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High-Sensitivity Cardiac Troponin, Statin Therapy, and Risk of Coronary Heart Disease

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ABSTRACT

BACKGROUND Cardiac troponin is an independent predictor of cardiovascular mortality in individuals without symptoms or signs of cardiovascular disease. The mechanisms for this association are uncertain, and a role for troponin testing in the prevention of coronary heart disease has yet to be established.

OBJECTIVES This study sought to determine whether troponin concentration could predict coronary events, be modified by statins, and reflect response to therapy in a primary prevention population.

METHODS WOSCOPS (West of Scotland Coronary Prevention Study) randomized men with raised low-density lipoprotein cholesterol and no history of myocardial infarction to pravastatin 40 mg once daily or placebo for 5 years. Plasma cardiac troponin I concentration was measured with a high-sensitivity assay at baseline and at 1 year in 3,318 participants.

RESULTS Baseline troponin was an independent predictor of myocardial infarction or death from coronary heart disease (hazard ratio [HR]: 2.3; 95% confidence interval [CI]: 1.4 to 3.7) for the highest (≥5.2 ng/l) versus lowest (≤3.1 ng/l) quarter of troponin (p < 0.001). There was a 5-fold greater reduction in coronary events when troponin concentrations decreased by more than a quarter, rather than increased by more than a quarter, for both placebo (HR: 0.29; 95% CI: 0.12 to 0.72 vs. HR: 1.95; 95% CI: 1.09 to 3.49; p < 0.001 for trend) and pravastatin (HR: 0.23; 95% CI: 0.10 to 0.53 vs. HR: 1.08; 95% CI: 0.53 to 2.21; p < 0.001 for trend). Pravastatin reduced troponin concentration by 13% (10% to 15%; placebo adjusted, p < 0.001) and doubled the number of men whose troponin fell more than a quarter (p < 0.001), which identified them as having the lowest risk for future coronary events (1.4% over 5 years).

CONCLUSIONS Troponin concentration predicts coronary events, is reduced by statin therapy, and change at 1 year is associated with future coronary risk independent of cholesterol lowering. Serial troponin measurements have major potential to assess cardiovascular risk and monitor the impact of therapeutic interventions.
Cardiac troponin is a specific marker of myocardial injury and an independent predictor of cardiovascular mortality in patients with and without cardiovascular disease (8–14). Novel high-sensitivity assays can now accurately measure plasma cardiac troponin I concentrations in everyone. Higher troponin concentrations may reflect subclinical coronary artery disease and identify those at greatest risk who could benefit from targeted preventative therapies. The aims of this study were to determine whether cardiac troponin I concentrations could predict future coronary events, be modified by statins, and assess response to therapy in WOSCOPS.

STATISTICAL ANALYSIS. The distribution of troponin I was skewed, and values were log-transformed before analysis. Participants were divided into quartiles of the distribution of baseline troponin concentration. Comparisons of baseline characteristics between groups were made using chi-square test for categorical variables and 1-way analysis of variance or the Kruskal-Wallis test for continuous variables. Multivariable Cox proportional hazards regression analyses were used to evaluate the associations between baseline and change in troponin concentration at 1 year with risk of coronary events over 5 and 15 years in the study population and a subgroup with no symptoms or signs of coronary heart disease at enrollment. Treatment effects (pravastatin vs. placebo) are expressed as hazard ratio (HR) with 95% confidence interval (CI). Percent participants were included. The research ethics committee of the University of Glasgow and all participating centers approved the trial design, and the participants provided written informed consent.
change in troponin was determined from the concentration at 1 year relative to the concentration at baseline, and the association with percent change in LDL cholesterol over the same period was assessed using the Pearson correlation coefficient. An independent-samples Student t test was used to compare the mean change between treatment groups. Participants who had a coronary event before the 1-year visit were excluded for the purpose of this analysis. The effect of change in troponin on coronary events at 5 years was explored further by splitting both treatments into 5 groups based on quintile cutpoints in the placebo group. Determinants of log-transformed baseline troponin I were investigated using stepwise linear regression at p-to-enter of 0.10 and p-to-stay of 0.05. Analyses were performed using SPSS version 20.0.0 (IBM Corp., Armonk, New York), SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, North Carolina), and R version 3.0.0 (R Project for Statistical Computing, Vienna, Austria). Statistical significance was taken as a 2-sided p < 0.05.

