Darapladib effect on circulating high sensitive troponin in patients with acute coronary syndromes

Héctor M. García-García[a,b,*,1], Rohit M. Oemrawsingh[a,1], Salvatore Brugaletta[a,c,1], Pascal Vranckx[d,1], Jennifer Shannon[e,1], Richard Davies[f,1], Eric Boersma[a,1], Patrick W. Serruys[a,1]

[a] Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands; [b] Cardialysis, Rotterdam, The Netherlands; [c] Thorax Institute, Department of Cardiology, Hospital Clinic, Barcelona, Spain; [d] Department of Cardiac Intensive Care and Interventional Cardiology, Hartcentrum Hasselt, Hasselt, Belgium; [e] GlaxoSmithKline, Research Triangle Park, NC, USA; [f] GlaxoSmithKline, Philadelphia, PA, USA

[1] These authors contributed equally.

ABSTRACT

Objectives: We compared the incidence of late increase in hs-cTnI between ACS and non-ACS patients treated with standard of care with or without darapladib.

Methods: A total of 323 (161 ACS and 162 non-ACS patients) were included. High sensitivity troponin I was measured at baseline and at 4, 13, 26 and 52 weeks.

Results: ACS patients had statistically higher hs-cTnI values during longer term follow-up at which these patients were no longer in the acute setting of myocardial ischemia, but were regarded to have stable CAD (mean hsTnI value in ACS patients: 1.180 versus 0.886 ng/L in non-ACS patients, $p = 0.02$). Multivariate logistic regression revealed three predictors of any 2-fold increase in hs-cTnI levels compared to the previous visit when interactions were not considered. Treatment with darapladib (adjusted OR 0.53; 95% CI: 0.30-0.92) and initial presentation with ACS (adjusted OR 0.42; 95% CI: 0.23-0.77) were associated with less frequent occurrence of a 2-fold increase in hs-cTnI levels. In contrast, diabetes was associated with a higher incidence of 2-fold increases in hs-cTnI levels (adjusted OR 2.20; 95% CI: 1.04-4.64). Logistic regression to predict any 2-fold increase in hs-cTnI by ACS status showed that in the ACS group, treatment with darapladib decreased the risk of elevation of hs-cTnI (OR 0.219; 95% CI: 0.087, 0.553, $p = 0.0013$).

Conclusion: In patients with ACS, treatment with darapladib is associated with less increase in cardiac troponin I compared to standard of care alone. This beneficial effect may be associated with darapladib's capability of reducing necrotic core in coronary plaques.

1. INTRODUCTION

Myocardial damage after either temporal or permanent suppression of the coronary blood flow has been reported to be prognostically relevant for patients. [1] Early detection of myocardial damage is highly encouraged to better assess risk of a new clinical event. Several markers of myocardial damage have been described (i.e creatinine kinase and cardiac troponin – cTn) as means of diagnosis of myocardial infarction [2]. Elevations of serum cardiac troponin levels above the detection limit have been associated with increased mortality and recurrent ischemic events in patients with acute coronary syndrome (ACS) and also in subjects without clinical evidence of cardiovascular disease [3-5]. As a consequence, the possibility that circulating troponin levels below the conventional detection limits might lead to further risk stratification for adverse cardiovascular outcome, led to the development of so-called high-sensitivity troponin (hs-cTn) assays. A post-hoc analysis of the PEACE trial demonstrated that, in patients with stable coronary artery disease (CAD), cardiac troponin T concentrations as measured with a highly sensitive assay were significantly associated with increased incidence of cardiovascular mortality and heart failure after adjustment for other independent prognostic indicators [6].

In addition, the serial assessment of c-Tn could also be a prognostically relevant marker of late events and its late suppression could become a therapeutical target.

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is a circulating enzyme bound predominantly to apoB-containing lipoproteins, and highly expressed in the necrotic core of atherosclerotic lesions [7,8]. Lp-PLA_2 rapidly degrades oxidatively modified phospholipids in LDL-c leading to formation of proinflammatory and cytotoxic products [9–11]. Because enhanced cell death and impaired clearance of apoptotic bodies are thought to be key mechanisms for necrotic core expansion [12], Lp-PLA_2 inhibition may favorably affect rupture-prone lesions.

