ORIGINAL RESEARCH

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Osteoprotegerin Is Associated With Major Bleeding But Not With Cardiovascular Outcomes in Patients With Acute Coronary Syndromes: Insights From the PLATO (Platelet Inhibition and Patient Outcomes) Trial

Thor Ueland, PhD; Axel Åkerblom, MD, PhD; Tatevik Ghukasyan, MSc; Annika E. Michelsen, PhD; Pål Aukrust, MD, PhD; Richard C. Becker, MD; Maria Bertilsson, MSc; Anders Himmelmann, MD, PhD; Stefan K. James, MD, PhD; Agneta Siegbahn, MD, PhD; Robert F. Storey, MD, DM; Frederic Kontny, MD, PhD; Lars Wallentin, MD, PhD; for the PLATO (Platelet Inhibition and Patient Outcomes) Trial Investigators*

***Background*—**Elevated levels of osteoprotegerin, a secreted tumor necrosis factor–related molecule, might be associated with adverse outcomes in patients with coronary artery disease. We measured plasma osteoprotegerin concentrations on hospital admission, at discharge, and at 1 and 6 months after discharge in a predefined subset (n=5135) of patients with acute coronary syndromes in the PLATO (Platelet Inhibition and Patient Outcomes) trial.

***Methods and Results*—**The associations between osteoprotegerin and the composite end point of cardiovascular death, nonprocedural spontaneous myocardial infarction or stroke, and non–coronary artery bypass grafting major bleeding during 1 year of follow-up were assessed by Cox proportional hazards models. Event rates of the composite end point per increasing quartile groups at baseline were 5.2%, 7.5%, 9.2%, and 11.9%. A 50% increase in osteoprotegerin level was associated with a hazard ratio (HR) of 1.31 (95% confidence interval [CI], 1.21–1.42) for the composite end point but was not significant in adjusted analysis (ie, clinical characteristics and levels of C-reactive protein, troponin T, NT-proBNP [N-terminal pro-B-type natriuretic peptide], and growth differentiation factor-15). The corresponding rates of non–coronary artery bypass grafting major bleeding were 2.4%, 2.2%, 3.8%, and 7.2%, with an unadjusted HR of 1.52 (95% CI, 1.36–1.69), and a fully adjusted HR of 1.26 (95% CI, 1.09–1.46). The multivariable association between the osteoprotegerin concentrations and the primary end point after 1 month resulted in an HR of 1.09 (95% CI, 0.89–1.33); for major bleeding after 1 month, the HR was 1.33 (95% CI, 0.91–1.96).

***Conclusions*—**In patients with acute coronary syndrome treated with dual antiplatelet therapy, osteoprotegerin was an independent marker of major bleeding but not of ischemic cardiovascular events. Thus, high osteoprotegerin levels may be useful in increasing awareness of increased bleeding risk in patients with acute coronary syndrome receiving antithrombotic therapy.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00391872. **(*J Am Heart Assoc*. 2018;7: e007009. DOI: 10.1161/JAHA.117.007009.)**

Key Words: acute coronary syndrome • bleeding • osteoprotegerin • prognosis

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From the Research Institute of Internal Medicine, The National Hospital (T.U., A.E.M., P.A.) and K. G. Jebsen Inflammatory Research Center (T.U., P.A.), University of Oslo, Norway; K. G. Jebsen–Thrombosis Research and Expertise Center, University of Tromsø, Norway (T.U., P.A.); Department of Medical Sciences, Cardiology (A.Å., S.K.J., L.W.), Uppsala Clinical Research Center (A.Å., T.G., M.B., S.K.J., A.S., L.W.), and Department of Medical Sciences, Clinical Chemistry (A.S.), Uppsala University, Uppsala, Sweden; Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital, Rikshospitalet, Oslo, Norway (P.A.); Division of Cardiovascular Health and Disease, Heart, Lung and Vascular Institute, University of Cincinnati College of Medicine, Cincinnati, OH (R.C.B.); AstraZeneca Research and Development, Gothenburg, Sweden (A.H.); Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, United Kingdom (R.F.S.); Department of Cardiology, Stavanger University Hospital, Stavanger, Norway (F.K.); and Drammen Heart Center, Drammen, Norway (F.K.).

An accompanying Appendix S1 is available at http://jaha.ahajournals.org/content/7/2/e007009/DC1/embed/inline-supplementary-material-1.pdf

*A complete list of the PLATO (Platelet Inhibition and Patient Outcomes) trial members is given in Appendix S1.

Correspondence to: Thor Ueland, PhD, Research Institute of Internal Medicine, Oslo University Hospital, Rikshospitalet, P.B. 4950 Nydalen, 0424 Oslo, Norway. E-mail: thor.ueland@medisin.uio.no

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Clinical Perspective

What Is New?

- In patients with acute coronary syndrome treated with dual antiplatelet therapy, osteoprotegerin was an independent marker of major bleeding after adjustment for clinical risk factors and multiple biomarkers prognostic for both cardiovascular events and bleeding, but it was not a marker of ischemic cardiovascular events.

What Are the Clinical Implications?

- High osteoprotegerin levels may be useful in increasing awareness of increased bleeding risk in patients with acute coronary syndrome receiving antithrombotic therapy.

Osteoprotegerin, a member of the tumor necrosis factor receptor superfamily, exerts pleiotropic effects on bone metabolism, endocrine function, and vascular inflammation,[1] at least partly through acting as a decoy receptor for the receptor activator of nuclear factor-κB ligand.[1] Osteoprotegerin may colocalize with von Willebrand factor (vWF) in platelets and on endothelial cells and is rapidly released by inflammatory stimuli.[2–4] Furthermore, osteoprotegerin is expressed within the failing myocardium in both experimental and clinical heart failure,[5] and osteoprotegerin expression has been observed in thrombotic material obtained from the site of plaque rupture during myocardial infarction (MI).[6] Thus, osteoprotegerin seems to be a multifaceted mediator with relevance for vascular and atherosclerotic disorders, although details of its pathways of actions are still sparsely understood.[2–4]

Circulating biomarkers provide independent information on risk for adverse outcomes on top of established demographic and clinical variables in patients with acute coronary syndromes (ACSs).[7–11] In addition to the established natriuretic peptides and cardiac troponins, which have been extensively evaluated and shown to be suitable biomarkers for prognosis and/or risk stratification of ACS,[12,13] the recently characterized inflammatory marker, growth differentiation factor-15 (GDF-15), may also provide additional clinically useful prognostic information in ACS.[14] Also, cystatin C, a marker of kidney function, has recently gained increasing relevance as an independent marker of mortality in ACS.[15] Accordingly, we have recently shown that NT-proBNP (N-terminal pro-B-type natriuretic peptide),[9,10] high-sensitivity troponin T (hs-TnT),[9,10] GDF-15,[8–10] and cystatin C[7] display independent associations with cardiovascular outcomes, including cardiovascular death, in the PLATO (Platelet Inhibition and Patient Outcomes) trial. Therefore, they represent important adjustment variables for evaluating the independent contribution of new biomarkers to prognosis.

Elevated osteoprotegerin levels have similarly been associated with all-cause mortality[16,17] and cardiovascular outcomes, like MI[18] and heart failure,[19] in patients with established coronary artery disease or ACS. In addition to the potential modulatory role of osteoprotegerin on hemostasis through interactions with vWF, elevated circulating osteoprotegerin concentrations have been associated with increased risk of bleeding complications in patients with polycythemia vera,[4] a condition with increased risk of both thrombotic and hemorrhagic complications. Nonetheless, the clinical importance of osteoprotegerin as a risk factor of bleeding complications has never been reported in patients with ACS.[8]

The PLATO trial encompassed a broad ACS population and proved ticagrelor to be superior to clopidogrel in reducing the composite end point of cardiovascular mortality, MI, or stroke. There was no difference in the overall rates of major bleeding, but there was an increase in bleeding unrelated to coronary artery bypass grafting (CABG).[20,21] In the current PLATO trial substudy, we evaluated osteoprotegerin levels on hospital admission and during 6 months of follow-up after ACS, together with important prognostic biomarkers, in relation to the composite end point of cardiovascular death, spontaneous MI, and stroke as well as to major non–CABG-related bleeding.[20,21] Finally, we explored the changes over time in osteoprotegerin concentrations from admission through 6 months of follow-up.

Methods

Design and Study Population

The randomized placebo-controlled PLATO trial included a total of 18 624 patients with ACS.[20,21] The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The patients presented with either ST-segment–elevation (STE) ACS or non-STE ACS and were randomized to either clopidogrel or ticagrelor treatment in addition to optimal medical therapy, including aspirin, and optional invasive therapy.[20,21] The need for additional oral anticoagulant therapy (ie, triple therapy) after inclusion was a contraindication in the PLATO trial. Patients were recruited between October 11, 2006 and July 17, 2008, and were followed up for up to 12 months after ACS.

Venous blood samples were obtained from all patients at randomization as part of the main study. In addition, there was a predefined substudy with serial blood sampling conducted at selected sites aiming to obtain samples from 4000 patients at hospital discharge and after 1 month and from at least 3000 of these patients also at 6 months.[20,21] All patients at these selected sites were continuously invited to

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the substudy, and inclusion of new patients proceeded until it was estimated that at least 3000 patients would be available for blood sampling at 6 months. Patients with a blood sample at baseline and at least 1 additional blood sample during follow-up were eligible for inclusion in the current analyses. The overall aims of the biomarker substudy program have previously been published.[20,21] The study adhered to the Declaration of Helsinki, the research protocol was approved by national and institutional regulatory and ethics committees, and written informed consent was obtained from the patients.

End Point Definition and Follow-Up

The prespecified primary end point of the present substudy was the composite of cardiovascular death (defined as any cardiovascular cause of death, sudden death, or any death with no clear attributable noncardiovascular cause), spontaneous MI (defined as non–procedure-related, nonfatal, MI type 1[22]), or stroke within 1 year of follow-up.[20] The components of the composite end point were also evaluated separately. The secondary end point was PLATO-defined non-CABG major bleeding, defined as follows: bleeding that was fatal, bleeding that was intracranial, bleeding that required ≥2 U of blood transfusion, or bleeding with a decrease in hemoglobin of >5 g/dL[20] (but not if directly related to a CABG operation).[20] All end points in the PLATO trial were centrally adjudicated by an independent and blinded clinical events adjudication committee (A.Å. and S.K.J.), comprising cardiologists or neurologists, to subclassify causes of death and to subdivide types of MI, stroke, and bleeding events.[20,22]

Sampling and Laboratory Analysis

Baseline venous blood samples were obtained within 24 hours of admission, before the administration of study medication. The venous blood was centrifuged, and the plasma samples were locally frozen in aliquots and stored at −70°C in a central repository at Uppsala Biobank until biochemical analyses were performed. Osteoprotegerin concentrations were determined by enzyme-linked immunoassay (R&D Systems, Stillwater, MN), as previously described and validated.[23] Briefly, wells were coated overnight with monoclonal mouse anti-human osteoprotegerin antibody in sterile PBS. The standard was recombinant osteoprotegerin. Subsequent steps included biotinylated polyclonal goat anti-human osteoprotegerin, streptavidin horseradish peroxidase, and tetramethylbenzidine as substrate (ThermoFisher Scientific, By, MA). The mean recovery of 2 samples spiked with different concentrations of recombinant osteoprotegerin was 93%. The intra-assay and interassay coefficients of variation of osteoprotegerin in the present study were 2.6% and 6.0%, respectively. The sensitivity, defined as the mean±3 SDs of the zero standard, was calculated to be 15 pg/mL.

Hs-TnT, NT-proBNP, and cystatin C were determined with sandwich immunoassays on the Cobas Analytics e601 Immunoanalyzer (Roche Diagnostics, Mannheim, Germany). White blood cell (WBC) count and high-sensitivity C-reactive protein (hs-CRP) were analyzed at the UCR Laboratory (Uppsala, Sweden), with a spectrophotometric analysis (Architect; Abbott, IL). GDF-15 was measured with a precommercial assay (Roche Diagnostics) using a monoclonal mouse antibody for capture and a monoclonal mouse antibody fragment for detection in a sandwich assay format. The results of these analyses in relation to outcomes and effects of study treatment have previously been reported.[8–10]

Statistical Analysis

Osteoprotegerin concentrations at all time points are presented as medians with interquartile ranges (IQRs). The changes of osteoprotegerin concentration over time were tested by Wilcoxon signed-rank test. Baseline characteristics are presented by osteoprotegerin quartile groups. Categorical baseline variables are presented as frequencies and percentages and compared by quartile groups of osteoprotegerin using χ^2 tests. Continuous baseline variables are presented as medians and IQRs and compared by quartile groups of osteoprotegerin using the Kruskal-Wallis test. Natural logarithmic transformations were performed for biomarker levels to obtain an approximate normal distribution. The relationship between osteoprotegerin and baseline characteristics and biomarkers was assessed by multivariable linear models. We calculated geometric means using the antilogarithms of the model-adjusted means (ie, predicted marginal means) and subsequently compared geometric means between groups (eg, men/women) using ratios.

