setting across a broad range of patient risk profiles encountered in routine clinical practice. The information supplements what is already known about rivaroxaban in clinical trials and demonstrates its true benefit in the general population.

In XANTUS, treatment and dosing decisions were at the discretion of the treating physicians and patients were followed-up for 1 year or until 30 days after premature discontinuation. By the end of the observation period, rivaroxaban demonstrated low rates of stroke/systemic embolism (SE) and major bleeding, including intracranial and gastrointestinal bleeding. In addition, 96.1% of rivaroxaban-treated patients did not experience any of the outcomes of stroke/SE, treatment-emergent major bleeding or all-cause death. The findings reaffirm the positive benefit/risk profile of rivaroxaban established in the phase III clinical trial ROCKET AF, in which rivaroxaban provided effective stroke prevention with a similar overall bleeding profile and significantly lower rates of intracranial and fatal bleeds compared with warfarin. Treatment persistence was high in XANTUS, with the majority (80%) of patients remaining on rivaroxaban throughout the 1-year study period. Other recent data on vitamin K antagonist (VKA) oral anticoagulants (OACs) have shown a persistence rate of ~60% after 1 year. Moreover, patient satisfaction was high, with 75% of rivaroxaban-treated patients in XANTUS reporting that they were satisfied with their treatment at year 1.

Dr Hammett is an Interventional Cardiologist at the Royal Brisbane and Women’s Hospital (RBWH). He has a major interest in cardiovascular research, and has been actively involved in the development of treatment guidelines and systems of care for ACS management within Queensland, with a focus on early triage and transfer of regional patients to PCI-capable hospitals.

He has also been the principal investigator in many landmark trials on novel antiplatelet and antithrombotic agents for both ACS and AF. He was the top Australian recruiter for PEGASUS, SOLID, APPRAISE, ATLAS-ACS and ATLAS-ACS2 trials, and the worldwide top recruiter for both the ATLAS-ACS and ATLAS-ACS2 trials (investigating the use of rivaroxaban in acute coronary syndromes). He was the Australian National Lead Investigator and co-author for the Atlantic Study, published in the New England Journal of Medicine last year (investigating the role of pre-hospital use of ticsagrelor in STEMI), and is the Australian National Lead Investigator for the upcoming Gemini ACS study (comparing the cardioprotective effects of different antiplatelet and antithrombotic strategies post-ACS).

Dr Hammett has an active ongoing research interest in the role of antithrombotic therapy in ACS, and in improving outcomes in stroke prevention for atrial fibrillation.


Clinical trial vs real-world data

The randomised controlled trial (RCT) is often considered to be the “gold standard” in clinical trials, superior to all other types of evidence, as it provides quantitative, comparative, controlled experiments in which treatment effect sizes may be determined with less bias than observational trials. This construct is reflected by the ‘pyramid of evidence’, in which different study designs are grouped according to a hierarchy, with studies most susceptible to threats to internal validity are at the bottom and those least prone are at the top (see Fig. 1). This hierarchy of study designs has traditionally been widely to evaluate the efficacy of a treatment or intervention and in the grading of evidence in practice guidelines.

![The pyramid of evidence](Image)

Figure 1. The pyramid of evidence. [Adapted from Ho M, et al. 2008]

However, it has increasingly been recognised that conclusions drawn from clinical trials lack an appreciation of how this new drug or technology impacts upon therapeutic management in a practical, real-life setting, i.e. a real-world situation. In other words, the traditional hierarchy of study designs cannot address critical questions on the safety and efficacy of therapies in real-world populations, the impact of risk factors on outcomes, or the effects of policy interventions. Thus, when interpreting results from major randomised trials evaluating non-vitamin K antagonist oral anticoagulants (NOACs) in AF, it must be recognised that the study participants were enrolled in a protected, controlled clinical trial environment that did not require regular monitoring. Moreover, clinical trial efficacy data relate to ‘ideal’ circumstances, in a situation that is seeking regulatory approval, using a fixed regimen with highly motivated patients, who are usually highly compliant with treatment (i.e. very unrepresentative of patients in the local community). Another important aspect to bear in mind is that while RCTs have to have internal validity (i.e. design and conduct must eliminate the possibility of bias), the data need to have external validity to be clinically useful (i.e. be relevant to patients with AF in day-to-day clinical practice). The clinical trial data of NOACs in AF may not reflect the “true” incidence of bleeding in the real world, which limits their external validity. RCTs cannot be expected to produce results that are directly relevant to all patients and all settings.

