High-sensitivity cardiac troponins in heart and kidney diseases: from lab to clinic

Citation for published version (APA):

Document status and date:
Published: 01/01/2015

DOI:
10.26481/dis.20150710ec

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:
• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

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Valorisation

Economic and Social Relevance

Cardiovascular diseases (CVD) are a major cause of death with a mortality rate of approximately 30% across Europe and America [1, 2]. CVD covers a wide range of disorders, including diseases of the cardiac muscle and of the vascular system. The majority of CVD that lead to mortality are due to acute myocardial infarction (AMI) and stroke. Cardiovascular research has already resulted into more interventions with significant reductions in morbidity and mortality [3, 4]. Regardless of this decline in mortality, more patients are at cardiovascular risk due to increased life expectancy and comorbidities related to an unhealthy lifestyle. Clinical care of these patients is already costly and is expected to further increase in the future. Additionally, treatments may also tremendously impact the quality of life of these patients. Future research should therefore focus on prevention and earlier detection of heart diseases.

Cardiac troponins are an essential component of the diagnostic criteria for myocardial infarction, especially when electrocardiographic results are inconclusive. According to the current guidelines a rise and/or fall in cardiac troponin (cTn) T or I concentrations, with at least one value above the 99th percentile of a healthy reference population, signifies myocardial damage and must be accompanied with also clinical indications such as ischemic symptoms or imaging evidence of myocardial damage [5]. Increasingly sensitive cTn assays enable an earlier diagnosis but severely impair the specificity towards AMI. When measuring with high-sensitivity (hs-) assays, elevated hs-cTn concentrations were also detected in a whole range of other pathologies [6]. Due to this lack in disease-specificity, unravelling the causes of hs-cTn positive results can therefore be challenging, especially in patients affected by more than one disease.

On the contrary, the increases in analytical sensitivity also gave rise to new opportunities for these assays. Even below the diagnostic cutoff, higher hs-cTn values are strongly associated with an increased risk on cardiovascular diseases and mortality, making them promising risk stratifying tools [7, 8].
Target groups

Cardiac troponins are important and highly used cardiac markers and their results are mainly interpreted by clinicians and laboratory specialists. Even before the publication of the current guidelines [5], a European survey demonstrated that 59% of the inquired laboratories were using cTnT or cTnI concentrations to diagnose AMI [9]. Results presented in this thesis can guide clinicians and laboratory specialists to a better understanding of hs-cTn results, by gaining insight into important clinical questions such as changes in renal clearance can affect hs-cTn results. Eventually a better interpretation of hs-cTn results can lead to an earlier diagnosis or rule out of patients. These advancements all have the potential to lead to more efficient, better and cost effective diagnostic process.

Activities and/or products

The results described in this thesis can be used for the development of various products or tools.

In this thesis we show that elevated cTn, especially hs-cTnT, concentrations were detected in elderly people without any evidence of heart and kidney diseases. These results support the concept that also other clinical indicators, besides acute myocardial damage, can greatly influence baseline hs-cTn results. As such, when considering individuals with non-acute symptoms, a young female individual without any cardiac history and a normal renal clearance will have lower baseline cTn concentrations as compared to an older male individual with decreases in renal clearance. For this reason, applying generalized cutoffs can result in under- or over-diagnosis within different patient cohorts [10-12], already implying that it is of great importance to interpret hs-cTn results to a more individual level. The development of a clinical algorithm might therefore be helpful to give direction of which hs-cTn result to expect in a patient, taken into account important factors (such as age, gender,
cardiovascular history, renal clearance, timing of blood collection, precision of the assay, etc.) Current guidelines also indicate the advantage of measuring more than one cTn concentration in time, although it remains unclear which delta to use for a safe rule out of a patient [5, 13-15]. Also here, a clinical algorithm might be helpful for a better indication what constitutes a significantly increased value that requires further clinical examinations.

Although cTn results are currently not used in the clinic to indicate the risk on future cardiovascular diseases and mortality, all current literature undeniably shows that higher troponin concentrations are significantly associated with the incidence of such a risk [16]. It seems therefore quite logic that hs-cTn results should be implemented in clinical risk scores that can be used in patients at risk for cardiovascular diseases. Potentially these clinical risk scores can serve guidance for preventive therapies in patients at high risk.

Furthermore, measuring multiple biomarkers have been proposed in the management of acute coronary syndromes. The combination of cTn measurements with more traditional biomarkers (C-reactive proteins, NTproBNP) and newly developed biomarkers (such as copeptin, heart-type fatty acid-binding protein) are widely investigated [17-19]. In this thesis, preliminary data shows that combining hs-cTnT and hs-cTnI assays might also be promising to further enhance the diagnostic potential of cardiac troponins.

We are the first to clearly show that the most prevalent molecular cTnT forms detected by the clinical cTnT assay are fragments. Moreover, different cTnT forms were observed during the early acute cTnT release following AMI (~29 kDa) as compared to chronic elevations seen in ESRD (<18 kDa) patients. New and unpublished results show that larger cTnT forms (≥29 kDa) still contain their C-terminal end, while the smaller fragments (<18 kDa) do not. This thesis therefore indicates that targeting the larger cTnT fragments have the potential to enhance the disease-specificity of the clinical assay. Adding a third antibody, directed against the C-terminal region of cTnT, to the current clinical ELISA
method can detect the proportion of these larger cTnT fragments, as illustrated in FIGURE 1. Future research has to indicate whether such a test can be used in addition to the current clinical hs-cTnT test, and might lead to a better differentiation between acute and chronic cTnT elevations.

![Figure 1 A. Conventional cTnT testing according to the ELISA method of the clinical assay. B. Incorporation of a third cTnT antibody directed against the C-terminal end.](image)

**FIGURE 1.** A. Conventional cTnT testing according to the ELISA method of the clinical assay. B. Incorporation of a third cTnT antibody directed against the C-terminal end.

**Implementation in clinical practice**

Cardiac troponins are already incorporated in clinical practice. Results obtained in this thesis show promising new opportunities for this biomarker in the clinic. Over the past years, increasingly more research is performed on the determinants and risk-stratification of hs-cTn results. However, specific algorithms incorporating more clinical indicators for high hs-cTn results are currently not available and still need to be developed. Also, many clinical scores have already been developed for the prediction of adverse events in high-risk
patients with ACS [20, 21], low-risk patients with symptoms of chest pain [22, 23] and even more general populations [24, 25]. However, most of these risk scores do not include hs-cTn results. Up till now, only one risk algorithm incorporates cTn concentrations when determining the risk in patients presenting with chest pain at the emergency department [23], which is still validated in the clinic trials. Whether hs-cTn concentrations can further improve these risk scores, also in more general populations, still merits further research.

Furthermore, the development of a new assay entails careful validation of the quantification, linearity and specificity of the results. To ensure the detection of cardiospecific cTnT isoforms, we propose the inclusion of a third antibody to the current hs-cTnT assay. For this reason, this new method must be developed in close collaboration with the manufacturer of the current hs-cTnT test (Roche Diagnostics).

Once these advancements are developed, the added value should be monitored in prospectively randomized control studies. Eventually, correct implementation of these tools requires that specialists should be educated on how to interpret the results through scientific exposure (peer-reviewed publications or international congresses) and guideline documents that are published by national and international societies in cardiology and biochemistry.
References


