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ORIGINAL RESEARCH

Prediction of Residual Risk by Ceramide-Phospholipid Score in Patients With Stable Coronary Heart Disease on Optimal Medical Therapy

Mika Hilvo, PhD*; Lars Wallentin, MD, PhD*; Tatevik Ghukasyan Lakic, MSc; Claes Held, MD, PhD; Dimple Kauhanen, MSc; Antti Jylhä, MSc; Johan Lindbäck, MSc; Agneta Siegbahn, MD, PhD; Christopher B. Granger, MD; Wolfgang Koenig, MD, PhD; Ralph A. H. Stewart, MD; Harvey White, MD; Reijo Laaksonen, MD, PhD; on behalf of the STABILITY Investigators†

BACKGROUND: Identification of patients with stable coronary heart disease who are at significant residual risk could be helpful for targeted prevention. Our aim was to determine the prognostic value of the recently introduced ceramide- and phospholipid-based risk score, the Cardiovascular Event Risk Test (CERT2), in patients with stable coronary heart disease on optimal medical therapy and to identify biological processes that contribute to the CERT2 score.

METHODS AND RESULTS: Plasma samples (n=11 222) obtained from the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial were analyzed using a tandem liquid chromatography-mass spectrometry method. STABILITY was a trial in patients with stable coronary heart disease randomized to the lipoprotein-associated phospholipase A2 inhibitor darapladib or placebo on optimized medical therapy at baseline, with a median follow-up of 3.7 years. Hazard ratios per SD for the CERT2 risk score were 1.32 (95% CI, 1.25–1.39) for major adverse cardiovascular event, 1.47 (95% CI, 1.35–1.59) for cardiovascular death, 1.32 (95% CI, 1.16–1.49) for stroke, 1.23 (95% CI, 1.14–1.33) for myocardial infarction, and 1.56 (95% CI, 1.39–1.76) for hospitalization due to heart failure, when adjusted for traditional cardiovascular risk factors. CERT2 showed correlation ($P<0.001$, $r>0.2$) with inflammatory markers high-sensitivity C-reactive protein, interleukin 6, the heart failure marker N-terminal pro-B-type natriuretic peptide, and low-density lipoprotein cholesterol. After also adjusting for levels of other prognostic biomarkers, the CERT2 score was still independently related to the risk of cardiovascular death but not to nonfatal events.

CONCLUSIONS: The CERT2 risk score can detect residual risk in patients with stable coronary heart disease and is associated with biomarkers indicating inflammation, myocardial necrosis, myocardial dysfunction, renal dysfunction, and dyslipidemia.

REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00799903.

Key Words: biomarker ■ cardiovascular ■ CERT2 ■ inflammation ■ lipid ■ risk

Distinct ceramide lipid species either alone or combined in a score have been shown to be associated with cardiovascular mortality both in primary and secondary prevention.[1,2] Recently, the ceramide score prognostic value was further improved by adding omega-3 fatty acid containing phospholipids into

Correspondence to: Lars Wallentin, MD, PhD, Uppsala Science Park, Dag Hammarskjölds väg 38, 751 85 Uppsala, Sweden. Email: lars.wallentin@ucr.uu.se or Reijo Laaksonen, MD, PhD, Zora Biosciences Oy, Tietotie 2C, 02150 Espoo, Finland. Email: reijo.laaksonen@zora.fi

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*Dr Hilvo and Dr Wallentin contributed equally to this work.

†A complete list of the STABILITY Investigators can be found in Appendix S1.

For Sources of Funding and Disclosures, see page 10.

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CLINICAL PERSPECTIVE

What Is New?

- The Cardiovascular Event Risk Test (CERT2) risk score can detect residual risk in patients with stable coronary heart disease on optimized medical therapy and is associated with inflammation, myocardial necrosis, myocardial dysfunction, renal dysfunction, and dyslipidemia.
- CERT2 showed robust performance in a study population covering various geographical locations worldwide.

What Are the Clinical Implications?

- The CERT2 risk score can be considered as a risk indicator in patients with stable coronary heart disease and it can be used in evaluating residual risk in patients taking guideline-recommended optimal medical therapy.
- CERT2 can be used to detect both lipid and inflammatory residual risk in patients with stable coronary heart disease.

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
CHD	coronary heart disease
DM	diabetes mellitus
HHF	hospitalization for heart failure
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
hs-TnT	high-sensitivity troponin T
IL-6	interleukin 6
LDL-C	low-density lipoprotein cholesterol
MI	myocardial infarction
NI	negative ionization
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PI	positive ionization
STABILITY	Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy

the risk algorithm.[3] It is not entirely clear why these lipid molecules, in several cohorts, have appeared to be significantly better prognostic markers than hs-CRP (high-sensitivity C-reactive protein) and low-density lipoprotein cholesterol (LDL-C).[1–3] It is known, however, that ceramides play a central role in controlling apoptosis.[4] In addition, ceramides have a bioactive role in inflammatory signaling, where there seems to be a vicious cycle between several cytokines and ceramides that maintain each other's biosynthesis, leading potentially to harmful chronic inflammation.[5,6] Furthermore, there is much evidence that certain ceramide species associate tightly with insulin resistance and diabetes mellitus (DM) risk.[7,8] Recently, sphingolipids, including ceramides, have been shown to accelerate low-density lipoprotein particle aggregation and infiltration into the arterial wall.[9]

All of the above mechanisms seem theoretically relevant and support the role of ceramides as potentially clinically important factors in patients with stable coronary heart disease (CHD). However, a better understanding of the associations between ceramides with cardiovascular outcomes and different biological processes would help in clinical interpretation and decision making. To this end, we analyzed the ceramide-phospholipid score (Cardiovascular Event Risk Test [CERT2]) and its components in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial, which is large-scale global trial with a rich biobank, including not only carefully defined cardiovascular phenotypes but also information on a large variety of other risk factors and biomarkers. These new data allowed us to investigate the associations between CERT2 and conventional cardiovascular risk factors and other prognostic biomarkers and also to evaluate the associations between CERT2 and cardiovascular outcomes. The purpose was to increase our understanding on the mechanisms behind the associations between CERT2 and its components and residual risk in patients with CHD.

METHODS

As a result of limitations in the informed consent obtained from the participants, the data of the study cannot be made publicly available. For research use, the data can be requested from the corresponding author Lars Wallentin, and the proposed collaborations will be handled in the STABILITY trial steering committee.

Study Population

STABILITY and its biomarker substudy have been previously described in detail.[10,11] In brief, the trial was performed in 39 countries to investigate the effect of darapladib, a selective inhibitor of lipoprotein-associated phospholipase A_2 for cardiovascular events in patients with stable CHD taking optimal secondary prevention treatment. The inclusion criteria were previous myocardial infarction (MI), percutaneous coronary intervention, coronary artery bypass grafting, or demonstrated multivessel coronary artery disease (CAD). In addition, patients had to be on statin treatment and have at least 1 of the following criteria: age ≥60 years, DM requiring

pharmacotherapy, high-density lipoprotein cholesterol <40 mg/dL, smoker (defined as at least 5 cigarettes per day on average) or a previous smoker (defined as at least 5 cigarettes per day on average when smoking) who discontinued within the past 3 months, moderate renal dysfunction, or concomitant cerebrovascular or peripheral arterial disease. STABILITY investigators were strongly encouraged to treat patients according to local guidelines for secondary prevention and to ensure that all patients were taking antiplatelet therapy and a statin. Investigators were also encouraged to address nonpharmacological preventive care measures to achieve risk factor targets for secondary prevention according to European Society of Cardiology, American Heart Association/American College of Cardiology, or national guidelines. The exclusion criteria were MI during the previous month, coronary revascularization during the previous 3 months, or planned coronary revascularization procedure. The median follow-up time was 3.7 years (interquartile range, 3.5–3.8). In patients included in the biomarker substudy, blood samples were obtained at randomization. Plasma aliquots were stored at –70°C until later analysis. The biomarkers in the STABILITY biomarker substudy program were analyzed at the Uppsala Clinical Research Center Laboratory as previously described.[11,12] The trial was approved by the institutional review boards and performed in accordance with the Declaration of Helsinki. All patients provided written informed consent for their participation. The trial was funded by GlaxoSmithKline and has been registered at ClinicalTrials.gov (NCT00799903; https://clinicaltrials.gov/ct2/show/NCT00799903).

Analysis of CERT2 Score Lipids

The CERT2 score comprises 7 lipids and is calculated based on the quartiles of 3 lipid ratios [ceramide(d18:1/24:1)/ceramide(d18:1/24:0), ceramide(d18:1/18:0)/phosphatidylcholine 14:0/22:6, and ceramide(d18:1/16:0)/phosphatidylcholine 16:0/22:5] and a single lipid (phosphatidylcholine 16:0/16:0). The score range was 0 to 12 points and stratified into 4 risk categories (0–3, low; 4–6, moderate; 7–8, increased; and 9–12, high). Details of CERT2 and CERT1 score calculation have been previously described.[3]

For the measurement of CERT2 lipids, baseline plasma samples from 11 222 participants were analyzed on a hybrid triple quadrupole/linear ion trap mass spectrometer (QTRAP 5500, AB Sciex), equipped with an ultra-high performance liquid chromatography (Nexera-X2, Shimadzu). Ceramide lipids were analyzed with a validated method, as previously described.[13] Phospholipids were analyzed from the same extract as ceramides and with a targeted phospholipid platform. The chromatography was performed on an ACQUITY UltraPerformance LCBEH C18, 2.1×50 mm id 1.7 µm column (Waters Corp). Mobile phases consisted of: (A) 10 mmol/L ammonium acetate in liquid chromatography-mass spectrometry grade water with 0.1% formic acid, and (B) 10 mmol/L ammonium acetate in acetonitrile:2-propanol (3:4, V/V) with 0.1% formic acid. The following liquid chromatography gradient was used: 0.5 min at 75% B, linear increase of B from 75% to 100% in 2.0 min, 1.0 min at 100% B, 100% to 75% B in 0.1 min, and 0.9 min equilibration at 75% before the next injection. The flow rate was 500 µL/min and column temperature was 60°C. The injection volume of all samples was 5 µL. Positive ionization (PI) was used for ceramide analysis and negative ionization (NI) for phospholipid analysis, and the data were collected using multiple reaction monitoring. Mass spectrometry settings were the same for all ions, except for ion spray voltage, declustering potential, entry potential, and collision exit potential. The conditions were as following: curtain gas (nitrogen) 25, collision-activated dissociation (nitrogen) 6, temperature 300 C, gas 1: 50, gas2: 50, interface heater on, ion spray voltage (PI 5000, NI –4500 V), declustering potential (PI 30, NI –100 V), entry potential (PI 10, NI –10 V), and collision exit potential (PI 20, NI –20 V). A 10-ms dwell time was applied to all analytes. Collision energy was applied specifically for each lipid (Table S1). Results were processed using Analyst 1.6 and MultiQuant 3.0 software (AB Sciex).

Statistical Analysis

Baseline characteristics and patient demographics were compared between CERT2 risk groups using Kruskall–Wallis test for continuous variables and chi-square test for categorical variables. The association between the components of the CERT2 risk score and other biomarkers were assessed by Spearman rank correlation coefficient. Biomarkers were logarithmic transformed when appropriate. The unadjusted association between CERT2 risk groups and clinical outcomes were presented by Kaplan–Meier curves.

Definitions of all outcome events were prespecified, as previously described,[10] and the events were adjudicated by an independent clinical events committee. We evaluated the models and the included biomarkers' prognostic performance for the primary outcome of major adverse cardiovascular event (ie, the composite of cardiovascular death, stroke and MI, and cardiovascular death), as well as secondary outcomes: major cardiovascular events, major coronary events, ie, the composite of coronary death, MI, urgent revascularization, all-cause death, MI, stroke, hospitalization for heart failure (HHF), the composite of cardiovascular

death and HHF, and the composite of major adverse cardiovascular events and HHF.

Cox proportional hazards models were used to investigate the covariate-adjusted association between CERT2 risk score and outcomes. Four models were used, with an incremental addition of covariates. Model 0 included CERT2 risk score and randomized treatment. Model 1 included CERT2 risk score, randomized treatment, age, sex, prior MI, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), multivessel CAD, DM, hypertension, history of smoking, polyvascular disease, race, geographic region, systolic blood pressure, and body mass index. Model 2 included hemoglobin, white blood cell count, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation, LDL-C, high-density lipoprotein cholesterol, and triglycerides in addition to model 1. The final model (3) included the following covariates in addition to model 2: high-sensitivity troponin T (hs-TnT), NT-proBNP (N-terminal pro-B-type natriuretic peptide), cystatin C, hs-CRP, and interleukin 6 (IL-6). All continuous variables were included as restricted cubic splines with 4 knots placed at the 5th, 35th, 65th, and 95th sample percentiles, as previously suggested.[14] The results were presented as the relative hazard for a 1-SD increase in CERT2 risk score. The proportional hazards assumption was assessed by visual inspection of Schoenfeld residual plots. The discriminative value of CERT2 risk score was assessed using the C-index. The models with and without CERT2 risk score were compared using likelihood ratio tests.

A statement of statistical significance implies a 2-sided $P<0.05$, and there were no adjustments for multiple comparisons. All statistical analyses were performed with SAS 9.4 (SAS Institute Inc). L.W. and T.G.L. had full access to all of the data in the study and take responsibility for the integrity and data analysis.

RESULTS

Characterization of Patients in CERT2 Risk Groups

CERT2 risk score (0–12) was determined using the previously established ceramides and phosphatidylcholines[3] that were measured from baseline plasma samples of 11 222 patients who participated in the STABILITY trial. Patients with renal dysfunction, polyvascular disease and multivessel CAD, current smokers, and those with high white blood cell count showed higher CERT2 risk score (Table 1). There were regional differences in the risk groups, as patients especially from Eastern Europe were enriched in the high-risk category (9–12), whereas an opposite trend was observed for patients from the Asia/Pacific region and North America (Table 1). Regarding race, white patients and patients of Central/South/South East Asian origin had a tendency for a higher CERT2 score, while the opposite was evident for black and East Asian/Japanese patients (Table 1). There was no clear trend for DM, body mass index, systolic blood pressure, or history of hypertension (Table 1). In contrast, patients with prior percutaneous coronary intervention/coronary artery bypass grafting had a tendency for a lower CERT2 score. Patients with higher CERT2 score were less likely to be taking statins and anti-inflammatory and antiplatelet therapy (aspirin, P2Y12) (Table 1). There were significant positive associations between CERT2 risk categories and increased concentrations of biomarkers associated with an increased cardiovascular risk, ie, LDL-C, triglycerides, lipoprotein-associated phospholipase A_2, white blood cell count, hs-CRP, IL-6, hs-TnT, NT-proBNP, growth differentiation factor-15, creatinine clearance, and cystatin C (Table 1).

