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Biomarkers and Coronary Lesions Predict Outcomes after Revascularization in Non–ST-Elevation Acute Coronary Syndrome

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BACKGROUND: Risk stratification in non–ST-elevation acute coronary syndrome (NSTE-ACS) is currently mainly based on clinical characteristics. With routine invasive management, angiography findings and biomarkers are available and may improve prognostication. We aimed to assess if adding biomarkers [high-sensitivity cardiac troponin T (cTnT-hs), N-terminal probrain-type natriuretic peptide (NT-proBNP), growth differentiation factor 15 (GDF-15)] and extent of coronary artery disease (CAD) might improve prognostication in revascularized patients with NSTE-ACS.

METHODS: In the PLATO (Platelet Inhibition and Patient Outcomes) trial, 5174 NSTE-ACS patients underwent initial angiography and revascularization and had cTnT-hs, NT-proBNP, and GDF-15 measured. Cox models were developed adding extent of CAD and biomarker levels to established clinical risk variables for the composite of cardiovascular death (CVD)/spontaneous myocardial infarction (MI), and CVD alone. Models were compared using *c*-statistic and net reclassification improvement (NRI).

RESULTS: For the composite end point and CVD, prognostication improved when adding extent of CAD, NT-proBNP, and GDF-15 to clinical variables (*c*-statistic 0.685 and 0.805, respectively, for full model vs 0.649 and 0.760 for clinical model). cTnT-hs did not contribute to prognostication. In the full model (clinical variables, extent of CAD, all biomarkers), hazard ratios (95% CI) per standard deviation increase were for cTnT-hs 0.93(0.81–1.05), NT-proBNP 1.32(1.13–1.53), GDF-15 1.20(1.07–1.36) for the composite end point, driven by prediction of CVD by NT-proBNP and GDF-15. For spontaneous MI, there was an association with NT-proBNP or GDF-15, but not with cTnT-hs.

CONCLUSIONS: In revascularized patients with NSTE-ACS, the extent of CAD and concentrations of NT-proBNP and GDF-15 independently improve prognostication of CVD/spontaneous MI and CVD alone. This information may be useful for selection of patients who might benefit from more intense and/or prolonged antithrombotic treatment.

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Patients admitted with suspected or definite non–ST-elevation acute coronary syndrome (NSTE-ACS)[16] are heterogeneous in terms of risk of recurrent nonfatal and fatal events. Several risk scores have therefore been developed to

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[16] Nonstandard abbreviations: NSTE-ACS, non–ST-elevation acute coronary syndrome; TIMI, Thrombolysis in Myocardial Infarction study group; GRACE, Global Registry of Acute Coronary Events; CK-MB, creatine kinase-MB; PCI, percutaneous coronary intervention; CAD, coronary artery disease; NT-proBNP, N-terminal probrain-type natriuretic peptide; GDF-15, growth differentiation factor 15; PLATO, Platelet Inhibition and Patient Outcomes trial; cTnT-hs, high-sensitivity cardiac troponin T; CVD, cardiovascular death; MI, myocardial infarction; CABG, coronary artery bypass graft; ECG, electrocardiogram; TIA, transient ischemic attack; IQR, interquartile range; UCR, Uppsala Clinical Research Center; 1VD, 1-vessel disease; 2VD, 2-vessel disease; 3VD, 3-vessel disease; LMD, left main disease; BMI, body mass index; HR, hazard ratio; LR, likelihood ratio; NRI, net reclassification improvement; 0/1VD, 0/1-vessel disease; STEMI, ST-elevation myocardial infarction; TRACER, Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes study.

estimate the prognosis and provide decision support regarding an early invasive or noninvasive management strategy *(1–4)*. In this setting, the Thrombolysis in Myocardial Infarction study group (TIMI) *(1)* and Global Registry of Acute Coronary Events (GRACE) *(2)* scores are the most commonly used, and are based mainly on disease history and clinical characteristics available on admission. Regarding biomarkers, both of these risk scores include a dichotomous estimate of myocardial damage [creatine kinase-MB (CK-MB) or troponin positive yes/no], and GRACE score also includes creatinine concentration as a crude estimate of renal function.

Since the development of the TIMI and GRACE scores, several aspects of NSTE-ACS treatment have evolved substantially. Based on more effective antithrombotic treatments, and improved outcomes with percutaneous coronary intervention (PCI), early angiography and subsequent revascularization has become the routine treatment in the majority of patients with NSTE-ACS and increased troponin concentrations in accordance with the current guidelines *(4, 5)*. As revascularization substantially reduces the risk of subsequent events *(6, 7)*, the tools developed before the invasive era might not be optimal for prognostication in the invasively managed population. In this setting, prognostication would rather be employed to guide secondary prevention measures, e.g., duration and intensity of antithrombotic treatment *(8–11)*. At the same time, additional information will be available which might be useful for prognostication, e.g., severity of coronary artery disease (CAD) in the coronary angiogram and results of measurements on biomarkers from blood samples obtained on admission.

In patients with NSTE-ACS, the extent of CAD is associated with risk of subsequent events *(12)*. During the last years several biomarkers have also been suggested to improve prognostication in patients with ACS, e.g., N-terminal probrain-type natriuretic peptide (NT-proBNP) *(13, 14)*, growth differentiation factor 15 (GDF-15) *(15)*, and cardiac troponins measured with high-sensitivity assays *(14, 16, 17)*. Few studies have, however, assessed the complementary data provided by combining clinical information, angiography findings, and biomarker measurements. In this substudy of the Platelet Inhibition and Patient Outcomes (PLATO) trial, we therefore investigated if measurements of these new biomarkers and the angiographic information on extent of CAD might improve prognostication of different outcomes in patients with NSTE-ACS managed with early revascularization.

