

Betrixaban compared with warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa)

Stuart J. Connolly^{1*}, John Eikelboom¹, Paul Dorian², Stefan H. Hohnloser³, Daniel D. Gretler⁴, Uma Sinha⁴, and Michael D. Ezekowitz⁵

¹Population Health Research Institute, 237 Barton Street East, Hamilton, Ontario, Canada L8L 2X2; ²University of Toronto, Toronto, Ontario, Canada; ³J. W. Goethe University, Frankfurt, Germany; ⁴Portola Pharmaceuticals, South San Francisco, CA, USA; and ⁵Lankenau Institute for Medical Research and the Heart Center, Wynnewood, PA, USA

Received 4 April 2012; revised 13 December 2012; accepted 20 January 2013; online publish-ahead-of-print 13 March 2013

Aims

Patients with atrial fibrillation (AF) are at increased risk of stroke. Betrixaban is a novel oral factor Xa inhibitor administered once daily, mostly excreted unchanged in the bile and with low (17%) renal excretion.

Methods and results

Patients with AF and more than one risk factor for stroke were randomized to one of three blinded doses of betrixaban (40, 60, or 80 mg once daily) or unblinded warfarin, adjusted to an international normalized ratio of 2.0–3.0. The primary outcome was major or clinically relevant non-major bleeding. The mean follow-up was 147 days. Among 508 patients randomized, the mean CHADS₂ score was 2.2; 87% of patients had previously received vitamin K antagonist therapy. The time in therapeutic range on warfarin was 63.4%. There were one, five, five, and seven patients with a primary outcome on betrixaban 40, 60, 80 mg daily, or warfarin, respectively. The rate of the primary outcome was lowest on betrixaban 40 mg (hazard ratio compared with warfarin = 0.14, exact stratified log-rank *P*-value 0.04, unadjusted for multiple testing). Rates of the primary outcome with betrixaban 60 or 80 mg were more similar to those of warfarin. Two ischaemic strokes occurred, one each on betrixaban 60 and 80 mg daily. There were two vascular deaths, one each on betrixaban 40 mg and warfarin. Betrixaban was associated with higher rates of diarrhoea than warfarin.

Conclusion

Betrixaban was well tolerated and had similar or lower rates of bleeding compared with well-controlled warfarin in patients with AF at risk for stroke.

Keywords

Betrixaban • Stroke • Atrial fibrillation

Introduction

Atrial fibrillation (AF) is an arrhythmia that affects an estimated 7 million people in the USA and the European Union with a median age of 75 years.¹ The greatest risk associated with AF is ischaemic stroke resulting from embolism of thrombus from the left atrium. Guidelines recommend treatment with a vitamin K antagonist for stroke prevention in patients with AF based on the results of randomized, controlled trials comparing warfarin with placebo or no warfarin.^{1–6} The use of warfarin is challenging because it has an unpredictable anticoagulant effect, a high

propensity for food and drug interactions, and a risk of significant bleeding. Indeed, a recent meta-analysis of contemporary randomized clinical trials comprising over 50 000 patient-years on warfarin revealed major bleeding rates ranging from 1.4 to 3.4% per year, and are likely higher outside the confines of a clinical trial.⁷ Routine coagulation monitoring is required, which is inconvenient for patients and costly for the health care system.²

Thrombin plays a key role in arterial and venous thromboses by activating platelets and facilitating the conversion of fibrinogen to fibrin. Recently, dabigatran, a direct thrombin inhibitor, has been shown to be superior to warfarin for the prevention of stroke

* Corresponding author. Tel: +1 905 527 4322, Fax: +1 905 527 44 563, Email: connostu@phri.ca

© The Author 2013. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits non-commercial use, distribution, and reproduction in any medium, provided that the original authorship is properly and fully attributed; the Journal, Learned Society and Oxford University Press are attributed as the original place of publication with correct citation details given; if an article is subsequently reproduced or disseminated not in its entirety but only in part or as a derivative work this must be clearly indicated. For commercial re-use, please contact journals.permissions@oup.com.

with improved ease of use; and is available in many countries.⁸ Factor Xa is also an attractive target for anticoagulant therapy as it is the enzyme responsible for the conversion of prothrombin to thrombin. Rivaroxaban and apixaban, factor Xa inhibitors, have been shown to be effective for stroke prevention in AF.^{9–11}

Betrixaban is an oral, once-daily, direct factor Xa inhibitor. It is rapidly absorbed with mean peak concentrations occurring 3 to 4 h after oral administration, a pharmacodynamic half-life of 20 h and a low peak-to-trough concentration ratio over each 24 h dosing period. Oral bioavailability of an 80 mg dose is 34% and protein binding is ~60%. Betrixaban is mostly excreted unchanged in bile, with low (17%) renal excretion. When administered immediately after a high-fat, high-calorie breakfast, C_{max} and AUC were reduced by ~50% compared with the fasting state. Betrixaban is a substrate for efflux proteins, including P-glycoprotein; however, it is not a substrate for major CYP enzymes.

Betrixaban has been studied in 215 patients in a phase II venous thrombo-embolism (VTE) prevention study (EXPERT) in patients undergoing total knee replacement.¹² Doses of 15 and 40 mg administered twice daily were compared with enoxaparin 30 mg twice daily for 10–14 days. Similar efficacy and safety were observed in all three groups, with a favourable safety profile. The present study was designed to assess the safety and tolerability of betrixaban at three different doses given orally once daily, compared with dose-adjusted [inter-quartile range (INR) 2.0–3.0] warfarin in patients with AF at risk of stroke.

