Although PCI is a lifesaving procedure for patients with STEMI, a feared potential complication is stent thrombosis. Dual antiplatelet therapy, which includes aspirin plus a P2Y12 antagonist inhibitor such as ticagrelor, is recommended to reduce the risk of stent thrombosis. The purpose of the ATLANTIC trial was to determine if the administration of ticagrelor in-ambulance is more effective than in-hospital administration in patients with STEMI.

In the international double-blind trial, 1862 patients with STEMI who were transferred for primary PCI were randomly assigned to receive 180 mg of ticagrelor in-ambulance or in-hospital with matching placebo. After PCI, all patients received ticagrelor (90 mg, BID) for 30 days. The mean time difference of receiving the loading dose of ticagrelor was 31 minutes. The primary end points of the trial were the proportion of patients not achieving ≥70% resolution of ST segment elevation prior to PCI or not achieving TIMI flow grade 3 in the suspected artery at the initial angiograph. Additional clinical end points included rates of definite stent thrombosis and major adverse cardiovascular events (MACEs). The primary safety end point was the rate of minor or major bleeding events.

In-ambulance administration of ticagrelor resulted in similar rates of lack of ≥70% resolution of ST segment elevation (OR, 0.93; 95% CI, 0.69 to 1.25; $P=.63$), TIMI flow grade 3 (OR, 0.97; 95% CI, 0.75 to 1.25; $P=.82$), or MACEs ($P=.91$) compared with patients who received in-hospital ticagrelor at 30 days. However, treatment with ticagrelor in-ambulance resulted in lower rates of definite stent thrombosis up to 24 hours ($P=.0008$) and 30 days (OR, 0.19; 95% CI, 0.04 to 0.86; $P=.0225$) compared with in-hospital treatment. Bleeding rates included minor, major, or life-threatening bleeding related to non–coronary artery bypass grafting for up to 30 days. In addition, rates of overall and serious adverse events were similar between both arms in the study.

Prof Montalescot concluded by stating that, in his opinion, the data from the ATLANTIC trial suggested that in-ambulance administration of ticagrelor was safe and reduced the risk of stent thrombosis in patients with STEMI undergoing PCI. The discussant, Paul Wayne Armstrong, MD, Edmonton, Alberta, Canada, stated that the reduction of stent thrombosis but also the failure to achieve the co–primary end points may be due to chance. In particular, the short time difference of 31 minutes between the pre- or in-hospital administration of ticagrelor may have undermined the results of this study. Therefore, Prof Armstrong suggested that the role of ticagrelor administered in-ambulance is yet to be established.

ODYSSEY FH I and FH II: Alirocumab Significantly Improves Cholesterol Levels in Patients With HeFH

Written by Nicola Parry

Michel Farnier, MD, PhD, Point Medical, Dijon, France, presented results from the Efficacy and Safety of Alirocumab SAR236553 (REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy trial [ODYSSEY FH I; NCT01623115] and the Study of Alirocumab (REGN727/ SAR236553) in Patients With HeFH (Heterozygous Familial Hypercholesterolemia) Who Are Not Adequately Controlled With Their LMT (Lipid-Modifying Therapy) trial [ODYSSEY FH II; NCT01709500]. These trials demonstrated that, in patients with heterozygous familial hypercholesterolemia (HeFH) whose low-density lipoprotein cholesterol (LDL-C) levels were inadequately controlled by statin and other lipid-lowering therapy (LLT), alirocumab produced significantly greater reductions in LDL-C compared with placebo.

Mutations in the LDL receptor gene, which cause HeFH, lead to elevated plasma levels of LDL-C and an increased risk of premature atherosclerosis and cardiovascular disease (CVD) [Pijlman AH et al. *Atherosclerosis*. 2010].

According to Prof Farnier, patients with HeFH are challenging to treat in clinical practice. Statins are the drug of first choice; however, even at the maximum tolerated dose, approximately 80% of adult patients with HeFH fail to reach the LDL-C target of <2.5 mmol/L (100 mg/dL) with monotherapy [Pijlman AH et al. *Atherosclerosis*. 2010]. The LDL-C target for adults with HeFH who also have coronary heart disease or diabetes is <1.8 mmol/L (<70 mg/dL) [Nordestgaard BG et al. *Eur Heart J*. 2013].

ODYSSEY FH I and II were double-blind, placebo-controlled trials, conducted in North America, Europe, and South Africa for ODYSSEY FH I and across Europe for ODYSSEY FH II, that enrolled a total of 735 participants (aged approximately 52 to 53 years). Inclusion criteria included patients who had HeFH, a history of CVD, LDL-C≥1.81 mmol/L (≥70 mg/dL), or no history of CVD and LDL-C≥2.59 mmol/L (≥100 mg/dL), and who were receiving a maximally tolerated daily statin dose with or without other LLT. Patients were randomized to alirocumab (75 to 150 mg subcutaneously Q2W; n=490 across both studies), or matching placebo (n=245 across both studies) for 78 weeks, in addition to current therapy.