Crude event rates at 1 year, by osteoprotegerin quartile groups at baseline, were estimated, as were Kaplan-Meier event rates. The functional form of the relationship between osteoprotegerin and outcomes was explored using cumulative sums of martingale residuals and restricted cubic splines.[24] The associations of osteoprotegerin concentrations (logarithm transformed), on admission, with the composite end point of cardiovascular death, spontaneous MI, or stroke and the secondary end points of cardiovascular death and bleeding were assessed by multivariable Cox proportional hazards models. The hazard was based on a 50% increase in biomarker concentration. Six models, with incremental addition of covariates, were used. Model 1 included the randomized treatment (ticagrelor or clopidogrel). Model 2 added the following clinical baseline risk factors: age, sex, body mass index, diabetes mellitus, chronic kidney disease, hypertension, smoking status, type of ACS, and history of heart failure,

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MI, percutaneous coronary intervention, CABG, stroke, or peripheral artery disease. Model 3 included all variables from model 2 together with hs-CRP level and WBC count. Model 4 included all the previously mentioned covariates with the addition of cystatin C, a marker of kidney dysfunction, which is strongly associated with an adverse outcome in this population.[7] Model 5 included all previously mentioned variables in addition to hs-TnT and NT-proBNP. Model 6 included all previously mentioned variables and GDF-15. For end points where osteoprotegerin was significantly associated in model 6, discrimination was assessed using the Harrell C-index. The multivariable models with and without osteoprotegerin were compared in terms of global model fit using likelihood ratio tests.

The effects of osteoprotegerin levels on outcomes in relation to predefined subgroup factors (ie, randomized treatment, ACS type, invasive/noninvasive in-hospital treatment approach, diabetes mellitus, sex, and smoking) were evaluated using Cox proportional hazards models. These models included quartile-divided osteoprotegerin levels, the respective subgroup factor, and the osteoprotegerin subgroup factor interaction term as independent variables. The proportional hazards assumption was assessed by visual inspection of Schoenfeld residual plots. A 2-sided $P<0.05$ was considered to be statistically significant, and there were no adjustments for multiple comparisons. All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

Results

Osteoprotegerin at Baseline and in Relation to Baseline Characteristics

Baseline osteoprotegerin concentrations were available in 5135 patients, with a median (IQR) of 2.65 (2.02–3.62) ng/mL. The blood samples for osteoprotegerin analysis were collected a median (IQR) of 15 (IQR, 8–21) hours after the index event or a median (IQR) of 10 (3–17) hours after admission.

The background characteristics for the entire study population with biomarkers available at baseline (n=16 401) have previously been reported.[7] Baseline characteristics by osteoprotegerin quartile groups are presented in Table 1 and showed that higher osteoprotegerin levels were associated with several demographic features and several biomarkers. Multivariable linear regression identified increasing age, female sex, STE ACS, increasing levels of hs-TnT, GDF-15, hs-CRP, and WBC, and lower cystatin C as the most prominent predictors of osteoprotegerin at baseline (Table 2). In contrast, the hs-TnT level was not associated with osteoprotegerin levels at 1 month. Age, female sex, GDF-15, and hs-CRP were the strongest predictors of osteoprotegerin at 1 month.

Osteoprotegerin Concentrations During Follow-Up

In patients with a baseline osteoprotegerin concentration and at least 1 follow-up sample (N=4679), the median (IQR) concentration was 2.65 (2.02–3.62) ng/mL at baseline. Figure 1 shows osteoprotegerin levels during 6 months of follow-up. No blood samples were obtained beyond 6 months of follow-up. Osteoprotegerin decreased significantly at hospital discharge (median [IQR], 2.33 [1.83–3.03] ng/mL; $P<0.0001$ versus baseline; n=4563) and further at 1 month (median [IQR], 2.24 [1.80–2.85] ng/mL; $P<0.0001$ versus baseline; n=4237), with a similar level at 6 months (median [IQR], 2.23 [1.81–2.80] ng/mL; $P<0.0001$ versus baseline; n=3084). No effects of randomized treatment were seen on osteoprotegerin levels at any time point (Table 3).

Osteoprotegerin and Cardiovascular Outcomes

During a predefined follow-up of 1 year (median, 9 months), the primary end point was observed in 434 patients (8.5%; 193 cardiovascular fatalities, 241 spontaneous MIs, and 62 stroke events). Restricted cubic spline analysis revealed a relatively linear association between high osteoprotegerin levels at baseline and incidence of the primary end point (Figure 2). Kaplan-Meier analysis (Figure 3A) revealed increasing event rates for the composite end point by quartiles of baseline osteoprotegerin: 5.2%, 7.5%, 9.2%, and 11.9% for quartiles 1 to 4, respectively. As shown in Figure 4A, the unadjusted hazard ratio (HR) and 95% confidence interval (CI), per 50% increase in baseline osteoprotegerin concentration, was 1.31 (1.21–1.42). The association remained significant after adjustment for clinical characteristics and biomarkers of inflammation (ie, hs-CRP and WBC count). However, after full multivariable adjustment, including the cardiac biomarkers and GDF-15, the HR (95% CI) was 0.98 (0.88–1.09). The HR for cardiovascular death alone was strongly attenuated and not significant after the addition of hs-CRP and WBC count. Admission osteoprotegerin levels were not associated with risk of stroke, whereas the association with spontaneous MI was not significant after adjustment for clinical characteristics (Table 4).

Osteoprotegerin and Major Bleeding

During follow-up, 200 patients had at least 1 non–CABG-related major bleeding event. Cubic spline analysis indicated an increase in risk of non–CABG-related major bleeding from the third quartile (>2.7 ng/mL) of osteoprotegerin at admission (Figure 2). As shown in the Kaplan-Meier graph (Figure 3B), a particularly high risk of bleeding was found among patients in the top quartile group of osteoprotegerin (>3.6 ng/mL), with an HR (95% CI) of 3.19 (2.12–4.79)

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Table 1. Baseline Characteristics and Biomarkers by Quartiles of Osteoprotegerin Concentrations at Baseline

Characteristic	Quartile 1 (<2.0 ng/mL) (n=1283)	Quartile 2 (2.0–2.7 ng/mL) (n=1284)	Quartile 3 (2.7–3.6 ng/mL) (n=1284)	Quartile 4 (>3.6 ng/mL) (n=1284)	*P* Value*
Age, y	56 (50–63)	62 (54–69)	65 (56–72)	67 (57–75)	<0.0001
Female sex	273 (21.3)	361 (28.1)	429 (33.4)	474 (36.9)	<0.0001
Weight, kg	82 (73–93)	81 (72–90)	80 (70–89)	78 (68–90)	<0.0001
BMI, kg/m^2	27.8 (25.3–30.8)	27.8 (25.3–30.9)	27.5 (24.8–30.4)	27.2 (24.7–30.5)	0.0005
Risk factors					
Habitual smoker	503 (39.2)	500 (38.9)	448 (34.9)	440 (34.3)	0.0104
Hypertension	787 (61.3)	846 (65.9)	884 (68.8)	870 (67.8)	0.0003
Dyslipidemia	569 (44.3)	558 (43.5)	551 (42.9)	495 (38.6)	0.0148
Diabetes mellitus	204 (15.9)	255 (19.9)	318 (24.8)	364 (28.3)	<0.0001
Medical history					
Angina pectoris	623 (48.6)	603 (47.0)	618 (48.1)	546 (42.5)	0.0080
Myocardial infarction	250 (19.5)	263 (20.5)	259 (20.2)	231 (18.0)	0.3893
Congestive heart failure	45 (3.5)	63 (4.9)	81 (6.3)	107 (8.3)	<0.0001
PCI	190 (14.8)	179 (13.9)	129 (10.0)	136 (10.6)	0.0002
CABG	51 (4.0)	68 (5.3)	71 (5.5)	66 (5.1)	0.2731
TIA	15 (1.2)	29 (2.3)	41 (3.2)	28 (2.2)	0.0066
Nonhemorrhagic stroke	34 (2.7)	35 (2.7)	57 (4.4)	49 (3.8)	0.0313
Peripheral arterial disease	69 (5.4)	84 (6.5)	101 (7.9)	92 (7.2)	0.0776
Chronic kidney disease	22 (1.7)	31 (2.4)	48 (3.7)	78 (6.1)	<0.0001
ST-segment–elevation MI	517 (40.3)	571 (44.5)	598 (46.6)	666 (51.9)	<0.0001
GRACE risk score	124.0 (109–139)	133.0 (117–149)	137.0 (120–154)	143.0 (126–162)	<0.0001
In-hospital medication					
Aspirin	1263 (98.4)	1266 (98.6)	1259 (98.1)	1264 (98.4)	0.7270
Unfractionated heparin	661 (51.5)	699 (54.4)	691 (53.8)	756 (58.9)	0.0021
LMWH	714 (55.7)	688 (53.6)	702 (54.7)	666 (51.9)	0.2539
Fondaparinux	16 (1.2)	24 (1.9)	21 (1.6)	12 (0.9)	0.1946
Bivalirudin	21 (1.6)	23 (1.8)	16 (1.2)	16 (1.2)	0.5656
Glycoprotein IIb/IIIa inhibitor	325 (25.3)	329 (25.6)	343 (26.7)	368 (28.7)	0.2135
β Blockers	1129 (88.0)	1118 (87.1)	1112 (86.6)	1112 (86.6)	0.6884
ACE inhibition and/or ARB	1103 (86.0)	1092 (85.0)	1131 (88.1)	1136 (88.5)	0.0265
Cholesterol lowering (statin)	1210 (94.3)	1193 (92.9)	1199 (93.4)	1209 (94.2)	0.4181
Biomarkers					
Hs-TnT, ng/L	119.0 (30.2–353.0)	158.0 (40.2–478.0)	135.0 (33.2–505.0)	274.5 (60.7–963.0)	<0.0001
NT-proBNP, pmol/L	260 (102–593)	402 (136–932)	458 (143–1269)	728 (200–2215)	<0.0001
Cystatin, mg/L	0.77 (0.65–0.90)	0.81 (0.65–0.97)	0.84 (0.69–1.05)	0.87 (0.69–1.11)	<0.0001
GDF-15	1214 (960.8–1601)	1447 (1126–1918)	1638 (1220–2263)	2026 (1465–2996)	<0.0001
Hs-CRP, mg/L	2.6 (1.3–6.0)	3.2 (1.4–6.9)	3.9 (1.6–10.0)	5.1 (2.1–16.0)	<0.0001

Data are given as median (quartile 1–quartile 3) or number (percentage). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; GDF-15, growth differentiation factor-15; GRACE, Global Registry of Acute Coronary Events; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

*P values from the χ^2 test (categorical variables) or the Kruskal-Wallis test (continuous variables).

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Table 2. Strongest Predictors of Osteoprotegerin Levels at Baseline and 1 Month

	Baseline			1 Month		
Background Characteristic	N		*P* Value	N		*P* Value
Ticagrelor				1509	0.999 (0.978–1.021)	0.9536
Age, 10-y increase	4406	1.096 (1.081–1.111)	<0.0001	3035	1.102 (1.087–1.116)	<0.0001
Female sex	1319	1.088 (1.059–1.117)	<0.0001	894	1.072 (1.045–1.100)	<0.0001
STE-ACS	2052	1.104 (1.075–1.134)	<0.0001	1471	0.972 (0.948–0.996)	0.0236
Hs-TnT, 10% increase	4406	1.002 (1.001–1.002)	<0.0001	3035	1.000 (0.998–1.002)	0.9237
GDF-15, 10% increase	4406	1.023 (1.020–1.026)	<0.0001	3035	1.013 (1.010–1.016)	<0.0001
Cystatin-C, 10% increase	4406	0.991 (0.987–0.995)	<0.0001	3035	1.003 (0.999–1.008)	0.1612
Hs-CRP, 10% increase	4406	1.004 (1.003–1.005)	<0.0001	3035	1.003 (1.002–1.004)	<0.0001
WBC count, 10% increase	4406	1.011 (1.007–1.015)	<0.0001	3035	1.007 (1.002–1.011)	0.0022

GDF-15 indicates growth differentiation factor-15; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; STE-ACS, ST-segment–elevation acute coronary syndrome; and WBC, white blood cell.

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versus the lowest quartile. When analyzed as a continuous variable (Figure 4B), there was a 1.52-fold (95% CI, 1.36–1.69) higher risk of bleeding per 50% increase in baseline osteoprotegerin, which also remained significant after full multivariable adjustment: HR, 1.26 (95% CI, 1.09–1.46). When added to the full multivariable model, osteoprotegerin contributed to discrimination about non–CABG-related major bleeding (C-index, 0.70 versus 0.71; *P*=0.0024 from the likelihood ratio test).

