

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Omland T, de Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 2009;361:2538-47. DOI: 10.1056/NEJMoa0805299.

A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease

Torbjørn Omland MD, PhD, MPH^{ab}, James A. de Lemos MD^c, Marc S. Sabatine MD, MPH^{de}, Costas A. Christophi PhD^f, Madeline Murguia Rice PhD^f, Kathleen A. Jablonski PhD^f, Solve Tjora MD^g, Michael J. Domanski^h, MD, Bernard J Gersh MB,ChB; D Philⁱ, Jean L. Rouleau MD^{j,k}, Marc A. Pfeffer MD, PhD^{de}, Eugene Braunwald MD^{de}, for the PEACE Investigators

^aDivision of Medicine, Akershus University Hospital, Lørenskog, Norway; ^bFaculty Division Akershus University Hospital and Center for Heart Failure Research, University of Oslo, Oslo, Norway; ^cDepartment of Medicine, UT Southwestern Medical Center, Dallas TX; ^dDepartment of Medicine, Harvard Medical School, Boston, MA; ^eCardiovascular Division, Brigham and Women's Hospital, Boston, MA; ^fThe Biostatistics Center, George Washington University, Rockville, MD; ^gCenter for Laboratory Medicine, Akershus University Hospital, Lørenskog, Norway; ^hNational Heart Lung and Blood Institute, Bethesda, MD; ⁱDivision of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, MN; ^jMontreal Heart Institute, Montreal, Quebec, Canada; and ^kFaculty of Medicine, University of Montreal, Montreal, Quebec, Canada

Address for correspondence:

Professor Torbjorn Omland
Division of Medicine
Akershus University Hospital
NO-1478
Lørenskog, Norway
Tel: +4740107050
Fax: +4767962190
e-mail: torbjorn.omland@medisin.uio.no

Supplementary Table 1. Eligibility Criteria.*

Inclusion criteria

Age 50 yr or older

Coronary artery disease documented by at least one of the following:

- Myocardial infarction at least 3 mo before enrollment
- Coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty at least 3 mo before enrollment
- Obstruction of $\geq 50\%$ of the luminal diameter of at least one native vessel on coronary angiography

Left ventricular ejection fraction $>40\%$ on contrast or radionuclide ventriculography or echocardiography, a qualitatively normal left ventriculogram, or the absence of left ventricular wall-motion abnormalities on echocardiography†

Toleration of the medication and successful completion of the run-in phase, with $\geq 80\%$ compliance with the medication

Exclusion criteria

Current use of or a current condition requiring use of an ACE inhibitor or a contraindication to ACE inhibitors

Current use of an angiotensin II–receptor antagonist

Hospitalization for unstable angina within the preceding 2 mo

Valvular heart disease deemed to require surgical intervention

Coronary-artery bypass grafting or percutaneous transluminal angioplasty within the preceding 3 mo

Planned elective coronary revascularization

Serum creatinine >2.0 mg/dl (177 $\mu\text{mol/liter}$)

Serum potassium >5.5 mmol/liter

Limited chance of 5-yr survival

Psychosocial condition precluding long-term adherence

Unable or unwilling to give consent

Female sex and of childbearing potential and not using contraception

Current use in a research trial of medication not approved by the U.S. Food and Drug Administration or the Health Protection Branch of the Canadian Department of National Health and Welfare

* ACE denotes angiotensin-converting enzyme.

† A subgroup of echocardiograms was reviewed by a core laboratory to confirm eligibility.

Details of biochemical analysis for hs-cTnT.

Levels of hs-cTnT were determined on a cobas e 411 (Roche Diagnostics, Germany). The samples were analyzed using a pre-commercial assay and the assay characteristics may differ slightly from the finalized commercial assay. According to the manufacturer, levels in serum and EDTA plasma are highly correlated ($n=30$, $R=0.998$), and both EDTA plasma and serum can be used for analysis of hs-cTnT. The new assay utilizes the same antibodies as the conventional 4th generation assay. The lower detection level of the hs-cTnT assay is $0.001 \mu\text{g/L}$ (1). According to the manufacturer, the intra- and inter-assay coefficients of variation above $0.01 \mu\text{g/L}$ were between 0.58 and 9.5% (intra-assay, 21 replicates) and 0.84 and 12.7% (total CV's, 20 runs, 40 replicates), respectively. Correlation coefficients with the conventional 4th generation assay in the concentration range between $0.001 \mu\text{g/L}$ and $9.76 \mu\text{g/L}$, were between 0.987 and 0.998 ($n=830$). The hs-cTnT level with 10% coefficient of variation was $0.012 \mu\text{g/L}$. The 99th percentile value in a sample of 1338 blood donors was $0.0133 \mu\text{g/L}$ (Roche Diagnostics, data on file). Comparison of the high sensitivity and the conventional assay demonstrates that absolute values do not match exactly. Thus, according to the manufacturer, the detection limit of the old assay ($0.01 \mu\text{g/L}$) corresponds to $0.03 \mu\text{g/L}$ with the new assay; $0.03 \mu\text{g/L}$ with the old assay corresponds to $0.05 \mu\text{g/L}$ with the new assay, etc. Accordingly, we estimate that only a minor proportion of samples (1.3%) in PEACE would have been detectable with the old assay.

