inappropriate shocks were associated with a particularly high risk of total mortality (HR, 4.7; p<0.001) due to increased non-SCD (HR, 9.9; p<0.001).

Current guidelines for primary prevention exclude ICD implantation in patients within the first 40 days after MI. However, this restriction excludes a vulnerable population, given that the SCD is significantly higher immediately post-MI, especially in patients with low left ventricular ejection fraction.

Discussant Christophe Leclercq, MD, Rennes University Hospital, Rennes, France, said that the new IRIS analysis did not answer the question of why ICD fails to reduce total mortality early after MI. As such, there is no evidence to support changes to the current guidelines for ICD implantation, he concluded.

Increased Bleeding Risk with Concomitant Use of Antiplatelet Therapy: Dabigatran vs Warfarin

Written by Maria Vinall

The RE-LY trial compared two doses of dabigatran (110 mg BID and 150 mg BID) with open label warfarin (target INR 2 to 3) in 18,113 patients with nonvalvular atrial fibrillation (AF). The primary results demonstrated that treatment with the 110-mg dose was associated with rates of stroke and systemic embolism (SSE) that were similar to those seen with warfarin but with a lower rate of major bleeding. Meanwhile, dabigatran, at a dose of 150 mg, reduced the rate of SSE compared with warfarin but had a similar rate of major bleeding [Connolly SJ et al. *N Engl J Med* 2009]. Antonio Miguel Dans, MD, University of the Philippines, Manila, Philippines, presented the results of post hoc subanalyses from RE-LY, comparing the efficacy and safety of dabigatran with warfarin in patients dependent upon use of concomitant antiplatelet therapy (APT).

Many patients who are on oral anticoagulant therapy also require APT. The specific objectives of these analyses were to compare the efficacy (SSE) and safety (major bleeding, as defined by the International Society of Thrombosis and Hemostasis) of each dose of dabigatran versus warfarin in subgroup of patients with and in the subgroup of patients without concomitant antiplatelet use and to determine the effect of concomitant APT on rates of bleeding. Other efficacy and safety endpoints included all stroke, hemorrhagic stroke, ischemic stroke, cardiovascular (CV) death, minor bleeding, major + minor bleeding, intracranial bleeding, and extracranial bleeding.

A total of 6952 (38.2%) patients received concomitant APT during the study, and in the majority of cases, this consisted of aspirin with or without clopidogrel. The hazard ratio of the primary efficacy endpoint (SSE) was significantly lower for the 150-mg dabigatran dose compared with warfarin both for patients who were not on APT (HR, 0.52; 95% CI, 0.38 to 0.72) and for those who were on APT (HR, 0.80; 95% CI, 0.59 to 1.05). However, the p-value for interaction was 0.058 indicating evidence of attenuation in the benefit of dabigatran in the group on APT. Meanwhile, the hazard ratio of the primary efficacy endpoint for the 110 mg dose was not significantly different than that for warfarin in either those who received or did not receive APT, and the p-value for interaction (p=0.74) indicated no effect modification by concomitant APT on the effect of the lower dose of dabigatran. Other findings were consistent for both doses across all efficacy endpoints that were evaluated.

Overall, the risk of major bleeding was higher for patients who were on concomitant APT, even after adjustment for important clinical factors (adjusted HR, 1.60; 95% CI, 1.41 to 1.81), that attempted to account for the higher risk profile of patients who require APT. The hazard for major bleeding was lower for dabigatran 110 mg compared with warfarin, regardless of the use of concomitant APT with no evidence of effect modification due to the use of concomitant APT (interaction p-value 0.79). Similarly, there was no evidence of an interaction (p = 0.87) between APT and the risk of major bleeding with dabigatran 150 mg, which was similar to that of warfarin. Thus, the findings with regard to major bleeding that were observed in the main trial (less bleeding with dabigatran 110 mg compared with warfarin, similar bleeding with 150 mg dabigatran compared with warfarin) also apply, whether concomitant APT was administered or not.

Results from this study underscore the increased risk of bleeding associated with the concomitant use of APT and anticoagulant therapy with an observed 60% increase in the adjusted hazard of bleeding in this post-hoc analysis. While the lowest rates of bleeding for patients taking concomitant APT were observed with dabigatran 110 mg, whether it is the optimal choice for patients with AF who need APT requires confirmation in a prospective randomized trial. Clinicians should note that the 110 mg dose is not commercially available in all countries (eg, USA). An additional limitation of the current analysis was that there was no assessment of different APT regimens (eg, aspirin monotherapy vs dual APT with aspirin +

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