Equal clinical performance of a novel point-of-care cardiac troponin I (cTnI) assay with a commonly used high-sensitivity cTnI assay

Citation for published version (APA):
Venge, P., van Lippen, L., Blaschke, S., Christ, M., Geier, F., Giannitsis, E., Hagström, E., Khellaf, M., Mair, J., Pariente, D., Scharnhorst, V., & Semjonow, V. (2017). Equal clinical performance of a novel point-of-care cardiac troponin I (cTnI) assay with a commonly used high-sensitivity cTnI assay. Clinica Chimica Acta, 469, 119-125. https://doi.org/10.1016/j.cca.2017.03.023

Document license:
CC BY

DOI:
10.1016/j.cca.2017.03.023

Document status and date:
Published: 01/06/2017

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

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.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.tue.nl/taverne

Take down policy
If you believe that this document breaches copyright please contact us at:
openaccess@tue.nl
providing details and we will investigate your claim.

Download date: 04. Oct. 2020
Equal clinical performance of a novel point-of-care cardiac troponin I (cTnI) assay with a commonly used high-sensitivity cTnI assay

Per Venge⁎, Lian van Lippen, Sabine Blaschke, Michael Christ, Felicitas Geier, Evangelos Giannitsis, Emil Hagström, Pierre Hausfater, Mehdi Khellafi, Johannes Mair, David Pariente, Volkmer Scharnhorst, Veronique Semjonow

Article Info

Keywords:
Cardiac troponin I
Acute myocardial infarction
Point-of-care
Emergency medicine

Abstract

Background: Efficient rule-out of acute myocardial infarction (MI) facilitates early disposition of chest pain patients in emergency departments (ED). Point-of-care (POC) cardiac troponin (cTn) may improve patient throughput. We compared the diagnostic accuracy of a novel cTnI test (Minicare cTnI, Philips), with current POC cTnI (I-Stat, Abbott) and high-sensitivity central laboratory cTnI (hs-cTnI; Architect, Abbott) assays.

Methods: The clinical performance of the assays were compared in samples from 450 patients from a previous clinical evaluation of Minicare cTnI.

Results: Minicare cTnI correlated with Architect hs-cTnI (r² = 0.85, p < 0.0001) and I-Stat cTnI (r² = 0.93, p < 0.0001). Areas under the receiver operating characteristics curves were 0.87–0.91 at admission (p = ns) and 0.96–0.97 h after admission (p = ns). The negative predictive values (NPV) at admission were 95% (92–97%, 95% CI) for Minicare cTnI and increased to 99% (97–100%) at 2–4 h, and similar to Architect hs-cTnI (98%, 96–100%), but higher than I-Stat cTnI (95%, 92–97%; p < 0.01). Negative likelihood ratios (LR–) after 2–4 h were 0.06 (0.02–0.17, 95% CI) for Minicare cTnI, 0.11 (0.05–0.24) for Architect hs-cTnI (p = 0.02) and 0.28 (0.18–0.43) for I-Stat cTnI (p < 0.0001). The clinical concordances between Minicare cTnI and Architect hs-cTnI were 92% (admission) and 95% (2–4 h), with lower concordances between Minicare cTnI and I-Stat cTnI (83% and 78%, respectively; p = 0.007).

Conclusions: The Minicare cTnI POC assay may become useful for prompt and safe ruling-out of AMI in ED patients with suspected AMI using a guideline supported 0/3 h sampling protocol.

1. Introduction

Achieving a prompt and accurate diagnosis of acute myocardial infarction (MI) is important, because early intervention saves lives. The diagnosis of MI is based on several criteria, including observation of circulating cardiac troponin I or T (cTnI or cTnT) above the upper reference limit (URL) [1–3].

