clopidogrel) on the efficacy and safety of dabigatran compared with warfarin.

While they are interesting, the results of this modestly sized exploratory subgroup should be interpreted with caution. Limitations include noncore lab assessment of mitral regurgitation (MR), nonrandomized treatment, and important baseline differences between those with and without moderate–severe MR. Larger randomized trials would provide stronger evidence to support current guidelines.

In the current European Society of Cardiology guidelines, mitral valve repair for patients with a primary indication for CABG is a class I recommendation for those with severe MR and left ventricular ejection fraction >30% and a Class IIa recommendation for patients with moderate MR.

ROCKET-AF: Rivaroxaban vs Warfarin in Patients with Moderate Renal Insufficiency

Written by Anne Jacobson

Patients with atrial fibrillation (AF) and moderate renal dysfunction have a higher risk of stroke and bleeding than patients with normal renal function, but respond favorably to reduced-dose rivaroxaban compared with warfarin, according to new findings from the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF; NCT00403767].

Keith A. A. Fox, MD, University of Edinburgh, Edinburgh, United Kingdom, presented results from the ROCKET-AF prespecified renal impairment substudy.

The ROCKET-AF trial compared the safety and efficacy of rivaroxaban 20 mg daily (15 mg for patients with a calculated creatinine clearance [CrCl] 30 to 49 ml/min) to standard dose-adjusted warfarin in 14,264 patients with AF and additional risk factors for stroke. In the primary study analysis in the "per protocol" cohort, rivaroxaban was non-inferior to warfarin in reducing the risk of stroke or systemic embolism ([SSE]; 1.71% vs 2.16% per year; HR, 0.79; 95% CI, 0.66 to 0.96; p<0.001 for noninferiority) [Patel M et al. *N Engl J Med* 2011]. Of note, there was no statistically significant difference between the treatment groups when all events between randomization and the end of the study were analyzed in an intention-to-treat analysis (2.1% vs 2.4%; p=0.12 for superiority).

Rivaroxaban is predominantly metabolized by the liver, although one-third of the drug is cleared by the kidneys and excreted unchanged in the urine. The current substudy evaluated the 2950 patients in the "per protocol" cohort with a baseline CrCl of 30 to 49 ml/min who received a reduced-dose of rivaroxaban (15 mg/day) compared to those treated with dose-adjusted warfarin with a target INR of 2.0 to 3.0.

Compared with patients with normal renal function, patients in the renal dysfunction substudy were older, had a higher $CHADS_2$ risk score, and were more likely to have a history of SSE. Patients with renal impairment had higher rates of stroke and bleeding than patients with preserved renal function, regardless of study treatment.

There was no evidence of a statistical interaction between renal function and the effect of rivaroxaban on the primary efficacy (interaction p=0.45) or safety endpoint (interaction p=0.76; Table 1). Among patients with moderate renal dysfunction, patients randomized to rivaroxaban, compared with those randomized to warfarin, had annualized rates of SSE 2.32% and 2.77% respectively (HR, 0.84; 95% CI, 0.57 to 1.23). For the primary safety endpoint of major plus non-major clinically relevant bleeding, the corresponding rates were 17.8% and 18.3% (HR, 0.98; 0.84 to 1.14).

Table 1. Primary Endpoints and Bleeding Rates.

Clinical Endpoint	CrCl 30 to 49 ml/min			CrCl ≥50 ml/min			p value (interaction)
	Rivaroxaban 15 mg (n=1474)[a]	Warfarin (n=1476)[a]	HR (95% CI)	Rivaroxaban 20 mg (n=5637)[a]	Warfarin (n=5640)[a]	HR (95% CI)	
Primary Principal Endpoint (SSE)	2.32	2.77	0.84 (0.57 to 1.23)	1.57	2.00	0.78 (0.63 to 0.98)	0.76
SSE, vascular death	4.64	4.83	0.96 (0.73 to 1.27)	2.76	3.32	0.83 (0.70 to 0.98)	0.38
SSE, vascular death, MI	5.58	6.54	0.85 (0.67 to 1.09)	3.55	4.16	0.85 (0.73 to 0.99)	0.98
Primary Safety Endpoint	17.82	18.28	0.98 (0.84 to 1.14)	14.24	13.67	1.04 (0.96 to 1.13)	0.4496
Major Bleeding	4.49	4.70	0.95 (0.72 to 1.26)	3.39	3.17	1.07 (0.91 to 1.26)	0.4800
Fatal Bleeding	0.28	0.74	0.39 (0.15 to 0.99)	0.23	0.43	0.55 (0.32 to 0.93)	0.5302
ICH	0.71	0.88	0.81 (0.41 to 1.60)	0.44	0.71	0.62 (0.42 to 0.92)	0.565

MI=Myocardial infarction; ICH=Intracranial hemorrhage.

