burden, with the majority of lesions comprising thin-cap fibroatheromas. In his concluding remarks, he also emphasized that although high-dose rosuvastatin therapy for 13 months is associated with a significant reduction of coronary atherosclerosis, it did not change the proportion of necrotic core in these arteries or the plaque phenotypes.

NO Fails to Reduce Myocardial IS: NOMI Results

Written by Emma Hitt Nichols, PhD

Inhaled nitric oxide (NO) did not reduce infarct size (IS) in patients who experienced STEMI and underwent percutaneous coronary intervention (PCI). Stefan P. Janssens, MD, PhD, University of Leuven, Leuven, Belgium, presented data from the Effects of Nitric Oxide for Inhalation in Myocardial Infarction Size study [NOMI; NCT01398384].

In animal models, inhalation of 40 to 80 ppm of NO decreased IS and area at risk and improved functional recovery [Liu X et al. *J Am Coll Cardiol.* 2007; Hataishi R et al. *Am J Physiol Heart Circ Physiol.* 2006]. The hypothesis of the NOMI study was that inhaled NO would decrease IS and improve left ventricular (LV) function in patients with STEMI who underwent primary PCI.

The NOMI trial was a multicenter double-blind phase 2 trial that randomized 248 patients with STEMI undergoing PCI within 12 hours to either inhaled NO (80 ppm) or placebo. All patients underwent magnetic resonance imaging to evaluate IS, LV function, and remodeling at 48 to 72 hours and again at 4 months. The primary end point was IS and secondary end points included myocardial salvage index, myocardial hemorrhage, LV remodeling at 48 to 72 hours, and LV remodeling at 4 months. The trial also examined the effects on prespecified subgroups, including TIMI flow grade, culprit artery, time between symptom onset and PCI, and troponin levels upon admission.

Inhaled NO failed to significantly reduce IS, and the IS/LV mass ratio was 19.4% in the control arm and 18% in the inhaled NO arm (estimate R effect, –1.48; 95% CI, –5.25 to 2.29; $P=.44$). There were no differences in the composite end point of death, recurrent ischemia, stroke, and rehospitalization at 150 days (log-rank $P=.1022$). NO treatment resulted in a significant improvement in LV remodeling at 4 months (OR, 0.90; 95% CI, 0.81 to 0.999; $P=.048$) compared with control. There were no significant differences in the other secondary end points.

Prof Janssens stated that the data from the NOMI trial show that inhaled NO is safe but did not decrease the IS, as measured by percentage LV mass. However, there were improvements in LV remodeling at 4 months.

TRO40303 Lacks Protective Effect in PCI: Results From MITOCARE

Written by Emma Hitt Nichols, PhD

TRO40303 failed to prevent reperfusion injury as measured by creatine kinase and troponin I levels in patients with STEMI when administered just prior to balloon inflation during percutaneous coronary intervention (PCI). Dan Atar, MD, Oslo University Hospital Ulleval, Oslo, Norway, presented data from the Safety and Efficacy Study of TRO40303 for Reduction of Reperfusion Injury in Patients Undergoing Percutaneous Coronary Intervention for Acute Myocardial Infarction [MITOCARE; Atar D et al. *Eur Heart J.* 2014].

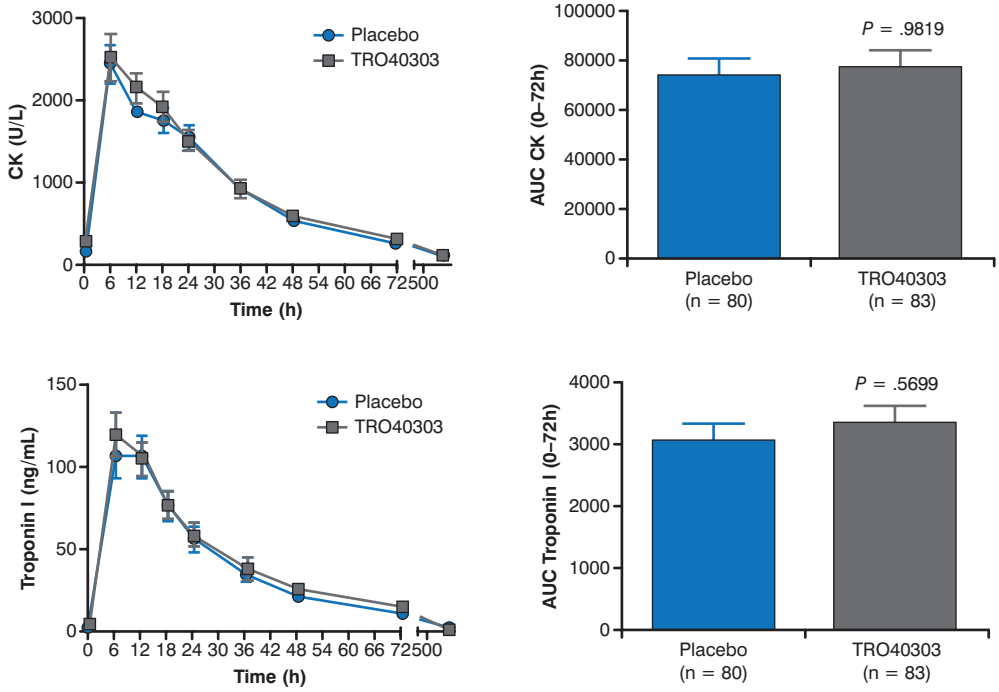
TRO40303 blocks the opening of the mitochondrial permeability transition pore and was thought to prevent reperfusion injury. In animal models, TRO40303 reduced infarct size by 50% [Le Lamer S et al. *J Transl Med.* 2013] and improved left ventricular ejection fraction (LVEF) at 24 hours and 1 month [Augeul L et al. ESC 2009 (poster P4491)]. The purpose of the MITOCARE study was to determine the efficacy and safety of TRO40303 when administered prior to balloon inflation during PCI.

