Darapladib Ineffective at Reducing Major Coronary Events After ACS

Written by Nicola Parry

Michelle O'Donoghue, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented primary results from The Stabilization of Plaques Using Darapladib-TIMI 52 trial [SOLID-TIMI 52; NCT01000727], demonstrating that darapladib is ineffective at reducing major coronary events when started within 30 days after an acute coronary syndrome (ACS) event.

By way of background, lipoprotein-associated phospholipase A_2 (Lp-PLA_2), a calcium-independent phospholipase A_2 that circulates in plasma in association with low-density lipoprotein particles, has been hypothesized to play a causal role in the development of atherosclerosis and to contribute to plaque instability through pathways related to inflammation. Darapladib is an enteric-coated, direct Lp-PLA_2 inhibitor that reduces enzyme activity in plasma and atherosclerotic plaques [Boekholdt SM et al. *Circulation.* 2008].

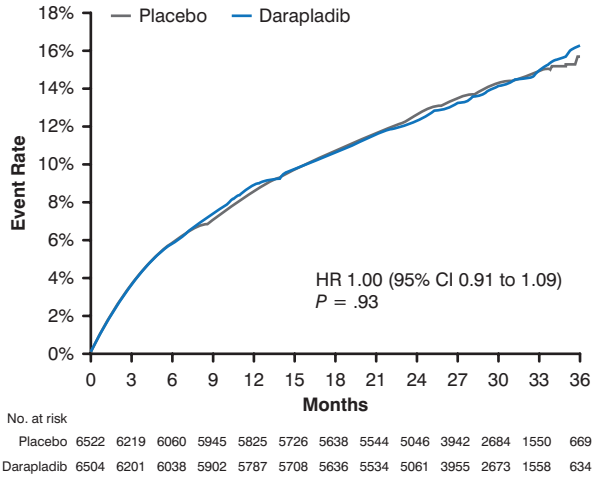
The SOLID-TIMI 52 trial was a double-blind, placebo-controlled, phase 3 study that was conducted at 868 sites in 36 countries to compare the safety and efficacy of darapladib with placebo for patients with ACSs if started within 30 days after hospitalization. It enrolled 13 026 participants within 30 days of hospitalization with ACSs. Qualifying events were most commonly STEMI (45.2%), NSTEMI (42.7%), and unstable angina (12.2%) and were balanced between the darapladib and placebo treatment arms.

Participants were randomized 1:1 to darapladib (160 mg once daily; n = 6504) or matching placebo (n = 6522), with a median follow-up duration of 2.5 years. The primary end point was the composite of coronary heart disease (CHD) death, myocardial infarction (MI), or urgent coronary revascularization for myocardial ischemia. Secondary end points included the composite of cardiovascular (CV) death, MI, or stroke; total coronary events; CHD death or MI; any coronary revascularization; individual components of the primary end point; and all-cause mortality.

After 3 years, the results demonstrated no significant difference in the occurrence of the primary end point between participants in the darapladib and placebo arms (16.3% vs 15.6%; HR, 1.00; 95% CI, 0.91 to 1.09; *P* = .93; Figure 1).

Similarly, darapladib did not significantly reduce the risk for the study's secondary end points of CV death, MI, or stroke (15.0% vs 15.0%; HR, 0.99; 95% CI, 0.90 to 1.09; *P* = .78). Additionally, there were no significant differences between the treatment arms for the individual components of the primary end points, for additional secondary and exploratory end points, or all-cause mortality (7.3% vs 7.1%; HR, 0.94; 95% CI, 0.82 to 1.08; *P* = .40).

Figure 1. Occurrence of the Primary End Point in the Darapladib and Placebo Treatment Arms



CHD, coronary heart disease; MI, myocardial infarction.
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Participants in the darapladib arm reported an odor-related complaint (predominantly of the urine, feces, and skin; 11.5% vs 2.5%) and diarrhea (10.6% vs 5.6%) more frequently than those in the placebo arm.

These data therefore do not support a strategy of targeted Lp-PLA_2 inhibition with darapladib on a background of optimal medical therapy in patients stabilized after ACS events, concluded Dr O'Donoghue. However, ongoing trials are evaluating the clinical utility of other novel therapeutics that target alternative pathways of inflammation.

Prehospital Ticagrelor Reduces Stent Thrombosis in STEMI

Written by Emma Hitt Nichols, PhD

Administration of ticagrelor in-ambulance resulted in reduced rates of stent thrombosis in patients with STEMI undergoing percutaneous coronary intervention (PCI) compared with patients who received ticagrelor in-hospital; however, the co–primary end points were not achieved. Gilles Montalescot, MD, PhD, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France, presented data from the 30-Day Study to Evaluate Efficacy and Safety of Pre-hospital vs In-hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for PCI [ATLANTIC; NCT01347580].

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