RESULTS

Baseline characteristics of the 3,318 participants in this analysis were similar to the full study population (Online Table 1).

DISTRIBUTION OF TROPONIN AT BASELINE. The median troponin concentration at baseline was 4.0 ng/l, with an interquartile range of 3.1 to 5.2 ng/l. Values were above the limit of detection (1.2 ng/l) in 3,318 participants (99.8%) and above the 99th-centile (34 ng/l) in 48 participants (1.5%). For the purpose of this analysis, 7 participants with undetectable troponin concentrations were assigned a value of 1.2 ng/l.

| TABLE 1 Baseline Characteristics of Participants Stratified by Troponin Concentration Quarters |
|-----------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Troponin concentration, ng/l            | Q1 (n = 748)    | Q2 (n = 889)    | Q3 (n = 843)    | Q4 (n = 838)    | p Value Trend   |
| All (N = 3,318)                         | 3.1-3.9         | 3.1-3.9         | 3.0-5.1         | 3.2-5.2         |                 |
| Age, yrs                                | 55.1 ± 5.5      | 53.8 ± 5.2      | 55.0 ± 5.5      | 55.4 ± 5.5      | <0.001          |
| Body mass index, kg/m²                  | 25.9 ± 3.2      | 25.6 ± 3.2      | 25.9 ± 3.0      | 26.0 ± 3.1      | <0.001          |
| Employed                                | 2,234 (71%)     | 2,177 (77%)     | 2,234 (72%)     | 2,177 (73%)     | <0.001          |
| Smoking and alcohol status              |                 |                 |                 |                 |
| Current smoker                          | 1,393 (42%)     | 333 (45%)       | 393 (44%)       | 343 (41%)       | 0.043           |
| Alcohol intake, ≥21 U/week              | 546 (17%)       | 121 (16%)       | 158 (18%)       | 138 (16%)       | 0.603           |
| Blood pressure and heart rate           |                 |                 |                 |                 |
| Systolic, mm Hg                         | 136 ± 17        | 133 ± 17        | 134 ± 17        | 136 ± 18        | <0.001          |
| Diastolic, mm Hg                        | 84 ± 11         | 83 ± 11         | 84 ± 11         | 84 ± 10         | <0.001          |
| Heart rate, beats/min                   | 65 ± 11         | 67 ± 11         | 66 ± 11         | 65 ± 11         | <0.001          |
| Past medical history                    |                 |                 |                 |                 |
| Hypertension                            | 544 (16%)       | 87 (12)         | 122 (14)        | 138 (16)        | <0.001          |
| Diabetes mellitus                       | 36 (1%)         | 8 (1%)          | 9 (1%)          | 10 (1%)         | 0.988           |
| Angina*                                 | 168 (5%)        | 23 (3%)         | 35 (4%)         | 48 (6%)         | <0.001          |
| Intermittent claudication               | 82 (3%)         | 20 (3%)         | 16 (2%)         | 18 (2%)         | 0.186           |
| Minor ECG abnormalities*                | 271 (8%)        | 36 (5%)         | 62 (7%)         | 63 (8%)         | <0.001          |
| Family history of CHD death             | 191 (6%)        | 44 (6%)         | 46 (5%)         | 42 (5%)         | 0.256           |
| Medication                              |                 |                 |                 |                 |
| Nitrate                                 | 74 (2%)         | 8 (1%)          | 14 (2%)         | 18 (2%)         | <0.001          |
| Beta-blocker                            | 241 (7%)        | 38 (5%)         | 46 (5%)         | 67 (8%)         | <0.001          |
| ACE inhibitor                           | 36 (1%)         | 4 (1%)          | 11 (1%)         | 8 (1%)          | 0.246           |
| Lipid levels                            |                 |                 |                 |                 |
| Total cholesterol, mg/dl                | 270 ± 22        | 268 ± 22        | 270 ± 22        | 272 ± 22        | <0.001          |
| LDL cholesterol, mg/dl                  | 191 ± 17        | 188 ± 16        | 190 ± 17        | 193 ± 17        | <0.001          |
| HDL cholesterol, mg/dl                  | 44 ± 9          | 43 ± 9          | 44 ± 10         | 44 ± 9          | 0.666           |
| Triglycerides, mg/dl                    | 154 ± 136       | 159 ± 138       | 151 ± 134       | 154 ± 136       | 0.249           |
| Treatment allocation                    |                 |                 |                 |                 |
| Placebo                                 | 1,647 (50%)     | 385 (51%)       | 456 (51%)       | 392 (47%)       | 0.150           |
| Pravastatin 40 mg                       | 1,671 (50%)     | 363 (49%)       | 433 (49%)       | 451 (53%)       | 0.150           |

