management by angiography alone. Colin Berry, FRCP, PhD, University of Glasgow, Glasgow, United Kingdom, presented data from the Fractional Flow Reserve Versus Angiographically Guided Management to Optimise Outcomes in Unstable Coronary Syndromes study [FAMOUS NSTEMI; NCT01764334].

Currently, visual interpretation of diagnostic angiography is important in determining the need for revascularization in patients with NSTEMI. FFR has a class I recommendation in stable coronary artery disease, but there is insufficient evidence for a recommendation in acute coronary syndromes. Lesion-level ischemia is associated with increased risk of ischemic events, as prior studies have shown that lesions with an FFR ≤0.80 benefit from revascularization with either coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). The hypothesis of the multicenter FAMOUS NSTEMI trial was that routine FFR is not only feasible in patients with NSTEMI but adds diagnostic, clinical, and economic benefits when compared with the current standard: angiography-guided management [Berry C et al. *Am Heart J.* 2013].

The primary outcome of the study was the proportion of patients who were administered medical management only at baseline. Secondary outcomes were the feasibility and safety of routine FFR, association between FFR and severity of stenosis, major adverse cardiac events (MACEs), resource use, and quality of life [Berry C et al. *Am Heart J.* 2013].

In this prospective clinical trial, 350 patients with intermediate- to high-risk NSTEMI were randomized to management that was guided by both angiography and FFR or by angiography alone. In the angiography-guided group, FFR was measured but not disclosed to clinicians or patients. Treatment decisions for any patient were left to the discretion of the treating physician. FFR was successful in 100% of patients, with a 0.03% rate of wire dissections. The treatment plan was altered in 22% of patients after FFR was disclosed, which decreased the number of patients treated with revascularization and type 4 myocardial infarctions (MIs).

FFR-guided management increased the number of patients allocated to medical therapy at the time of angiography (22.7% vs 13.2%; $P=.02$). A similar relationship was seen at 1 year, although this did not achieve statistical significance.

The rate of MACEs at 1 year was similar in both arms (log rank $P=.79$). The rates of procedure-related type 4 MIs and spontaneous MIs were similar in both arms; however, there was evidence that procedure-related type 4 MIs were greater in the FFR-guided arm compared with the angiography-guided arm ($P=.12$).

In conclusion, Prof Berry stated that the data from the FAMOUS NSTEMI trial suggest that FFR is feasible and safe and that the results can influence clinical decision making for patients with NSTEMI. However, Prof Berry noted that a larger trial is needed to further evaluate the clinical outcomes and cost-effectiveness of FFR-guided management of patients with NSTEMI.

STABILITY: Darapladib and Lp-PLA$_2$ Levels in Treatment of Atherosclerosis

Written by Brian Hoyle

The Stability of Atherosclerotic Plaque by Initiation of Darapladib Therapy trial [STABILITY; NCT00799903] showed that darapladib, an oral inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$), compared with placebo, did not significantly reduce the composite primary end point of cardiovascular (CV) death, myocardial infarction (MI), and stroke (HR, 0.94; 95% CI, 0.85 to 1.03; $P=.20$) in 15 828 patients with stable coronary heart disease (CHD) on optimal medical therapy [White HD et al. *N Engl J Med.* 2014]. The mean follow-up duration was 3.7 years. The secondary end point of major coronary events (CHD death, MI, and urgent coronary revascularization) was significantly reduced with treatment versus placebo (HR, 0.90; 95% CI, 0.82 to 1.00; $P=.045$).

Lars Wallentin, MD, PhD, Uppsala Clinical Research Center, Uppsala, Sweden, presented data from a predefined analysis of STABILITY designed to examine factors that contribute to high levels of Lp-PLA$_2$ activity, whether its activity predicted outcomes or identified patients who would have a greater benefit with darapladib, and whether darapladib would provide persistent, long-term reduction of Lp-PLA$_2$ activity.

For this analysis, blood samples were collected at baseline from 14 500 patients; of these, samples were also collected at all follow-up visits (months 1, 3, 6, and 18 and end of treatment) in 100 patients. The mean activity level of Lp-PLA$_2$ was 172 nmol/min/mL, with a normal distribution in relation to baseline demographics. The patients were evenly divided by tertiles of Lp-PLA$_2$ activity (tertile 1, ≤153.6 nmol/min/mL; tertile 2, 153.7–192.5 nmol/min/mL; tertile 3, >192.5 nmol/min/mL).

