Defining cardiovascular risk in diabetes: the emerging role of troponin assays

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Atherosclerotic cardiovascular disease (ASCVD), including acute coronary syndrome (ACS), myocardial infarction (MI), angina, arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease, is the leading cause of mortality for individuals with type 2 diabetes (T2D) and is the largest contributor to the economic costs of diabetes. Main ASCVD risk factors include hypertension, dyslipidemia, smoking, a family history of premature coronary disease, and albuminuria (1). Numerous studies have confirmed the benefits of controlling ASCVD risk factors with T2D, especially addressed simultaneously.

Furthermore, biomarkers have substantial utility in modern cardiovascular diagnosis, prognosis, and therapy. Brain natriuretic peptide (BNP) and N terminal (NT)-proBNP not only support diagnostic certainty, but offer prognostic value in heart failure (HF), and may be helpful to trend throughout hospitalization to predict likelihood of readmission (2). In the vast majority of cases, elevated circulating troponin is a marker for myocyte necrosis, whether from ischemia or other causes. In the presence of prolonged ischemia, myocytes are irreversibly damaged releasing myofibril-bound cytosolic complexes, and both troponin I (cTnI) and troponin T (cTnT) are widely utilized to diagnose ACS (3). The higher sensitivity assays (hs-cTnT and hs-cTnI) can detect extremely trace amounts of elevation, diagnostic for myocardial injury or necrosis (4). For the definition of MI, the 2012 Joint European Society of Cardiology/American College of Cardiology/American Heart Association/World Health Federation Task Force optimally includes both elevated cardiac biomarkers and clinical evidence for myocardial ischemia (5,6). The rise and fall of troponin with at least one value above the 99th percentile of the upper reference limit is diagnostic for MI along with supportive ECG and echocardiographic findings of ischemia (5,6).

Elevated troponin concentrations in HF, even without overt coronary artery disease (CAD), are well-established to be associated with worse clinical outcomes and higher risk of death (2). Although, troponins I and T respond similarly for ACS and acute decompensated HF, elevated high-sensitivity troponin assays in the setting of T2D without acute cardiac disease have prognostic significance and may justify more intensive risk reduction. In this editorial, we reflect on the recent troponin data reported from the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial. In the EXAMINE trial, with T2D and established ischemic heart disease outside of an acute setting, detectable levels of high sensitivity troponin were predictive for cardiovascular morbidity and mortality (7). In contrast to the prior 2001 Adult Treatment Panel III (ATP III) cholesterol guidelines (8), T2D is not always a CAD "risk equivalent" by today's standards (9). However, the EXAMINE trial suggests that clinicians in the future can utilize elevated troponin assays to identify patients with diabetes at higher risk of cardiovascular disability and death, thereby mandating more intensive risk reduction (7).

Particularly, clinical studies have demonstrated that troponin elevation in patients with T2D and stable ischemic heart disease can be useful in identifying a higher risk cohort. We consider the significant consequences and

future impact of recent data from the EXAMINE trial which demonstrated dynamic or persistently elevated hs-cTnl at 1, 3 and 6 months following an acute cardiac event may more precisely identify high ASCVD risk in persons with T2D (7).

Elevated hs-cTnl and ASCVD risk in T2D: implications of the EXAMINE trial

In the general population, as shown in the Dallas Heart Study, elevated cTnT is an ASCVD marker (10). Specifically for persons with diabetes, elevated troponin appears predictive of CAD events. The West of Scotland Coronary Prevention Study (WOSCOPS) trial measured baseline hs-cTnT level in 3,318 men without a prior MI. At one year, for the highest versus the lowest quartile of troponin, the finding of elevated cTnT levels well within reference range (but higher in comparison to other patients in the cohort) was an independent predictor of CAD death, or first MI (hazard ratio 2.3, 95% CI: 1.4–3.7) (11). Moreover, a fall in troponin levels predicted lower nonfatal MI or mortality, beyond the benefits of statin treatment. Interestingly, independent of low density lipoprotein cholesterol (LDL-C) lowering, patients randomized to pravastatin had greater troponin reduction and fewer coronary events (11). This recent WOSCOPS trial analysis suggests that hs-cTnI levels can be a guide for escalation of statin therapy. Additionally, The Bypass Angioplasty Revascularization Investigation (BARI 2D) trial demonstrated that elevated hs-cTnT level in 2285 patients with T2D and stable ischemic disease was predictive of higher cardiovascular morbidity and mortality (12). Comparing patients with abnormal hs-cTnT at baseline with those with normal concentrations, the five-year rate of the composite endpoint of death, MI, or stroke was significantly increased (27.1 versus 12.9 percent; adjusted hazard ratio 1.85, 95% CI: 1.48–2.32). This adverse prognosis was not altered by those who received an invasive strategy (12). Therefore, in T2D, there are significant data confirming that elevated troponin is a marker for CAD morbidity and mortality, which may be modified by statin therapy.

