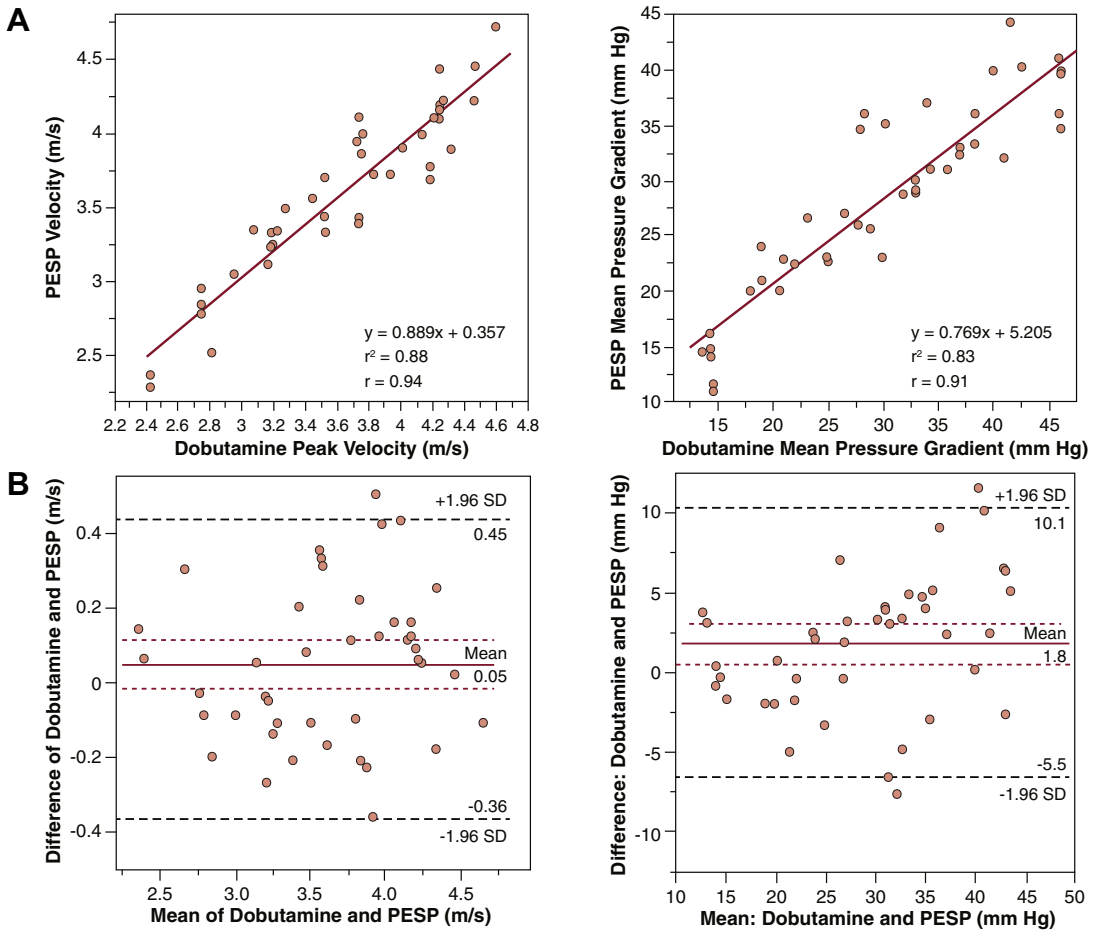
FIGURE 1 Correlation of PESP and Dobutamine Transaortic Gradients



(A) Pearson correlation of gradients. **(B)** Bland-Altman analysis of gradients. PESP = post-extrasystolic potentiation.

provided promising potential for the use of PESP gradients in evaluation of patients with LFLG-AS and reduced LVEFs.

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High-Sensitivity Troponin I Is Associated With High-Risk Plaque and MACE in Stable Coronary Artery Disease

Cardiac troponin I (cTnI) is a marker of myocardial injury, and improvements to assay sensitivity allow for precise quantification at extremely low concentrations. In stable coronary artery disease (CAD),

high-sensitivity (hs)-cTnI concentrations are independently associated with subsequent cardiac death and myocardial infarction (MI). However, the underlying pathological mechanism remains unknown.

