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EDITORIAL COMMENT

Predicting Incident CVD Risk With High-Sensitivity Cardiac Troponin

Mainstream, Niche, or Neither?

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The potential of high-sensitivity cardiac troponin (hs-cTn) assays to augment cardiovascular disease (CVD) prediction in primary prevention has long been an area of interest. Numerous prospective studies and meta-analyses of these studies have demonstrated independent associations between hs-cTn concentrations and incident adverse CVD outcomes.[1-4] Intriguingly, more recent data also indicate that commercial assays testing the T and I subunits of hs-cTn can provide independent and complementary prognostic information in primary prevention.[5,6]

However, guidelines do not currently endorse hs-cTn measurement in the routine clinical care of primary prevention adults. This is due in large part to the absence of any randomized trials demonstrating a reduction in downstream clinical events among asymptomatic patients who undergo hs-cTn testing compared to usual care (with the latter typically including 10-year CVD risk prediction using traditional CVD risk factors entered into risk estimating equations). Further dampening enthusiasm, a prominent 2024 meta-analysis reported that the incremental improvement in CVD risk prediction metrics like discrimination was relatively small when hs-cTn was added to traditional risk equations.[7] This small improvement in discrimination on adding hs-cTn to traditional risk factors, which arguably translates into low "bang for your buck," was despite the same meta-analysis again confirming independent associations between hs-cTn and adverse CVD outcomes. Therefore, though hs-cTn is an independent novel risk factor for incident CVD, the incremental prognostic information provided by this biomarker over and above traditional risk factors may not be substantial enough to justify widespread testing. Pending more convincing research data, it seems unlikely that hs-cTn testing to augment CVD risk prediction in primary prevention will penetrate into routine clinical care any time soon.

But what about in selected subgroups of interest? Especially subgroups of the population in whom the risk of CVD is known to be elevated despite the absence of traditional CVD risk factors? For example, traditional risk equations are known to underestimate CVD risk in people infected with human immunodeficiency virus (HIV) and it is possible that hs-cTn may improve risk prediction in this particular setting. Furthermore, the recent REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) validated the clinical efficacy of statin therapy in primary prevention adults with HIV who had nonelevated low density lipoprotein cholesterol (mean 2.8 mmol/L [108 mg/dL]) and who were also at low predicted CVD risk by traditional risk scores.[8] In REPRIEVE, the incidence of a major adverse cardiovascular event was 4.81 per 1000 person-years in the pitavastatin group and 7.32 per 1000 person-years in the placebo group (HR: 0.65; 95% CI: 0.48-0.90; $P = 0.002$). While one could consequently argue for statin therapy in all eligible adults with HIV, the number needed to treat in REPRIEVE was 100 to prevent 1 CVD event and so it may be useful for clinicians and patients to have access to a biomarker that can identify adults with HIV who are at higher absolute risk for CVD and in whom

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the expected number needed to treat for statin therapy would be lower. There is no doubt but that hs-cTn has strong potential to serve in this biomarker role. In this issue of *JACC: Advances*, the REPRIEVE authors add to our understanding of hs-cTn as a potential biomarker of CVD risk in persons with HIV by reporting on the cross-sectional association between high-sensitivity cardiac troponin-T (hs-cTnT) and subclinical coronary plaque assessed using coronary computed tomography angiography.[9]

The premise that troponins rise in tandem with progressive coronary disease and risk is both intellectually and practically appealing. However, previous studies in this area, including work from our group, have failed to consistently demonstrate an association between hs-cTn and coronary plaque in persons with HIV.[10] In this planned mechanistic substudy of REPRIEVE, a nonrandom subsample of participants went on to have computed tomography coronary angiography for plaque characterization. Of note, 48% of REPRIEVE participants had some coronary plaque present. This is higher than would be expected in a non-HIV population of primary prevention adults. Participants with no detectable hs-cTnT had a prevalence of coronary plaque of 38%, whereas the prevalence was 54% among those with detectable hs-cTnT (>6 ng/L).[9] After adjustment for traditional CVD risk factors, the OR of any coronary plaque in the top quartile of hs-cTnT (>9.64 ng/L) was 1.37 (95% CI: 1.12-1.67) compared to persons without detectable hs-cTnT. The associations of hs-cTnT >9.64 ng/L with both vulnerable plaque (OR: 1.47) and with coronary artery calcium score >100 (OR: 2.58) were even stronger. As such, these results support the hypothesis that at least some of the association between hs-cTn and incident CVD is mediated by atherosclerotic mechanisms. This is relevant because hs-cTn (particularly the hs-cTnT subunit tested in REPRIEVE) is more strongly associated with heart failure and CVD death than coronary heart disease outcomes.[3]

So—in the final analysis—does the current substudy of the REPRIEVE trial dataset advance knowledge in the field and to what extent? On the pro side of the argument, the current results do demonstrate that hs-cTn is associated with atherosclerotic mechanisms that underlie at least some of the link between hs-cTn and prognosis in persons with HIV. As such, among selected subgroups like persons with HIV, hs-cTn may have a niche role in triaging the allocation of atherosclerotic prevention therapies like statins, but also perhaps aspirin, intensive blood pressure targets, and even glucagon-like peptide 1 agonists. However, on the other hand, the con side of the argument is that for such a medication triage approach to be justifiable there would need to be at least evidence of effect modification on the efficacy of preventive treatments according to hs-cTn concentration (which has never been reported to our knowledge) or, even better, one could argue that hs-cTn needs a trial similar to the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) design[11]; ie, a randomized trial demonstrating benefit for hs-cTn testing within the context of preventive care—either in general primary prevention or in the primary CVD prevention of select subgroups of at-risk adults like those with HIV.

For now, the scales seem to be balanced on the side of the con argument. Indeed, practically speaking, the majority of low-risk asymptomatic persons with HIV will not be assessed in dedicated preventive or cardiovascular clinics, so there must be some caution in using a biomarker traditionally associated with acute coronary syndrome in an asymptomatic population. Noting the varied causes of elevated hs-cTn in this group, we should also be wary of triggering diagnostic cascades. It is possible that a more typical non-trial HIV population would be at higher risk—for example with intercurrent illness, uncontrolled hypertension, and chronic kidney disease—and consequently that higher troponin results could be returned in a more "real-world" sample of asymptomatic persons with HIV and lead to significant and unindicated downstream testing.

Unfortunately, pending further data and preferably data from dedicated trials, we therefore believe the jury is still out on whether the application of hs-cTn testing to predict incident CVD risk in clinical care has the potential to become mainstream or niche; or whether hs-cTn in primary prevention will just remain a topic for academics to write papers on.

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