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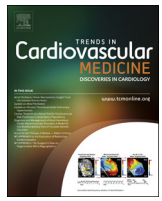

# Cardiac troponin as a novel tool for cardiovascular risk prediction in ambulatory populations

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ABSTRACT

Assays for cardiac troponin have become increasingly sensitive, and are now able to detect very low concentrations of circulating cardiac troponin in a substantial proportion of stable patients who are not suspected of having an acute myocardial infarction. These low concentrations of cardiac troponin are frequently well within the range of what is considered normal but are nonetheless associated with a significant increase in the risk of major cardiovascular events, including heart failure, myocardial infarction, and death in patients with and without established cardiovascular disease. The strength and consistency of these associations, and the fact that adding cardiac troponin to traditional risk factors improves the accuracy of existing cardiovascular risk prediction algorithms, raises the possibility of using cardiac troponin for therapeutic decision-making in ambulatory populations. Cardiac troponin is a powerful predictor of cardiovascular risk on the population level, but a specific intervention that can mitigate cardiac troponin-associated risk has not been identified. Thus, the therapeutic implications of cardiac troponin elevations for individual patients remain unclear. Ongoing research seeks to better understand the underlying cause of cardiac troponin release and to identify therapeutic interventions that can effectively mitigate cardiac troponin-associated cardiovascular risk. The development of high-sensitivity assays for cardiac troponin offers the opportunity to gain tremendous insight into the causes and consequences of chronic myocardial injury, and may, in the future, help guide therapy directed at improving the outcomes of ambulatory patients at high risk for cardiovascular events.

**Key words:** Cardiac troponin, Myocardial injury, Risk prediction, Prevention, Coronary heart disease.



## Introduction

Cardiac troponin is the preferred marker of myocardial necrosis, and has revolutionized the diagnosis of myocardial infarction in patients being evaluated for chest pain suspected to be cardiac in etiology [1].

Over the past decade, manufacturers have developed increasingly sensitive assays that allow the detection of very low concentrations of cardiac troponin with a high degree of accuracy in otherwise healthy or stable patients. As outlined here, these low-cardiac troponin concentrations have been associated with future cardiovascular events, including myocardial infarction (MI), heart failure, and cardiovascular death, in a wide array of populations with and without established cardiovascular disease.

The strong and consistent relationship between baseline concentrations of cardiac troponin—even concentrations that are within the putative normal range—and future major cardiovascular events has raised the possibility that high-sensitivity assays for cardiac troponin may have clinical utility for risk stratification and risk prediction in stable outpatients. This article will provide an overview of the clinically relevant performance characteristics of the high-sensitivity cardiac troponin assays, review the published

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associations with cardiovascular events in primary and secondary populations, and outline a number of key unanswered questions that will have to be addressed before cardiac troponins can demonstrate clinical utility in stable patients.

### A primer on high-sensitivity assays for cardiac troponin

Both cardiac troponin I and T are key protein components of the contractile apparatus in cardiac myocytes. The vast majority of cardiac troponin I and T mass in the cardiac myocyte is bound to the contractile apparatus and is released to the circulation only after irreversible cell death [2]. Troponin I and T are also produced in skeletal muscle, but there are important differences in their isoforms that allow diagnostic tests to distinguish between the skeletal and cardiac myocyte derived proteins.

Since they were first introduced into clinical use in the 1990s, and then included in the consensus definition of myocardial infarction in 2000, the ongoing improvement of the operating characteristics of the assays for cardiac troponin I and T have allowed the detection of lower and lower concentrations of cardiac troponin in the peripheral circulation. For example, clinically available assays for cardiac troponin I are now able to detect concentrations that are 100-fold lower than the first commercially available assay for cardiac troponin I [1–3]. Contemporary assays are also reasonably precise at these lower concentrations, with coefficients of variation that fall below 20% at the 99th percentile (or upper reference limit) for most assays [2]. This level of precision is one that experts in the field consider acceptable [4].

