SUPPLEMENTAL MATERIAL

Supplemental Methods

Patient population

In the overall PEACE trial, a total of 8290 patients with documented stable coronary artery disease and preserved left ventricular ejection fraction were randomized at 187 clinical centers in the United States, Canada, and Europe to trandolapril or placebo from November 1996 through June 2000. Subjects were followed for a median of 4.8 years. As part of the study protocol, a sample of venous blood was obtained in EDTA-treated tubes at the time of enrollment. Participation in the biomarker substudy was at the discretion of each clinical center and there were no clinically relevant differences between patients included in the substudy and the overall trial population (Supplemental Table 1). The plasma component was aspirated and frozen at -20 ^{o}C at individual centers. Within 3 months after collection, plasma samples were shipped on dry ice to a central laboratory for storage at -70 ^{o}C or colder until thawed for determination of biomarkers.

Biomarker analyses

Levels of MR-proANP, MR-proADM, CT-proET-1, and copeptin were determined using the Time-Resolved-Amplified-Cryptate-Emission (TRACE) technology on the Kryptor Compact analyzers (B.R.A.H.M.S. GmbH, Henningsdorf, Germany). NT-proBNP levels were determined with an electrochemiluminescence immunoassay on a Modular platform (Roche Diagnostics, Bsel, Switzerland). Cardiac troponin T (cTnT) levels were measured with a highly sensitive assay on an autoanalyzer (cobas e 411, Roche Diagnostics, Penzberg, Germany).

Outcomes

All clinical events were confirmed by a review of medical records. Cardiovascular death, MI, and stroke underwent blinded review by an outcomes committee. Heart failure was classified by centrally trained local staff and confirmed by staff at the coordinating center through a review of hospital records. For an event to be classified as heart failure, hospitalization with a primary cause of heart failure was required.

Statistical analyses

As described by Pencina and colleagues, the integrated discrimination improvement (IDI) is a method to quantify the differences in the probabilities for events and non-events based on the addition of the new biomarkers to the model and can be viewed as difference between the improvement in average sensitivity and any potential increase in average "one minus specificity". The net re-classification improvement (NRI) is the probability that patients are appropriately assigned to a higher or lower risk. We calculated NRI using Harrell's technique, as programmed in R, which evaluates the change in the estimated risk as a continuous variable and therefore is not dependent on *a priori* categorization.

Supplemental Table 1. Baseline Characteristics of Patients in the PEACE Trial

Baseline Characteristic	**All patients (n=8290)**	**Patients in the biomarker substudy (n=3717)**	**Patients not in the biomarker substudy (n=4573)**
Age, y	64.3±8.2	64.1±8.2	64.5±8.2
Female sex	1494 (18.0)	701 (18.9)	793 (17.3)
Weight, kg	83.4±15.7	83.9±15.7	83.1±15.7
Hypertension	3764 (45.4)	1658 (44.6)	2106 (46.1)
Diabetes	1380 (16.7)	602 (16.2)	778 (17.0)
Current smoker	1177 (14.2)	564 (15.2)	613 (13.4)
Prior MI	4552 (55.0)	2087 (56.2)	2465 (54.0)
Prior PCI or CABG	5971 (72.1)	2697 (72.6)	3274 (71.7)
Aspirin	7519 (90.7)	3389 (91.2)	4130 (90.4)
Beta-blocker	4965 (59.9)	2303 (62.0)	2662 (58.3)
Lipid-lowering therapy	5801 (70.0)	2667 (71.8)	3134 (68.6)
SBP, mmHg	133.4±16.6	133.4±16.8	133.5±16.4
DBP, mmHg	77.7±9.7	78.1±10.0	77.4±9.6
GFR, ml/min/1.73 m^2	77.6±19.1	77.9±19.4	77.3±18.8
ApoB, mg/dl	107.2±23.1	107.2±23.1	106.8±26.3
ApoA, mg/dl	138.2±24.6	138.2±24.6	133.2±21.4
LVEF, %	58.2±9.4	58.7±9.6	57.7±9.1

Data presented are mean ±SD for normally distributed continuous variables and n (%) for dichotomous variables. CABG = coronary artery bypass grafting; DBP = diastolic blood pressure; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