Relative to this editorial, in addition to baseline levels, the trend of troponin over time was also important in the EXAMINE trial. One in four clinically stable patients had a greater than 25% increase in hs-cTnI and a significantly higher risk of major CV events (7). On the other hand, patients with undetectable hs-cTnI levels at the two-time points were at low risk of cardiac events over 2 years. Moreover, there was a 3-fold risk of CV death/MI/stroke in the group between 1.9 to 26 ng/L compared to those with undetectable troponin. Those patients within the highest (>99th percentile) tier of baseline troponin elevation fared even worse, with a 3- to 9-fold higher risk of major cardiovascular events within this cohort (7). In future conventional clinical care, the EXAMINE trial confirms that troponin assays have important prognostic implications outside of the acute hospital setting, identifying T2D patients who will benefit from more aggressive secondary prevention measures, especially intensive LDL-C reduction. Additionally, hs-cTnl may identify at-risk individual candidates for more intensive primary prevention who have not yet suffered from an index cardiovascular event (11).

T2D as a "CAD equivalent" reconsidered

In 1998, Haffner *et al.* noted in Finnish cohort data that patients with T2D, but with no prior MI, had the same risk of future MI as an individual without T2D, but with a previous MI (13). This was the basis upon which the 2001 ATP III guidelines first labeled diabetes as a "coronary disease equivalent" (8). Nevertheless, based on several population studies, the more recent American Heart Association and American College of Cardiology (AHA/ACC) 2013 cholesterol guidelines more accurately classified diabetes as an ASCVD predictor, rather than an automatic CAD equivalent (1). These guidelines recommend the use of moderate to high intensity statin therapy for any person with diabetes 40 to 75 years of age. This recommendation reflects a substantially increased lifetime risk for ASCVD events and death in persons with diabetes, as well as greater morbidity and worse survival following the onset of clinical ASCVD (9).

In a Kaiser Permanente study of 80,012 new coronary heart disease (CHD) events, prior CAD was associated with triple the risk of new cases of CAD, whereas T2D was associated with double the risk than that of patients with no history of either TD2 or MI. Therefore, prior CAD is substantially more predictive of future coronary events (22.5 per 1,000 person years) and T2D cannot exactly be regarded as equivalent to prior CAD (12.2 per 1,000 person years). The risk of future CHD with a history of either T2D or CHD was similar only among those with diabetes of long duration (≥10 years) (14). Cardiac imaging studies also confirm heterogeneity in CAD prevalence in patients with diabetes by coronary calcium computed tomography (CT) scans. In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, 38% of patients with T2D had no coronary artery

calcium (CAC) and the absence of CAC was associated with low annual rate of CHD events (15).

It is clear that patients with T2D do not have the same level of CVD risk as the general population, with varying degrees of cardiovascular morbidity and mortality and 80% of persons with T2D dying from CVD (16). Nevertheless, this CVD burden is greatly affected by comorbid conditions such as length and severity of hyperglycemia, hyperlipidemia, hypertension, smoking and age. Therefore, the use of hs-cTnl assays may greatly assist cardiovascular specialists and other clinicians with unveiling patients with T2D who are at "extreme risk" for cardiac events, a new category identified by the 2017 Association of Clinical Endocrinologists and American College of Endocrinology (AACE) on the Comprehensive T2D Management Algorithm. The AACE unique category of "extreme risk" represents progressive ASCVD including, unstable angina after achieving an LDL-C <70 mg/dL or established clinical CVD in patients with T2D, chronic kidney disease stages 3 or 4, or family history of premature ASCVD (17). The robust AACE goal suggests achieving a LDL-C <55 mg/dL, using intensive pharmacotherapy, including the recently approved proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