Methods

STUDY POPULATION

The PLATO trial (www.clinicaltrials.gov identifier: NCT00391872) randomized 18624 patients with ST-elevation and non–ST-elevation acute coronary syndromes to ticagrelor or clopidogrel for the prevention of cardiovascular events. Patients were followed for up to 12 months and the primary end point was the composite of cardiovascular death (CVD), myocardial infarction (MI, excluding silent), and stroke. Details of study design, outcome definitions and overall results have been published *(18, 19)*. A predefined biomarker substudy was also part of the PLATO program including the safety population (i.e., those who received at least one dose of the study drug) of 18421 patients. In the present study, 5174 patients in the biomarker substudy with available results of highly-sensitive cardiac troponin T (cTnT-hs), NT-proBNP, and GDF-15 at baseline; an admission diagnosis of NSTE-ACS; in-hospital management including coronary angiography and revascularization (by PCI or coronary artery bypass graft [CABG] surgery); and prespecified clinical characteristics were included (see Fig. S1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol63/issue2).

NSTE-ACS was defined by absence of both persistent ST-segment elevation and new (or presumed new) left bundle-branch block in entry ECG. Additionally, 2 or more of the following inclusion criteria were required: 1) ST-segment changes on electrocardiogram (ECG) indicating ischemia [ST-segment depression or transient elevation ($\geq$1 mm) in at least 2 contiguous leads]; 2) positive biomarker indicating myocardial necrosis (troponin I or T or CK-MB above the upper reference limit); 3) one of the following: $\geq$60 years of age, previous MI or CABG surgery, CAD with $\geq$50% stenosis in $\geq$2 vessels, previous ischemic stroke, transient ischemic attack (TIA), carotid stenosis, cerebral revascularization, diabetes mellitus, peripheral artery disease, or chronic renal dysfunction. The trial was conducted in accordance with the Declaration of Helsinki. All patients provided informed consent to participate.

BIOMARKERS

Blood samples were taken by direct venipuncture at randomization at a median of 7.6 h after admission [interquartile range (IQR): 2.0–15.9]. This was at a median of 15.3 h (IQR: 8.3–21.1) after the start of symptoms. The samples were centrifuged within 30 min and aliquots of plasma (EDTA) were frozen and stored at −70 °C or lower until central analysis at the Uppsala Clinical Research Center (UCR) laboratory. GDF-15, cTnT-hs, and NT-proBNP were analyzed using the Cobas® Analytics e601 and c501 Immunoanalyzer (Roche Diagnostics).

According to the manufacturer, the cTnT-hs assay has an analytical measurement range of 3–10000 ng/L, limit of detection 5 ng/L, and limit of quantification of

13 ng/L, based on the 10% CV, with a local CV of 3% at 27 ng/L in the UCR laboratory.

The NT-proBNP assay has, according to the manufacturer, an analytical measurement range of 5–35 000 ng/L, a reported total CV ranging between 2.9 and 6.1%, and the lowest concentration corresponding to a 10% CV is 30 ng/L. The local CV was 3% at 125 ng/L.

The precommercial Elecsys® GDF-15 assay (Roche Diagnostics) has been described previously *(20)*. According to the manufacturer, it has an interassay CV of 2.3% at 100 ng/L and 1.8% at 17 200 ng/L, an intraassay CV of 0.8% at 1100 ng/L and 0.9% at 18 600 ng/L, and a lower detection limit of 10 ng/L. In the UCR laboratory, the local CV was 3% at 928 ng/L.

All biomarkers were entered into the models as continuous variables, i.e., no specific cutoffs were used.

EXTENT OF CAD

At coronary angiography, the presence of a coronary stenosis of ≥50% was reported for the following locations: left main, left anterior descending, left circumflex, right coronary, and bypass graft. Information on whether the coronary anatomy was left or right dominant was not available in the database. For the purpose of this analysis, 1-vessel disease (1VD) was defined as a ≥50% stenosis in any of the above locations (except left main), 2-vessel disease (2VD) at 2 locations (except left main), and 3-vessel disease (3VD) as stenosis at ≥3 locations and/or in the left main [left main disease (LMD)].

END POINTS

The primary end point for this study was the composite of CVD and spontaneous MI. We also analyzed CVD and spontaneous MI individually. A central adjudication committee blinded to treatment assignment assessed all events.

STATISTICAL ANALYSES

Baseline and inhospital characteristics are presented in the subgroup of patients with an inhospital management that included revascularization and available biomarker and coronary angiography data, as well as data on prespecified clinical characteristics for the clinical base model. Continuous variables are presented as median and Q1-Q3, categorical variables as number and percentage. To assess any association between biomarkers and extent of CAD, χ^2 tests (with biomarker quartiles) and Spearman correlations (with biomarkers as continuous variables) were conducted.

Kaplan–Meier estimated event rates were plotted by biomarker quartile as well as by extent of CAD for the primary end point of CVD or spontaneous MI. Multivariable Cox proportional hazards models were developed using clinical variables, extent of CAD, and continuous biomarker measurements as independent variables. The clinical variables included in the models were: age; body mass index (BMI); heart rate; systolic blood pressure; male gender; habitual smoking; ST-depression in ECG; T-wave inversion in ECG; if patients had experienced hypertension, dyslipidemia, diabetes mellitus, chronic renal disease, or congestive heart failure before the index event; family history of coronary artery disease; and randomized treatment (ticagrelor or clopidogrel). Hazard ratios (HRs) and 95% CIs were expressed per SD increase in the respective log-transformed biomarker measurement. The assumption of proportional hazards for the biomarkers and extent of CAD was assessed visually using log-cumulative hazard plots. Model calibration was evaluated using the Grønnesby–Borgan test *(20)*. The cumulative sums of Martingale-based residuals indicated that a log transformation was adequate for the biomarkers.