Supplemental Table 2. Biomarker Assay Specifications

Biomarker	**MR-proANP**	**MR-proADM**	**CT-proET-1**	**Copeptin**
Assay specifications				
Units of measurement	pmol/L	nmol/L	pmol/L	pmol/L
Detection limit	2.1	0.05	3	5
Direct measurement upper limit	1000	10	500	500
Coefficient of variation	20-80 pmol/L: <8% >80 pmol/L: <5%	0.2-0.5 nmol/L: <20% 0.5-2.0 nmol/L: <11% 2-6 nmol/L: <10% >6 nmol/L: <6%	40-80 pmol/L: <10% >80 pmol/L: <6%	15-20 pmol/L: <15% 20-50 pmol/L: <13% >50 pmol/L: <8%
Values in Healthy Population*				
Median	46.1	0.39	45.5	5.0
97.5 percentile	163.9	0.52	73.9	17.4
Values in PEACE				
Median (25^{th}-75^{th} %ile)	90.45 (63.68-128.3)	0.5301 (0.4486-0.6353)	47.82 (39.04-57.02)	6.467 (0-10.67)
Mean±SD of log transformed values†	4.627±0.460	2.356±0.016	4.036±0.301	2.765±0.422
Values in Heart Failure Population[1]				
Median (25^{th}-75^{th} %ile)	206 (127-322)	0.75 (0.58-0.97)	81 (64-105)	13.8 (7.6-24.2)

*Data are from the package inserts for each assay.

† Raw values were natural log transformed. For MR-proADM, as the raw values were <1, a constant (10) was added to all values prior to log transformation.

Supplemental Table 3. Baseline Characteristics by MR-proANP Quartiles

	Quartiles of MR-proANP (pmol/L)				
Baseline Characteristic	**≤63.68 (n=930)**	**63.69-90.45 (n=929)**	**90.46-128.3 (n=930)**	**≥128.4 (n=928)**	**P value**
Age, y	59.5±6.8	62.1±7.3	65.3±7.5	69.6±7.4	<0.001
Female sex	140 (15.1)	160 (17.2)	193 (20.8)	208 (22.4)	<0.001
Weight, kg	87.5±16.0	84.8±15.0	83.1±15.7	80.4±15.1	<0.001
Hypertension	363 (39.0)	376 (40.5)	447 (48.1)	472 (50.9)	<0.001
Diabetes	179 (19.2)	152 (16.4)	135 (14.5)	136 (14.7)	0.004
Current smoker	228 (24.5)	165 (17.8)	95 (10.2)	76 (8.2)	<0.001
Prior MI	519 (55.8)	517 (55.7)	510 (54.9)	541 (58.3)	0.36
Prior PCI or CABG	661 (71.1)	676 (72.8)	669 (72.0)	691 (74.5)	0.15
Aspirin	865 (93.0)	865 (93.1)	842 (90.7)	817 (88.0)	<0.001
Beta-blocker	419 (45.1)	531 (57.2)	646 (69.6)	707 (76.2)	<0.001
Lipid-lowering therapy	681 (73.3)	692 (74.5)	661 (71.2)	633 (68.2)	0.005
SBP, mmHg	130.7±14.7	131.6±16.2	133.9±16.9	137.3±18.5	<0.001
DBP, mmHg	80.0±9.8	78.2±10.1	77.6±9.6	76.7±10.1	<0.001
GFR, ml/min/1.73 m^2	84.8±20.6	80.6±18.6	76.1±17.2	70.2±17.9	<0.001
ApoB, mg/dl	109.8±23.4	108.2±23.8	106.0±22.3	104.7±22.4	<0.001
ApoA, mg/dl	137.2±23.4	137.3±23.6	139.3±25.0	139.2±26.3	0.12
LVEF, %	59.5±9.6	59.3±9.6	58.7±9.8	57.5±9.4	<0.001

Data presented are mean ±SD for normally distributed continuous variables and n (%) for dichotomous variables. BMI = body mass index; CABG = coronary artery bypass grafting; DBP = diastolic blood pressure; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