Darapladib (GlaxoSmithKline, Philadelphia PA) which is a Lp- PLA_2 inhibitor has been studied in the Integrated Biomarkers and Imaging Study-2 trial (NCT00268996) [13]. One of the key findings was that Lp-PLA_2 inhibition with darapladib interferes with necrotic core expansion.

The primary objective of this exploratory post-hoc analysis is to compare hs troponin I levels between darapladib and placebo subjects in the IBIS 2 study, and to describe the differences in patterns of troponin levels between patients presenting with ACS and those presenting with non-ACS as measured longitudinally with a high sensitivity immunoassay during one-year follow-up.

2. METHODS

2.1. Study design

The Integrated Biomarkers and Imaging Study-2 trial has been published elsewhere [13]. Briefly, it was an international, multicenter, randomized, double blind, placebo-controlled study in patients with confirmed CHD. Institutional review boards at each center approved the protocol, and patients provided written informed consent.

2.2. Patient population

Patients 18 years of age or older undergoing cardiac catheterization for acute coronary syndrome (ACS) or non-ACS were eligible.

In the protocol, ACS is defined as: patients with enzymatic evidence of myocardial necrosis [chest pain or chest pain equivalent lasting greater than or equal to 20 min within past 72 h with elevated pre-catheterization levels of troponin I or T (i.e. >99th percentile of reference control group)]. Non-ACS is defined as: patients with coronary heart disease other than troponin-positive acute coronary syndrome.

Randomization allocated patients into darapladib vs. placebo groups and was stratified according to ACS status and center. Key exclusion criteria were planned surgical revascularization, stroke in the past 6 months, chronic hepatic disorder or abnormal ALT, bilirubin (ALT >2.5 or bilirubin >1.5 upper limit of normal), serum creatinine >2.0 mg/dL, blood pressure >160/100 mm Hg, poorly controlled diabetes mellitus (HbA_{1c} >10%), severe heart failure or left ventricular ejection fraction <30%, and current life-threatening condition. Patients were ineligible if angiography demonstrated left main coronary stenosis >50% or coronary anatomy was inappropriate for IVUS.

2.3. IVUS imaging

The ECG-gated IVUS-RF acquisition was performed using EagleEye catheter (20 MHz) at pullback speed of 0.5 mm/s as described. The quantitative IVUS analysis was performed by the Core Imaging Laboratory (Cardialysis, Rotterdam, The Netherlands) using customized software (pcVH 2.1, Volcano Therapeutics). After selection of the region of interest in the nonculprit vessel, vessel and lumen area data were obtained for every cross-section throughout the region of interest by semiautomatic planimetry of the leading edges of the luminal and external elastic membrane borders. Necrotic core was identified with autoregressive classification system that showed sensitivity and specificity of 92% and 97% for detection of necrotic core, respectively. The intra- and interobserver variability of necrotic core measurements: the mean absolute difference for necrotic core area was 0.01 mm^2 (SD 0.06) for the intraobserver and 0.02 mm^2 (SD 0.08) for the interobserver variability, respectively.

2.4. Biomarkers

Plasma samples were drawn at baseline (prior to the cardiac catheterization), weeks 4, 13, 26, 52 and at the follow-up visit. Cardiac troponin I was measured using the ultrasensitive Singulex Erenna System (Singulex Inc., Berkeley, CA, USA) which is an ultrasensitive flow-based immunoassay that uses single-molecule counting [14]. It has been standardized to National Institute of Standards and Technology Material and validated with a lower limit of detection of 0.0002 ng/mL (0.20 ng/L). The inter-assay coefficient of variation (CV) is 10% at 0.91 ng/L, and the 99th percentile in a healthy control population is 9 ng/L [15].

2.5. Statistical analysis

Baseline characteristics are reported as mean values (+/– standard deviation) for continuous variables, whereas discrete variables are presented in terms of frequencies and percentages.