To assess the discriminatory ability of the models, the Harrell *c*-index was used. Models were compared in terms of global model fit improvement using likelihood ratio (LR) tests. The continuous net reclassification improvement (NRI) *(21)* was calculated to estimate the degree of correct reclassification when adding biomarkers and extent of CAD to the clinical base model, with each component presented individually (NRI among events, and NRI among non-events) and as a total measure. Censored observations were handled using Kaplan–Meier estimation. As a sensitivity analysis, we also entered mode of revascularization (PCI or CABG) as an interaction term in the models.

A 2-sided *P* value of 0.05 was used to denote statistical significance. No adjustments for multiple testing were performed and all analyses should be considered as exploratory. All analyses were conducted using SAS version 9.4.

Results

For this substudy, 5174 patients met the inclusion criteria of NSTE-ACS, had available angiography data, inhospital revascularization, available biomarker measurements, and available data on clinical characteristics (see online Supplemental Fig. S1). The baseline and inhospital characteristics are shown in Table 1. Compared to previously published data on the overall revascularized NSTE-ACS population from PLATO *(22)*, there were no apparent differences in demographics, risk factors, or comorbidities. On the basis of angiography, 2051 (39.6%) patients had 0/1-vessel disease (0/1VD), 1529 patients (29.6%) had 2VD, and 1594 patients (30.8%) had 3VD/LMD.

Biomarker concentrations by quartile in relation to extent of CAD are shown in Fig. 1 and online Supplemental Table S1. There was no apparent association between concentrations of cTnT-hs and extent of CAD.

Table 1. Baseline and in-hospital characteristics.

	Characteristic	Total, n = 5174[a]
Demographics	Age, years, median (Q1–Q3)	63 (55–71)
	Female	1296 (25.0%)
	Weight, kg, median (Q1–Q3)	80 (71–90)
	BMI, kg/m^2, median (Q1–Q3)	27.5 (24.9–30.7)
Randomized treatment group	Ticagrelor	2603 (50.3%)
	Clopidogrel	2571 (49.7%)
Risk factor	Habitual smoker	1758 (34.0%)
	Hypertension	3381 (65.3%)
	Dyslipidemia	2797 (54.1%)
	Diabetes mellitus	1351 (26.1%)
	Family history of CAD	1942 (37.5%)
Medical history	Angina pectoris	2411 (46.6%)
	MI	1107 (21.4%)
	Congestive heart failure	189 (3.7%)
	PCI	908 (17.5%)
	CABG	370 (7.2%)
	TIA	157 (3.0%)
	Nonhemorrhagic stroke	173 (3.3%)
	Peripheral arterial disease	335 (6.5%)
	Chronic renal disease	196 (3.8%)
Physical findings	Diastolic blood pressure, mmHg, median (Q1–Q3)	80 (70–88)
	Systolic blood pressure, mmHg, median (Q1–Q3)	135 (120–150)
	Heart rate beats per min, median (Q1–Q3)	71 (63–80)
ECG findings	ST-segment depression ≥1 mm	2825 (54.6%)
	T-wave inversion in ECG	1690 (32.7%)
Delays	Delay from start of pain to randomization, h, median (Q1–Q3)	15.3 (8.3–21.1)
	Delay from admission to randomization, h, median (Q1–Q3)	7.6 (2.0–15.9)
Medications at randomization	Aspirin	4916 (95.0%)
	Beta-blockade	4173 (80.7%)
	ACE[a]-inhibition and/or ARB[b]	3276 (63.3%)
	Cholestrol lowering (statin)	4271 (82.5%)
	Calcium antagonist	813 (15.7%)
	Diuretic	1039 (20.1%)
Invasive procedures inhospital	Coronary angiography	5174 (100.0%)
	PCI before discharge for index event	4537 (87.7%)
	CABG predischarge	661 (12.8%)

[a] Data are n (%) unless otherwise noted.
[b] ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

For both NT-proBNP and GDF-15, quartile-divided biomarker concentrations were significantly related to extent of CAD ($P < 0.0001$ for both). However, the correlations with extent of CAD were weak, with Spearman correlation coefficients of $r = 0.117$ and $r = 0.121$ for NT-proBNP and GDF-15, respectively.

Kaplan–Meier estimates of the composite end point of CVD and spontaneous MI are found in Fig. 2A–C. Both NT-proBNP and GDF-15 were associated with the composite end point driven by strong prediction of CVD, with HR 8.00 (95% CI, 3.99–16.03) and 7.61 (95% CI, 3.64–15.93) when comparing the highest to