The primary end point was the percentage change in LDL-C from baseline to week 24. At week 24, alirocumab significantly reduced LDL-C levels compared with placebo

in both FH I and II trials (−48.8% and −48.7% vs 9.1% and 2.8%, respectively; $P<.0001$). To reach a prespecified LDL-C level <1.81 mmol/L (70 mg/dL), an uptitration to 150 mg Q2W at week 12 was necessary in 43.4% and 38.6% of patients receiving alirocumab treatment in both trials.

Similarly, by week 24, significantly more alirocumab-treated patients compared to those on placebo had reached the LDL-C goal of a level <2.59 mmol/L (100 mg/dL) in high-risk patients or <1.81 mmol/L (70 mg/dL) in very high-risk patients (72.2% vs 2.4% in FH I, and 81.4% vs 11.3% in FH II; both $P<.0001$). Most patients receiving alirocumab achieved their LDL-C goals at week 24 in both trials (72.2% and 81.4% vs 2.4% and 11.3%; $P<.0001$), and this reduction was maintained to 52 weeks (1.7 mmol/L and 1.9 mmol/L [65.9 mg/dL and 74.3 mg/dL]).

In an analysis of pooled data from the 2 trials at week 52, alirocumab appeared to be well tolerated. Treatment-emergent adverse events (TEAEs) occurred in a similar proportion of patients treated with alirocumab and placebo (74.8% vs 75.4%) and led to discontinuation in 3.1% and 3.7% of patients, respectively. The most commonly reported TEAEs (occurring in ≥5% of patients in each treatment arm) were injection-site reactions, nasopharyngitis, influenza, and headaches.

With such a large proportion of patients achieving their target LDL-C levels, and the lack of major adverse safety signals compared with placebo, alirocumab represents a very promising treatment approach for this very high-risk patient population, concluded Prof Farnier.

IBIS-4: High-Dose Rosuvastatin Reduces Plaque Burden in Patients With STEMI

Written by Nicola Parry

Lorenz Räber, MD, Bern University Hospital, Bern, Switzerland, presented results from the Integrated Biomarker and Imaging Study-4 [IBIS-4; Räber L et al. *Eur Heart J*. 2014], a prospective substudy embedded in the COMFORTABLE trial [Räber L et al. *JAMA*. 2012] comparing biolimus-eluting stents vs bare-metal stents in patients with STEMI undergoing percutaneous coronary intervention (PCI). Data from IBIS-4 demonstrated that high-dose daily rosuvastatin was associated with a significant reduction in atherosclerotic burden in the non–infarct-related epicardial coronary arteries (non-IRAs) in patients with STEMI who underwent successful primary PCI.

For the past 2 decades, statins have been the mainstay of therapy in patients with high levels of low-density lipoprotein cholesterol (LDL-C), potently reducing cardiovascular events with acute coronary syndromes [Roth EM, Diller P. *Future Cardiol*. 2014]. According to Prof Räber, however, although statins are a key component of treatment for patients with acute STEMI, their long-term impact on coronary atherosclerosis is unknown. This study therefore aimed to investigate the effect of high-dose statin therapy on plaque burden, composition, and phenotype in the non-IRAs of patients with STEMI undergoing primary PCI.

IBIS-4 included 103 patients with STEMI who underwent intravascular ultrasonography (IVUS) and radiofrequency ultrasonography (RF-IVUS) of the 2 non-IRAs following successful primary PCI. Exclusion criteria included subjects with either non-IRA with >50% stenosis.

All patients received rosuvastatin 20 mg/d for the first 2 weeks, followed by a dose increase to 40 mg/d for the remainder of the study period. Atherosclerotic burden was evaluated in the proximal arterial segments at baseline and 13 months using IVUS and RF-IVUS.

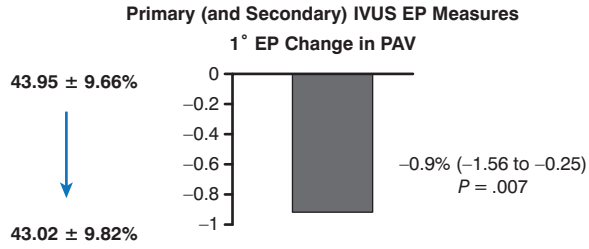
The primary IVUS end point was the change in percent atheroma volume (PAV), and the primary RF-IVUS end point was the change in percent necrotic core, both at 13 months. Successful serial imaging was available for 82 patients with 146 analyzed non-IRAs at both time points.

From baseline to 13 months, LDL-C had decreased from a median of 3.29 to 1.89 mmol/L ($P<.001$). With regard to the primary end point, IVUS demonstrated a significant reduction of atheroma volume (43.95% to 43.02%; 95% CI, −1.56 to −0.25, $P=.007$; Figure 1).

There was no significant change, however, in percent necrotic core with RF-IVUS (21.14% to 21.02%; 95% CI, −1.05 to 0.96; $P=.93$). Similarly, the proportions of plaques with necrotic core and different plaque phenotypes were unchanged.

Dr Räber noted that the proximal segments of non-IRAs in these patients contained a high atherosclerotic plaque

Figure 1. Effect of Rosuvastatin on Atheroma Volume



EP, end point; IVUS, intravascular ultrasonography; PAV, percent atheroma volume.
Source: Räber L et al. *Eur Heart J*. 2014.
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