Efficient rule-out of MI in patients presenting with symptoms of cardiac ischemia facilitates early disposition of the patient to outpatient care, and helps to relieve the increasing crowding of the emergency...
2. Materials and methods

2.1. Patients

Patients admitted with suspected MI were enrolled prospectively at EDs or coronary care units/chest pain units of seven hospitals in Germany, France, Austria and the Netherlands as described previously [7]. Patients eligible for enrolment were adults (age ≥ 18 years) who had presented with symptoms suggestive of MI. Only patients who presented for the first time and < 12 h from onset of symptom onset were included. The study was approved by local ethical committees and all patients provided written, informed consent.

2.2. Study outcome and definitions

The primary outcome of the study was MI, based on evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, defined according to the Third universal definition of myocardial infarction [1]. MI secondary to coronary procedures (MI type 4a or 5) or patients who died prior to biomarkers being obtained (MI type 3) were not included. Cases of MI were further sub-classified according to ST-segment changes to ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI).

Serial blood samples for cTn analyses were drawn at three different time points: admission, 2–4 h, and 6–24 h after the first blood draw/admission. The time window of blood sampling was set according to local hospital standard procedures.

2.3. Adjudication process

The pre-specified primary outcome was documented and reported by the Minicare cTnI study investigators, and adjudicated by an independent clinical events committee (CEC). The CEC adjudication process and precision of adjudicated diagnoses has been presented previously [8]. Only the data from patients with at least one central laboratory cTnT result above the 99th percentile upper reference limit (URL) using the hospital hs-cTnT test were adjudicated. Patients without elevated hs-cTnT levels were not considered as having an MI and were not adjudicated.

The final diagnosis of MI was based on the adjudication performed independently by two CEC cardiologist reviewers (Phase I review), who were blinded to the outcome of the Minicare cTnI test. Each reviewer assessed the information in the event package (e.g. ECG, clinical records) and the results from the hospital standard cTnT assay. If the two reviewers disagreed on the diagnosis or time of event in Phase I, the event was assessed at a second review in a CEC committee meeting (Phase II review). At least three cardiologist reviewers adjudicated the event and reached a consensus decision on the final diagnosis.

2.4. Measurement of cTn

The concentrations of cTnT in lithium-heparin plasma were measured at the local hospital laboratories using a hs-cTnT assay (Roche); cTnI was measured in fresh lithium-heparinised whole blood and plasma samples using the Minicare cTnI assay at admission and 2–4 h after admission. Lithium-heparin plasma samples were frozen and shipped to Department of Clinical Chemistry, Uppsala University Hospital, Uppsala, Sweden, for the analysis by the Abbott Architect® hs-cTnI and the Abbott I-Stat® cTnI assays. Analysis of plasma samples occurred within 4 h of thawing.

The 99th percentile URLs provided by manufacturers were 43 ng/L for the Minicare cTnI assay, 26.2 ng/L for the Architect hs-cTnI assay, and 80 ng/L for the I-Stat cTnI assay [6,9]. The analytical specifications of the Minicare cTnI were LoB (level of blank) 6.5 and 8.5 ng/L, LoD (level of detection) 18 and 17 ng/L for two different lots, respectively and LoQ (level of quantitation) at 20% CV was 38 ng/L (95% CI 28.3–47.7 ng/L). The CV at 99th percentile URL was calculated to be 18.6% [7].

2.5. Statistics

Non-parametric statistics were used for comparisons between groups and comparisons between assays were made using Passing-Bablok regression analysis. The clinical performance was evaluated by receiver operating characteristics (ROC) curve analysis, which in addition to area under the ROC curve (AuROC) provides information on sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive (LR +) and negative (LR-) likelihood ratios. The cut-off points used to calculate these parameters were the URLs (26.2 ng/L for Architect hs-cTnI, 80 ng/L for I-Stat cTnI and 43 ng/L for Minicare cTnI). Differences between AuROC were calculated according to DeLong et al. [10] and differences between proportions by Chi²-testing. The statistical programmes MedCalc (MedCalc Statistical Software version 16.8.4, MedCalc Software bvba, Ostend, Belgium) and SAS™ were used.