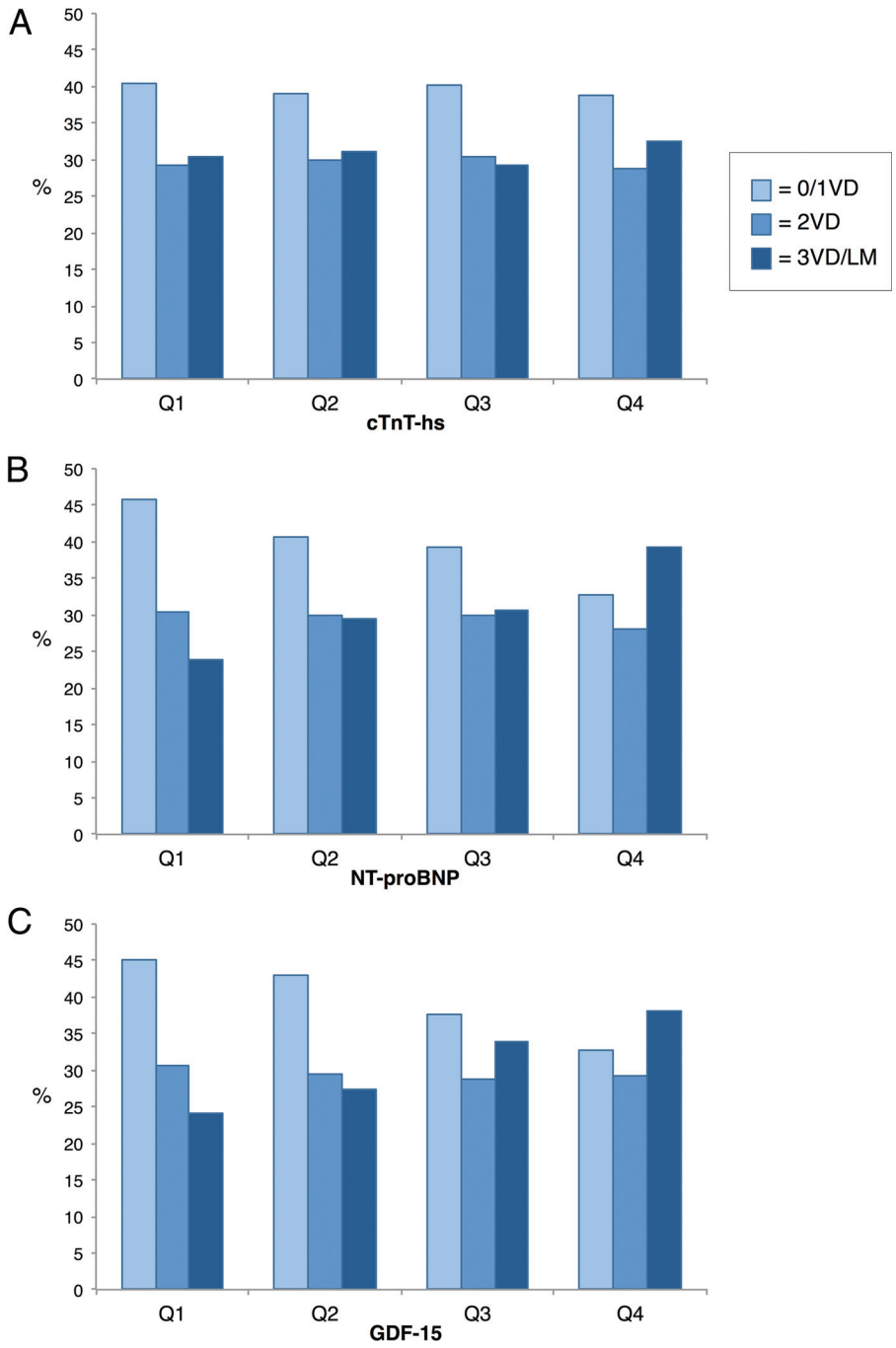

Fig. 1. Extent of CAD per biomarker quartiles.

Proportion of patients with 0/1VD, 2VD, and 3VD/LM in each quartile of (A) cTnT-hs, (B) NT-proBNP, and (C) GDF-15. χ^2 Tests were performed to assess if there were relationships between the extent of CAD and biomarkers by quartile: cTnT-hs ($P = 0.68$), NT-proBNP ($P < 0.0001$), and GDF-15 ($P < 0.0001$).

