High-sensitivity troponin I concentrations are associated with high-risk plaque and future major adverse cardiovascular events in patients with stable coronary artery disease

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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 undergoing PCI for stable CAD in the Virtual Histology in Vulnerable Atherosclerosis trial were included (n=99)(1). Baseline three-vessel virtual-histology intravascular ultrasound (IVUS) was performed, recording plaque burden (PB). Plaque ruptures were cavity-containing plaques with overlying tissue fragments. Thin-cap fibroatheroma (TCFA) had >10% confluent necrotic core in luminal contact for three consecutive frames, with ≤10% dense calcium(1). A hs-cTnI assay (ARCHITECT$_{STAT}$, Abbott Laboratories) quantified concentrations on serum samples taken before intervention (limit of detection = 1.2ng/L, 99th centile = 34ng/L men and 16ng/L women(2)). Patients were grouped based on hs-cTnI concentration into low (≤3.0ng/L), intermediate (3.1-5.9ng/L) and high (≥6.0ng/L). MACE was determined at follow-up (mean 1104±348, 1247±366 and 1086±405 days for increasing group, p=0.25) and defined as composite of death, MI, unstable angina or unplanned revascularization. hs-cTnI was naturally log-transformed, with linear regression models including variables that predict serum hs-cTnI (age, gender and renal function). Univariable and multivariable analyses for MACE were performed using Cox regression. All calculations were performed in SPSS 21.0.0, with $p<0.05$ considered significant.

Serum hs-cTnI concentrations were above the limit of detection in 95 patients (96.0%) and >99th centile in 2 men and 1 woman (3.0% of whole population). Patient age increased progressively through hs-cTnI groups (p=0.006), as did smoking (p=0.01) and prior MI

(p=0.04). 98% of patients received statins and therapy duration was similar between groups (p=0.44).

IVUS pullback length between groups was similar (182.9±39.4mm vs. 201.1±59.2mm vs. 181.5±57.4mm; p=0.35). In total, 657 plaques were analyzed (median 6.0 [4.0-8.0] plaques per patient). Mean PB was 49.7±7.2% vs. 51.1±7.0% vs. 50.7±7.5% (p=0.12) for increasing hs-cTnI group. 98 plaques were classified as TCFA (14.9%) and 28 patients had ≥2 TCFA. Although plaque numbers were similar across 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**). Plaque rupture was observed in 12 non-target lesions, but the frequency of non-target lesion rupture similar across groups (8.0% vs. 9.1% vs. 22.2%, p=0.20 for inter-group 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 (β 0.15, 95%CI 0.03-0.27, p=0.014).

At follow-up, 18 patients sustained MACE including 3 deaths, 5 MIs, 12 unplanned revascularizations and 12 unstable angina presentations. hs-cTnI concentration was associated with MACE in univariable analysis (HR 1.43, 95%CI 1.11-1.84, 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, 1.13-1.95, p=0.004).

In PROSPECT, non-culprit lesions with PB≥70%, MLA≤4mm^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, while those

patients with ≥2 high-risk plaques had increased hs-cTnI concentrations. Furthermore, hs-cTnI was independently associated with TCFA frequency. These results imply hs-cTnI may therefore have clinical potential in identifying the so-called 'vulnerable patient' in the absence of unstable symptoms, allowing tailored preventative therapies to 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 non-target lesion rupture on IVUS, there was no statistical difference between 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 potential to identify stable CAD patients who display an adverse pattern of coronary atherosclerosis and worse clinical outcomes.

FIGURE

Plaque characteristics according to hs-cTnI concentration

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

L, low; IM, intermediate and H, high

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