There was also a significant association between osteoprotegerin and non–procedure-related major bleeding in the fully adjusted model (n=99; HR, 1.24 [95% CI, 1.02–1.50]; *P*=0.0325). There were no interactions between osteoprotegerin levels and outcomes by randomized treatment or by other tested subgroups, including type of ACS (STE or non-STE ACS), diabetes mellitus, age, or sex.

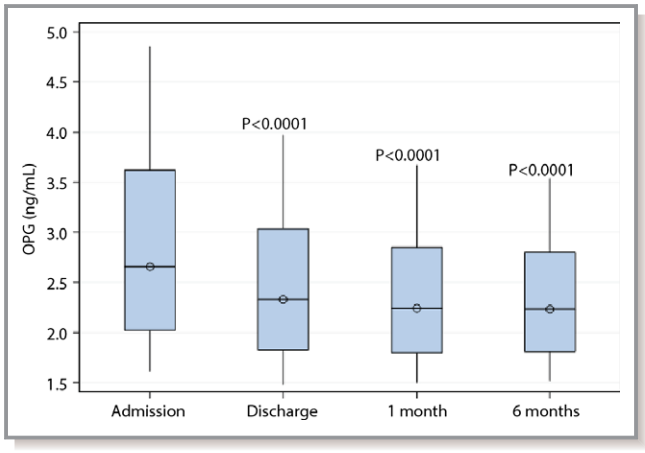

Figure 1. Box plots of osteoprotegerin levels on hospital admission and during follow-up.

Osteoprotegerin Concentrations and Outcomes at 1 Month

Osteoprotegerin levels at 1 month were associated with the occurrence of the primary composite end point after 1 month (n=240), with an HR (95% CI) of 1.59 (1.38–1.83). After adjusting for inflammatory markers, the association between osteoprotegerin at 1 month and the composite end point was not significant: HR (95% CI), 1.19 (0.98–1.66) (Figure 4A). The number of non–CABG-related major bleeding events after 1 month was low (n=75). Nonetheless, the randomized treatment-adjusted and fully adjusted HRs (95% CIs) were 1.78 (1.38–2.28) and 1.33 (0.91–1.96), respectively, per 50% increase in osteoprotegerin at 1 month (n=47) (Figure 4B). The number of nonprocedural major bleeding events after 1 month was 58. This limited further statistical analyses.

Discussion

In patients with ACS treated with dual antiplatelet treatment, the osteoprotegerin concentration was independently associated with increased risk of bleeding after adjustment for clinical risk factors and multiple biomarkers prognostic for both cardiovascular events and bleeding. In contrast, although there were independent associations between the osteoprotegerin level on admission and after 1 month and the primary composite cardiovascular end point of cardiovascular death, spontaneous MI, or stroke after adjustment for clinical characteristics and biomarkers of inflammation, these were not sustained after complete adjustment for biomarkers of cardiac function and GDF-15.

This study, for the first time in patients with ACS, showed that increasing levels of osteoprotegerin were associated with

Table 3. Effect of Randomized Treatment on Mean Osteoprotegerin Levels at Discharge and at 1 and 6 Months After Randomization

Visit	Treatment	n*	Mean (SD)	Geometric Mean†	Ratio of Geometric Means (95% CI)	*P* Value‡
Discharge	Ticagrelor	2263	2.62 (1.24)	2.39	1.01 (0.99–1.02)	0.5958
	Clopidogrel	2300	2.56 (1.15)	2.38		
Month 1	Ticagrelor	2103	2.46 (0.98)	2.28	0.99 (0.97–1.01)	0.2507
	Clopidogrel	2134	2.43 (0.91)	2.30		
Month 6	Ticagrelor	1513	2.46 (0.94)	2.30	1.01 (0.99–1.04)	0.1730
	Clopidogrel	1571	2.39 (0.91)	2.26		

CI indicates confidence interval.
*n includes patients with osteoprotegerin samples available at both baseline and the respective visit.
†The geometric means are calculated using the antilogarithms of the model-adjusted means of the logarithm-transformed data.
‡*P* values from an ANCOVA model with the natural logarithm of osteoprotegerin as the outcome variable and logarithm baseline osteoprotegerin and randomized treatment (ticagrelor or clopidogrel) as independent variables.

bleeding complications during antiplatelet treatment. The magnitude of the association between osteoprotegerin at admission and bleeding was only marginally affected by the addition of any biomarker and significantly improved the performance of the multivariable model, indicating that the role of osteoprotegerin on bleeding outcomes may be exerted via pathways not reflected by other biomarkers. The final addition of novel biomarker GDF-15 was crucial because this marker has a proven strong association with bleeding outcomes.[8] A low circulating level of the endothelial activation marker vWF is a risk factor for bleeding.[25] Osteoprotegerin binds vWF with high affinity, and this complex is present in vivo and may influence bleeding risk.[2,3] In addition, osteoprotegerin may bind vWF reductase, thrombospondin-1, and in late stages of thrombus formation, this interaction may promote proteolysis of vWF multimers and prevent platelet aggregation.[2] This may be beneficial in limiting further plaque progression; however, it could also promote bleeding. Finally, osteoprotegerin is a modulator of vascular calcification and is correlated with coronary calcium scores in the

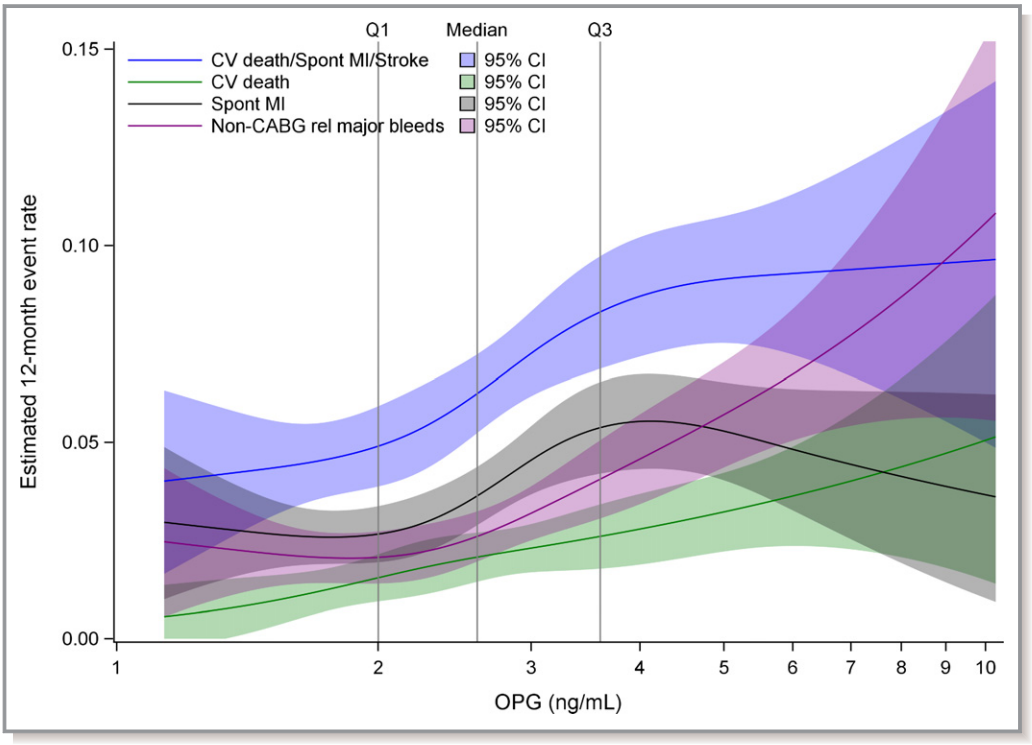

Figure 2. Restricted cubic splines for osteoprotegerin in all patients at baseline on the investigated outcomes. CABG indicates coronary artery bypass grafting; CI, confidence interval; CV, cardiovascular; and MI, myocardial infarction.

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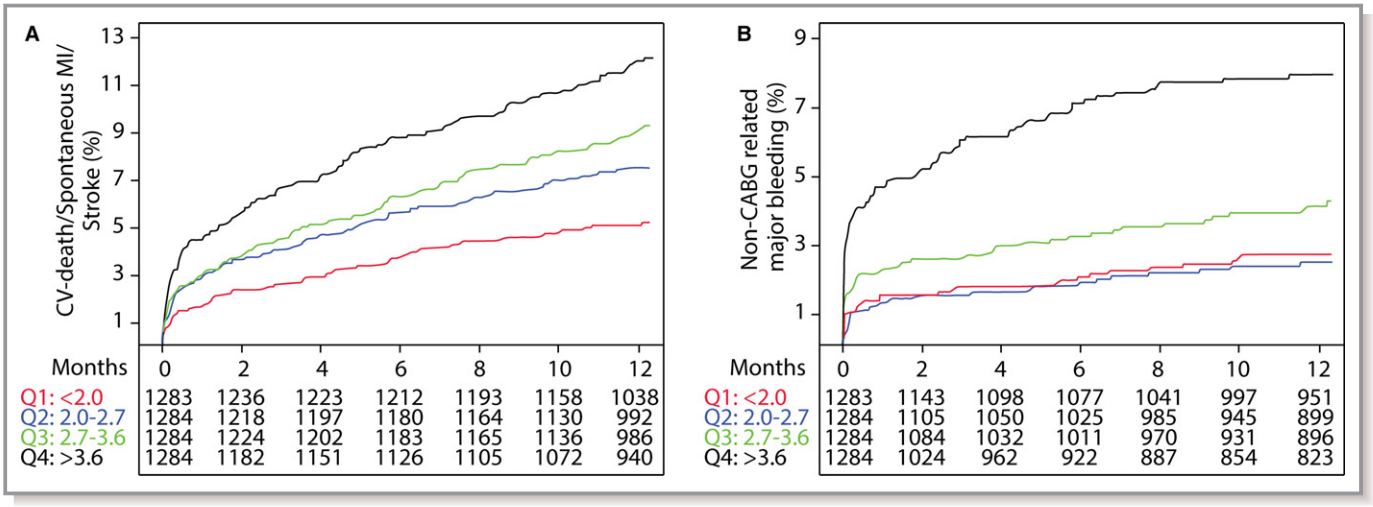

Figure 3. Kaplan-Meier estimated event rates of the primary outcome (composite of cardiovascular death, spontaneous myocardial infarction [MI], and stroke; A) and non–coronary artery bypass grafting (CABG)-related major bleeding (B) by quartiles of osteoprotegerin. OPG indicates osteoprotegerin.

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general populations[26] and in patients with coronary artery disease.[27] Because the degree of coronary calcification is a risk factor for non–CABG-related major bleeding in ACS,[28] it is conceivable that the association between osteoprotegerin and bleeding risk in our study could reflect effects of calcified arteries on bleeding. Such interactions between osteoprotegerin, hemostasis, and calcification warrant further exploration. The serial analyses of osteoprotegerin revealed a decrease in median levels that stabilized at the 1-month follow-up. The effect of osteoprotegerin on bleeding and the univariate association with ischemic end points and mortality all exhibited numerically greater point estimates at 1 month. However, the number of events, especially bleeding events, rapidly decreases after the first month of the follow-up, and this is reflected by the large CIs at 1 month. Thus, although the association with bleeding was not significant in the fully adjusted model at 1 month, our data support that osteoprotegerin may be a novel and stable marker for major bleeding in the setting of ACS and antithrombotic therapy. However, we are unable to draw any conclusions on a possible causative role of osteoprotegerin on ischemic events or bleeding in patients with ACS receiving antithrombotic therapy. Furthermore, it would also be of interest in forthcoming studies to evaluate if osteoprotegerin could be a bleeding biomarker in patients not taking dual antiplatelet therapy or aspirin monotherapy.