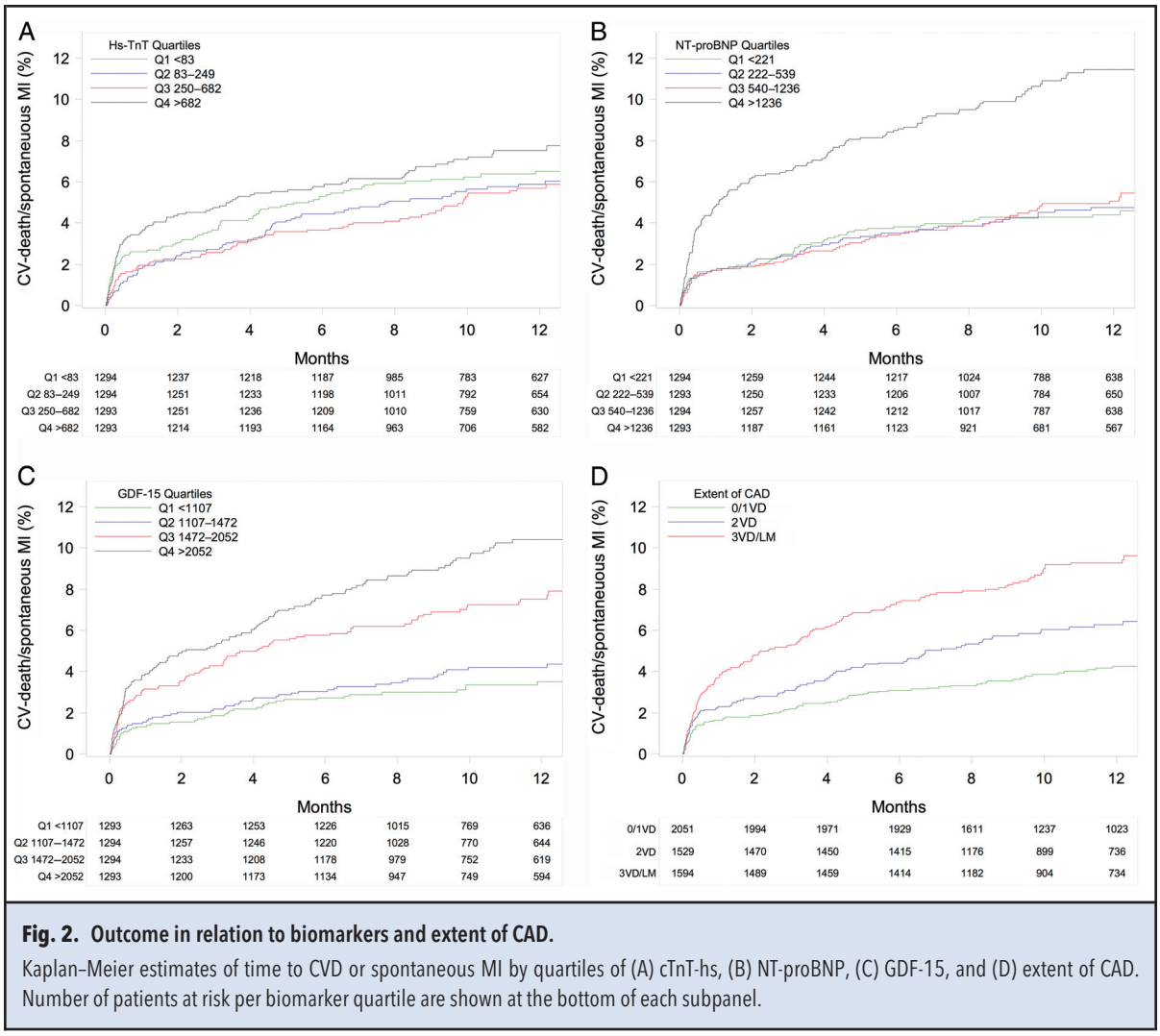

Fig. 2. Outcome in relation to biomarkers and extent of CAD.

Kaplan–Meier estimates of time to CVD or spontaneous MI by quartiles of (A) cTnT-hs, (B) NT-proBNP, (C) GDF-15, and (D) extent of CAD. Number of patients at risk per biomarker quartile are shown at the bottom of each subpanel.

the lowest quartile of NT-proBNP and GDF-15, respectively. The highest compared to the lowest quartile of NT-proBNP was also associated with a higher risk of spontaneous MI, unadjusted HR 1.77 (95% CI, 1.24–2.53). For GDF-15 there was a gradual association of higher rates of spontaneous MI with higher concentrations of GDF-15. Thus, the third and the highest quartile compared to the lowest quartile of GDF-15 had unadjusted HRs 1.91 (95% CI, 1.28–2.87) and 2.19 (1.47–3.25), respectively (Table 2, Fig. 2B–C). There was no apparent association between concentrations of cTnT-hs and the composite end point of CVD and spontaneous MI, or with spontaneous MI alone. For CVD alone, the highest compared to the lowest quartile of cTnT-hs was associated with worse outcome, unadjusted HR 1.75 (95% CI, 1.09–2.81) (Table 2).

The extent of CAD was associated with the primary composite end point, with an unadjusted HR 1.46 (95% CI, 1.08–1.97) for 2VD and a HR 1.97 (95% CI, 1.48–2.60) for 3VD/left main disease, when compared with 0/1VD. This was driven by corresponding associations with both CVD and MI. (Table 2, Fig. 2D).

MULTIVARIABLE EVALUATION OF PROGNOSTIC VALUE OF CAD AND BIOMARKERS

Concerning the composite end point of CVD and spontaneous MI, adding extent of CAD to clinical variables improved the model with a *c* index increasing from 0.649 to 0.673 (LR-test: $P < 0.0001$). Further adding either NT-proBNP or GDF-15 improved the model's performance to a similar degree, with a *c* index of 0.679 and 0.683, respectively (both $P < 0.0001$). NT-proBNP contributed mainly by reclassifying patients to a higher risk, whereas GDF-15 contributed mainly by reclassifying patients to a lower risk (Table 3). cTnT-hs did

Table 2. Occurrence of endpoints according to extent of CAD and biomarker quartiles (unadjusted).

		Cardiovascular death or spontaneous MI		Cardiovascular death		Spontaneous MI	
	No. of patients	Events, n (%)	HR (95% CI)	Events, n (%)	HR (95% CI)	Events, n (%)	HR (95% CI)
Extent of CAD							
0VD/1VD	2051	80 (3.9)	Reference	21 (1.0)	Reference	64 (3.1)	Reference
2VD	1529	90 (5.9)	1.46 (1.08–1.97)	29 (1.9)	1.75 (1.00–3.07)	67 (4.4)	1.37 (0.97–1.93)
3VD/LMD	1594	140 (8.8)	1.97 (1.48–2.60)	64 (4.0)	3.02 (1.82–5.00)	91 (5.7)	1.68 (1.21–2.33)
cTnT-hs (ng/L)							
Q1: <83	1294	80 (6.2)	Reference	27 (2.1)	Reference	58 (4.5)	Reference
Q2: 83–249	1294	72 (5.6)	0.88 (0.64–1.21)	23 (1.8)	0.84 (0.48–1.47)	57 (4.4)	0.96 (0.67–1.39)
Q3: 250–682	1293	67 (5.2)	0.83 (0.60–1.15)	18 (1.4)	0.66 (0.37–1.21)	52 (4.0)	0.89 (0.61–1.29)
Q4: >682	1293	91 (7.0)	1.16 (0.86–1.57)	46 (3.6)	1.75 (1.09–2.81)	55 (4.3)	0.97 (0.67–1.40)
NT-proBNP (ng/L)							
Q1: <221	1294	56 (4.3)	Reference	9 (0.7)	Reference	48 (3.7)	Reference
Q2: 221–539	1293	57 (4.4)	1.03 (0.71–1.49)	17 (1.3)	1.92 (0.86–4.30)	45 (3.5)	0.95 (0.63–1.43)
Q3: 540–1236	1294	62 (4.8)	1.11 (0.77–1.60)	19 (1.5)	2.13 (0.96–4.70)	49 (3.8)	1.02 (0.69–1.53)
Q4: >1236	1293	135 (10.4)	2.55 (1.87–3.48)	69 (5.3)	8.00 (3.99–16.03)	80 (6.2)	1.77 (1.24–2.53)
GDF-15 (ng/L)							
Q1: <1107	1293	42 (3.2)	Reference	8 (0.6)	Reference	36 (2.8)	Reference
Q2: 1107–1472	1294	52 (4.0)	1.23 (0.82–1.85)	15 (1.2)	1.87 (0.79–4.40)	44 (3.4)	1.22 (0.78–1.89)
Q3: 1472–2052	1294	93 (7.2)	2.27 (1.58–3.27)	32 (2.5)	4.06 (1.87–8.81)	67 (5.2)	1.91 (1.28–2.87)
Q4: >2052	1293	123 (9.5)	3.07 (2.16–4.36)	59 (4.6)	7.61 (3.64–15.93)	75 (5.8)	2.19 (1.47–3.25)