Abbreviations used in this issue: AE = adverse event; AF = atrial fibrillation; bid = twice daily; CHADS, score = combined risk factors of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke/transient ischaemic attack/thromboembolism; CHA2DS–VASc score = extends CHADS, (vascular disease, age 65–74 years, female sex); NOAC = non-vitamin K antagonist oral anticoagulant; NVAF = non-valvular atrial fibrillation; OAC = oral anticoagulant; ed = once daily; PRO = patient-reported outcome; SAE = serious adverse event; SE = systemic embolism; VKA = vitamin K antagonist.
Another important point to consider is that none of the large clinical trials comparing NOACs with warfarin inform clinicians as to which NOAC to select for an individual patient. Instead, clinicians have to make sense of the data from pharmacological analyses and clinical trials on aspects of dosing, adjustment for renal impairment, side effects, and they must also take other clinical and socioeconomic factors into consideration. It is very difficult to make a balanced assessment of the risks and benefits of NOACs in clinical trials, when taking into account the differences in study design (double-blind in ROCKET-AF and ARISTOTLE® vs open-label in RE-LY), patient populations (average CHADS2 stroke risk scores 3.5 in ROCKET-AF vs 2.1 in RE-LY and ARISTOTLE), methods of calculating anticoagulation time in the therapeutic range (including or excluding warfarin initiation and interruption periods), endpoint determination during transition to standard warfarin care at the end of the studies and subtle differences in bleeding definitions (strict or modified International Society on Thrombosis and Haemostasis [ISTH], or other criteria). The lack of comparative effectiveness studies makes it difficult to determine the superiority of one anticoagulant over another. It is almost impossible to estimate relative efficacy and safety across agents within an indication, such as NVAF, without trials specifically designed to make an unbiased comparison of the different NOACs. This raises the possibility that treatment decisions will be subject to the influence of subjective factors (including marketing). Many questions therefore surround the safety and efficacy of NOACs in broad clinical use outside the context of clinical trials. Data are needed that demonstrate the impact of NOACs and their performance under usual circumstances in real-world clinical practice, where regular day-to-day clinic patients tend to have lower treatment adherence and persistence compared with their clinical trial counterparts. While RCTs have excellent internal validity, due to the strength of randomisation, which allows only the exposure to treatment to differ between two treatment arms, additional biases may mean that RCTs have limited external validity (e.g. specialised centres of excellence with regulated protocols often means that patients, providers and care settings differ markedly from the general population). Health care decision-makers need non-RCT information as well, to overcome the limitation of the controlled experimental environment of the RCT, which may not generalise to populations, settings, or conditions not reflected in the trial. A number of research groups have developed evidence hierarchies that reflect the primary data from RCTs and allow researchers to systematically grade the evidence, as with for example the system used by the US Agency for Healthcare Research and Quality (AHRQ) that grades evidence in order from most to least rigorous: 1) systematic reviews and meta-analyses of RCTs; 2) nonrandomised intervention studies; 3) observational studies; 4) nonexperimental studies; and 5) expert opinion. There are weaknesses with this system of evidence grading. The US Preventive Services Task Force (USPSTF) recognised that decision-makers require information not only on the rigour of the research design but also on the magnitude of the net benefit in support of a particular technology or health service for the target population. The Scottish Intercollegiate Guidelines Network (SIGN) has also recognised the limitations of the AHRQ grading system, pointing out that evidence hierarchies may not account for the methodological quality of individual studies or they may fail to reflect the overall strength of the evidence base. There are other groups, such as the American College of Cardiology, that maintain their own evidence grading and classification systems, combining judgements about evidence quality with judgements about the usefulness of the intervention.

**Defining real-world data**

The terminology used by authoritative bodies about real-world data are fairly consistent: an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force considers that real-world data are data used for decision-making that are not collected in conventional RCTs; the European Forum “Relative Effectiveness” Working group (part of the European Commission) offers a similar explanation of real-world data as “a measure in understanding health care data collected under real life practice circumstances”, while at the payer level a real-life study has been defined as “anything that is not interventional”.