Prediction of Cardiovascular Risk by CERT2 Risk Score

There were statistically significant associations between CERT2 and all cardiovascular outcomes. For CERT2, the highest unadjusted hazard ratios (HRs) per SD were observed for cardiovascular death (HR, 1.57; 95% CI, 1.45–1.69), all-cause death (HR, 1.54; 95% CI, 1.45–1.64), and HHF (HR, 1.52; 95% CI, 1.35–1.70) (Table 2). Statistically significant associations were also observed for all other cardiovascular end points, including the primary composite end point for major adverse cardiovascular events or HHF and major coronary events, as well as MI and stroke separately (Table 2). The HRs were attenuated only slightly when the models were adjusted for multiple traditional cardiovascular risk factors and lipid biomarkers (Table 2). However, the HRs decreased more when additional biomarkers (hs-TnT, NT-proBNP, cystatin C, hs-CRP, and IL-6) were included in the models, after which only the end points including cardiovascular death remained significant (Table 2). In addition, the previous version of the ceramide score (CERT1) showed significant results for all of the end points (Table 3) but did not show as robust HRs as the improved CERT2 version. The unadjusted associations between CERT2 risk groups and the occurrence of major adverse cardiovascular events, HHF, and cardiovascular death are illustrated in Figure 1.

Addition of CERT2 on top of traditional risk factors improved the C index for all investigated end points. However, the CERT2 score provided very limited if any

Table 1. Patient Characteristics at the Time of Randomization by CERT2 Risk Score Categories

	CERT2: 0 to 3	CERT2: 4 to 6	CERT2: 7 to 8	CERT2: 9 to 12	*P* Value
No.	1708	4943	2795	1776	
Age, y	64 (58–70)	65 (59–71)	65 (59–71)	65 (58–72)	0.0004
Men, No. (%)	1405 (82.3)	4028 (81.5)	2287 (81.8)	1428 (80.4)	0.520
Geographic region, No. (%)					
Asia/Pacific	327 (19.1)	734 (14.8)	321 (11.5)	198 (11.1)	<0.0001
Eastern Europe	317 (18.6)	1341 (27.1)	974 (34.8)	784 (44.1)	
North America	524 (30.7)	954 (19.3)	384 (13.7)	184 (10.4)	
South America	49 (2.9)	167 (3.4)	121 (4.3)	55 (3.1)	
Western Europe	491 (28.7)	1747 (35.3)	995 (35.6)	555 (31.3)	
Race, No. (%)					
Black	66 (3.9)	108 (2.2)	50 (1.8)	23 (1.3)	<0.0001
Central/South/South East Asian	93 (5.4)	331 (6.7)	202 (7.2)	152 (8.6)	
East Asian/Japanese	202 (11.8)	317 (6.4)	91 (3.3)	40 (2.3)	
Other	40 (2.3)	114 (2.3)	44 (1.6)	31 (1.7)	
White	1307 (76.5)	4073 (82.4)	2408 (86.2)	1530 (86.1)	
Diabetes mellitus, No. (%)	677 (39.6)	1855 (37.5)	1064 (38.1)	736 (41.4)	0.023
Body mass index, kg/m^2	28.4 (25.8–31.7)	28.3 (25.6–31.5)	28.5 (25.8–32.0)	28.4 (25.3–32.0)	0.154
Systolic blood pressure, mm Hg	130 (120–142)	131 (121–143)	131 (120–143)	131 (120–144)	0.029
History of hypertension, No. (%)	1217 (71.3)	3513 (71.1)	1962 (70.2)	1270 (71.5)	0.765
Significant renal dysfunction, No. (%)*	416 (24.4)	1416 (28.6)	868 (31.1)	615 (34.6)	<0.0001
Prior MI, No. (%)	1025 (60.0)	3012 (60.9)	1761 (63.0)	1125 (63.3)	0.062
Prior percutaneous coronary intervention or coronary artery bypass grafting, No. (%)	1309 (76.6)	3606 (73.0)	2025 (72.5)	1230 (69.3)	<0.0001
Family history of premature CHD, No. (%)	456 (26.7)	1256 (25.5)	665 (23.9)	415 (23.4)	0.057
Polyvascular disease, No. (%)	191 (11.2)	738 (14.9)	478 (17.1)	375 (21.1)	<0.0001
Multivessel CAD, No. (%)	205 (12.0)	700 (14.2)	440 (15.7)	294 (16.6)	<0.0001
Smoking status, No. (%)					
Never smoked	570 (33.4)	1540 (31.2)	802 (28.7)	488 (27.5)	<0.0001
Current smoker	255 (14.9)	874 (17.7)	590 (21.1)	434 (24.4)	
Former smoker	882 (51.7)	2529 (51.2)	1403 (50.2)	854 (48.1)	
Missing		8 (0.2)	7 (0.3)	4 (0.2)	
Statin treatment, No. (%)	1677 (98.2)	4838 (97.9)	2733 (97.8)	1708 (96.2)	0.0002
High-intensity statin treatment, No. (%)	119 (7.0)	326 (6.6)	168 (6.0)	101 (5.7)	0.329
Aspirin, No. (%)	1622 (95)	4591 (92.9)	2557 (91.5)	1579 (88.9)	<0.0001
P2Y12, No. (%)	609 (35.7)	1662 (33.6)	917 (32.8)	556 (31.3)	0.047
ACEI or ARB, No. (%)	1340 (78.5)	3831 (77.5)	2189 (78.3)	1426 (80.3)	0.111
β-Blocker, No. (%)	1323 (77.5)	3907 (79.0)	2318 (82.9)	1457 (82.0)	<0.0001
Randomization to darapladib, No. (%)	823 (48.2)	2441 (49.4)	1388 (49.7)	933 (52.5)	0.059
White blood cell count, Gl/L	6.3 (5.4–7.3)	6.5 (5.5–7.7)	6.8 (5.7–8.0)	7.1 (5.9–8.4)	<0.0001
LDL-C, mmol/L	1.90 (1.53–2.33)	2.10 (1.66–2.61)	2.21 (1.76–2.82)	2.42 (1.90–3.08)	<0.0001
HDL-C, mmol/L	1.17 (1.00–1.36)	1.19 (1.00–1.40)	1.15 (0.98–1.37)	1.14 (0.95–1.36)	<0.0001
Triglycerides, mmol/L	1.44 (1.06–1.95)	1.52 (1.10–2.10)	1.53 (1.12–2.19)	1.57 (1.12–2.29)	<0.0001

(*Continued*)

Table 1. Continued

	CERT2: 0 to 3	CERT2: 4 to 6	CERT2: 7 to 8	CERT2: 9 to 12	*P* Value
eGFR (Chronic Kidney Disease Epidemiology Collaboration), mL/min/1.73 m^2	76.6 (64.4–88.1)	75.1 (63.3–86.9)	73.7 (61.0–86.2)	73.3 (59.1–86.1)	<0.0001
hs-CRP, mgL	0.9 (0.5–1.9)	1.2 (0.6–2.6)	1.8 (0.8–3.8)	2.5 (1.1–5.8)	<0.0001
hs-TnT, ng/L	8.4 (5.7–12.4)	8.9 (6.1–13.5)	10.0 (6.5–15.0)	10.9 (6.9–17.3)	<0.0001
NT-proBNP, ng/L	130 (64–262)	163 (82–344)	214 (103–464)	283 (123–691)	<0.0001
IL-6, pg/mL	1.7 (1.2–2.4)	2.0 (1.4–2.9)	2.3 (1.6–3.5)	2.7 (1.8–4.5)	<0.0001
Cystatin C, mg/L	0.96 (0.85–1.11)	0.99 (0.86–1.16)	1.03 (0.89–1.21)	1.06 (0.92–1.99)	<0.0001
GDF15, pg/mL	1138 (861–1654)	1198 (887–1711)	1283 (942–1852)	1438 (1040–2170)	<0.0001
Lp-PLA_2 activity, μmol/min per L	161 (134–191)	169 (141–200)	178 (149–209)	190 (156–224)	<0.0001

Chi-square or Kruskal–Wallis test. CAD indicates coronary artery disease; CERT, Cardiovascular Event Risk Test; CHD, coronary heart disease; GDF15, growth differentiation factor-15; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; IL-6, interleukin 6; LDL-C, low-density lipoprotein cholesterol; Lp-PLA_2, lipoprotein-associated phospholipase A_2; MI, myocardial infarction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Significant renal dysfunction defined as estimated glomerular filtration rate [eGFR] ≥30 and ≤59 mL/min per 1.73 m^2 OR urine albumin creatinine ratio ≥30 mg albumin/g creatinine.

incremental prognostic information when added to a model of 21 risk factors including also hs-TnT, NT-proBNP, cystatin C, hs-CRP, and IL-6 (Table 2).

Correlation of CERT2 Components With Other Cardiovascular Risk Biomarkers

Association of CERT2 and its components with other biomarkers was investigated, and the highest correlations for the score were observed for hs-CRP, IL-6, NT-proBNP, and LDL-C (Figure 2). Of the CERT2 components, ceramide(d18:1/24:1)/ceramide(d18:1/24:0) showed only modest correlation with any other biomarker, whereas ceramide(d18:1/18:0)/phosphatidylcholine(14:0/22:6) and ceramide(d18:1/16:0)/phosphatidylcholine(16:0/22:5) lipid ratios were especially correlated with the inflammatory markers hs-CRP and IL-6. The fourth component, phosphatidylcholine 16:0/16:0 showed a strong correlation with LDL-C, as did individual ceramide molecules that were also associated with triglycerides (Figure 2).

DISCUSSION

The present results confirmed an earlier association between CERT2 and cardiovascular events, especially all-cause and cardiovascular death.[3] In addition, for the first time we report an association between CERT2 and HHF. CERT2 was associated with clinical characteristics, cardiovascular risk factors and contemporary biomarkers, but, despite this, showed independent prognostic value after adjustment with numerous clinical variables including randomized treatment, age, sex, prior MI, prior percutaneous coronary intervention or coronary artery bypass grafting, presence of multivessel CAD, DM, history of hypertension, history of smoking, peripheral vascular disease, geographic region, systolic blood pressure, and body mass index. Furthermore, addition of standard laboratory information such as hemoglobin, white blood cell count, estimated glomerular filtration rate, LDL-C, high-density lipoprotein cholesterol, and triglycerides on top of the above-listed clinical parameters did not attenuate the predictive value of CERT2. However, after adding hs-TnT, NT-proBNP, cystatin C, hs-CRP, and IL-6 as adjusting factors, CERT2 was significantly associated only with fatal outcomes.

A clear strength of the present study was the validation of the performance of the CERT2 score in a large (N=11 222) clinical trial, which was conducted across different geographic regions and has a rich database of cardiovascular phenotypes and biomarkers. A limitation of the study was that the mass spectrometry method did not include standard compounds for all CERT2 components.

Future research will show whether patients with high CERT2 score will benefit from more aggressive lipid lowering by highest statin doses or PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors. In the present study, patients with high CERT2 score were significantly less frequently treated with aspirin. It remains to be evaluated whether aspirin treatment truly affects CERT2 score and serum concentrations of its components and whether the association is attributable to anti-inflammatory or antithrombotic processes, or both. In contrast, patients with high CERT2 risk score were more frequently treated with β-blockers. This observation, together with the other results, warrants systematic clinical and mechanistic investigations on how different medications affect ceramides and phosphatidylcholines. Moreover, systematic lifestyle intervention studies are needed to evaluate their usefulness in risk reduction in patients with high CERT2 score. Importantly, a ceramide synthesis inhibitor has

Table 2. HRs Per 1-SD (2.4) Increase of CERT2 for Different End Points and C-Indices for Models With and Without CERT2

End Point	HR (95% CI)	C-Statistic –CERT2	C-Statistic +CERT2	*P* Value
MACE or HHF				
Model 0	1.32 (1.26–1.39)	0.510 (0.498–0.522)	0.579 (0.565–0.594)	<0.0001
Model 1	1.35 (1.28–1.42)	0.665 (0.651–0.678)	0.684 (0.671–0.697)	<0.0001
Model 2	1.26 (1.20–1.33)	0.693 (0.680–0.706)	0.701 (0.688–0.715)	<0.0001
Model 3	1.08 (1.02–1.15)	0.750 (0.737–0.763)	0.751 (0.738–0.764)	0.009
MACE				
Model 0	1.30 (1.24–1.37)	0.508 (0.495–0.521)	0.575 (0.559–0.590)	<0.0001
Model 1	1.32 (1.25–1.39)	0.654 (0.640–0.669)	0.672 (0.658–0.686)	<0.0001
Model 2	1.23 (1.16–1.31)	0.682 (0.667–0.696)	0.689 (0.675–0.704)	<0.0001
Model 3	1.08 (1.02–1.15)	0.731 (0.717–0.745)	0.732 (0.718–0.746)	0.012
Major coronary event				
Model 0	1.26 (1.19–1.33)	0.515 (0.502–0.529)	0.566 (0.550–0.582)	<0.0001
Model 1	1.28 (1.21–1.36)	0.642 (0.627–0.657)	0.656 (0.641–0.671)	<0.0001
Model 2	1.20 (1.13–1.27)	0.671 (0.656–0.687)	0.676 (0.661–0.692)	<0.0001
Model 3	1.07 (1.00–1.14)	0.717 (0.702–0.732)	0.717 (0.702–0.732)	0.053
Cardiovascular death				
Model 0	1.57 (1.45–1.69)	0.510 (0.490–0.529)	0.625 (0.602–0.648)	<0.0001
Model 1	1.47 (1.35–1.59)	0.729 (0.710–0.749)	0.752 (0.733–0.770)	<0.0001
Model 2	1.38 (1.26–1.50)	0.760 (0.741–0.779)	0.771 (0.752–0.789)	<0.0001
Model 3	1.14 (1.04–1.26)	0.831 (0.815–0.847)	0.831 (0.815–0.847)	0.005
MI				
Model 0	1.16 (1.08–1.25)	0.512 (0.493–0.531)	0.542 (0.521–0.564)	0.0001
Model 1	1.23 (1.14–1.33)	0.649 (0.628–0.670)	0.657 (0.636–0.678)	<0.0001
Model 2	1.15 (1.06–1.25)	0.675 (0.655–0.696)	0.680 (0.659–0.700)	0.0009
Model 3	1.06 (0.97–1.16)	0.707 (0.687–0.728)	0.708 (0.688–0.729)	0.176
HHF				
Model 0	1.52 (1.35–1.70)	0.523 (0.495–0.551)	0.619 (0.587–0.652)	<0.0001
Model 1	1.56 (1.39–1.76)	0.761 (0.736–0.787)	0.787 (0.763–0.811)	<0.0001
Model 2	1.45 (1.28–1.64)	0.800 (0.777–0.822)	0.811 (0.789–0.833)	<0.0001
Model 3	1.02 (0.89–1.17)	0.892 (0.875–0.909)	0.892 (0.875–0.909)	0.763
Stroke				
Model 0	1.29 (1.15–1.46)	0.499 (0.470–0.529)	0.575 (0.541–0.610)	<0.0001
Model 1	1.32 (1.16–1.49)	0.655 (0.623–0.687)	0.672 (0.640–0.703)	<0.0001
Model 2	1.29 (1.14–1.48)	0.678 (0.644–0.711)	0.687 (0.655–0.720)	0.0001
Model 3	1.15 (0.99–1.33)	0.719 (0.689–0.750)	0.722 (0.692–0.752)	0.059
All-cause death				
Model 0	1.54 (1.45–1.64)	0.502 (0.486–0.518)	0.624 (0.605–0.643)	<0.0001
Model 1	1.44 (1.35–1.54)	0.711 (0.695–0.727)	0.736 (0.721–0.752)	<0.0001
Model 2	1.34 (1.25–1.44)	0.743 (0.727–0.758)	0.754 (0.738–0.770)	<0.0001
Model 3	1.12 (1.04–1.21)	0.800 (0.785–0.815)	0.801 (0.786–0.815)	0.003