3. Results

3.1. Patients

Table 1 shows clinical characteristics of all 450 patients included in the study; a more detailed table of clinical characteristics is reported in Supplementary Table 1. Results from all three cTn assays were obtained from 417 patients at admission and from 353 patients 2–4 h after admission. The comparative results given below are based on these cohorts. Supplementary Fig. 1 shows the number of patients included at admission and 2–4 h after admission as well as the numbers of patients given the diagnosis of MI by the adjudication panel.

3.2. Correlations and correspondences between cTnI analysers

Significant (p < 0.0001) correlations were observed using Passing-Bablok regression analysis for cTn concentrations measured on the Minicare cTnI, either as whole blood or plasma, compared with the Architect hs-cTnI and I-Stat cTnI (Fig. 1). There was evidence of bias for both comparisons: 0.59 (whole blood) and 0.48 (plasma) for the Architect hs-cTnI and 0.48 (whole blood) and 0.43 (plasma) for the I-Stat cTnI. The correspondences relative to the cut-offs of the respective assay at admission were 92% between the Minicare cTnI and the Architect hs-cTnI, 83% between the Minicare cTnI and the I-Stat cTnI, and 81% between Architect hs-cTnI and I-Stat cTnI. The 8% discordant results among MI patients between Minicare cTnI and Architect hs-cTnI were almost equally distributed with 3% showing elevated concentrations with Minicare cTnI and 5% showing elevated results with Architect hs-cTnI, but non-elevated results with the other. The 17%
discordant results among MI patients between Minicare cTnI and I-Stat cTnI showed a much more skewed distribution since all discordant results had elevated Minicare cTnI results but non-elevated I-Stat cTnI results. Similarly, all 19% discordant results among MI patients between Architect hs-cTnI and I-Stat cTnI were due to elevated Architect hs-cTnI results and non-elevated I-Stat cTnI results. These differences were significant ($p < 0.0001$).

3.3. Clinical performance

The comparisons between the clinical performances of the three assays are illustrated in Fig. 1 in which the results of patients with and without MI are compared by the findings with the Minicare cTnI whole blood assay and the Architect hs-cTnI and I-Stat cTnI assays at admission and 2–4 h after admission, respectively. The correlations between concentrations of cTnI in the MI patients are highly significant between all three assays ($p < 0.0001$). However, discrepancies were seen relative to the cut-offs of the assays. Sixteen patients with MI (25%) had normal cTnI according to either Minicare cTnI or Architect hs-cTnI at admission and reduced to 3 patients (5%) after 2–4 h ($p = 0.003$ vs. admission; see Table 2). The overall concordance (Table 2) between Minicare cTnI whole blood and Architect hs-cTnI was 92% (admission) and 95% (2–4 h), with a lower concordance between Minicare cTnI and I-Stat cTnI of 83% and 78% ($p = 0.007$), respectively. The proportions of patients with adjudicated MI who had normal (false negative) cTnI 2–4 h after admission were 28% for the I-Stat cTnI and 5% for Minicare cTnI whole blood ($p = 0.009$). Similar results were obtained in the comparison with Minicare cTnI plasma and Architect hs-cTnI. False negative cTnI at admission were 27–30% for Minicare cTnI and Architect hs-cTnI and 47% for I-Stat cTnI ($p < 0.05$). The clinical concordances between the assays relative to delay from onset of symptoms to admission are given in the supplementary file, Tables 2a and b. The concordances between the Minicare cTnI and Architect hs-cTnI were similar to the above results and with lower concordances to I-Stat cTnI when the patients were divided into those admitted < 4 h from onset and those admitted > 4 h from onset of symptoms.