Several biomarkers, on admission for ACS, provide clinically important information on risk for cardiovascular morbidity and mortality, including NT-proBNP (myocardial dysfunction),[9,10] cardiac troponins (myocardial necrosis),[29] and cystatin C (kidney function).[7,11] Circulating osteoprotegerin has been reported to be associated with cardiovascular outcomes, including mortality, MI, and incident heart failure, in several ACS cohorts.[16–19] However, although most of these studies include natriuretic peptides,[16,17,19] troponins,[16–18] and CRP[16–18] in their adjustment strategy, none include GDF-15, which increases in response to myocardial stress associated with inflammation and tissue damage[30] and is becoming a recognized biomarker in ACS.[9,10,14] In this large study population, the association between high osteoprotegerin levels at admission and risk of the primary end point or cardiovascular death was markedly attenuated and no longer significant after addition of NT-proBNP, hs-TnT, and GDF-15 to the model that included clinical variables and inflammatory biomarkers. This finding suggested that osteoprotegerin in the short-term phase could reflect a local or systemic inflammatory response to myocardial necrosis, but could not independently predict prognosis. Osteoprotegerin is strongly expressed within the failing myocardium,[5] correlates with infarct size after ACS,[31] and was strongly associated with cardiac troponin levels in the short-term phase in our study. Thus, a strong influence of the short-term phase reaction could attenuate the association with adverse ischemic events, as is seen for CRP.[32] At 1 month, hs-CRP and, in particular, GDF-15 were among the strongest predictors of osteoprotegerin; they are more closely related to adverse cardiovascular outcomes in our cohort and could, therefore, partly explain the lack of association with outcomes, compared with other studies that lack GDF-15 measurements. Differences compared with our previous report in 897 patients with ACS, in whom an association between high osteoprotegerin levels at admission and all-cause mortality was observed, could also be attributable to the markedly longer follow-up time (89 months) and, thus, a larger proportion and incidence of fatalities.[17] Nonetheless, similar to the present study, the

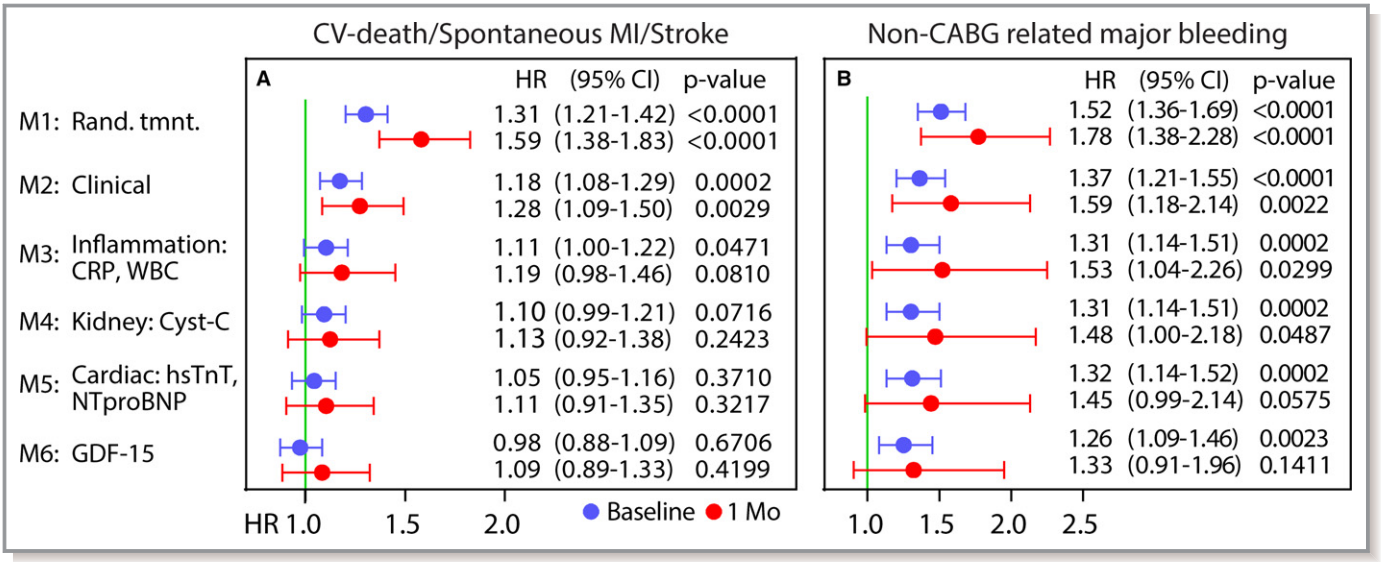

Figure 4. Forest plot of hazard ratios (HRs) and 95% confidence intervals (CIs) per 50% increase in osteoprotegerin concentration on the primary composite end point (A) and the secondary end point of non–coronary artery bypass grafting (CABG) major bleeding (B) during up to 1 year of follow-up. HRs are presented per 50% increase in biomarker level and are presented after incremental addition of covariates, as detailed left of A and in Statistical Analysis. Point estimates in blue indicate baseline levels, whereas red indicates 1-month samples. CRP indicates C-reactive protein; CV, cardiovascular; GDF-15, growth differentiation factor-15; hs-TnT, high-sensitivity troponin T; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and WBC, white blood cell.

relationship between osteoprotegerin and MI was not significant in adjusted analysis.[17] Also, in a study by Roysland et al, who evaluated osteoprotegerin in 4463 patients with non-STE ACS with a similar follow-up as our study,[16] the association with MI was not present in adjusted analysis, although an association with cardiovascular death persisted in adjusted analysis.

Limitations

The current study provides insights to the role of osteoprotegerin in a population with ACS, but it has some limitations. The PLATO trial comprises a broad population with ACS. However, patients requiring dialysis or with recent significant bleeding were not eligible. Furthermore, because mortality

Table 4. Associations Between Continuous (HRs per 50% Increase in Osteoprotegerin) or Quartiles of Osteoprotegerin at Baseline (n=5135) and 1 Month (n=4233) and Outcome

		Cardiovascular Death		MI		Stroke	
Model	Time	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
1	Baseline	1.47 (1.31–1.64)	<0.0001	1.19 (1.07–1.33)	0.0019	1.21 (0.98–1.50)	0.0773
	1 Mo	1.87 (1.48–2.35)	<0.0001	1.50 (1.25–1.78)	<0.0001	1.76 (1.23–2.51)	0.0019
2	Baseline	1.25 (1.10–1.42)	0.0007	1.11 (0.98–1.25)	0.1054	1.10 (0.86–1.39)	0.4460
	1 Mo	1.30 (0.99–1.70)	0.0603	1.22 (1.00–1.50)	0.0517	1.55 (1.02–2.34)	0.0384
3	Baseline	1.05 (0.92–1.22)	0.4604	1.09 (0.95–1.26)	0.2037	1.09 (0.83–1.43)	0.5330
	1 Mo	1.05 (0.74–1.50)	0.7886	1.20 (0.94–1.53)	0.1399	1.25 (0.74–2.12)	0.4047
4	Baseline	1.04 (0.90–1.20)	0.6005	1.09 (0.95–1.25)	0.2382	1.08 (0.82–1.41)	0.5947
	1 Mo	0.90 (0.63–1.27)	0.5414	1.16 (0.91–1.49)	0.2255	1.22 (0.72–2.08)	0.4567
5	Baseline	0.97 (0.84–1.12)	0.7054	1.04 (0.90–1.20)	0.5700	1.09 (0.83–1.43)	0.5484
	1 Mo	0.88 (0.63–1.24)	0.4753	1.14 (0.90–1.46)	0.2835	1.22 (0.72–2.08)	0.4567
6	Baseline	0.90 (0.78–1.05)	0.1853	0.99 (0.86–1.15)	0.9088	1.16 (0.68–1.98)	0.5785
	1 Mo	0.89 (0.64–1.25)	0.5092	1.14 (0.89–1.46)	0.2995	1.49 (0.96–2.29)	0.0722

CI indicates confidence interval; HR, hazard ratio; and MI, myocardial infarction. Models are described in the Statistical Analysis section in the Methods.

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was lower in the group randomized to ticagrelor, a survival bias with ticagrelor may have been present. This is important because ticagrelor is known to have bleeding as an adverse effect. Also, the number of bleeding events was not sufficient for subgroup analysis, evaluating the association between osteoprotegerin levels and different types of bleeding. Finally, although we evaluated interactions between osteoprotegerin levels and outcomes by several subgroups (eg, diabetes mellitus status and type of ACS), increased osteoprotegerin levels have been observed in a wide range of diseases and comorbidities,[23,33] also associated with adverse outcome (eg, aortic stenosis[33]). Because we were unable to account for these diseases and comorbidities, we cannot exclude that they would influence our results. However, our cohort is a representative population with ACS (ie, no inclusion/exclusion criteria to expect any particular selection).

Conclusion

In patients with ACS treated with dual antiplatelet therapy, we observed an independent association between osteoprotegerin concentrations and the risk of major bleeding both at baseline and after 1 month. Osteoprotegerin levels were also associated with ischemic cardiovascular outcomes, even when adjusting for clinical characteristics and biomarkers of inflammation and kidney function (but not for cardiac biomarkers and GDF-15). High osteoprotegerin levels may be useful in increasing awareness of increased bleeding risk in patients with ACS receiving antithrombotic therapy.

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National coordinators: Diego Ardissino (Ospedale Maggiore di Parma, Parma, IT), Phil Aylward (Flinders Medical Centre, Bedford Park, AU), Noe Babilonia (Philippine Heart Center, Quezon City, PH), Jean-Pierre Bassand (University Hospital Jean Minjoz, Besancon, FR), Andrzej Budaj (Grochowski Hospital, Warsaw, PL), Zaza Chapichadze (Institute of Cardiology, Tblisi, GE), Marc J Claeys (University Hospital Antwerp, Edegem, BE), Patrick Commerford (Groote Schuur Hospital, Cape Town, ZA), Jan H Cornel (Medisch Centrum Alkmaar, Alkmaar, NL), Tibor Duris (Hospital Nove Zamky, Nove Zamky, SK), Runlin Gao (Cardiovascular Inst & Fu Wai Hosp, Beijing, CN), Armando (García Castillo, Hospital de Cardiologia UMAE, Nuevo Leon, MX), Evangelos Giannitsis (University of Heidelberg, Heidelberg, DE), Paul Gurbel (Sinai Hospital, Baltimore, MD, US), Robert Harrington (Duke Clinical Research Institute, Durham, NC, US), Magda Heras (Hospital Clinic of Barcelona, Barcelona, ES), Steen Husted (Aarhus University Hospital, Aarhus, DK), Stefan James (Uppsala University Hospital, Uppsala, SE), Matyas Keltai (Semmelweis University, Budapest, HU), Neil Kleiman (Baylor College of Medicine, Houston, TX, US), Frederic Kontny

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(Volvat Medical Center, Oslo, NO), Dimitrios Kremastinos (Attikon University General Hospital, Athens, GR), Riitta Lassila (Helsinki University Central Hospital, FI), Basil S Lewis (Lady Davis Carmel Medical Center, Haifa, IL), Jose Lopez Sendon (Hospital Universitario La Paz, Madrid, ES), Cheuk Man Yu (Chinese University of Hong Kong, HK), Gerald Maurer (Medical University of Vienna, Vienna, AT), Bernhard Meier (University Hospital, Bern, CH), João Morais (Santo Andrés Hospital, Leiria, PT), José Nicolau (Heart Institute (InCor), São Paulo, BR), Alexander Nikolaevich Parkhomenko (Research Institute of Cardiology, Kiew, UA), Ali Oto (Hacettepe Univ School of Medicine, Ankara, TR), Prem Pais (St.John's Medical College, Bangalore, IN), Ernesto Paolasso (Estudios Clinicos Latin America, Rosario, AR), Dimitar Raev (Medical Institute, Ministry of Interior, Sofia, BG), Dato Seri Robaayah Zambahari (National Heart Institute, Kuala Lumpur, MY), Mikhail Ruda (Cardiology Research Center, Moscow, RU), Marc Sabatine (Brigham & Women's Hospital, Boston, MA, US), Anwar Santoso (Udayana School of Medicine, Denpasar, ID), Ki-Bae Seung (Kangnam St. Mary's Hospital, Seoul, KR), Lim Soo Teik (Heart Centre, Singapore, SG), Jindrich Spinar (University Hospital Brno, Brno, CZ), Piyamitr Sritara (Ramathibodi Hospital, Bangkok, TH), Robert Storey (University of Sheffield, Sheffield, UK), Pierre Théroux (Montreal Heart Institute, Montreal, CA), Douglas Weaver (Henry Ford Heart & Vascular Inst, Detroit, MI, US), Freek Verheugt (UMC St Radboud, Nijmegen, NL), Marius Vintila (St Pantelimon University Hospital, Bucharest, RO), Delon Wu Wu (Chang Gung Memorial Hospital-Linkou, Tao-Yuan, TW)

DSMB members:

Chairman: Jeffrey L Anderson (Intermountain Medical Center, Murray, UT, US)

Voting members: David DeMets (University of Wisconsin Medical School, Madison, WI, US), Maarten Simoons (Erasmus Medical Centre, Rotterdam, NL), Robert Wilcox (Nottingham University Hospital, Nottingham, UK), Frans Van de Werf (University Hospital Leuven, Leuven, BE)

DSMB statisticians: Susan Anderson (University of Wisconsin Medical School, Madison, WI, US), Erik Iverson (University of Wisconsin Medical School, Madison, WI, US)

ICAC members and operational personnel:

Co-chairmen: Kenneth W Mahaffey (Duke Clinical Research Institute, Durham, NC, US), Claes Held (Uppsala Clinical Research Center, Uppsala, SE)

Coordinators: Sheila Dickerson (Duke Clinical Research Institute, Durham, NC, US), Matts Högberg (Uppsala Clinical Research Center, Uppsala, SE), Debra Montgomery (Duke Clinical Research Institute, Durham, NC, US)