Model 0 includes the Cardiovascular Event Risk Test (CERT2) score and randomized treatment. Model 1 includes CERT2 score, randomized treatment, age, sex, prior myocardial infarction (MI), coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), multivessel coronary artery disease), diabetes mellitus, hypertension, history of smoking, polyvascular disease, geographic region, systolic blood pressure, and body mass index. Model 2 includes the following covariates in addition to model 1: hemoglobin, white blood cell count, Chronic Kidney Disease Epidemiology Collaboration, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Model 3 includes the following covariates in addition to model 2: high-sensitivity troponin T, pro-B-type natriuretic peptide, cystatin C, high-sensitivity C-reactive protein, and interleukin 6. *P* value relates to the significance of the hazard ratio (HR). HHF indicates hospitalization for heart failure; and MACE, major adverse cardiovascular event.

been shown to significantly reduce lipid-induced insulin resistance.[15] Thus, it would be interesting to perform studies evaluating the effect of ceramide inhibition on the occurrence of complications in patients with stable CHD. CERT2 score contains omega-3 fatty acid–containing phosphatidylcholine molecules. Thus, the

Table 3. HRs Per 1-SD (3.4) Increase of CERT1 for Different End Points and C-Indices for Models With and Without CERT1

End Point	HR (95% CI)	C-Statistic –CERT	C-Statistic +CERT	*P* Value
MACE or HHF				
Model 0	1.20 (1.14–1.26)	0.510 (0.498–0.522)	0.554 (0.540–0.569)	<0.0001
Model 1	1.24 (1.18–1.31)	0.664 (0.650–0.677)	0.674 (0.661–0.688)	<0.0001
Model 2	1.21 (1.14–1.27)	0.693 (0.680–0.706)	0.697 (0.684–0.711)	<0.0001
Model 3	1.09 (1.03–1.15)	0.750 (0.737–0.763)	0.751 (0.738–0.763)	0.0031
MACE				
Model 0	1.19 (1.13–1.25)	0.508 (0.495–0.522)	0.551 (0.536–0.566)	<0.0001
Model 1	1.22 (1.16–1.29)	0.653 (0.639–0.668)	0.663 (0.649–0.677)	<0.0001
Model 2	1.18 (1.11–1.24)	0.682 (0.667–0.696)	0.685 (0.671–0.699)	<0.0001
Model 3	1.08 (1.02–1.15)	0.731 (0.717–0.745)	0.732 (0.718–0.746)	0.0126
Major coronary event				
Model 0	1.17 (1.11–1.23)	0.515 (0.502–0.529)	0.549 (0.533–0.565)	<0.0001
Model 1	1.21 (1.15–1.28)	0.641 (0.626–0.656)	0.649 (0.634–0.664)	<0.0001
Model 2	1.16 (1.10–1.24)	0.671 (0.656–0.686)	0.674 (0.658–0.689)	<0.0001
Model 3	1.08 (1.02–1.15)	0.716 (0.701–0.731)	0.717 (0.702–0.732)	0.0107
Cardiovascular death				
Model 0	1.26 (1.17–1.36)	0.511 (0.491–0.530)	0.566 (0.543–0.589)	<0.0001
Model 1	1.25 (1.16–1.35)	0.727 (0.707–0.747)	0.734 (0.715–0.754)	<0.0001
Model 2	1.22 (1.12–1.33)	0.758 (0.739–0.778)	0.761 (0.742–0.781)	<0.0001
Model 3	1.07 (0.98–1.17)	0.831 (0.815–0.847)	0.830 (0.814–0.847)	0.1462
MI				
Model 0	1.15 (1.07–1.24)	0.512 (0.493–0.531)	0.543 (0.522–0.565)	0.0001
Model 1	1.22 (1.13–1.32)	0.648 (0.627–0.669)	0.657 (0.636–0.678)	<0.0001
Model 2	1.15 (1.06–1.25)	0.675 (0.655–0.696)	0.678 (0.658–0.699)	0.0008
Model 3	1.10 (1.01–1.20)	0.706 (0.686–0.727)	0.708 (0.688–0.729)	0.0242
HHF				
Model 0	1.33 (1.20–1.49)	0.523 (0.495–0.551)	0.590 (0.558–0.621)	<0.0001
Model 1	1.39 (1.25–1.56)	0.762 (0.736–0.787)	0.779 (0.754–0.803)	<0.0001
Model 2	1.39 (1.23–1.56)	0.800 (0.777–0.822)	0.808 (0.786–0.830)	<0.0001
Model 3	1.09 (0.96–1.23)	0.892 (0.875–0.909)	0.892 (0.875–0.909)	0.1892
Stroke				
Model 0	1.24 (1.10–1.39)	0.499 (0.470–0.529)	0.567 (0.534–0.600)	0.0002
Model 1	1.28 (1.13–1.44)	0.655 (0.623–0.687)	0.669 (0.638–0.701)	<0.0001
Model 2	1.27 (1.12–1.44)	0.678 (0.645–0.712)	0.688 (0.655–0.720)	0.0003
Model 3	1.16 (1.02–1.33)	0.720 (0.689–0.750)	0.723 (0.692–0.753)	0.028
All-cause death				
Model 0	1.29 (1.21–1.37)	0.503 (0.487–0.519)	0.574 (0.555–0.593)	<0.0001
Model 1	1.25 (1.17–1.33)	0.710 (0.693–0.726)	0.720 (0.704–0.736)	<0.0001
Model 2	1.21 (1.13–1.29)	0.742 (0.726–0.758)	0.746 (0.730–0.762)	<0.0001
Model 3	1.07 (1.00–1.15)	0.800 (0.785–0.815)	0.800 (0.785–0.815)	0.0663

Model 0 includes the Cardiovascular Event Risk Test (CERT) score and randomized treatment. Model 1 includes CERT score, randomized treatment, age, sex, prior myocardial infarction (MI), coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), multivessel coronary artery disease, diabetes mellitus, hypertension, history of smoking, polyvascular disease, geographic region, systolic blood pressure, and body mass index. Model 2 includes the following covariates in addition to model 1: hemoglobin, white blood cell count, Chronic Kidney Disease Epidemiology Collaboration, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Model 3 includes the following covariates in addition to model 2: high-sensitivity troponin T, pro-B-type natriuretic peptide, cystatin C, high-sensitivity C-reactive protein, and interleukin 6. HHF indicates hospitalization for heart failure; and MACE, major adverse cardiovascular event.

protective effect of fish oils[16] might be associated with these particular phosphatidylcholines and they may serve as a proxy of supplementation efficacy.

Evaluation of associations between CERT2 score and clinical characteristics as well as other biomarkers revealed no significant relationship between CERT2

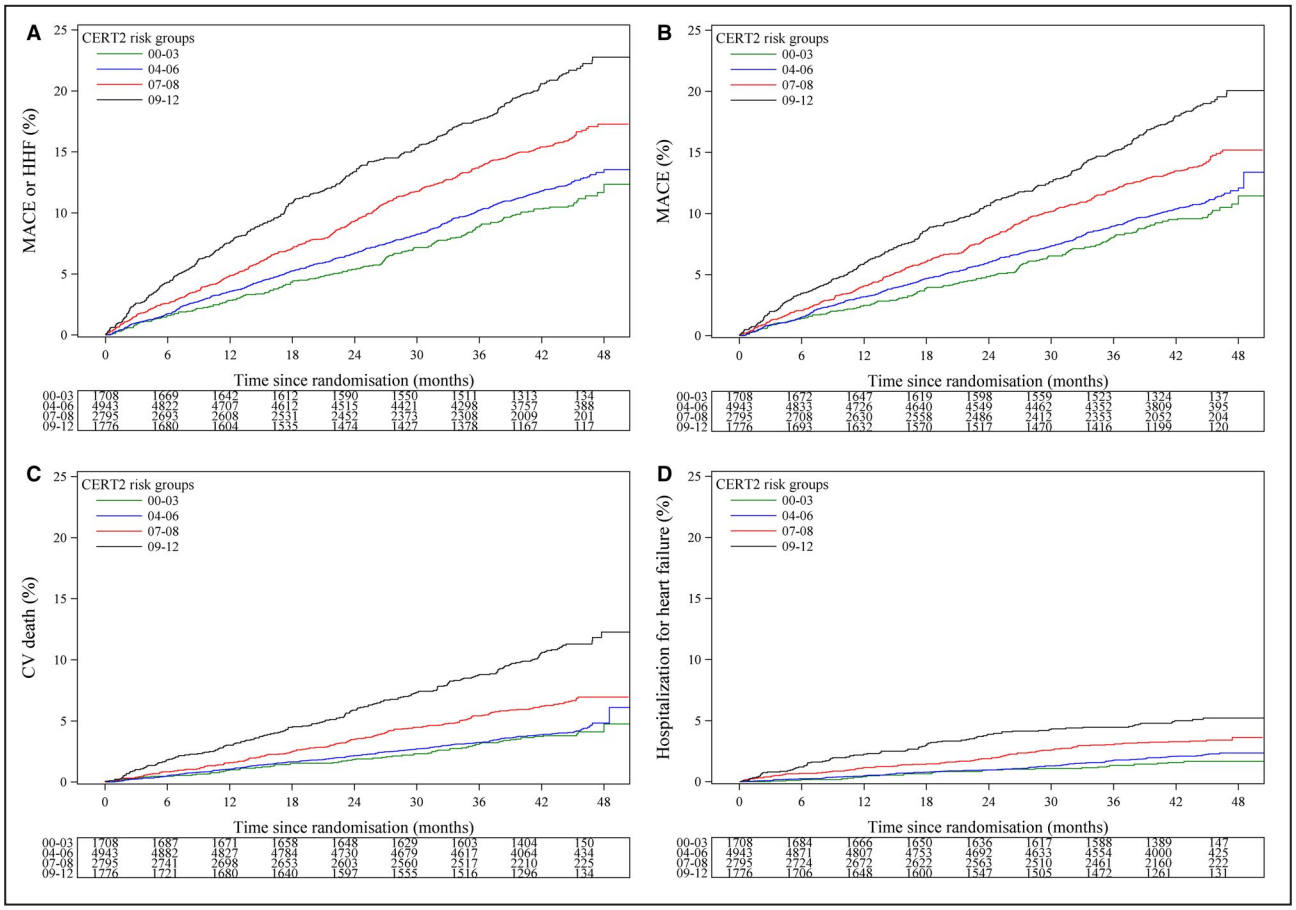

Figure 1. CERT2 is associated with the risk of future cardiovascular events.
Kaplan–Meier curves of the cumulative event rate by the Cardiovascular Event Risk Test (CERT2) risk groups for (**A**) major adverse cardiovascular event (MACE)/hospitalization for heart failure (HHF), (**B**) MACE, (**C**) cardiovascular (CV) death, and (**D**) HHF.

score and age or sex. For the first time, CERT2 was tested and showed robust performance in a study population covering various geographical locations worldwide. Nevertheless, there were differences in the score distribution in different locations, and further investigations are needed to investigate the factors behind this phenomenon. Here, we showed that the CERT2 score was associated with smoking as well as polyvascular disease and multivessel CAD. Patients with renal dysfunction had higher CERT2 scores, while the association with high blood pressure and DM was much weaker. CERT2 was strongly associated with the levels of lipid biomarkers (LDL-C and triglyceride), which is in line with recently published lipidomic data,[17] and suggests that ceramides, constituents of the circulating lipoproteins, are associated with hyperlipidemia. However, it is noteworthy that the CERT2 score was prognostic even after adjustment for LDL-C and triglyceride levels. This indicates that the sphingolipids might have additional pathophysiologic importance for cardiovascular disease beyond conventional lipids. The CERT2 score was also significantly associated with inflammatory markers (hs-CRP and IL-6), suggesting that variations in ceramide levels might be a reflection of vascular inflammation. Thus, these findings imply that CERT2 could reflect both lipid and inflammatory residual risk in patients with stable CHD. Higher CERT2 score was also associated with higher hs-TnT and NT-proBNP concentrations. These findings indicate that alterations of ceramides might be associated with, and possibly contribute to, myocardial necrosis and myocardial dysfunction. Thus, CERT2 score could potentially be useful as a tool to determine residual risk in patients with stable CHD as it is associated with all cardiovascular events and reflects disturbances of several key mechanisms for cardiovascular disease such as dyslipidemia, inflammation, myocardial necrosis, and myocardial and renal dysfunction.

CONCLUSIONS

The CERT2 risk score is associated with all cardiovascular outcomes and with biomarkers related to

	LDL-C	HDL-C	TG	hs-TnT	proBNP	Cyst-C	hs-CRP	IL-6	Lp-PLA$_2$	GDF15	eGFR
CERT2	0.208	-0.046	0.066	0.130	0.221	0.145	0.270	0.262	0.191	0.143	-0.069
Cer(d18:1/24:1) / Cer(d18:1/24:0)	-0.109	0.009	-0.075	0.085	0.140	0.075	0.016	0.091	-0.076	0.068	-0.078
Cer(d18:1/18:0) / PC 14:0/22:6	-0.040	-0.201	0.021	0.110	0.134	0.134	0.248	0.254	0.135	0.147	-0.042
Cer(d18:1/16:0) / PC 16:0/22:5	0.131	-0.183	-0.031	0.067	0.151	0.100	0.264	0.218	0.180	0.050	-0.019
PC 16:0/16:0	0.507	0.273	0.243	0.041	0.083	0.025	0.097	0.047	0.205	0.065	-0.023
Cer(d18:1/16:0)	0.562	0.058	0.366	0.031	0.078	0.028	0.236	0.127	0.323	0.064	-0.035
Cer(d18:1/18:0)	0.344	-0.031	0.420	0.001	-0.017	-0.049	0.266	0.140	0.183	0.028	0.000
Cer(d18:1/24:0)	0.539	0.060	0.445	-0.037	-0.103	-0.094	0.136	-0.027	0.266	-0.055	0.041
Cer(d18:1/24:1)	0.379	0.069	0.330	0.045	0.047	-0.012	0.141	0.066	0.166	0.015	-0.042
PC 14:0/22:6	0.267	0.197	0.258	-0.120	-0.157	-0.179	-0.099	-0.187	-0.030	-0.140	0.047
PC 16:0/22:5	0.227	0.224	0.278	-0.050	-0.105	-0.089	-0.117	-0.139	0.025	-0.009	0.002

Color legend:	p ≥ 0.001 or -0.1 ≤ r < 0.1	r < -0.1	0.1 ≤ r < 0.2	0.2 ≤ r < 0.3	r ≥ 0.3

Figure 2. CERT2 is associated with lipid and inflammatory biomarkers.
The figure presents Spearman correlations of the Cardiovascular Event Risk Test (CERT2) and its components with other biomarkers. eGFR indicates estimated glomerular filtration rate; GDF15, growth differentiation factor-15; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; IL-6, interleukin 6; LDL-C, low-density lipoprotein cholesterol; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; and proBNP, N-terminal pro-B-type natriuretic peptide.

inflammation, myocardial necrosis, myocardial dysfunction, dyslipidemia, and renal dysfunction. The CERT2 risk score can be considered as a risk indicator in patients with stable CHD and it could be useful in evaluating residual risk in patients on guideline-recommended evidence-based optimal medical therapy.