The clinical performances of the Minicare cTnI whole blood and plasma assays were further evaluated in comparison to the two plasma cTnI assays by ROC curve analysis (Table 3, Fig. 2). The AuROC (95%CI) for the Minicare cTnI whole blood was 0.88 (0.83–0.94) at admission and 0.97 (0.95–0.99) 2–4 h after admission. The AuROC for Minicare cTnI plasma was 0.87 (0.81–0.93) and 0.97 (0.95–0.99), respectively. Corresponding figures were 0.91 (0.87–0.95) and 0.97 (0.95–0.99) for the Architect hs-cTnI and 0.88 (0.82–0.94) and 0.96 (0.92–0.99), respectively, for the I-Stat cTnI. AuROCs were not statistically different between the three assays at the two different time points. Significant differences were observed in terms of clinical performance in relation to their respective cut-offs (43 ng/L for Minicare cTnI, 26.2 ng/L for Architect hs-cTnI and 80 ng/L for I-Stat cTnI, as shown in Table 3. Thus, the sensitivities of the Minicare cTnI and Architect hs-cTnI assays were significantly higher at admission or 2–4 h after admission, compared with the sensitivity of I-Stat cTnI ($p < 0.0001$) whereas the specificity of the I-Stat cTnI assay was higher ($p < 0.0001$). The NPV at admission was 95% for the Minicare cTnI and Architect hs-cTnI, which was not significantly different from that of the I-Stat cTnI (92%). NPV increased to 99% for Minicare cTnI in whole blood, to 98% for Minicare cTnI in plasma and to 98% for Architect hs-cTnI at 2–4 h, whereas the NPV of the I-Stat cTnI was lower, 95% ($p = 0.002$ and $p = 0.03$, respectively). The corresponding LR− after 2–4 h was lower for the Minicare cTnI whole blood (0.06) than for Architect hs-cTnI (0.11) ($p = 0.02$) and for I-Stat cTnI (0.28).
Minicare cTnI plasma (0.08) was not different from Architect hs-cTnI, but significantly different from I-Stat cTnI (p < 0.0001).

The time between onset of symptoms and admission varied considerably among the patients and it was therefore of interest to relate cTnI concentrations to the duration of symptoms before admission (Supplementary file, Tables 3–6). The majority of patients with MI were admitted within 1–4 h after start of symptoms. Concentrations of cTnI increased in line with the duration of symptoms for all assays (Fig. 3). Non-elevated cTnI levels were seen with either Minicare cTnI or Architect hs-cTnI in 4–8% of patients with MI admitted > 4 h after start of symptoms, in contrast to 21% with I-Stat cTnI. The proportions of patients without a diagnosis of MI who had elevated cTnI concentrations at admission were about 1% for the I-Stat cTnI, 7–8% for the Minicare cTnI and Architect hs-cTnI respectively (Supplementary Fig. 2). Elevation of cTnI in the absence of MI was seen in 10% of patients with a prior history of coronary artery disease. Clinical performance characteristics in relation to onset of symptoms i.e. < 4 h or > 4 h, are further given in Supplementary Tables 7a and b.

### 4. Discussion

The present study is the first prospective evaluation using fresh whole blood POC assays that demonstrated equal clinical performance with a hs-cTnI laboratory assay for cTnI measurements made at 0 h or 3 h after admission. The clinical performance of the POC Minicare cTnI assay suggests that this assay, whether used as a whole blood assay or as a plasma assay, has comparable clinical performance to the Architect hs-cTnI assay, in terms of diagnosis of MI. This is remarkable in the light of the modest analytical sensitivity of Minicare cTnI, which can measure cTnI in about 5% of a healthy population [7], compared with the Architect hs-cTnI assay which can measure cTnI in 95% of a healthy population.