### Rationale for observational registries

Observational registries can contribute in important ways to the real-world evidence base, by recording long-term efficacy and safety data on newer drugs in a heterogeneous patient population, with large patient numbers that potentially reveal rare adverse events and information about the effect of co-morbidities that were not observed in the clinical trial environment. Since 2001, several major registries have been launched to assess real-world outcomes in patients with AF. These registries include:

- The Dresden NOAC registry (Germany) — for more information: Dresden NOAC register: [http://www.noragregist.de/index.html](http://www.noragregist.de/index.html) [Website in German]
- GARFIELD-AF – Global Anticoagulant Registry in the FIELD – for more information: Thrombosis Research Institute. [http://www.tri-london.ac.uk/garfield](http://www.tri-london.ac.uk/garfield)
- PREFER in AF – PREvention of thromboembolic events – European Registry in Atrial Fibrillation.
- Fushimi AF Registry – a community-based survey of current AF management in Fushimi-ku (an urban community in Japan)

Having multiple sources of real-world data to consult provides health care decision-makers with the following evidence that is essential for sound coverage and reimbursement decisions:

- Estimates of effectiveness as opposed to efficacy in a variety of typical practice settings;
- Comparison of multiple alternative interventions (e.g. older vs newer drugs) or clinical strategies to inform optimal therapy choices beyond placebo comparators;
- Estimates of the evolving risk-benefit profile of a new intervention, including long-term (and rare) clinical benefits and harms;
- Examination of clinical outcomes in a diverse study population that reflects the range and distribution of patients observed in clinical practice;
- Results on a broader range of outcomes (e.g. patient-reported outcomes [PROs], HRQoL, and symptoms) than have traditionally been collected in RCTs (i.e. major morbidity and short-term mortality);
- Resource use data that enable the costing of health care services and economic evaluation;
- Information on how a product is dosed and applied in clinical practice and on levels of compliance and adherence to therapy;
- Data in situations where it is not possible to conduct an RCT (e.g. narcotic abuse);
- Substantiation of data collected in more controlled settings;
- Data in circumstances where there is an urgency to provide reimbursement for some therapies because it is the only therapy available and may be life-saving;
- Interim evidence – in the absence of RCT data — upon which preliminary decisions can be made;
- Data on the net clinical, economic, and PRO impacts following implementation of coverage or payment policies or other health management programmes.
Various issues with collection of real-world data include the lack of good quality and sufficiently representative databases in many countries, incomplete databases, presence of many asymptomatic cases in real world (an issue with retrospective observation of data), the potential for bias and confounding with all nonrandomised data, and suchlike.5,13 Nevertheless, real-world data play an important role in the evaluation of epidemiology and burden of disease, treatment patterns, compliance, persistence, and health outcomes of different treatments.5 The traditional hierarchy of evidence collated from RCTs is enhanced by real-world evidence studies that provide information on how new products perform and benefit patients in the real world.

Expert commentary:

Randomised clinical trials are the bedrock of clinical knowledge and evidence-based practice – they are essential for evaluating the efficacy and associated risk of potential new treatments. However, by necessity most RCTs restrict recruitment to a fairly homogenous group of patients; those with the greatest likelihood of benefit from the new treatment, and the lowest risk of adverse events (i.e. without co-morbidities or other potential complicating factors). They are conducted in a rigorous manner with careful control of dosing, measurement of compliance, and restriction of other medications that could confound the results. They also involve a degree of patient self-selection in that patients most likely to take part are motivated about their healthcare, understanding of the benefits of treatment, and vigilant about potential competing health risks. Consequently, after the initial optimism that accompanies RCT results confirming new and better therapy, uncertainties and unanswered questions often surface. This was especially true of NOACs (dabigatran, rivaroxaban, and apixaban), all breakthrough therapies with significant advantages, equal or better efficacy, and less risk than the existing standard of care (warfarin) in their respective RCTs. Common questions included: how do the trial results relate to my patient, with co-morbidities and several other medications? Will these shorter-acting agents still look as favourable against warfarin in patients who are more sporadic with their dosing? Can I truly get by without monitoring anticoagulant effect? What if my patient needs cardioversion? What will happen if my patient suffers trauma, needs emergent surgery, or develops significant bleeding? Registry data helps answer these questions. It can confirm the generalisability of RCT results to a broader, unscreened ‘real world’ population (or identify potential issues, if the outcomes are not as favourable as those seen in the initial RCT results).