ARTICLE INFORMATION

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Affiliations

From Zora Biosciences Oy, Espoo, Finland (M.H., D.K., A.J., R.L.); Department of Medical Sciences, Uppsala University, Uppsala, Sweden (L.W., C.H., A.S.); Uppsala Clinical Research Center, Uppsala, Sweden (L.W., T.G.L., C.H., J.L., A.S.); Medical Center, Duke University, Durham, NC (C.B.G.); Deutsches Herzzentrum München, Technische Universität München, München Germany and DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany (W.K.); Institute of Epidemiology and Medical Biometry, University of Ulm, Germany (W.K.); N Green Lane Cardiovascular Service, Auckland City Hospital and University of Auckland, New Zealand (R.A.H.S., H.W.); Finnish Cardiovascular Research Center, University of Tampere, Finland (R.L.); Finnish Clinical Biobank Tampere, Tampere University Hospital, Tampere, Finland (R.L.).

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Supplementary Materials

Table S1
Appendix S1

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SUPPLEMENTAL MATERIAL

Table S1. Precursor ion, product ion, dwell time and collision energy applied for ceramides and phospholipids.

Precursor ion (m/z)	Product ion (m/z)	Dwell Time	Lipid	Collision Energy
Positive polarity				
538.5	264.25	10	Cer(d18:1/16:0)	40
566.5	264.25	10	Cer(d18:1/18:0)	40
650.6	264.25	10	Cer(d18:1/24:0)	40
648.6	264.25	10	Cer(d18:1/24:1)	40
545.5	271.25	10	IS d7-Cer(d18:1/16:0)	40
573.5	271.25	10	IS d7-Cer(d18:1/18:0)	40
657.6	271.25	10	IS d7-Cer(d18:1/24:0)	40
655.6	271.25	10	IS d7-Cer(d18:1/24:1)	40
Negative polarity				
782.6	255.2	10	IS D4-PC 32:0-16:0	-50
778.6	255.2	10	PC 32:0-16:0	-50
822.5	227.2	10	PC 36:6-14:0	-50
852.6	255.2	10	PC 38:5-16:0	-50

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Alvaro Avezum (Dante Pazzanese Institute of Cardiology, São Paulo, BR)

Philip E Aylward (South Australian Health and Medical Research Institute, Flinders University and Medical Centre, Adelaide, AU)

Alfonso Bryce (Cardiogolf/Clinica El Golf, Lima, PE)

Hong Chen (Peking University People's Hospital, Beijing, CN)

Ming-Fong Chen (National Taiwan University Hospital, Taipei, TW)

Ramon Corbalan (Pontificia Universidad Catolica de Chile, Santiago, CL)

Anthony John Dalby (Milpark Hospital, Johannesburg, ZA)

Nicolas Danchin (AP-HP and Université Paris Descartes, Paris, FR)

Robbert J De Winter (University of Amsterdam, Amsterdam, NL)

Stefan Denchev (University Hospital Alexandrovska, Sofia, BG)

Rafael Diaz (ECLA Estudios Cardiológicos, Latinoamérica, Rosario, AR)

Moses Elisaf (University of Ioannina, Ioannina, GR)

Marcus D Flather (University of East Anglia and Norfolk and Norwich University Hospital, UK)

Assen R Goudev (Queen Giovanna University Hospital, Sofia, BG)

Christopher Granger (Duke University, Medical Center, Durham, NC, US; the VIGOUR Organization)

Liliana Grinfeld (University of Buenos Aires, School of Medicine, Buenos Aires, AR)

Claes Held (Uppsala Clinical Research Center and Uppsala University, Uppsala, SE)

Judith S. Hochman (NYU Langone Medical Center, New York, NY, US)

Steen Husted (Hospital Unit West, Herning/Holstbro, DK)

Hyo-Soo Kim (Seoul National University Hospital, Seoul, KR)

Wolfgang Koenig (University of Ulm Medical Center, Ulm, DE)

Ales Linhart (Charles University in Prague, Prague, CZ)

Eva Lonn (McMaster University, Hamilton, Ontario, CA)

José López-Sendón (Hospital Universitario La Paz, Madrid, ES)

Athanasios J Manolis (Asklepeion Hospital, Athens, GR)

Emile R. Mohler, III (University of Pennsylvania, Philadelphia, PA, US)

José C. Nicolau (University of São Paulo Medical School, São Paulo, BR)

Prem Pais (St. John's Medical Collage, Bangalore, IN)

Alexander Parkhomenko (Institute of Cardiology, Kiev, UA)

Terje R Pedersen (University of Oslo and Oslo University Hospital, Oslo, NO)

Daniel Pella (PJ Safarik University, Kosice, SK)

Marco Antonio Ramos-Corrales (San Jose Satelite Hospital, Naucalpan, MX)

Mikhail Ruda (Russian Cardiologic Research and Production Complex of Rosmedtechnology, Moscow, RU)

Mátyás Sereg (St. George Hospital, Székesfehérvár, HU)

Saulat Siddique (Shaikh Zayed Postgraduate Medical Institute, Lahore, PK)

Peter Sinnaeve (University Hospitals Leuven, Leuven, BE)

Piyamitr Sritara (Mahidol University, Bangkok, TH)

Ralph Stewart (Green Lane Cardiovascular Service, Auckland City Hospital, and Auckland University, Auckland, NZ)

Henk P Swart (Antonius Hospital Sneek, NL)

Rody G Sy (University of the Philippines, Manila, PH)

Tamio Teramoto (Teikyo Academic Research Center, Itabashi-ku, Tokyo, JP)

Hung-Fat Tse (University of Hong Kong, Hong Kong SAR, CN)

W Douglas Weaver (Henry Ford Heart and Vascular Institute, Wayne State University, Detroit, MI, US)

Robert Weiss (Maine Research Associates, Auburn, ME, US)

Margus Viigimaa, Tallinn (University of Technology, Tallinn, EE)

Dragos Vinereanu (University of Medicine and Pharmacy, University and Emergency Hospital, Bucharest, RO)

Jun-ren Zhu (Fudan University, Shanghai, CN)

Independent Data Monitoring Committee members (IDMC):

Chairman: Rory Collins (University of Oxford, Oxford, UK)

Voting members:

Jeffrey Anderson, (Intermountain Medical Center, Murray, UT, US)

David DeMets (University of Wisconsin–Madison, Madison, WI, US)

Peter Ganz (University of California-San Francisco, San Francisco, CA, US)

Peter Sandercock (Western General Hospital, Edinburgh, UK)

Michael Weber (SUNY Downstate College of Medicine, New York, NY, US)

Statistical Data Analysis Center

Department of Biostatistics and Medical Informatics, University of Wisconsin–Madison, Madison, WI, US

Staff members:

Marian Fisher (Director); Kevin Buhr, Scott Diegel, and Melissa Schultz (Contributing Statisticians)

Clinical Endpoint Classification (CEC) - Cardiology

Chairman - CEC Cardiology: Claes Held, Uppsala Clinical Research Center and Uppsala University, Uppsala, SE

Co-chair - CEC Cardiology: Ken Mahaffey, Duke Clinical Research Institute, Durham, NC, US

CEC adjudicators Cardiology

John Alexander (Duke University School of Medicine, Durham, NC, US)

Sana Al-Khatib (Duke University School of Medicine, Durham, NC, US)

Tomasz Baron (Uppsala University Hospital, Uppsala, SE)

Olle Bergström (Växjö Hospital, Växjö, SE)

Cheryl Bushnell (Duke University School of Medicine, Durham, NC, US)

Christina Christersson (Uppsala University Hospital, Uppsala, SE)
Kai Eggers (Uppsala University Hospital, Uppsala, SE)
Bengt-Olov Fredlund (Sahlgrenska University Hospital, Gothenburg, SE)
Emil Hagström (Uppsala University Hospital, Uppsala, SE)
Ziad Hijazi (Uppsala University Hospital, Uppsala, SE)
Lovisa Holm Örndahl (Uppsala University Hospital, Uppsala, SE)
Stefan James (Uppsala University Hospital, Uppsala, SE)
Tomas Jernberg (Karolinska University Hospital, Stockholm, SE)
Nina Johnston (Uppsala University Hospital, Uppsala, SE)
Renato Lopez (Duke University School of Medicine, Durham, NC, US)
Rajendra H Mehta (Duke University School of Medicine, Durham, NC, US)
Kristin L Newby (Duke University School of Medicine, Durham, NC, US)
Örjan Nordmark (Uppsala University Hospital, Uppsala, SE)
Jonas Oldgren (Uppsala University Hospital, Uppsala, SE)
Matthew T Roe (Duke University School of Medicine, Durham, NC, US)
Katarina Saldéen (Sahlgrenska University Hospital, Gothenburg, SE)
Anna Stenborg (Uppsala University Hospital, Uppsala, SE)
Karolina Szummer (Karolinska University Hospital, Stockholm, SE)
Christoph Varenhorst (Uppsala University Hospital, Uppsala, SE)
Axel Åkerblom (Uppsala University Hospital, Uppsala, SE)

Coordinating sites – CEC Cardiology:
Lead coordinating site: Uppsala Clinical Research Center (UCR), Uppsala University, Uppsala, SE
Duke Clinical Research Institute (DCRI), Durham, NC, US
GLCC Research Organization Ltd, Auckland, NZ

Staff members – CEC Cardiology
UCR: Charlotta Elfström (CEC Project Lead); Ulrika Bodén and Pernilla Holmgren (CEC Coordinators); Christina Alm, Theresa Hallberg, and Margareta Forsman (CEC Monitors); Hanna Ljung and Camilla Svanberg (CEC Assistant)
DCRI: Patrick F Loebs (CEC Project Lead); Karen Atwater, Robert Baldwin, Maria Butts, Tuan Chan, Patricia Connolly, Gerry Esposito, Jacalyn B Hillier, Marla Jordan, Kathleen Lane, Debra Eckart Kimberly O'Malia, Grace Ryan, Patsy Smitheran, Maunette Tait, and Sachin Vyas (CEC Monitors); Jessy Frazilus (CEC Assistant)

GLCC: Olga Bucan, Sarah Douglas (CEC Project Leads); Caroline Alsweiler, Lorinda Ball, Ana Bucan, and Laura Mackay (CEC Monitors)

Clinical Endpoint Classification (CEC) - Oncology

Chairman CEC - Oncology: Stephen Wiviott (Brigham and Women's Hospital, Boston, MA, US)

CEC adjudicators - Oncology

Gretchen Gignac (Boston Medical Center, Boston, MA, US)

Wolfram Goessling (Brigham and Women's Hospital, Boston, MA, US)

Ephraim Hochberg (Massachusetts General Hospital, Boston, MS, US)

Andrew Lane (Dana Farber Cancer Institute, Boston, MA, US)

Carol Rosenberg (Harvard Vanguard, Boston, MA, US)

Andrew Wagner (Dana Farber Cancer Institute, Boston, MA, US)

Brian M Wolpin (Dana Farber Cancer Institute, Boston, MA, US)

Coordinating site – CEC Oncology:

Lead coordinating site: Thrombolysis in Myocardial Infarction (TIMI) Study Group, CEC Department, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Uppsala Clinical Research Center (UCR), Uppsala University, Uppsala, SE

Duke Clinical Research Institute (DCRI), Durham, NC, US

GLCC Research Organization Ltd, Auckland, NZ

Staff members – CEC Oncology:

TIMI Study group: Cheryl Lowe (CEC Director); Kristen Mills (CEC Manager); Maria Alkhalil and Jessica Ruvido (CEC Coordinators); Mian Qasim Rehman, Margarita Shimmer, and Irina Stebletsova (Medical Reviewers)

Statistical Centers and involved statisticians:

Allison Barnes, GlaxoSmithKline, Research Triangle Park, NC, US

Rebekkah Brown, GlaxoSmithKline, Research Triangle Park, NC, US

Karen Chiswell, Duke Clinical Research Institute, Durham, NC, US

Rich Davies, GlaxoSmithKline, King of Prussia, PA, US

Amanda Stebbins, Duke Clinical Research Institute, Durham, NC, US

Central laboratory

Quest Diagnostics Clinical Laboratories, Inc., Valencia, CA , US

Data coordination:

Data management: GlaxoSmithKline, R&D Projects Clinical Platforms & Sciences, King of Prussia, PA, US

Registration And Medication Ordering System [RAMOS] interactive voice response system: GlaxoSmithKline, R&D Platform Technology & Science, Upper Providence, PA, US

Web-based data capture vendor: Oracle Health Sciences, Boston, MA, US

STABILITY Investigators by country

Listed are investigators recruiting at least 1 patient. Number of patients included is listed in brackets. FPI = Former Principal Investigator at site

Argentina

Bustamante Labarta, Miguel, Instituto Medico de la Comunidad (IMEC), Buenos Aires (19); Cartasegna, Luis R, Hospital Italiano de La Plata, Buenos Aires (6); Chekherdemian, Sergio, Complejo Médico de la Policia Federal Argentina Churruca-Visca, Ciudad Autonoma de Buenos Aires (16); Cuello, Jose L, Instituto de Investigaciones Clinicas Bahia Blanca, Buenos Aires (42); Elías, Pedro, INSARES, Mendoza (22); Giordano, Jorge, Clinica Instituto Medico Adrogue, Buenos Aires (23); Hirschson, Alfredo, CENIT- Centro de Neurociencias y Tratamiento- Buenos Aires, Buenos Aires (14); Hominal, Miguel Angel, Centro de Investigaciones Clinicas del Litoral S.R.L., Santa Fe, Santa Fe (47); Ibañez, Julio O, Instituto de Hipertension y Corazon, Corrientes (21); Jure, Horacio O, Clinica Chutro SRL, Córdova (49); Litvak, Marcos, Instituto Medico Especializado, Ciudad Autonoma de Buenos Aires (25); Macin, Stella M, Instituto de Cardiologia JF Cabral, Corrientes (16); MacKinnon, Ignacio Jorge, Instituto de Investigacion Clinica de Mar del Plata, Buenos Aires (56); Maffei, Laura Elena, Consultorios Asociados de Endocrinología (CADE), Buenos Aires (43); Montaña, Oscar R, Clinica DIM Privada, Buenos Aires (39); Prado, Aldo D, Investigaciones Clinicas Tucuman, Tucuman (18); Sala, Jorgelina M, Gorosito, Vanina (FPI) Instituto de Investigaciones Clinicas Rosario, Santa Fe (68); Sanchez, Ramiro A, Fundapres, Ciudad Autonoma de Buenos Aires (18).

Australia

Brieger, David, Concord Hospital, Concord (6); Chew, Derek, Flinders Medical Centre, Bedford Park (9); Cross, David, The Wesley Research Institute, Auchenflower (20); De Looze, Ferdinandus J, Aus trials Pvt Ltd, Sherwood (36); Farshid, Ahmad, The Canberra Hospital, Garran (10); Hall, Stephen, Emeritus Research, Malvern (17); Krum, Henry, CCRE Clinical Trials Centre, Monash University, Caulfield Hospital, Caulfield (22); Lane, Geoff K, Fremantle Hospital, Fremantle (15); Oqueli Flores, Ernesto, Stickland, John (FPI), Ballarat Health Service - Ballarat Base Hospital, Ballarat (6); Purnell, Peter W, Joondalup Clinical Trials Foundation Inc., Joondalup (55); Szto, Gregory YF, Peninsula Heart Centre, Peninsula Private Hospital, Frankston (20); Thompson, Peter L, Sir Charles Gairdner Hospital, Nedlands (22); Waites, Jonathan, Coffs Harbour Health Campus, Coffs Harbour (55); William, Maged, Gosford Hospital, Gosford (13).