Supplementary Table 2. Baseline characteristics of entire PEACE trial cohort, compared with the subgroup having hs-cTnT data.*

| Baseline Characteristic | Cardiac Troponin T Subsample (n=3679) | PEACE Cohort (n=8290) | P-value |
|---|---------------------------------------|-----------------------|---------|
| Demographic characteristics | | | |
| Age, years | 63.6± 8.2 | 63.9± 8.2 | 0.18 |
| Female sex, % of patients | 696 (18.9) | 1494 (18.0) | 0.24 |
| White race, % of patients† | 3371 (91.6) | 7666 (92.5) | 0.11 |
| Body-mass index‡ | 28.5± 4.7 | 28.4± 4.7 | 0.11 |
| Medical history (% of patients) | | | |
| Documented myocardial infarction | 2070 (56.3) | 4553 (55.0) | 0.18 |
| Angina pectoris | 2689 (73.1) | 5843 (70.5) | 0.004 |
| Percutaneous coronary intervention | 1677 (45.6) | 3462 (41.8) | <0.001 |
| Coronary-artery bypass grafting | 1318 (35.8) | 3234 (39.0) | <0.001 |
| Diabetes mellitus | 604 (16.4) | 1386 (16.7) | 0.68 |
| Previous hypertension | 1649 (44.8) | 3765 (45.4) | 0.55 |
| Stroke | 158 (4.3) | 357 (4.3) | 0.98 |
| Current smoker | 550 (15.0) | 1177 (14.2) | 0.53 |
| Mean blood pressure, mm Hg | | | |
| Systolic | 134±16.9 | 133±16.6 | 0.86 |
| Diastolic | 78± 9.8 | 78± 9.6 | 0.04 |
| Laboratory determinations | | | |
| eGFR, ml/min/1.73m ² | 77.9±19.3 | 77.6±19.4 | 0.52 |
| Serum cholesterol, mg/dl§ | 193±39.1 | 192±38.9 | 0.79 |
| LV ejection fraction of 40-50%, % of patients | 531 (14.4) | 1236 (14.9) | 0.50 |
| Medications (% of patients) | | | |
| Assignment to trandolapril | 1835 (49.9) | 4158 (50.2) | 0.78 |
| Calcium-channel blocker | 1224 (33.3) | 2938 (35.5) | 0.02 |
| Beta-blocker | 2277 (61.9) | 4965 (59.9) | 0.04 |
| Aspirin or other antiplatelet medication | 3353 (91.2) | 7520 (90.7) | 0.44 |
| Lipid-lowering drug | 2643 (71.9) | 5802 (70.0) | 0.04 |
| Potassium-sparing diuretic | 123 (3.3) | 258 (3.1) | 0.51 |
| Other diuretic | 337 (9.2) | 853 (10.3) | 0.06 |
| Digitalis | 122 (3.3) | 291 (3.5) | 0.59 |

* eGFR denotes estimated glomerular filtration rate, LV left ventricular.

† Race was reported by patients.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

Supplementary Table 3. Association between high sensitivity cardiac troponin T as a categorical variable and cardiovascular outcomes.

| Absolute number of events | | | | |
|----------------------------------|---------------------|---------------------|---------------------|--------------------------------|
| Outcome | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile |
| Cardiovascular mortality | 9 | 15 | 34 | 67 |
| Fatal/non-fatal MI | 53 | 51 | 58 | 71 |
| Fatal/non-fatal CHF | 5 | 9 | 25 | 65 |
| CHF deaths | 0 | 0 | 3 | 10 |
| CV deaths except CHF deaths | 9 | 15 | 31 | 57 |