Supplemental Table 4. Baseline Characteristics by MR-proADM Quartiles

	Quartiles of MR-proADM (nmol/L)				
Baseline Characteristic	**≤0.4486 (n=930)**	**0.4487-0.5301 (n=930)**	**0.5302-0.6353 (n=928)**	**≥0.6354 (n=929)**	**P value**
Age, y	60.1 ± 7.0	62.5 ± 7.6	65.2 ± 7.8	68.7 ± 7.6	<0.001
Female sex	148 (15.9)	125 (13.4)	173 (18.6)	255 (27.4)	<0.001
Weight, kg	80.6 ± 14.5	83.8 ± 14.6	85.1 ± 16.0	86.3 ± 16.8	<0.001
Hypertension	377 (40.5)	350 (37.6)	435 (46.9)	496 (53.4)	<0.001
Diabetes	148 (15.9)	133 (14.3)	139 (15.0)	182 (19.6)	0.03
Current smoker	145 (15.6)	130 (14.0)	160 (17.2)	129 (13.9)	0.75
Prior MI	506 (54.4)	534 (57.4)	526 (56.7)	521 (56.1)	0.54
Prior PCI or CABG	705 (75.8)	688 (74.0)	649 (69.9)	655 (70.6)	0.003
Aspirin	863 (92.8)	866 (93.1)	840 (90.6)	820 (88.4)	<0.001
Beta-blocker	525 (56.5)	554 (59.6)	601 (64.8)	623 (67.1)	<0.001
Lipid-lowering therapy	713 (76.8)	689 (74.1)	649 (70.1)	616 (66.4)	<0.001
SBP, mmHg	131.4 ± 16.1	131.0 ± 16.3	134.5 ± 16.9	136.6 ± 17.4	<0.001
DBP, mmHg	78.8 ± 10.2	77.9 ± 9.8	78.5 ± 9.6	77.2 ± 10.6	0.01
GFR, ml/min/1.73m^2	84.9 ± 20.0	81.2 ± 18.5	77.4 ± 17.2	68.2 ± 17.6	<0.001
ApoB, mg/dl	106.9 ± 21.7	106.2 ± 22.2	108.5 ± 24.8	107.2 ± 23.4	0.64
ApoA, mg/dl	138.1 ± 24.5	136.7 ± 23.3	138.4 ± 24.4	139.7 ± 26.1	0.08
LVEF, %	58.9 ± 9.6	58.6 ± 9.4	59.0 ± 9.9	58.5 ± 9.7	0.39

See footnote to Supplemental Table 3 for details.

Supplemental Table 5. Baseline Characteristics by CT-proET-1 Quartiles

	Quartiles of CT-proET-1 (pmol/L)				
Baseline Characteristic	**≤39.04 (n=930)**	**39.05-47.82 (n=929)**	**47.83-57.02 (n=929)**	**≥57.03 (n=929)**	**P value**
Age, y	62.0±7.6	63.1±8.0	64.6±8.2	66.8±8.0	<0.001
Female sex	191 (20.5)	155 (16.7)	145 (15.6)	210 (22.6)	0.37
Weight, kg	82.3±15.5	84.3±15.4	84.4±15.4	84.8±16.1	0.001
Hypertension	384 (41.3)	385 (41.4)	403 (43.4)	486 (52.3)	<0.001
Diabetes	162 (17.4)	125 (13.5)	153 (16.5)	162 (17.4)	0.57
Current smoker	127 (13.7)	132 (14.2)	140 (15.1)	165 (17.8)	0.01
Prior MI	493 (53.0)	551 (59.3)	516 (55.6)	527 (56.7)	0.31
Prior PCI or CABG	701 (75.4)	685 (73.7)	647 (69.7)	664 (71.5)	0.02
Aspirin	859 (92.4)	854 (91.9)	852 (91.9)	824 (88.7)	0.008
Beta-blocker	557 (59.9)	567 (61.0)	573 (61.8)	606 (65.2)	0.02
Lipid-lowering therapy	699 (75.2)	676 (72.8)	650 (70.1)	642 (69.1)	0.001
SBP, mmHg	131.1±16.1	132.9±16.5	133.4±17.2	136.0±17.2	<0.001
DBP, mmHg	77.8±9.7	78.7±10.1	78.4±9.6	77.7±10.4	0.61
GFR, ml/min/1.73 m^2	84.6±21.2	80.6±17.3	76.9±17.9	69.6±17.6	<0.001
ApoB, mg/dl	106.0±22.6	107.0±22.0	107.0±23.3	108.7±24.3	0.04
ApoA, mg/dl	139.6±25.3	139.1±24.5	137.3±24.7	136.9±23.8	0.01
LVEF, %	58.7±9.5	59.2±9.7	58.8±9.7	58.3±9.7	0.21