not improve prediction of the composite end point (Fig. 3; also see online Supplemental Table S2). In a model comprising clinical variables, extent of CAD, and NT-proBNP, the addition of GDF-15 further improved the model to *c* index 0.685 ($P = 0.0026$) (Table 3). In the full model (including clinical variables, extent of CAD, and all biomarkers), the HRs (95% CIs) per SD increase in biomarker concentration were cTnT-hs 0.93 (0.81–1.05), NT-proBNP 1.32 (1.13–1.53), and GDF-15 1.20 (1.07–1.36) for the prediction of the composite end point of CVD or spontaneous MI (Fig. 3).

Regarding the prediction of CVD alone, adding extent of CAD to clinical variables improved the model, with the *c* index rising from 0.760 to 0.791 ($P < 0.0001$) (Table 3). The addition of cTnT-hs to clinical variables improved the model minimally, with an increase in *c* index from 0.760–0.762 (see online Supplemental Table S2), while the addition of NT-proBNP or GDF-15 increased the *c* index to 0.776 and 0.772, respectively (both $P < 0.0001$). In a model including clinical variables and extent of CAD, adding NT-proBNP or GDF-15 increased the *c* index to 0.799 or 0.804, respectively (both $P < 0.0001$). In a model comprising clinical variables, extent of CAD, and NT-proBNP, adding GDF-15 further improved the model to *c* index 0.805 ($P = 0.0062$). In the final model, the HRs (95% CIs) per SD increase in biomarker concentration were cTnT-hs 1.00 (0.80–1.23), NT-proBNP 1.61 (1.24–2.08), and GDF-15 1.31 (1.09–1.58) for the prediction of CVD (Fig. 3).

For spontaneous MI alone, NT-proBNP and GDF-15 were associated with the outcome in a model adjusting for clinical variables and extent of CAD. No association was apparent between concentrations of cTnT-hs and spontaneous MI. In a model adjusting for clinical variables and extent of CAD, the HRs (95% CIs) per SD increase in biomarker concentration were cTnT-hs 0.89 (0.76–1.04), NT-proBNP 1.28 (1.07–1.53), and GDF-15 1.10 (0.95–1.28) for the prediction of spontaneous MI.

Similar results were found when assessing the prognostic impact per biomarker doubling instead of per SD increase (see online Supplemental Fig. S2). There were no significant interactions between the prognostic performance of the biomarkers and mode of revascularization (PCI vs CABG, data not shown).

Table 3. Model improvement by adding extent of CAD and biomarkers to clinical characteristics.

Outcome	Model	Predictor added	Harrell *c* (95% CI) Model without predictor added	Harrell *c* (95% CI) Model with predictor added	NRI			LR test
					Total	Among events	Among nonevents	*P* value
Cardiovascular death or Spontaneous MI (number of events = 309)	Clinical	Extent of CAD	0.649 (0.617–0.681)	0.673 (0.642–0.704)	0.233	0.238	−0.005	<0.0001
	Clinical	NT-proBNP	0.649 (0.617–0.681)	0.661 (0.629–0.693)	0.253	0.188	0.065	<0.0001
	Clinical	GDF-15	0.649 (0.617–0.681)	0.662 (0.630–0.694)	0.205	0.011	0.194	<0.0001
	Clinical + extent of CAD	NT-proBNP	0.673 (0.642–0.704)	0.679 (0.647–0.711)	0.170	0.124	0.046	<0.0001
	Clinical + extent of CAD	GDF-15	0.673 (0.642–0.704)	0.683 (0.652–0.714)	0.191	0.006	0.185	<0.0001
	Clinical + extent of CAD + NT-proBNP	GDF-15	0.679 (0.647–0.711)	0.685 (0.653–0.716)	0.101	−0.010	0.111	0.0026
Cardiovascular death (number of events = 113)	Clinical	Extent of CAD	0.760 (0.713–0.806)	0.791 (0.749–0.833)	0.428	0.241	0.186	<0.0001
	Clinical	NT-proBNP	0.760 (0.713–0.806)	0.776 (0.730–0.823)	0.428	0.256	0.172	<0.0001
	Clinical	GDF-15	0.760 (0.713–0.806)	0.772 (0.727–0.817)	0.273	0.038	0.235	<0.0001
	Clinical + extent of CAD	NT-proBNP	0.791 (0.749–0.833)	0.799 (0.755–0.842)	0.355	0.215	0.140	<0.0001
	Clinical + extent of CAD	GDF-15	0.791 (0.749–0.833)	0.804 (0.764–0.844)	0.234	0.003	0.230	<0.0001
	Clinical + extent of CAD + NT-proBNP	GDF-15	0.799 (0.755–0.842)	0.805 (0.763–0.846)	0.107	0.028	0.079	0.0057
Spontaneous MI (number of events = 222)	Clinical	Extent of CAD	0.629 (0.592–0.667)	0.645 (0.609–0.681)	0.149	0.251	−0.102	0.0072
	Clinical	NT-proBNP	0.629 (0.592–0.667)	0.636 (0.598–0.673)	0.169	0.141	0.029	0.0013
	Clinical	GDF-15	0.629 (0.592–0.667)	0.635 (0.598–0.672)	0.119	−0.036	0.155	0.0203
	Clinical + extent of CAD	NT-proBNP	0.645 (0.609–0.681)	0.649 (0.612–0.686)	0.162	0.144	0.017	0.0037
	Clinical + extent of CAD	GDF-15	0.645 (0.609–0.681)	0.650 (0.614–0.686)	0.128	−0.017	0.145	0.0298
	Clinical + extent of CAD + NT-proBNP	GDF-15	0.649 (0.612–0.686)	0.652 (0.615–0.688)	0.055	−0.035	0.090	0.1722