Summary statistics were calculated for the natural log of the area under the curve (AUC) high sensitive troponin I, weighted by day, excluding baseline and week 4 (thus from week 13 to week 52). Treatment group comparisons were based on the general linear model with terms for treatment group and ACS status. Pearson correlations between the change from baseline to week 52 in necrotic core volume and the weighted area under the curve of hs troponin (excluding the baseline and week 4 visits) were calculated.

The proportions of subjects with 2-,3- and 4- fold increases in hs-cTnI from the previous visit were examined by treatment group and ACS status. These proportions were examined excluding the baseline value and the week 4 hs-cTnI values because ACS subjects would be expected to have high hs-cTnI at entry into the study. Thus, solely the late increase/suppression (>13 weeks) was explored.

Logistic regression modeling was performed to predict any 2- fold increase in hs-cTnI from the previous visit. The following terms were included in the model: treatment group, ACS status, treatment group by ACS status interaction, age, smoking status, presence of a stent at baseline, previous MI, hypertension, HDL <1.03, LDL <1.81 mmol/L, and diabetes. In this model, only treatment group, ACS status, and the treatment group by ACS status interaction were significant at the 5% level. Due to the significant interaction between treatment group and ACS status, odds ratios for treatment group are presented within ACS status.

All statistical tests were two-sided with a type I error level of 0.05. Analyses were performed with SAS version 9.1.

3. RESULTS

A total of 323 patients constituted the Intent-to-Treat population (patients who took at least 1 dose), 161 patients had an acute coronary syndrome (ACS) and 162 had a non-ACS. At baseline, 252 patients had at least one stenting procedure in a non-study vessel. Table 1 contains the baseline characteristics of patients in the ITT population.

Table 1. Baseline characteristics

Clinical characteristics	Placebo (*n* = 151)	Darapladib (*n* = 172)
Age (y)	57.3 ± 10.9	59.4 ± 9.8
Males (*n*, %)	126 (83)	140 (81)
Body-mass index (kg/m^2)	27.8 ± 3.8	27.5 ± 4.0
Diabetes mellitus (*n*, %)	22 (15)	22 (13)
Hypertension (*n*, %)	89 (59)	115 (67)
Low HDL cholesterol (<40 mg/dL) (n, %)	40 (26)	45 (26)
Hypercholesterolemia (*n*, %)	95 (63)	108 (63)
Current smoker (*n*, %)	57 (38)	64 (37)
Prior medical history (*n*, %)		
Prior myocardial infarction	49 (32)	51 (29)
Prior coronary revascularization	47 (31)	50 (29)
Peripheral artery disease	7 (5)	17 (10)
Prior stroke	3 (2)	4 (2)
Index hospitalization (*n*, %)		
PCI during index hospitalization	122 (81)	130 (76)
ACS	74 (49)	87 (51)
STEMI	35 (23)	40 (23)
Non-STEMI	39 (26)	47 (27)
Cardiovascular medications at randomization (*n*, %)		
Aspirin	138 (91)	149 (87)
Clopidogrel or ticlopidine	122 (81)	136 (79)
Any antiplatelet medication	150 (>99)	170 (99)
ACE inhibitors or ARBs	88 (58)	101 (59)
Beta-blockers	119 (79)	138 (80)
Statins	134 (89)	157 (91)
Laboratory values		
Cholesterol (mg/dL)		
Total	187.3 ± 47.6	182.3 ± 43.2
LDL	108.2 ± 41.4	103.6 ± 37.4
HDL	46.8 ± 11.2	48.0 ± 12.4

Table 1. *(continued)*

Clinical characteristics	Placebo (n = 151)	Darapladib (n = 172)
Triglycerides (mg/dL)		
Median	141	136
IQR	97-202	96-193
hsC-reactive protein (mg/L)		
Geometric mean	2.4	2.4
95% CI	1.9, 3.1	1.9, 3.0
Lp-PLA_2 activity ($\mu mol/min^{-1}/L^{-1}$)[a]		
Geometric mean	159	160
95% CI	152, 167	153, 167
Blood pressure		
Systolic-mm Hg	125.7 ± 16.9	128.0 ± 16.1
Diastolic-mm Hg	75.2 ± 10.1	75.6 ± 9.9
Study vessel[b]-no. (%)		
LAD	44 (36)	56 (39)
LCX	32 (26)	37 (26)
RCA	45 (37)	51 (35)
Diameter stenosis[c] (%)	28.0 (10.5)	26.6 (10.3)
Mean lumen diameter[c] (mm)	2.9 ± 0.5	3.0 ± 0.6