See footnote to Supplemental Table 3 for details.

Supplemental Table 6. Baseline Characteristics by Copeptin Quartiles

	Quartiles of Copeptin (pmol/L)				
Baseline Characteristic	**0 (n=1382)**	**5-6.467 (n=477)**	**6.468-10.67 (n=929)**	**≥10.68 (n=929)**	**P value**
Age, y	63.7±7.9	63.7±8.3	63.4±8.2	65.7±8.3	<0.001
Female sex	342 (24.8)	89 (18.7)	143 (15.4)	127 (13.7)	<0.001
Weight, kg	82.3±15.2	84.6±15.9	84.6±15.9	85.4±15.7	<0.001
Hypertension	629 (44.1)	218 (45.7)	380 (40.9)	451 (48.6)	0.20
Diabetes	205 (14.8)	78 (16.4)	135 (14.5)	184 (19.8)	0.01
Current smoker	183 (13.2)	64 (13.4)	176 (19.0)	141 (15.2)	0.02
Prior MI	754 (54.6)	268 (56.2)	539 (58.0)	526 (56.7)	0.18
Prior PCI or CABG	1011 (73.2)	338 (70.9)	684 (73.6)	664 (71.6)	0.60
Aspirin	1273 (92.1)	439 (92.0)	853 (91.9)	824 (88.8)	0.02
Beta-blocker	849 (61.4)	292 (61.2)	583 (62.8)	579 (62.4)	0.52
Lipid-lowering therapy	1006 (72.9)	348 (73.0)	666 (71.8)	647 (69.7)	0.11
SBP, mmHg	132.7±16.9	134.3±17.0	132.0±16.4	135.3±16.9	0.01
DBP, mmHg	77.9±9.8	78.9±9.9	78.2±10.1	78.0±10.2	0.99
GFR, ml/min/1.73 m^2	80.0±18.8	78.9±18.9	78.6±20.0	73.7±19.3	<0.001
ApoB, mg/dl	107.0±23.1	108.1±24.0	105.8±21.7	108.4±23.8	0.67
ApoA, mg/dl	140.4±25.7	138.2±23.0	137.6±24.1	135.7±23.9	<0.001
LVEF, %	59.3±9.7	58.4±9.1	58.6±9.6	58.3±9.7	0.01

See footnote to Supplemental Table 3 for details.

Supplemental Table 7. Correlation between biomarkers

	MR-proANP	MR-proADM	CT-proET-1	Copeptin	NT-proBNP	cTnT
MR-proANP	. . .	0.44	0.30	0.12	0.76	0.37
MR-proADM	<0.001	. . .	0.63	0.23	0.38	0.30
CT-proET-1	<0.001	<0.001	. . .	0.21	0.25	0.22
Copeptin	<0.001	<0.001	<0.001	. . .	0.10	0.20
NT-proBNP	<0.001	<0.001	<0.001	<0.001	. . .	0.35
cTnT	<0.001	<0.001	<0.001	<0.001	<0.001	. . .

Values above and to the right of the diagonal line of identity are Spearman's correlation coefficients, values to the left and below are the corresponding P values.