### Table 2

Clinical concordance of the three assays: numbers of MI diagnoses in relation to assay cut-offs.

| Test          | Admission 2–4 h after admission | 2–4 h after admission |
|---------------|---------------------------------|-----------------------|
|               | No. with Minicare cTnI ≤ 43 ng/L | No. with Minicare cTnI > 43 ng/L | Concordance | No. with Minicare cTnI ≤ 43 ng/L | No. with Minicare cTnI > 43 ng/L | Concordance |
| Architect hs-cTnI | ≤ 26.2 ng/L³ | 16 | 2 | 92% | 3 | 3 | 95% |
|                | > 26.2 ng/L | 3 | 43 | 0 | 52 | |
| I-Stat cTnI    | ≤ 80 ng/L²  | 19 | 11 | 83% | 3 | 13 | 78% |
|                | > 80 ng/L   | 0 | 34 | 0 | 42 | |

³ Clinical cut-offs (99th percentile upper reference limit for cTnI from healthy populations). POC: point-of-care.
population [6,11]. We also compared the clinical performance of the Minicare cTnI and the I-Stat cTnI, a POC assay used worldwide in the ED setting. The performance of I-Stat cTnI was inferior to the Minicare cTnI when adopting the cut-off given by the manufacturer. Moreover, the Minicare cTnI assay can be used equally with whole blood, capillary blood or plasma [7].

The analytical and clinical sensitivities of the Minicare cTnI appear difficult to reconcile with the reported imprecision of the assay at its clinical cTnI cut-off, which is < 20% CV as required in guidelines, and above the 10% CV required for a hs-cTn assay [7]. One explanation could be overestimation of the imprecision, which was determined by the Clinical & Laboratory Standards Institute protocol and not by the

| Table 3  |
|----------|
| AuROC | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | LR+ | LR- |
|----------|-----------------|-----------------|---------|---------|-----|-----|
| Minicare TnI, whole blood, cut-off 43 ng/L |
| Admission | 0.88 (0.83–0.94) | 70 (58–81) | 93 (89–95) | 63 (51–75) | 95 (92–97) | 10 (6–15) | 0.32 (0.22–0.47) |
| 2–4 h | 0.97 (0.95–0.99) | 95 (86–99) | 91 (87–94) | 68 (57–78) | 99 (97–100) | 11 (7–17) | 0.06 (0.02–0.17) |
| Minicare TnI, Plasma, cut-off 43 ng/L |
| Admission | 0.87 (0.81–0.93) | 73 (61–84) | 92 (89–95) | 64 (52–74) | 95 (92–97) | 9 (6–15) | 0.29 (0.19–0.43) |
| 2–4 h | 0.97 (0.95–0.99) | 93 (83–98) | 90 (86–93) | 66 (55–76) | 98 (96–100) | 10 (6–15) | 0.08 (0.03–0.20) |
| Architect® hs-cTnI, Plasma, cut-off 26.2 ng/L |
| Admission | 0.91 (0.87–0.95) | 72 (59–82) | 92 (88–94) | 61 (49–72) | 95 (92–97) | 9 (6–13) | 0.31 (0.21–0.45) |
| 2–4 h | 0.97 (0.95–0.99) | 90 (79–96) | 91 (87–94) | 67 (55–77) | 98 (95–99) | 10 (7–16) | 0.11 (0.05–0.24) |
| I-Stat® POC cTnI, cut-off plasma, 80 ng/L |
| Admission | 0.88 (0.82–0.94) | 53 (40–66) | 99 (97–100) | 89 (75–97) | 92 (89–95) | 47 (17–128) | 0.47 (0.37–0.62) |
| 2–4 h | 0.96 (0.92–0.99) | 72 (59–83) | 98 (96–99) | 89 (77–96) | 95 (92–97) | 43 (17–106) | 0.28 (0.18–0.43) |

AuROC: area under the receiver operating characteristics curve; PPV, positive predictive value; NPV, negative predictive value; LR +, positive likelihood ratio; LR −, negative likelihood ratio. Figures in parentheses are 95% CI. *P-values as compared to Minicare cTnI whole blood; **⁎⁎⁎= p < 0.001, **⁎⁎= p < 0.01, * = p < 0.05.

