Biological variation of cardiac troponins in chronic kidney disease

RA Jones1, J Barratt2, EA Brettell3, P Cockwell4, RN Dalton5, JJ Deeks3,6,7, G Eaglestone8, T Pellatt-Higgins9, PA Kalra10, K Khunti11, FS Morris8, RS Ottridge3, AJ Sitch6,7, PE Stevens8, CC Sharpe12, AJ Sutton13, MW Taal14 and EJ Lamb1; on behalf of the eGFR-C Study Group

Abstract

Background: Patients with chronic kidney disease often have increased plasma cardiac troponin concentration in the absence of myocardial infarction. Incidence of myocardial infarction is high in this population, and diagnosis, particularly of non ST-segment elevation myocardial infarction (NSTEMI), is challenging. Knowledge of biological variation aids understanding of serial cardiac troponin measurements and could improve interpretation in clinical practice. The National Academy of Clinical Biochemistry (NACB) recommended the use of a 20% reference change value in patients with kidney failure. The aim of this study was to calculate the biological variation of cardiac troponin I and cardiac troponin T in patients with moderate chronic kidney disease (glomerular filtration rate [GFR] 30–59 mL/min/1.73 m²).

Methods and results: Plasma samples were obtained from 20 patients (median GFR 43.0 mL/min/1.73 m²) once a week for four consecutive weeks. Cardiac troponin I (Abbott ARCHITECT® i2000SR, median 4.3 ng/L, upper 99th percentile of reference population 26.2 ng/L) and cardiac troponin T (Roche Cobas® e601, median 11.8 ng/L, upper 99th percentile of reference population 14 ng/L) were measured in duplicate using high-sensitivity assays. After outlier removal and log transformation, 18 patients' data were subject to ANOVA, and within-subject (CVI), between-subject (CVG) and analytical (CVA) variation calculated. Variation for cardiac troponin I was 15.0%, 105.6%, 8.3%, respectively, and for cardiac troponin T 7.4%, 78.4%, 3.1%, respectively. Reference change values for increasing and decreasing troponin concentrations were +60%–38% for cardiac troponin I and +25%–20% for cardiac troponin T.

Conclusions: The observed reference change value for cardiac troponin T is broadly compatible with the NACB recommendation, but for cardiac troponin I, larger changes are required to define significant change. The incorporation...
of separate RCVs for cardiac troponin I and cardiac troponin T, and separate RCVs for rising and falling concentrations of cardiac troponin, should be considered when developing guidance for interpretation of sequential cardiac troponin measurements.

**Keywords**

Troponin, renal disease

*Accepted: 17th January 2020*

**Introduction**

Chronic kidney disease (CKD) is common: 4.5% of the UK population have a glomerular filtration rate (GFR) below 60 mL/min/1.73 m$^2$.1 The majority of individuals with CKD have moderate disease (CKD category G3) defined by a GFR of 30 to 59 mL/min/1.73 m$^2$. People with CKD have an increased prevalence of cardiovascular disease2,3 and an increased cardiovascular mortality risk with declining renal function.4–8 Consequently, patients with moderate CKD are more likely to die from cardiovascular complications than progress to renal failure requiring renal replacement therapy.

Diagnosis of acute myocardial infarction requires: (a) evidence of myocardial injury by observing at least one measure of cardiac troponin concentration exceeding the upper 99th percentile of a healthy reference population; (b) confirmation that such injury is acute, through observing a rise and/or fall of cardiac troponin concentration and (c) evidence of myocardial ischaemia as demonstrated by accompanying characteristic symptoms and signs of myocardial infarction (e.g. electrocardiogram changes).9 Patients with CKD are frequently observed to have concentrations of cardiac troponin that exceed the 99th percentile in the absence of myocardial infarction.9–12 The increased plasma troponin concentration observed in CKD is most likely a reflection of the multifaceted burden of cardiovascular disease and creates a significant diagnostic problem.9,10,13–15 The diagnosis of myocardial infarction in patients with CKD is most likely a reflection of the multifaceted burden of cardiovascular disease and creates a significant diagnostic problem.9,10,13–15 In this situation, observation of changing cardiac troponin concentration over time is a useful pointer towards myocardial infarction, although acute volume overload or heart failure may also cause this pattern.9