Fatal bleeding was reduced with rivaroxaban compared to warfarin among both patients with moderate renal dysfunction (0.28% vs 0.74%; HR, 0.39; 0.15 to 0.99) and in those with mild/normal renal function (0.23% vs 0.43%; HR, 0.55; 0.32 to 0.93), with no evidence of statistical heterogeneity (interaction p=0.53). The rates of intracranial hemorrhage in the rivaroxaban versus warfarin groups for patients with renal impairment were 0.71% versus 0.88% (HR, 0.81; 0.41 to 1.60) and among

those with normal renal function 0.44% versus 0.71% (HR, 0.62; 0.42 to 0.92). Despite the numeric difference in the hazard ratios, the statistical test for interaction was not significant (p=0.51), in part related to the small absolute number of events in the former group. Gastrointestinal bleeding was more common with rivaroxaban than warfarin, both for patients with renal impairment (2.88% vs 1.77%; p=0.02) and normal renal function (1.79% vs 1.12%; p=0.0002).

Findings from this ROCKET-AF substudy were consistent with those from the overall trial. In patients with moderate renal impairment, reduced-dose rivaroxaban preserved the benefit of warfarin in preventing SSE, and in the "per protocol analysis" yielded lower rates than warfarin. The rates of bleeding and adverse events with reduced dose rivaroxaban compared with warfarin were similar, with fewer fatal bleeds.

Additional reading: Fox KAA et al. *Eur Heart J* 2011.

ONTARGET: Treatment Nonadherence Rapidly Increases CV Event Risk

Written by Anne Jacobson

Patients who are at high risk for cardiovascular (CV) events face a vicious cycle in which treatment nonadherence increases event rates while events themselves reinforce nonadherence, according to new findings from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET).

ONTARGET included 25,620 patients with coronary heart disease or diabetes plus two additional risk factors for vascular events. In the main study analysis, telmisartan was noninferior to ramipril for the primary composite endpoint of CV death, myocardial infarction (MI), stroke, or heart failure (HF) hospitalization (p=0.0045) and for the secondary endpoint of CV death, MI, or stroke (p=0.001) [Yusuf S et al. *N Engl J Med* 2008].

The current ONTARGET analysis focused on risk factors and outcomes that are associated with nonadherence, the latter defined as premature permanent discontinuation of all study medications. Michael Böhm, MD, University of the Saarland, Saarbrücken, Germany, presented findings from the study.

Throughout ONTARGET, there was a continuous increase in the proportion of patients who permanently discontinued treatment. After 72 months of follow-up, 4629 patients (18.6%) had discontinued treatment. Increasing age, female gender, black race, physical inactivity, smoking status, diabetes, and depression were significantly associated with non-adherence.

The strongest factor that was associated with premature permanent drug cessation was the occurrence of a non-fatal event during trial follow-up. Premature discontinuation significantly increased after nonfatal MI (HR, 2.24; 95% CI, 1.95 to 2.57; p<0.0001), stroke (HR, 2.28; 95% CI, 1.98 to 2.63; p<0.0001), and HF hospitalization (HR, 2.85; 95% CI, 2.49 to 3.27; p<0.0001). Other nonfatal events, such as revascularization, angina, end-stage renal disease, malignancy, and new-onset HF, diabetes, and atrial fibrillation also increased the risk of treatment discontinuation (p<0.0001 for each event). The risk of premature permanent cessation also increased with early events and with an increasing number of total events.

Over time, the risk of CV events increased sharply and soon after premature cessation of study medication. Compared with patients who remained on treatment, patients who stopped were 29% more likely to reach the primary endpoint of CV death, MI, stroke, or HF hospitalization (HR, 1.298; 95% CI, 1.181 to 1.427; p<0.0001) and 38% more likely to reach the secondary endpoint of CV death, MI, or stroke (HR, 1.385; 95% CI, 1.255 to 1.528; p<0.0001). Premature permanent cessation was also strongly associated with the individual endpoints of CV death (HR, 2.050; 95% CI, 1.824 to 2.303; p<0.0001) and HF hospitalization (HR, 1.464; 95% 1.228 to 1.745; p<0.0001).

The authors conclude that the ONTARGET trial revealed a deleterious "nonadherence-event" cycle, in which stopping study medications increased CV events, leading to increased morbidity, less trust in therapy, and further nonadherence. To break this cycle, interventions that promote treatment adherence are needed for patients who are at high risk of nonadherence, and for all patients immediately after a CV event, Prof. Böhm concluded.

Editors Note: While these observations raise an important hypothesis, it is important to note that the strongest predictors of premature cessation were the occurrences of clinical events during the trial. Patients who experience events (eg non-fatal MI) are at a heightened risk of a recurrent event and therefore it is unclear that treatment cessation led to recurrent events or was just associated with sicker patients. In addition, it is important to recognize that patients may stop therapy prematurely for many reasons in a trial, including related adverse events and acute illnesses for which treatment cessation may be medically indicated (eg, cessation of anti-hypertensive patients who are in shock). Thus while drug discontinuation may be followed shortly by a clinical event (eg, MI), therefore suggesting a temporal association, establishing a true causal relationship may be difficult. Additional analyses that show consistency in patients with no preceding hospitalization or CV event as well a description of reasons for treatment cessation would strengthen the overall findings.