AstraZeneca members: Jan Healy (Wilmington, DE, US), Nardev Khurmi (Wilmington, DE, US), Seva Paniflov (Mölndal, SE), Frank Senk (Wilmington, DE, US), LuAnn Vanaman (Wilmington, DE, US),

Adjudicators:

North America, India and Australia: John Alexander (Duke University School of Medicine, Durham, NC, US), Sana Al-Khatib (Duke University School of Medicine, Durham, NC, US), Jeffrey Berger (Duke

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University School of Medicine, Durham, NC, US), Cheryl Bushnell (Wake Forest University Baptist Medical Center, US), Derek Chew (Flinders Medical Center, Australia), Mauricio Cohen (University of North Carolina, Chapel Hill, NC, US), Jeffrey Craig (Wake Forest University Baptist Medical Center, Winston-Salem, NC, US), James De Lemos (Texas Southwestern Medical Center, Dallas, TX, US), John French (Liverpool Hospital, Sidney, AU), Robert Giugliano (Brigham and Women´s Hospital, Boston, MA, US), Shaun Goodman (St Michaels Hospital, Toronto, CA), Adam Greenbaum (Henry Ford Hospital, Detroit, MI, US), Adrian Hernandez, (Duke University School of Medicine, Durham, NC, US), Jason Katz (Duke University School of Medicine, Durham, NC, US), Renato Lopes (Duke University School of Medicine, Durham, NC, US), Mina Madan (Sunnybrook Health Sciences Centre, Canada), Kenneth Mahaffey (Duke University School of Medicine, Durham, NC, US), Peter McCullough (William Beaumont Hospital, Royal Oak, MI, US), Darren McGuire (Texas Southwestern Medical Center, Dallas, TX, US), Rajendra Mehta (Duke University School of Medicine, Durham, NC, US), Chiara Melloni (Duke University School of Medicine, Durham, NC, US), David Morrow (Brigham and Women´s Hospital, Boston, MA, US), Kristen Newby (Duke University School of Medicine, Durham, NC, US), Matthew Roe (Duke University School of Medicine, Durham, NC, US), Stuart Russell (Johns Hopkins School of Medicine, Baltimore, MD, US), Benjamin Scirica (Brigham and Women´s Hospital, Boston, MA, US), Bimal Shah (Duke University School of Medicine, Durham, NC, US), Lynda Szczech (Duke University School of Medicine, Durham, NC, US), David Whellan (Duke University School of Medicine, Durham, NC, US), David Wiviott (Brigham and Women´s Hospital, Boston, MA, US)

Sweden: Marie Bennermo (Danderyd Hospital, Stockholm, SE), Christina Christersson (Uppsala University Hospital, Uppsala, SE), Kai Eggers (Uppsala University Hospital, Uppsala, SE), Bengt-Olof Fredlund (Sahlgrenska University Hospital, Gothenburg, SE), Matthias Götberg (Lund University Hospital, Lund, SE), Emil Hagström (Uppsala University Hospital, Uppsala, SE), Claes Held (Uppsala University Hospital, Uppsala, SE), Ziad Hijazi (Uppsala University Hospital, Uppsala, SE), Mikael Holmgren (Sahlgrenska University Hospital, Gothenburg, SE), Stefan James (Uppsala University Hospital, Uppsala, SE), Tomas Jernberg (Karolinska University Hospital, Stockholm, SE), Nina Johnston (Uppsala University Hospital, Uppsala, SE), Birgitta Jönelid (Uppsala University Hospital, Uppsala, SE), Sasha Koul (Lund University Hospital, Lund, SE), Pia Lundman (Danderyd Hospital, Stockholm, SE), Jonas Oldgren (Uppsala University Hospital, Uppsala, SE), Katarina Saldeen Nilehn (Sahlgrenska University Hospital, Gothenburg, SE), Ola Samuelsson (Sahlgrenska University Hospital, Gothenburg, SE), Karolina Szummer (Karolinska University Hospital, Stockholm, SE), Christoph Varenhorst (Uppsala University Hospital, Uppsala, SE), Axel Åkerblom (Uppsala University Hospital, Uppsala, SE)

Statistical centre and involved statisticians: Richard Cairns (Worldwide Clinical Trials, Inc; Nottingham, GB), Allan Skene (Worldwide Clinical Trials, Inc; Nottingham, GB), Karen Pieper (Duke Clinical Research Institute, Durham, NC, US), Sylvia Olofsson (Uppsala Clinical Research Center, Uppsala, SE), Joseph Ycas (AstraZeneca R&D, Wilmington, DE, US)

Academic coordinating centers and operational personnel:

Duke Clinical Research Institute (DCRI; Durham, NC, US): Richard Becker, Robert A Harrington

Uppsala Clinical Research Center (UCR; Uppsala, SE): Inger Ekman, Stefan James, Lars Wallentin

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Central laboratory: Quintiles Central Laboratory, Scotland (Livingston, UK)

Data coordination: AstraZeneca R&D, Cognizant Technology Solutions, Stockholm, SE (data management partner), Medidata Solutions Inc, New York, NY, US (web-based data capture vendor), ICON Clinical Research, LP, Philadelphia, PA, US (interactive web/voice response system, vendor)

All principal investigators by country, PLATO

Argentina: Pablo Schygiel (Instituto Médico Adrogúe, Adrogué; 6), Oscar Allall (Hospital Córdoba, Córdoba; 16), Hugo Ramos (Clínica Privada Caraffa, Córdoba; 12), Julio Bono (Sanatorio Allende, Córdoba; 9), Juan Fuselli (CEMIC, Buenos Aires; 4), Carlos Cuneo (Hospital San Bernardo, Salta; 1), Hugo Colombo (Clínica Privada Colombo, Córdoba; 6), José Navarro Estrada (Hospital Italiano, Autonomous City of Buenos Aires; 7), Carlos Pasinato (Complejo Médico-Policial "Churruca-Visca", Buenos Aires; 3), Daniel Nul (PBA - I Medico Constituyentes - Cardiology, Morón; 20), Mario Berli (Hospital Cullen, Santa Fé; 37), Rodolfo Milesi (Instituto Cardiovascular Santa Fé, Santa Fé; 38), Miguel Hominal (Sanatorio Médico de Diagnóstico y Tratamiento, Santa Fé; 17), Ricardo Fernandez (Sanatorio San Gerónimo, Santa Fé; 52), Adrian Hrabar (Sanatorio Modelo de Quilmes, Quilmes; 13), Hector Luciardi (Hospital Centro de Salud, Tucuman; 6), Juan Muntaner (Centro Modelo de Cardiologia, Tucuman; 22), Gerardo Zapata (Instituto Cardiovascular de Rosario, Rosario; 20), Stella Macin (Instituto de Cardiología de Corriente "J.F.Cabral", Corrientes; 24), Marcelo Bettinoti (Sanatorio Güemes, Buenos Aires; 27), Jorge Julio Bluguermann (Policlinica Bancaria, Autonomous City of Buenos Aires; 16), Eduardo Gabriel Hasbani (Centro Privado de Cardiología, San Miguel de Tucumán; 21), Ruben Piraino (Sanatorio Plaza, Rosario; 18), Fernando Colombo Berra (Sanatorio de la Trinidad Quilmes, Quilmes; 14), Alejandro Garcia Escudero (Clinica Espora, Adrogue; 1)

Australia: Julian Vaile (Flinders Medical Centre, Bedford Park; 9), Darren Walters (Prince Charles Hospital, Chermside; 22), Tony Dart (Alfred Hospital, Melbourne; 4), Chris Hii (Calvary Health Care ACT, Melbourne; 12), Paul Garrahy (Princess Alexandra Hospital, Woolloongabba; 21), John Amerena (Geelong Hospital, Geelong; 4), John Counsell (Dandenong Hospital, Dandenong; 4), Leonard Arnolda (Royal Perth Hospital, Perth; 7)

Austria: Gerald Maurer (AKH Wien, Wien; 20), Kurt Huber (Wilhelminenspital der Stadt Wien, Wien; 63), Franz Roithinger (Thermenklinikum Mödling, Mödling; 5), Josef Hofer (LKH Freistadt, Freistadt; 9), Helmut Brussee (Med.-Univ. Graz, Graz; 9), Heinz Krappinger (LKH Villach, Villach; 1), Joachim Nesser (KH Elisabethinen Linz, Linz; 3), Peter Siostrzonek (KH der Barmherzigen Schwestern Linz, Linz; 8), Otmar Pachinger (Med.-Univ. Innsbruck, Innsbruck; 19), Heinz Drexel (LKH Feldkirch, Feldkirch; 7)

Belgium: Frank Cools (A.Z. Klina, Brasschaat; 15), Michel Eycken (AZ Sint Augustinus, Wilrijk; 2), Marcelo Goldstein (Clinique Sainte-Anne Saint-Remi, Brussels; 14), Patrizio Lancellotti (Centre Hospitalier Universitaire Sart Tilman, Liège; 11), Frédéric Mathieu, Pierre Materne (Centre Hospitalier Régional de la Citadelle, Liège; 15), Erwin Raymenants (AZ Sint-Maarten, Mechelen; 10), Walter Van Mieghem (Ziekenhuis-Oost Limburg Campus Sint-Jan, Genk; 11), Mark Claeys (Universitair Ziekenhuis Antwerpen, Edegem; 11), Edouard Benit (Virga Jesse Ziekenhuis, Hasselt; 3), Philippe Dubois (Centre Hospitalier Universitaire de charleroi, Charleroi; 5), Dia El Allaf (Centre Hospitalier Hutois, Nuy; 36), Guy Heynickx

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(O.L.V. Ziekenhuis, Aalst; 15), Harry Striekwold (Heilig Hartziekenhuis Mol, Mol; 18), Patrick Timmermans (Clinique Saint-Luc, Bouge; 4)

Brazil: Felipe Lima (HC FMUSP Incor, São Paulo; 63), Leopoldo Piegas (Instituto Dante Pazzanese, São Paulo; 6), Paulo Lotufo Hospital (Universitário da Universidade de São Paulo, São Paulo; 17), Valdir Golin (Hospital Irmandade Santa Casa de Misericordia de Sao Paulo, São Paulo; 8), Antônio Carvalho (Universidade Federal de São Paulo, São Paulo; 11), Lilia Maia (Fundacao da Faculdade Regional de Sao Jose do Rio Preto, São José do Rio Preto; 14), Gilmar Greque (Instituto de Moléstias Cardiovasculares, São José do Rio Preto; 6), José Francisco Saraiva (Hospital e Maternidade Celso Pierro, Campinas; 16), Peo Filho (Hospital Conceição, Porto Alegre; 29), Oscar Dutra (Instituto de Cardiologia do Rio Grande do Sul, Porto Alegre; 54), Jorge Ribeiro (Hospital de Clinicas de Porto Alegre, Porto Alegre; 4), Paulo Leaes Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre; 28), Euler Manenti (Hospital Mãe de Deus, Porto Alegre; 4), Jose Antonio Abrantes (Santa Casa de Misericórdia de Pelotas, Porto Alegre; 34), Paulo Roberto Rossi (Hospital Universitário Evangélico de Curitiba, Curbita; 18), Harry Filho (Inst. Cardiologia de Santa Catarina, São José; 10), Denilson Albuquerque (Fundacao Cardio Vascular Pedro Ernesto, Rio de Janeiro; 6), Gilmar Reis (Irmandade Santa Casa de Misericordia de Belo Horizonte, Belo Horizonte; 60), Álvaro Rabelo (Fundação Baiana de Cardiologia, Salvador; 16), Marcelo Teixeira (Hospital Português, Salvador; 2), Délcio Júnior Hospital Universitário da Univ. Federal de Mato Grosso, Campo Grande; 33), Maria Fernanda Garcia (Instituto do Coração do Distrito Federal, Brasília; 4), Ludmilla Almeida Oliveira (Pro Matre - Instituto do Coração (InCor), Natal; 11), Maria Sanali Paiva (Natal Hospital Center, Natal; 11), Yorghos Michalaros (Instituto Previdência Servidores de Minas Gerais, Belo Horizonte; 40), João Batista Júnior (Hospital Agamenon Magalhães, Recife; 31), Raul Júnior (Hospital Santa Rita, Maringá; 32), Hans Fernando Dohmann (Hospital Pró-Cardíaco (PROCEP), Rio de Janeiro; 3), Salvador Rassi (Hospital das Clínicas da Universidade Federal de Goiás, Goiânia; 18), Antonio Carlos Sousa (Hospital São Lucas, Aracaju; 23), Marco Gomes (Hospital Memorial Arthur Ramos, Maceió; 22), Eduardo Maia (Sociedade Espanhola de Beneficencia, Rio de Janeiro; 2), José Neto (Irmandade Santa Casa de Misericórdia de Curitiba (PUC-PR), Curitiba; 16), Roberto Botelho (Hospital Santa Catarina, Uberlândia; 41)

