MATRIX: Comparison of Transradial and Transfemoral Access and Bivalirudin to Unfractionated Heparin

Written by Eleanor Mayfield

The MATRIX trial [NCT01433627] was performed in patients with acute coronary syndrome (ACS) who underwent coronary angiography, percutaneous coronary intervention (PCI), or both, and the trial was designed to determine the optimal access site and anticoagulation strategy. There were no differences between transradial (TR) and transfemoral (TF) access with regard to the primary efficacy end point, but TR access reduced mortality and major bleeding [Valgimigli M et al. *Lancet.* 2015]. In addition, there were no differences in the incidence of the primary end point between bivalirudin and unfractionated heparin (UFH); however, bivalirudin reduced death and major bleeding. The findings from both programs were presented by the principal investigator, Marco Valgimigli, MD, PhD, Erasmus Medical Center, Rotterdam, The Netherlands.

Compared with the femoral artery, the radial artery's superficial location and smaller caliber allow better hemostasis, but the use of radial arterial catheterization can be more technically challenging to perform, Prof Valgimigli said. Because previous trials had reached differing conclusions, it was unclear whether TR access improved outcomes in patients with ACS who were managed invasively when compared with TF access [Hsieh V, Jolly S. *J Comp Eff Res.* 2013; Michael TT et al. *JACC Cardiovasc Interv*. 2013].

A second unresolved question in this patient population was which antithrombotic regimen most effectively prevented ischemic complications while limiting bleeding risk. Previous studies comparing bivalirudin and UFH used with or without glycoprotein IIb/IIIa inhibitors had also produced conflicting results [Abtahian F et al. *Catheter Cardiovasc Interv.* 2015; Capodanno D et al. *Eur Heart J Acute Cardiovasc Care*. 2015].

MATRIX was a phase 3, prospective, randomized, open-label trial conducted at 78 sites in Italy, The Netherlands, Spain, and Sweden. Participants, recruited between October 2011 and November 2014, were randomized in a 2-step process. In the MATRIX Access Site program, 8404 patients with ACS who were candidates for coronary angiography and PCI were randomly assigned to TR access (n = 4197) or TF access (n = 4207). In the MATRIX Antithrombin program, patients (n = 7213) who underwent PCI were then randomly assigned to anticoagulation with UFH (n = 3603) or bivalirudin (n = 3610).

Primary and secondary end points were identical in both programs; co-primary end points were major adverse cardiovascular events (MACEs), a composite of death, myocardial infarction (MI), and stroke at 30 days; and net adverse clinical events (NACEs), a composite of MACEs plus major bleeding (BARC 3 or 5) at 30 days. Secondary end points were each component of the co-primary end points; any bleeding as measured by the BARC, TIMI, or GUSTO scales; and stent thrombosis.

Participants in the Access Site program were >70% men, with a mean age of 67; 30% were aged ≥75 years; 48% had a diagnosis of STEMI; 46%, NSTEMI; and 6%, unstable angina. Participants in the Antithrombin program were >75% men, with a mean age of 65; 25% were aged ≥75 years; 55% had a diagnosis of STEMI; 40%, NSTEMI; and <5%, unstable angina.

Interventional cardiologists conducting study procedures were required to have performed a total of at least 75 TR coronary interventions and performed at least 50% of all their interventional procedures by the TR route during the year preceding initiation of the MATRIX study.

Among patients in the Access Site program, 8.8% of the TR group experienced the co-primary end point MACEs compared with 10.3% of the TF group (rate ratio [RR], 0.85; 95% CI, 0.74 to 0.99; 2-sided $P = .031$). The P value was considered nonsignificant at the prespecified α of 0.025 that was utilized given the 2 primary comparisons of the trial. In the TR group, 9.8% of participants met the NACEs end point vs 11.7% of those in the TF group, which was statistically significant (RR, 0.83; 95% CI, 0.73 to 0.96; $P = .009$). The factors contributing to this outcome were statistically significant differences in death (Table 1) and major bleeding (Table 2), in favor of the TR approach.

In the Antithrombin program, there were no statistically significant differences between the UFH and bivalirudin groups for either of the co-primary end points

Table 1. Access Site Program: All-Cause Mortality

End Point	Transradial Access, % of Patients	Transfemoral Access, % of Patients	Significance Level, Rate Ratio (95% CI)	*P* Value
All-cause mortality[a]	1.6	2.2	0.72 (0.53 to 0.99)	.045
CV death	1.5	2.1	0.75 (0.54 to 1.04)	.08
Non-CV death	0.1	0.1	—	

CV, cardiovascular.

[a]Number needed to benefit 1 person, 167.

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.