Baseline characteristics were similar between treatment arms. The average age was 58 years, 80% of patients had at least 1 CV risk factor, and 25% had known vascular disease. A majority (70%) of patients were receiving statins, mostly (62%) of high or moderate intensity.

Treatment with evolocumab resulted in a 61% reduction in LDL-C at 12 weeks (95% CI, 59% to 63%; $P < .001$) as compared to standard therapy. The absolute reduction in LDL-C was 73 mg/dL (95% CI, 71 to 76), with a median achieved LDL-C of 48 mg/dL. All lipid parameters were significantly affected, including decreased non-high-density lipoprotein cholesterol (HDL-C), apolipoprotein B, lipoprotein(a), and triglycerides, and increased HDL-C and apolipoprotein A1 ($P < .001$ for all).

Using a composite CV end point, including death, coronary events, cerebrovascular events, and heart failure requiring hospitalization, the Kaplan-Meier 1-year rates of CV events were 0.95% for patients receiving evolocumab and 2.18% for patients receiving standard of care alone (HR, 0.47; 95% CI, 0.28 to 0.78; $P = .003$). Separation of the Kaplan-Meier plots was evident after 2 to 3 months of follow-up.

This decrease in CV end points was consistent across all types of CV outcomes and was consistent across all patient subgroups with no heterogeneity of effect. Rates of AEs were balanced between treatment arms, except for neurocognitive AEs, which were higher in the evolocumab arm although they were low in both arms (< 1%). Notably, these events did not appear related to achieved LDL-C.

Further study on evolocumab is underway with the FOURIER trial, for which results are expected in 2017. Dr Sabatine concluded that in the interim, the OSLER data support the potential for PCSK9 inhibition with evolocumab to reduce the risk of CV outcomes through lowered LDL-C levels.

EMBRACE: Bendavia Has No Effect on Reperfusion Injury in STEMI

Written by Aimee Spevak

C. Michael Gibson, MD, MS, Harvard Medical School, Boston, Massachusetts, USA, presented results from the EMBRACE trial [NCT01572909], which investigated the effect of bendavia administration on reperfusion injury in patients receiving percutaneous coronary intervention (PCI) and stenting for STEMI. EMBRACE was an international, multicenter trial designed to investigate the effect of bendavia on infarct size in patients with first-time anterior STEMI. Patients were required to present with a closed artery and a TIMI flow of 0 or 1 in proximal or mid left anterior descending lesions, and within 4 hours of symptoms. Patients with shock were excluded. The primary analysis population was smaller than planned due to low numbers of patients presenting with complete obstruction on angiography.

Mitochondria present a potential target for pharmacotherapy to lower reperfusion injury. In animal studies, bendavia, a mitochondria-targeting peptide, has reduced infarct size following ischemic events up to 42% [Kloner RA et al. *J Am Heart Assoc*. 2012], and improvements occur with no changes in heart rate or blood pressure [Sabbah HN et al. *Eur Heart J*. 2013 (abstr P3286)]. These results showed promise of improved mitochondrial bioenergetics without increased demands on the heart.

Patients were randomized 1:1 and were blinded to treatment with bendavia (n = 150) or volume-matched placebo (n = 147). Bendavia IV was administered at 0.05 mg/kg/h at least 15 minutes prior to, and 60 minutes following, PCI. The primary end point was the area under the curve (AUC) for serum creatine kinase MB (CK-MB) levels over 72 hours post-PCI. The clinical end point was a composite of all-cause death, new-onset congestive heart failure (CHF), and CHF rehospitalization. Secondary end points included infarct size by the AUC for troponin I, magnetic resonance imaging outcomes, TIMI perfusion grade and corrected TIMI frame count post-PCI, and ST-elevation resolution.

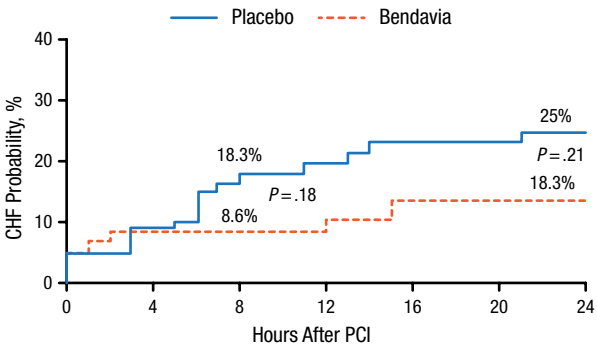
Of 297 randomized patients, an unexpected 117 (40%) had an open artery at angiography (pre-PCI TIMI flow grade > 1) and were excluded from the analysis. After satisfying all patient exclusions, the primary analysis population was 118; patients were excluded from the treatment arms equally. Baseline characteristics were similar except hypertension (60% in placebo group vs 37.9% in treatment group). Other clinical and angiographic characteristics were similar.