Medication access denial in high risk CVD: potential role of troponin assays

Unfortunately, it is common clinical practice to regard low levels of elevated troponin as inconsequential when observed outside of the context of an acute ACS event. This so called "troponin leak" minimizes mildly elevated troponin values that may be found incidentally in patients with left ventricular hypertrophy, hypertensive emergency, uncontrolled atrial fibrillation, severe sepsis, or acute decompensated HF (18). Similarly in the outpatient setting, clinicians may consider mildly elevated circulating troponin as not being reflective of acute plaque rupture and therefore less clinically significant. On the contrary, we propose that the recent EXAMINE analysis and the preponderance of data implicate hs-cTnI as a prognostic marker for ASCVD outcomes in an already high-risk population, specifically those with T2D (7). Thus, clinicians should not succumb to the common practice of discounting mild troponin elevations as merely incidental, and these patients continue to be a population that deserves special attention in terms of implementing intensive medical therapy. Along with hyperglycemia and other conventional risk factors, elevated troponin levels may significantly elevate patient risk to the level of CAD equivalent (8).

Despite consensus statements that LDL-C lowering is critical to both familial hypercholesterolemia (FH) and high risk ASCVD patients, a recent study indicates in contemporary clinical care of high-risk patients, including those with presumptive FH or ASCVD, experience high rates of rejection for PCSK9 inhibitor prescriptions even when there is sufficient evidence that they have inadequately controlled LDL-C despite concurrent appropriate statin-based therapy (19). These high rejection rates highlight potential challenges in operationalizing the results of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial. This recent landmark study randomized 27,564 high risk individuals, 36.7% with T2D, demonstrating a significant reduction in ASCVD outcomes with evolocumab, a PCSK9 inhibitor (20). The AACE algorithm confirms PCSK9 inhibitors fulfill a large unmet need for more aggressive lipid-lowering therapy beyond statins (17).

In the recent FH Optimal Care of the US (FOCUS) study, 237 presumptive FH patients with LDL-C >190 mg/dL despite evidence of statin-based lipid lowering therapy were prescribed PCSK9 inhibitors. Unfortunately, 63.3% of the prescriptions for PCSK9 inhibitors were rejected. Furthermore, in 1,622 patients with ASCVD and LDL-C value >100 mg/dL despite evidence of being treated with appropriate lipid lowering therapy, 57.5% of PCSK9 inhibitor prescriptions were also rejected (19).

In an era of navigating the maze of health insurance prior authorization, we propose high sensitivity troponin assays may be of great utility in qualifying particular high-risk patients who need intensive therapy, including PCSK9 inhibition from restricted formulary medications. Perhaps, troponin assays could be incorporated into insurance prior authorizations to allocate these admittedly costly but extremely effective agents. Perhaps hs-cTnI assays can provide a concrete means of allocating new and emerging pharmacotherapy to patients in the highest tier of risk, regardless of socioeconomic status.

Future opportunities in precision medicine: high sensitivity troponin assays

In January 2017, the FDA approved the first U.S. high-sensitivity troponin assay, (Elecsys Troponin T Gen 5 STAT, Roche Diagnostics), despite availability of such technology in other countries for several years. The FDA specifies different cutoff values for men and women, above the 99th percentile

upper reference limit, 14 ng/L for women and 22 ng/L for men. Beyond the rapid diagnosis of the presence or absence of acute MI, hs-cTnT and hs-cTnI may usher a paradigm shift in cardiovascular preventive care (21).

The EXAMINE analysis has proven that serial measurements of hs-cTnI can precisely identify a subset of patients with diabetes who are high risk (7). The AACE 2017 unique category of "extreme risk" proposes an aggressive goal of LDL-C <55 mg/dL (17). Ambulatory persons with TD2 and elevated serum hs-TnI assays are a distinct high-risk population that could benefit from intensive risk factor modification with high intensity statins and improved access to PCSK9 inhibitors.

