of simvastatin with or without ezetimibe, to either ERN 2 g plus LRPT 40 mg daily (n=12,838) or placebo (12,835). Lipid stabilization was achieved prerandomization using simvastatin 40 mg daily (with or without ezetimibe) to target total cholesterol of 135 mg/dL and patients were followed for 4 years. The primary endpoint was time to first major vascular event, defined as a nonfatal MI or coronary death, nonfatal or fatal stroke, or revascularization. Mean baseline total cholesterol, direct-LDL, HDL, and triglycerides levels were 128, 63, 44, and 125 mg/dL, respectively, which were below the targets for such high-risk patients.

By the end of the 4-year study, 25% of the ERN/LRPT and 17% of the placebo-treated patients had discontinued study treatment and the average overall compliance with ERN/LRPT was 78%. SAEs, including new-onset diabetes, occurred significantly more often in the ERN/LRPT group versus placebo (Table 1). In addition, myopathy was more common in the ERN/LPRT arm (0.6%) versus placebo (0.1%; 95% CI, 2.62 to 7.50; p<0.0001) and much higher in China than in Europe (0.13%/year vs 0.04%/year; p=0.001).

Table 1. SAEs With ERN/LRPT

SAE	ERN/LRPT (n=12,838)	Placebo (n=12,835)	Risk Ratio (95% CI)
Diabetes			
Any diabetic complication[1]	460 (11.1)	311 (7.5)	1.55 (1.34 – 1.78)
New onset diabetes[2]	792 (9.1)	632 (7.3)	1.27 (1.14 – 1.41)
Infections	1031 (8.0)	853 (6.6)	1.22 (1.12 – 1.34)
Gastrointestinal	620 (4.8)	491 (3.8)	1.28 (1.13 – 1.44)`
Bleeding (any)	326 (2.5)	238 (1.9)	1.38 (1.17 – 1.62)
Musculoskeletal	481 (3.7)	385 (3.0)	1.26 (1.10 – 1.44)
Skin[3]	86 (0.7)	51 (0.4)	1.67 (1.20 – 2.34)

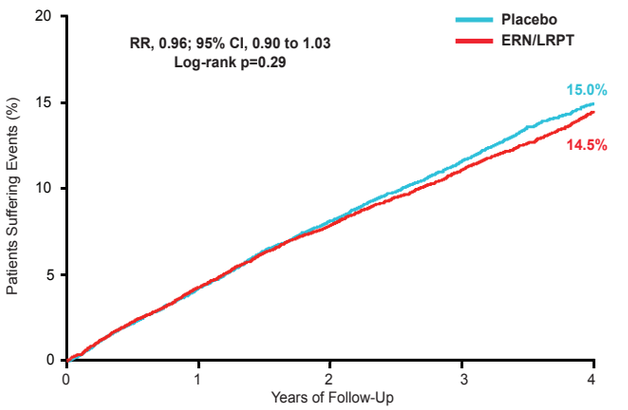
ERN/LRPT=extended-release niacin plus laropiprant; SAE=serious adverse event.

[1]Among participants with diabetes at randomization (n=8299); [2]Among participants without diabetes at randomization (n=17,374); [3]Skin = rash, ulcer, other

On average, treatment with ERN/LRPT decreased LDL-C by 10 mg/dL and triglycerides by 33 mg/dL, while increasing HDL-C by 6 mg/dL. There was no significant reduction in the primary endpoint (major coronary event, stroke, or revascularization) with ERN/LRPT compared with placebo after 4 years (14.5% vs 15.0%, RR, 0.96; 95% CI, 0.90 to 1.03; p=0.29; Figure 1).

There was an overall significant reduction in revascularizations with ERN/LRPT versus placebo (revascularization events, 6.3% vs 7.0%; p=0.03) with no significant differences in any of the other components of the primary endpoint, including coronary death, nonfatal MI, ischemic stroke, or hemorrhagic stroke. All-cause death tended to occur more frequently with ERN/LRPT than placebo (6.2% vs 5.7%; RR, 1.09; 95% CI, 0.99 to 1.21; p=0.08).

Figure 1. Effect of ERN/LRPT on Major Vascular Events



ERN/LRPT=extended-release niacin plus laropiprant.

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There were no significant differences in any of the subgroup comparisons based on age, sex, baseline disease category, or type of statin-based therapy, except for an excess of statin-related myopathy in Chinese patients.

The findings of HPS-THRIVE are consistent with those of previous niacin trials, including AIM-HIGH [AIM-HIGH Investigators. *N Engl J Med* 2011], and suggest lack of clinical benefit with niacin in the treatment and prevention of cardiovascular disease among patients receiving statin therapy. Whether other therapies (eg, CETP inhibitors, PCSK9 inhibitors) that increase HDL-C and/or lower LDL-C may be beneficial in addition to statins are being explored in ongoing Phase 3 trials.

High-Dose Rosuvastatin Reduces Contrast-Induced Nephropathy

Written by Phil Vinall

Among statin-naïve patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) managed with an early invasive strategy, pretreatment with high-dose rosuvastatin was associated with a significant reduction in the incidence of contrast-induced acute kidney injury (CI-AKI). In addition, pretreatment with rosuvastatin was also associated with a reduction in adverse clinical events at 30 days compared with placebo. Anna Toso, MD, Misericordia e Dolce Hospital, Prato, Italy, presented the results of the Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induced Acute Kidney Injury and Myocardial Damage in Patients With Acute Coronary Syndrome study [PRATO-ACS; NCT01185938] on behalf of the trial investigators.

