Urban Rural Epidemiology [PURE] study. Reporting on the study, Rafael Diaz, MD, Estudios Cardiológicos Latinoamérica, Rosario, Argentina, noted that the overall prevalence of hypertension was approximately 41%, with fewer than half of people with hypertension being aware of the diagnosis or being treated for it, and only 13% of those with a diagnosis of hypertension having controlled blood pressure (BP).

The PURE study included 153,996 adults (ages 35 to 70 years; mean age, 50.4 years) from 628 rural and urban communities in 3 high–income countries (HIC), 10 upper- (UMIC) and lower–middle-income countries (LMIC), and 4 low-income countries (LIC). Hypertension was defined as an average systolic BP (SBP) ≥140 mm Hg or a diastolic BP (DBP) ≥90 mm Hg, the self-report of a medical diagnosis of hypertension, or the use of BP-lowering medications. The mean SBP for the study population was 131.23 mm Hg, and the mean DBP was 81.99 mm Hg. Most individuals (36.8%) had prehypertension; 21.9% had stage 1 hypertension, and 13.4% had stage 3 or 4 hypertension. Approximately 28% of the population had an optimal BP.

Awareness, treatment, and control of hypertension varied among rural and urban areas within the 3 categories of countries. In HIC and MIC, there was a greater prevalence of hypertension in rural areas than in urban areas; in LIC, the reverse was true, with a higher prevalence in urban areas. The prevalence of hypertension was greater among men in HIC and MIC, but was greater among women in LIC.

The investigators also assessed prevalence, awareness, treatment, and control among subgroups categorized by the presence of other cardiovascular risk factors (eg, diabetes, current or past smoking, obesity, age >65 years, and male sex). Rates were highest among individuals with ≥2 risk factors (compared with no or 1 risk factors). Hypertension was controlled in 15% of individuals with ≥2 risk factors, in 12% with 1 risk factor, and in 8% with no risk factors.

The low rates of BP control may be related to the low use of ≥2 BP-lowering medications. Although the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure notes that ≥2 medications are required for most people with hypertension, the control rates in PURE ranged from 15.7% in HIC to 13.1% in MIC to 1.6% in LIC.

Prof. Diaz noted that novel strategies to detect hypertension (such as systematic screening), simplified treatment algorithms, and facilitation of the early use of combination therapies may be helpful in improving the global control of hypertension, particularly in LIC.

The comparisons were adjusted for age and sex. The urban-rural differences in awareness (LIC and LMIC), treatment (LIC, LMIC, and UMIC), and control (LIC, LMIC, and UMIC) were significant ($p<0.001$).

Genetic Determinants of Variability in Dabigatran Exposure

Written by Lori Alexander

Genetic factors may be responsible for some of the inter-individual variability in dabigatran exposure, according to findings from the Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY] Genetics study. The RE-LY trial demonstrated that dabigatran 150 mg BID was superior to warfarin, while the 110 mg dose was noninferior to warfarin in the reduction of stroke in patients with atrial fibrillation [Connolly SJ et al. *N Engl J Med* 2009]. The lower dose was associated with less major bleeding when compared with warfarin, while the higher dose (150 mg) had a similar rate of major bleeding.

Dabigatran etexilate is an oral prodrug that is rapidly converted by esterases (carboxylesterase-1 [CES1]) to the active agent dabigatran, explained Guillaume Pare, MD, McMaster University, Hamilton, Ontario, Canada, who presented the findings of the study. CES1 is a serine esterase that can activate or deactivate various drugs. Prof. Pare and colleagues hypothesized that genetic variability in the pathways required for bioactivation of dabigatran might be responsible for some of the 30% variability in dabigatran exposure.

In the first phase of the study, a genome-wide analysis (551,203 markers) was performed on biologic samples from 1490 patients of European ancestry enrolled in the RE-LY trial randomized to dabigatran to identify the genetic determinants of peak and trough concentrations of dabigatran. Another 807 patients from RE-LY treated with warfarin also underwent genotyping. Identified genetic determinants were tested for their association with efficacy and safety outcomes in an overlapping sample of 1694 patients. The primary efficacy endpoint was stroke or systemic embolism, and the primary safety endpoint was any bleeding (minor or major).

Genome-wide analysis demonstrated 2 variants associated with peak concentration of dabigatran, one at the ABCB1 locus (rs4148738) and one at the CES1 locus (rs8192935). The ABCB1 polymorphism was associated with a 12%

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 ($p=1.2x10^{-8}$).

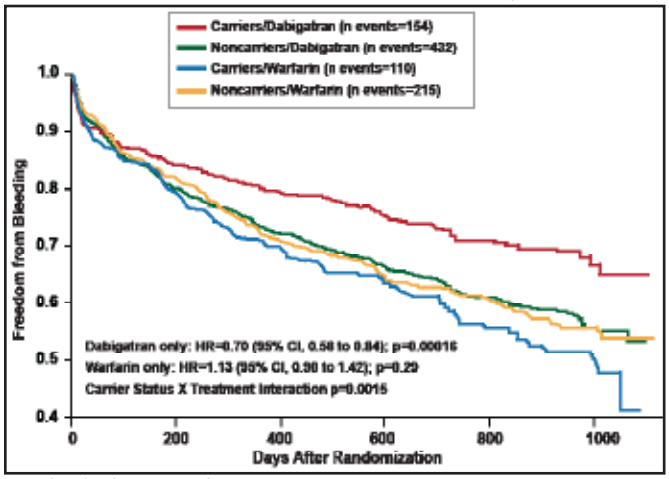
None of these genetic determinants had a significant association with efficacy, but the CES1 rs2244613 variant did have a significant association with bleeding (Table 1). A significant interaction by treatment arm was also noted: the odds of bleeding with dabigatran decreased 33% for carriers of the 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