Serum biomarkers can provide patients with tangible evidence of disease activity and severity. For example, serum-based markers of colorectal cancer are now routinely used for monitoring patients following the surgical removal of malignant colorectal tumors, in order to more precisely detect any cancer recurrences or metastases (22). In a similar fashion, perhaps high sensitivity troponin assays can provide skeptical patients with concrete evidence of their disease state and the need for therapeutic intervention. We propose, one of the greatest benefits to cardiovascular medicine may be increasing use of high sensitivity troponin assays to target the highest risk individuals with T2D and help providers overcome therapeutic inertia.

Unfortunately, it is a daily clinical struggle to convince patients that controlling their ASCVD risk is so critically important for primary and secondary prevention. Adherence to cardiovascular medications is uniformly suboptimal and leads to increase in CVD morbidity and mortality (23). Perhaps the information obtained from a high sensitivity troponin assay may be another precision medicine tool that will encourage patients to meet these LDL-C targets and to demonstrate to them that they truly are at the highest risk and warrant the most intensive medical therapy.

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References

1. American Diabetes Association. Standards of Medical Care in Diabetes. Journal of Clinical Applied Research and Education 2017;40:S75-87.
2. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACC/AHA/HFSA Guideline for the Management of Heart Failure. Circulation 2017. [Epub ahead of print].
3. Daubert MA, Jeremias A. The utility of troponin measurement to detect myocardial infarction: review of the current findings. Vasc Health Risk Manag 2010;6:691-9.
4. Kavsak PA, MacRae AR, Yerna MJ, et al. Analytic and Clinical Utility of a Next-Generation, Highly Sensitive Cardiac Troponin I Assay for Early Detection of Myocardial Injury. Clin Chem 2009;55:573-7.
5. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.
6. Thygesen K, Alpert J, White H, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634-53.
7. Cavender MA, White WN, Jarolim P, et al. Serial Measurement of High Sensitivity Troponin I and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus in the EXAMINE Trial. Circulation 2017;135:1911-21.
8. Third Report of the National Cholesterol Education

Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation 2002;106:3143.
9. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S1-45.
10. Wallace TW, Abdullah SM, Drazner MH, et al. Prevalence and determinants of troponin T elevation in the general population. Circulation 2006;113:1958-65.
11. Ford I, Shah AS, Zhang R, et al. High-Sensitivity Cardiac Troponin, Statin Therapy, and Risk of Coronary Heart Disease. JACC 2016;68:2719-28.
12. Everett BM, Brooks MM, Vlachos HE, et al. Troponin and Cardiac Events in Stable Ischemic Heart Disease and Diabetes. NEJM 2015;373:610-20.
13. Haffner SM, Lehto S, Rönnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. NEJM 1998;339:229-34.
14. Rana JS, Liu JY, Moffet HH, et al. Diabetes and Prior Coronary Heart Disease are Not Necessarily Risk Equivalent for Future Coronary Heart Disease Events. J Gen Intern Med 2016;31:387-93.
15. Malik S, Budoff MJ, Katz R, et al. Impact of Subclinical Atherosclerosis on Cardiovascular Disease Events in Individuals With Metabolic Syndrome and Diabetes: The Multi-Ethnic Study of Atherosclerosis. Diabetes Care 2011;34:2285-90.
16. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
17. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2017 Executive Summary. Endocr Pract 2017;23:207-38.
18. Kelley WE, Januzzi JL, Christenson RH, et al. Increases of Cardiac Troponin in Conditions other than Acute Coronary Syndrome and Heart Failure. Clin Chem 2009;55:2098-112.
19. Knowles JW, Howard WB, Karayan L, et al. Access to Non-Statin Lipid Lowering Therapies in Patients at High Risk of Atherosclerotic Cardiovascular Disease. Circulation 2017;135:2204-6.
20. Sabatine MS, Giugliano R, Wiviott S, et al. Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. NEJM 2015;372:1500-9.
21. Food and Drug Administration 510(k) Review: Decision Summary. Available online: https://www.accessdata.fda.gov/cdrh_docs/reviews/K162895.pdf. Accessed May 24, 2017.
22. Engstrom PF, Benson AB, Saltz L, et al. National Comprehensive Cancer Network. Colon cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 2003;1:40-53.
23. Ferdinand KC, Senatore FF, Clayton-Jeter H, et al. Improving Medication Adherence in Cardiometabolic Disease Practical and Regulatory Implications. J Am Coll Cardiol 2017;69:437-51.

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