Bulgaria:

Dimitar Raev (Central Clinical Hospital, Sofia; 30), Assen Goudev (MHAT Queen Joanna, Sofia; 24), Sotir Marchev (5th MHAT, Sofia; 22), Atanas Mihov (MHAT St. Ekaterina, Dimitrovgrad; 20), Anastas Popov (MHAT Haskovo, Haskovo; 13), Maria Cekova (MHAT “Georgi Stranski” Cardiology Dept and ICU, Pleven; 52), Silvia Dimitrova (MHAT Russe, Ruse; 13), Stefan Denchev (MHAT Alexandrovska, Sofia; 30), Mladen Grigorov (2nd MHAT, Sofia; 23), Snezhanka Tisheva (MHAT “Georgi Stranski” Cardiology and Rheumatology, Pleven; 55), Atanas Penev (MHAT ‘St. Marina’, Varna; 13), Dobri Hazarbasanov (MHAT ‘St. Anna’, Sofia; 16), Stanislav Petranov (MHAT Burgas, Burgas; 20), Stanislav Petranov (MHAT Plovdiv , Plovdiv; 11), Boicho Boichev (MHAT Kazanlak, Kazanlak; 25), Nina Shehova (MHAT Dr.Bratan Shukerov, Smolian; 35), Varbitza Hergeldjieva (MHAT Russe, Russe; 10), Toma Vladimirov (MHAT Gabrovo, Gabrovo; 2), Fedya Nikolov, Atanas Djurdjev (UMHAT St.Georgi, Plovdiv; 37)

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Canada: Pierre Theroux (Institut de Cardiologie de Montreal, Montréal; 12), James Swan (Scarborough Cardiology Research, Scarborough; 64), Barry Rose (The Health Science Centre, St John´s; 9), Christian Constance (Hopital Maisonneuve-Rosemont, Montreal; 27), Krishnan Ramanathan (Diamond Health Care Centre, Vancouver; 6), Wolf Peter Klinke (Victoria Heart Institute, Victoria; 18), Warren Cantor (Southlake Regional Health Centre, Newmarket; 21), Robert Welsh (Edmonton University Hospital, Edmonton; 9), John Ducas (St Boniface General Hospital, Winnipeg; 1), Petr Polasek (Kelowna Cardiology Research, Kelowna; 2), Thao Huynh Thanh (Hopital General de Montreal, Montreal; 5), Rakesh Bhargava (Lakeridge Health Oshawa, Oshava; 16), Robert Teskey (N.B. Heart Centre, Saint John; 20), Saul Vizel (Cambridge Memorial Hospital, Cambridge; 23), John Paul Deyoung (Medical Centre Cornwall, Cornwall; 19), Hubert Comtois (Cite de la Sante de Laval, Laval; 18), Patrick Ma (Rockyview Hospital, Calgary; 5), Robert Dupuis (Centre Hospitalier de la Region de I Amiante, Thetford mines; 10), John Heath (Campbell River Hospital, Campbell River; 2), Danielle Dion (Centre Hospitalier Beauce-Etchemin, Saint-Georges; 4), David Cleveland (Penticton Regional Hospital, Penticton; 3), Dennis Rupka (Fraser Clinical Trials, New Westminster; 10), Shyam Radhakrishnan (Sunnybrook Health Sciences Centre, Toronto; 9), Jayant Bhatt Brockville (General Hospital, Brockville; 28), Rodney Zimmermann (Regina General Hospital, Regina; 13), Michel Nguyen (C.U.S.E. Site Fleurimont, Sherbrooke; 2), Josep Rodes Cabau (Hopital Laval, Quebec City; 22), Michel Le May (Ottawa Heart Institute, Ottawa; 8), William Kostuk (London Health Sciences Centre, London; 12), Jan Kornder (Surrey Memorial Hospital, Surrey; 3)

China: Jilin Chen (Fu Wai Hospital, Beijing; 11), Xinchun Yang (Beijing Chaoyang Hospital, Beijing; 61), Shuzheng Lv (Anzhen Hospital, Beijing; 22), Yong Huo (Peking University First Hospital, Beijing; 28), Jianhua Zhu (Hospital of Zhejiang, Hang Zhou; 19), Zhanquan Li (The Peoples Hospital of Liaoning Province, Shenyang; 66), Dejia Huang (Chengdu Hua Xi Hospital, Chengdu; 50), Jiyan Chen (Guang Dong Provincial Peoples Hospital, Guangzhou; 41), Ben He (Renji Hospital, Shanghai; 42), Qi Hua (Xuanwu Hospital, Beijing; 65), Yaling Han (Shenyang SY P.L.A General Hospital, Shenyang; 13)

Czech Republic: Jindrich Spinar (Fakultni nemocnice Brno-Bohunice, Brno; 93), Milos Holub (Nemocnice Jihlava, Jihlava; 8), Eva Mandysova (Nemocnice Na Homolce, Prague; 11), Jan Belohlavek (Vseobecna fakultni nemocnice, Prague; 120), Petr Reichert (Nemocnice Teplice, Teplice; 57), Ondrej Cermak (Nemocnice Slany, Slany; 55), Vratislav Dedek (Nemocnice Usti nad Orlici, Usti nad Orlici; 33), Pavel Cervinka (Masarykova nemocnice, Usti nad Labern; 50), David Horak, Frantisek Holm (Krajska nemocnice Liberec, Liberec; 161), Ladislav Groch (Fakultni nemocnice u Sv. Anny, Brno; 87), Zuzana Motovska (Fakultni nemocnice Kralovske Vinohrady, Prague; 145), Rudolf Spacek (Nemocnice na Frantisku, Prague; 4), Jan Matejka Nemocnice (Pardubice, Pardubice; 45), Leos Pleva, Roman Stipal (Ostrava-Poruba - FN, Ostrava-Poruba; 14), Marek Richter (Fakultni nemocnice Olomouc, Olomouc; 17), Jiri Povolny (Nemocnice Kladno, Kladno; 7), Jan Vojacek (Fakultni nemocnice Hradec Kralove, Hradec Kralove; 20), Jiri Vejvoda (FN Motol, Kardiovaskulární centrum FN Motol, Prague; 55), Zdenek Coufal (Zlin - Krajska nem. T.Bati, a.s, Zlin; 12), Zdenek Monhart (Nemocnice Znojmo, Znojmo; 27)

Denmark: Per Dahl Christensen (Viborg-Kjellerup Sygehus, Viborg; 6), Else Sørensen, Karen Dodt (Horsens Sygehus, Horsen; 5), Lars Frost (Regionshospitalet Silkeborg, Silkeborg; 17), Dorthe Dalsgaard (Regionshospitalet Herning, Herning; 12), John Markenvard (Fredericia Sygehus, Fredericia; 5), Ole Nyvad (Fredericia og Kolding Sygehuse, Kolding; 1), Knud Pedersen (Odense Universitetshospital, Odense; 8),

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Roman Sykulski (Storstrømmens sygehus, Næstved; 26), Kim Klarlund (Køge Sygehus, Køge; 35), Carl Dahlstrøm (Sygehus Syd, Slagelse; 14), Thomas Melchior (Roskilde Sygehus, Roskilde; 8), Tomas Jakobsen (Hillerød Sygehus, Hillerød; 10), Jan Jensen (Gentofte Amtssygehus, Hellerup; 39), Knud Skagen (Herlev Hospital, Herlev; 10), Søren Rasmussen (Hvidovre Hospital, Hvidorvre; 9), Jens Erik Nielsen (Glostrup Hospital, Glostrup; 32), Jens Brønnum-Schou (Amager Hospital, Copenhagen; 26), Peer Grande (Rigshospitalet, Copenhagen; 55), Christian Tuxen (Frederiksberg Hospital, Frederiksberg; 12), Tonny Nielsen (Sydvestjysk sygehus, Esbjerg; 26), Jens Petersen (Sygehus Vendsyssel, Hjørring; 8), Natasha Roseva-Nielsen (Sygehus Vestsjælland Holbæk, Holbæk; 13), Allan Mcnair, Margrethe Ege Olsen (Frederikssund Sygehus, Frederikssund; 3), Henrik Nielsen (Bispebjerg Hospital, Copenhagen; 2)

Finland: Ilkka Tierala (HUS, Meilahden sairaala, Helsinki; 6), Antti Ylitalo (Satakunnan keskussairaala, Pori; 10), Seppo Utriainen (Etelä-Karjalan keskussairaala, Lappeenranta; 2), Juha Hartikainen (Kuopin yliopistollinen sairaalam, Kuopio; 15), Juhani Airaksinen (Turun Yliopistollinen Keskussairaala, Turku; 30), Seppo Voutilainen (Päijät-Hämeen keskussairaala, Lahti; 14), Kai Nyman (Keski-Suomen keskussairaala, Jyväskylä; 44), Mikko Halkosaari (Keski-Pohjanmaan keskussairaala, Kokkola; 9), Alexandre Hadjikov (Lapin keskussairaala, Rovaniemi; 24)

France: Jean-Pierre Bassand (Hopital Jean Minjoz, Besancon; 18), Jean-Ernst Poulard (Centre Hospitalier Général dAbbeville, Abbeville; 10), Nourredine El Mansour (Nouvel Hôpital - Usic, Valenciennes; 73), Fabrice Leroy (Centre Hospitalier de Douai, Douai; 11), Gilles Traisnel (Polyclinique du Bois, Lille; 13), Eric Decoulx (Hopital de Tourcoing Guy Chatiliez, Tourcoing ; 20), Damien Maes (Clinique du Parc, Croix ; 2), Xavier Lamit (Hôpital Intercommunal de Fréjus Saint Raphaël, Fréjus; 2), Eric Maupas (Hôpital Privé les Franciscaines, Nîmes; 4), Gilles Bayet (Clinique Rhone Durance, Avignon; 10), Karim Gacem (H Marengo, Chloet; 11), Claude Cassat (CHU Dupuytren, Limoges; 4), Pierre Coste (Hôpital Cardiologique du Haut Lévêque, Pessaq; 7), Nicolas Delarche (Centre Hospitalier François Mitterrand, Pau; 11), Laurent Ledain (Centre Hospitalier St Louis, La Rochelle; 3), Gilles Mougeot (CHG de Senlis, Senlis; 13), Gery Hannebicque (Centre Hospitalier d´Arras, Arras; 17), Riadh Rihani (Centre Hospitalier Saint Philibert, Lomme; 13), François Philippe (Institut Mutualiste Montsouris, Paris; 4), Jean-Jacques Blanc (Hopital de la cavale Blanche, Brest; 15), Bruno Farah (Clinique Pasteur, Toulouse; 17), Hervé Le Breton (Che Pontchaillou, Rennes; 3), René Koning (Clinique Saint Hilaire, Rouen; 5), Patrick Henry (Hopital Lariboisiere, Paris; 7), Michèle Escande (CH Allauch, Allauch; 5), Jean-Luc Dubois-Rande (Hôpital Henri Mondor, Creteil; 7), Simon Elhadad (Centre Hospitalier de Lagny sur Marne, Lagny sur Marne; 48), Gilles Grollier (CHU Côte de Nacre, Caen; 9), Yves Cottin (CHU Bocage, Dijon; 15), Philippe Garot (Hôpital Claude Galien, Quincy sous Sénart; 10), Olivier Dibon (Hôpital de la Source, Orleans; 16), Jean-François Rousseau (CHG Bercagnes, Falaise; 3), Jean Noel Labeque (Centre Hospitalier Cote Basque, Bayonne; 3), Patrick Ohlmann (Hôpital de Hautepierre, Strasbourg; 7), Patrick Khanoyan (Hôpital Saint Joseph, Marseille; 8)

Georgia: Vakhtang Chumburidze (National Center of Therapy, Tblisi; 35), Kakhi Paposhvili (Clinical Hospital 2, Tblisi; 42), Irakli Megreladze (Cardiology Clinic, Tblisi; 70), Bondo Kobulia (Institute of Cardiology, Tblisi; 17), Nodar Emukhvari (Clinic 1, Tblisi; 39), Anzor Melia (Cardiological Clinic "GULI", Tblisi; 25), Merab Mamatsashvili (Clinic "ADAPTI", Tblisi; 52), Gulnara Chapidze (Emergency Cardiology Centre, Tblisi; 101), George Khabeishvili (Diagnostic Services Clinic, Tblisi; 138)

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Greece: Dimitrios Kremastinos (Attikon University General Hospital, Athens; 14), Stefanos Foussas (Tzaneio, General Hospital of Piraeus, Piraeus; 3), Antonis Manolis (Evangelismos General Hospital of Athens, Athens; 19), Panagiotis Vardas (University Hospital of Heraklion, Heraklion; 5), Georgios Theodorakis, Vassilis Voudris (Onassis Cardiac Surgery Center, Athens; 8), Filippos Triposkiadis (District University General Hospital of Larissa, Larissa; 7), Dimitrios Alexopoulos (University Hospital of Patra, Patra; 13), Georgios Parharidis (AHEPA Hospital of Thessaloniki, Thessaloniki; 21)

