International Journal of Cardiology 288 (2019) 25–26

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

The rise and fall of the 99th percentile decision limit for cardiac troponins?

Kristin Moberg Aakre [a,b], Torbjørn Omland [c,d,*]

[a] Hormone Laboratory, Haukeland University Hospital, Bergen, Norway
[b] Department of Clinical Science, University of Bergen, Bergen, Norway
[c] Division of Medicine, Akershus University Hospital, Oslo, Norway
[d] Center for Heart Failure Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

ARTICLE INFO

Article history:
Received 20 February 2019
Accepted 27 February 2019
Available online 14 March 2019

Keywords:
Acute coronary syndrome
Age
Diagnostic cut off
Gender
Man
Woman

According to the 4th universal definition of acute myocardial infarction (AMI), a rise and fall in serial cardiac troponin (cTn) concentrations with at least one value exceeding the upper reference limit, defined as the 99th percentile in a healthy population, is an obligate criterion for the diagnosis of AMI [1]. The decision to use the 99th percentile as the decision limit was originally based on the desire to balance sensitivity and specificity. An important concern was to avoid overdiagnosis of AMI. Accordingly, biologically the 99th percentile does not represent a clear distinction between health and disease; the association between concentrations of cTn and cardiovascular risk is a continuum.

With the introduction of high sensitivity cTn assays for clinical use, it soon became clear that low levels of cTn circulate in patients with stable coronary heart disease and in the normal state [2,3]. It also became evident that circulating concentrations of cTnI and cTnT increase with age and are higher in men than in women [4,5]. These observations have obvious implications for the determination of the 99th percentile value. For instance, the 99th percentile is commonly determined by measuring a cohort of presumably healthy individuals, e.g. 600 individuals, and then removing the six highest concentrations in this cohort. As men generally have higher values compared to women, the sex-independent 99th percentile concentration will typically be based on observations from male subjects and consequently be much closer to the male specific cut-off than to the female cut-off. Based on this and other concerns, the authors of the 4th definition of myocardial infarction recently recommended the use of gender stratified cut offs for diagnosing AMI [1]. Although this seems logical, perhaps surprisingly, most studies examining the potential consequences of their use have not been able to document a clear benefit of sex-specific cut-offs [6]. An important factor contributing to the lack of effect relates to the fact that women are older when they develop atherosclerotic coronary artery disease, offsetting the effect of sex differences. In this perspective, it is commendable and of interest that Widera and colleagues in the current volume of the *Journal* examine the diagnostic and prognostic value of both sex-specific and age-specific cut-offs for cTnT in a retrospective cohort of patients with non-ST elevation acute coronary syndrome (NSTE-ACS) [7].

NSTE-ACS comprises non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris. Both are characterised by acute myocardial ischemia and may have similar clinical presentation, the distinction being that NSTEMI encompasses dynamic cTn changes and at least one concentration that exceeds the 99th percentile. Patients with elevated cTn have been shown to be at higher risk and in early studies to benefit more from an early invasive strategy [8,9]. In contemporary clinical practice, however, both patients with NSTEMI and unstable angina pectoris will commonly undergo coronary angiography and if appropriate, percutaneous coronary intervention during the index hospitalization, reducing the risk for early recurrent ischemic events. In order to assess future risk of the patient, the "ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation" recommend calculation of the Global Registry for Acute Coronary Events (GRACE) score to guide treatment decisions [10]. Widera and colleagues in their study evaluate the consequences of using sex-independent (i.e. 14 ng/L), sex-dependent (i.e. 9 ng/L in women, 15.5 ng/L in men) and sex- and age-dependent (i.e. 9 ng/L in women younger than 65 years, 17 ng/L in women 65 years or older and in men 50–64 years old and 31 ng/L in men 65 years or older) cut-offs for cTnT for diagnosing NSTEMI and subsequently calculation of the GRACE score. As anticipated, use of the

Abbreviations: Cardiac troponin, cTn; Cardiac troponin I, cTnI; Cardiac troponin T, cTnT; AMI, Acute myocardial infarction; NSTE-ACS, non-ST elevation acute coronary syndrome; NSTEMI, non-ST elevation myocardial infarction; GRACE, Global Registry for Acute Coronary Events; IDI, Integrated discrimination improvement.

DOI of original article: https://doi.org/10.1016/j.ijcard.2018.12.001.

