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EDITORIAL COMMENT

# High-Sensitivity Cardiac Troponin and Primary Prevention

## An Important New Role*

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Measurements of cardiac troponins (cTn) have revolutionized the diagnosis of acute myocardial infarction (MI), and high-sensitivity cTn (hscTn) assays will improve that further (1). However, an even greater potential benefit of hscTn assays will be in evaluating the long-term risk of cardiovascular comorbidities, a relatively untapped area. This is because values of hscTn rise in response to comorbidities such that higher, although still normal values of hscTn identify those patients with hypertension, diabetes, obesity, and sleep-disturbed breathing who are at risk to develop more overt cardiovascular disease (1–4). These minor increases in high sensitivity troponin indicate ongoing, low-level myocyte injury that could be due to mechanisms such as volume or pressure overload, myocardial strain, inflammation, and/or direct myocyte toxicity (5). The hscTn findings are analogous to the situation with natriuretic peptides where higher, albeit normal, values have been used to identify those at risk for heart failure. Importantly, interventions in response to these minor increases improve outcomes (6). hscTn, because it is not a physiological activator like B-type natriuretic peptide, and varies less over time, and might be a better biomarker to use to monitor such processes (7). In addition, there is synergism between hscTn and B-type natriuretic peptide assays (4). In addition, we would suggest that the response to preventative therapies may well be reflected by changes in cTn as observed in patients with heart failure (8).

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Ford et al. (9) now provide provocative new insights into this fertile environment with data about how hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins) influence patient outcomes during primary prevention in an analysis of the WOSCOPS (West of Scotland Coronary Prevention Study) (9). Neither baseline low-density lipoprotein cholesterol (LDLc) nor its change over the first year was associated with adverse outcomes. Instead, outcomes tracked with changes in hscTnI values. Baseline hscTnI values that were greater but well within the normal range conferred an increased risk for nonfatal MI and cardiovascular death at 5 and 15 years (hazard ratio [HR]: 2.27; interquartile range [IQR]: 1.42 to 3.65 and HR: 1.54; IQR: 1.16 to 2.05, respectively) between those in the highest and lowest hscTnI quartile. This was abolished by randomization to statin treatment but persisted in the untreated group (Table 2 in the article by Ford et al. [9]). These effects are similar to those reported with the baseline values from the JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, which used the same hscTnI assay (10). The HR based on sex-specific quartile values were similar for the development of cardiovascular events but in contrast to the present report, a differential response to rosuvastatin was not observed across the quartiles of hscTnI results (10).

However, and most importantly, individuals whose hscTnI values diminished over the first year had fewer events than those in whom the values did

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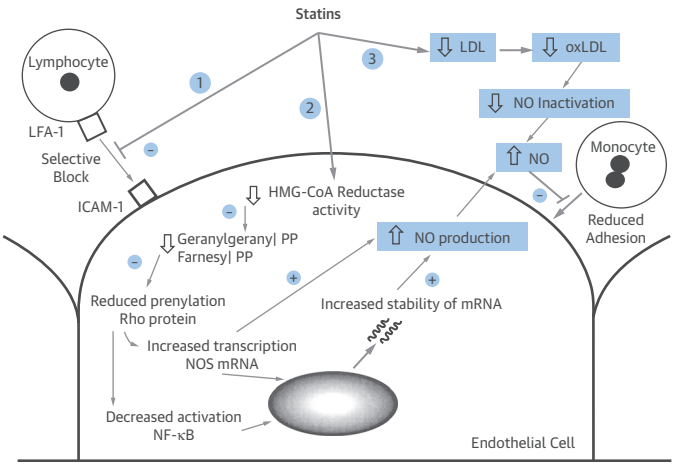
**FIGURE 1 Anti-Inflammatory Actions of Statins**