Methods

Patients with new or existing non-valvular AF were recruited from outpatient clinics. They were eligible for enrolment if they fulfilled the following criteria: male or female aged ≥ 18 years, in AF or atrial flutter at the time of enrolment or documented within the previous year by Holter, ECG, rhythm strip, pacemaker, or other intracardiac recording, and with one or more risk factor(s) for stroke, resulting in an indication for anticoagulation with a vitamin K antagonist. Subjects on warfarin were required to have an INR ≤ 2.2 at the time of randomization. Major exclusion criteria included: body weight of < 40 kg, need for either haemodialysis or peritoneal dialysis, AF due to reversible causes, active bleeding; history of congenital or acquired bleeding disorders or vascular malformation; history of intracranial, retroperitoneal, or intraocular bleeding within the last 6 months; high risk of bleeding for other reasons including from significant liver disease; conditions other than AF that required chronic anticoagulation; persistent uncontrolled hypertension. Patients on verapamil were excluded pending a formal drug interaction study. Patients with renal insufficiency were not excluded unless they were on dialysis.

Outcomes

The primary outcome was the time to occurrence of major or clinically relevant non-major (CRNM) bleeding. The secondary outcomes were any bleeding (including major, CRNM, and any other reported bleeding) and the time to occurrence of death, ischaemic or non-ischaemic stroke, MI, or other systemic embolism. An independent adjudicator, blinded to treatment groups, adjudicated all major bleeds, CRNM bleeds, strokes, MI, other systemic embolism, and deaths.

Major bleeding was defined as clinically overt bleeding that was associated with a reduction in haemoglobin of ≥ 20 g/L or transfusion of ≥ 2 units of blood or packed cells, or symptomatic bleeding in a critical

area or organ: intraocular, intracranial, intraspinal, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome or a fatal outcome. Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or discomfort for the patient such as pain or impairment of activities of daily life. All other overt bleeding episodes were classified as minimal bleeding events, and were not adjudicated. Diagnosis of stroke required acute onset of a focal neurological deficit of presumed vascular origin that lasted for ≥ 24 h or resulted in death. A stroke was categorized as ischaemic, haemorrhagic, or unknown, based on CT or MR scanning or autopsy. Deaths were classified as vascular (including bleeding), non-vascular, due to other specific causes (e.g. malignancy), or unknown. Vascular death was considered to occur when there was no obvious non-vascular event to explain death, such as cancer, trauma, or respiratory failure. Sudden or un-witnessed deaths were considered vascular.

Safety monitoring

A data safety monitoring committee was appointed to independently review all safety and efficacy data at regular intervals during the study and make recommendations, as appropriate. No formal analyses of efficacy were performed.

Randomization and follow-up

Patients were randomly assigned (1:1:1 allocation) to betrixaban 40, 60, 80 mg orally, once daily, or warfarin (target INR of 2.0–3.0). Assignment to betrixaban or warfarin was not blinded, but the betrixaban dose was double-blinded. Subjects assigned to betrixaban were instructed to take the drug at bedtime, preferably at least 2 h after the evening meal. A dynamic randomization was used to assign and balance patients by country, concurrent aspirin use, and antecedent warfarin. Aspirin (up to 162 mg daily), clopidogrel, ticlopidine, and any concomitant medications or treatments deemed necessary by the investigator to provide adequate supportive care were allowed during the study. Verapamil use was not allowed, as a drug interaction study had not been performed. The study was conducted according to ethical standards, local laws, and GCPs in the USA, Canada, and Germany. Subjects were assessed at screening, and at weeks 0, 1, 2, 4, 8, and 12 and then every 2 months thereafter for a maximum of 1 year.

Laboratory analyses

Study measurements included plasma betrixaban concentrations, D-dimer concentrations, and thrombin generation (TG). Inhibition of tissue factor-initiated TG was measured as previously described.¹² D-dimer levels were assessed in both warfarin naive (13%) and experienced patients (87%) at baseline and at 12 weeks.

Statistical analyses

Under the assumptions that the event rate for the composite of major and CRNM bleeding would be 5.7% in the warfarin group at 3 months, the enrolment period would be 8 months, and the total study duration would be 11 months, enrolment of 500 patients was planned to provide 80% power to detect a hazard ratio (HR) of 2.27 in the primary endpoint for an individual betrixaban dose vs. warfarin using a two-sided log-rank test at the 0.05 significance level. Continuous parameters were summarized by n (number of non-missing observations), mean, standard deviation, median, minimum, maximum, and the first and third quartiles. Categorical parameters were summarized by count and per cent. Time in therapeutic range (TTR) of the INR was calculated by linear interpolation.¹³ Survival estimates were computed

using the Kaplan–Meier method. Differences in the primary and other outcomes, between treatment groups, were formally tested using individual exact log-rank tests and stratified by country and concurrent aspirin use. Secondary analyses used Cox proportional hazards models. There was no adjustment for testing multiplicity. Significance testing was two-sided. Adverse event rates were compared using Fisher's exact tests. Statistical analyses were performed on an intent-to-treat population basis, using the SAS® software version 9.1.3 or StatXact® PROCs for SAS version 8.