Values are presented as mean ± SD unless otherwise specified; to convert to mmol/L multiply values of cholesterol by 0.02586 and triglycerides by 0.0113; PCI, percutaneous coronary intervention; ACS, acute coronary syndromes.

[a] Plasma Lp-PLA2 activity was measured by a colorimetric method with an intraassay precision of 1.7% and interassay precision of 4.8%.

[b] Imaging evaluable population: placebo 121 patients; darapladib 146 patients.

[c] Quantitative coronary angiography: placebo 121 patients; darapladib 144 patients.

Higher high sensitivity troponin AUCs were observed in patients presenting with an ACS as compared to those without (mean hsTnI values: 3.7 ± 1.8 versus 1.1 ± 0.1.2 ng/L, $p < 0.001$), when measurements at all timepoints were taken into account. (Fig. 1) ACS patients also had statistically higher hs-TnI values during longer term follow-up, at which these patients were no longer in the acute setting of myocardial ischemia (>4 weeks), but were regarded to have stable CAD (mean hsTnI value in ACS patients: 1.180 versus 0.886 ng/L in non-ACS patients, $p < 0.02$).

3.1. High-sensitivity troponin I levels over time

When hsTnI measurements at all timepoints were considered, 18% of ACS subjects vs. 33% of non-ACS subjects had a 2-fold increase in hsTnI levels compared to the previous sample collection. As mentioned earlier, hsTnI levels are known to be elevated at

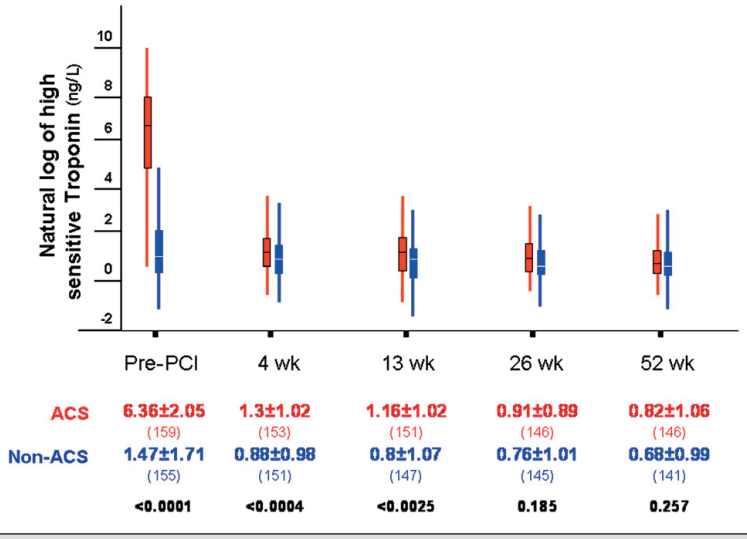

Fig. 1. High sensitivity troponin I levels by visit and acute coronary syndrome (ACS) status.

baseline in the ACS patients, followed by a period of normalization (i.e. decrease instead of increase). A second model was therefore used to assess whether the lower incidence of 2-fold increases in hsTnI levels would persist in the ACS patients when only changes between visits from week 13 onwards were evaluated. This also demonstrated that 2-fold increases in hsTnI levels during follow-up occurred less frequently in ACS patients (15% of ACS subjects vs. 26% of non-ACS subjects) (Online Supplement Table 1).