Belgium

Beauloye, Christophe, Cliniques Universitaires Saint-Luc, Brussels (28); Boland, Jean, Centre Hospitalier Régional de la Citadelle, Liège (10); Charlier, Filip, Imelda Ziekenhuis, Bonheiden (26); De Raedt, Herbert JLP, Onze-Lieve-Vrouwziekenhuis Aalst, Aalst (17); Dens, Joseph AY, Ziekenhuis Oost-Limburg, Genk (21); Dujardin, Karl, H.-Hartziekenhuis, Roeselare (23); Friart, Alain, Centre Hospitalier Universitaire de Tivoli, La Louvière (18); Scheen, André, Centre Hospitalier Universitaire de Liège, Liège (14); Schröder, Erwin, CHU Mont-Godinne, Yvoir (5); Sinnaeve, Peter R, Universitair Ziekenhuis Gasthuisberg, Leuven (17); Verheye, Stefan, LRAZNA Campus Middelheim, Antwerpen (3); Vranckx, Pascal, Jessa Ziekenhuis, Hasselt (20).

Brazil

Abrantes, José A M, Santa Casa de Pelotas, Pelotas (23); Albuquerque, Denilson, Campos De Hospital Universitário Pedro Ernesto, Rio de Janeiro (24); Ardito, Wilma Roberta, Instituto de Moléstias Cardiovasculares – IMC, São José do Rio Preto (6); Baracioli, Luciano M, Instituto do Coracaodo HCFMUSP (INCOR), Sao Paulo (16); Bertolami, Marcelo C, Instituto Dante Pazzanese de Cardiologia, São Paulo (32); Bodanese, Luiz C, Hospital São Lucas da PUC-RS, Porto Alegre (19); Dos Santos Filho, Raul D, Instituto do Coração - INCOR, São Paulo (2); Maia, Lilia N, Fundação Faculdade Regional de Medicina de São José do Rio Preto, São José do Rio Preto (9); Manenti, Euler RF, Hospital Mãe de Deus, Instituto de Medicina Vascular, Porto Alegre (29); Marino, Roberto L, Madre Teresa - Cardiologia Clinica & Intervencionista, Belo Horizonte (2); Ogawa Indio do Brasil, Clarisse K, Instituto Dante Pazzanese de Cardiologia, São Paulo (21); Paiva, Maria Sanali de Oliveira, Natal Hospital Center, Natal (59); Rabelo, Alves Junior, Álvaro, Fundação Bahiana de Cardiologia, Salvador (10); Rassi, Salvador, Hospital das Clínicas da Universidade Federal de Goiás, Goiânia (31); Reis, Gilmar, Santa Casa da Misercórdia de Belo Horizonte, Belo Horizonte (45); Rossi, Paulo R F, Unicardios - Unidade de Atendimento do Coração S/S, Curitiba (42); Saraiva, José Francisco K, Hospital e Maternidade Celso Pierro da PUC Campinas, Campinas (14).

Bulgaria

Benov, Haralambi, MHAT Dr. Stefan Cherkezov, Veliko Tarnovo (26); Chompalova, Boryana, MHAT Plovdiv, Plovdiv (5); Denchev, Stefan, Cardiology Clinic at MHAT Alexandrovska, Sofia (23); Goudev, Assen, Cardiology Clinic at MHAT Tsaritsa Yoanna, Sofia (24); Grigorova, Valentina, 1st internal ward at 1st MHAT Sofia, Sofia (29); Mihov, Atanas, Internal Department at MHAT Sveta Ekaterina, Dimitrovgrad (26); Mincheva, Valentina, Clinic of Cardiology at National Multiprofile Transport Hospital Tzar Boris III, Sofia (23); Petrova, Sylvia, Internal Cardiology Department at MHAT Ruse, Ruse (20); Staneva, Angelina, Raev, Dimitar (FPI), Clinic of cardiology and intensive treatment, Sofia (3); Tisheva, Snezhanka, Cardiology clinic at MHAT "Dr. Georgi Stranski", Pleven (43);

Canada

Aronson, Ronnie, LMC Endocrinology Centres, Toronto (17); Bedard, Jacques, Recherche Clinique London/London Clinical Research, Sherbrooke (25); Bhargava, Rakesh K, Heart Care Research, Oshawa (10); Borts, David, Brampton Research Associates, Brampton (48); Constance, Christian, Clinique Sante Cardio MC, Montreal (50); Cusson, Jean, Hopital Charles LeMoyne, Greenfield Park (12); Davies, Richard F, University of Ottawa Heart Institute, Ottawa (14); Ducas, John, Saint Boniface General Hospital, Winnipeg (19); Ferguson, Murdo ER, Colchester Research Group, Truro (20); Goldenberg, Ronald M, LMC Endocrinology Centres (Thornhill) Limited, Thornhill (35); Grondin, Francois, Clinique de Cardiologie de Levis, Levis (17); Gyenes, Gabor, University of Alberta Hospital, Edmonton (10); Halperin, Frank, Kelowna Cardiology Research, Kelowna (13); Kornder, Jan, SMH Cardiology Clinical Trials Inc., Surrey (18); Kouz, Simon, Centre de sante et de services sociaux de Nord de Lanaudiere, Saint Charles-Borromee (51); Lainesse, Andre Y, Centre Investigation Clinique de la Mauricie Inc., Trois Rivieres (23); Leader, Rolland, Leader Medicine Professional Corporation, Ajax (20); Leiter, Lawrence A, Saint Michael's Hospital, Toronto (8);

Lonn, Eva M, Hamilton Health Sciences, Hamilton (35); Milot, Alain, CHUQ Pavillon Saint Francois D'Assise, Quebec City (4); Pearce, Murray E, Murray Pearce Medicine Professional Corporation, Kitchener (5); Pliamm, Lew, Canadian Phase Onward Inc, Toronto (30); Powell, Calvin N, Dr. Calvin Powell Professional Medical Corporation, Bay Roberts (25); Rose, Barry F, Health Sciences Centre, St. John's (5); Rupka, Dennis W, Fraser Clinical Trials, Inc., New Westminster (35); Siega, Anthony JD, Klinke, Peter W (FPI), Victoria Heart Institute Foundation, Victoria (57); St-Amour, Eric, Q&T Research Outaouais Inc., Gatineau (49); Talbot, Paul, Centre de recherche clinique de Quebec Inc., Quebec City (45); Tardif, Jean-Claude, Montreal Heart Institute, Montreal (3); Tishler, Steven J, Mississauga Clinical Research Centre, Mississauga (29); Title, Lawrence, Queen Elizabeth II Health Sciences Center, Halifax (9); Wong, Graham C, Buller, Christopher E (FPI), Diamond Health Care Centre, Vancouver (39).

Chile

Acevedo Blanco, Monica Andrea, Hospital Clinico Universidad Catolica de Chile, Santiago (14); Albornoz Alarcon, Francisco Javier, Hospital Las Higueras, Talcahuano (87); Escobar, Edgardo, Hospital San Borja Arriaran, Santiago (12); Florenzano Urzua, Fernando, Hospital Salvador, Santiago (17); Pedemonte Villablanca, Oneglio Antonio, Hospital Gustavo Fricke, Viña del Mar (14); Prieto Dominguez, Juan Carlos, Hospital Clinico Universidad de Chile, Santiago (28); Sanhueza Cardemil, Patricio, Centro de Estudios Clínicos Santiago Oriente, Santiago (10); Varleta Olivares, Paola Elena, Hospital Dipreca, Santiago (13).

China

Chen, Hong, People's hospital of Peking University, Beijing (30); Chen, Jiyan, Guangdong General Hospital, Guangzhou (26); Dong, Yugang, 1st Affiliated Hospital of Sun Yat-Sen University, Guangzhou (19); Ge, Junbo, Zhongshan Hospital Affilliated to Fudan University, Shanghai (10); He, Ben, Ren Ji Hospital Affiliated to Shanghai Jiao Tong University, Shanghai (5); Huo, Yong, 1st Affiliated Hospital of Beijing University, Beijing (19); Li, Weimin, 1st Affiliated Hospital of Harbin Medical University, Haerbin (137); Li, Xin-li, Jiangsu Province Hospital, Nanjing (1); Liao, Yuhua, Wuhan Union Hospital, Wuhan (23); Wei, Meng, The Sixth Hospital of Shanghai Jiaotong University, Shanghai (12); Yan, Xiaowei, Peking Union Medical College Hospital, Beijing (17); Ye, Ping, Beijing 301 PLA Hospital, Beijing (3); Yuan, Zuyi, 1st Affiliated Hospital, Xian Jiaotong University, Xian (36); Zhang, Yun, Shandong University Qi Lu Hospital, Jinan (18); Zhu, Jianhua, 1st Affiliated Hospital of Zhejiang University, Hang Zhou (13).

Czech Republic

Cermak, Ondrej, Nemocnice Slany, Slany (93); Dedek, Vratislav, Orlickoustecka nemocnice, Usti nad Orlici (72); Francek, Lumir, Kromerizska nemocnice, Kromeriz (57); Grunfeldova, Hana, Mestska nemocnice Caslav, Caslav (37); Hubac, Jan, Franc, Pavel (FPI), Chrudimska nemocnice, Chrudim (12); Kellnerova, Ivana, Svitavska nemocnice, Svitavy (63); Klimsa, Zdenek, Nemocnice Jihlava as, Jihlava (55); Kroupa, Josef, Oblastni nemocnice Kolin, Kolin (35); Kuchar, Ladislav, Vseobecna interni ambulance, Milevsko (51); Linhart, Ales, Vseobecna Fakultni Nemocnice - II. interni klinika, Praha 2 (64); Malecha, Jan, Ordinace pro choroby srdce, Chomutov (114); Povolny, Jiri, Cardiomed, s.r.o., P-P Klinika Kladno, Kladno (9); Velimsky, Tomas, Kardiologicka ambulance, Pisek (55); Volf, Roman, Jirka, Vladimir (FPI), Nemocnice Tabor, Tabor (57).

Denmark

Bang, Lia, Grande, Peer (FPI), Rigshospitalet Hjerternedicinsk Forskningsenhed, Kobenhavn (36); Frost, Lars, Regionshospitalet Silkeborg, Silkeborg (30); Husted, Steen E, Aarhus Sygehus, Aarhus (16); Laursen, Rikke V, Nielsen, Tonny (FPI), Sydvestjysk Sygehus Esbjerg, Esbjerg (20).

Estonia
Hedman, Anu, East-Tallinn Central Hospital, Tallinn (26); Muda, Piibe, Tartu University Clinic, Tartu (21); Planken, Ulle, North Estonia Regional Hospital, Tallinn (30).

France
Barnay, Claude, Centre Hospitalier du Pays d'Aix, Aix en Provence cedex 1 (1); Bauters, Christophe, Hôpital Cardiologique, Lille Cedex (2); Bayet, Gilles, Clinique Rhône-Durance, Avignon (5); Bonnet, Jacques, Hôpital Cardiologique du Haut Lévêque, Pessac (20); Bruckert, Eric, Groupe Hospitalier PITIE-Salpetriere, Paris Cedex 13 (14); Cottin, Yves, CHU de Dijon - Complexe du Bocage, Dijon cedex (3); Courreges, Jean-Pierre, Centre Hospitalier de Narbonne, Narbonne Cedex (11); Danchin, Nicolas, Hôpital Européen Georges Pompidou Pole B, Paris (8); Decoulx, Eric, Centre Hospitalier Hôpital Chatilliez, Tourcoing cedex (71); Demarcq, Jean-Michel, Hôpital Victor Provo, Roubaix (5); Dubois-Rande, Jean-Luc, Hôpital Henri Mondor, Créteil Cedex (3); Elbaz, Meyer, CHU Hôpital de Rangueil, Toulouse Cedex (26); Khalife, Khalifé, CHR De Metz-Thionville-Hospital De Mercy, Metz Cedex (24); Krempf, Michel, CHU de Nantes - Hôtel Dieu, Nantes cedex (20); Maupas, Eric, Hôpital Privé les Franciscaines, Nimes (5); Ovize, Michel, Groupe Hospitalier Est, Bron Cedex (11); Roul, José Gérald, Nouvel Hôpital Civil (NHC), Strasbourg cedex (3); Schiele, François, Bassand, Jean-Pierre (FPI), CHU - Hôpital Jean Minjoz, Besançon Cedex (6); Steg, Gabriel, Hôpital Bichat Claude Bernard, Paris cedex 18 (8); Vaisse, Bernard, CHU de Marseille - Hôpital de la Timone, Marseille cedex 5 (4).

Germany
Aigner, Ulrich Michael, Praxis Dr. med. Ulrich Aigner, Sulzbach-Rosenberg (5); Bavendiek, Udo, Fischer, Dieter (FPI), Medizinische Hochschule Hannover, Hannover (3); Benedix, Gisela, Dr.med. Gisela Benedix, Berlin (5); Boeneke, Hilmar, Dr. med. Hilmar Boeneke, Lienen-Kattenvenne (9); Bott, Jochen, Praxis Dr.med. Jochen Bott, Berlin (37); Brado, Bernadett, Praxis Dr. med. Bernadett Brado, Heidelberg (8); Buhr, Marianne, Praxis Dr. med. Marianne Buhr, Berlin (2); Butter, Christian, Heart Center Brandenburg in Bernau, Bernau (2); Fischer, Steffen, Praxisgemeinschaft Dr.med. Steffen Fischer, Leipzig (43); Foerster, Andreas PD, Dr.med Andreas Foerster, Berlin (44); Grad, Marc Oliver, Polikum Friedenau MVZ GmbH, Berlin (9); Grosskopf, Josef, Dr.med. Josef Grosskopf, Wallerfing (10); Hanefeld, Markolf, GWT-TUD GmbH, Dresden (68); Hoeltz, Susanne, Frick, Horst-Michael (FPI), Susanne Hoeltz, Rhaunen (7); Illies, Gabriele, SMO. MD GmbH Zentrum fuer Klinische Studien, Magdeburg (88); Jung, Thomas WGE, Praxis Dr. med. Thomas Jung, Deggingen (24); Kademann, Barbara, Praxis Dr.med Barbara Kademann, Leipzig (11); Kahrmann, Gert, Bourrat, Alexandra (FPI), Horacek, Thomas (FPI), Reusch, Regina (FPI), Dr.med Gerd Kahrmann, Witten (9); Klausmann, Gerhard, Studienzentrum Haematologie/Onkologie/Diabetologie, Aschaffenburg (28); Klein, Christiane, Gem. Praxis Dr.med Christiane Klein, Kuenzing (14); Koenig, Wolfgang, Universitaetsklinikum Ulm/Oberer Eseslsberg, Ulm (4); Krause, Karl Heinz, MedicoKIT Goch Institut fuer klinische Arzneimittelpruefungen, Goch (23); Kuesters, Detlev, Praxis Dr.med. Detlev Kuesters, Eschweiler (17); Mellwig, Klaus-Peter, Kardiologische Klinik, Bad Oeynhausen (25); Menke, Thomas, Praxis Dr. Thomas Menke, Goch (16); Mueller, Steve, Gem. Praxis Dr.med Steve Mueller, Gueglingen (24); Neumann, Gerhard, Praxis Dr. med. Gerhard Neumann, Delitzsch (52); Nischik, Ruth Medamed GmbH, Leipzg (31); Preusche, Andreas, Praxis Dr.med. Andreas Preusche, Schmiedeberg (20); Prohaska, Martin, Dr.med. Martin Prohaska, Muehldorf (4); Regner, Stefan Franz, Gem. Praxis Dr.med. Stefan Regner, Mainz (8); Rein, Wilfried, Dr.med. Wilfried Rein, Herford (24); Rummel, Reinhard, Dr.med Reinhard Rummel, Berlin (20); Samer, Holger, Praxis Dr.med. Holger Samer, Haag (18); Schaefer, Thomas, Praxis Dr. med. Thomas Schaefer, Kelkheim (19); Schenkenberger, Isabelle, Isabelle Schenkenberger, Berlin (60); Schmidt, Ekkehard, Dr.med. Ekkehard Schmidt, Hamburg (71); Schoen, Norbert, Kardiologisch-angiologiscbe Schwerpunktpraxis, Muehldorf (3); Schreckenberg, Andreas, Dr.med. Andreas Schreckenberg, Weyhe-Leeste (15); Schulze, Uwe, Wunderlich, Joachim (FPI), Vivantes MVZ Praxis Dr. med. Uwe Schulze, Berlin (21); Sohn, Hae-Young, Klauss, Volker

(FPI), Universitaetsklinikum Muenchen, Muenchen (3); Toursarkissian, Nicole, Praxis Dr. med. Nicole Toursarkissian, Berlin (66); Voigt, Jan-Gerrit, Dr.med. Jan-Gerrit Voigt, Dorsten (13); Weber, Dirk, Praxis Dr. med.Dirk Weber, Essen (65); Winkelmann, Bernhard R Dr.med, Prof. Dr.med. Bernhard Winkelmann, Hessen (11); Zuechner, Dirk, Dr.med. Dirk Zuechner, Berlin (30).