Patients (n = 99) who underwent percutaneous coronary intervention for stable CAD in the Virtual Histology in Vulnerable Atherosclerosis trial (1) were included in this study. Baseline 3-vessel intravascular ultrasound (IVUS) virtual histology was performed, which recorded plaque burden (PB). Plaque ruptures were cavity-containing plaques with overlying tissue fragments. Thin-cap fibroatheroma (TCFA) had a >10% confluent necrotic core in luminal contact for 3 consecutive frames, with ≤10% dense calcium (1). A hs-cTnI assay (ARCHITECT$_{STAT}$, Abbott Laboratories, Abbott Park, Illinois) quantified concentrations on serum samples taken before intervention (limit of detection: 1.2 ng/l; 99th percentile: 34 ng/l in men and 16 ng/l in women) (2). Patients were grouped based on hs-cTnI concentrations into low (≤3.0 ng/l), intermediate (3.1 to 5.9 ng/l), and high (≥6.0 ng/l) levels. Major adverse cardiac events (MACE) were determined at follow-up (mean: 1,104 ± 348 days, 1,247 ± 366 days, and 1,086 ± 405 days for the increasing group; p = 0.25) and were defined as a composite of death, MI, unstable angina, or unplanned revascularization. hs-cTnI was naturally log-transformed, with linear regression models that included variables that predicted serum hs-cTnI (age, sex, and renal function). Univariable and multivariable analyses for MACE were performed using Cox regression. All calculations were performed in SPSS version 21.0.0 (IBM, Armonk, New York), with p < 0.05 considered significant.

Serum hs-cTnI concentrations were above the limit of detection in 95 patients (96.0%) and >99th percentile in 2 men and 1 woman (3.0% of whole population). Patient age increased progressively through the hs-cTnI groups (p = 0.006), as did smoking (p = 0.01), and previous MI (p = 0.04). Ninety-eight percent of patients received statins, and therapy duration was similar among the groups (p = 0.44).

IVUS pullback length among the groups was similar (182.9 ± 39.4 mm vs. 201.1 ± 59.2 mm vs. 181.5 ± 57.4 mm; p = 0.35). A total of 657 plaques were analyzed (median 6.0; range 4.0 to 8.0 plaques per patient). Mean PB was 49.7 ± 7.2% versus 51.1 ± 7.0% versus 50.7 ± 7.5% (p = 0.12) for the group in which hs-cTnI increased. Ninety-eight plaques were classified as TCFA (14.9%), and 28 patients had ≥2 TCFAs. Although plaque numbers were similar across the groups (p = 0.90), there were more high-risk plaques per patient with increasing hs-cTnI, namely, PB ≥70% (p = 0.02) and TCFA (p = 0.048) (**Figure 1**). Plaque rupture was observed in 12 nontarget lesions, but the frequency of nontarget lesion rupture was similar across the groups (8.0% vs. 9.1% vs. 22.2%; p = 0.20 for intergroup comparison). Serum hs-cTnI concentrations were increased in patients with ≥2 high-risk plaques, including PB ≥70% (p = 0.03) and TCFA (p = 0.002). TCFA number remained the only variable independently associated with hs-cTnI concentration on multivariable linear regression (beta = 0.15; 95% confidence interval [CI]: 0.03 to 0.27; p = 0.014).

