increase in peak concentration per minor allele, while the CES1 polymorphism was associated with a 12% decrease in peak concentration per minor allele ($p=8.2x10^{-8}$ and $p=3.2x10^{-8}$, respectively). Two variants were associated with trough concentration: rs4580160 at the CES1P2 locus and rs2244613 at the CES1 locus. The CES1 polymorphism had a significant effect, with a 15% decrease in trough concentration per minor allele ($p=1.2x10^{-8}$).

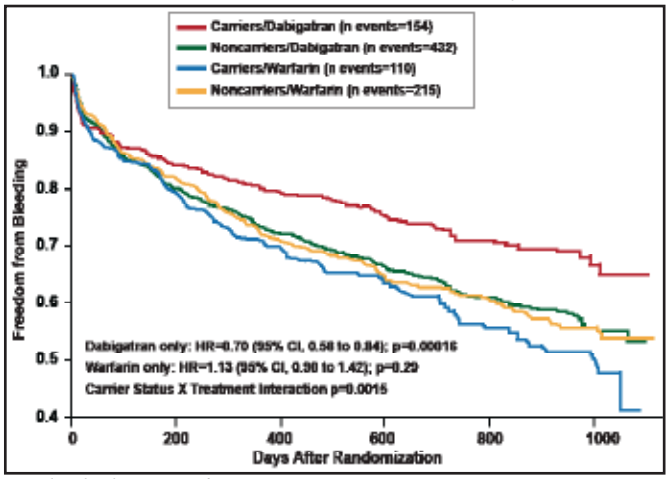
None of these genetic determinants had a significant association with efficacy, but the CES1 rs2244613 variant did have a significant association with bleeding (Table 1). A significant interaction by treatment arm was also noted: the odds of bleeding with dabigatran decreased 33% for carriers of the CES1 rs2244613 polymorphism, while there was no impact of this genetic variant on bleeding for those receiving warfarin (Figure 1). Approximately one third of Europeans are carriers of this polymorphism, said Prof. Pare.

Table 1. Association of Significant Genetic Determinants with Efficacy and Safety.

Event	Peak Concentration				Trough Concentration	
	ABCB1 rs4148738		CES1 rs8192935		CES1 rs2244613	
	Odds Ratio (95% CI)	p value	Odds Ratio (95% CI)	p value	Odds Ratio (95% CI)	p value
Ischemic stroke or SE	0.88 (0.53-1.46)	0.62	0.76 (0.43-1.34)	0.34	0.70 (0.33-1.47)	0.34
Any bleeding	0.94 (0.82-1.09)	0.44	0.89 (0.76-1.03)	0.13	0.67 (0.55-0.82)	$7x10^{-5}$
Major bleeding	1.14 (0.85-1.52)	0.40	0.88 (0.64-1.21)	0.44	0.66 (0.43-1.01)	0.06
Minor bleeding	0.94 (0.81-1.09)	0.38	0.89 (0.76-1.05)	0.17	0.70 (0.57-0.85)	$4x10^{-4}$

SE=sytemic embolism.

Figure 1. Freedom from Bleeding According to CES1 rs2244613 Carrier Status in the RE-LY Study.



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This analysis provides evidence supporting the idea of dose modification of dabigatran based on genotype but requires additional study.

The RE-LY AF Registry

Written by Lori Alexander

Around the world, the average 1-year mortality rate is 10% for patients with a diagnosis of atrial fibrillation (AF) who present to an emergency department (ED) for any reason. The rate is highly variable among different countries, noted Jeffrey S. Healey, MD, McMaster University, Hamilton, Ontario, Canada, who reported on the study.

Prof. Healey said that, although AF is a major global disease, most of what is known about the disorder is based on studies conducted in Europe and North America. The baseline results from the Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY AF] registry, which were presented at the European Society of Cardiology Congress 2012, demonstrated important regional variations in risk factors and treatment of AF across 47 countries. Dr. Healey and colleagues followed patients for 1 year to document cause-specific mortality and clinical outcomes—most notably, stroke.

Of the 18,113 patients enrolled in the RE-LY AF trial, 15,408 (85%) were entered in the registry. The vast majority (98%) had AF (while 2% had atrial flutter), and most (79%) had a prior history of AF. For patients presenting to an ED, AF was the primary diagnosis for 44% of patients and the secondary diagnosis for 56%; for those with a secondary diagnosis of AF, the primary diagnosis varied widely between regions, but heart failure (HF) was the most common.

The global average crude mortality rate was 10%, with the highest rates in Africa, South America, and China. When adjustments were made for several variables, the differences were somewhat attenuated, and the rates were highest in Southeast Asia, China, and Eastern Europe (Figure 1). The rates were substantially higher (2-3 fold overall) in all regions when AF was a secondary diagnosis (Figure 2). HF was the primary cause of death overall (34%), followed by infection (12%), and stroke (9.5%). Other causes of death were respiratory failure, cancer, sudden death, and myocardial infarction (all less than 9%).

The rate of stroke within 1 year varied among regions, from approximately 8% in Africa to less than 1% in India; the global average was 4%. When adjusted for confounders (age, stroke/transient ischemic attack, HF, hypertension, diabetes, and use of vitamin K antagonists [VKAs]), there

was substantially less variation in the stroke rate, ranging from approximately 5% in China and Southeast Asia to 3% in India. Most of the difference in stroke rates could be explained by differences in VKA use.