| Univariate model | | | | |
|-----------------------------|---|---|---|---|
| Outcome | 2nd vs. 1st quartile HR (95% CI) | 3rd vs. 1st quartile HR (95% CI) | 4th vs. 1st quartile HR (95% CI) | p-value for trend across quartiles |
| Cardiovascular mortality | 1.70 (0.74-3.89) | 3.90 (1.87-8.12) | 7.85 (3.91-15.75) | <0.001 |
| Fatal/non-fatal MI | 0.98 (0.66-1.43) | 1.12 (0.77-1.62) | 1.41 (0.99-2.01) | 0.05 |
| Fatal/non-fatal CHF | 1.91 (0.64-5.70) | 5.27 (2.02-13.77) | 14.42 (5.81-35.84) | <0.001 |
| CV deaths except CHF deaths | 1.70 (0.74-3.88) | 3.54 (1.69-7.44) | 6.67 (3.30-13.48) | <0.001 |

| Multivariate model 1 | | | | |
|-----------------------------|---|---|---|--|
| Outcome | 2nd vs. 1st quartile HR (95% CI) | 3rd vs. 1st quartile HR (95% CI) | 4th vs. 1st quartile HR (95% CI) | p-value for trend across categories |
| Cardiovascular mortality | 1.50 (0.65-3.44) | 2.97 (1.40-6.30) | 5.04 (2.42-10.47) | <0.001 |
| Fatal/non-fatal MI | 0.96 (0.65-1.41) | 1.05 (0.71-1.55) | 1.21 (0.82-1.78) | 0.30 |
| Fatal/non-fatal CHF | 1.74 (0.58-5.21) | 4.13 (1.56-10.91) | 9.20 (3.60-23.54) | <0.001 |
| CV deaths except CHF deaths | 1.51 (0.66-3.47) | 2.77 (1.30-5.93) | 4.43 (2.11-9.31) | <0.001 |

| Multivariate model 2 | | | | |
|-----------------------------|---|---|---|--|
| Outcome | 2nd vs. 1st quartile HR (95% CI) | 3rd vs. 1st quartile HR (95% CI) | 4th vs. 1st quartile HR (95% CI) | p-value for trend across quartile |
| Cardiovascular mortality | 1.37 (0.60-3.14) | 2.45 (1.15-5.23) | 3.73 (1.77-7.87) | <0.001 |
| Fatal/non-fatal MI | 0.94 (0.64-1.38) | 1.01 (0.68-1.49) | 1.12 (0.75-1.67) | 0.54 |
| Fatal/non-fatal CHF | 1.56 (0.52-4.67) | 3.32 (1.24-8.84) | 6.09 (2.34-15.83) | <0.001 |
| CV deaths except CHF deaths | 1.39 (0.60-3.19) | 2.32 (1.08-5.00) | 3.34 (1.57-7.15) | <0.001 |

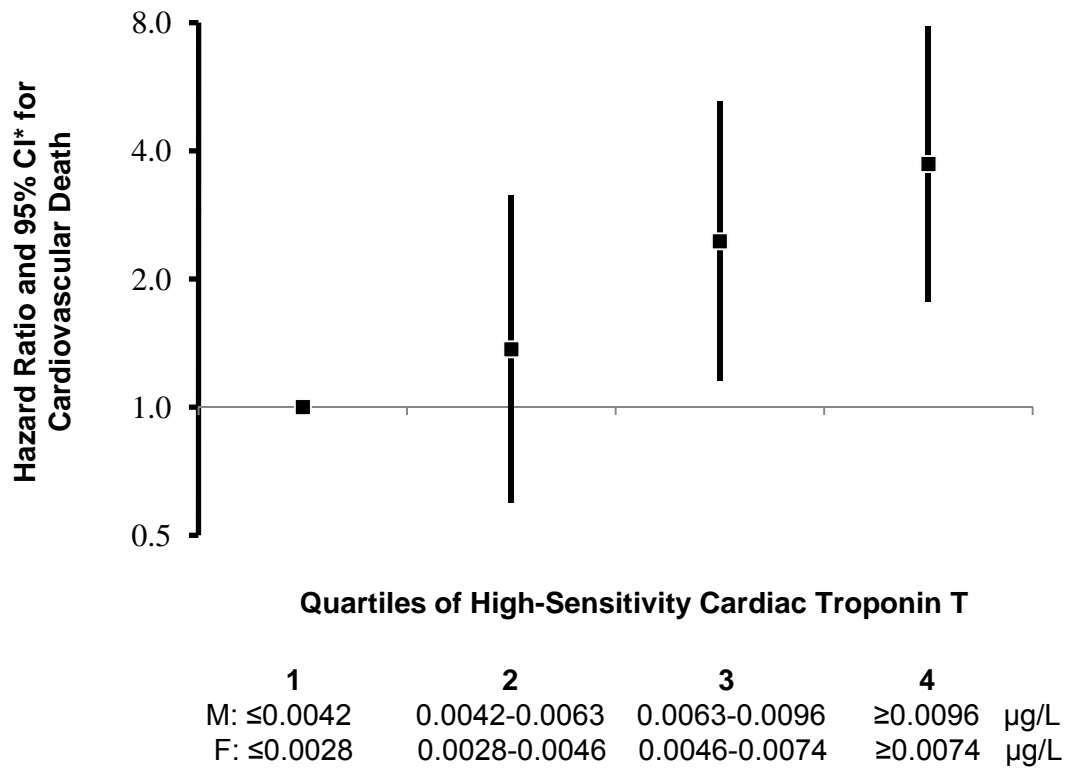
HR: hazard ratio; CI: confidence interval; MI: myocardial infarction; CHF: congestive heart failure

