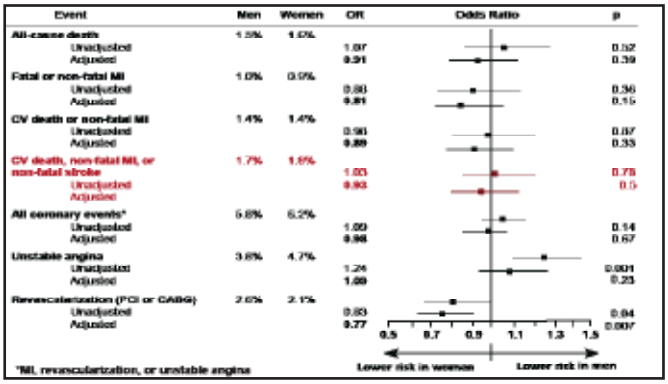
The risk profile differed substantially by gender, with women more likely to have hypertension or diabetes (Table 1). Women were also more likely to have angina but were less likely to have had diagnostic non-invasive testing or coronary angiography, to have received evidence-based pharmacologic treatments, or to have had revascularization (Table 1).

Figure 1. Major CV Outcomes at 1 Year.



CABG=coronary artery bypass grafting; CV=cardiovascular; MI=myocardial infarction; PCI=percutaneous coronary intervention.

Table 1. Gender Differences in Stable CAD in CLARIFY.

Characteristics	Men (%)	Women (%)	p value
Risk Factors			
Family history of premature CAD	28	31	<0.0001
Treated hypertension	69	78	<0.0001
Diabetes	28	33	<0.0001
Medical History			
Angina	21	29	<0.0001
Coronary angiography	86	80	<0.0001
Noninvasive test for MI	63	58	<0.0001
MI	62	51	<0.0001
Peripheral artery disease	10	8	<0.0001
Stroke	4	4	0.24
TIA	3	4	0.0033
PCI	59	55	<0.0001
CABG	25	17	<0.0001
Pharmacologic Treatments			
Lipid-lowering drugs	93	90	<0.0001
Aspirin	88	87	0.048
ACE inhibitor and/or ARB	76	76	
β-blocker	75	75	

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; CABG=coronary artery bypass grafting; CAD=coronary artery disease; MI=myocardial infarction; PCI=percutaneous coronary intervention; TIA=transient ischemic attack.

Prof. Steg noted several limitations to the study. The primary limitation was the relatively low number of women, which he noted may have been related to the inclusion criteria required by the study. In addition, the cohort sample may not be representative of a population-based sample, as physician and patient participation in the CLARIFY registry is voluntary. Also, despite adjustments for potential confounders, residual confounding cannot be excluded.

HPS2-THRIVE Results

Written by Lori Alexander

Approximately two thirds of patients can tolerate extended-release (ER) niacin when combined with laropiprant, according to a prespecified interim safety and tolerability analysis of the Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE; NCT00461630] study. The addition of niacin/laropiprant to statin therapy offers a dual goal of decreasing low-density lipoprotein-cholesterol (LDL-C) and increasing high-density lipoprotein-cholesterol (HDL-C).

Niacin, the first lipid-modifying drug, is one of the most effective agents for increasing HDL-C levels. However, its use has been limited by its side effects, particularly flushing. Coadministration of laropiprant, a selective prostaglandin D antagonist, has been shown to reduce flushing. However, the drug may not reduce this side effect in all patients, as flushing can occur through other pathways.

HPS2-THRIVE includes more than 25,000 patients in Europe and China who have cardiovascular disease (CVD) and are at high risk for recurrent vascular events. The patients were randomly assigned to ER niacin 2 g/laropiprant or to placebo. All patients also received LDL-C reducing therapy with simvastatin 40 mg, with or without ezetimibe 10 mg. The study is the largest one to date to evaluate the CV benefits of increasing HDL-C levels. Jane Armitage, MD, Oxford Clinical Trial Service, Oxford, United Kingdom, reported on the safety and tolerability of the combination drug.

Patients were treated with ER niacin/laropiprant or placebo during an 8-week run-in phase prior to randomization. During this phase, 25.4% of patients in the ER niacin/laropiprant group withdrew from therapy for any medical reason; the primary reasons were cutaneous effects (primarily flushing, 11.3%) and gastrointestinal symptoms (5.5%). An additional 8.7% of patients in this group withdrew during the randomized treatment phase, again primarily because of cutaneous effects (5.1%) and gastrointestinal symptoms (3.6%). Among patients in the placebo group, 1.2% withdrew during the treatment phase because of cutaneous effects and 1.6% because of gastrointestinal symptoms.

Prof. Armitage noted that ER niacin/laropiprant was associated with a high rate of myopathy (1.13% vs 0.18% in the placebo group). This finding was seen primarily in patients of Chinese descent (62 of 69 patients with myopathy were from China). Overall, rhabdomyolysis was rare (0.05% in the treatment group and 0.02% in the placebo group). The identification of an increased risk of myopathy with niacin and simvastatin prompted the following change to the simvastatin label: "Patients of Chinese descent should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products."