Greece
Alexopoulos, Dimitrios, University Hospital of Patras, Patras (13); Anastasiou-Nana, Maria, Kremastinos, Dimitrios (FPI), University General Hospital Attikon, Athens (19); Elisaf, Moses, University General Hospital of Ioannina, Ioannina (21); Geleris, Parashos, Peripheral General Hospital Ippokratio, Thessaloniki (17); Kallikazaros, Ioannis, General Hospital of Athens Ippokratio, Athens (2); Kranidis, Athanasios, General Hospital of West Attica "Agia Varvara", Agia Varvara, Athens (18); Manolis, Athanasios, General Hospital Asklipieio Voulas, Voula / Athens (15); Mantas, Ioannis, General Hospital of Chalkida, Chalkida (34); Olympios, Christoforos, General Hospital of Elefsina Thriasio, Magoula (17); Tziakas, Dimitrios, University General Hospital of Alexandroupolis, Alexandroupolis (19); Voudris, Vassilis, Onassis Cardiac Surgery Center, Athens (12).

Hong-Kong
Lam, Yat Yin Homer, Yip, Wai Kwok Gabriel (FPI), Prince of Wales Hospital, Shatin, New Territories (56); Siu, Chung Wah David, Queen Mary Hospital, Hong Kong (61).

Hungary
Benczúr, Béla, Jász-Nagykun-Szolnok Megyei Hetényi Géza Kórház-Rendelőintézet, Szolnok (15); Hornyik, Andrea, CRU Hungary Kft- II. Rakoczi Ferenc Korhaz, Szikszó (96); László, Zoltán, Fovarosi Onkormanyzat Szent Janos Korhzaa es Eszak-budai Egyesitett Korhazai, Budapest (26); Papp, András, ClinExpert kft, Kaszásdűlő u. 5., Budapest (14); Papp, Anikó, Területi Kórház, Berettyóújfalu (13); Plés, Zsolt, Piros, Annamária (FPI), CEE Research Kft, Sátoraljaújhely (113); Szakál, Imre Selye János Kórház, Komárom (16); Túri, Tibor, Sereg, Mátyás (FPI), Fejér Megyei Szent György Kórház, Székesfehérvár (67); Vértes, András, Fovarosi Onkormanyzat Egyesitett Szent Istvan es Szent Laszlo Korhaz, Budapest (50).

India
Abraham, Sunitha, Narayana Hrudayalaya Institute of Medical Sciences, Bangalore (1); Banker, Darshan N, Bankers Heart Institute, Vadodara (47); Chandwani, Prakash, Heart & General Hospital, Jaipur (25); Gupta, Rajeev, Fortis Escorts Hospital, Jaipur (17); Hiremath, Jagdish, Poona Hospital & Research Centre, Pune (33); Jayadev, Santhosh, St John's Medical College Hospital, Bangalore (9); Joseph, Stigimon, Menon, Jaideep (FPI), Little Flower Hospital and Research Centre, Angamaly (28); Keshavamurth, C, Srinivas, Arun (FPI), Vikram Hospital & Heart Care, Mysore (10); Parikh, Keyur, Care Institute of Medical Science, Ahmedabad (113); Pothineni, Ramesh B, Dr. Ramesh Cardiac & Multispeciality Hospital Limited, Vijayawada (52); Sathe, Shireesh P, Deenanath Mangeskar Hospital & Research Center, Pune (15); Sawhney, Jitendra P, Sir Ganga Ram Hospital, New Delhi (37); Sethi, Sumeet, Chandra, Praveen Kumar (FPI), Department of Cardiology, New Delhi (4); Varma, Sudhir, Sadbhavna Medical and Heart Institute, Patiala (7).

Italy
Ardissino, Diego, Azienda Ospedaliero-Universitaria di Parma, Parma (47); Bobbio, Marco, Azienda Ospedaliera S.Croce e Carle, Cuneo (7); Bongo, Angelo S, Azienda Ospedaliera Maggiore della Carità, Novara (32); Cipollone, Francesco, Mezzetti, Andrea (FPI), Fondazione G. D'Annunzio-Centro Studi sull'Invecchiamento (Ce.S.I.), Chieti (32); Colivicchi, Furio, Santini, Massimo (FPI), Azienda Ospedaliera San Filippo Neri, Roma (24); Esposito, Giovanni, Chiariello, Massimo (FPI), Università degli Studi di Napoli Federico II, Dipartimento di medicina clinica, Napoli (15); Marzilli, Mario, Azienda Ospedaliero-Universitaria Pisana Ospedale di Cisanello, Pisa (19); Merlini, Piera,

Ospedale Niguarda Ca' Granda - Dipartimento De Gasperis, Milano (28); Moretti, Luciano, Presidio Ospedaliero C.G. Mazzoni, Ascoli Piceno (25); Olivari, Zoran, Ospedale S. Maria di Ca' Foncello, Struttura Complessa di Cardiologia- Presidio Ospedaliero di Treviso, Treviso (13); Patrizi, Giampiero, Ospedale "B. Ramazzini", Carpi (5); Valgimigli, Marco, Azienda Ospedaliera-Universitaria Arcispedale S.Anna di Ferrara, Ferrara (9).

Japan

Amemiya, Hiroshi, Hayama Heart Center, Kanagawa (23); Ando, Kenji, Iwabuchi, Masashi (FPI), Kokura Memorial Hospital, Fukuoka (3); Endo, Masahiro, Nagashima, Hirotaka (FPI), Tokyo Heart Center, Tokyo (18); Kametani, Ryosuke, Nagoya Tokushukai General Hospital, Aichi (7); Koike, Akihiro, National Hospital Organization Fukuoka-Higashi Medical Center, Fukuoka (8); Kuramochi, Takehiko, Chibanishi General Hospital, Chiba (20); Nakamura, Yuichiro, Nakamura Cardiovascular Clinic, Fukuoka (17); Oku, Koji, National Hospital Organization Nagasaki Medical Center, Nagasaki (18); Okutsu, Masaaki, Nozaki Tokushukai Hospital, Osaka (20); Sueyoshi, Atsushi, Uji Tokushukai Hospital, Kyoto (30); Takahashi, Wataru, Sasaki, Yasuyuki (FPI), National Hospital Organization Shinshu Ueda Medical Center, Nagano (16); Tanabe, Jun, National Hospital Organization Shizuoka Medical Center, Shizuoka (5); Tanaka, Hideki, Kashima, Katsuro (FPI), National Hospital Organization Kagoshima Medical Center, Kagoshima (16); Tanaka, Yutaka, Takeshita, Satoshi (FPI), Shonan Kamakura General Hospital, Kanagawa (23); Teranishi, Junichi, Betsuyaku, Tetsuo (FPI), National Hospital Organization Hokkaido Medic058187al Center, Hokkaido (24); Yamamoto, Takashi, Shiga University of Medical Science Hospital, Shiga (19); Yamazaki, Seiji, Sapporo Higashi Tokushukai Hospital, Hokkaido (20); Yano, Shoji, Oita city Medical Association's ALMEIDA Memorial Hospital, Oita (11); Yoshida, Kazuro, National Hospital Organization Nagasaki Kawatana Medical Center, Nagasaki (20).

Korea

Chae, Jei-Keon, Chonbuk National University Hospital, Jeonju-si, Jeollabuk-Do (8); Chae, Shung-Chull, Kyungpook National University Hospital, Dae-Gu (28); Cho, Myeong-Chan, Chungbuk National University Hospital, Cheongju (53); Choi, Dong-Hoon, Yonsei University Health System, Seoul (22); Choi, Dong-Ju, Seoul National University Bundang Hospital, Seongnam-si Gyeonggi-do (10); Hong, Taek-Jong, Pusan National Univ. Hospital, Seo-gu Busan (61); Jeon, Hui-Kyung, The Catholic University of Korea, Uijeongbu-si (53); Jeong, MyungHo, Chonnam National University Hospital, Gwangju (30); Kim, Hyo-Soo, Seoul National University Hospital, Seoul (93); Kim, Hyun-Joong, Ryu, Kyu-Hyung (FPI), Konkuk University Medical Center, Seoul (11); Kim, Woo-Shik, Kim, Kwon-Sam (FPI), KyungHee University Medical Center, Seoul (29); Lee, Sang-Hoon, Samsung Medical Center, Gangnam-gu (26); Lim, Do-Sun, Korea University Anam Hospital, Seoul (43); Park, Seong-Wook, Asan Medical Center, Seoul (26); Seung, Ki-Bae, The Catholic Univ of Korea Seoul St. Mary's Hospital, Seoul (10).

Mexico

Cervantes-Escárcega, Jose-Luis, Hosptial Angeles del Pedregal, Mexico (74); Hernández-Santamaría, Ismael, Hospital Juárez de México, México D.F (12); Sánchez-Díaz, Carlos Jerjes, Unidad de Investigación Clínica en Medicina S.C., Monterrey (18); Uribe-Rios, Marittza-Arasely, Alvarado-Ruiz, Ricardo (FPI), Cardioprevent, Durango (37).

Netherlands

De Winter, Robbert J, Academisch Medisch Centrum, Amsterdam (17); Dijkgraaf, René, St. Jansdal Ziekenhuis, Harderwijk (24); Jansen, Rutger M.G, Slingeland Ziekenhuis, Doetinchem (19); Knufman, Nicole M.J, Frederiks, Joost (FPI), Bronovo Ziekenhuis, S-Gravenhage (12); Kuijper, Adrianus, F.M Spaarne Ziekenhuis, Hoofddorp (24); Post, Johannes C, Michels, Herman R (FPI), Catharina Ziekenhuis, Eindhoven (17); Roeters van Lennep, Hendrik W.O, Liem, AnHo (FPI), Admiraal de Ruyter Ziekenhuis, Goes (28); Smits, Pieter C, Maasstad Ziekenhuis, Rotterdam (6);

Swart, Hendrik P, Antonius Ziekenhuis, Sneek (48); Van Boven, Adrianus J, Medisch Centrum Leeuwarden, Leeuwarden (107); Van Daele, Marc ERM, Orbis Medisch Centrum, Sittard-Geleen (28); Van der Zwaan, Coenraad, Ziekenhuis Rivierenland, Tiel (36); Von Birgelen, Clemens, Medisch Spectrum Twente locatie Haaksbergerstraat, Enschede (64); Westendorp, Iris C.D, Rode Kruis Ziekenhuis, Beverwijk (14).

New Zealand
Davidson, Laura, Palmerston North Hospital, Palmerston North (19); Devlin, Gerard P, Waikato Hospital, Hamilton (22); Elliott, John M, Christchurch Hospital, Christchurch (17); Hamer, Andrew W, Nelson Hospital, Nelson (3); Harrison, Nigel A, Rankin, Richard J (FPI), Whangarei Hospital, Whangarei (11); Hart, Hamish H, North Shore Hospital, Auckland (9); Hills, Matthew J, Timaru Hospital, Timaru (6); O'Meeghan, Timothy J, Hutt Hospital, Lower Hutt (16); Scott, Douglas S, Middlemore Hospital, Auckland (14); Stewart, Ralph AH, Auckland City Hospital, Auckland (46); Tisch, Jonathan G, Tauranga Hospital, Tauranga (21); Williams, Michael JA, Chen, Victor HT (FPI), Dunedin Hospital, Dunedin (18).

Norway
Berge, Christ, Helse Bergen HF, Bergen (25); Istad, Helge, Radhuset Spesialistsenter, Oslo (60); Pedersen, Terje R, Ullevål Universitetssykehus, Oslo (8); Sirnes, Per Anton, 0stlandske Hjertesenter, Moss (20).

Pakistan
Hanif, Bashir, Tabba Heart Institute, Karachi (35); Ishaq, Riaz, The Indus Hospital, Karachi (31); Kayani, Azhar Mahmood, Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi Cantt Rawalpindi Institute of Cardiology Rawalpindi (46); Qureshi, Muhammad Bilal Ahsan, Ch PervaizElahi Institute of Cardiology, Multan (33); Siddique, Saulat, Shaikh Zayed Hospital, Lahore (80); Yaqub, Zia, National Institute of Cardiovascular Diseases, Karachi (25).

Peru
Doig, Rafael, Britto, Frank. (FPI), Centro de Investigación INCOR, Lima (27); Yanac, Pedro, Horna, Manuel (FPI), Valdivia, José (FPI), Hospital Nacional Alberto Sabogal Sologuren, Callao (41); Zubiate, Mario Cesar, Hospital Nacional Edgardo Rebagliati Martins, Lima (10).

Philippines
Abelardo, Nelson S, Manila Doctors Hospital, Manila (9); Abola, Maria Teresa B, Philippine Heart Center, Quezon City (23); Añonuevo, John C, Philippine General Hospital, Manila (35); Atilano, Alberto A, Perpetual Succor Hospital, Manila (44); Cheng, Federick C, St. Luke's Medical Center, Quezon City (15); Gaspar-Trinidad, Emma Y, Medical Center Manila, Manila (9); Sison, Jorge A, Mezzannine 24, Manila (32); Sulit, Dennis Jose V, Quirino Memorial Medical Center, Quezon City (10); Sy, Rody G, Cardinal Santos Medical Center, San Juan (24); Uy, Norbert Lingling, UERM Memorial Medical Center, Quezon City (18).