Values are mean ± SD or n (%). *Symptoms consistent with angina on Rose questionnaire and minor ST-segment or T-wave abnormalities on resting 12-lead ECG defined by Minnesota codes (4–2, 4–3, 5–2, 5–3).

ACE = angiotensin-converting enzyme; CHD = coronary heart disease; ECG = electrocardiogram; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Q = quarter.
Participants were stratified into quarters of the baseline troponin concentration (Table 1). Compared to the lowest quarter, participants in the upper quarters were older and were more likely to have a history of hypertension, symptoms of angina, and minor abnormalities on the electrocardiogram (\(p < 0.001\) for all). Those in the highest quarter had higher systolic and diastolic blood pressures (139 ± 18 mm Hg vs. 133 ± 17 mm Hg and 85 ± 11 mm Hg vs. 83 ± 11 mm Hg, respectively), and there were small differences in total and LDL cholesterol concentrations across the quarters (4 and 5 mg/dl, respectively). In contrast, there were no significant differences in high-density lipoprotein cholesterol and triglyceride concentrations or the prevalence of diabetes mellitus. In a stepwise linear regression model, higher baseline troponin concentrations were associated with increased risk of coronary heart disease (CHD) at both 5- and 15-year follow-up. Compared to the lowest quarter (≤3.1 ng/l), patients in the highest quarter (≥5.2 ng/l) were at the highest risk for nonfatal myocardial infarction or death from CHD at 5 and 15 years (hazard ratio: 2.27; 95% confidence interval: 1.42 to 3.65; and hazard ratio: 1.54; 95% confidence interval: 1.16 to 2.05, respectively; \(p < 0.001\) for both). Cardiovascular death was also associated with baseline troponin concentration (\(p < 0.001\)), but noncardiovascular death was not (\(p = 0.890\)).
echocardiographic abnormalities (minor ST-segment and T-wave abnormalities) (Online Table 2).

**BASELINE TROPONIN AND RISK OF CORONARY HEART DISEASE EVENTS.** Higher troponin concentrations at baseline were associated with increased risk of coronary heart disease at both 5- and 15-year follow-up (Figure 1, Online Table 3). Compared to the lowest quarter ($\leq$3.1 ng/l), patients in the highest quarter ($\geq$5.2 ng/l) were at the highest risk for nonfatal myocardial infarction or death from coronary heart disease at 5 and 15 years (HR: 2.27; 95% CI: 1.42 to 3.65 and HR: 1.54; 95% CI: 1.16 to 2.05, respectively; $p < 0.001$ for both). All-cause mortality and cardiovascular death were also associated with baseline troponin concentration, but non-cardiovascular death was not. In a sensitivity analysis, similar relationships were observed for the primary endpoint in 2,882 men without symptoms or signs of coronary heart disease at enrollment (Online Figure 1).