Prof. Armitage reported that during the run-in phase, LDL-C levels were reduced by 20% and HDL-C levels were increased by 17%. These results differ from those in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes [AIM-HIGH] trial, in which LDL-C levels were reduced 5.5% and HDL-C levels were increased by 13.2% [AIM-HIGH Investigators. *N Engl J Med* 2011]. The AIM-HIGH trial was stopped early because of a lack of benefit of niacin. Whether the more favorable effects on LDL-C lowering and HDL-C raising in HPS2-THRIVE and better tolerability of niacin when combined with laropiprant will translate into a reduction in vascular events will have to wait until the presentation of the study's primary efficacy results in 2013.

PRoFESS Study Results

Written by Lori Alexander

A landmark analysis is providing insight into the relationship between resting heart rate and outcomes after ischemic stroke. An analysis of data from the 20,165 patients enrolled in the Prevention Regimen for Effectively Avoiding Second Stroke [PRoFESS] study showed that heart rate is associated with mortality among patients with stroke and that a low heart rate is associated with a better functional outcome and less cognitive decline after an ischemic stroke.

PRoFESS was a 2x2 factorial trial that evaluated the safety and efficacy of aspirin and extended-release dipyridamole compared with clopidogrel (as noninferiority first then superiority), and the safety and efficacy of telmisartan compared with placebo (superiority) [Diener HC et al. *Cerebrovasc Dis* 2007]. The primary results of both comparisons have been previously published [Yusuf et al. *N Engl J Med* 2008; Sacco et al. *N Engl J Med* 2008].

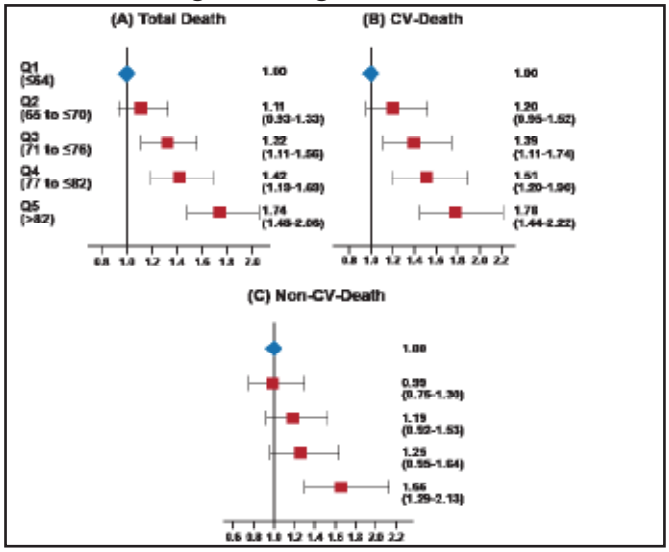
Prior studies have shown an association between resting heart rate and cardiovascular (CV) events along the CV continuum, and stress models have shown that reducing heart rate may reduce the size of a stroke, explained Michael Böhm, MD, Universitätskliniken des Saarlandes, Klinik für Innere Medizin III, Homburg/Saar, Germany, who presented the findings of the study. Thus, the current study was designed to answer the questions of whether baseline heart rate predicts recurrent stroke, myocardial infarction (MI), heart failure, or death after stroke or is associated with functional outcome or cognitive decline after recurrent stroke [Böhm M et al. *Eur Heart J* 2012].

The patients were grouped according to baseline heart rates, with quintiles of ≤64, 65 to 70, 71 to 76, 77 to 82, and >82 beats per minute (bpm). The predefined endpoints were disability after a recurrent stroke, as assessed with the modified Rankin Scale score and the Barthel Index, and cognitive function, as assessed with the Mini-Mental State Examination (MMSE) score. Disability was assessed at 3 weeks, and the MMSE score was determined at 4 weeks after randomization and at the penultimate visit.

Overall, increasing quartile of heart rate was associated with female gender and diabetes mellitus. β-blocker use, statin use, hypertension, and age were associated with lower heart rates.

All-cause mortality was higher among patients in the 3 highest quintiles of heart rate compared with the lowest quintile (71 to 76 bpm: HR, 1.32; 95% CI, 1.11 to 1.56; 77 to 82 bpm; HR, 1.42; 95% CI, 1.19 to 1.69; and >82 bpm: HR, 1.74; 95% CI, 1.48 to 2.06; p<0.0001 for both). Prof. Böhm noted that the heart rate threshold differed for CV and non-CV mortality (Figure 1). Baseline heart rate was not associated with MI, recurrent stroke, or new or worsening heart failure.

Figure 1. All-Cause Mortality, CV Death, and Non-CV Death According to Resting Heart Rate.



CV=cardiovascular.