Poland
Budaj, Andrzej, Szpital Grochowski im. dr med. Rafala Masztaka- Samodzielny Publiczny Zaklad Opieki Zdrowotnej, Warszawa (22); Chmielinski, Arkadiusz, Poradnia Rodzinna Zdrowie, Plonsk (31); Czepiel, Aleksandra, Poradnia Rodzinna Zdrowie, Warszawa (27); Guzniczak, Ewa M, Siminiak, Tomasz (FPI), Szpital Rehabilitacyjno-Kardiologiczny, Oborniki (7); Kania, Grzegorz, NZOZ Przychodnia Zdrowia Zadebie, Skierniewice (71); Kincel, Krzysztof, Wielospecjalistyezny Niepubliczny Zaklad Opieki Zdrowotnej, Slaskie (11); Kopaczewski, Jerzy, Szpital Wojewodzki we Wloclawku, Wloclawek (50); Kubica, Jacek, Niepubliczny Zaklad Opieki Zdrowotnej MEDICUS Jacek Kubica, Bydgoszcz (7); Lysek, Roman, Lecznica CITOMED Sp. z o.o., Torun (43); Miekus, Pawel, Gabinet Kardiologiczny MEDIPULS, Gdynia (53); Mlodziankowski, Adam, American Heart

of Poland, Mielec (26); Napora, Piotr, NZOZ Centrum Badań Klinicznych, Wroclaw (32); Prochaczek, Fryderyk, Niepubliczny Specjalistyczny Zaklad Opiekii Zdrowotnej, Tychy (18); Ruscika, Teresa, Vitamed - A. Galaj R. Cichomski Sp. j., Bydgoszcz (67); Tarchalski, Janusz, Niepubliczny Specjalistyczny Zaklad Opiekii Jantar, Ostrow Wielkopolski (14); Tracz, Wieslawa, Krakowski Szpital Specjalistyczny im. Jana Pawla II w Krakowie, Krakow (24); Wrzosek, Bozena, Wojewodzki Szpital Specjalistyczny Samodzienly Publiczny Zakald opieki Zdrowotnej, Radom (7).

Romania

Basarab, Gheorghe V, Spitalul Clinic Judetean de Urgenta Deva, Deva (26); Benedek, Imre, Spitalul Clinic Judetean de Urgenta Targu Mures, Targu Mures (59); Cinteza, Mircea, Spitalul Universitar de Urgenta Bucuresti, Bucharest (32); Cristea, Madalina I, CMDTAMP, Bucharest (14); Dimulescu, Doina R, Spitalul Universitar de Urgenta Elias, Bucharest (12); Dragusin, Daniela, Spitulal Clinic Judetean de Urgenta "Sf. Ap. Andrei", Galati (22); Gabor, Iulia, Spitalul Clinic de Urgenta "Sf. Ioan" Bucuresti, Bucharest (44); Ginghina, Carmen D, Institutul de Boli Cardiovasculare C.C. Iliescu, Bucuresti (25); Macarie, Cezar E, Institutul de Boli Cardiovasculare C.C. Iliescu, Bucuresti (93); Sinescu, Crina, Spitalul Clinic de Urgenta Bagdasar-Arseni, Bucharest (17); Tatu-Chitoiu, Gabriel, Cardiomed Clinic, Bucharest (13); Vinereanu, Dragos, Spitalul Universitar de Urgenta Bucuresti, Bucharest (54).

Russia

Andryushina, Natalya A, Baum, Svetlana R (FPI), Non-state Institution of healthcare “Road clinical hospital on station Novosibirsk-Glavny of OAO "Russian Railways", Novosibirsk (9); Arkhipov, Mikhail V, LLC Medical Association "New hospital", Yekaterinburg (26); Barbarash, Olga L, Municipal Health care Institution "Kemerovo Cardiological Dispensary", Kemerovo (28); Boldueva, Svetlana, State educational institution of higher professional education Saint-Petersburg's State Medical Academy n.a.I.I.Mechnikov, Saint Peterburg (25); Boyarkin, Mikhail V, Saint Petersburg State Institution of Healthcare, Alexandrovskaya city hospital, Saint Petersburg (6); Demko, Arkady P, Non State Institution of heathcare Department hospital on station Kemerovo of OAO “Russian Railway”, Kemerovo (18); Freydlin, Marina S, State financed Institution of healthcare of Sverdlovsk’s Region “Scientific practical center for special kinds of medical care" Ural Institution of Cardiology, Yekaterinburg (14); Golitsyn, Sergei P, Federal State Institution Russian Cardiology Research Complex Institute of Clinical Cardiology, Moscow (20); Gordeev, Ivan, State Institution of healthcare of Moscow, Moscow Clinical Hospital No.15 n.a.O.M Filatov, Moscow (38); Gratsiansky, Nikolay, State Institution of healthcare of Moscow, City clinical hospital No. 29 n.a., Moscow (31); Karpov, Yuri A, Federal State Institution Russian Cardiology Research Complex, Institute of Clinical Cardiology, Moscow (23); Kobalava, Zhanna, State Institution of healthcare of Moscow, City clinical hospital No.64, Moscow (21); Konstantinov, Vladimir, State educational institution of higher professional education, Saint Petresburg (14); Kuimov, Andrey D, State Educational Institution for higher professional education Novosibirsk State Medical University based at Muncipal Institution of healthcare City Clinical Hospital No.1, Novosibirsk (23); Kukharchuk, Valery V, Federal State Institution Russian Cardiology Research Complex Institute Of Clinical Cardiology, Moscow (9); Panov, Alexey, Federal State Institution ” Federal center of heart blood and endocrinology n.a.V.A Almazov of Rosmedtechnologies, Saint-Petersburg (43); Ruda, Mikhail Y, Federal State Institution Russian Cardiology Research Complex Institute of Clinical Cardiology, Moscow (45); Sayganov, Sergey A, Saint-Petersburg State Institution of healthcare Pokrovskaya city hospital, Saint-Petersburg (55); Simanenkov, Vladimir, Saint-Petersburg State Institution of Healthcare City Hospital No. 26, Saint-Petersburg (14); Smolenskaya, Olga G, City Hospital No. 41, Yekaterinburg (13); Tsyba, Larisa P, Municipal Institution of healthcare Novosibirsk’s municipal clinical hospital of Emergency Call Service No.2, Novosibirsk (17); Vishnevsky, Alexander Y, Saint-Petersburg State Instituion of healthcare Pokrovskaya city hospital, Saint-Petersburg (57); Yakhontova, Polina K, State financed Institution of healthcare of Novosibirsk’s Region “Novosibirsk's Regional Clinical Cardiological Dispensary”, Novosibirsk (21); Yakushin, Sergey S, State Institution of healthcare Ryazan Regional

Clinical Cardiology Dispensary, Ryazan (53); Zateyshchikov, Dmitry A, State Institution of healthcare of Moscow City Hospital No. 17, Moscow (31).

Slovakia
Gaspar, Ludovit, Univerzitna nemocnica Bratislava, Bratislava (12); Hranai, Marian, Kardiocentrum Nitra, Nitra (52); Kokles, Martin, Univerzitna nemocnica Bratislava, Bratislava (16); Pella, Daniel, Cardio D&R, s.r.o., Kosice (40).

South Africa
Badat, Aysha, Sliwa-Hahnle, Karen (FPI), Chris Hani Baragwanath Clinical Trial Centre, Soweto (2); Blignaut, Suzanne, Paarl Research Centre, Paarl (32); Burgess, Lesley, Tygerberg Hospital, Cape Town (69); Dalby, Anthony, Millpark Hospital, Suite C, Johannesburg (6); Dawood, Saleem Y, Vincent Pallotti Hospital, Pinelands (52); Gray, Thomas, Scion Clinical Research, Pretoria (10); Horak, Adrian R, Vincent Pallotti Hospital, Pinelands (5); Mabin, Thomas, Vergelegen Medi Clinic, Somerset West (18); Manga, Pravin, Wits Donald Gordon Clinical Trial Site, Gauteng (15); Moodley, Rajendran, Netcare Umhlanga Medical Centre, Umhlanga (11); Pretorius, Maria M, Hough, Frans S (FPI), Karl Bremer Hospital, Bellville (19); Roodt, Andre, ClinResco Centre, Kempton Park (3); Saaiman, Jan, Kuils River Private Hospital, Kuils River (117); Theron, Hendrik D, Netcare Universitas Hospital, Bloemfontein (27).

Spain
Alonso Karlezi, Rodrigo, Mata López, Pedro (FPI), Fundación Jiménez Díaz, Madrid (2); Aranda Granados, Pedro, Hospital Carlos Haya, Malaga (5); Berrazueta Fernández, José Ramón, Hospital Marques de Valdecilla, Santander (2); Carnevali Ruiz, Daniel, Hospital Quirón Madrid, Pozuelo de Alarcón/Madrid (13); Castro Conde, Almudena, Hospital de Cantoblanco La Paz, Madrid (45); Cruz Fernández, José Mª, Hospital Virgen de la Macarena, Sevilla (36); De Teresa Galván, Eduardo, Hospital Clinico Universitario Virgen Victoria, Malaga (19); De Teresa Parreño, Luis, Camino Viejo Alicante-Elche s/n, Alicante (26); Díaz Buschmann, Isabel, Hospital Infanta Elena, Valdemoro/Madrid (26); Domínguez Escribano, José Ramón, Hospital San Juan, Alicante (18); Garcia Puig, Juan, Hospital la Paz, Madrid (24); Gil Extremera, Blas, Hospital Clínico San Cecilio, Granada (67); Gómez Cerezo, Jorge, Hospital Infanta Sofía, San Sebastián de los Reyes/Madrid (10); Macaya, Carlos Miguel, Hospital Clinico San Carlos, Madrid (20); Mostaza Prieto, José Mª, Instituto de Salud Carlos III, Madrid (13); Muñoz Aguilera, Roberto, Hospital Infanta Leonor, Madrid (15); Pérez Muñoz, Carlos, Hospital General de Jerez de la Frontera, Jerez de la Frontera (60); Querejeta Iraola, Ramón, Hospital de Donostia, San Sebastián (17); Romero Hinojosa, José Antonio, Hospital Virgen de las Nieves, Granada (9); Ruilope Urioste, Luis Miguel, Hospital Doce De Octubre, Madrid (6); Sabán Ruiz, José, Hospital Ramon Y Cajal, Madrid (14); Sobrino Martínez, Javier, Hospital Espiritu Santo, Sta. Coloma de Gramanet/Barcelona (6); Suárez Suárez, Enma Concepción, Lozano Martínez-Luengas, Iñigo (FPI), Hospital Central de Asturias, Oviedo (21).

Sweden
Al-Khalili, Faris, Stockholm Heart Center, Stockholm (22); Bandh, Stellan, Hjärtmottagningen, Västerås (4); Bennermo, Marie, Hjärt kärllaboratoriet, Stockholm (9); Dellborg, Mikael, Klin Exp Forskningslab, Göteborg (15); Held, Claes, Uppsala Kliniska Forskningscentrum UCR, Uppsala (8); Herlitz, Johan, Johanson, Per (FPI), Kardiologens forskningsenhet, Göteborg (10); Hjelmaeus, Lars, City Heart, Stockholm (39); Landergren, Karl, Forskningsmottagning Avd. 4, Västervik (11); Linderfalk, Carina, Eksjö Företagshälsovård, Eksjö (38); Lindholm, Carl-Johan, Hjärtmottagningen, Lund (35); Lindmark, Krister, Kliniskt forskningscentrum, Umeå (20); Mooe, Thomas, Hjärtenhetens Mottagning, Östersund (35); Nilsson, Jan, Klinisk forskningsenhet, Malmö (42); Wodlin, Peter, Kardiologiska kliniken, Linköping (11).

Taiwan
Ho, Yi-Lwun, National Taiwan University Hospital, Taipei (41); Hou, Charles, Mackay Memorial Hospital, Taipei City (15); Hsia, Chien-Hsun, Changhua Christian Hospital, Changhua (41); Lin, Shing-Jong, Taipei Veterans General Hospital, Taipei (15); Tsai, Liang-Miin, National Cheng Kung University Hospital, Tainan (49); Wang, Kuo-Yang, Taichung Veterans General Hospital, Taichung (39).

Thailand
Chotinaiwattarakul, Chunhakasem, Her Majesty Cardiac Centre, Siriraj Hospital, Bangkok (13); Kuanprasert, Srun, Maharajnakorn Chiangmai Hospital, Amphoe Muang, Chiang Mai (80); Sansanayudh, Nakarin, Phramongkutklao Hospital, Bangkok (56); Sritara, Piyamitr, Ramathibodi Hospital, Mahidol University, Bangkok (36); Suithichaiyakul, Taworn, Chulalongkorn University, Bangkok (22).

Ukraine
Andriyevska, Svitlana, Odesa Regional Cardiodispensary, Odesa (5); Basylevych, Andriy Y, Lviv City Municipal Clinical Hospital No. 5, Lviv (16); Denesiuk, Vitaliy I, Vinnytsia City Clinical Hospital #1, Vinnytsia (46), Kononenko, Lyudmyla G, City Clinical Hospital No 27, Kharkiv (39); Korzh, Oleksii M, Multifield Clinical Hospital 17 n.a. Malyshev, Kharkiv (21); Kovalenko, Volodymyr M, National Scientific Centre M.D.Strazhesko Institute of cardiology of AMS of Ukraine, Kyiv (9); Kraiz, Igor G, Kharkiv State Treatment and Preventive Institution "Central Clinical Hospital of Ukrzaliznytsia", Kharkiv (52); Lishnevska, Viktoriia Y, Institute of Gerontology of AMS of Ukraine, Kyiv (15); Lutay, Mykhaylo I, Strazgesko Research Institute of Cardiology, Kyiv (4); Parkhomenko, Oleksandr M, National Scientific Centre "M.D.Strazhesko Institute of cardiology", Kyiv (25); Rudenko, Leonid V, Kyiv Emergency Care Hospital, Kyiv (21); Telyatnikova, Zinaida Y, Odesa City Polyclinic No.20, Odesa (13); Tseluyko, Vira Y, City Clinical Hospital # 8, Kharkiv (47); Vatutin, Mykola T, Institute of Urgent and Reconstructive Surgery, Donetsk (19); Vizir, Vadym A, Zaporizhzhia City Clinical Hospital No.7, Zaporizhzhia (21).

United Kingdom
Bakhai, Ameet, Barnet Hospital, Barnet (18); Bijral, Harbal S, Stewart, Edmund (FPI), Central Health Centre, Cumbernauld (8); Dargie, Henry, Barlow, Marion G (FPI), Clinical Research Initiative, Glasgow (2); Dutka, David P, Addenbrooke's Hospital, Cambridge (3); Findlay, Iain N, Royal Alexandra Hospital, Paisley (6); Fisher, Michael, Royal Liverpool University Hospital, Liverpool (32); Gorog, Diana A, Queen Elizabeth II Hospital, Hertfordshire (5); Jacques, Adam M, Beeton, Ian (FPI), St Peter's Hospital, Chertsey (4); Logie, Brian, Orchard Medical Centre, Motherwell (20); Pepper, John R, Flather, Marcus D (FPI), Royal Brompton Hospital, Chelsea (6); Purcell, Ian F, Freeman Hospital, Newcastle-upon-Tyne (29); Scullion, William, Thompson, James F (FPI), Waverley Medical Practice, Coatbridge Health Centre, Coatbridge (8); Senior, Roxy, Northwick Park Hospital, Harrow (3); Simpson, David A, Low Waters Medical Centre, Hamilton (13); Thackray, Simon DR, Alamgir, Mohammed F (FPI), Castle Hill Hospital, Cottingham (4); Wilding, John PH, University Hospital Aintree, Liverpool (6); Wong, Yuk-ki, St. Richard's Hospital, Chichester (17).