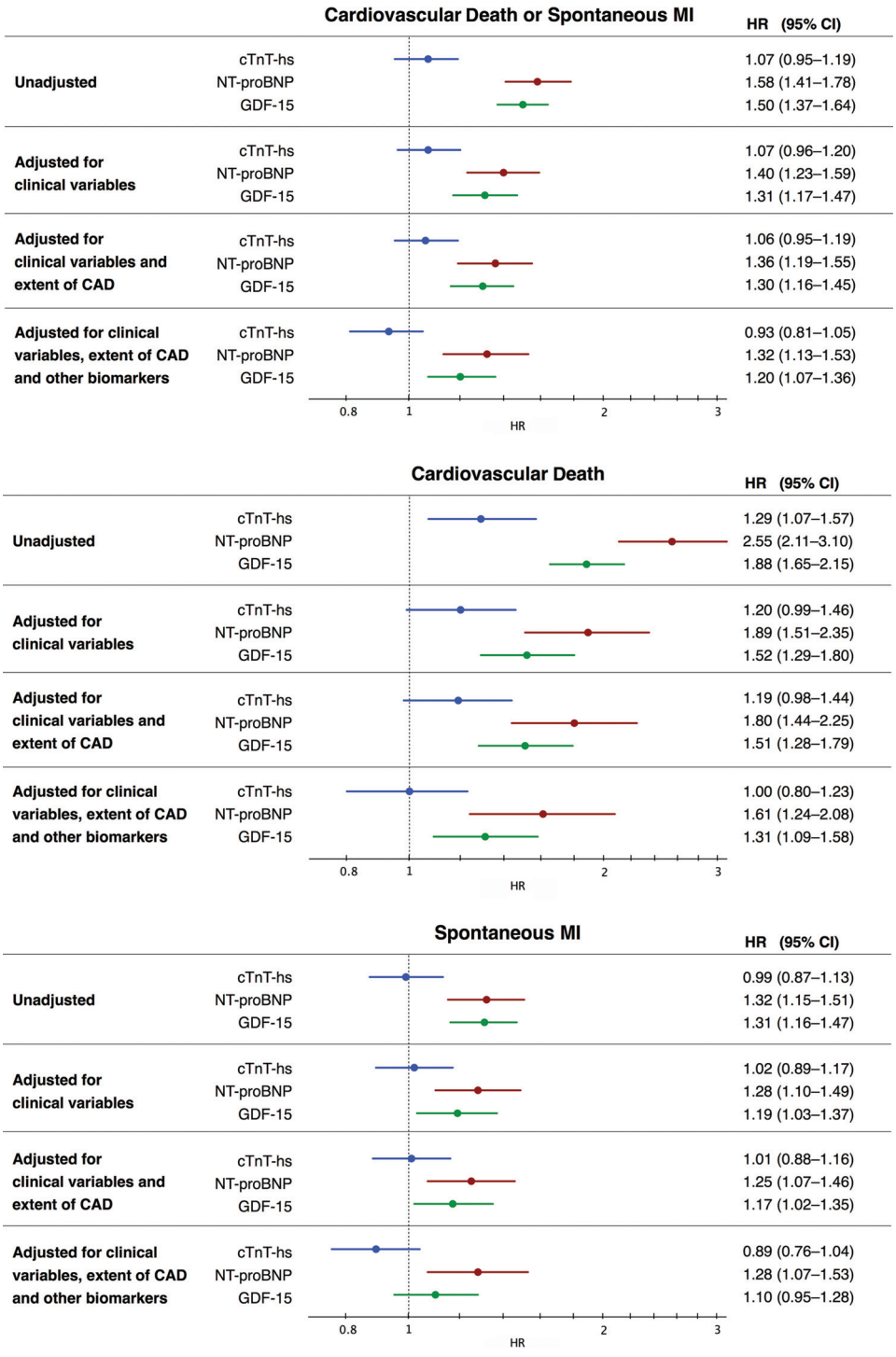

Fig. 3. Adding biomarkers to risk prediction models.

HRs per SD increase in biomarker concentration in different Cox proportional hazards models. The unadjusted model includes no other variable than randomized treatment. The clinical variables included were age; BMI; heart rate; systolic blood pressure; male sex; habitual smoking; ST-depression in ECG; T-wave inversion in ECG; history of hypertension, dyslipidemia, diabetes mellitus, chronic renal disease, congestive heart failure; family history of coronary artery disease; and randomized treatment (ticagrelor or clopidogrel).

Discussion

Early coronary angiography and, if feasible, revascularization is currently the routine treatment in patients with NSTE-ACS with increased troponin concentrations without further risk stratification. There is a need for better information on the risk for different events after the invasive procedure as support for the decision making on continuing medical treatments, e.g., intensity and duration of antithrombotic treatment *(8–11)*. In this PLATO substudy focusing on patients with NSTE-ACS managed with early revascularization, we showed that the extent of CAD at coronary angiography and the entry concentrations of NT-proBNP and GDF-15 independently improved the prediction of CVD alone and CVD or spontaneous MI. The models combining clinical characteristics, extent of CAD, and biomarkers outperformed a model based on clinical characteristics alone. NT-proBNP, GDF-15, and the extent of CAD all independently contributed to the prognostication of both CVD and spontaneous MI. In contrast, cTnT-hs concentrations at the time of presentation were not independently associated with either the composite end point of CVD and spontaneous MI, or its individual components (when adjusting for clinical variables) in NSTE-ACS patients managed with revascularization.