The primary end point in the study showed no significant difference between the study drug group and the placebo group. No differences were seen in the clinical composite end point or any secondary end points. The exploratory end point of CHF was numerically lower with bendavia at 8 hours following treatment; however, this difference was not statistically significant (Figure 1).

Non-prespecified, exploratory analyses found potential benefit in patients with hypertension who received bendavia for infarct volume and ST-segment resolution, and a trend toward benefit for edema volume. Exploratory analyses showed several protective renal outcomes associated with bendavia.

Dr Gibson concluded by reiterating that no differences were seen between bendavia and placebo in terms of the CK-MB AUC, but added that these data generated

Figure 1. CHF Probability for 24 Hours Following PCI



CHF, congestive heart failure; PCI, percutaneous coronary intervention.
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hypotheses toward the potential for bendavia to reduce CHF symptoms within 8 hours following PCI, which is under investigation for patients with systolic heart failure in additional clinical trials. The potential renal protective effects of bendavia are also under investigation.

REGULATE-PCI Trial: Safety Concerns Cause Early Termination

Written by Aimee Spevak

The REG1 anticoagulant system—which includes pegnivacogin, an active anticoagulant, and anivamersen, a complementary control agent to neutralize the effect of pegnivacogin, for patients undergoing percutaneous coronary intervention (PCI)—was compared with bivalirudin in the REGULATE-PCI trial [NCT01848106], presented by Roxana Mehran, MD, Icahn School of Medicine at Mount Sinai, New York, New York, USA. Due to increased severe allergic reactions, including 1 death, the trial was terminated early, with only about 24% of the anticipated sample size enrolled.

While antithrombotic therapies have improved safety and efficacy outcomes of PCI, available therapies may lead to adverse events (AEs) such as bleeding [Steg PG et al. *N Engl J Med*. 2009]. Research continues to investigate novel antithrombotic regimens for PCI that might have the ideal balance of efficacy, safety, and ease of use.

The REG1 anticoagulant system was designed to provide rapid, predictable antithrombotic action with quick reversibility by near-complete factor IXa inhibition. The phase 2 randomized active-controlled RADAR trial [Povsic TJ et al. *Eur Heart J*. 2013] had showed promising results for the REG1 anticoagulant system to allow for early vascular sheath removal with similar bleeding rates to heparin. Although the study was not designed to evaluate an effect on ischemic end points, the number of adverse cardiovascular (CV) end points was lower in the REG1 arm. In the RADAR trial, 3 patients had allergic-like reactions shortly after drug administration (2 were serious).

In REGULATE-PCI, patients were randomized 1:1 to receive either the REG1 system or bivalirudin during PCI. The primary efficacy outcome was a composite rate of death, nonfatal myocardial infarction, nonfatal stroke, and urgent target-lesion revascularization through day 3 following PCI, and the primary safety end point was the rate of bleeding through day 3, unassociated with coronary artery bypass graft (CABG) surgery. Additional follow-up continued through day 30, with data on allergic AEs collected.

Patients were stratified by risk group and placed into high-, medium-, and low-risk subgroups based on indicators of CV risk. Recruitment began in September 2013 with medium- and low-risk patients; in April 2014, investigators expanded enrollment of high-risk patients following a safety review for approximately 1000 patients enrolled in the study.

However, in June 2014, the study enrollment was suspended due to increased reports of severe allergic reactions, with 3232 of the planned 13 200 patients enrolled. Ten serious allergic events, 1 fatal, were observed in the REG1 treatment group, compared with

Table 1. Allergic Events End Points Through 3 Days Following Percutaneous Coronary Intervention

End Point by Day 3	REG1 (n = 1605)	Bivalirudin (n = 1601)
Serious allergic events	10 (0.6)	1 (< 0.1)
Fatal event	1	0
Severe event (anaphylactic reaction)	9	1
Organ system involvement		
Mucocutaneous	9	1
Respiratory	8	1
Circulatory	6	1
Gastrointestinal or genitourinary	4	0
Nonserious allergic events	14 (0.9)	9 (0.5)
Severe event (anaphylactic reaction)	8	3
Nonsevere event	6	6

Data presented in n or n (%).
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