XANTUS STUDY DESIGN

Overview

As part of the post-approval plan for rivaroxaban, the European Medicines Agency (EMA) required observational studies to be conducted to provide a comprehensive data set to support the safety and clinical utility of rivaroxaban for reducing the risk of stroke in patients with AF in routine practice (i.e. beyond the strict confines of the RCT environment), across different geographic regions, care settings, patient populations, and health care systems.18 The EMA approved the design of XANTUS (Xarelto® for Prevention of Stroke in Patients with Atrial Fibrillation; NCT01606995) as a single-arm observational, noninterventional cohort study. The XANTUS study serves as the prototype for a series of four separate phase IV studies designed to cover different global regions, collectively comprising the XANTUS programme. XANTUS-EL (NCT01800006) and XANAP (NCT01750786) are ongoing in the EMEA (Europe, the Middle East and Africa), Latin America and Asia-Pacific regions. XANTUS-CN (NCT identifier not yet available) is in the planning stages and will be conducted in the People’s Republic of China.

Patient population, enrolment, medication and follow-up

Patients eligible for the study were adults aged ≥18 years with NVAF newly started on rivaroxaban to reduce the risk of stroke or SE. All patients were screened sequentially and documented in an anonymous log file independently of treatment. Enrolment took place from June 2012 to December 2013 in 311 centres in Europe, Canada, and Israel, involving a total of 6784 patients with AF.

Decisions about rivaroxaban prescription were at the discretion of the treating physician, including dose and duration of therapy. In Europe, label-recommended rivaroxaban doses for stroke prevention in NVAF are 20 mg od for patients with normal renal function or mild impairment (creatinine clearance [CrCl] ≥50 mL/min) and 15 mg od for patients with moderate or severe renal impairment (CrCl 15–49 mL/min).19 Importantly, the Australian registration and product information concerning the use of rivaroxaban for stroke prevention in AF recommends 15 mg od for patients with moderate renal impairment only (CrCl 30–49 mL/min); rivaroxaban is contraindicated in Australia for patients with CrCl <15 mL/min.20 As XANTUS followed the European labelling (which allows use of rivaroxaban with more marked degrees of renal impairment), a small number of patients with CrCl between 15–29 mL/min were included; these represented only 1% of the cohort and did not affect the overall result.

After the initial screening visit for XANTUS, follow-up visits were scheduled at the time of hospital discharge, if applicable, and approximately every 3 months thereafter. The overall follow-up period was 1 year, concluding with a final patient visit. For patients who discontinued therapy before the end of the 1-year follow-up, the observation period ended approximately 30 days after the last dose of rivaroxaban.

Study outcomes

The primary outcomes were related to the safety of rivaroxaban in clinical practice, recorded as adverse events (AEs) or serious AEs (SAEs); SAEs were followed-up until a final outcome was available. AEs and SAEs included major bleeding events (ISTH definition), all-cause death, and any other AEs and SAEs.18 Secondary outcomes included:

- symptomatic thromboembolic events (stroke, non-central nervous system SE, transient ischaemic attack [TIA], and myocardial infarction [MI])
- non-major bleeding events (defined as any bleeding event not meeting the criteria for a major haemorrhage)
- rates of AEs and SAEs across patients with different baseline risk profiles for stroke or bleeding.

Intracranial bleeding that met the definition of stroke was included in both stroke and major bleeding endpoints. Haemorrhagic transformations of ischaemic stroke were counted as a major bleeding event regardless of whether symptomatic or not. Other outcomes included treatment persistence, patient satisfaction (reported by patients using standardised questionnaires completed at quarterly intervals), health care resource use, details of interventions and how they were managed, and reasons for any switch from or interruption of rivaroxaban therapy, including assessment of persistence with therapy.

Study conduct

At every patient visit, physicians were asked to record AEs and SAEs on the AE report form and document the seriousness, duration, actions taken, outcomes, and relation to rivaroxaban therapy for each AE. Documentation concerning AEs was required to cover the 30-day period after cessation of therapy for patients discontinuing rivaroxaban early. AEs were considered treatment-emergent when they occurred from the day of the first dose of rivaroxaban, and up to 2 days after the last dose in the event of discontinuation.

Five expert physicians (not directly involved in the care of XANTUS study patients) formed an independent Central Adjudication Committee (CAC) in order to adjudicate major bleeding, stroke, SE, TIA, MI, and all-cause death. The CAC had access to all patient records. The CAC also adjudicated the type of stroke and occurrence of a haemorrhagic transformation of ischaemic stroke. Clinical cause of death was centrally adjudicated. Reporting standards were confirmed by performing quality assessment and source data verification visits at 61 (19.6%) sites between 04–13 and 03–14, and by reviewing documentation related to 581 patients (8.6%).

