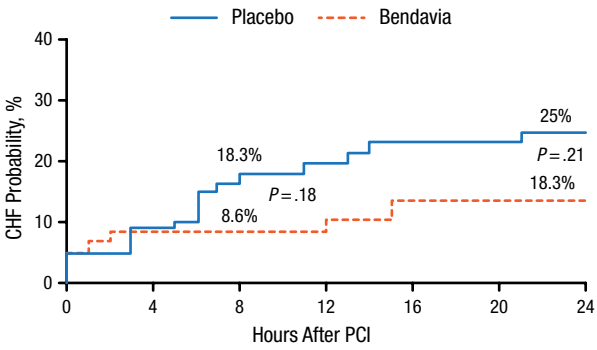
Figure 1. CHF Probability for 24 Hours Following PCI



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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1 in the bivalirudin treatment group (Table 1). In August 2014, upon recommendation from the Data Safety Monitoring Board, the study was permanently terminated due to excess allergic reaction rates associated with REG1 with a clear offsetting benefit to the drug.

No significant differences were observed in the primary efficacy end point with the data available; however, the exploratory end point of stent thrombosis was lower with REG1 at both days 3 and 30 (0.8% vs 0.1% with REG1; $P < .01$). Regarding the primary safety end point, major non-CABG-associated bleeding (BARC type 3 or 5) did not differ between the 2 groups (0.4% vs 0.1%; $P = .10$). Nevertheless, minor and major bleeding rates were higher in REG1, with 6.5% compared with 4.1% at day 3 ($P < .002$).

Dr Mehran concluded with a word of caution in interpreting the efficacy and bleeding data, as early termination limited the number of participants and events. She reiterated that REG1, as currently formulated, resulted an infrequent but unacceptably high rate of severe allergic reactions.

SCOT-HEART: CTCA Potential to Improve Angina Diagnosis, Treatment, and Outcomes

Written by Aimee Spevak

The SCOT-HEART trial [SCOT-HEART Investigators. *Lancet*. 2015] was conducted to determine whether rapid-access chest pain centers would benefit from the addition of computed tomography coronary angiography (CTCA) to diagnose patients presenting with suspected angina due to coronary heart disease (CHD). Use of CTCA improved the provider certainty of diagnosis, influenced changes in treatment, and showed a potential to decrease CHD-related death and nonfatal myocardial infarction (MI).

Clinicians at rapid-access chest pain centers can accurately identify patients with chest pain at high risk for CHD. However, a need remains to reduce the number of patients felt to be at lower risk who are misdiagnosed with noncardiac chest pain, as these patients compose roughly one-third of fatal and nonfatal MI cases within 6 months of presenting with chest pain [Sekhri N et al. *Heart*. 2007].

David Newby, MD, PhD, University of Edinburgh, Edinburgh, Scotland, United Kingdom, presented data from SCOT-HEART, which randomized patients presenting with suspected angina due to CHD to receive diagnosis by standard care alone or standard care plus CTCA. The primary end point of the study was the change in diagnosis of angina due to CHD when using CTCA. The study included patient groups previously excluded from angina trials, as no restrictions were put on presence of arrhythmia, obesity, or calcium score. Patients with renal failure, allergy to contrast media or other inability to undergo computed tomography scanning, pregnancy, or acute coronary syndrome within 3 months were excluded.

Data were collected at 12 centers across Scotland. A total of 4146 patients were recruited and randomized 1:1, half to standard of care and half to standard of care plus CTCA. Baseline characteristics were similar between the 2 groups.

The addition of CTCA to standard testing improved provider diagnosis certainty nearly 4-fold (RR, 3.76; 95% CI, 3.61 to 3.89), while diagnosis (angina due to CHD) frequency decreased (RR, 0.78; 95% CI, 0.70 to 0.86). At 6 weeks of follow-up, clinicians reported further increased certainty in diagnosis; during the follow-up period, CTCA use led to a significant increase in change in diagnosis (23% vs 1% in the standard care group; $P < .001$).

Use of CTCA resulted in a 14% increase in further investigations ($P < .0001$) and an 18% increase in treatment changes ($P < .0001$). Patients were followed up for a median of 1.7 years (range, 0.1 to 4.1); CTCA was associated with a 38% reduction in CHD death and nonfatal MI, which for the prespecified analysis was just under statistical significance (HR, 0.62; 95% CI, 0.38 to 1.01; $P = .0527$).

Prof Newby concluded that the use of CTCA for patients with suspected angina due to CHD was beneficial in a variety of ways: it clarified diagnosis, aided in treatment decision making, increased further testing, and increased diagnosis of CHD. Use of CTCA may improve treatment decisions, reducing fatal and nonfatal MI.

SAPIEN 3 TAVR System Produces Excellent Clinical Outcomes in PARTNER II Trial

Written by Aimee Spevak

The PARTNER II trial [NCT01314313] enrolled high-risk operable, inoperable, and intermediate-risk operable patients with symptomatic severe aortic stenosis (AS) to receive the most recently available transcatheter heart valve (THV). Both patient groups experienced lower-than-expected mortality and stroke outcomes, with low rates of adverse events (AEs) and paravalvular leak.

Since their introduction in 2003, balloon-expandable THVs have continued to evolve. The current SAPIEN 3 (S3) valve, available since 2013, is size 14 French and has several modified features in the valve and its delivery system. To investigate this new iteration of transcatheter aortic valve replacement, the PARTNER II trial was designed to evaluate safety and efficacy outcomes for