In this subset of the original study, the HR for the overall relative treatment effect for the primary endpoint at 5 years was 0.45 (95% CI: 0.32 to 0.65; $p < 0.001$) and for the outcome of coronary death or hospitalized myocardial infarction at 15 years was 0.68 (95% CI: 0.56 to 0.83; $p < 0.001$). There was no evidence of an interaction between treatment effect and quarters of baseline troponin concentration ($p = 0.67$ and $p = 0.19$, respectively, for the 5- and 15-year outcomes) (Online Table 4). At 15 years, the absolute risk reduction in nonfatal myocardial infarction or death from coronary heart disease was greatest in the highest quarter (9.0%) compared to the lower three quarters (2.6% to 3.0%) (Online Table 4).

**CHANGE IN TROPONIN AND LDL CHOLESTEROL WITH TREATMENT.** At 1 year, participants taking pravastatin had a greater reduction in troponin concentration (19%) (95% CI: 17% to 20%) than those receiving placebo (6%) (95% CI: 4% to 8%; $p < 0.001$) (Figure 2). The absolute change in troponin concentration from baseline with pravastatin was 2.0 ng/l (interquartile range: 1.2 to 2.8 ng/l; $p < 0.001$). Change in troponin concentration on treatment correlated weakly with change in LDL cholesterol ($r = 0.20; p < 0.001$).

**CHANGE IN TROPONIN AND CORONARY HEART DISEASE RISK REDUCTION.** After adjustment for multiple variables (including baseline troponin concentration, and baseline and change in LDL cholesterol), change in troponin concentration at 1 year was an independent predictor of nonfatal myocardial infarction or death from coronary heart disease at both 5 and 15 years in both treatment arms (Table 2). To explore this relationship further, participants were divided into fifths based on the change in troponin concentration in the placebo group. There was a clear gradient of risk across change in troponin. In the placebo group, relative to the referent (middle) fifth, those in the top fifth (>$26\%$ increase) had a higher risk of the primary endpoint over 5 years, and those in...
the bottom fifth (≥27% decrease) had a lower risk (p < 0.001 for trend) (Figure 3). In those taking pravastatin, a similar trend was observed, but twice as many men were in the lowest-risk group, with ≥27% reductions in troponin concentration (645 vs. 320 on placebo; p < 0.001), and 30% fewer were in the highest risk group, with >26% increase in troponin concentration (223 vs. 320 on placebo; p < 0.001). The risk of the primary endpoint in participants on pravastatin was 5-fold lower in those with the greatest reduction in troponin concentration (HR 0.23; 95% CI: 0.10 to 0.53) compared to those with the greatest increase in troponin concentration (HR 1.08; 95% CI: 0.53 to 2.21; p < 0.001 for trend) despite similar reductions in LDL cholesterol concentration (22% to 28%). Compared to placebo, participants taking pravastatin with the greatest reduction in troponin at 1 year (highest quarter: ≥38% reduction vs. lowest quarter: >3% increase) had the largest reduction in cardiovascular events (HR: 0.21. 95% CI: 0.08 to 0.52 vs. HR: 0.82; 95% CI: 0.51 to 1.32, respectively; p = 0.002), whereas the reduction in events was similar across quarters of change in LDL cholesterol (p = 0.823) (Online Figure 3).

**DISCUSSION**

We observed a strong, specific, and independent association between baseline and 1-year change in plasma troponin I concentration and the onset of coronary heart disease over 5 and 15 years in WOSCOPS. Troponin concentrations were reduced by pravastatin therapy, which doubled the number of men whose troponin fell by more than a quarter and were at the lowest risk for future coronary events. Thus, pravastatin treatment caused similar relative risk reductions in each category of troponin change and increased the propensity for troponin concentrations to fall, leading to additive decrements in future risk that appeared to be independent of LDL cholesterol lowering. We conclude that high-sensitivity cardiac troponin assays can be used to predict future risk of coronary heart disease and to assess response to statin therapy (Central Illustration). Therefore, serial troponin measurements appear to have major potential to monitor risk and assess the impact of established or novel therapeutic interventions on future coronary heart disease risk.