There is little published data relating to the biological variation of cardiac troponin in patients with moderate CKD. Knowledge of the biological (and analytical) variation can be used to calculate reference change values (RCVs), which can be used to determine whether a change in serial measures of a biomarker are statistically significant.19 This is pertinent to the diagnosis of acute coronary syndromes since other medical conditions, including CKD, increase cardiac troponin concentrations in the absence of myocardial infarction. Defining significant change in cardiac troponin concentration is an area of active debate. In 2007, the National Academy of Clinical Biochemistry (NACB) suggested a change of 20% should be considered significant among dialysis patients, although this recommendation predated the use of high-sensitivity cardiac troponin assays and did not consider biological variation.20 The recent Fourth Universal Definition of Myocardial Infarction considers the difficulties of defining significant change. While a troponin concentration change $>$50% has been considered to exceed that which could be attributed to biological and analytical variability, smaller changes ($>$20%) are significant when the initial baseline value exceeds the 99th percentile of the reference population. Furthermore, there is a move towards defining change in absolute (concentration) rather than relative (percentage) terms, although it is acknowledged that such values will be assay dependent.9,21 Generally, definitions of significant change have not discriminated between cardiac troponin T (cTnT) and cardiac troponin I (cTnI). The aim of the present study was to establish the total variation (CV$_T$), within-subject biological variation (CV$_I$) and analytical variation (CV$_A$) of cTnT and cTnl using high-sensitivity assays in patients with clinically stable moderate CKD in order to derive RCVs.

**Study participants and methods**

Patients were recruited from nephrology clinics at the Kent Kidney Care Centre, Canterbury, UK, between August 2014 and July 2015. Twenty white participants with moderate CKD were invited to participate in the biological variability substudy of the multicentre UK prospective longitudinal eGFR-C study.22 Inclusion criteria comprised an estimated GFR between 30 and 59 mL/min/1.73 m$^2$ sustained over at least 90 days prior
to the study. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation and an enzymatic creatinine assay (Abbott Laboratories) standardized to the reference materials NIST SRM 967 and 914. Exclusion criteria were age <18 years, pregnancy, breastfeeding, an episode of acute kidney injury within the last six months, known current alcohol or drug abuse, amputee (whole or part-limb), kidney transplant recipient and cognitive impairment. Patients provided written informed consent. The study had ethical approval (South-East Coast Research Ethics Committee, reference 11/LO/1304). The study conforms to the internationally agreed checklist for the reporting of studies of biological variation.

Blood was collected into ethylenediaminetetraacetic acid (EDTA) (Vacuette®, Greiner Bio-One International) tubes using standard venepuncture procedures. Samples were obtained once a week for four consecutive weeks with standardization to the same time of day (morning) and day of the week to minimize preanalytical variables. Samples were centrifuged within 6 h of venepuncture and plasma pipetted into 2 mL microtubes (Sarstedt). Plasma was stored at −80°C for approximately 24 months before cardiac troponins were measured in a single batch.

Cardiac troponin I was measured in duplicate using two high-sensitivity assays. On the morning of analysis, samples were thawed at room temperature and mixed by inversion. Immediately prior to analysis, samples were centrifuged at 3300 g for 10 min. Plasma cTnI was measured using the ARCHITECT® STAT high-sensitivity cTnI chemiluminescent microparticle immunoassay (Abbott Laboratories, Chicago, IL, USA, product code 3P25) assay (upper 99th percentile of a healthy reference population: female [15.6 ng/L], male [34.2 ng/L], combined [26.2 ng/L]) on the Abbott ARCHITECT® i2000SR module. Plasma cTnT was measured using the Elecsys® high-sensitivity cTnT electrochemiluminescent sandwich immunoassay on the Roche Cobas® e601 (Roche Diagnostics, Risch-Rotkreuz, Switzerland) analyser platform (upper 99th percentile of a healthy reference population 14 ng/L). The measurement of both cardiac troponins was undertaken on the same day by a single operator using one instrument that had been calibrated using a single batch of standards, reagents and quality controls. The samples for each patient were analysed in duplicate in random order to minimize any effects of assay drift.