Results

Patient disposition

There were 561 patients screened, and 508 were randomized to the four treatment groups (Figure 1). All patients received at least one dose of study medication and the rate of premature withdrawal from study medication was similar between betrixaban 40, 60, and 80 mg per day and warfarin (8.7, 9.4, 8.7, 6.3%, respectively). There were 113, 119, 117, and 113 patients who completed a minimum follow-up of 90 days for betrixaban 40, 60, and 80 mg per day and warfarin, respectively. The maximum follow-up duration was 329 days and the median follow-up was 150 days. There were 127 patients enrolled from Canada, 369 from the USA, and 12 from Germany.

Baseline characteristics and compliance

Baseline patient risk factors were well balanced (Table 1). The mean age of patients was 73 years, 33.5% were female, and most

patients were Caucasian. The overall mean weight was 90.9 kg. Only 13% of patients had never previously received a vitamin K antagonist. Baseline estimated calculated glomerular filtration rate (GFR) was >70 mL/min in 53.5% of patients, and 8.1% of patients had a GFR <40 mL/min. The mean CHADS₂ score was 2.2.

Concomitant antiplatelet therapy was used in 42, 39, 40, 41% of patients in the betrixaban 40, 60, 80 mg, and warfarin groups, respectively. The mean TTR for patients receiving warfarin was 63.4%. The mean compliance with betrixaban therapy (based on pill counts at follow-up visits) was 96.6, 96.5, and 96.0% on betrixaban 40, 60, and 80 mg per day, respectively.

Bleeding outcomes

The numbers of patients with a major or CRNM bleed were one, five, five, and seven on betrixaban 40, 60, 80 mg, and warfarin, respectively (Table 2).

The rates of the primary outcome were lowest with betrixaban 40 mg [hazard ratio (HR) compared with warfarin = 0.14, exact stratified log-rank *P*-value unadjusted for multiple testing = 0.04; 95% confidence interval 0.017–1.135]. Betrixaban 60 mg per day and betrixaban 80 mg per day had rates of the primary outcome, which were more similar to warfarin. The outcome of any bleeding event occurred in 22, 32, 24, and 40 patients on betrixaban 40, 60, 80 mg, and warfarin, respectively. With betrixaban 40 mg and betrixaban 80 mg per day, the rates of any bleeding were reduced compared with warfarin [exact stratified log-rank *P*-values of 0.01 and 0.02 (unadjusted for multiple testing), respectively].

