

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

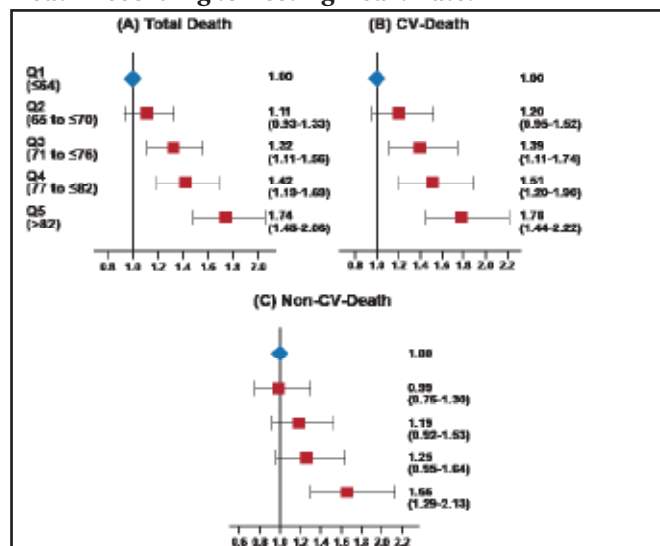
heart rate may reduce the size of a stroke, explained Michael Böhm, MD, Universitätskliniken des Saarlandes, Klinik für Innere Medizin III, Homburg/Saar, Germany, who presented the findings of the study. Thus, the current study was designed to answer the questions of whether baseline heart rate predicts 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.

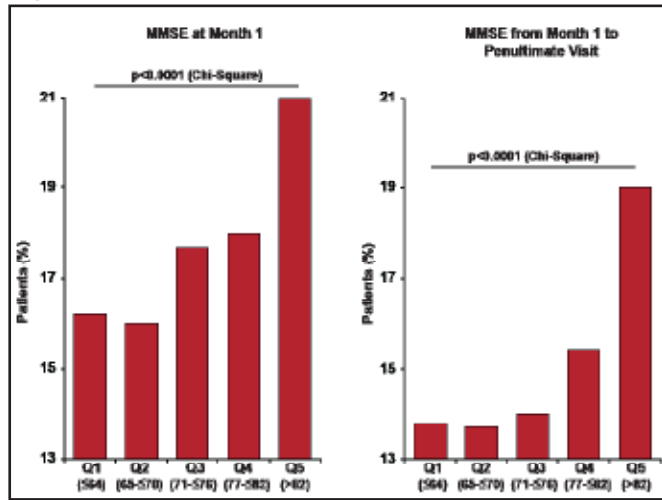
All-cause mortality was higher among patients in the 3 highest quintiles of heart rate compared with the lowest quintile (71 to 76 bpm: HR, 1.32; 95% CI, 1.11 to 1.56; 77 to 82 bpm; HR, 1.42; 95% CI, 1.19 to 1.69; and >82 bpm: HR, 1.74; 95% CI, 1.48 to 2.06; p<0.0001 for both). Prof. Böhm noted that 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.



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Figure 2. Mini-Mental State Examination ≤24 Points.



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Among 1627 patients who had a recurrent stroke, the functional outcome at 3 months was better in patients with a lower heart rate at baseline. The baseline heart rate was also significantly associated with cognitive decline according to the MMSE score (≤ 24 points; $p=0.0001$; Figure 2); more patients with a heart rate >82 bpm had a decrease of 2 points on the MMSE between the 1 month and penultimate visits.

Prof. Böhm interpreted these findings as suggestive that lower heart rates may be associated with smaller strokes rather than fewer recurrent strokes. Further study will be needed to better understand whether heart rate plays a causative role in outcomes after stroke and whether therapies to reduce heart rate will be beneficial in patients experiencing a first stroke.

Outcomes from the CARDia Trial

Written by Lori Alexander

No clear evidence supports routine percutaneous coronary intervention (PCI) for patients with diabetes and multivessel disease, according to 5-year follow-up data from the Coronary Artery Revascularisation in Diabetes [CARDia; ISRCTN19872154] trial. Coronary artery bypass graft (CABG) surgery is favored, unless clinical features indicate that PCI is clearly preferable.

The CARDia trial was designed in the early 2000s as the first randomized comparison of PCI and CABG for patients with diabetes and multivessel (or complex disease of the left anterior descending) coronary artery disease [Kapur A et al. *J Am Coll Cardiol* 2010]. A total

of 510 patients were randomized to CABG ($n=254$) or to PCI plus stenting and routine abciximab ($n=256$). The primary endpoint was a composite of all-cause mortality, myocardial infarction (MI), and stroke; the main secondary outcome included the addition of repeat revascularization to the primary outcome events. According to noninferiority analysis, PCI proved not to be noninferior to CABG at 1 year of follow-up (13.0% in the PCI group vs 10.5% in the CABG group; HR, 1.25; 95% CI, 0.75 to 2.09; $p=0.39$). The rates of all-cause mortality were similar for the 2 groups (3.2%).

Roger Hall, MD, Duke University, Durham, North Carolina, USA, reported the most recent findings of the trial. At a median of 5.1 years of follow-up, conventional intention-to-treat analysis did not show a significant difference in the primary endpoint for the 2 groups (26.6% in the PCI group vs 20.5% in the CABG group; HR, 1.34; 95% CI, 0.94 to 1.93), but Dr. Hall said the study was underpowered for this comparison. PCI was associated with significantly higher rates of repeat revascularization (21.9% vs 8.3%; $p<0.001$), nonfatal MI (14% vs 6.3%; $p=0.007$), and a composite of death, MI, stroke, or repeat revascularization (37.5% vs 26%; $p=0.005$). There was no difference in nonfatal stroke ($p=0.48$). The similar all-cause mortality rates at 1 year continued at 5 years (14% in the PCI group and 12.6% in the CABG group; $p=0.53$; Table 1).

Table 1. Comparison of CABG and PCI at 5 Years of Follow-Up.

Adjudicated Events after Randomization	Patients (%)		p value	HR (95% CI)
	CABG	PCI		
Primary endpoint*	20.5	26.6	0.11	1.34 (0.94-1.93)
Non-fatal MI	6.3	14.0	0.007	2.26 (1.25-4.08)
Non-fatal stroke	4.3	3.1	0.48	0.72 (0.29-1.79)
Repeat revascularization	8.3	21.9	<0.001	2.87 (1.74-4.74)
Primary endpoint or repeat revascularization	26.0	37.5	0.005	1.56 (1.14-2.14)
All-cause mortality	12.6	14.0	0.53	1.17 (0.73-1.87)

*Composite of death, nonfatal MI, or nonfatal stroke; CABG=coronary artery bypass graft; MI=myocardial infarction; PCI=percutaneous coronary intervention.

Dr. Hall noted that the findings did not confirm the results of other studies showing much higher mortality at 5 years in association with PCI, and thus, PCI may be an option in carefully selected patients with diabetes and multivessel disease as an alternative to CABG, although the latter remains the preferred method of revascularization for the majority of these patients.