Our analysis has a number of important and distinctive strengths that distinguish it from previous studies of troponin in coronary heart disease risk prediction. First, we evaluated plasma troponin concentration in a primary prevention setting rather than in populations that included patients with established coronary heart disease. Second, we had access to prolonged robust clinical follow-up of well-characterized participants over a 15-year period. Third, we used the latest-generation high-sensitivity cardiac troponin I assay, which detected troponin in 99.8% of the study population. Finally, in addition to exploring associations with baseline troponin concentration, we were able to critically assess dynamic changes in troponin concentrations as part of a major randomized placebo-controlled trial of statin therapy.

In WOSCOPS, a number of biomarkers have been assessed for cardiovascular risk stratification (17-19). In previous analyses, C-reactive protein predicted both cardiovascular and noncardiovascular events (19), whereas troponin is a specific biomarker for the...
prediction of coronary heart disease outcomes. Interestingly, in contrast to recent studies of patients with established coronary heart disease (8), we found that troponin predicted fatal and nonfatal myocardial infarction rather than heart failure events. Similar associations were recently reported in individuals without cardiovascular disease who participated in the JUPITER (Justification for the Use of Statins in Primary Prevention) trial (20). This finding likely reflects differences in the extent of coronary heart disease at enrollment, the use of concomitant therapies, and the low prevalence of heart failure events.

The association between troponin and coronary heart disease risk is nonlinear, with an apparent threshold at 5.2 ng/l that identifies those 2 to 3 times more likely to have a coronary event over 15 years. This is consistent with findings from other cohorts using the same assay (21), in which receiver-operating curve analysis identified a threshold of 6 ng/l in a randomized trial population with established coronary heart disease (14) and 7 ng/l in men who participated in the Scottish Heart Health Study (12). Interestingly, troponin concentrations <5 ng/l also identify patients as low risk in the emergency department (21), and increasingly this approach is being used to rule out myocardial infarction in clinical practice. Primary prevention guidelines recommend statins for the prevention of cardiovascular disease in any individual with a 10-year estimated risk of a cardiovascular event >7.5% (22). This approach has been widely debated, with the benefits and risks for the individual more evenly balanced (5-7). We believe cardiac troponin may help to better stratify those healthy individuals at risk for coronary heart disease who would benefit most from statin therapies and that this approach should be formally addressed in prospective trials.

We hypothesized that statin therapy would reduce cardiac troponin concentrations. However, the observations that a large majority of participants on pravastatin had lower troponin concentrations at 1 year and that this reduction correlated with the decrease in LDL cholesterol were unexpected. White et al. (23) reported that cardiac troponin concentrations were reduced with pravastatin in patients with coronary heart disease. However, troponin concentrations were measured by a contemporary sensitive assay and were undetectable in more than one-third of patients and were below the limit of analytical precision in the majority. As such, the assay had insufficient sensitivity to evaluate the relationship among pravastatin therapy, troponin concentration, and LDL cholesterol. In contrast, we used a novel high-sensitivity assay that was able to measure cardiac troponin in >99% of our study population.

FIGURE 3 Change in Troponin Concentration at 1 Year Stratified by Treatment Allocation and Nonfatal Myocardial Infarction or Coronary Heart Disease Death at 5 Years

(Top) Nonfatal myocardial infarction or death from coronary heart disease (CHD) at 5 years in those taking pravastatin (orange) and placebo (blue) stratified into fifths by change in troponin concentration in the placebo group: Q1 = >26% increase; Q2 = 2% to 25% increase; Q3 = 2% increase to 13% decrease; Q4 = 13% to 27% decrease; Q5 = >27% decrease. (Middle) Twice as many participants were in the lowest-risk group (Q5), with >27% reductions in troponin concentration (645 vs. 320 on placebo; p < 0.001), and 30% fewer were in the highest-risk group (Q1) with >26% increase in troponin concentration (223 vs. 320 on placebo; p < 0.001). (Bottom) Using participants in the placebo group whose troponin concentrations were unchanged as a referent (Q3), hazard ratios for the primary outcome were determined for each fifth after adjustment for age, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, high-density lipoprotein and low-density lipoprotein (LDL) cholesterol, symptoms of angina, diabetes, hypertension, family history of premature coronary heart disease, minor electrocardiographic abnormalities, nitrate use, and smoking status. The risk of the primary endpoint in participants taking pravastatin was 5-fold lower in those with the greatest reduction in troponin concentration (hazard ratio: 0.23; 95% confidence interval: 0.10 to 0.53) compared to those with the greatest increase in troponin concentration (hazard ratio: 1.08; 95% confidence interval: 0.53 to 2.21, p < 0.001 for trend) despite similar reductions in LDL cholesterol concentration (22% to 28%).
This allowed us to explore associations among change in troponin, LDL cholesterol, and coronary events.