Statins, due to their lipid-lowering and pleiotropic properties, may have a renal-protective effect after contrast medium administration for patients undergoing an angiographic procedure. However, the dose, type, timing and target population for statin use is uncertain. This study tested the hypothesis that high doses of rosuvastatin given before an angiographic procedure would protect against the development of CI-AKI.

In the PRATO-ACS trial, statin-naïve NSTE-ACS patients admitted to the cardiac care unit (CCU) between July 2010 and August 2012 managed with an early invasive strategy were eligible for the study. Exclusion criteria were: emergent angiography, acute renal failure or early-stage renal disease requiring dialysis, a baseline serum creatinine ≥3 mg/dL, contraindications to statin treatment, or exposure to contrast medium within the last 10 days. After admission to the CCU, 271 patients were randomized to receive rosuvastatin (loading dose of 40 mg, then 20 mg/day) or a placebo. The primary endpoint was the development of CI-AKI defined as a rise in serum creatinine ≥0.5 mg/dL absolute or ≥25% increase relative to baseline that occurred within 72 hours of contrast exposure.

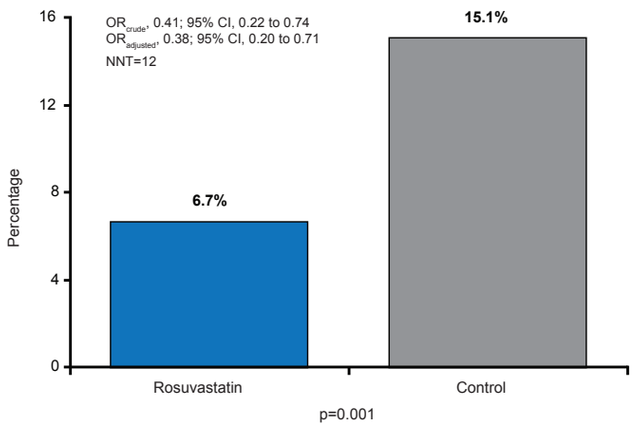
Serum creatinine increases ≥25%, ≥0.5 mg/dL, and ≥0.3 mg/dL within 48 and 72 hours, as well as a decrease in estimated glomerular filtration rate ≥25% within 72 hours were additional biomarker endpoints. Other clinical endpoints included acute renal failure requiring dialysis, persistent renal damage, all-cause mortality, myocardial infarction, and stroke through 30 days.

All patients were treated with dual antiplatelet therapy (aspirin+clopidogrel) prior to coronary angiography (±percutaneous coronary intervention) and after discharge. In addition, all patients received oral N-acetylcysteine and hydration both pre- and 24 hours post contrast medium (nonionic, dimeric iso-osmolar) administration. CI-AKI analysis was performed in 252 patients in each group after 72 hours. At discharge patients in the rosuvastatin pretreatment group continued rosuvastatin 20 mg, while those in control group received atorvastatin 40 mg daily.

There were no significant differences in baseline clinical, biochemical, or demographic characteristic, time from randomization to angiography, procedural success, or CI-AKI Mehran risk score, a validated risk prediction model for the development of CI-AKI, between the 2 groups.

CI-AKI was significantly less frequent in patients pretreated with rosuvastatin compared with placebo (6.7% vs 15.1%; adjusted OR, 0.38; 95% CI, 0.20 to 0.71; p=0.001; Figure 1). Compared with placebo, pretreatment with rosuvastatin was associated with significant reductions in all of the CI-AKI endpoints and the effect was consistent across all prespecified subgroups.

Figure 1. Primary Endpoint: CI-AKI



CK-AKI=contrast-induced acute kidney injury; NNT=number needed to treat.
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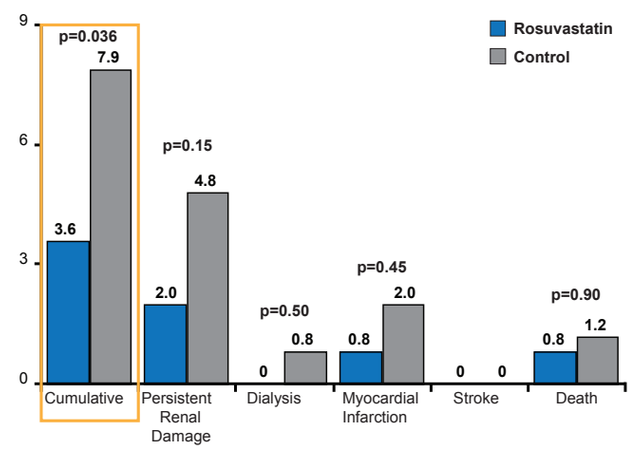
In addition, rosuvastatin pretreatment reduced the rate of acute renal failure requiring dialysis, persistent renal damage, all-cause mortality, myocardial infarction, and stroke at 30 days (3.6% vs 7.9%; p=0.036) compared with placebo (Figure 2).

Figure 2. Adverse Clinical Events (30 Days)



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To date, there have been few effective strategies to protect patients from developing CI-AKI. The findings from the PRATO-ACS trial are notable and further studies are needed to both corroborate these results and potentially evaluate whether this is a class-effect of statins or unique to rosuvastatin.