Multivariate model 1: adjusted for treatment assignment, age, sex, current smoking, C-reactive protein AHA-CDC categories.

Multivariate model 2: Same as model 1 with additional adjustment for sex-specific quartiles of N-terminal pro-B-type natriuretic peptide.

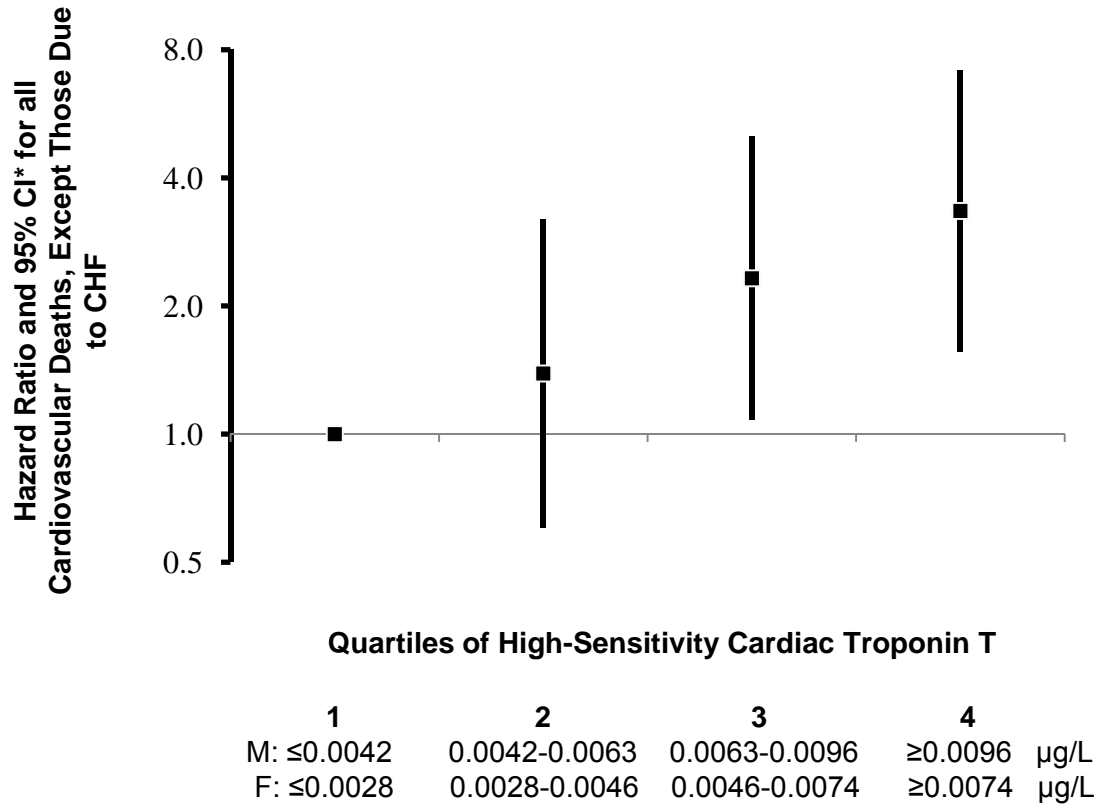
Supplementary Figure 1. Association between quartiles of high sensitivity cardiac troponin T and the risk of (Panel A) cardiovascular death and (Panel B) all cardiovascular deaths except those due to heart failure after adjustment for other significant predictors of this outcome in patients with stable coronary artery disease.

Panel A. Cardiovascular death.