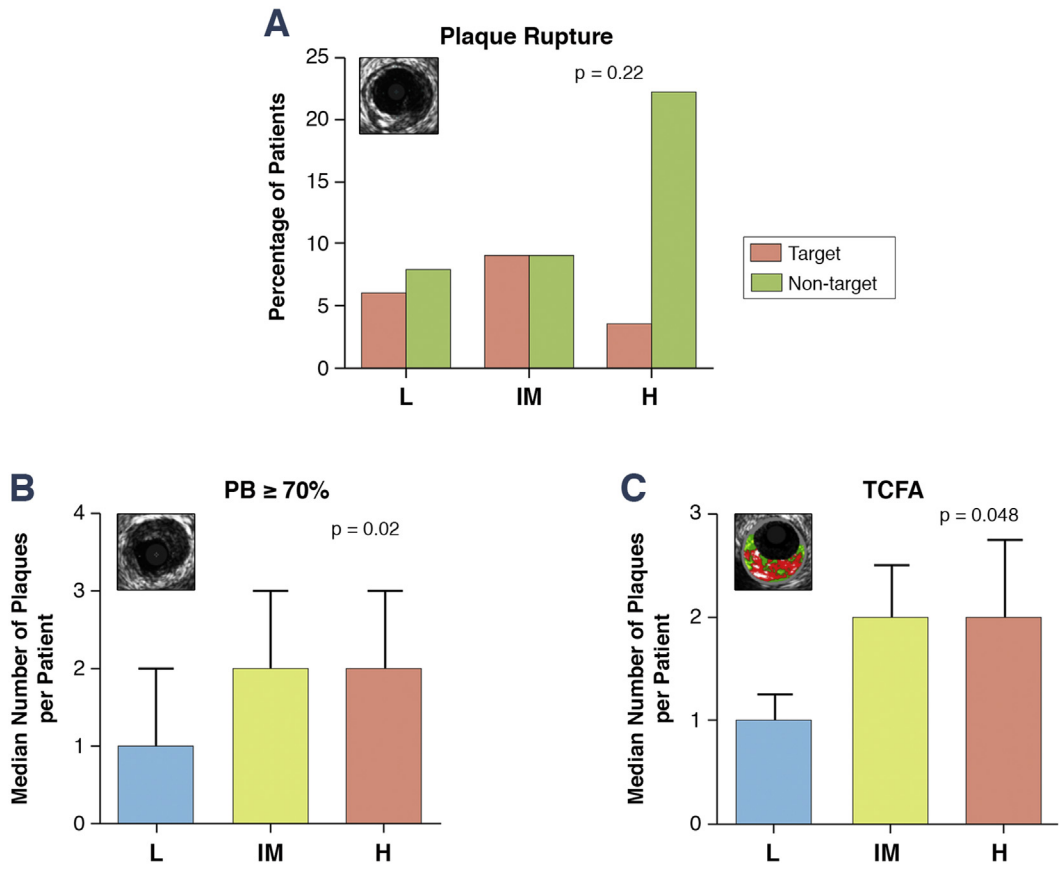
At follow-up, 18 patients had MACE, including 3 deaths, 5 MIs, 12 unplanned revascularizations, and 12 unstable angina presentations. hs-cTnI concentration was associated with MACE in univariable analysis (hazard ratio [HR] 1.43; 95% CI: 1.11 to 1.84; p = 0.006). This association persisted despite adjustment for age, sex, and the number of high-risk plaques per patient (HR: 1.48; 95% CI: 1.13 to 1.95; p = 0.004).

In the PROSPECT (Prospective Natural-History Study of Coronary Atherosclerosis) study, nonculprit lesions with PB ≥70%, minimal luminal area ≤4 mm^2, and TCFA predicted MACE at 3.4 years with rates of 9.6%, 5.3%, and 4.9%, respectively (3). We found that stable CAD patients in the highest hs-cTnI group had more PB ≥70% and TCFA plaques, whereas those patients with ≥2 high-risk plaques had increased hs-cTnI concentrations. Furthermore, hs-cTnI was independently associated with TCFA frequency. Therefore, these results might imply that hs-cTnI has clinical potential for identifying the "vulnerable patient" in the absence of unstable symptoms, which would allow tailored preventative therapies for those at highest risk of future events.

Approximately 60% of ischemic coronary events are precipitated by plaque rupture followed by thrombosis, but not all ruptures result in clinical symptoms. Although we found a higher frequency of nontarget lesion ruptures on IVUS, there was no statistical difference among the groups. Future studies should consider using novel imaging methods that better detect rupture to assess whether elevated hs-cTnI concentrations in patients with stable CAD is associated with plaques undergoing repetitive cycles of subclinical rupture and repair.

In conclusion, increased hs-cTnI concentrations in patients with stable CAD are associated with high-risk plaques and independently with MACE. Although these data should be viewed as hypothesis-generating, hs-cTnI measurement has the potential to identify stable CAD patients who display an adverse pattern of coronary atherosclerosis and worse clinical outcomes.

FIGURE 1 Plaque Characteristics According to hs-cTnI Concentration



(A) With increasing high-sensitivity troponin-I (hs-cTnI), the frequency of nontarget lesion rupture was similar, but there were higher numbers of lesions with **(B)** plaque burden (PB) ≥70% and **(C)** classified thin-cap fibroatheroma (TCFA). H = high; IM = intermediate; L = low.