**Data analysis**

Samples with measures below the limit of detection for either the cTnI assay (≤1.2 ng/L) or the cTnT assay (≤5 ng/L) were excluded. Normality was assessed using the Shapiro-Wilk test (Analyse-it Software Ltd, Leeds, UK) which showed a non-Gaussian distribution. The data were therefore log-transformed using a natural logarithm as recommended. For both cardiac troponins, Cochran’s test identified two values that differed markedly between duplicate measures and one value that differed markedly between the series of replicate measures; these were therefore removed. Where one duplicate of a sample was excluded (or absent), both duplicate results were excluded from statistical analysis. The data-set of each patient was then subject to outlier removal by Reed’s test; no subjects were excluded based on this test. The data-set belonging to any patient with less than three (out of four) duplicate cardiac troponin measures available were completely excluded from statistical analysis. On this basis, a total of three patients were excluded; one individual was excluded from all analysis; one individual was excluded from cTnI analysis only and one individual was excluded from cTnT analysis only. Details of excluded measures are shown in supplementary Table S1. The log-transformed data from 18 patients were subject to ANOVA (Minitab Statistical Software, Minitab Ltd, Coventry, UK) and estimates of biological variation were generated for CV_T, CV_A and CV_I. Data were then back-transformed allowing derivation of the exact CV values \[ \sqrt{\exp(S^2) - 1} \times 100 \] .

Power (>80%) and width of confidence intervals (CI) for the CV_I were estimated according to standard methods. Calculation of bidirectional (positive and negative) RCVs was appropriate for the definition of acute myocardial infarction (a rise and/or fall in cardiac troponin). Furthermore, since it cannot be assumed that the positive RCV (rise) is the same as the negative RCV (fall), asymmetrical (log-normal) RCVs were calculated using the approach for log-normal data proposed by Fokkema et al.

**Results**

Characteristics of the study participants are shown in Table 1. Three patients had type 2 diabetes mellitus, seven ischaemic heart disease, one angina and two had heart failure. One participant was a current smoker and 10 were ex-smokers. Antihypertensive and cholesterol-reducing drugs were being taken by 15 and 13 patients, respectively. Seven of the participants had urine albumin concentrations between 3 and 30 mg/mmol creatinine, and a further four had urine albumin concentrations >30 mg/mmol. No participants had a significant change in kidney function during the study nor an acute cardiac event.
The median concentration overall (all patients, all study points) of both cardiac troponins was below the relative 99th percentile derived from a healthy reference population. For cTnT, the median cTnT concentration of seven patients exceeded the 99th percentile (Figure 1(a)), whereas for cTnI, no individual patient had a median concentration over all study points exceeding the 99th percentile (Figure 1(b)). The highest median concentration of cTnT observed in an individual was 37.6 ng/L, whereas the highest median value for an individual for cTnI was 13.7 ng/L.

Biological and analytical variation data are shown in Table 2. The within-subject and analytical variability of cTnT was approximately half that of cTnI. Consequently, the positive and negative RCVs were lower for cTnT (25%/–20%) than for cTnI (60%/–38%).

**Discussion**

Defining a statistically significant change in serial troponin concentrations should be established from biological variability studies. There is a literature describing the biological variation of cardiac troponins in patients with kidney failure treated by dialysis but, to the best of our knowledge, this is the first study to report the biological variation of both cTnT and cTnI measured using high-sensitivity assays in patients with moderate CKD. We observed within-subject biological variation of 7.4% (CI 5.9% to 9.8%) and 15.0% (CI 11.6% to 20.2%) for cTnT and cTnI, respectively. RCVs for increasing and decreasing troponin concentrations were +25%/–20% for cTnT and +60%/–38% for cTnI.