The study complied with the Declaration of Helsinki, was approved by the appropriate Health Authorities, independent Ethics Committees, and Independent Review Boards as required, and was conducted in accordance with Good Pharmacoepidemiological Practice (GPP). An independent academic Steering Committee oversaw the design, execution, and conduct of the study, was responsible for manuscript development, had full access to all data, and approved all versions of the manuscript. Patients provided written informed consent that included the permission for data collection and analysis.

Statistical analysis

Statistical analyses were descriptive, exploratory, and generally limited to frequency tables or summary statistics (e.g. means ± standard deviation or medians ± quartiles). The primary analysis population was the full safety population, defined as all patients who took at least one dose of rivaroxaban.
Results

Baseline demographics and clinical characteristics of the cohort approximated everyday clinical practice. Mean patient age was 71.5 years (range 19–99), 41% were female, and 9.4% had documented severe or moderate renal impairment (CrCl <50 mL/min). The mean CHADS, and CHA₂DS-VASc scores were 2.0 and 3.4, respectively; 859 (12.7%) patients had a CHA₂DS-VASc score of 0 or 1.

Over a mean 329 days of follow-up, the vast majority (96.1%) of patients did not experience treatment-emergent major bleeding, all-cause mortality, or stroke/SE; overall numbers increased progressively over time (see Fig. 2). A total of 2709 patients (39.9%) had a treatment-emergent AE and 1200 (17.7%) had a treatment-emergent SAE. Treatment-emergent major bleeding occurred in 128 patients (2.1 events per 100 patient-years). Rates and patterns of major bleeding in XANTUS were uncommon and generally consistent with phase III study data (see Table 1). The annual stroke rate of 0.7% was lower than that in the ROCKET-AF on-treatment population (1.7 events per 100 person-years). Eleven patients (0.2%) had a primary haemorrhagic stroke and 32 (0.5%) a primary ischaemic stroke. Left atrial thrombus was recorded in 6 patients (0.1 events per 100 patient-years). All-cause death occurred in 118 patients (1.9 events per 100 patient-years) within the study treatment period, with the adjudicated cause of death due primarily to cardiovascular causes (41.5% of patients), mainly heart failure (20.3%), followed by cancer (19.5%).

Table 1. XANTUS study outcomes: adjudicated treatment-emergent thromboembolic and bleeding events and all-cause death.

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Incidence proportion,* n (%)</th>
<th>Incidence rate, events per 100 patient-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>118 (1.7)</td>
<td>1.9 (1.8 to 2.3)</td>
</tr>
<tr>
<td>Thromboembolic events (stroke, SE, TIA, and MI)</td>
<td>108 (1.6)</td>
<td>1.8 (1.5 to 2.1)</td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>51 (0.8)</td>
<td>0.8 (0.6 to 1.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>43 (0.6)</td>
<td>0.7 (0.5 to 0.9)</td>
</tr>
<tr>
<td>SE</td>
<td>8 (0.1)</td>
<td>0.1 (0.1 to 0.3)</td>
</tr>
<tr>
<td>TIA</td>
<td>32 (0.5)</td>
<td>0.5 (0.4 to 0.7)</td>
</tr>
<tr>
<td>MI</td>
<td>27 (0.4)</td>
<td>0.4 (0.3 to 0.6)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>128 (1.9)</td>
<td>2.1 (1.8 to 2.5)</td>
</tr>
<tr>
<td>Fatal</td>
<td>12 (0.2)</td>
<td>0.2 (0.1 to 0.3)</td>
</tr>
<tr>
<td>Critical organ bleeding</td>
<td>43 (0.6)</td>
<td>0.7 (0.5 to 0.9)</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>26 (0.4)</td>
<td>0.4 (0.3 to 0.6)</td>
</tr>
<tr>
<td>Mucosal bleeding*</td>
<td>60 (0.9)</td>
<td>1.0 (0.7 to 1.3)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>52 (0.8)</td>
<td>0.9 (0.6 to 1.1)</td>
</tr>
<tr>
<td>Haemoglobin decrease ≥2 g/dL,5,6</td>
<td>52 (0.8)</td>
<td>0.9 (0.6 to 1.1)</td>
</tr>
<tr>
<td>Non-major bleeding events</td>
<td>878 (12.9)</td>
<td>15.4 (14.4 to 16.5)</td>
</tr>
</tbody>
</table>

*Rivaroxaban (n=6784) - VASc risk scores showed that stroke/SE, major bleeding, and all-cause death generally increased with higher risk scores. The baseline stroke risk of patients in XANTUS was lower than in patients in the ROCKET-AF trial, with mean CHADS, scores were 2.0 and 3.5, respectively. Moreover, fewer patients enrolled in XANTUS compared with patients in ROCKET-AF had experienced prior stroke/SE or TIA (19% vs 55%).

