Risk Prediction in Acute Coronary Syndrome using the US vs non-US 99th Percentile Threshold of the 5th Generation Troponin T Assay

TO THE EDITOR:

Acute myocardial infarction (AMI)[1] is a common reason for seeking emergency medical attention. According to the universal definition of MI (*1*), cardiac troponin T or I are the cornerstones in defining AMI. In addition to increasing/decreasing troponin levels, the 99th percentile concentration of a healthy reference population is recommended as a diagnostic threshold. Further, recommendations on assay total imprecision are provided. With the availability of assays fulfilling these criteria, improved AMI diagnosis has been demonstrated, especially in European cohorts. Subsequently, highly sensitive troponin assays were introduced in several international markets and have since been adopted as standard. Improved assay sensitivity has led to accelerated diagnostic algorithms that are recommended by the European Society of Cardiology (*2*). In addition to their diagnostic value, cardiac troponin values inform risk stratification in acute coronary syndrome (ACS). Higher assay sensitivity improves prognostic besides diagnostic utility (*3*).

In January 2017, a 5th generation troponin T assay (Roche) was cleared by the US Food and Drug Administration (FDA) for use in the US (*4*). Notably, clinical application based on the FDA information is not as straightforward as one might expect. First, the overall 99th percentile provided for AMI diagnosis (19 ng/L) differs from the value used in most published studies and guidelines (14 ng/L). Second, for the first time, sex-specific cut-offs for troponin T are provided (females 14 ng/L, males 22 ng/L), which are comparable to sex-specific cut-offs of highly sensitive troponin I assays (*5*). Third, the 5th generation troponin T assay was not FDA-cleared for risk stratification in ACS, whereas the previous-generation assay might be used in this context.

We sought to stress this third aspect by evaluating the prognostic value of the 5th generation troponin T assay in ACS. The newly published US 99th percentile and the established non-US 99th percentile were compared with the last-generation assay that was cleared for risk stratification by the FDA.

Troponin T was measured in 1023 patients (30.4% female) enrolled consecutively in the Bad Nauheim ACS registry using the highly sensitive and last-generation (clinical cutoff 30 pg/mL) assays as published (*6*). The study was approved by the local ethic board; all patients provided informed consent. Patients were transferred for a coronary angiography, leading to a cohort with high AMI prevalence (826 AMI patients). The present analysis does not focus on the diagnostic ability of the current-generation troponin T assay but on its prognostic value.

Risk factors were comparable to those of other cohorts, with 67% hypertension, 42% hyperlipidemia, and 22% diabetes. Median time between chest pain onset and admission was 7 h (range: 3–15 h). Median troponin T on admission was 210 ng/L (range: 10–749 ng/L) using the 4th generation Roche assay and 232 ng/L (42–752 ng/L) using the 5th generation assay. Outcome measures were the combined endpoint of death and nonfatal AMI (excluding index event). Eighty events (72/9 deaths/AMI) were documented during 183.7 ± 46.9 days of follow-up. The 5th generation assay using the non-US 99th percentile yielded an HR of 4.9 (95% confidence interval: 1.55–15.53; $P = 0.007$) compared to 4.48 (1.64–12.24; $P = 0.003$)

[1] **Nonstandard abbreviations:** AMI, acute myocardial infarction; ACS, acute coronary syndrome; FDA, Food and Drug Administration.

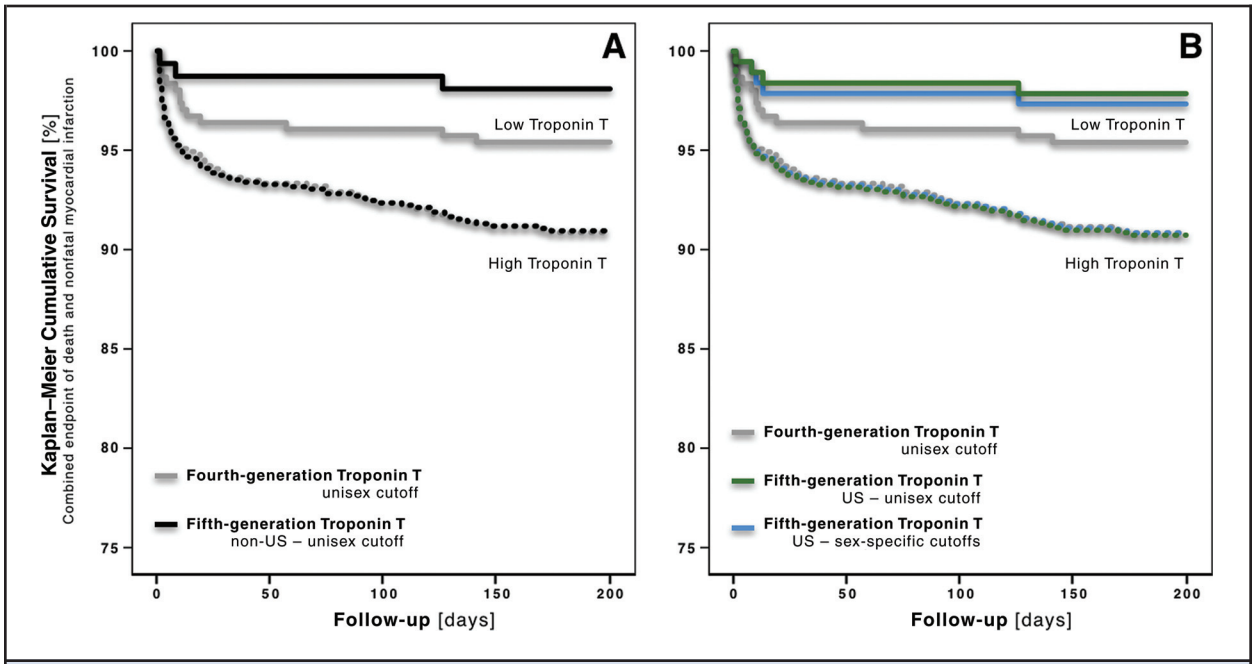

Fig. 1. Comparing the prognostic information of the last generation and the current generation troponin T assay in ACS using US and non-US cut-offs.

associated with the US unisex threshold. Applying the sex-specific US 99th percentile led to an HR of 3.55 (1.44–8.78; P = 0.006). The HR of the 4th generation assay was 2.03 (1.14–3.63; P = 0.016). Kaplan–Meier survival curves are illustrated in Fig. 1, comparing the last- with the current-generation assay applying the non-US, the US unisex, as well as the sex-specific 99th percentile cut-offs. The 5th generation assay, used as continuous parameter, showed a slightly higher Harrell C statistic, with an area under the curve of 0.653 compared to 0.642 when using the 4th generation assay. Application of the unisex non-US cutoff identified 15, the unisex US cutoff 14, and the sex-specific US 99th percentile cutoff 13 more patients at risk with the 5th generation assay as compared to those identified with the use of the earlier-generation assay.

A potential limitation of the present study is that prognosis was evaluated in a population with high ACS probability. Therefore, the sex-specific US 99th percentile cut-offs may not perform similarly to the non-US unisex cutoff with respect to prognosis in US-based emergency department populations with lower expected ACS probability.

To conclude, the 5th generation troponin T assay provides additional prognostic information using either the US or the non-US 99th percentile cutoffs compared to the 4th generation assay. With respect to risk stratification in ACS, the US sex-specific cut-offs performed comparable to the unisex cut-offs.

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