United States
Ahmed, Abdel M, Altru Health System Clinic, Grand Forks, North Dakota (15); Antonishen, Mark C, Northern Michigan Regional Hospital, Petoskey, Michigan (15); Atassi, Keith, Northwest Indiana Cardiovascular Physicians, Valparaiso, Indiana (4); Azocar, Jose, Northgate Medical P.C., Springfield, Massachusetts (5); Ball, Eric M, Walla Walla Clinic, Walla Walla, Washington (17); Ballantyne, Christie M, Baylor College of Medicine, Houston, Texas (19); Bays, Harold E, L-Marc Research Center, Louisville, Kentucky (30); Beavins, Jill E, American Health Network of Indiana, LLC, Franklin, Indiana (30); Benjamin, Sabrina A, Universal Research Group, Tacoma, Washington

(20); Benson, Mark R, American Health Network of Indiana, Avon, Indiana (27); Berger, Peter B, Buckley, Jeremy W (FPI), Geisinger Medical Center, Danville, Pennsylvania (32); Betz, William R Lake Erie Medical Group, PC, Erie, Pennsylvania (13); Biederman, Robert WW, Allegheny General Hospital, Pittsburgh, Pennsylvania (21); Bisher III, Edward W, Baptist Heart Specialists, Jacksonville, Florida (40); Bittner, Vera A, Dr. Vera Bittiner, The University of Alabama at Birmingham, Birmingham, Alabama (13); Breton, Cristian F, International Research Associates, LLC, Miami, Florida (14); Buttaci, Salvatore, Changlani, Mahesh (FPI), Patterson, John B (FPI), Cardiovascular Institute of the South, New Iberia, Louisiana (21); Byrd, Leroy J, Rowan Research, Spokane, Washington (12); Canaday, Donald B, Rockwood Inland Cardiology Associates, Spokane, Washington (27); Cashion, Jr, William R, Austin Heart P.L.L.C, Harker Heights, Texas (14); Chandna, Harish, Victoria Heart and Vascular Center, Victoria, Texas (14); Chang, Anna R, John Muir Physicians, Network Clinical Research Center, Concord, California (11); Chin, John, Regional Cardiology Associates, Sacramento, California (6); Claybrook, Harry P, Martin, Frederick A (FPI), Internal Medicine and Pediatric Associates of Bristol, PC, Bristol, Tennessee (21); Cohen, Kenneth R, New West Physicians, PC, Golden, Colorado (18); Colan, David R, Internal Medical Associates of Grand Island, PC, Grand Island, Nebraska (18); Coodley, Gregg O, Fanno Creek Clinic, LLC, Portland, Oregon (14); Corson, Marshall A, Knopp, Robert H (FPI), Paramsothy, Pathmaja (FPI), Harborview Medical Center, Seattle, Washington (19); Cottiero, Richard A, Hypertension and Nephrology Inc., Providence, Rhode Island (17); Dandona, Paresh, Diabetes-Endocrinology Center of Western New York, Williamsville, New York (9); Davidson, Michael H, Kamaradt, Kent T (FPI), Radiant Research, Inc., Chicago, Illinois (18); Davuluri, Ashwini K, Baptist Heart Spealists, P.A., Jacksonville, Florida (16); Desai, Vikas S, Garson, Glen D (FPI), Charles River Medical Associates, Natick, Massachusetts (14); East, Cara Soltero Cardiovascular Research Center, Dallas, Texas (19); Ebrahimi, Ramin, Ramin Ebrahimi, M.D. lnc., Los Angeles, California (6); Ellison, Howard S, Rockdale Medical - Research Associates, Conyers, Georgia (28); Erickson, Bernard R, CentraCare Heart and Vascular Center at St Cloud Hospital, St Cloud, Minnesota (25); Fernandes, Valerian L, Ralph H Johnson VA Medical Center, Charleston, South Carolina (21); Flores, Angel R, Heritage Valley Medical Group, Inc., Beaver, Pennsylvania (64); Folkerth, Steven D, Clinical Research Center of Nevada, Las Vegas, Nevada (2); Foster, Robert E, Birmingham Heart Clinic, PC, Birmingham, Alabama (9); Gaona, Sr., Raul E, Briggs Clinical Research, LLC, San Antonio, Texas (8); Gardner, Timothy J, Northside Internal Medicine, Spokane, Washington (19); George, William H, Cadillac Clinical Research LLC., Cadillac, Michigan (5); Gessler, Carl J JR, The Heart Center Research LLC, Huntsville, Alabama (9); Gill, Santosh K, Fox Valley Clinical Research LLC, Aurora, Illinois (13); Go, Alan S, Kaiser Permanente Santa Clara Medical Center, Santa Clara, California (17); Go, Alan S, Kaiser Permanente Division of Research, Oakland, California (19); Goldberg, Anne C, Washington University School of Medicine, St. Louis, Missouri (17); Goldschmidt, Marc E, New Jersey Cardiology Associates, West Orange, New Jersey (6); Gorman, Timothy A, Brautigam, Donald F (FPI), Great Lakes Medical Research, Westfield, New York (44); Guyton, John R, Duke University Medical Center, Durham, North Carolina (17); Haffey, Thomas, Western Cardiology Associates, Thornton, Colorado (6); Henry, Sheldon D, Geisinger Clinic, Geisinger Medical Group-Grays Woods, Port Matilda, Pennsylvania (28); Hermany, Paul R, Grand View - Lehigh Valley Health Services, Sellersville, Pennsylvania (28); Hoekstra, John A, National Clinical Research-Richmond Inc., Richmond, Virginia (14); Hudson, Michael, Henry Ford Hospital, Detroit, Michigan (7); Iteld, Bruce J, Louisiana Heart Center, Slidell, Louisiana (16); Jack, David B, Lonepeak Family Medicine, Draper, Utah (14); Johnson Jr., Frank P, Advanced Therapeutics Inc., Johnson City, Tennessee (26); Joswig, Bill C, Arch Health Partners, Poway, California (19); Kaissar, Amy J, Dawes Frietzin Clinical Research Group, LLC, Indianapolis, Indiana (10); Karns, Adam D, Karns, Robert M (FPI), Adam D Karns, MD, Los Angeles, California (28); Kaster, Steven R, Wenatchee Valley Medical Center, Wenatchee, Washington (31); Kerzner, Boris, Health Trends Research LLC, Baltimore, Maryland (76); Khan, Mohammed S, Ahmed, Ismail S (FPI), North Ohio Research Ltd, Westlake, Ohio (10); Kieval, Joshua, ZASA Clinical Research, Atlantis, Florida (5); Kim, Edward, Eastside Cardiology Associates, Kirkland, Washington (10); Klaff, Leslie J, Rainer Clinical Research Center Inc, Renton,

Washington (16); Klein, Eric J, Capital Clinical Research Center, Olympia, Washington (21); Koren, Michael J, Jacksonville Center for Clinical Research, Jacksonville, Florida (25); Kosinski, Edward J, Connecticut Clinical Research, Bridgeport, Connecticut (26); Krumian, Razmig, Portnoy, Edward B (FPI), Westlake Medical Research, Thousand Oaks, California (2); Kuvin, Jeffrey T, Tufts Medical Center, Boston, Massachusetts (6); Langer, Michael M, North Ohio Research, Ltd., Elyria, Ohio (16); Letts, Dustin P, Caro Mont Heart, Gastonia, North Carolina (55); Lipetz, Robert S, Encompass Clinical Research, Spring Valley, California (11); Long, William J, Thomas, Ignatius (FPI), Medical Research Institute, Slidell, Louisiana (33); Lopes-Virella, Maria, Medical University of South Carolina, Charleston, South Carolina (10); Lubin, Barry C, National Clinical Research-Norfolk, Inc., Norfolk, Virginia (23); Martin, Richard A, Geisinger Clinic, Geisinger Medical Group-Lake Scranton, Scranton, Pennsylvania (9); Masri, Bassem, Weill Medical College of Cornell University/NYPH, New York, New York (11); Matthews, George, Corbelli, John C (FPI), Buffalo Cardiology and Pulmonary Associates,P.C, Williamsville, New York (15); McCullum, Kevin, York Hospital Wellspan, York, Pennsylvania (14); Meholick, Alan W, Buffalo Heart Group, Buffalo, New York (28); Mitchell, Jerry R, Texas Center for Drug Development, PA, Houston, Texas (18); Modares, Fariba, Geisinger Clinic, Geisinger Medical Group-Kistler, Wilkes-Barre, Pennsylvania (16); Mohler, Emile, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania (2); Morcos, Charle N, Apex Research Institute, Santa Ana, California (31); Murdock, David K, Aspirus Cardiovascular Associates, Wausau, Wisconsin (20); Narayan, Puneet, Clinical Research Institute of Northern Virginia, Burke, Virginia (25); Oberoi, Mandeep S, Central Jersey Medical Research Center, Elizabeth, New Jersey (46); O'Connor, Thomas, Schnecker, Robert J (FPI), American Health Network of Indiana, LLC, Greenfield, Indiana (36); O'Donnell, Philip J, Selma Medical Associates, Winchester, Virginia (40); Ong, Stephen T, MD Medical Research, Oxon Hill, Maryland (11); Parang, Pirouz Deborah Heart and Lung Centre, Browns Mills, New Jersey (4); Pasquini, John A, Mid Carolina Cardiology/Novant Health-NMG, Charlotte, North Carolina (58); Patel, Rajesh J, Lycoming Internal Medicine, Inc., Jersey Shore, Pennsylvania (30); Patlola, Raghotham, Cardiovascular Institute of the South, Lafayette, Louisiana (19); Penny, William, VA San Diego Healthcare System, San Diego, California (14); Pepine, Carl J, University of Florida, Gainesville, Florida (18); Pierce, Charles H, Stein, Evan A (FPI), Metabolic and Atherosclerosis Research Center, Cincinnati, Ohio (55); Popeil, Larry R, Magnolia Research Group Inc., Ocala, Florida (12); Pratt, Stephen E, West Coast Research, LLC, San Ramon, California (14); Price, Robert W, Mid Carolina Cardiology PA, Matthews, North Carolina (47); Raikhel, Marina, Torrence Clinical Research, Lomita, California (20); Ravi, Ram C, Cho, Donald (FPI), North Ohio Research, Ltd., Middleburg Heights, Ohio (22); Rhyne, James M, The Lipid Center, Statesville, North Carolina (15); Richards, Mary K, Mary K. Richards, MD, PA, Little Rock, Arkansas (16); Rivera, Ernesto, Amarillo Heart Group, Amarillo, Texas (11); Robinson, Jennifer G, Preventive Intervention Center, Iowa City, Iowa (67); Roth, Eli M, Sterling Research Group Ltd, Cincinnati, Ohio (33); Rubenstein, Carl J, Oklahoma Cardiovascular Research Group, Oklahoma City, Oklahoma (15); Sandoval, Jaime D, Padre Coast Clinical Research, Corpus Christi, Texas (25); Sangrigoli, Renee A, Doylestown Cardiology Associates VIAA, Doylestown, Pennsylvania (22); Schramm, Erichn L, St. Johns Clinical Research Center, Ponte Vedra, Florida (23); Schwartzbard, Arthur, New York University, New York (10); Serfer, Gregory T, South Florida Clinical Research Center, Hollywood, Florida (3); Shah, Dhiren H, Shah Associates, PA, Prince Frederick, Maryland (25); Shalek, Marc S, Legacy Heart Center, Plano, Texas (45); Shanes, Jeffrey G, Consultants in Cardiovascular Medicine, Melrose Park, Illinois (16); Sharma, Marigene S, Bretton, Elizabeth M (FPI), Albuquerque Clinical Trials, Inc., Albuquerque, New Mexico (15); Sheikh, Zafar, Internal Medicine Associates, Madera, California (3); Sklaver, Neal L, Medical Specialists Associated, Dallas, Texas (18); Solano, Maria Del Pilar, Goldberg, Ronald B (FPI), University of Miami, Diabetes Research Institute, Miami, Florida (6); Srivastava, Nalin K, South Carolina Pharmaceutical Research, Spartanburg, South Carolina (7); Staniloae, Cezar S, Gotham Cardiovascular Research, PC, New York (37); Staub, Jonathan S, Wilmington Medical Research, Wilmington, North Carolina (18); Stillabower, Michael E, Christiana Care Health System, Christiana Care Hospital, Newark, Delaware (17); Suresh, Damodhar P, St. Elizabeth Physicians,

Crestview Hills, Kentucky (19); Szulawski, Ireneusz, Geisinger Clinic, Geisinger Medical Group-Lewistown, Lewistown, Pennsylvania (16); Thompson, Paul, Polk, Donna M (FPI), Hartford Hospital, Hartford, Connecticut (14); Tinkel, Jodi L, Pandya, Utpal H (FPI), University of Toledo Medical Centre, Toledo, Ohio (9); Toth, Phillip T, Midwest Institute For Clinical Research, Indianapolis, Indiana (17); Traboulssi, Mourhaf, North Ohio Heart Centre, Inc, Sandusky, Ohio (53); Tuohy IV, Edward R, Bridgeport Hospital, Bridgeport, Connecticut (8); Uusinarkaus, Kari T, Clinical Research Advantage, Inc, Colorada Springs, Colorado (7); Vijay, Nampalli K, Aurora Denver Cardiology Associates, Denver, Colorado (18); Voyce, Stephen, Advanced Cariology Specialists, Scranton, Pennsylvania (18); Wainwright, William, RHancock, Holly (FPI), Baptist Heart Specialists, Jacksonville Beach, Florida (28); Walder, James S, Black Hills Cardiovascular Research Group Cardiology Associates, P.C., Rapid City, South Dakota (56); Wang, Tracy Yu-Ping, Duke University Medical Center, Durham, North Carolina (15); Watkins, Stanley P, Alaska Heart Institute, Anchorage, Alaska (11); Weiss, Robert J, Maine Research Associates, Auburn, Maine (66); Whitney, Edwin J, BHS Speciality Network, Inc., San Antonio, Texas (7); Wickemeyer, William J, Iowa Heart Center, West Des Moines, Iowa (55); Willis, John G, San Gabriel Clinical Research, Georgetown, Texas (12); Wilson, Dennis F, Abrams, Cyril (FPI), Mid Carolina Cardiology, Salisbury, North Carolina (23); Wiseman, Alan, Eastern Maine Medical Centre, Bangor, Maine (17); Wolfson, Eric, Wolfson Medical Centre, Las Vegas, Nevada (14); Wright, David, Central Texas Clinical Research, Austin, Texas (19); Zawada, Jr. Edward T, Verma, Suneet (FPI), Avera Research Institute, Sioux Falls, South Dakota (14).