Editorial Commentary

Is twice better than once?—challenges of troponin measurements for risk prediction in the general population

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Comment on: Lyngbakken MN, Røsjø H, Holmen OL, *et al.* Temporal Changes in Cardiac Troponin I Are Associated with Risk of Cardiovascular Events in the General Population: The Nord-Trøndelag Health Study. Clin Chem 2019;65:871-81.

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Troponins and especially high-sensitive troponins (hs-cTn) have become a crucial part in every day clinical practice for more than 15 years to reliably diagnose myocardial infarctions and guide further therapeutic interventions in the acute setting (1). In addition to the predictive value, hs-cTn not only support the clinician while dealing with an acute coronary syndrome (ACS) but also help to identify individuals at risk for future cardiovascular events. Such prognostic value has been established in the general population (2) and also in patients with known coronary heart disease (CHD) (3). While the first reports on the prognostic value of troponins were derived from single measurements (2,4), increasing evidence has been accumulated in favor of serial measurements of hs-cTn. For example, in patients with known CHD, hs-cTn (either hs-cTnI or hs-cTnT) measured 12-month after an acute event (myocardial infarction, coronary bypass surgery) had an even stronger association with recurrent cardiovascular disease (CVD) events (fatal and non-fatal) than the hs-cTn obtained about 9 weeks after the initial event (5). Patients with incremental values of either hs-cTnI or hs-cTnT showed higher incidences of cardiovascular events compared to individuals with the greatest decremental values.

In the general population, reports about serial measurements point into a similar direction. McEvoy *et al.* found an increase in hs-cTnT detected at 6 years of follow-up to be independently associated with clinical endpoints such as incident CHD, heart failure and all-cause mortality in 9,000 individuals (6). Accordingly, Hughes *et al.* evaluated the prognostic role of hs-TnI in 3,875 individuals while taking 3 samples 5 years apart from each other (7). An increase of hs-cTnI was also associated with an increase of fatal- and non-fatal cardiovascular events. Interestingly, in this study serial measurements did not improve the risk prediction models when compared to the most recent hs-cTnI measurement.

Recently, Lyngbakken *et al.* added interesting data to the growing body of evidence emphasizing the role of hs-cTn in risk prediction models: They measured hs-cTnI in 4,805 individuals initially free from CVD from the Nord-Trøndelag Health Study at 2 time points 10 years apart from each other and assessed clinical endpoints [risk of incident heart failure (HF), myocardial infarction (MI), and cardiovascular death] (8). Their main finding was a temporal relative increase in hs-cTnI which was associated with male gender, higher age and elevated systolic blood pressure. *Vice versa* a relative decrease went along with female gender, lower blood pressure, and lower body mass index.

An increase in hs-cTnI associated with significant risk of admission for MI or HF in adjusted models (HR 1.68; 95% CI, 1.16–2.42). Yet, a decrease did not significantly protect from such events (HR 1.19; 95% CI, 0.84–1.68). Importantly, the most recent assessment of hs-cTnI had an

even stronger predictive value than the relative or absolute changes of hs-cTnI.

These findings are comparable to those obtained by Hughes *et al.* (7), although the relative number of CVD events within the cohort of Lyngbakken *et al.* was smaller (as correctly mentioned by Lyngbakken *et al.* and expected, given the different time frames of the studies and subsequently different incidences of CVD events due to optimized primary prevention).

Nevertheless, in both studies the serial measurement of hs-cTnI during long-term follow-up was not superior in its prognostic value compared to the most recent single measurement in the general population.

As mentioned by the authors, an important limitation of the data presented by Lyngbakken *et al.* addresses the use of statins within the study population which was not assessed. Statins—compared to placebo—led to a reduction of hs-cTnI and cardiovascular events as recently reported by Ford *et al.* (9). Presumably, individuals with an unfavourable lipid profile were treated with HMG-CoA reductase inhibitors which might have influenced their values of hs-cTnI and CVD events even within this cohort. Interestingly, changes in hs-cTnI were not concordantly associated with an increased burden from traditional cardiovascular risk factors (such as total cholesterol, BMI or hypertension) emphasizing the potential of hs-cTnI to mirror cardiovascular risk beyond established risk factors. This is also reflected by the notion that the proportion of cardiovascular events which is not explained by traditional risk factors varied from 10–35% (10). Hence, there is ongoing interest and medical need in precise risk prediction tools integrating traditional risk factors and novel biomarker (such as hs-cTn) as well to reliably identify individuals being at high risk for cardiovascular events (4,11).

In summary, the study presented by Lyngbakken *et al.* enrolling an impressive number of almost 5,000 individuals followed for more than 10 years adds important information regarding the predictive impact of hs-cTnI in the general population during long-term follow-up. Although the relative and absolute changes of hs-cTnI associated with the risk of cardiovascular events, the most recent values were most informative for assessing individuals' cardiovascular risk. However, given the current data regarding hs-cTn and risk prediction, a general advice for the ideal time points of recurrent hs-cTn measurements cannot be given at this moment. Moreover, the ideal scenario of a (multi-) biomarker risk prediction model, which reliably categorizes individuals in accordance to their future CHD risk, needs more such studies allowing to identify subjects who might benefit from tailored and personalized preventive strategies and should include beside the description of the associated risk estimates of the adverse health outcomes also an evaluation of the incremental prognostic value of the biomarker if added to well established risk prediction models.

Acknowledgments

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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