Figure 1. 1-Year Mortality for Patients with AF by Region.

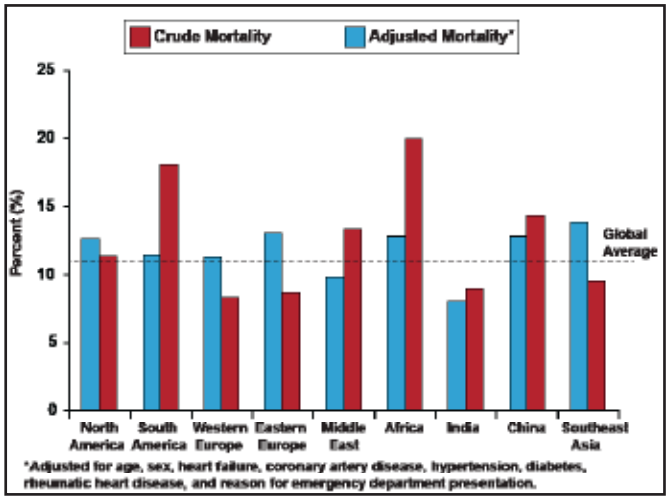

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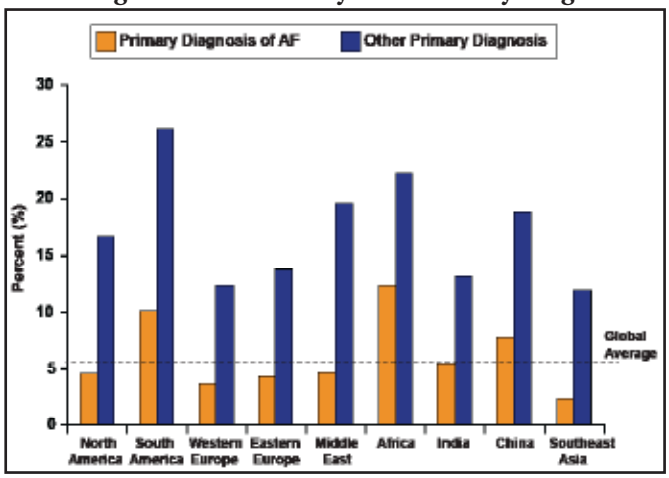
Figure 2. Regional Variation in 1-Year Mortality According to AF as a Primary or Secondary Diagnosis.



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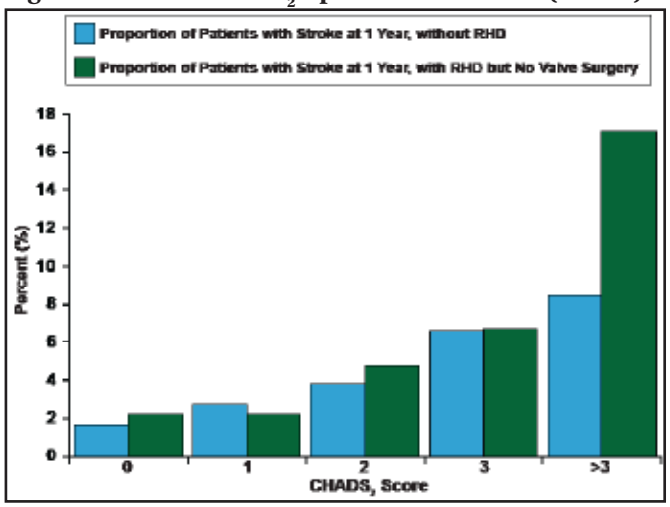
About one third of the patients from India in the registry had documented rheumatic heart disease (RHD). Overall, 1788 patients had RHD, and when the data for this population were analyzed, the risk of stroke was higher for patients with a history of RHD (adjusted rates, 4.3% vs 2.5%). Globally, the $CHADS_2$ score had a greater influence on risk of stroke than the presence of RHD (Figure 3).

The authors concluded that the 1-year RELY AF registry results underscore the large unmet medical needs and large opportunities for improvement in outcomes for patients with AF. Consistent global application of currently available modalities for diagnosis, risk stratification, and treatment of patients presenting with AF is crucial in reducing the morbidity and mortality of this condition.

Figure 3. Global $CHADS_2$-Specific Stroke Rate (1-Year).



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TRA 2°P-TIMI 50 Results

Written by Lori Alexander

For patients with a history of myocardial infarction (MI) who are stable, the addition of vorapaxar to the standard of care reduced the long-term risk of cardiovascular (CV) death or ischemic events and increased the risk of moderate or severe bleeding. These findings are among the first to show a benefit of adding intense antiplatelet treatment to standard therapies for long-term secondary prevention in patients with a history of MI.

Vorapaxar inhibits platelet activation by antagonizing thrombin-mediated activation of the protease activated receptor-1 (PAR-1) expressed on platelets. The efficacy and safety of the drug were evaluated for secondary prevention in a broad group of patients with prior MI, prior stroke, or peripheral artery disease in the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis in Myocardial Infarction 50 [TRA 2°P-TIMI 50] trial. Benjamin M. Scirica, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the primary results in the subgroup of patients who were randomized with a qualifying MI (type 1 MI within the previous 2 weeks to 12 months), with publication timed to coincide with the presentation at the European Society of Cardiology Congress 2012 [Scirica BM et al. *Lancet* 2012].