Multivariate logistic regression revealed three predictors of any 2-fold increase in hsTnI levels compared to the previous visit. After adjustment for clinically relevant variables, treatment with darapladib (adjusted OR 0.53; 95% CI: 0.30-0.92) and initial presentation with ACS (adjusted OR 0.42; 95% CI: 0.23-0.77) were associated with less frequent occurrence of a 2-fold increase in hsTnI levels. In contrast, diabetes was associated with a higher incidence of 2-fold increases in hsTnI levels (adjusted OR 2.20; 95% CI: 1.04-4.64). No other clinical baseline characteristic was significantly associated with hsTnI increases, either in univariate or multivariate analyses. (Table 2) However, due to the presence of a significant treatment by ACS status interaction, a logistic regression model to predict any 2-fold increase in troponin by ACS status was performed. In the ACS group, treatment with darapladib reduced the risk of hs-TnI elevation (OR 0.219; 95% CI: 0.087, 0.553, $p = 0.0013$) (Table 3).

No significant correlations were found between change in necrotic core volume and the weighted area under the curve of hscTnI in the overall study population or in subgroups of ACS-status or treatment allocation (Online Supplement Table 2).

Table 2. Details of logistic regression modeling to predict any 2-fold increase in troponin from the previous visit full model (no interaction terms).

	Estimate	*p*-value	OR (95% CI)
Treatment group (darapladib vs placebo)	−0.32	0.024	0.526 (0.301, 0.919)
ACS status (ACS vs non-ACS)	−0.43	0.005	0.420 (0.230, 0.765)
Age	0.005	0.745	1.005 (0.976, 1.034)
Smoker (yes vs no)	−0.03	0.857	0.944 (0.502, 1.773)
Stent at baseline (yes vs no)	−0.25	0.138	0.609 (0.316, 1.173)
Previous MI (yes vs no)	−0.12	0.423	0.780 (0.425, 1.433)
Hypertension (yes vs no)	−0.14	0.366	0.763 (0.424, 1.373)
HDL (<1.03 vs >=1.03)	0.13	0.447	1.305 (0.657, 2.595)
LDL (<1.81 vs >=1.81)	−0.21	0.157	0.663 (0.375, 1.172)
Diabetes (yes vs no)	0.40	0.038	2.200 (1.044, 4.636)

Table 3. Details of logistic regression modeling to predict any 2-fold increase in troponin from the previous visit model by ACS status.

	Estimate	*p*-value	OR (95% CI)
ACS subgroup ($n = 159$)			
Treatment group (darapladib vs placebo)	−0.7583	0.0013	0.219 (0.087, 0.553)
Non-ACS subgroup ($n = 159$)			
Treatment group (darapladib vs placebo)	−0.1228	0.4683	0.782 (0.403, 1.519)

Additionally, examination of the incidence of clinical events in those patients who had a 2-fold increase of hs-cTnI from the previous visit ($n = 80$), showed that 27.5% of these patients had at least one MACE (cardiovascular death, MI, stroke, coronary revascularization) event. (Table 4). The timing of the determination of hsTnI and MACE event is reported in the Online Supplement Table 3. A 2-fold increase in hs-cTnI was not related to the date of the MACE events in the majority of events.

4. DISCUSSION

In this exploratory post-hoc analysis of the IBIS 2 trial, there was a marked suppression of the late elevation (>13 weeks) of high sensitivity troponin I in patients treated with darapladib. This was more apparent in patients that had ACS at the time of randomization to darapladib, when compared with non-ACS patients.

In a substudy from the FRISC-II trial(5), persistent minute elevation (levels >0.01 µg/L) of cTnI, predicted mortality during long-term follow-up. In our study, an association with mortality cannot be done due to the nature of the IBIS study (i.e. imaging vs. outcome trial). Nevertheless, it is expected that treatment with darapladib may have an effect

Table 4. **Summary of subjects with a MACE event and a two-fold increase in troponin in IBIS-2.**	
Subjects with MACE	58/323 (18%)
Death	0
Myocardial infarction	11
Stroke	2
Coronary revascularization	57
Subjects with 2 MACE	13
Subjects with a two-fold increase in troponin from the previous visit	80/323 (25%)
Subjects with a two-fold increase in troponin from the previous visit:	
And a MACE event[a]	22/80 (27.5%)
And no MACE event	58/80 (72.5%)