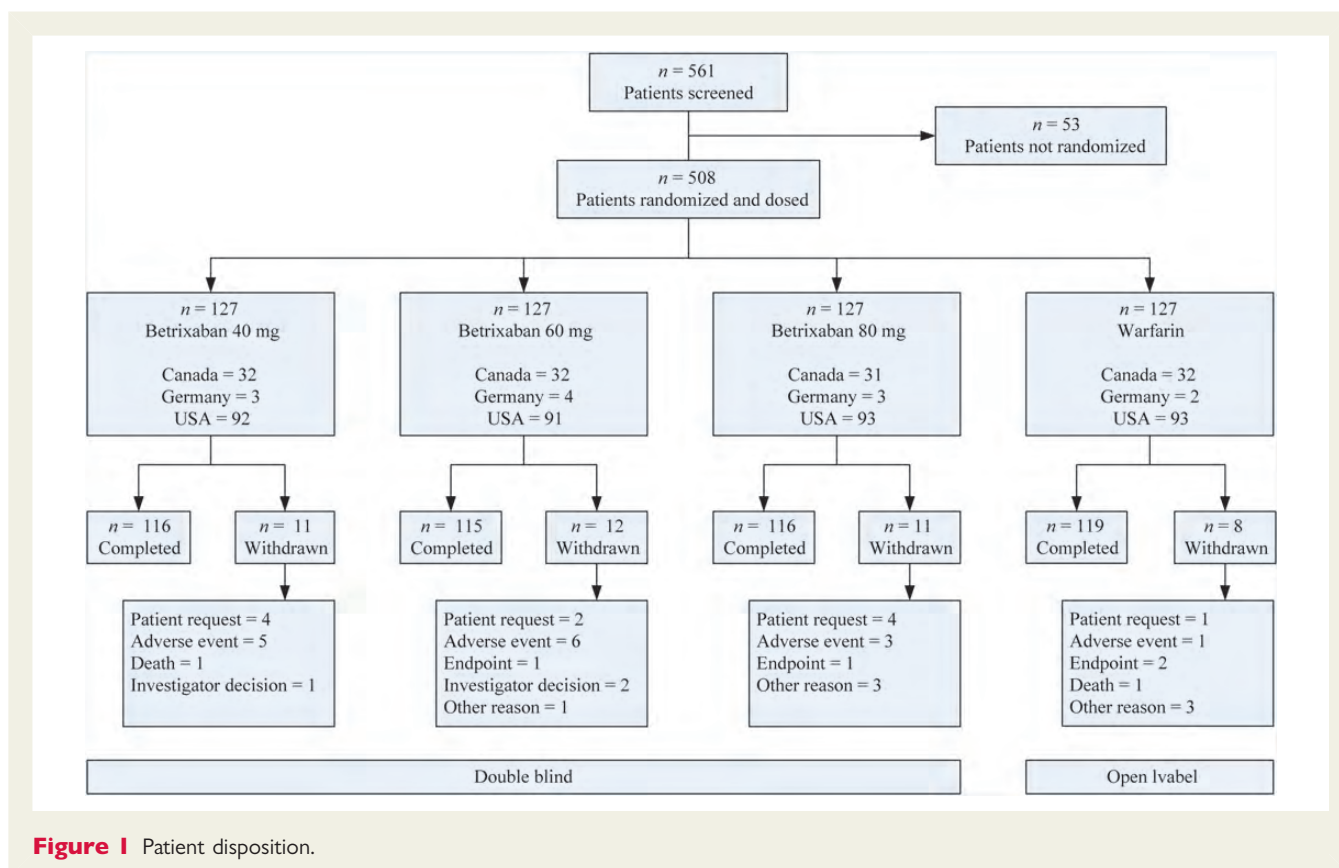


Table 1 Baseline demographics and patient characteristics

Demographic or baseline measure	Betrixaban 40 mg (n = 127)	Betrixaban 60 mg (n = 127)	Betrixaban 80 mg (n = 127)	Warfarin (n = 127)	Overall (n = 508)
Age (years)					
Mean (SD)	73.3 (8.50)	73.8 (8.35)	72.0 (7.65)	72.7 (8.75)	73.0 (8.32)
Age category [n (%)]					
≥75 years	63 (49.6)	66 (52.0)	51 (40.2)	60 (47.2)	240 (47.2)
Gender/race [n (%)]					
Female	48 (37.8)	46 (36.2)	38 (29.9)	38 (29.9)	170 (33.5)
White	125 (98.4)	123 (96.9)	123 (96.9)	126 (99.2)	497 (97.8)
Other	2 (1.6)	4 (3.1)	4 (3.1)	1 (0.8)	11 (2.2)
Weight (kg)					
Mean (SD)	89.58 (21.409)	89.14 (23.438)	91.25 (20.690)	93.73 (24.337)	90.93 (22.523)
Weight category [n (%)]					
>90 kg	53 (41.7)	54 (42.5)	65 (51.2)	62 (48.8)	234 (46.1)
Prior use of vitamin K antagonist [n (%)]					
No	15 (11.8)	17 (13.4)	16 (12.6)	18 (14.2)	66 (13.0)
Concomitant antiplatelet therapies [n (%)]					
At least one antiplatelet therapy	53 (41.7)	49 (38.6)	51 (40.2)	52 (40.9)	205 (40.4)
Exactly one antiplatelet therapy	49 (38.6)	47 (37.0)	46 (36.2)	49 (38.6)	191 (37.6)
Two or more antiplatelet therapies	4 (3.1)	2 (1.6)	5 (3.9)	3 (2.4)	14 (2.8)
GFR level (Cockcroft–Gault) [n (%)]					
<40 mL/min	14 (11.0)	14 (11.0)	7 (5.5)	6 (4.7)	41 (8.1)
40–70 mL/min	47 (37.0)	50 (39.4)	50 (39.4)	48 (37.8)	195 (38.4)
>70 mL/min	66 (52.0)	63 (49.6)	70 (55.1)	73 (57.5)	272 (53.5)
Classification of AF [n (%)]					
Permanent	49 (38.6)	34 (26.8)	35 (27.6)	52 (40.9)	170 (33.5)
Persistent	28 (22.0)	25 (19.7)	26 (20.5)	26 (20.5)	105 (20.7)
Paroxysmal	50 (39.4)	68 (53.5)	66 (52.0)	49 (38.6)	233 (45.9)
CHADS ₂ score ^a [n (%)]					
0–1	28 (22.0)	36 (28.3)	43 (33.9)	37 (29.1)	144 (28.3)
2	52 (40.9)	45 (35.4)	55 (43.3)	42 (33.1)	194 (38.2)
3–6	47 (37.0)	46 (36.2)	29 (22.8)	48 (37.8)	170 (33.5)

AF, atrial fibrillation; GFR, glomerular filtration rate.

^aThe CHADS₂ score is used to predict the risk of stroke in AF. It ranges from 0 to 6. One point is given for each of congestive heart failure, hypertension, age ≥75, and diabetes mellitus. Two points are given for either stroke or transient ischaemic attack. The CHADS₂ score was computed regardless of timing of component events and diagnoses

Stroke and death

There was one stroke on betrixaban 60 mg and one on betrixaban 80 mg (both ischaemic) and no strokes on betrixaban 40 mg or warfarin (Table 2). There were two deaths, both vascular, one on betrixaban 40 mg and one on warfarin. There were no occurrences of myocardial infarction, systemic embolic events, or pulmonary embolism during the study.