Fig. 2. Receiver operating characteristics curves for diagnosis of acute myocardial infarction with the three assays at admission and at 2–4 h after admission.
construction of an imprecision profile based on duplicates of a large number of patient samples. We argued previously that the latter procedure probably better reflects the actual imprecision of the day-to-day use of the assay [12]. Indeed in recent evaluations, after the completion of the present study, of the imprecision of the Minicare cTnI, lower imprecision was reached and reported by the manufacturer (Philips). The unique antibody configuration of the assay, which includes an antibody against troponin C, may also be relevant to the discussion of the sensitivity of the assay, as we showed earlier that the clinical performance of another cTnI assay was dramatically improved by such measures [13]. For example, the Vidas cTnI assay was judged not clinically useful due to its inability to measure cTnI in the blood of any of a population of healthy subjects [14]. Nevertheless, its clinical performance matched contemporary cTnI assays. Thus, the inclusion of an anti-TnC antibody in the Minicare cTnI assay may detect processes in the ischemic myocardium that increase the expression and release of troponin C [15]. Alternatively, TnC antibodies may increase the epitope recognition of cTnI-cTnC complexes in the assay.

Prompt and accurate rule-out of MI for a patient presenting with symptoms suggestive of MI is a major goal in the crowded emergency room. The introduction of laboratory hs-cTnT assays supports rule-out of MI within 3 h [3], or as little as 1 h, after admission [16]. The use of laboratory assays often incurs a delay in response time, typically of 1–2 h after blood draw; the availability of a sufficiently sensitive POC cTnT assay could support earlier discharge by providing a rapid cTnI measurement [4]. This has not been achieved to date, apparently due to the seemingly insurmountable challenge of achieving the analytical sensitivity of the hs-cTnI laboratory assays in a POC test. The clinical performance of the Minicare cTnI POC assay therefore seems unique, having achieved a negative predictive value of 99% and clinical diagnostic performance equivalent to one of the most sensitive cTnI laboratory assays currently available. As discussed above, the clinical performance of the Minicare cTnI arose from its clinical specificity, rather than its analytical sensitivity in measuring very low cTnI levels. The Minicare cTnI assay may be the first POC assay suitable for safe rule-out of patients with suspicion of MI 3 h after admission [3]. However, until the clinical performance of the Minicare cTnI assay has been confirmed in further studies, the diagnosis of AMI should be based on the results of this assay only when the results of sensitive laboratory assays are not available.

Most patients (60%) were admitted to the hospital < 4 h after start of symptoms, consistent with the lower negative predictive value at admission. It was interesting that, in the group of patients with MI and longer (> 6 h) duration of symptoms pre-admission all patients had Architect hs-cTnI or Minicare cTnI plasma concentrations above their respective clinical cut-offs except one patient at the cut-off as measured by Minicare cTnI in whole blood. Several patients without an MI diagnosis had elevated cTnI concentrations i.e. “false positives” (7.2%), in a diagnostic sense. As might be expected about 50% of these patients had a history of coronary artery disease and the raised cTnI therefore were consistent with a degree of myocardial ischaemia.

Our study focussed on the clinical performance of the respective assays, in terms of their ability to identify a level of cTnI that would support a diagnosis of MI (i.e. above the 99th percentile cut-off from a healthy population) in patients with an adjudicated diagnosis of MI, independently of the assays discussed here. Current guidelines for the diagnosis of non–ST elevation MI also require observation of dynamic changes (rise and/or fall) in cTnI [1,3]. This aspect of MI diagnosis is beyond the scope of our study, which represents a limitation of the current analysis. However, our observations are directly relevant to the clinical use of these cTnI tests: clinical performance depends on the identification of cTnI levels above the diagnostic cut-off, irrespective of the precise diagnostic protocol used with respect to dynamic changes in cTnI. Other limitations of the study were the moderate size of the cohort and the post-hoc analysis of the prospective trial, which also precluded any conclusions as to gender-specific cut-offs. However, these limitations were counterbalanced by the input of very high quality data of the patients and by the state-of-the art diagnostic process.