The estimates of within-subject biological variation for cardiac troponin reported in the present study are similar to those previously reported in patients undergoing haemodialysis. For example, Fahim et al. reported a CVI for cTnT of 7.9% in dialysis patients. Among studies that simultaneously measured both cTnI and cTnT, including the present study, the within-subject variability has been consistently lower for cTnT than for cTnI. In patients with renal failure undergoing haemodialysis treatment Mbagaya et al. reported slightly higher CVI values compared with the present study for cTnT and cTnI of 10.5% and 20.2%, respectively. Aakre et al. estimated the CVI of cardiac troponins among stable haemodialysis patients and reported values of 8.3% and 14.3% for cTnT and cTnI, respectively. In the same study, CVI values among healthy individuals of 8.3% (cTnT) and 14.3% (cTnI) were reported. Corte et al. observed within-subject biological variation for cTnT of 14.7% among patients with kidney failure compared with 5.9% among healthy individuals, although the study design was somewhat different between the two groups. Among patients with CKD not receiving dialysis (median estimated GFR 17 mL/min/1.73 m²), within-day biological variability for cTnT of 8% to 9% has been reported. Overall, the reported variability appears comparable between studies including haemodialysis patients, CKD patients and healthy individuals.

When considering any change in a patient’s results, health-care practitioners need to be able to distinguish true change (‘signal’) from the ‘noise’ of variability. In clinical practice, biological variation is best considered in terms of the RCV, which takes both biological and analytical variation into account. RCVs for cTnT in the present study (25%/–20%) are generally comparable to those previously reported in dialysis patients: 33%/–25%, 32°/–26% and 34°/–26%. The RCVs for cTnT reported in the present study are also broadly compatible with the NACB’s definition of a significant change of 20%.

For cTnI, however, our data suggest that a larger difference (60%/–38%) is required to define significant change. Similarly, reported RCVs for cTnI among
dialysis patients were 53%/–35%33 and 80%/–44%,34 and among CKD patients not receiving dialysis 34%/–26%.36 The reported positive and negative RCV values therefore consistently exceed the 20% critical difference recommended by the NACB, in some cases by several fold, and would stretch the critical relative differences discussed within the Fourth Universal Definition of Myocardial Infarction.9,20 The use of a 20% critical difference to interpret serial measures of cTnI could contribute to misleading diagnoses of acute myocardial infarction in patients with moderate CKD. It is also clear that the data do not have a symmetric distribution, i.e. the same critical difference cannot be applied to rising and falling troponin concentrations. Our data and that of others,33,34,36 particularly for cTnI, demonstrate that the biological variation of troponin concentration is non-Gaussian and that RCVs will differ between rising and falling concentrations. Similarly, should absolute, as opposed to relative, delta values be used to detect change, as has been suggested,

Table 2. Summary of the components of variation of cardiac troponin I and T.

| Components of variation       | Cardiac troponin I       | Cardiac troponin T       |
|-------------------------------|--------------------------|--------------------------|
| Analytical variation (CVA)    | 8.3% (7.0%, 10.2%)       | 3.1% (2.6%, 3.8%)       |
| Within-subject variation (CVI)| 15.0% (11.6%, 20.2%)    | 7.4% (5.9%, 9.8%)       |
| Between-subject variation (CVG)| 105.6% (72.0%, 210.8%)  | 78.4% (55.6%, 139.4%)  |
| Total variation (CVT)         | 17.2%                    | 8.0%                     |
| Positive log-normal RCV (rise)| 60%                      | 25%                      |
| Negative log-normal RCV (fall)| –38%                     | –20%                     |

Note: Values are % (95% CI).

CI: confidence interval; CVA: analytical variation; CVI: within-subject biological variation; CVG: between-subject biological variation; RCV: reference change value.
the same issue will pertain regarding different rising and falling troponin concentrations.\(^5\)

As previously reported, particularly among dialysis patients,\(^{32-34}\) but also in earlier studies of non-dialysis CKD patients,\(^{10,11}\) cTnT is more commonly increased above the 99th percentile than cTnI. The reason for this is not the main focus of the present study, but various explanations have been proposed including different cTnI and cTnT release kinetics or differences in clearance from the circulation. This observation is reinforced by the present study with concentrations of cTnT commonly exceeding the 99th percentile reference interval, while cTnI concentrations were predominantly normal.

