Table 2. Bleeding Outcomes.

Outcome	Apixaban (n=9088)*	Warfarin (n=9052)*	HR (95% CI)	p value
Primary outcome: ISTH major bleeding	2.13	3.09	0.69 (0.60 to 0.80)	<0.001
Intracranial	0.33	0.80	0.42 (0.30 to 0.58)	<0.001
Gastrointestinal	0.76	0.86	0.89 (0.70 to 1.15)	0.37
Other locations	1.79	2.27	0.79 (0.68 to 0.93)	0.004
Major or clinically relevant nonmajor bleeding	4.07	6.01	0.68 (0.61 to 0.75)	<0.001
GUSTO severe bleeding	0.52	1.13	0.46 (0.35 to 0.60)	<0.001
GUSTO moderate or severe bleeding	1.29	2.18	0.60 (0.50 to 0.71)	<0.001
TIMI major bleeding	0.96	1.69	0.57 (0.46 to 0.70)	<0.001
TIMI major or minor bleeding	1.55	2.46	0.63 (0.54 to 0.75)	<0.001
Any bleeding	18.1	25.8	0.71 (0.68 to 0.75)	<0.001
Net clinical bleeding				
SSE or major bleeding	3.17	4.11	0.77 (0.69 to 0.86)	<0.001
SSE, major bleeding, or all-cause death	6.13	7.20	0.85 (0.78 to 0.92)	<0.001

*Event rate - %/year; ISTH=International Society of Thrombosis and Hemostasis; GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries; TIMI=Thrombolysis in Myocardial Infarction, SSE=stroke, systemic embolism; Source: Granger CB, Alexander JH, McMurray JJV et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. Aug 28, 2011.

ARISTOTLE is the third recently completed Phase 3 trial that has compared a novel oral anticoagulant with warfarin in patients with AF. These findings are important, in that they represent the first double-blind trial that has demonstrated superiority of a novel oral anticoagulant over warfarin in terms of both efficacy and safety and a reduction in mortality. All three agents that have been tested to date (apixaban, rivaroxaban, and dabigatran) have demonstrated a favorable safety profile with a primary benefit of reducing intracranial bleeding compared with warfarin. Whether newer agents can further reduce ischemic/thrombotic stroke and how these novel drugs compare with warfarin managed with a higher TTR are two important unanswered questions. As more treatment options become available for patients with AF, clinicians and medical systems will need to carefully weigh their respective characteristics as well as cost-effectiveness. Head-to-head comparisons in terms of efficacy and safety are needed.

Further reading: Granger et al. *N Engl J Med* 2011.

Benefits of Apixaban over Warfarin are Consistent, Irrespective of TTR

Written by Maria Vinall

Results from the ARISTOTLE (Apixaban for Reduction In STrOke and other ThromboemboLic Events in atrial fibrillation [NCT00412984]) trial showed that treatment with apixaban results in a lower rate of stroke or systemic embolism (SSE), less bleeding, and lower mortality compared with warfarin therapy [Granger CB et al. *N Engl J Med* 2011]. Lars Wallentin, MD, Uppsala University, Uppsala, Sweden, discussed the results of a subanalysis of data from ARISTOTLE, which demonstrated that the benefit of apixaban over warfarin was not related to the quality of INR control at the individual ARISTOTLE study centers.

A total of 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke from 1034 centers in 39 countries were randomized to double-blind, double-dummy treatment with apixaban 5 mg BID versus warfarin (target INR 2.0 to 3.0). In the main trial results, both the primary efficacy outcome of SSE (HR, 0.79; 95% CI, 0.66 to 0.95; p=0.01) and the primary safety outcome of ISTH major bleeding (HR, 0.69; 95% CI, 0.60 to 0.80; p<0.001) were reduced with apixaban compared with warfarin. The purpose of the current analysis was to assess whether the benefits of apixaban were consistent among centers that achieved similar time-in-therapeutic range (TTR). Each center's TTR was calculated as the median of all individuals' TTRs in warfarin-treated patients and then assigned as a measure of quality of INR control for all patients. Analyses were adjusted for differences in baseline variables with the potential to influence TTR and/or outcome (eg, age, sex, body weight, $CHADS_2$ score, prior stroke, diabetes mellitus, hypertension, heart failure, and baseline medications).

Consistent with the main trial results, when stratified by the centers' TTRs, there was a directionally consistent reduction in the primary endpoint with apixaban compared with warfarin in each stratum (Table 1). There was no significant interaction between efficacy and the quartile of center-based TTR (p interaction=0.29). Similarly, the primary safety endpoint of ISTH major bleeding was reduced in each center-based TTR stratum with apixaban compared with warfarin, with a trend toward greater reduction at centers with lower TTRs but with no statistically significant interaction (p interaction=0.10; Table 2). The secondary safety endpoint of major or clinically relevant minor bleeding was also reduced with apixaban, with a more robust reduction at centers with lower TTRs and significant interaction (p interaction=0.005; Table 2).

Table 1. SSE in Relation to Centers' TTRs.