Adverse events and liver function tests

There were similar rates of serious adverse events in the four treatment arms: 9.4, 9.4, 8.7, 9.4% on betrixaban 40, 60, 80 mg, and warfarin, respectively. There were significantly higher rates of diarrhoea in the pooled betrixaban group vs. warfarin, 6.0 vs. 0.8%, respectively. Rates of premature study discontinuation (for any cause) were higher on betrixaban compared with warfarin,

Table 2 Outcome events

Outcome	Betrixaban 40 mg (n = 127), events	Betrixaban 60 mg (n = 127), events	Betrixaban 80 mg (n = 127), events	Warfarin (n = 127), events	Betrixaban 40 mg vs. warfarin [HR (95% confidence interval)]	Betrixaban 60 mg vs. warfarin [HR (95% confidence interval)]	Betrixaban 80 mg vs. warfarin [HR (95% confidence interval)]
Major or CRNM bleeding	1	5	5	7	0.140 (0.017–1.135)	0.711 (0.225–2.243)	0.755 (0.239–2.389)
Major bleeding	0	0	3	5	NA (NA)	NA (NA)	0.609 (0.145–2.557)
CRNM bleeding	1	5	2	4	0.264 (0.030–2.364)	1.257 (0.337–4.684)	0.538 (0.098–2.937)
Minimal bleeding	22	28	23	36	0.572 (0.336–0.974)	0.752 (0.458–1.235)	0.584 (0.346–0.986)
Any bleeding	22	32	24	40	0.508 (0.301–0.856)	0.767 (0.481–1.224)	0.551 (0.332–0.914)
Stroke	0	1 (ischaemic)	1 (ischaemic)	0	–	–	–
Death	1 (vascular)	0	0	1 (vascular)	–	–	–

HR and 95% confidence interval values are from a secondary analysis using a Cox proportional hazards model with treatment, country, and concurrent aspirin use effects. CRNM, clinically relevant non-major; rate per year, rate per 100 patient years of follow-up; n, number of patients randomized; HR, hazard ratio.

8.9 vs. 6.3%. Liver function tests were measured in all patients at each visit. The per cent of patients with an elevated alanine aminotransferase greater than three times the upper limit of normal on betrixaban (all doses) and on warfarin were 1.8 vs. 0.8%, respectively. There was no dose-related increase in these numbers with 3 (2.4%), 3 (2.4%), and 1 (0.8%) cases in the 40, 60, and 80 mg betrixaban group, respectively.

Pharmacodynamic data

Figure 2 shows the levels of TG associated with increasing concentrations of betrixaban based on blood sample collection at ~13 h (median) after dosing (range 2–18 h) for up to 11 occasions throughout the study. The inset shows the TG associated with increasing intensity of anticoagulation with warfarin, as measured by the INR. Levels of TG similar to those seen with therapeutic warfarin (INR 2.0–3.0) are achieved with betrixaban at plasma concentrations between 12 and 30 ng/mL. The geometric mean betrixaban plasma concentrations, at steady state (week 4), were 6, 9.6, and 12 ng/mL for betrixaban 40, 60, and 80 mg, respectively.

Figure 3 shows the plasma D-dimer concentrations in study patients after 12 weeks of treatment. Because warfarin therapy reduces D-dimer concentration, patients who were warfarin-naïve at baseline are displayed separately from the overall study population. In the warfarin-naïve population, there is a reduction in D-dimer levels on treatment relative to their respective baseline level with betrixaban (all doses combined) ($P \leq 0.001$) and with warfarin ($P = 0.08$). The reductions in the three betrixaban groups are not significantly different from that seen with warfarin (P -values of 0.91, 0.49, and 0.19 for the three comparisons).

Discussion

Betrixaban is a novel once-daily factor Xa inhibitor which has been shown to competitively bind to factor Xa and to inhibit its activity.

A dose ranging study in 215 patients at risk for VTE events after orthopedic surgery reported that betrixaban demonstrated clinical antithrombotic activity comparable with that of enoxaparin 30 mg s.c. given every 12 h.¹² Patients with AF have an increased risk of stroke, and vitamin K antagonist therapy is recommended in those at moderate or high risk of stroke.

The EXPLORE-Xa study was designed to evaluate the safety and tolerability of betrixaban compared with warfarin in patients with AF who are receiving or are eligible for vitamin K antagonist therapy. Patients enrolled were typical of AF patients who would typically receive warfarin for the prevention of stroke. Unlike other similar studies with novel factor Xa inhibitors, patients with renal insufficiency were allowed to be enrolled unless they were on dialysis. The main findings of the study are the rates of the primary outcome (major or CRNM bleeding) were numerically lower with all three doses of betrixaban compared with warfarin; and betrixaban 40 mg daily has a statistically significant lower rate than with warfarin. These findings suggest that there may be a dose–response relationship for bleeding with betrixaban. Thus, all three doses of betrixaban studied, 40, 60, and 80 mg once daily, appear to have an acceptable safety profile in comparison with warfarin.

The effectiveness of warfarin and its safety have been shown to be associated with the control of the INR.¹⁴ This is often measured by the TTR, which can be calculated by linear interpolation of the INR values over time. The average TTR reported in a recent meta-analysis of surveys of clinical practice in the USA is 55%, with somewhat high levels achieved using anticoagulation clinics.¹⁵ In the EXPLORE Xa study, most patients were experienced with warfarin and would therefore be expected to have a somewhat higher TTR than naïve patients. The INR control achieved in this study was good, and was similar to that achieved in recent randomized trials of warfarin therapy in AF patients.^{8,10,11,16} Therefore, one would have expected a rate of major bleeding