Supplemental Table 8. Association of biomarker levels and individual components of primary outcome in the placebo arm

Biomarker	Model	CV Death		Heart Failure	
		HR (95% CI)	P value	HR (95% CI)	P value
MR-proANP	*Unadjusted*	2.12 (1.69-2.67)	<0.001	2.52 (1.96-3.23)	<0.001
	Adjusted	1.76 (1.31-2.37)	<0.001	2.35 (1.72-3.20)	<0.001
MR-proADM	*Unadjusted*	1.74 (1.52-1.99)	<0.001	1.68 (1.44-1.96)	<0.001
	Adjusted	1.56 (1.27-1.90)	<0.001	1.47 (1.17-1.84)	0.001
CT-proET-1	*Unadjusted*	2.07 (1.55-2.77)	<0.001	2.13 (1.55-2.93)	<0.001
	Adjusted	1.52 (1.10-2.10)	0.012	1.70 (1.20-2.42)	0.003
Copeptin	*Unadjusted*	1.29 (1.03-1.62)	0.026	1.23 (0.96-1.58)	0.10
	Adjusted	1.03 (0.80-1.32)	0.83	1.08 (0.83-1.40)	0.57

Of the 1868 patients allocated to placebo, 67 experienced cardiovascular death and 56 heart failure. HR is per 1-SD increase in the log-transformed value of the biomarker. Each biomarker was analyzed separately.

Supplemental Table 9. Association of biomarker levels and other outcomes in the placebo arm

Biomarker	Model	All-Cause Death		Acute MI		Acute Stroke		Revascularization	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
MR-proANP	*Unadjusted*	1.59 (1.37-1.86)	<0.001	1.10 (0.91-1.33)	0.31	1.50 (1.11-2.03)	0.008	0.96 (0.87-1.06)	0.44
	Adjusted	1.30 (1.06-1.58)	0.011	1.07 (0.84-1.35)	0.59	1.51 (1.01-2.24)	0.043	0.96 (0.84-1.10)	0.55
MR-proADM	*Unadjusted*	1.57 (1.41-1.74)	<0.001	1.27 (1.08-1.50)	0.003	1.12 (0.84-1.51)	0.44	0.98 (0.88-1.09)	0.72
	Adjusted	1.41 (1.22-1.64)	<0.001	1.19 (0.96-1.48)	0.11	0.91 (0.65-1.27)	0.58	0.95 (0.84-1.08)	0.43
CT-proET-1	*Unadjusted*	1.56 (1.29-1.89)	<0.001	1.25 (1.00-1.55)	0.046	0.94 (0.69-1.27)	0.69	0.92 (0.83-1.02)	0.12
	Adjusted	1.29 (1.05-1.59)	0.016	1.12 (0.89-1.40)	0.35	0.84 (0.63-1.12)	0.23	0.91 (0.81-1.01)	0.08
Copeptin	*Unadjusted*	1.23 (1.06-1.44)	0.007	1.11 (0.92-1.33)	0.27	0.92 (0.67-1.28)	0.64	1.00 (0.90-1.11)	0.96
	Adjusted	1.06 (0.90-1.26)	0.48	1.01 (0.83-1.24)	0.88	0.84 (0.60-1.17)	0.30	0.98 (0.88-1.10)	0.78

Of the 1868 patients allocated to placebo, 153 died from any cause, 109 had an acute MI, 40 had an acute stroke, and 372 underwent coronary revascularization. HR is per 1-SD increase in the log-transformed value of the biomarker. Each biomarker was analyzed separately.

Supplemental Table 10. Adjusted multivariable, multimarker models in the placebo arm

	Model 1 **Clinical factors + NT-proBNP**		**Model 2** **Clinical factors + cTnT**		**Model 3** **Clinical factors + NT-proBNP & cTnT**		**Model 4** **Clinical factors + NT-proBNP, cTnT, & MR-proANP**		**Model 5** **Clinical factors + NT-proBNP, cTnT, & MR-proADM**		**Model 6** **Clinical factors + NT-proBNP, cTnT, MR-proANP, & MR-proADM**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
NT-proBNP	1.73 (1.42-2.12)	<0.001	n/a	n/a	1.68 (1.35-2.08)	<0.001	1.22 (0.89-1.68)	0.21	1.58 (1.27-1.97)	<0.001	1.22 (0.89-1.67)	0.22
cTnT	n/a	n/a	1.37 (1.18-1.60)	<0.001	1.21 (1.02-1.44)	0.026	1.22 (1.02-1.45)	0.027	1.15 (0.96-1.38)	0.14	1.15 (0.96-1.38)	0.14
MR-proANP	n/a	n/a	n/a	n/a	n/a	n/a	1.59 (1.14-2.22)	0.007	n/a	n/a	1.50 (1.06-2.12)	0.021
MR-proADM	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1.25 (1.04-1.50)	0.017	1.20 (0.99-1.44)	0.06