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India: Prem Pais (St. Johns Medical College Hospital, Bangalore; 9), Ramesh Babu Byrapaneni (Medwin Hospital, Hyderabad; 10), Ramesh Babu Pothineni (Citi Cardiac Research Center Ltd, Vijayawada; 7), Darshan Banker (Bankers Heart Institute, Vadodara; 79), Praveen Chandra (Max Heart & Vascular Hospital, New Delhi; 9), Prakash Chandwani (Tongia Heart & General Hospital, Jaipur; 1), Haridas Kottaram (Amrita Institute of Medical Sciences, Kochi; 8), Rajendra Kumar Premchand (Krishna Institute of Medical Sciences, Hyderabad; 26), Sharad Jain (Apollo Hospitals International Ltd., Gandhinagar; 10), Harshawardhan Mardikar (Spandan Heart Institute and Research Centre, Nagpur; 58), Padinhare Mohanan (West Fort Hi-Tech Hospital, Thrissur; 13), Arumugam Chandrakasu, Pradeep Nayar (Frontier Life Line Pvt. Ltd, Chennai; 4), Ashok Omar (Escorts Heart Institute & Research Center, New Dehli; 17), Raja Panwar (S.P. Medical College & Hospital, Bikaner; 70), Keyur Parikh (SAL Hospital & Medical Institute, Ahmedabad; 97), Swapan Kumar Paul (Peerless Hospital & B.K. Roy Research Center, Kolkata; 2), Robin Pinto (Holy Family Hospital, Mumbai; 11), Ramesh Srinivasaiah Saligrama (Bhagwan Mahaveer Jain Heart Centre, Bangalore; 20), Jitendra Pal Singh Sawhney (Sir Gangarams Hospital, New Dehli; 15), Skand Trivedi (Bhopal Memorial Hospital & Research Center, Bhopal; 68), Sudhir Varma (Sadbhavna Medical & Heart Institute, Patiala; 21), Subramaniam Bhuvaneswaran (PSG Hospitals, Coimabatore; 20)

Indonesia: Anwar Santoso (Sanglah Hospital, Denpasar; 18), Sunarya Soerianata (National Cardiovascular Center Harapan Kita Hospital, Jakarta; 12), Erwinanto Erwinanto (Hasan Sadikin Hospital, Bandung; 7), Sodiqur Rifqi (Telogorejo Hospital, Semarang; 8), I Gde Suryawan (Soetomo Hospital, Surabaya; 17)

Israel: Ariel Finkelstein (Tel Aviv Sourasky Medical Center, Tel Aviv; 171), Oscar Kracoff (Kaplan Medical Center, Rehovot; 27), Shmuel Gottlieb (Bikkur Cholim Hospital, Jerusalem; 23), Yonatan Hasin (Baruch Padeh Medical Center, Poriya; 133), Doron Zahger (Soroka Medical Center, Beer Sheva; 20), Basil Lewis (Lady Davis Carmel Medical Center, Haifa; 13), Chaim Lotan (Hadassah Ein Kerem Medical Center, Jerusalem; 56), Lev Bloch(Haemek Medical Center, Afula; 7), Uri Rosenschein (Bnai Zion Medical Center, Haifa; 34), Yoseph Rozenman (Wolfson Medical Center, Holon; 2), Simcha Meisel (Heart institute Hillel Yafe Medical Center, Hadera; 36), Marc Klutstein (Shaarei Zedek Medical Center, Jerusalem; 99), Amos Katz (Barzilai medical center, Ashkelon; 17), Zvi Vered (Assaf Harofeh Medical Center, Zerifin; 3)

Italy: Giampiero Perna (Ospedali Riunti Umberto I - Lancisi- Salesi, Ancona; 7), Italo De Luca (Azienda Ospedaliera " Ospedale Policlinico Consorziale", Bari ; 20), Antonello Gavazzi (Ospedali Riuniti di Bergamo, Bergamo; 13), Corrado Tamburino (Azienda Ospedalieria Universitario Vittorio Emanuele -

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Malaysia: Robaayah Zambahari (Institute Jantung Negara, Kuala Lumpur; 11), Kui Sim (Sarawak General Hospital, Kuching; 25), Omar Ismail (Penang General Hospital, Penang; 12), Wan Azman Wan Ahmad (University Malaya Medical Centre, Kuala Lumpur; 10)

Mexico: Armando García (MTY, IMSS34, Monterrey; 29), Mario Benavides (Hospital Universitario Eleuterio Gómez, Monterrey; 10), Gabriel Ramos (Hospital Civil De Guadalajara Dr Juan I Menchaca, Guadalajara; 49), Ernesto Cardona (Hospital Jardines de Guadalupe, Zapopan; 1), Pedro Gutierrez Fajardo (Hospital Bernardette, Guadalajara; 1), Alberto Romo (Centro Médico Nacional de Occidente, Guadalajara; 10), Carlos Martinez (DF, Cardio, CV, Tlalpan; 18), Alejandra Meaney (Hospital 1 de Octubre, ISSSTE, Mexico City; 1), Alejandra Meaney (Hospital Regional Dr Valentin Gomez Farias, ISSSTE, Zapopa; 1), Raul Velasco (GDL, Angel L., GI, Guadalajara; 2), Juan Carlos Nuñez (Hospital General de Durango, Durango; 9), Juan Perez (Hospital General de Puebla SSA, Puebla; 6)

Netherlands: Jan Hein Cornel (Medisch Centrum Alkmaar, Alkmaar; 86), Freek Verheugt (Universitair Medisch Centrum St. Radboud, Nijmegen; 5), Marco Alings (Amphia Ziekenhuis, Breda; 27), Peter Bendermacher (Elkerliek Ziekenhuis, Helmond; 67), Bryan Van Den Berg (IJsselland Ziekenhuis, Capelle aan den IJssel; 9), Hugo Beyerbacht (Röpcke-Zweers Ziekenhuis, Hardenberg; 9), Rolf Michels (Catharina Ziekenhuis, Eindhofen; 6), René Dijkgraaf (Ziekenhuis Sint Jansdal, Harderwijk; 26), Marcel Van Der Linde (Ziekenhuis Nij Smellinghe, Drachten; 28), Reginald Groutars (Sint Lucas Andreas Ziekenhuis, Amsterdam; 18), Bas Hamer (Meander Medisch Centrum, Amersfoort; 37), Frank Den Hartog (Ziekenhuis Gelderse Vallei, Ede; 24), Rob Van Der Heijden (Vlietland Ziekenhuis, Vlaardingen; 20), Klaas Holwerda (Sint Elisabeth Ziekenhuis, Tilburg; 9), Maarten Janssen (Kennemer Gasthuis, Haarlem; 11), Debbie Nicastia, W. Jap-Tjoen-San (Gelre Ziekenhuis, locatie Lukas, Apeldoorn; 2), Wim Aengevaeren (Rijnstate Ziekenhuis, locatie Arnhem, Arnhem; 34), Ben Gho (Atrium Heerlen, Heerlen; 22), Martin De Leeuw

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Norway: Leif Erik Erdal, Ole Rolstad (Sykehuset Innlandet HF Lillehammer, Lillehammer; 32), Ulf Hurtig (Sykehuset Innlandet HF Tynset, Tynset; 5), Kjell Andersen (Sykehuset Innlandet HF Hamar, Hamar; 18), Geir Høgalmen (Sykehuset Innlandet HF Gjøvik, Gjøvik; 10), Bjørn Jørgensen (Asker og Bærum sykehus HF, Rud; 10), Geir Heggelund (Universitetssykehuset i Nord-Norge HF, Tromsø; 7), Rune Fanebust (Helse Bergen HF Haukeland universitetssykehus, Bergen; 8), Gunvald Eivindson (Sørlandet sykehus HF Kristiansand, Kristiansand; 5), Torstein Gundersen (Sørlandet sykehus HF Arendal, Arendal; 14), Tor Omland (Sørlandet sykehus HF Flekkefjord, Flekkefjord; 11), Knut Tore Lappegård (Nordlandssykehuset HF Bodø, Bodø; 4), Erik Gjertsen (Sykehuset Buskerud HF, Drammen; 11), Pål Smith (Akershus universitetssykehus HF, Nordbyhagen; 5), Kjell Berget (Blefjell Sykehus HF Kongsberg, Kongsberg; 9), Dan Atar (Aker universitetssykehus HF, Oslo; 5), Nils Lid (Blefjell sykehus Notodden, Notodden; 4), Lars Gullestad (Rikshospitalet HF, Oslo; 1)

Phillipines: Noe Babilonia (Philippine Heart Center, Quezon City; 28), John Anonuevo (Philippine General Hospital, Manila; 1), Richard To (The Medical City, Pasig City; 9), Gregorio Rogelio (St. Lukes Medical Center, Quezon City; 10), Edgar Molleno (Perpetual Succour Hospital, Cebu City; 11), Cesar Estalilla Iii (Cebu Doctors University Hospital, Cebu City; 4), Raul Martin Coching (Davao Doctors Hospital, Davao City; 15)

Poland:

Andrzej Budaj (SPZOZ. Szpital Grochowski im. dr med. Rafała Masztaka, Warszawa; 52), Pawel Buszman (Wieńcowych SP Szpital, Katowice; 133), Maciej Dalkowski (Miedziowe Centrum Zdrowia SA, Lubin; 207), Robert Gil (Centralny Szpital Kliniczny MSWiA, Warszawa; 5), Andrzej Kleinrok (Szpital Wojewódzki im. Jana Pawła II, Zamosc; 12), Wlodzimierz Krasowski (Szpital Specjalistyczny św. Wojciecha Adalberta, Gdansk; 34), Jerzy Lewczuk (Wojewódzki Szpital Specjalistyczny ul, Wroclaw; 53), Wladyslaw Pluta (Wojewódzkie Centrum Medyczne, Opole; 59), Roman Szelemej (Specjalistyczy Szpital im.dr Sokołowskiego, Walbrzych; 39), Hanna Szwed (KlinikaChoroby Wieńcowej, Warszawa; 90), Jacek Gessek (Szpital Miejski im. M. Kopernika, Torun; 81), Pawel Miekus (Szpital Miejski im. J. Brudzińskiego, Gdynia; 78), Jacek Kubica (Klinika Kardiologii, Bydgoszcz; 97), Zygfryd Reszka (Wojewódzki Szpital Zespolony Ul, Elblag; 44), Malgorzata Krzciuk (Krzciuk Oddział Kardiologii ul, O. Swietokrzyski; 14), Barbara Kusnierz

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Portugal: João Morais(Hospital de Santo André, Leiria; 13), Isabel Arroja (Centro Hospitalar Lisboa Ocidental-HSF Xavier, Lisboa; 7), Nunes Diogo (Hospital de Santa Maria, Lisboa; 16), José Ferreira Santos (Hospital de São Bernardo, Setúbal; 11), Leitão Marques (Centro Hospitalar Coimbra, Coimbra; 19), Gonçalo Proença (Hospital Amadora-Sintra, Amadora; 8), Graça Da Silva (Hospital Distrital de Santarém, Santarém; 7), Luís Gonçalo (Hospital Padre Américo/Vale do Sousa, Penafiel; 13), Santos Mendes (Hospital de São Sebastião, Santa Maria da Feira; 4), Carlos Gonçalves (Centro Hosp Vila Nova Gaia, Vila Nova de Gai; 29), Pedro Cardoso (Hospital Infante D. Pedro, Aveiro; 17), Ilídio Moreira (Centro Hospitalar Trás os Montes e Alto Douro, Vila Real; 5), Luís Miguel Pereira (Hospital S Marcos, Braga; 3)

Romania: Marius Vintila (Sf.Pantelimon, Bucharest; 54), Mircea Cinteza (UCH Bucharest, Bucharest; 103), Catalina Arsenescu Georgescu (Centrul de Cardiologie Iasi, Isai; 1), Radu Capalneanu (Institutul Inimii "Niculae Stancioiu", Cluj Napoca; 2), Mariana Radoi (Cardiology Brasov, Brasov; 3), Dan Ionescu (Cardiology Center Craiova, Craiova; 52), Gabriela Stanciulescu (County Hospital Arges, Pitesti; 110), Bogdan Minescu (County Hospital Braila, Braila; 34), Marilena Spiridon (Spitalul Clinic Judetean de Urgenta"Sf.Spiridon", Isai; 20), Mihai Creteanu (Spitalul Clinic Judetean de Urgenta, Suceava; 11), Mircea Constantinescu (Spitalul Judetean Buzau, Buzau; 7)