An association between angiographic extent of CAD and subsequent events has previously been shown for ACS overall *(23)*, NSTE-ACS *(12)*, and ST-elevation myocardial infarction (STEMI) *(24)*. The conventional risk scores, e.g., TIMI and GRACE scores, were developed for identification of patients at high risk at entry who might benefit from early revascularization. However, these scores may be less appropriate for risk prediction in the invasively managed NSTE-ACS population. The present findings of an independent prognostic value of extent of CAD is in agreement with the ACUITY-PCI score which, including angiographic findings (extent of CAD, small vessel disease, bifurcation lesion) and clinical variables (baseline cardiac biomarker elevation or ST-deviation, insulin-treated diabetes, renal insufficiency), performed better than both TIMI and GRACE scores, with *c* indices of 0.70 vs 0.56 and 0.51, respectively, for the prediction of 1-year mortality or MI in NSTE-ACS patients undergoing PCI *(25)*.

In previous studies of heterogeneous patient cohorts with NSTE-ACS, troponin levels have generally been associated with subsequent ischemic events and mortality *(26–28)*. However, these studies reflect the variable revascularization practices from when they were conducted, including patients who, despite increased troponin concentrations and higher risk of subsequent events, still were managed with a noninvasive management strategy. We have previously reported the finding of a strong association between cTnT-hs and the composite end point of CVD/MI/stroke in the nonrevascularized NSTE-ACS cohort in PLATO, in contrast to a lack of association in the present revascularized cohort *(6)*. These contrasting findings are most likely due to the substantial risk reduction of early thrombotic events caused by the stenting of the culprit lesion in the revascularized patients. In GUSTO (global utilization of strategies to open occluded arteries)-IV, patients with increased troponin concentrations who underwent revascularization had almost identical risk of death as patients with nonincreased troponin concentrations *(29)*. Similar findings have recently been reported from the contemporary thrombin-receptor antagonist vorapaxar in acute coronary syndromes (TRACER) study, where peak troponin concentrations were associated with mortality only in patients who did not undergo revascularization, while in revascularized patients, peak troponin concentrations failed to predict 2-year mortality *(30)*.

NT-proBNP is a well-established risk marker that predicts mortality in several different settings: ACS *(31, 32)*, heart failure *(33)*, and even atrial fibrillation *(34)*. Similarly, GDF-15 has also demonstrated prognostic value in patients with heart failure *(35)*, atrial fibrillation *(36)*, and in the general population *(37, 38)*. Additionally, GDF-15 has been shown to predict mortality in NSTE-ACS, with added prognostic value when combined with NT-proBNP *(15, 39)*. In a recent study, the addition of NT-proBNP and GDF-15 to the GRACE score improved the prediction of all-cause mortality or MI at 6 months in NSTE-ACS patients *(40)*. In the present study focusing only on invasively managed NSTE-ACS patients, we showed for the first time the independent prognostic value of extent of CAD as well as the biomarkers NT-proBNP and GDF-15. GDF-15 was shown to contribute to risk prediction to a similar extent as NT-proBNP. However, while NT-proBNP improved identification of patients at higher risk, GDF-15 contributed mainly by reclassifying patients to a lower risk level. The reason for this is unknown, but could be related to the fact that primarily the top quartile of NT-proBNP identified patients at increased risk, whereas GDF-15 provided a more gradual increase in risk by increasing quartiles.

The current European NSTE-ACS guidelines recommend only troponin in the assessment of a patient with NSTE-ACS, mainly to establish the diagnosis; and risk scores (either TIMI or GRACE) for risk assessment *(5)*. In the present study of invasively managed NSTE-ACS patients, we show that extent of CAD, NT-proBNP, and GDF-15, but not cTnT-hs, add substantial prognostic information when compared with clinical characteristics alone. As current clinical practice may shift toward longer term antiplatelet therapy and/or anticoagulant use based on recent studies *(8–11, 36)*, the complementary information from angiographic burden

of CAD and biomarkers could help us better understand which patients benefit the most from more intense and/or prolonged treatment.

There are limitations to this study. First, it was a post hoc analysis of the revascularized NSTE-ACS subgroup. The analyses were based on patients who underwent coronary angiography and revascularization based on a decision by the treating physician as in the real life setting. This decision was no doubt influenced by troponin levels measured locally. Therefore, increased troponin concentrations likely influenced the selection of the presently studied subgroup, although the concentration at entry was not significantly related to outcomes in the revascularized population. Finally, in this study only biomarker measurements at the time of randomization were studied. The possible added prognostic information of serial measurements of biomarkers is acknowledged.

In conclusion, in this PLATO substudy, the extent of CAD at coronary angiography and entry concentrations of NT-proBNP and GDF-15 independently improved the prediction of subsequent CVD or spontaneous MI beyond clinical characteristics in patients with NSTE-ACS managed with early revascularization. The extent of CAD and the concentrations of NT-proBNP and GDF-15 all independently contributed to prognostication of both CVD and spontaneous MI. In contrast, the cTnT-hs concentration at entry was not associated with the composite of CVD and spontaneous MI or spontaneous MI alone after early revascularization. This information therefore might be useful to include in decision algorithms for selection of NSTE-ACS patients who might benefit from more intense and/or prolonged antithrombotic treatment, or for identification of patients who might do well with less intense treatment after revascularization.

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