The study was adequately powered based on essential elements of the study design (number of individuals, samples and replicates).\(^{26}\) In relation to analytical performance specifications defined by the ratio of CV\(_A\) to CV\(_I\), the cTnT (0.4) and cTnI (0.5) assays met desirable and minimum quality specifications, respectively.\(^{26}\) The study followed a strict design to minimize preanalytical and analytical variation and investigator bias.\(^{24}\) Outliers in the data were excluded using a formal exclusion protocol, and a strength of this study is that few data were excluded prior to ANOVA. Estimation of components of variation was derived using a nested ANOVA approach, which takes into account analytical variation for estimation of within-subject biological variation. The participants were derived from a patient group which is a major population in which detection of myocardial infarction is a clinically relevant issue. Participants had stable kidney disease, suggesting that the variation we have reported is physiological and not pathological in nature. The methods used to measure cTnT and cTnI met criteria for the definition of high-sensitivity assays\(^{31,37}\) and are recommended by the National Institute for Health and Care Excellence for the early rule out of myocardial infarction.\(^{38}\)

Our study has some limitations. The cohort studied was recruited from a single centre and was exclusively Caucasian: biological variability estimates may therefore not be transferable to other ethnic groups. Our study comprised participants with moderate CKD and the results may not be transferable to more advanced kidney disease. However, as discussed above, comparison with other studies of patients receiving dialysis for kidney failure suggests similar levels of biological variability.\(^{32-34}\) The RCV is a value derived under idealized conditions which are often not replicated in typical clinical practice (e.g. multiple operators and batches of reagents will increase the value of CV\(_A\) and hence increase the RCV). Furthermore, sampling time was standardized to some extent in our study. In the clinical setting, change in cTnT concentrations will also be influenced by the known circadian variation, with peak concentrations occurring in the early morning and a nadir in the evening.\(^{39,40}\) RCVs should therefore be considered a minimum clinically significant change. Individual laboratories may need to adjust RCVs to take into account the analytical variation of their own troponin assay. However, the values generated in this study are useful to guide understanding of change in cardiac troponin concentration in patients among whom interpretation can often be challenging. Although the recommended approach, the outlier removal process may inadvertently remove values representing true biological variation, albeit, as noted above, relatively few outliers were removed in this study. Myocardial infarction was not a measured outcome in this cohort of CKD patients. However, in a renal dialysis population, Aakre et al. demonstrated successful use of the RCV to identify patients with acute cardiac events.\(^{33}\) Serial changes in concentration of cTnT exceeded the RCV in all four patients who experienced cardiac events and in three of four patients for cTnI.\(^{33}\) Finally, our samples were stored for up to two years at –80°C prior to analysis. We are unaware of published data supporting storage over this period. However, Egger et al. report good stability over one year at –80°C for both cTnT and cTnI in EDTA plasma, including through two freeze–thaw cycles, measured using the Abbott and Roche assays, respectively, suggesting good stability of these markers.\(^{41}\)

A further consideration is the timescale over which variability is studied to generate the RCV. We have used samples obtained at weekly intervals. Variability over shorter periods of time may be more relevant when addressing the issue of diagnosis of myocardial infarction. Among healthy volunteers, for both cTnT and cTnI, within-subject biological variability does seem to be higher when studies are conducted over periods of days/weeks compared with studies of within-day (hourly) variability.\(^{33,42,43}\) Literature on this point is less clear among patients with kidney disease. Aakre et al. studied variability in haemodialysis patients and observed lower within-subject variability when troponins were studied at 90 min intervals over 6 h (cTnT 1.9% and cTnI 3.3%).\(^{33}\) Conversely, estimates of CV\(_I\) for cTnI obtained by van der Linden et al. from hourly measurements over 24 h in patients with and without CKD were 8.7% and 9.4%, respectively, closer to the results we report in the present study.\(^{36}\) These authors observed that the CV\(_I\) did not differ significantly irrespective of whether hourly, 3-hourly or 6-hourly sampling intervals were considered.\(^{36}\)

In conclusion, we describe the biological variability of cTnT and cTnI in a carefully designed study using...
high-sensitivity assays in patients with moderate CKD. Our data suggest that independent RCVs for cTnI and cTnT should be incorporated into guidance for the interpretation of cardiac troponin in patients with CKD. Furthermore, we recommend that separate positive and negative RCVs should be considered, particularly for cTnI. While not the focus of our study, the same considerations would apply to the use of absolute concentration changes. Research should continue to elucidate reasons for the observed difference in prevalence of increased concentrations of cTnT compared with cTnI in relation to the respective 99th percentile of a healthy reference population, and of the difference in biological variability between the two troponins, which cannot currently be explained.