Russia: Alexey Duda (Altay Regional Cardiology Dispensary, Barnaul; 28), Olga Lesnyak (Sverdlovsk Regional Clinical Hospital 1, Ekaterinburg; 24), Mikhail Arkhipov (New Hospital Medical Union, Ekaterinburg; 40), Elena Ovcharenko (Irkutsk Regional Clinical Hospital after Znak Pocheta Order, Irkutsk; 20), Svatlana Akhunova (Interregional Clinical and Diagnostic Center, Kazan; 20), Anna Dembitskaya (Kaliningrad Regional Hospital, Kaliningrad; 25), Olga Barbarash (Kemerovo Cardiology Dispensary,

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Kemerovo; 36), Prokhor Pavlov (Khanty-Mansiysk Regional Clinical Hospital, Khanty-Mansiysk; 18), Sergey Ustyugov, Galina Nechepurenko (Karpovich City Clinical Hospital, Krasnoyarsk; 2), Kirill Linev (Regional Clinical Hospital, Krasnoyarsk; 3), Vladimir Shulman (Berzon City Clinical Hospital 20, Krasnoyarsk; 44), Ivan Gordeev (City Filatov Clinical Hospital 15, Moscow; 36), Mikhail Ruda (Russian Cardiology Research and Manufacturing Complex, Moscow; 4), Dmitry Zateyshchikov (Moscow State Healthcare Institution City Hospital 17, Moscow; 28), Boris Sidorenko (Moscow State Healthcare Institution, City Clinical Hosp 51, Moscow; 2), Garry Klein (Bayandin Murmansk Regional Clinical Hospital, Murmansk; 29), Igor Fomin (City Clinical Hospital 5, Nizhniy Novgorod; 12), Elena Kosmachova (Krasnodar Ochapovsky Regional Clinical Hospital 1, Krasnodar; 13), Dmitry Belenky (Novosibirsk Clinical Hospital for Emergency Care 2, Novosibirsk; 22), Vladimir Ganyukov (Novosibirsk Regional Clinical Cardiology Dispensary, Novosibirsk; 15), Svetlana Baum (Road Clinical Hospital at Novosibirsk-Glavniy Station, Novosibirsk; 11), Larisa Khaisheva, Ludmila Katelnitskaya (City Hospital for Emergency Care 2, Rostov-naDonu; 25), Rumiya Miftyakhova (Samara Regional Clinical Cardiology Dispensary, Samara; 27), Natalia Burova (Federal Research Center of Heart, Blood and Endocrin, St Petersburg; 32), Svetlana Boldueva (St.Petersburg Mechnikov State Medical Academy, St Petersburg; 19), Alexey Sherbak (St.Petersburg City Multiservice Hospital 2, St Petersburg; 6), Alexander Petrov (Leningrad Regional Clinical Hospital, St Petersburg; 7), Victor Kostenko (St.Petersburg Dzhanelidze Research Inst for Emergency Care, St Petersburg; 24), Alexander Filippov (Kirov Military Medical Academy under the Ministry of Defence, St Petersburg; 2), Alexander Vishnevsky (St.Petersburg City Pokrovskaya Hospital, St Petersburg; 28), Valentin Markov (Research Cardiology Institute Tomsk Scientific Center, Tomsk; 45), Vadim Kuznetsov (Tyumen Cardiology Center, Tuymen; 26), Vladimir Verin (Primorskaya Regional Clinical Hospital 1, Vladivostok; 5)

Singapore: Soo Teik Lim (National Heart Centre, Singapore; 36), Dinesh Nair, Ing Haan Lim, Jimmy Lim (Tan Tock Seng Hospital, Singapore; 28)

Slovakia: Tibor Duris (Interna klinika FNsP, Nove Zamky; 15), Viliam Fridrich (Oddelenie intervencnej kardiológie NUSCH, BA, Bratislava; 17), Pavel Vahala (Interna klinika FN, Nitra; 11), Pavel Cuncik (Nemocnica A, Wintera, Piestany; 3), Margita Belicova (Interna klinika, Martinska fakultna nemoc, Martin; 73), Martin Studencan (Kardiologicke oddelenie VUSCH Kosice, Kosice; 85), Stanislava Remisova (IV, interna klinika FN a LF, Bratislava; 4), Peter Kycina (Interne oddelenie NsP, Liptovsky Mikulas; 12), Vladimir Macek (Interne oddelenie FN, Trnava; 34), Vladimir Spisak (Interne odd, a odd, arytmii NsP, Zilina; 1), Miroslav Urban (Interna klinika Ustredna vojenska nemocnica SNP,Ruzomberok ; 23), Marian Hranai (Kardiocentrum s.r.o Nitra, Nitra; 60)

South Africa: Edmund Brice, Hellmuth Weich (Tygerberg Hospital, Cape Town; 38), Jacobus Badenhorst (Unitas Hospital, Pretoria; 10), Adrian Horak (Vincent Palloti, Cape Town; 28), Saleem Dawood (SY Dawood, Cape Town; 27), Hendrik Theron (Netcare Private Hospital, Bloemfontein; 32), Tom Mabin (CT, Somerset West, Vergelen, Somerset West; 14)

South Korea: Ki Bae Seung (Kangnam St. Marys Hospital, Seoul; 21), In Ho Chae, Young-Seok Cho (Seoul National University Bundang Hospital, Seongnam; 3), Cheol-Whan Lee (Asan Medical Centre, Seoul; 19), Seung-Jea Tahk (Ajou University Hospital, Suwon; 12), Jung Han Yoon (Yonsei University Wonju Christian

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Switzerland: Bernhard Meier (Inselspital, Bern; 14), Tiziano Moccetti (Cardiocentro Ticino, Lugano; 151), Michael Pieper (Herz- und Neuro-Zentrum Bodensee, Kreuzlingen; 28), Marco Roffi, Vitali Vérin (Hôpital universitaire Genève, Genève; 4), Alberto Pagnamenta (Ospedale Regionale di Mendrisio Beata Vergine, Mendrisio; 11), Augusto Gallino (Ospedale San Giovanni, Bellinzona; 3), Martin Brack, Hans-Rudolf Baur (Tiefenauspital, Bern; 3)

Taiwan: Ming-Shien Wen (Chang Gung Memorial Hospital - Linkou, Kweishan Shiang; 11), Wen-Jone Chen (National Taiwan University Hospit, Taipei; 20), Ying-Hwa Chen (Veterans General Hospital, Taipei; 15), Charles Hou (Macaky Memorial Hospital, Tapei; 22), Mien-Cheng Chen (Chang-Gung Memorial Hospital- Kaohsiung, Niao-Song-Shiang; 24)

Thailand:

Piyamitr Sritar (Ramathibodi Hospital, Bankok; 25), Suphot Srimahachota (Chulalongkorn, Bangkok; 24), Srun Kuanprasert (Maharajnakorn Chiang Mai, Chiang Mai; 55), Chaiyasit Wongvipaporn (Srinagarind Hospital, Khon Kaen; 30), Nakarin Sansanayudh (Phramongkutklao, Bankok; 19)

Turkey: Ali Oto (Hacettepe University, Ankara; 2), Fatih Ertas (Ankara University Medicine Faculty, Ankara; 3), Ahmet Temizhan (SB Turkiye Yuksek Ihtisas Training and Research Hospital, Ankara; 1), Zerrin Yigit (Istanbul University, Istanbul; 13), Mesut Demir (Cukurova University, Adana; 10), Gokhan Cin

(Mersin University, Mersin; 5), Aytul Belgi (Akdeniz University, Antalya; 5), Bengi Yaymaci (Kartal Yuksek Ihtisas Education and Research Hospital, Istanbul; 12)

Ukraine: Igor Krayz (Ukrainian Railway Central Clinical Hospital, Kharkov; 58), Lyudmila Kononenko (Kharkov City Clinical Hospital 27, Kharkov; 20), Vira Tseluyko (Kharkov City Clinical Hospital 8, Kharkov; 14), Alexander Parkhomenko (Institute of Cardiology, Emergency and Intensive Therapy, Kiev; 15), Oleksandr Karpenko (Kiev City Clinical Hospital 1; 16), Olena Koval Dnepropetrovsk (Emergency Hospital, Dnepropetrovsk; 23), Leonid Rudenko (Kiev City Clinical Emergency Hospital, Kiev; 17), Mykola Vatutin (Inst of Urgent and Recovery Surgery DNMU Int Medicine, Donetsk; 4), Natalyia Kalinkina(Makiyivka City Clinical Hospital No 1 DNMU Int. Dis., Makiyivka; 2)

United Kingdom: Robert Storey (Northern General Hospital, Sheffield; 91), Greg Lip (City Hospital, Birmingham; 11), Ranjit More (Victoria Hospital, Blackpool; 46), Rajdeep Khattar (Manchester Royal Infirmary, Manchester; 15), Ian Hudson (Glenfield Hospital, Leicester; 3), Iain Squire (Leicester Royal Infirmary, Leicester; 13), Mark De Belder (James Cook University Hospital, Middlesborough; 6), Alastair Pell (Monklands Hospital, Airdrie; 3), Keith Oldroyd (Western Infirmary, Glasgow; 23), Chim Lang (Ninewells Hospital, Dundee; 17), Keith Fox (Edinburgh Royal Infirmary, Edinburgh; 8), Niall Herity (Belfast City Hospital, Belfast; 13), Andrew Moriarty (Craigavon Area Hospital, Belfast; 7), Mark Ramsey (Morriston Hospital, Swansea; 16), Patrick O'Callaghan (Royal London Hospital, London ; 1), Martin Wilkins (Hammersmith Hospital, London; 4), Diane Bruce (Poole General Hospital, Poole; 1), Andrew Bishop (North Hampshire Hospital, Basingstoke; 3)

United States of America: Salvador Lanza (Florida Hospital Altamonte, Orlando; 1), Theodore Lau (FHS Research Center, Tacoma; 19), David Henderson, John Walker (Cardiology Research Associates, Ormond Beach; 49), Michael Imburgia (Louisville Cardiology Medical Group, PSC, Louisville; 21), Paul Gurbel (Sinai Centre for Thrombosis Research, Baltimore; 10), Joseph Raffeto (Peninsula Cardiology Associates, Salisbury; 8), James Donovan (Norton Suburban Hospital Cardiovascular Associates, Louisville; 10), Venkatesh Nadar (Heritage Cardiology Associates, Camp Hill; 6), Steven Minor (Austin Heart P.A., San Marcos; 7), William Rogers (University of Alabama at Birmingham, Birmingham; 2), Frank Lester (IMC Diagnostic & Medical Clinic Mobile Infirmary, Mobile; 1), James Bengston (St. Joseph Mercy Oakland Hospital, Pontiac); 8), Wayne Leimbach (Oklahoma Heart Institute, Tulsa; 7), Vibhuti Singh (Suncoast Cardiovascular Research, St Petersburg; 10), Ernesto Rivera (Amarillo Heart Clinical Research Institute, Amarillo; 6), Ralph Vicari (Holmes Regional Medical Center, Melbourne); 7), Jerome Anderson (Integris Heart Hospital, Oklahoma City; 2), Vasilios Papademetriou (VA Medical Center - DC, Washington; 4), Michael Rich (St Marys Duluth Clinic, Duluth; 8), Drew Purdy (Black Hills Clinical Research Ctr, Rapid City; 3), Paul Casale (Lancaster General Hospital, Lancaster; 8), John Corbelli (Buffalo Cardiology & Pulmonary Associates, Williamsville; 4), Steven Guidera (Doylestown Hospital, Doylestown; 57), John Murphy (South County Cardiology Associates Inc, Wakefield; 5), William Wu (Central Cardiovascular Research Foundation, San Antonio; 4), John Gordon (San Diego Cardiac Ctr, San Diego; 3), Biswajit Kar (VA Medical Center - TX, Houston; 16), Diwakar Lingham, Jorge Davidenko (New York Heart Center, Syracuse; 4), Brian Friedman (Olathe Medical Center, Olathe; 1), Michael Lim (St. Louis University Health Sciences Center, St Louis; 16), Magdi Ghali (Iowa Heart Center PC, West Des Moines; 19), John Sinden, Marc Silver (Raleigh Cardiology, Raleigh; 3), Henry Lui (APEX Cardiology PC, Jackson; 22), Steven Yakubov (Midwest

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Hospital, Kansas City; 3), Thomas Stuckey (LeBauer CV Research Foundation, Greensboro; 19), Atul Aggarwal (Nebraska Heart Institute, Lincoln; 2)

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Osteoprotegerin Is Associated With Major Bleeding But Not With Cardiovascular Outcomes in Patients With Acute Coronary Syndromes: Insights From the PLATO (Platelet Inhibition and Patient Outcomes) Trial

Thor Ueland, Axel Åkerblom, Tatevik Ghukasyan, Annika E. Michelsen, Pål Aukrust, Richard C. Becker, Maria Bertilsson, Anders Himmelmann, Stefan K. James, Agneta Siegbahn, Robert F. Storey, Frederic Kontny, Lars Wallentin and the PLATO (Platelet Inhibition and Patient Outcomes) Trial Investigators

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