We conclude that the novel Minicare cTnI POC assay equals the clinical performance in our patient cohort of a hs-cTnI assay. The diagnostic performance of the assay may arise from the inclusion of a monoclonal antibody directed against troponin C. If confirmed by future clinical studies our data suggest that the clinical performance of the Philips Minicare cTnI assay, with a very high negative predictive value, may become suitable for prompt and safe rule-out of MI for patients with symptoms suggestive of MI in the emergency setting using a 0/3 h sampling protocol.

Acknowledgements

Dr. Mike Gwilt (GT Communications) edited the manuscript written by the authors for English and style (funded by Philips).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.cca.2017.03.023.

References

[1] K. Thygesen, J.S. Alpert, A.S. Jaffe, et al., Third universal definition of myocardial infarction, Eur. Heart J. (2012).
[2] P.G. Steg, S.K. James, D. Atar, et al., ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, Eur. Heart
[3] M. Roffi, C. Patrono, J.P. Collet, et al., 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC), Eur. Heart J. 37 (2016) 267–315.

[4] R. Bingisser, C. Cairns, M. Christ, et al., Cardiac troponin: a critical review of the case for point-of-care testing in the ED, Am. J. Emerg. Med. 30 (2012) 1639–1649.

[5] B.E. Amundson, F.S. Apple, Cardiac troponin assays: a review of quantitative point-of-care devices and their efficacy in the diagnosis of myocardial infarction, Clin. Chem. Lab. Med. 53 (2015) 665–676.

[6] F.S. Apple, R. Lier, M.M. Murakami, Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population, Clin. Chem. 58 (2012) 1574–1581.

[7] D.W. Kemper, V., de T.F. Semjonow, et al., Analytical evaluation of a new point of care system for measuring cardiac troponin I, Clin. Biochem. 50 (2017) 174–180.

[8] K.W. Mahaffey, R.A. Harrington, M. Akkerhuis, et al., Disagreements between central clinical events committee and site investigator assessments of myocardial infarction endpoints in an international clinical trial: review of the PURSUIT study, Curr. Control. Trials Cardiovasc. Med. 2 (2001) 187–194.

[9] V. Palamalai, M.M. Murakami, F.S. Apple, Diagnostic performance of four point of care cardiac troponin I assays to rule in and rule out acute myocardial infarction, Clin. Biochem. 46 (2013) 1631–1635.

[10] E.R. DeLong, D.M. DeLong, D.L. Clarke-Pearson, Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach, Biometrics 44 (1988) 837–845.

[11] I. Thorsteindottir, T. Aspelund, E. Gudmundsson, et al., High-sensitivity cardiac troponin I is a strong predictor of cardiovascular events and mortality in the AGES-Reykjavik community-based cohort of older individuals, Clin. Chem. 62 (2016) 623–630.

[12] P. Venge, N. Johnston, B. Lindahl, S. James, Normal plasma levels of cardiac troponin I measured by the high-sensitivity cardiac troponin I access prototype assay and the impact on the diagnosis of myocardial infarction, J. Am. Coll. Cardiol. 54 (2009) 1165–1172.

[13] P. Venge, B. Lindahl, Cardiac troponin assay classification by both clinical and analytical performance characteristics: a study on outcome prediction, Clin. Chem. (2013).

[14] F.S. Apple, A new season for cardiac troponin assays: it’s time to keep a scorecard, Clin. Chem. 55 (2009) 1303–1306.

[15] M.Y. White, A.S. Tchen, H.C. McCarron, R.D. Hambly, R.W. Jeremy, S.J. Cordwell, Proteomics of ischemia and reperfusion injuries in rabbit myocardium with and without intervention by an oxygen-free radical scavenger, Proteomics 6 (2006) 6221–6233.

[16] C. Mueller, E. Giannitsis, M. Christ, et al., Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T, Ann. Emerg. Med. 68 (2016) 76–87.