Acknowledgements
We are grateful to the pathology staff at the Pembury Hospital, Pembury, Kent UK for assistance with the cTnT measurements. We acknowledge Birmingham Clinical Trials Unit for trial coordination and data management, and the Research Governance teams at the University of Birmingham and East Kent University Hospitals NHS Foundation Trust for research governance and Sponsor duties.

Declaration of conficting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The eGFR-C study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme 11/13/01. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. AS and JJD are supported by the NIHR Birmingham Biomedical Research Centre at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham.

Ethical approval
The study had ethical approval (South-East Coast Research Ethics Committee, reference 11/LO/1304).

Guarantor
EJL.

Contributorship
All authors contributed to the design, analysis and production of the article. Laboratory work was undertaken by RAJ.

ORCID iD
EJ Lamb https://orcid.org/0000-0002-5154-7351

Supplemental material
Supplemental material for this article is available online.

References
1. Carter JL, Stevens PE, Irving JE, et al. Estimating glomerular filtration rate: comparison of the CKD-EPI and MDRD equations in a large UK cohort with particular emphasis on the effect of age. QJM 2011; 104: 839–847.
2. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003; 108: 2154–2169.
3. Druke TB and Massy ZA. Atherosclerosis in CKD: differences from the general population. Nat Rev Nephrol 2010; 6: 723–735.
4. Wheeler DC, Townend JN and Landray MJ. Cardiovascular risk factors in predialysis patients: baseline data from the Chronic Renal Impairment in Birmingham (CRIB) study. Kidney Int Suppl 2003; S201–S203.
5. Thompson S, James M, Wiebe N, et al. Cause of death in patients with reduced kidney function. J Am Soc Nephrol 2015; 26: 2504–2511.
6. Baigent C, Burbury K and Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000; 356: 147–152.
7. Matushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010; 375: 2073–2081.
8. Tonelli M, Munster P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet 2012; 380: 807–814.
9. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019; 40: 237–269.
10. Abbas NA, John RI, Webb MC, et al. Cardiac troponins and renal function in nondialysis patients with chronic kidney disease. Clin Chem 2005; 51: 2059–2066.
11. Lamb EJ, Kenny C, Abbas NA, et al. Cardiac troponin I concentration is commonly increased in nondialysis patients with CKD: experience with a sensitive assay. Am J Kidney Dis 2007; 49: 507–516.
12. Lamb EJ, Webb MC and Abbas NA. The significance of serum troponin T in patients with kidney disease: a review of the literature. Ann Clin Biochem 2004; 41: 1–9.
13. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and preven-
14. Parikh RH, Seliger SL and deFilippi CR. Use and interpretation of high sensitivity cardiac troponins in patients with chronic kidney disease with and without acute myocardial infarction. Clin Chem 2015; 48: 247–253.
15. Eggers KM, Lindahl B, Carrero JJ, et al. Cardiac troponins and their prognostic importance in patients with suspected acute coronary syndrome and renal dysfunction. Clin Chem 2017; 63: 1409–1417.
16. Rolfi M, Patrono C, Collet JP, 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.
17. Sauby L, Poulsen TS, Hosbond S, et al. Classification of myocardial infarction: frequency and features of type 2 myocardial infarction. Am J Med 2013; 126: 789–797.
18. Twemerbold R, Wildi K, Jaeger C, et al. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. Circulation 2015; 131: 2041–2050.
19. Fraser CG. Making better use of differences in serial laboratory results. Ann Clin Biochem 2012; 49: 1–3.
20. National Academy of Clinical Biochemistry National Academy of Clinical Biochemistry laboratory medicine practice guidelines: use of cardiac troponin and B-type natriuretic peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute coronary syndromes and heart fail-
