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.

Furthermore, BID dosing was associated with numerically higher bleeding rates compared with the same QD dose across the three total study doses (10 mg, 30 mg, 60 mg). Relative to placebo (3.1%), the increase in bleeding was statistically significant (p=0.002) for the darexaban 30-mg BID dose (11.3%). No cases of fatal bleeding or intracranial hemorrhage were reported in either study group. TIMI major bleeding rates were low in all groups; however, the rate for any TIMI bleeding followed the same dose-dependent increase as was seen for the primary endpoint. There was no difference in the composite efficacy endpoint of all-cause mortality, nonfatal MI, nonfatal stroke, and severe recurrent ischemia in any of the darexaban dose groups, individually or combined, when compared with placebo (p=NS).

Darexaban is a novel anti-Xa anticoagulant, similar to rivaroxaban and apixaban, which have already been evaluated in Phase 2 studies. While the Phase 3 APPRAISE-2 trial that evaluated apixaban in ACS was halted early due to excess bleeding risk, the ATLAS-2 trial (rivaroxaban in ACS) is ongoing. Insights from these Phase 3 trials will help clinicians understand whether there is a role for oral anticoagulant therapy in addition to antiplatelet therapy in patients with ACS and how to dose these new agents appropriately.

Additional reading: Steg G et al. *Eur Heart J* 2011.

EMPHASIS-HF: An Analysis of the High-Risk Groups

Written by Maria Vinall

Recent results from the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF) trial showed that eplerenone, compared with placebo, significantly reduced the risk of the composite of cardiovascular (CV) death and hospitalization for heart failure (HF) in patients with chronic systolic NYHA class II HF [NCT00232180; Zannad F et al. *N Engl J Med* 2011]. Subjects were randomized to eplerenone (up to 50 mg daily) or placebo, in addition to recommended background therapy. Enrollment in the trial, which randomized 2737 patients, was stopped prematurely after a median follow-up of 21 months, when an overwhelming benefit (HR, 0.63; p<0.001) with eplerenone on the primary endpoint of death from CV causes and hospitalization for HF was observed in the secondary interim analysis. After the trial was prematurely stopped for efficacy in May 2010, a subgroup of patients (58% of the patients who were randomized; n=1597) were followed for an additional 10 months on blinded therapy through March 2011, resulting in a mean follow-up of 25 months in the extended follow-up subgroup.

Bertram Pitt, MD, University of Michigan, Ann Arbor, Michigan, USA, presented three sets of new data from the trial: 1) safety and efficacy results of the extended follow-up of the EMPHASIS-HF study; 2) an exploratory analysis of recurrent hospitalization; and 3) analyses in five high-risk subgroups. The five subgroups of individuals who were considered to be at high risk were independently analyzed, including subjects with: age ≥75 years (n=184), left ventricular ejection fraction (LVEF) <30% (n=440), estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 (n=270), diabetes (n=240), and systolic blood pressure (SBP) <123 mm Hg (n=339).

Consistent with the main study, the primary composite endpoint of CV death or hospitalization for HF was reduced with eplerenone compared with placebo (HR, 0.66; 95% CI, 0.57 to 0.77; p<0.001) in the extended follow-up subgroup. An analysis of the cumulative number of hospitalization for HF (recurrent event analysis) also favored eplerenone (HR, 0.62; 95% CI, 0.53 to 0.72; p<0.001).

There were consistent reductions with eplerenone in the primary endpoint in each of the five individual high-risk groups (Table 1). Additionally, in each of the five subgroups, there were significant reductions with eplerenone in the secondary endpoints of all-cause hospitalization and in hospitalization for HF (p<0.01 for all comparisons).

Table 1. Rates of CV Death or HF Hospitalization During Study Extension.

	HR (95% CI)	p value
All Subjects	0.63 (0.54 to 0.74)	p<0.0001
≥75 years of age (n=184)	0.66 (0.49 to 0.88)	p=0.0044
LVEF <30% (n=440)	0.65 (0.54 to 0.78)	p<0.0001
eGFR<60 ml/min/1.73 m^2 (n=270)	0.62 (0.49 to 0.79)	p=0.0001
Diabetes mellitus (n=240)	0.54 (0.42 to 0.70)	p<0.0001
SBP <123 mm Hg (n=339)	0.63 (0.51 to 0.79)	p=0.0001

HR=hazard ratio; LVEF=left ventricular ejection fraction; eGFR=estimated Glomerular Filtration Rate; SBP=systolic blood pressure.

The safety endpoint of serum potassium greater than 5.5 mmol/L was more frequent with eplerenone overall and among each of the individual high-risk groups (p<0.05 for each comparison). There was no significant increase in serious hyperkalemia (K+ >6.0 mmol/L), hyperkalemia that led to drug discontinuation, hospitalization for hyperkalemia, or hospitalization for worsening renal function for eplerenone patients relative to placebo patients.