The newest assays for cardiac troponin I and T are now termed "high-sensitivity" assays. This term specifically refers to two performance characteristics of an assay. First, the assay must have a total imprecision of $\leq$10% at the upper limit of normal [2], which is defined by consensus as the 99th percentile in a reference population (the upper reference limit) [3,5]. Second, a high-sensitivity assay is one that is able to measure cardiac troponin concentrations that are lower than the established 99th percentile for that assay, but above the assay's limit of detection, in at least half of all healthy individuals [2]. The sensitivity of these assays has allowed the detection of smaller amounts of myocardial injury in acute coronary syndromes, improving the diagnosis of myocardial infarction in some populations [6,7], and potentially eliminating the diagnosis of unstable angina [8]. However, the enhanced clinical sensitivity is accompanied by a reduction in clinical specificity, which may be part of the reason that no high-sensitivity assay is yet approved by the Food and Drug Administration for clinical use in the United States [9,10].

While the lack of specificity of the high-sensitivity assays is a significant concern when they are being used to diagnosis myocardial infarction in a patient with chest pain, this limitation is less important when cardiac troponin is used as a tool for risk stratification in a stable outpatient population. The enhanced sensitivity of the high-sensitivity assays has also allowed the detection of very low concentrations of cardiac troponin in these patients. As will be described below, strong associations with future cardiovascular events are seen across the spectrum of cardiac troponin concentrations, including among those with concentrations that are well within the range of what is considered "normal."

### Etiology of cardiac troponin release in stable patients

The enhanced sensitivity of newer assays for cardiac troponin has opened a window into the presence of ongoing myocardial injury in otherwise stable outpatients. Depending on the high-sensitivity assay used and the population sampled, a substantial proportion, or even a majority, of these stable patients have measurable concentrations of cardiac troponin in their peripheral blood. The vast majority of the measured cardiac troponin values are below the 99th percentile of the upper reference limit, and thus are considered "normal." The prevalence of these low, but detectable concentrations of cardiac troponin has led to a developing understanding of the causes and correlates of this cardiac troponin release. Most experts believe that the cardiac troponin release does represent myocardial necrosis, but mechanisms such as myocardial cell apoptosis, myocyte strain, and transient increases in myocyte cell wall permeability have been proposed as alternative mechanisms [8]. In addition to the differential diagnosis provided in the most recent Universal Definition of MI, other pathologic processes have newfound importance as possible causes for alterations in cardiac troponin, as displayed in the Table [1]. This list can provide a framework for considering the etiology of a detectable cardiac troponin concentration in patients with and without an acute rise in cardiac troponin concentrations, particularly for those with concentrations of cardiac troponin that are higher than the 99th percentile of the upper reference limit, or "abnormal." While the proportion with an abnormal cardiac troponin is low in healthy patients without established cardiovascular disease, the prevalence of an abnormal high-sensitivity cardiac troponin can be remarkably high in select groups of patients. For example, we found that 39% of patients with stable ischemic heart disease and type 2 diabetes had high-sensitivity cardiac troponin T concentrations in the abnormal range [11]. Fig. 1 outlines one possible framework for clinicians to use when evaluating a patient with an abnormal cardiac troponin [1,12,13].

### Cardiac troponin for risk prediction in the community: Primary prevention

Standard cardiac troponin assays have little utility in ambulatory populations with a low prevalence of cardiovascular disease, because the assays are not sensitive enough to detect cardiac troponin in most of these patients. However, in spite of these limitations, a number of separate European populations have reported that cardiac troponin concentrations measured with standard assays have significant associations with future cardiovascular disease and improve measures of CVD risk prediction in those without established CVD, particularly when combined with other biomarkers (such as NT-proBNP) [14,15].

The development of more sensitive assays has allowed investigators to detect circulating cardiac troponin in a broader range of individuals, including those who are younger or who do not have established cardiovascular