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A Randomized Trial of Reminders of Past High BNP to Increase Measurement of LVEF

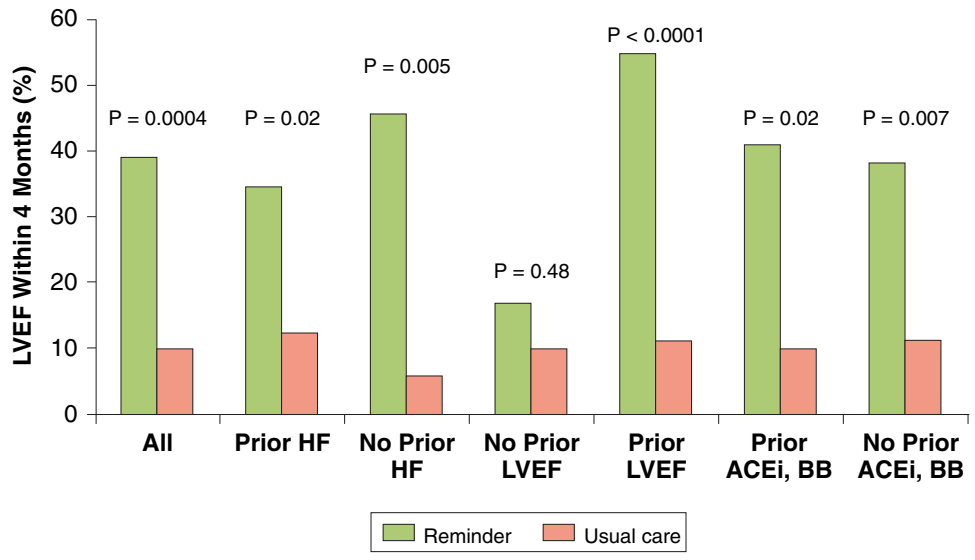
Patients with a high B-type natriuretic peptide (BNP) level have an increased prevalence of a reduced left ventricular ejection fraction (LVEF) (e.g., <40%) and may benefit from life-prolonging therapies (1). However, BNP testing may occasionally go unnoticed by the patient's primary care provider (2). Thus, patients with elevated levels may not have follow-up measurement of LVEFs. Those with depressed LVEFs will not be identified and cannot benefit from several life-prolonging therapies (1). The objective of this study was to determine the impact of a clinical reminder to physicians of patients who have a BNP >200 pg/ml, no previous systolic dysfunction, and no follow-up imaging. We randomized consecutive patients (inpatient or outpatient) from January 1, 2011 to February 15, 2012 with a BNP value of at least 200 pg/ml, with no previous diagnosis of systolic dysfunction (LVEF <40%) and no LVEF measurement recorded in the chart after the BNP measurement for at least 6 months. The primary outcome was measurement of LVEF by any imaging at 4 months after randomization obtained through chart review. A waiver of consent was granted by the Stanford Institutional Review Board.

The mean age of the 115 patients was 77 ± 12 years, 99% were men, 6% were black, and the mean BNP was 485 ± 457 pg/ml. In the 2 years before randomization, 65% had a diagnosis of heart failure, 55% had diabetes, 86% had hypertension, and 55% had ischemic heart disease. A previous LVEF value was known in 61% (mean 55 ± 8%). Overall, 39% of patients were hospitalized in the previous 12 months.

Among the patients randomized to the physician reminder, 39% (22 of 57 patients) had an LVEF measurement within 4 months compared with 10% (6 of 58 patients) of those randomized to usual care ($p = 0.0005$) (**Figure 1**). In another 15 patients in the reminder group, the physician accepted the order for echocardiography, but it was never performed due to patient cancellation (n = 12) or subsequent physician discontinuation (n = 3).

At 4 months of follow-up, a new diagnosis of moderate or greater depressed systolic dysfunction (LVEF <40%) was made in 6 patients: 5 of 57 (9%) patients in the reminder group compared with 1 of 57 (2%) patients in the usual care group ($p = 0.11$). This corresponded to a rate of a low LVEF of 23% (5 of 22 patients) among those who underwent imaging during follow-up. The number needed to remind to

FIGURE 1 Measurement of LVEF



Left ventricular ejection fraction (LVEF) is shown for the reminder and usual care groups, and in 3 subgroups (history of heart failure [HF], previous LVEF measurement, and previous use of angiotensin-converting enzyme inhibitors [ACEi] and guideline recommended beta-blockers [BB]).