We observed that change in troponin predicted risk with an approximately 5-fold range in HRs when comparing men with the greatest increases and decreases in troponin concentration. We observed the lowest rate of coronary heart disease events (1.4% over 5 years) in men treated with pravastatin whose troponin concentration fell by more than a quarter and the highest in those taking placebo with an increase in troponin of more than a quarter (11.6% over 5 years). Although LDL cholesterol level is currently used to select patients for statin therapy and to monitor treatment response, it was notable that neither baseline nor change in LDL cholesterol predicted future coronary events. Importantly, pravastatin more than doubled the likelihood of a reduction in troponin concentration and this appeared to be independent of LDL cholesterol lowering. In addition to reducing serum cholesterol concentrations, statins reduce the levels of other oxidized proteins, improve endothelial nitric oxide bioavailability, and slow progression of atherosclerosis (24). Our observations suggest the preventative effects of statin therapy are mediated in part by these other mechanisms. It was surprising that change in troponin concentration at 1 year was an independent predictor of risk in the placebo group, in which LDL cholesterol concentrations were unchanged. It is possible that cardiac troponin concentrations are modulated by a minor fraction, such as oxidized LDL, that is not reflected when measuring total LDL concentration. Such oxidized lipoproteins may influence troponin concentration directly through a toxic effect on cardiomyocytes or indirectly through their effects on nitric oxide bioavailability and myocardial perfusion. We speculate that recruitment to WOSCOPS may have increased awareness of cardiovascular risk in some trial participants, thereby inducing lifestyle modifications that both lower cardiac troponin concentration and improve outcomes.

A biomarker that can dynamically track the risk of coronary heart disease over time would be a major step forward. Indeed, previous studies have failed to demonstrate that changes in inflammatory, hemostatic, or lipid biomarkers can predict future cardiovascular risk (17–19). This unique property of change of troponin with time has major ramifications and suggests that serial high-sensitivity troponin measurements could represent a major surrogate biomarker to help manage our patients and evaluate coronary heart disease risk with established or novel cardiovascular and noncardiovascular therapies.

**STUDY LIMITATIONS.** The trial was conducted in middle-aged men with raised cholesterol levels, and the findings may not be applicable to the wider population including women. This is an important point, as the threshold of 5.2 ng/l that identified men at increased risk in our study population may not apply to women or to other groups (16). We were able to obtain results from only 3,318 participants, and the requirement for a 1-year sample restricted the study population to those who were compliant with the
CONCLUSIONS

Cardiac troponin I is an independent predictor of coronary heart disease events in middle-aged hypercholesterolemic men without prior myocardial infarction. Troponin concentrations are reduced by statin therapy, and reductions in troponin concentrations are associated with better outcomes independent of LDL cholesterol lowering. These findings suggest that high-sensitivity cardiac troponin has major potential to identify those at greatest risk and to assess their response to interventions for the prevention of coronary heart disease. Finally, serial high-sensitivity troponin concentrations may represent a new paradigm in the assessment of the efficacy and safety of novel cardiovascular and noncardiovascular therapies.

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REFERENCES


KEY WORDS cardiac troponin, cardiovascular risk, primary prevention, statins

APPENDIX For exclusion criteria for participation in WOSCOPS as well as supplemental tables and figures, please see the online version of this article.