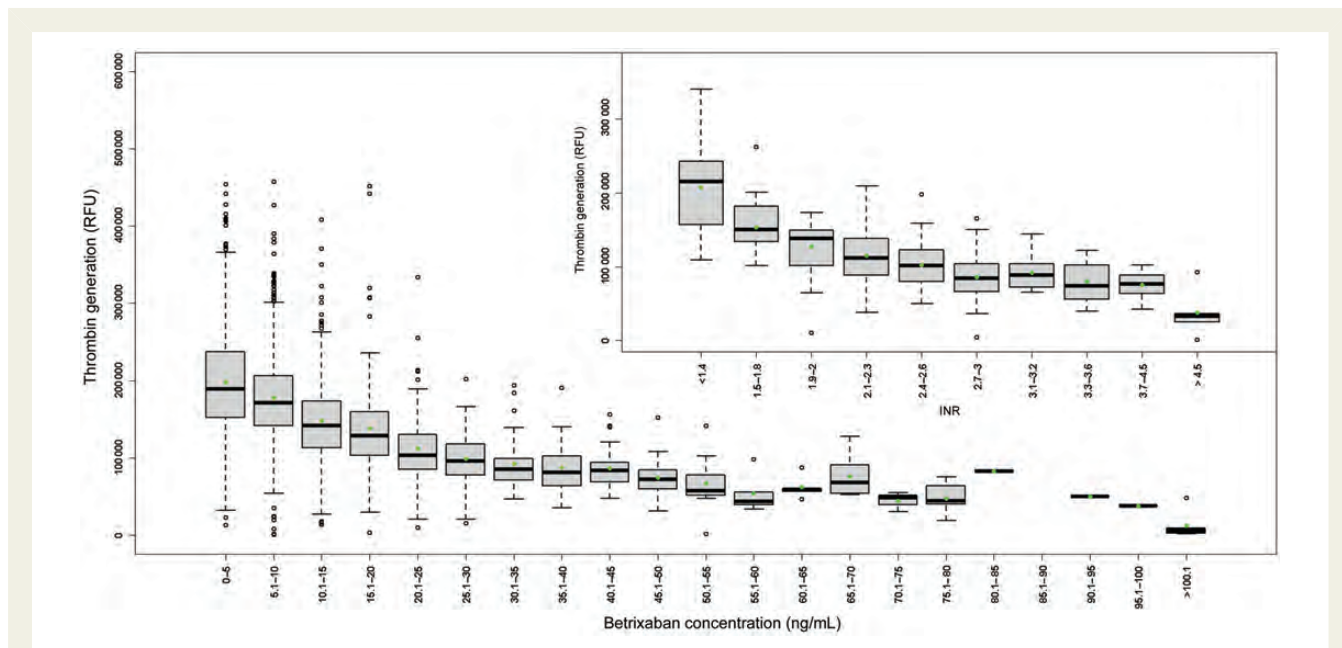


Figure 2 Box and whiskers plot of dose responsive effect of betrixaban on thrombin generation in patient plasma at around a median 13 h (2–18 h) post-dose. Thrombin activity is measured following cleavage of a specific fluorogenic substrate for thrombin. The figure depicts the fluorescence signal vs. the range of betrixaban plasma concentrations. The boxes represent first and third quartile of the population and the whiskers extend to 1.5 inter-quartile range. The inset represents the effect of anticoagulation by warfarin (inter-quartile range) on thrombin generation.