21. Mueller M, Biener M, Vafaiia M, 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: 209–218.
22. Lamb EJ, Brettell EA, Cockwell P, et al. The eGFR-C study: accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease-prospective longitudinal study in a multiethnic population. BMC Nephrol 2014; 15: 13.
23. Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007; 53: 766–772.
24. Bartlett WA, Braga F, Carobene A, et al. A checklist for critical appraisal of studies of biological variation. Clin Chem Lab Med 2015; 53: 879–885.
25. Fokkema MR, Herrmann Z, Muskiet FA, et al. Reference change values for brain natriuretic peptides revisited. Clin Chem 2006; 52: 1602–1603.
26. Fraser CG and Harris EK. Generation and application of data on biological variation in clinical chemistry. Crit Rev Clin Lab Sci 1989; 27: 409–437.
27. Cole TJ. Sympercents: symmetric percentage differences on the 100 log(e) scale simplify the presentation of log transformed data. Stat Med 2000; 19: 3109–3125.
28. Roraas T, Petersen PH and Sandberg S. Confidence intervals and power calculations for within-person biological variation: effect of analytical imprecision, number of replicates, number of samples, and number of individuals. Clin Chem 2012; 58: 1306–1313.
29. Burdick RK and Graybill FA. Confidence intervals on variance components. Abingdon: Taylor & Francis, 1992.
30. Rowe C, Sitch AJ, Barratt J, et al. Biological variation of measured and estimated glomerular filtration rate in patients with chronic kidney disease. Kidney Int 2019; 96: 429–435.
31. Wu AHB, Christenson RH, Greene DN, et al. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem 2018; 64: 645–655.
32. Fahim MA, Hayen AD, Horvath AR, et al. Biological variation of high sensitivity cardiac troponin-T in stable dialysis patients: implications for clinical practice. Clin Chem Lab Med 2015; 53: 715–722.
33. Aakre KM, Roraas T, Petersen PH, et al. Weekly and 90-minute biological variations in cardiac troponin T and cardiac troponin I in hemodialysis patients and healthy controls. Clin Chem 2014; 60: 838–847.
34. Mbaga W, Luva A and Lopez B. Biological variation of cardiac troponin in stable haemodialysis patients. Ann Clin Biochem 2015; 52: 562–568.
35. Corte Z, Garcia C and Venta R. Biological variation of cardiac troponin T in patients with end-stage renal disease and in healthy individuals. Ann Clin Biochem 2015; 52: 53–60.
36. van der Linden N, Hilderink JM, Cornelis T, et al. Twenty-four-hour biological variation profiles of cardiac troponin I in individuals with or without chronic kidney disease. Clin Chem 2017; 63: 1655–1656.
37. Apple FS, Sandoval Y, Jaffe AS, et al. Cardiac troponin assays: guide to understanding analytical characteristics and their impact on clinical care. Clin Chem 2017; 63: 73–81.
38. National Institute for Health and Care Excellence. Myocardial infarction (acute): early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnIþ3 assays). 2014; DG15, www.nice.org.uk/guidance/dg15 (accessed 31 January 2020).
39. Klinkenberg LJ, van Dijk JW, Tan FE, et al. Circulating cardiac troponin T exhibits a diurnal rhythm. J Am Coll Cardiol 2014; 63: 1788–1795.
40. Fourrier S, Ijen L, Marques-Vidal P, et al. Circadian rhythm of blood cardiac troponin T concentration. Clin Res Cardiol 2017; 106: 1026–1032.
41. Egger M, Dieplinger B and Mueller T. One-year in vitro stability of cardiac troponins and galectin-3 in different sample types. Clin Chim Acta 2018; 476: 117–122.
42. Wu AH, Lu QA, Todd J, et al. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. Clin Chem 2009; 55: 52–58.
43. Frankenstein L, Wu AH, Hallermayer K, et al. Biological variation and reference change value of high-sensitivity troponin T in healthy individuals during short and intermediate follow-up periods. Clin Chem 2011; 57: 1068–1071.