* Corresponding author at: Division of Medicine, Akershus University Hospital, NO-1478 Lørenskog, Norway.
E-mail address: torbjorn.omland@medisin.uio.no (T. Omland).

https://doi.org/10.1016/j.ijcard.2019.02.071
0167-5273/© 2019 Elsevier B.V. All rights reserved.

sex-specific cut-offs resulted in a substantially higher number of women diagnosed with NSTEMI, increasing diagnostic sensitivity at the cost of decreasing specificity. In men, the effect of sex-specific cut-offs was less pronounced, but tended to decrease sensitivity and increase specificity. The use of the combined age- and sex-specific cut-off values resulted in a moderate reduction of the number of NSTEMI diagnoses in men aged 65 years or older and a more marked reduction in women aged 65 years or older and in men aged 50–64 years. The more novel aspects of the study of Widera and colleagues relate to the effect of sex-specific and combined age- and sex-specific cut-off values on reclassification of patients between GRACE low-risk and high-risk strata. According to this analysis, the use of sex-specific cut-off values had negligible effects on reclassification while the use of the combined age- and sex-specific cut-off values resulted in reclassification of women at low-risk to the correct GRACE risk stratum. This benefit was also supported by higher integrated discrimination improvement (IDI) index in women. Still, the clinical implications of these changes appear to be modest, as the incidence of cardiovascular events within 6 months in those reclassified was low.

When considering the potential introduction of age- and sex-specific decision limits, practical issues related to the adoption of such limits must be taken into consideration. A common, unisex decision limit is easy for clinicians to remember and to use. On the other hand, clinicians have readily accepted the rationale for and use of the estimated glomerular filtration rate equation (i.e. an automatically reported age, race and gender adjustment of the creatinine value), as a superior index of renal function compared to serum creatinine measurements reported with age and gender stratified reference intervals. With appropriate education, it is therefore likely that clinicians will accept the future use of algorithms that include and automatically report important determinants of cTn levels. Rather than using the current simplistic approach of dichotomizing cTn concentrations to define risk, future approaches may include tools such as machine learning and take into account factors such as the magnitude and velocity of change in cTn concentrations, as well as confounding factors such as age and sex. The use of a single cTn cut-off that is independent of sex and age may therefore become obsolete in the not too distant future.

Disclosure statement

Kristin M Aakre has served on an advisory board for Roche Diagnostics. Torbjørn Omland has served on advisory boards for Abbott Diagnostics and Roche Diagnostics and has received research support from Abbott Diagnostics, Novartis, Roche Diagnostics, Singulex and SomaLogic via Akershus University Hospital, and speaker's honoraria from Roche Diagnostics and Siemens.

Acknowledgements

None.

Sources of funding

None.

References

[1] K. Thygesen, J.S. Alpert, A.S. Jaffe, B.R. Chaitman, J.J. Bax, D.A. Morrow, et al., Fourth universal definition of myocardial infarction (2018), Circulation. 138 (2018) (e618-e51).
[2] J.A. de Lemos, M.H. Drazner, T. Omland, C.R. Ayers, A. Khera, A. Rohatgi, et al., Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population, JAMA. 304 (2010) 2503–2512.
[3] T. Omland, J.A. de Lemos, M.S. Sabatine, C.A. Christophi, M.M. Rice, K.A. Jablonski, et al., A sensitive cardiac troponin T assay in stable coronary artery disease, N. Engl. J. Med. 361 (2009) 2538–2547.
[4] T. Omland, J.A. de Lemos, O.L. Holmen, H. Dalen, J.S. Benth, S. Nygard, et al., Impact of sex on the prognostic value of high-sensitivity cardiac troponin I in the general population: the HUNT study, Clin. Chem. 61 (2015) 646–656.
[5] M.O. Gore, S.L. Seliger, C.R. Defilippi, V. Nambi, R.H. Christenson, I.A. Hashim, et al., Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay, J. Am. Coll. Cardiol. 63 (2014) 1441–1448.
[6] K.M. Eggers, B. Lindahl, Impact of sex on cardiac troponin concentrations-a critical appraisal, Clin. Chem. 63 (2017) 1457–1464.
[7] C. Widera, E. Giannitsis, M. Mueller-Hennessen, I. Reimann, A. Guba-Quint, I. Marquardt, et al., Diagnostic and prognostic value of sex- and age-specific cutpoints for highsensitivity troponin T in non-ST-elevation acute coronary syndrome, Int. J. Cardiol. 275 (2019) 13–19.
[8] D.A. Morrow, C.P. Cannon, N. Rifai, M.J. Frey, R. Vicari, N. Lakkis, et al., Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial, JAMA. 286 (2001) 2405–2412.
[9] L. Wallentin, D. Lindholm, A. Siegbahn, L. Wernroth, R.C. Becker, C.P. Cannon, et al., Biomarkers in relation to the effects of ticagrelor in comparison with clopidogrel in non-ST-elevation acute coronary syndrome patients managed with or without in-hospital revascularization: a substudy from the prospective randomized platelet inhibition and patient outcomes (PLATO) trial, Circulation. 129 (2014) 293–303.
[10] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, 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. 2016;37:267–315.