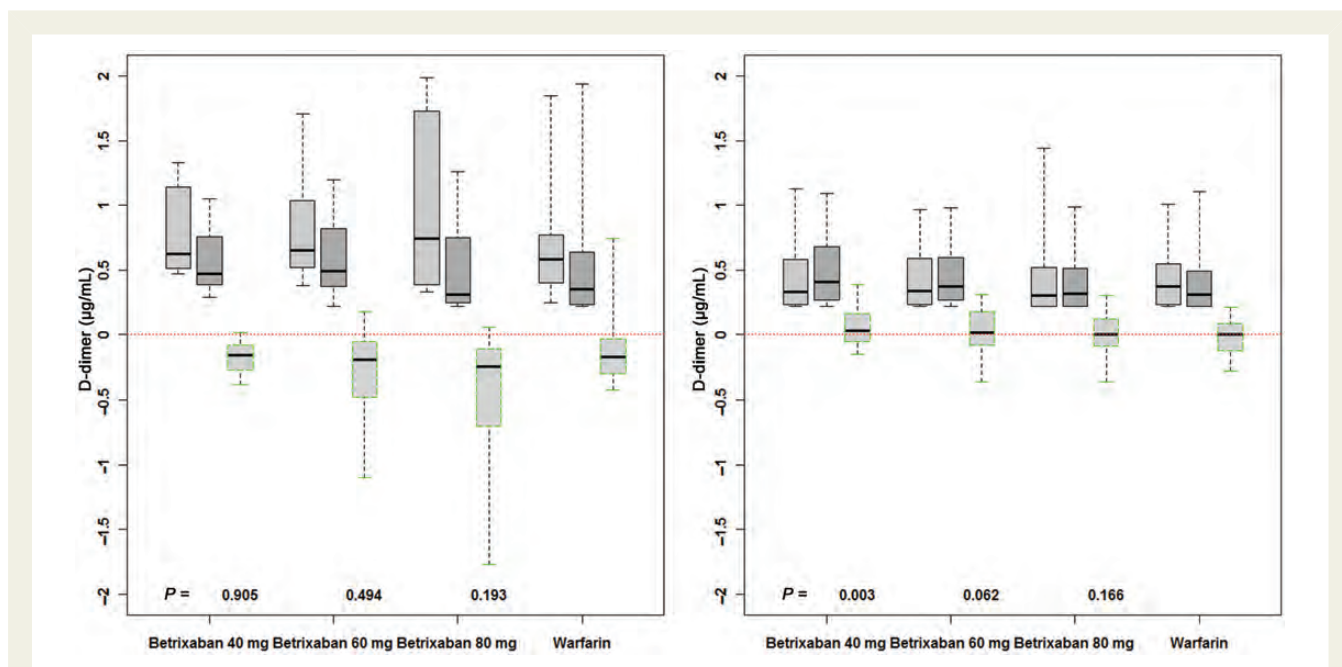


Figure 3 Changes in D-dimer levels in the overall patient population (right panel) and warfarin-naïve patients (left panel) after 12 weeks of treatment. Box and whiskers plots represent levels at baseline, 12 weeks, and changes relative to baseline. Each betrixaban group is compared with the warfarin group; *P*-values were determined by non-parametric test (Kruskal–Wallis).

on warfarin similar to rates recently reported in these trials. However, the rate of major bleeding on warfarin in this study was 10.3% per year which is unexpectedly higher.^{8,10,11,16}

Rates of ischaemic stroke would be expected to be low on warfarin in patients with a mean CHADS₂ score of 2 and with good INR control. There were two ischaemic strokes observed in the

study and no systemic embolic events, myocardial infarctions, or pulmonary emboli. One stroke occurred in each of the betrixaban 60 and 80 mg arms; no strokes occurred on betrixaban 40 mg or on warfarin. Given the mean duration of follow-up (0.4 years), risk profile of the patients, and the INR control achieved, one would expect about 0–1 strokes in such well-managed warfarin patients, consistent with the overall stroke rate observed in this study.

The evaluation of the TG data indicates that betrixaban has an anticoagulant effect at the concentrations achieved by the doses used in this study and that this effect is comparable with that of warfarin. This supports the clinical findings and suggests that at the same level of TG as therapeutic warfarin, betrixaban may have a lower risk of bleeding than warfarin. However, this will need to be evaluated in an adequately powered study. Warfarin suppresses D-dimer concentrations.¹⁷ Patients enrolled in this study who were treated with a vitamin K antagonist at baseline had lower D-dimer levels than naïve patients. In vitamin K antagonist-naïve patients, the three doses of betrixaban and warfarin reduced D-dimer levels, thus demonstrating anticoagulant activity of the betrixaban doses tested. Of particular importance, the reduction in D-dimer for betrixaban patients on 60 and 80 mg resulted in levels within the 0.5 µg/mL concentration, which has been shown to correlate with a reduction in thromboembolic, cardiovascular, and bleeding events.¹⁸

Betrixaban was well tolerated in this relatively short-term study. Patients in this study had mostly used warfarin before enrolment, which would be expected to result in a low rate of intolerance to warfarin. Nonetheless, betrixaban was as well tolerated as warfarin with similar rates of serious adverse effects. Betrixaban was associated with reports of gastro-intestinal symptoms in some patients, especially diarrhoea. These symptoms were mild and did not result in discontinuation of therapy.

The main limitation of this study is its small size. Hence, it was statistically underpowered to provide definitive conclusions regarding the safety or efficacy of any particular betrixaban dose vs. warfarin. For example, no statistical adjustment was made for multiple comparisons (each dose vs. warfarin) in the primary endpoint. Nevertheless, this study provides some guidance regarding dose of betrixaban for evaluation in larger clinical trials. The lowest rate of bleeding was seen with betrixaban 40 mg. The pharmacodynamic and kinetic data indicated that all betrixaban doses tested reduce TG and that the 80 mg daily had a similar reduction in TG as would be expected with therapeutic warfarin (INR 2.0–3.0). All three betrixaban doses reduced D-dimer to levels expected to be associated with clinical benefit using warfarin therapy.

In conclusion, betrixaban at doses of 40–80 mg per day was well tolerated in AF patients at risk for stroke with a risk of bleeding that was similar to, or lower than, that of well-managed warfarin. A larger and definitive phase 3 trial of betrixaban is indicated.

Funding

The trial was funded by Portola Pharmaceuticals, South San Francisco, CA, USA.

Conflict of interest: S.J.C.: grant—Boehringer Ingelheim, Bristol Myers Squibb, Bayer; consulting fee or honorarium—Boehringer

Ingelheim, Bristol Myers Squibb, Bayer, Portola. J.E.: consulting fee or honorarium—Portola, Bayer, Boehringer Ingelheim, sanofi-aventis, Daiichi Sanyko; consultancy—Bayer, Boehringer Ingelheim; sanofi-aventis, Bristol Myers Squibb; GlaxoSmithKline, McNeil, Daiichi Sankyo; grants/grants pending—Bayer, Boehringer Ingelheim; payment for lectures including service on speakers bureaus—Bayer, Boehringer Ingelheim, Portola; sanofi-aventis, Bristol Myers Squibb; GlaxoSmithKline, McNeil, Daiichi Sankyo. U.S.: employment—Portola Pharmaceuticals; patents (planned, pending or issued)—Portola Pharmaceuticals, Inc.; stock/stock options—Portola Pharmaceuticals, Inc. M.D.E.: consultant and speaker: Boehringer Ingelheim; consultant—ARYx Therapeutics, Pfizer, sanofi-aventis, Bristol Myers Squibb, PORTOLA, Bayer, Diachi Sanko, Medtronics, Eisai, Merck, J&J, Gilead, Janssen Scientific Affairs, Pozen, Inc., CohereX. D.D.G. is an employee of Portola Pharmaceuticals.