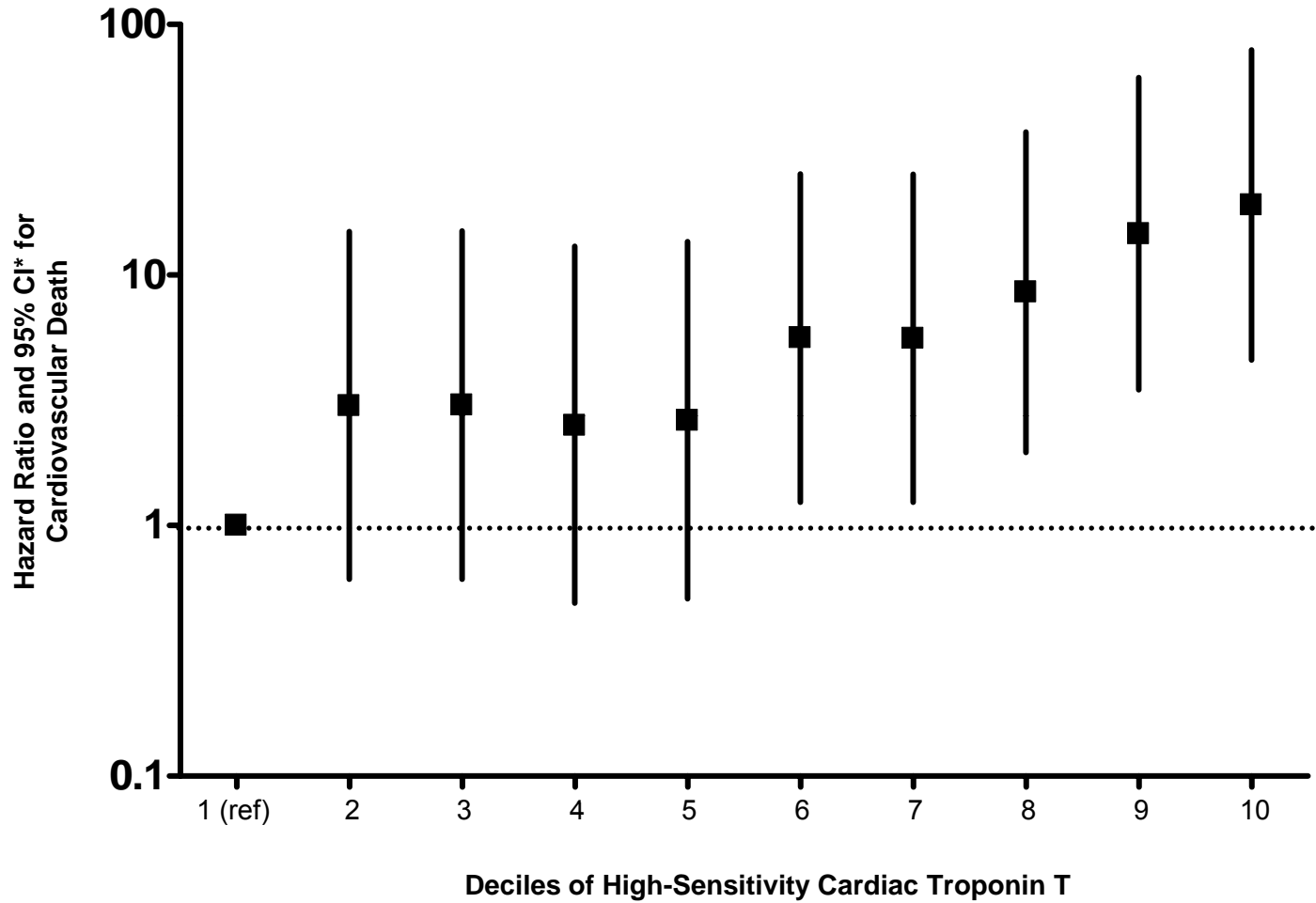


*Adjusted for treatment assignment, age, sex, current smoking, C-reactive protein and N-terminal pro-B-type natriuretic peptide.

Panel B. All cardiovascular deaths except those due to heart failure.



Supplementary Figure 2. Association between deciles of high sensitivity cardiac troponin T and the risk of cardiovascular death after adjustment for treatment assignment only.



M: <0.0027 - 0.0037 - 0.0046 - 0.0054 - 0.0063 - 0.0073 - 0.0087 - 0.0106 - 0.0143 >0.0143 $\mu\text{g/L}$
F: <0.0015 - 0.0024 - 0.0032 - 0.0039 - 0.0046 - 0.0055 - 0.0065 - 0.0084 - 0.0114 >0.0114 $\mu\text{g/L}$

*Adjusted for treatment assignment.

Reference List

- (1) Latini R, Masson S, Anand IS et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation* 2007; 116(11):1242-1249.