**(1)** Statins inhibit lymphocyte adhesion to ICAM-1 and impair T-cell stimulation by binding to the LFA-1 site, a nonHMG-CoA reductase-related mechanism. **(2)** Through inhibition of HMG-CoA reductase, statins inhibit the mevalonate pathway and reduce the intracellular isoprenoids, downregulating prenylation. Reduced prenylation of Rho downregulates activation of NF-κB and increases transcription of NOS, which combined with increased stability of NOS mRNA, induce elevations in the endothelial production of NO. **(3)** Statins reduce LDL levels, decreasing the substrate available for oxidized LDL. Oxidized LDL inactivates NO and downregulates endothelial NOS expression (not shown). These effects increase NO bioavailability and decrease monocyte adhesion to endothelial cells. HMG-CoA = hydroxymethylglutaryl-coenzyme A; ICAM = intercellular adhesion molecule; LDL = low-density lipoprotein; LFA = lymphocyte function-associated antigen; mRNA = messenger RNA; NF-κB = nuclear factor kappa beta; NO = nitric oxide; NOS = nitric oxide synthase; oxLDL = oxidized low-density lipoprotein; PP = diphosphate. Reprinted with permission from Sposito and Chapman (13).

not change. There was an impressive 5-fold greater reduction in coronary events when hscTnI results decreased to the lowest quartile with some suggestion of a trend toward benefit whenever hscTnI values declined. Those subjects whose troponin levels rose or failed to drop had no benefit or, if the increase was marked, apparent detrimental. These data suggest a potential role for hscTnI values as a measurement of whether primary prevention strategies are working or will ultimately fail at halting disease progression. This occurred for both placebo and pravastatin groups, although there were twice as many subjects in the pravastatin group who manifested such changes. Thus, as opposed to what one might have anticipated, that is, a relationship to lipid lowering, these investigators found no association with changes in LDLc but a strong relationship to changes in hscTnI results. The changes were modest but likely sufficient to be analytically detected. The critical issue in this regard has to do with biological variation, which includes analytical as well as biological changes over time. If the changes in hscTnI values are within those metrics, one cannot be sure they are not due to variation alone. The values for biological variation for hscTnI results are generally in the range of 50% (11). The values reported by Ford et al. (9) are on the margin of the biological variation data assuming that biological variation does not increase to greater values over the course of 1 year. Thus, repeated testing as suggested by the authors or a longer period of observation before the second sample may be necessary.

How might these reductions occur in each group? Those in prevention would suggest that the effects in the placebo group may be due to a healthier life style. There are data in older individuals showing that regular modest exercise (12) reduces hscTn values. It is unlikely, however, that randomization to a statin increased those behaviors; so what worked in that group? The benefit of statin therapy is thought to be largely due to reductions in LDLc over time. We do not take issue with the important effects of statins on cholesterol homeostasis. However, there has been a growing body of evidence supporting additional disease-altering mechanisms as well. The data from Ford et al. (9) showing that change in hscTnI and not LDLc values were associated with outcomes are more compatible with novel mechanisms. It is speculative to invoke these mechanistic explanations, but prior work supports the existence of these effects (13), as outlined in **Figures 1** and **2**.

Why did statins not work in all subjects? There are likely many explanations including insufficient LDLc reductions and failure of the nonlipid-lowering properties of statins with regard to altering inflammation, thrombosis, and nitric oxide levels. Although the mechanistic insights into the success and failure of statin therapy in this study population will be debated, there is little room for the argument that measurement of small differences of hscTnI values within the “normal range” identified those in whom the disease was suppressed or would progress. Could it be that troponin is also a marker of low-level disease activity and should be incorporated into our assessments of primary prevention therapies? Data from Ford et al. (9) endorse a prospective evaluation of a strategy of using changes in troponin levels as a marker of effectiveness of disease mitigation.

How may we use these data to further the care of patients? The values at baseline in both the present study and the Jupiter study are too low and overlap too substantially with normal values to be used to determine risk in individual patients. Thus, if used, a STOP-HF (Screening to Prevent Heart Failure) approach of using higher values within that range