Cauterine clearance values were reported in 4452 (65.6%) patients, 14.4% of whom had CrCl <50 mL/min and 85.6% had CrCl ≥50 mL/min. The lowest incidence proportion for major bleeding (0.6%) was observed in patients for whom no CrCl test results were recorded. Of 3812 patients with a documented CrCl of ≥50 mL/min, 15% received the lower rivaroxaban dose of 15 mg od; conversely, the 20 mg od dose was received by 36% of the 640 patients who had moderate or severe renal impairment documented at any time during the study.

Treatment persistence was high throughout the 1-year study period; 80% of patients were still on study treatment at the end of the observation period. The majority (75.1%) of patients reported to their physicians that they were ‘very satisfied’ or ‘satisfied’ with their treatment. The main reason for premature discontinuation (7.9% of all patients) was because of an AE.

Table 2. XANTUS study outcomes: adjudicated treatment-emergent thromboembolic and bleeding events and all-cause death.

The incidence rate of major bleeding was lower than that in ROCKET-AF (3.6 events per 100 patient-years). The incidence rates of fatal bleeding, critical organ bleeding, and intracranial haemorrhage were similar to those observed in ROCKET-AF (XANTUS vs ROCKET-AF 0.2 vs 0.2 events per 100 patient-years, 0.7 vs 0.5 events per 100 patient-years, and 0.4 vs 0.5 events per 100 patient-years, respectively), whereas major gastrointestinal bleeding occurred less frequently (0.9 events per 100 patient-years) than in ROCKET-AF (2.0 events per 100 patient-years).

Figure 2. Cumulative rates (Kaplan–Meier) for treatment-emergent all-cause death, major bleeding events, and stroke/systemic embolism in the XANTUS study. [Adapted from Camm AJ, et al. 2016]
Expert Commentary:

XANTUS is a prospective, ‘real world’ observational study that fills an important gap in our understanding of the use of rivaroxaban for stroke prevention in AF. The initial randomised controlled trial, ROCKET-AF, studied a particularly high-risk group of patients (median age 73 years, 90% hypertensive, and over 55% with prior stroke, systemic embolus or TIA; mean CHADS2 score 3.5). These are risk factors not just for stroke, but for bleeding; given this, the major bleeding rate in ROCKET-AF was reassuringly low (3.9% in patient-years). The trial confirmed the efficacy and safety of rivaroxaban, and led to its registration and PBS reimbursement in Australia. However, important questions remained, including the outcomes with rivaroxaban in lower-risk patients. The unselected prospective cohort in XANTUS is more representative of the patients we see in everyday practice; mean age of 71, prior stroke rate of 19%, mean CHADS2 score 2.0. The event rates were low, with 96.1% of patients having no major adverse events over the 1-year follow-up. The rate of stroke/systemic embolisation was only 0.8%, and major bleeding 2.1%. A particular strength of the study is the regular follow-up and independent central adjudication of major events, more in keeping with the rigour of a randomised trial than a standard overview. Overall consistency with rivaroxaban therapy was high, as was patient satisfaction. The XANTUS trial provides reassurance that the results from ROCKET-AF are reproducible in everyday practice, and are generalisable to a broader patient cohort than that studied in ROCKET-AF.

Take-home messages – Christopher Hammett

XANTUS provides important additional information on the use of rivaroxaban for stroke prevention. It shows that rivaroxaban is safe and effective in AF patients at moderate stroke risk. The mean CHADS2 score in XANTUS was 2.0, akin to the cohorts studied in the randomised trials of dabigatran (RE-LY trial) and apixaban (ARISTOTLE trial), which both had a baseline mean CHADS2 score of 2.1. The rate of major adverse events was low throughout the 1-year follow-up, and stroke and major bleeding rates were lower than those seen in the ROCKET-AF trial (which was a higher-risk population), and comparable or better than those seen in the randomised trials for both dabigatran and apixaban. XANTUS provides reassurance that outcomes with rivaroxaban remain good in the ‘real world’, without attrition control on patient selection or concomitant treatments. It adds to a growing body of registry and administrative dataset information confirming favourable safety and efficacy results for all three NOACs currently available on the Australian market.

References