In this multicenter phase 2a trial, 167 patients with STEMI were randomized to either TRO40303 or placebo prior to PCI. The baseline characteristics were similar in both groups, although the TRO40303 arm had a higher mean age (64 vs 60 years) compared with the placebo arm. The mean time from the onset of pain to balloon time was 180 minutes, and the mean door-to-balloon time was 38 minutes.

The primary outcome of the study was infarct size as measured by area under the curve for creatine kinase and troponin I. The secondary outcome was infarct size as measured by magnetic resonance imaging. Patients were eligible for the study if they had no prior STEMI, presented with chest pain within 6 hours, and were to be treated with primary PCI, and there was TIMI 0/1 flow in the culprit artery. Patients were excluded if they had experienced cardiac arrest, ventricular fibrillation, cardiogenic shock, previous coronary artery bypass graft, or atrial fibrillation or they had a pacemaker.

There were no significant differences in creatine kinase ($P=.98$) or troponin I ($P=.57$) levels between the TRO40303 and placebo groups at 72 hours (Figure 1). In addition, the secondary end points—including myocardial salvage index, infarct size, microvascular obstruction, left ventricular end diastolic volume and end systolic volume, and LVEF—were similar between arms.

Figure 1. Effect of TRO40303 on CK and Troponin I Levels



AUC, area under the curve; CK, creatine kinase.
Reproduced with permission from D Atar, MD.

The rate of adverse events was similar between the TRO40303 and placebo arms. However, 25% of patients experienced at least 1 adverse event in the TRO40303 arm, compared with 10% in the placebo arm ($P = .01$). For example, more patients in the TRO40303 group required repeat revascularization.

In conclusion, Prof Atar stated that the MITOCARE trial showed that TRO40303 does not reduce infarct size in patients with STEMI.

ENGAGE AF-TIMI 48: Tailoring Edoxaban Dose Preserves Drug Efficacy and Safety

Written by Brian Hoyle

The Effective Anticoagulation With Factor Xa Next Generation in the Atrial Fibrillation–TIMI 48 trial [ENGAGE AF-TIMI 48; Giugliano RP et al. *N Engl J Med*. 2013] of 21 105 patients with atrial fibrillation and $CHADS_2$ scores ≥2 reported the noninferiority of the oral factor Xa inhibitor edoxaban 30 and 60 mg once daily versus warfarin and dose-related decreases in major bleeding. Christian T. Ruff, MD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the results of a subanalysis showing that the protocol-driven dose adjustments in ENGAGE AF maintained the efficacy of edoxaban and reduced bleeding.

By way of background, the novel oral anticoagulants (NOACs), such as edoxaban, unlike warfarin, seem to provide fixed dosing therapeutic anticoagulation without the need for routine monitoring. However, an emerging question is whether the drug concentration or anticoagulant activity should be measured to optimize the risk/benefit ratio of a NOAC. Therefore, this subanalysis correlated the trough plasma concentrations of edoxaban in 6780 study patients and the anti–factor Xa activity in 2865 of the 6780 patients, measured 1 month after randomization with the edoxaban dose. The efficacy and safety outcomes were compared in the no dose reduction (NDR) and dose reduction (DR) groups in the edoxaban arms against warfarin.

The primary efficacy outcome was stroke or systemic embolic events (SEEs), and the primary safety outcome was major bleeding defined by International Society on Thrombosis and Haemostasis criteria. At baseline, or if any factors developed during the trial, doses in both edoxaban arms were reduced by 50% for patients with