The baseline characteristics and biomarkers that increased or decreased Lp-PLA$_2$ activity on multivariate analysis are shown in Table 1. In the subset of 100 patients, there was a 65% relative risk reduction in Lp-PLA$_2$ activity with darapladib that was seen 1 month after treatment began and persisted through the end of follow-up.

Table 1. Effect of Baseline Characteristics and Biomarkers on Lp-PLA$_2$ Activity on Multivariate Analysis

Variable	Effect Tested	Change in Mean Lp-PLA$_2$	*P* Value
LDL-C, mmol/L	≥2.58 vs <1.80	+60.3	<.001
	1.80–2.58 vs <1.80	+27.3	<.001
Gender	Male vs female	+25.5	<.001
Race	Asian vs white	−23.2	<.001
HDL-C <1.03 mmol/L	Yes vs no	+17.8	<.001
Geographic region	East Europe/West Europe/South America vs North America	−15/−20/−11	<.001
Smoker	Yes vs no	+7.6	<.001
Age, y	≥75 vs <65	+4.1	<.001
Hs-CRP, mg/L	>1.0 vs <1.0	+2.5	.002
Renal dysfunction	Yes vs no	+2.2	.005
Diabetes	Yes vs no	−5.5	<.001
Statin	Yes vs no	−9.7	<.001
P2Y$_{12}$ inhibitor	Yes vs no	−2.1	<.004

HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$.

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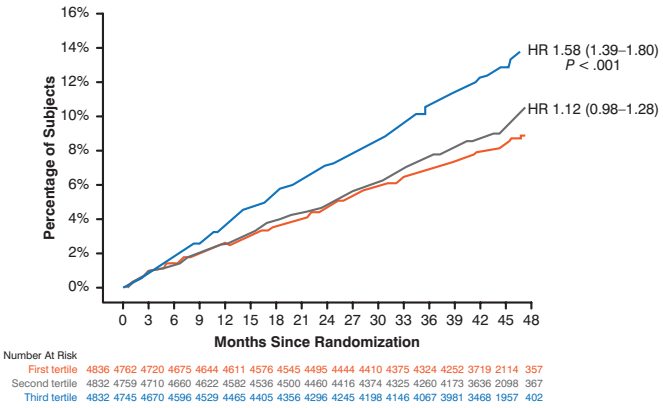
For the primary end point, the baseline level of Lp-PLA$_2$ activity predicted an increased risk for events, with a significant increase in tertile 3 versus tertile 1 (P<.001) and a nonsignificant (NS) increase in tertile 2 versus tertile 1 (Figure 1). A similar prognostic effect was seen for the secondary end point of major coronary events for tertile 3 versus tertile 1 (HR, 1.52; 95% CI, 1.34 to 1.73; P<.001) and tertile 2 versus tertile 1 (HR, 1.12; 95% CI, 0.97 to 1.28; P=NS).

No relation was found between treatment with darapladib and the composite primary or secondary outcomes in any tertile of Lp-PLA$_2$ activity (Table 2).

In addition to traditional risk factors that increased the risk for a primary outcome event, Lp-PLA$_2$ activity increased this risk (tertile 3 vs tertile 1; HR, 1.45; 95% CI, 1.25 to 1.69; P<.001). Darapladib versus placebo treatment did not influence the risk for the primary outcome (HR, 0.92; 95% CI, 0.83 to 1.03; P=.14).

Figure 1. Lp-PLA$_2$ Activity in Relation to Primary Outcome



CV, cardiovascular; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; MI, myocardial infarction.

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Table 2. Treatment Outcomes in Relation to Lp-PLA$_2$ Activity

Variable	Placebo (n = 7904)	Darapladib (n = 7924)	HR (95% CI)	Interaction *P* Value
CV death, MI, stroke				.526
Tertile 1	8.7%	7.7%	0.88 (0.73 to 1.08)	
Tertile 2	9.2%	9.1%	1.00 (0.83 to 1.20)	
Tertile 3	13.4%	11.7%	0.87 (0.74 to 1.02)	
Major coronary event				.748
Tertile 1	8.4%	7.8%	0.93 (0.76 to 1.14)	
Tertile 2	9.8%	8.3%	0.84 (0.70 to 1.02)	
Tertile 3	12.8%	11.1%	0.87 (0.73 to 1.02)	

CV, cardiovascular; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; MI, myocardial infarction.

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This analysis of the STABILITY study showed that Lp-PLA$_2$ activity is an independent predictor of CV events, but its baseline activity did not predict the effect of darapladib on coronary events.

Further evaluation is needed to determine the value of measuring Lp-PLA$_2$ activity to predict CV risk in the absence of an indication for a specific treatment, stated Prof Wallentin.