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

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 alghorithm 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.

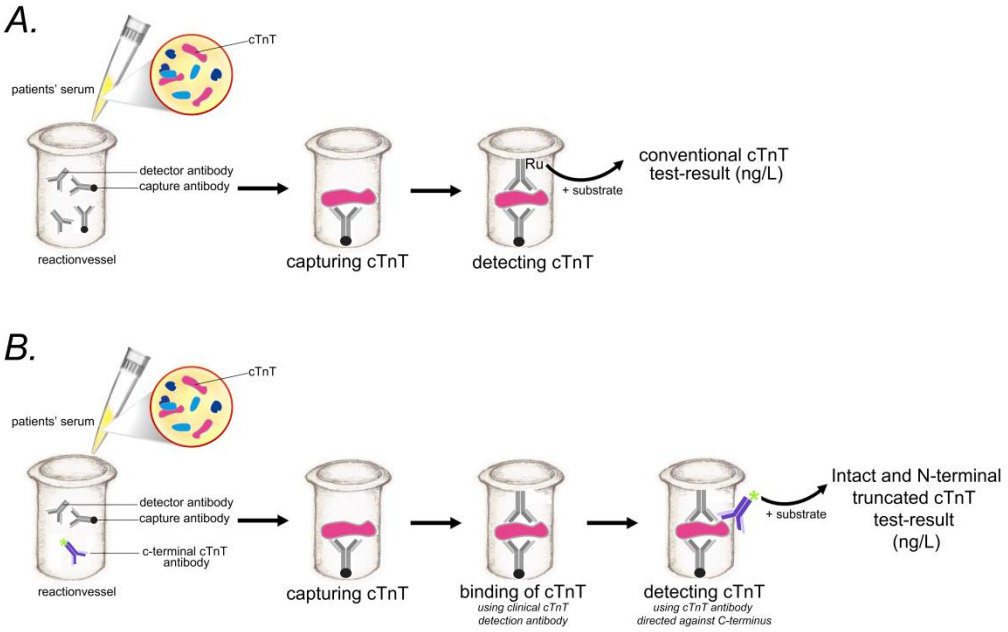

FIGURE 1. ***A.*** Conventional cTnT testing according to the ELISA method of the clinical assay. ***B.*** Incorporation of a third cTnT antibody directed against the C-terminal end.

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

patiens 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

1. Nichols, M., N. Townsend, P. Scarborough, et al. European Cardiovascular Disease Statistics. European Society of Cardiology (www.escardio.org).
2. Go, A.S., D. Mozaffarian, V.L. Roger, et al., Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation, 2014. 129(3): p. e28-e292.
3. Heart Protection Study Collaborative, G., MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet, 2002. 360(9326): p. 7-22.
4. Keeley, E.C., J.A. Boura, and C.L. Grines, Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet, 2003. 361(9351): p. 13-20.
5. Thygesen, K., J.S. Alpert, A.S. Jaffe, et al., Third universal definition of myocardial infarction. Eur Heart J, 2012. 33(20): p. 2551-67.
6. Kelley, W.E., J.L. Januzzi, and R.H. Christenson, Increases of cardiac troponin in conditions other than acute coronary syndrome and heart failure. Clin Chem, 2009. 55(12): p. 2098-112.
7. de Lemos, J.A., M.H. Drazner, T. Omland, et al., Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA, 2010. 304(22): p. 2503-12.
8. Mills, N.L., A.M. Churchhouse, K.K. Lee, et al., Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. JAMA, 2011. 305(12): p. 1210-6.
9. Collinson, P.O., M.P. van Dieijen-Visser, K. Pulkki, et al., Evidence-based laboratory medicine: how well do laboratories follow recommendations and guidelines? The Cardiac Marker Guideline Uptake in Europe (CARMAGUE) study. Clin Chem, 2012. 58(1): p. 305-6.
10. Shah, A.S., M. Griffiths, K.K. Lee, et al., High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ, 2015. 350: p. g7873.
11. Reiter, M., R. Twerenbold, T. Reichlin, et al., Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. Eur Heart J, 2011. 32(11): p. 1379-89.
12. Olivieri, F., R. Galeazzi, D. Giavarina, et al., Aged-related increase of high sensitive Troponin T and its implication in acute myocardial infarction diagnosis of elderly patients. Mech Ageing Dev, 2012. 133(5): p. 300-5.
13. Reichlin, T., A. Irfan, R. Twerenbold, et al., Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation, 2011. 124(2): p. 136-45.
14. Mueller, M., M. Biener, M. Vafaie, et al., Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. Clin Chem, 2012. 58(1): p. 209-18.
15. Keller, T., T. Zeller, F. Ojeda, et al., Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA, 2011. 306(24): p. 2684-93.
16. Newby, L.K., R.L. Jesse, J.D. Babb, et al., ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on Clinical Expert Consensus Documents. J Am Coll Cardiol, 2012. 60(23): p. 2427-63.
17. Sabatine, M.S., D.A. Morrow, J.A. de Lemos, et al., Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation, 2002. 105(15): p. 1760-3.
18. Kellens, S., F.H. Verbrugge, M. Vanmechelen, et al., Point-of-care heart-type fatty acid binding protein versus high-sensitivity troponin T testing in emergency patients at high risk for acute coronary syndrome. Eur Heart J Acute Cardiovasc Care, 2015.

19. Jacobs, L.H., M. van Borren, E. Gemen, et al., Rapidly rule out acute myocardial infarction by combining copeptin and heart-type fatty acid-binding protein with cardiac troponin. Ann Clin Biochem, 2015.
20. Granger, C.B., R.J. Goldberg, O. Dabbous, et al., Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med, 2003. 163(19): p. 2345-53.
21. Boersma, E., K.S. Pieper, E.W. Steyerberg, et al., Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation, 2000. 101(22): p. 2557-67.
22. Antman, E.M., M. Cohen, P.J. Bernink, et al., The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA, 2000. 284(7): p. 835-42.
23. Backus, B.E., A.J. Six, J.H. Kelder, et al., Risk scores for patients with chest pain: evaluation in the emergency department. Curr Cardiol Rev, 2011. 7(1): p. 2-8.
24. D'Agostino, R.B., Sr., R.S. Vasan, M.J. Pencina, et al., General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation, 2008. 117(6): p. 743-53.
25. Assmann, G., P. Cullen, and H. Schulte, Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation, 2002. 105(3): p. 310-5.