Table 2. Access Site Program: Bleeding End Points

Bleeding End Point	Transradial Access, % of Patients	Transfemoral Access, % of Patients	Significance Level, Rate Ratio (95% CI)	*P* Value
BARC 3/5	1.6	2.3	0.67 (0.49 to 0.92)	.013
Access site (BARC 3/5)	0.4	1.1	0.37 (0.21 to 0.66)	.0004
Nonaccess site (BARC 3/5)	1.1	1.2		.68
BARC 3	1.3	2.1	0.64 (0.45 to 0.90)	.0098
BARC 5	0.2	0.3		.82
TIMI (major or minor)	1.2	1.7	0.72 (0.50 to 1.04)	.08
GUSTO (moderate or severe)	1.1	1.4	0.78 (0.53 to 1.14)	.20

Table 3. Antithrombin Program: Results for All Bleeding End Points

Bleeding End Point	Bivalirudin, % of Patients	UFH, % of Patients	Significance Level, Rate Ratio (95% CI)	*P* Value
Access site (BARC 3/5)	0.6	0.9	0.59 (0.33 to 1.04)	.07
Nonaccess site (BARC 3/5)	0.8	1.6	0.53 (0.34 to 0.83)	.005
BARC 3	1.3	2.1	0.61 (0.42 to 0.88)	.008
BARC 5	0.1	0.4	0.31 (0.11 to 0.85)	.0016
TIMI (major or minor)	1.0	1.9	0.50 (0.33 to 0.75)	.002
GUSTO (moderate or severe)	0.9	1.5	0.61 (0.39 to 0.95)	.027

UFH, unfractionated heparin.

(MACEs, $P = .45$; NACEs, $P = .122$). Rates of all-cause mortality were significantly reduced in the bivalirudin group compared with the UFH group at 30 days (1.7% vs 2.3%; RR, 0.71; 95% CI, 0.51 to 0.99; $P = .042$). Bleeding risk was also significantly reduced in the bivalirudin group, across all scales and including fatal events and nonaccess site events (Table 3).

One possible explanation for the finding that the co-primary composite end point of neither trial was met despite significant reductions in mortality and bleeding is that the MI rate was much higher than expected and there were no differences in the rates of MI between the 2 groups, Prof Valgimigli said.

In conclusion, the MATRIX trial found that TR access reduced the occurrence of NACEs, which was 1 of 2 co-primary composite end points, and it reduced all-cause mortality and major bleeding when compared to TF access. Bivalirudin did not reduce the occurrence of either of the co-primary composite end points, but exploratory analyses found that death and bleeding were reduced with bivalirudin when compared with UFH.

Evolocumab Effectively Lowers LDL-C, Decreases Cardiovascular Outcomes in OSLER

Written by Aimee Spevak

Marc S. Sabatine, MD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented data on the OSLER studies [Sabatine MS et al. *N Engl J Med.* 2015], 2 open-label, randomized extension studies of evolocumab phase 2 and phase 3 trials. OSLER showed that evolocumab, a proprotein convertase subtilisinkexin type 9 (PCSK9) inhibitor, effectively decreased low-density lipoprotein cholesterol (LDL-C) levels and reduced cardiovascular (CV) outcomes. The drug was well tolerated, with no gradient of adverse events (AEs) across all levels of minimum achieved LDL-C.

Available data on evolocumab, a fully human monoclonal antibody against PCSK9, demonstrate its ability to lower LDL-C by about 60% on top of statin therapy; additionally, the drug has been well tolerated by patients [Raal FJ et al. *Lancet.* 2015; Robinson JG et al. *JAMA.* 2014; Stein EA et al. *Eur Heart J.* 2014]. However, the effect of evolocumab on CV outcomes of patients was previously undefined.

Patients were randomized in a 2:1 ratio to receive evolocumab plus standard of care (n = 2976) or standard of care alone (n = 1489). Evolocumab was administered by subcutaneous injections of either 140 mg every 2 weeks or 420 mg once monthly. Median follow-up was 11.1 months (interquartile range, 11.0 to 12.8); the vast majority of patients (96%) completed follow-up and 7% discontinued evolocumab early. The primary end point was the incidence of AEs, and the secondary outcome was the percent change in LDL-C levels. A prespecified, exploratory analysis of adjudicated CV clinical outcomes was performed.

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