	Apixaban		Warfarin			
Center TTR (%)	Events	Rate/100 person years	Events	Rate/100 person years	HR (95% CI)	Adjusted Interaction
<58.0	70	1.75	88	2.28	0.77 (0.56 to 1.06)	0.29
58.0 to 65.7	54	1.30	68	1.61	0.80 (0.56 to 1.15)	
65.7 to 72.2	51	1.21	65	1.55	0.79 (0.54 to 1.13)	
>72.2	36	0.83	44	1.02	0.81 (0.52 to 1.26)	

TTR=Time-therapeutic range; HR = Hazard ratio; CI = Confidence interval

There were consistent reductions in mortality and the composite efficacy endpoint of SSE and myocardial infarction with apixaban in each stratum, with no

interaction, based on TTR (p interaction=0.39 and 0.27, respectively). There was also a reduction in the incidence of hemorrhagic stroke and an improved net clinical benefit with apixaban, neither of which was related to the quartile of center-based TTR.

Table 2. Bleeding in Relation to Centers' TTRs.

	Apixaban		Warfarin			
Center TTR (%)	Events	Rate/100 person years	Events	Rate/100 person years	HR (95% CI)	Adjusted Interaction p value
Major Bleeding						0.10
<58.0	61	1.75	115	3.34	0.53 (0.39 to 0.72)	
58.0 to 65.7	61	1.60	102	2.68	0.60 (0.43 to 0.82)	
65.7 to 72.2	103	2.68	109	2.89	0.93 (0.71 to 1.21)	
>72.2	98	2.49	136	3.46	0.72 (0.55 to 0.93)	
Major and clinically relevant bleeding						0.005
<58.0	115	3.19	207	6.13	0.53 (0.42 to 0.66)	
58.0 to 65.7	125	3.32	195	5.24	0.64 (0.51 to 0.80)	
65.7 to 72.2	179	4.75	220	5.99	0.79 (0.65 to 0.97)	
>72.2	191	4.96	255	6.68	0.74 (0.62 to 0.90)	

TTR=Time-therapeutic range; HR = Hazard ratio; CI = Confidence interval

Prof. Wallentin concluded, "In patients with atrial fibrillation, treatment with apixaban is more effective and safer than treatment with warfarin across a wide range of warfarin management." It should be noted that the comparisons of results by center-based TTR in trials that have compared novel anticoagulants that do not use INR with warfarin that is being titrated to the INR are challenging and have several limitations. A patient's TTR may be modified by many factors, including region, center, logistical issues, and individual patient characteristics. The current analysis grouped patients across a group of centers into one of four quartiles, according to the center's average TTR for all patients who were treated with warfarin at that center, and does not represent an adjustment at the patient level. These results should be applied with caution by clinicians, especially when faced with individual patients who have been able to achieve excellent therapeutic control with warfarin.

Safety and Tolerability Darexaban in Patients with ACS: The RUBY-1 Trial

Written by Maria Vinall

Results from the RUBY-I trial [NCT00994292] showed a dose-related, 2- to 4-fold increase in bleeding when the factor Xa inhibitor darexaban was added to standard treatment (aspirin with or without clopidogrel) for the secondary prevention of ischemic vascular events in patients with recent acute coronary syndrome (ACS). These result are consistent with the findings of other factor Xa inhibitor trials in patients with ACS and, thus, not unexpected in this Phase 2 dose-ranging safety trial that compared darexaban with placebo. Gabriel Steg, MD, Hôpital Bichat, Université Paris Diderot, Paris, France, who presented the results of the RUBY-1 trial, stated that "investigating the potential role of low-dose darexaban in preventing major cardiac events after ACS will require a large Phase 3 trial to test whether or not it might achieve clinical efficacy on top of dual antiplatelet therapy (DAPT) without an unacceptable increase in the risk of bleeding."

The RUBY-1 trial was a prospective Phase 2, multicenter, double-blind, randomized, multiple-dose, placebo-controlled, parallel-group, 26-week study in 1279 patients with recent non-ST-segment elevation (NSTEMI) and ST-segment elevation (STEMI). Patients with NSTEMI were also required to have one additional risk factor for recurrent ischemic events. Key exclusion criteria included the need for ongoing anticoagulant therapy, fibrinolytic administration, glycoprotein IIb/IIIA antagonists or other antiplatelet drugs (aspirin and clopidogrel were allowed), heightened bleeding risk, stroke or transient ischemic attack within 12 months prior to index event, and persistent systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg at baseline. After discontinuation of parenteral antithrombotic therapy, subjects received one of six regimens of darexaban (5 mg BID, 10 mg QD, 15 mg BID, 30 mg QD and BID, 60 mg QD) or placebo in addition to DAPT. The primary study outcome was the incidence of major or clinically relevant nonmajor bleeding events. Secondary endpoints included a composite of all-cause mortality, nonfatal myocardial infarction (MI), nonfatal stroke, and severe recurrent ischemia.

Approximately 70% of subjects had STEMI and nearly three-quarters had undergone PCI for their index event prior to study enrollment. The mean subject age was 57 years, and 80% was male. Approximately 96% of subjects were on DAPT with aspirin + clopidogrel. Of the 23% of patients who discontinued prematurely, 137 (11%) did so because of adverse events (AEs), which were more frequent in the groups that received high doses of darexaban. Overall AEs were similar between arms, including alanine transaminase, aspartate transaminase, and bilirubin levels.

Major and clinically relevant nonmajor bleeding events at 6 months were numerically higher in all darexaban arms compared with the placebo group (pooled HR, 2.28; 95% CI, 1.13 to 4.60; p=0.022) [Steg PG et al. *Eur Heart J* 2011]. There was a dose-response relationship (p=0.009) for increased bleeding rates with increasing darexaban dose.