References

- Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, ACC/AHA Task Force Members, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, ESC Committee for Practice Guidelines, Priori SG, Bland JJ, Budaj A, Camm AJ, McGregor VK, Metzra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;**114**:e257–e354.
- Ansell J, Hirsh J, Hylek E, Jacobson A, Crowley M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-based Clinical Practice Guidelines (8th edition). *Chest* 2008;**133** (6 Suppl.):160S–198S.
- Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK Study. *Lancet* 1989;**1**:175–179. PubMed PMID: 2563096.
- Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;**343**:687–691.
- Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;**323**:1505–1511.
- Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, Krause-Steinrauf H, Kurtzke JF, Nazarian SM, Radford MJ. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med* 1992;**327**:1406–1412.
- Agarwal S, Hachamovitch R, Menon V. Current trial-associated outcomes with warfarin in prevention of stroke in atrial fibrillation: a meta-analysis. *Arch Int Med* 2012;**172**:623–631.
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
- Connolly SJ, Eikelboom J, Joyner C, Diener H, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser S, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, San Tan R, Sim K, Lewis B, Van Mieghem W, Lip G, Kim JH, Lananas-Zanetti F, Gonzalez-Hermosillo A, Dans A, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S, for the AVERROES Steering Committee Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–817.
- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
- Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell JA, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Ghalib M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L,

- The ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
12. Turpie AGG, Bauer KA, Davidson BL, Fisher WD, Fent M, Huo MH, Sinha U, Gretler DD, EXPERT Study Group. A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). *Thromb Haemost* 2009;**101**:68–76.
 13. Rosendaal FR, Cannegieter SC, van der Meer FJM, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;**69**:236–239.
 14. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S; ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008;**118**:2029–2037.
 15. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm* 2009;**15**:244–252.
 16. ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomized controlled trial. *Lancet* 2006;**367**:1903–1912.
 17. Nozawa T, Inoue H, Iwasa A, Okumura K, Jong-dae L, Shimizu A, Hayano M, Yano K. Effects of anticoagulation intensity on hemostatic markers in patients with non-valvular atrial fibrillation. *Circ J* 2004;**68**:29–34. PubMed PMID: 14695462.
 18. Sadanaga T, Sadanaga M, Ogawa S. Evidence that D-dimer levels predict subsequent thromboembolic and cardiovascular events in patients with atrial fibrillation during oral anticoagulant therapy. *Cardiol J Am Coll* 2010;**55**: 2225–31.

CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehs092

Online publish-ahead-of-print 21 March 2013

Isolated persistent left superior vena cava draining into the left atrium of an otherwise normal heart

Dominik C. Benz¹, Nazmi Krasniqi^{1,2}, Ute Wagnetz¹, Ruedi Steiger³, Felix C. Tanner^{1,2}, and Urs Eriksson^{1,2,4*}

¹Department of Medicine, GZO – Zurich Regional Health Centre, Wetzikon, Switzerland; ²Department of Cardiology, Cardiovascular Center, University Hospital, Zurich, Switzerland; ³Rosenklinik am See AG, Rapperswil, Switzerland; and ⁴Division of Cardioimmunology, Department Cardiovascular Research, Institute of Physiology, University of Zurich, Switzerland

*Corresponding author. Email: urs.eriksson@gzo.ch

A 63-year-old male presented with progressive right-sided hemiparesis, facial palsy, and aphasia. He had been scheduled for neoadjuvant chemotherapy for relapsing adenocarcinoma of the left colic flexure, and a left-sided port-a-cath was implanted 7 days ago. The CCT scan revealed several already well-demarcated ischaemic brain lesions. Treatment with aspirin and statin was initiated.

Chest X-ray revealed an unusual left-sided downward course of the port-a-cath catheter to the left atrium. Injection of agitated saline into the left cubital vein showed microbubbles in the left atrium (Panel A). In contrast, injection into the right arm resulted in opacification of the right atrium (Panel B). TEE demonstrated an isolated left-sided superior vena cava draining into the left atrium between the left atrial appendage and the left upper pulmonary vein (Panel C). The innominate vein was absent, while there was normal course of the right superior vena cava. Except for a very small left ventricular diverticulum, cardiac anatomy was otherwise normal. Retrospective analysis of a former thoracic CT scan (Panel D) and MR angiography (Panel E) confirmed the persistent left superior vena cava (PLSVC).

To our knowledge, there has not been described yet an isolated defect of LSVC draining into the left atrium as single anomaly without atresia of coronary sinus, any septal defects and any valvular abnormalities.

PLSVC draining to the left atrium is clinically relevant as it predisposes to paradoxical embolism, particularly in the context of venous injections into the left arm, device implantation, or central vein cannulation from the left side.

Supplementary material is available at *European Heart Journal* online.