Note: MACE includes death, myocardial infarction, stroke, and coronary revascularization.
[a] Includes subjects with both a MACE and a two-fold troponin increase at any time. Troponin increase may have been before or after MACE.

on clinical outcomes not only by preventing late elevations of troponin (this report), but also for halting progression of necrotic core assessed by IVUS-virtual histology [13]. One can hypothesize that the late elevation of cardiac TnI is caused by several factors: 1. increased demand ischemia due to volume and pressure overload that can occur in patients with high prevalence of co-morbidities (congestive heart failure, left ventricular hypertrophy, diabetes mellitus, and chronic kidney disease) [16,17]. In the context of a randomized control trial such as IBIS 2, the distribution of these diseases is expected to be equal in both treatment arms; 2. Apoptosis of cardiomyocytes could be another explanation for measurable troponin levels in the long term after index procedure. This phenomenon is specific for patients who had an ACS in whom the apoptotic processes persist for months after an AMI. [18]. In humans, circulating Lp-PLA2 is bound predominantly to LDL. Lp-PLA2 acts on oxidized phospholipids within modified LDL to generate lysophosphatidylcholine and oxidized fatty acids. Both products have proinflammatory effects that contribute to the initiation and progression of atheroma, in large part, through the recruitment and activation of monocyte-macrophages. The products of Lp-PLA2 activity can also induce apoptosis among macrophages. Although the exact mechanism has not been yet completely elucidated, monocytes activated by transient hypoxia protect cardiomyocytes during hypoxia and re-oxygenation through expression of CD11b receptors [19]. Thus, this process can be affected by darapladib by preventing the formation of lysophosphatidylcholine and oxidized fatty acids, thereby avoiding monocyte apoptosis and therefore protecting myocytes; 3. Late TnI increase is marked in non-ACS patients treated with and without darapladib, and in ACS patients treated with standard of care, but not in those ACS patients treated with darapladib. Whether ACS patients receiving darapladib represent a subset of patients with enhanced

reduction in major adverse cardiovascular events is currently being investigated in the SOLID-TIMI 52 trial [20]. As mentioned above, a possible explanation is that ACS patients exhibit a more significant inflammatory process post-ACS with activation of monocytes and macrophages, as compared with non-ACS patients. In such environment darapladib is hypothesized to play a major role, reducing the apoptosis of these cells with eventual protection of cardiomyocytes. 4. Asymptomatic coronary plaque ruptures with subsequent microembolization of the resulting thrombus may also represent a cause of late increase in hs-cTnI. It has been reported that patients with ACS have additional asymptomatic ruptured plaques beyond the culprit lesions, showing the multifocal nature of the disease [21]. The size of the necrotic core is one important determinant for the rupture of those plaques [22]. In the IBIS 2, the progression of the expansion of necrotic core was halted by darapladib [13]. In this subset of patients (i.e. ACS), darapladib also decreases the incidence of a two-fold increase in high sensitive troponin; 5. Another simpler reason for the late increase in cTn is the occurrence of thrombotic events in this population. In this report, the 2-fold increase in hsTnI occurred in 25% (80/323) of the total population, and of these patients only 27.5% (22/80) had at least a MACE event. The raise in high sensitive troponin was most of the time unrelated to the time of the event (Online Supplement Table 3).

4.1. Study limitations

This exploratory post-hoc subanalysis has several limitations: 1. blood samples were not processed at short-term which might have caused increase variability in the assessment of the high sensitivity troponin I as it has been described [23,24]; 2. this report includes the total population included in IBIS 2 study but the sample size is too small to investigate a potential relationship between elevations in high sensitivity troponin and clinical events and; 3. likewise, the observations regarding the effect of darapladib on levels of high sensitive troponin are hypothesis-generating and require further exploration.

5. CONCLUSIONS

In patients with acute coronary syndrome, addition of darapladib to standard of care therapy is associated with a lower incidence of a two-fold increase in cardiac troponin I over time when compared to standard of care alone. This beneficial effect may be associated with darapladib's capability of reducing necrotic core in coronary plaques, and thus warrants further study.