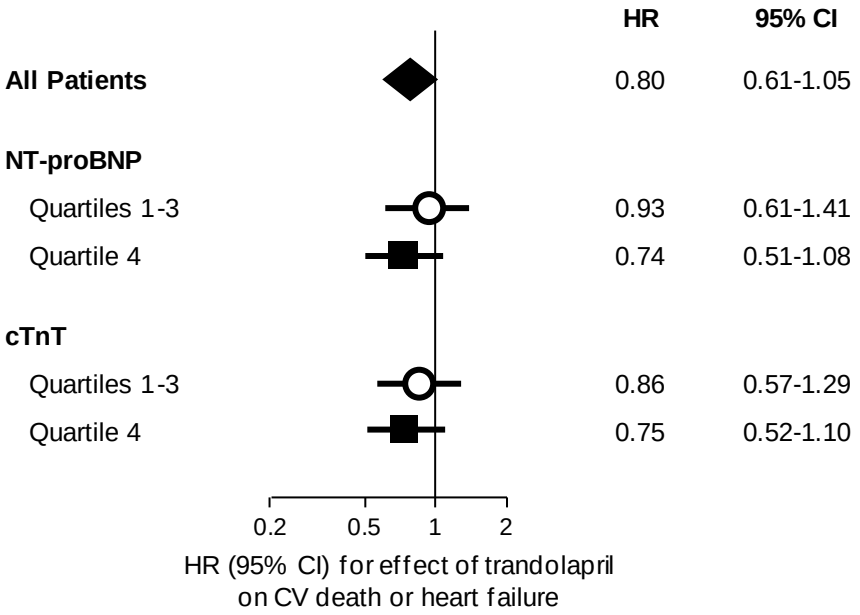
Each model contains the standard clinical factors used in prior models (age, sex, weight, history of hypertension, history of diabetes mellitus, current tobacco use, prior MI, prior PCI or CABG, systolic blood pressure, estimated GFR, ratio of apoB/apoA, LVEF, aspirin use, beta-blocker use, lipid-lowering medication use) as well as those biomarkers shown with data. HR is for the risk per 1-SD of log-transformed biomarker.

Supplemental Table 11. C-statistics in adjusted multimarker models in the placebo arm

	Without MR-proANP, MR-proADM, CT-proET-1	**With MR-proANP, MR-proADM, CT-proET-1**	
Clinical model alone	**0.768**	**0.809**	*P=0.0005*
Clinical + NT-proBNP	**0.793** *P=0.03*	**0.810** *P=0.82*	*P=0.02*
Clinical + cTnT	**0.783** *P=0.03*	**0.810** *P=0.49*	*P=0.007*
Clinical + NT-proBNP + cTnT	**0.797** *P=0.0004*	**0.810** *P=0.63*	*P=0.03*

Each model contains standard clinical factors (listed in the Methods and in the footnote to Table 3 in the main paper).
P values to the right of c-statistics represent the significance of adding MR-proANP, MR-proADM, and CT-proET-1 to the model.
P values below the c-statistics represent the significance of adding NT-proBNP, cTnT or both to the model.

Supplemental Figure 1



Supplemental Figure Legend

Supplemental Figure. Benefit of trandolapril on the risk of the composite of cardiovascular death or heart failure in 3717 patients from the PEACE trial, categorized as to their levels of biomarkers of cardiovascular stress. Patients are categorized as to whether their level of each biomarker was in the top quartile (quartile 4) or not (quartiles 1-3). The P values for interaction were 0.43 and 0.63 for NT-proBNP and cTnT, respectively. The diamond indicate the effect in the entire biomarker cohort, with the center indicating the point estimate and the left and right ends indicating the 95% CI. The squares and circles indicate the point estimate and the horizontal lines indicate the 95% CIs for the effect in each subgroup.

Supplemental References

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