APPENDIX

Core Laboratories: imaging (Cardialysis, Rotterdam, The Netherlands).
Participating Centers (number of patients enrolled): Austria: Hanusch Krankenhaus, Georg Gaul [6]. Belgium: Centre Hospitalier Universitaire Sart-Tilman, Victor Legrand [10]; ZNA Campus Middelheim, Stefan Verheye (25); Cardiovascular Center, Aalst, William Wijns [14]. Czech Republic: V_seobecná Fakultní Nemocnice, Michael Aschermann [23]. Denmark: Skejby University Hospital, Hans Erik Bøtker [18]. Germany: West German Heart Center, Raimund Erbel [7]; Kerckhoff Klinik, Christian Hamm [7]; Universitätsklinikum Heidelberg, Stefan Hardt, Helmut Kücherer (1); Universitätsklinikum München, Volker Klauss [14], Universitätsklinikum Ulm, Wolfgang Koenig [9]; Segeberger Kliniken, Gert Richardt [3]. The Netherlands: Medisch Spectrum Twente, Clemens von Birgelen [14]; Medisch Centrum Leeuwarden, Adrianus Johannes van Boven [12]; Catharina Hospital and Catherine R&D, Herman Rolf Michels [14], Erasmus Medical Center, Patrick Serruys [20]; Medisch Centrum Rijnmond Zuid, Pieter Smits [11]. Norway: Haukeland Sykehus, Oyvind Bleie [20]. Poland: Upper Silesian Heart Center, Pawel Buszman (40); Szpital Uniwersytecki, Dariusz Dudek [19]. Spain: Hospital Marques de Valdecilla, Thierry Colman [9]; Hospital Clinico San Carlos, Carlos Macaya [9]. Switzerland: Kantonsspital Luzern, Paul Erne (25).

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.atherosclerosis.2012.06.064.

Disclosures

Jennifer Shannon and Rich Davies are employees of GlaxoSmithKline. The rest of the authors declare no conflicts of interest relevant to the content of this paper.

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SUPPLEMENTARY MATERIAL

Table 1. Summary of subjects with an increase in high sensitive troponin from the previous visit at weeks 26, 52 by acute coronary syndrome (ACS) Status

	Placebo		Darapladib		Total	
ACS	**71**		**83**		**154**	
2-Fold	17	24%	6	7%	23	15%
3-Fold	11	15%	3	4%	14	9%
4-Fold	6	8%	3	4%	9	6%
Non-ACS	**73**		**80**		**153**	
2-Fold	20	27%	20	25%	40	26%
3-Fold	7	10%	15	19%	22	14%
4-Fold	6	8%	8	10%	14	9%

Table 2. Correlation between the Change from Baseline to Week 52 in Necrotic Core Volume and Weighted Area Under the Curve of hs Troponin (Excluding the Baseline and Week 4 Visits)

	n	Pearson Correlation
Overall	239	0.109 (p=0.09)
Placebo Treatment Group	110	0.115 (p=0.23)
Darapladib Treatment Group	129	0.133 (p=0.13)
ACS	118	0.172 (p=0.06)
Placebo Treatment Group	56	0.182 (p=0.18)
Darapladib Treatment Group	62	0.249 (p=0.05)
Non-ACS	121	–0.048 (p=0.60)
Placebo Treatment Group	54	–0.071 (p=0.60)
Darapladib Treatment Group	67	–0.131 (p=0.29)

ACS, acute coronary syndrome; hs, high sensitive

Table 3. Summary of Subjects with a MACE event and a two-fold increase in Troponin in IBIS-2

Subjects with MACE and two-fold increase in troponin	22
Time from first MACE to two-fold increase in troponin:	
Increase prior to MACE	
>=100 days prior	4
>50 to <100 days prior	2
... 1 day prior	1
Two-fold increase followed first MACE or same day as MACE	
Same day as MACE	3
<=10 days after MACE	2
>10-<30 days after MACE	7
… >100 days after MACE	3

Note: MACE includes death, myocardial infarction, stroke, and coronary revascularization