Biotin interference in high-sensitivity cardiac troponin T testing

ESC European Society of Cardiology
Cardiovascular Research (2019) **115**, 1950–1951
doi:10.1093/cvr/cvz277

RESEARCH LETTER

Biotin interference in high-sensitivity cardiac troponin T testing: a real-world evaluation in acute cardiac care

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Received 21 July 2019; revised 18 September 2019; editorial decision 13 October 2019; online publish-ahead-of-print 30 October 2019

The United States Food and Drug Administration recently issued a safety communication to warn for biotin interference in cardiac troponin assays.[1] Cardiac troponins are the gold standard biomarkers for diagnosing acute myocardial infarction (AMI). Cardiac troponin concentrations can be falsely low in patients using dietary supplements containing high levels of biotin.[1] Since the prevalence of dietary supplement intake is ≥30% in the USA and Europe, substantial clinical concern has risen that AMI might be missed.[1,2] Analytical interference of biotin especially applies to cardiac troponin immunoassays exploiting the biotin–streptavidin interaction in the assay configuration.[3] Therefore, we evaluated the real-world prevalence of biotin interference in high-sensitivity cardiac troponin T (hs-cTnT, Roche Diagnostics, Basel, Switzerland) testing in acute cardiac care.

This analysis included 572 consecutive patients of our acute cardiac care unit over a 3 month period and was carried out according to the principles of the Declaration of Helsinki. This biotin interference analysis was conducted anonymously as part of an assay verification protocol by our clinical laboratory. Hence, no additional patient informed consent was acquired. For a representative characterization of the study population, we refer to the CARMENTA trial (NCT01559467), which was carried out in the same acute cardiac care unit.[4] Lithium-heparin plasma samples were collected for routine hs-cTnT concentration assessment. The hs-cTnT assay has a limit of blank of 3 ng/L, a limit of detection of 5 ng/L, a limit of quantitation of 13 ng/L, and a linear measuring range of 5–10 000 ng/L. To directly assess the effect of biotin-driven hs-cTnT assay interference, hs-cTnT concentrations were assessed before and after biotin depletion using an excessive amount of streptavidin-coated magnetic micro-particles. To validate our biotin depletion protocol, biotin concentrations (IDK® Biotin ELISA, Immundiagnostik AG, Bensheim, Germany) were assessed in a sub-cohort of 100 patients before and after biotin depletion. Considering the applied sample dilution factor (1:2), the biotin ELISA has a limit of blank of 50 ng/L, a limit of detection of 64.8 ng/L, limit of quantitation of 96.2 ng/L, and a linear measuring range of 96.2–2200 ng/L.

Median [inter-quartile range] baseline biotin concentration in the 100 patients sub-cohort was 331 [219–521] ng/L. Our biotin depletion protocol effectively removed almost all free circulating plasma biotin, reducing levels to below the detection limit (96.2 ng/L) in 97% of the samples. In the total population, no detectable biotin-associated bias was observed as absolute hs-cTnT concentration differences (before minus after biotin depletion) were equally distributed around zero (*Figure 1*). A Wilcoxon signed-rank test supported unchanged hs-cTnT values after biotin depletion (11.8 [5.6–24.2] ng/L vs. 11.8 [5.6–24.1] ng/L, $P = 0.95$).

This study is the first to evaluate the real-world prevalence of biotin interference in the hs-cTnT immunoassay in acute cardiac care.

No patient within the sub-cohort showed biotin levels in the range where assay interference would be suspected, suggesting a very low a priori probability of biotin-driven assay interference in this patient group. In our total acute cardiac care unit population, no single case of biotin interference was found as no relevant change in hs-cTnT concentration after biotin depletion was observed in any patient.

Although biotin's potency at high levels to interfere with various immunoassays is undisputed from an analytical perspective, the present analysis shows that biotin interference is in fact rare. In terms of absolute risk, the probability of a missed AMI diagnosis due to biotin interference is lower than other relatively common sources of risks such as blood sample haemolysis, heterophilic antibodies, patient/blood sample misidentification, or even biological variation of cardiac troponin T.[5]

Three limitations of our study merit attention. First, dietary supplement intake information was not collected. However, considering the number of patients included in this analysis and, a dietary supplement intake prevalence of ≥30% in The Netherlands, a substantial population prone for biotin interference in hs-cTnT testing was studied. Second, specific patient groups may receive extremely high-dosages of biotin, e.g. patients with multiple sclerosis and other inflammatory diseases.[3] Even though the risk of a missed AMI diagnosis at a population level may be low, the risk in these specific patient groups is conceivable. Third, we evaluated the effect of biotin interference on the Roche assay only, and

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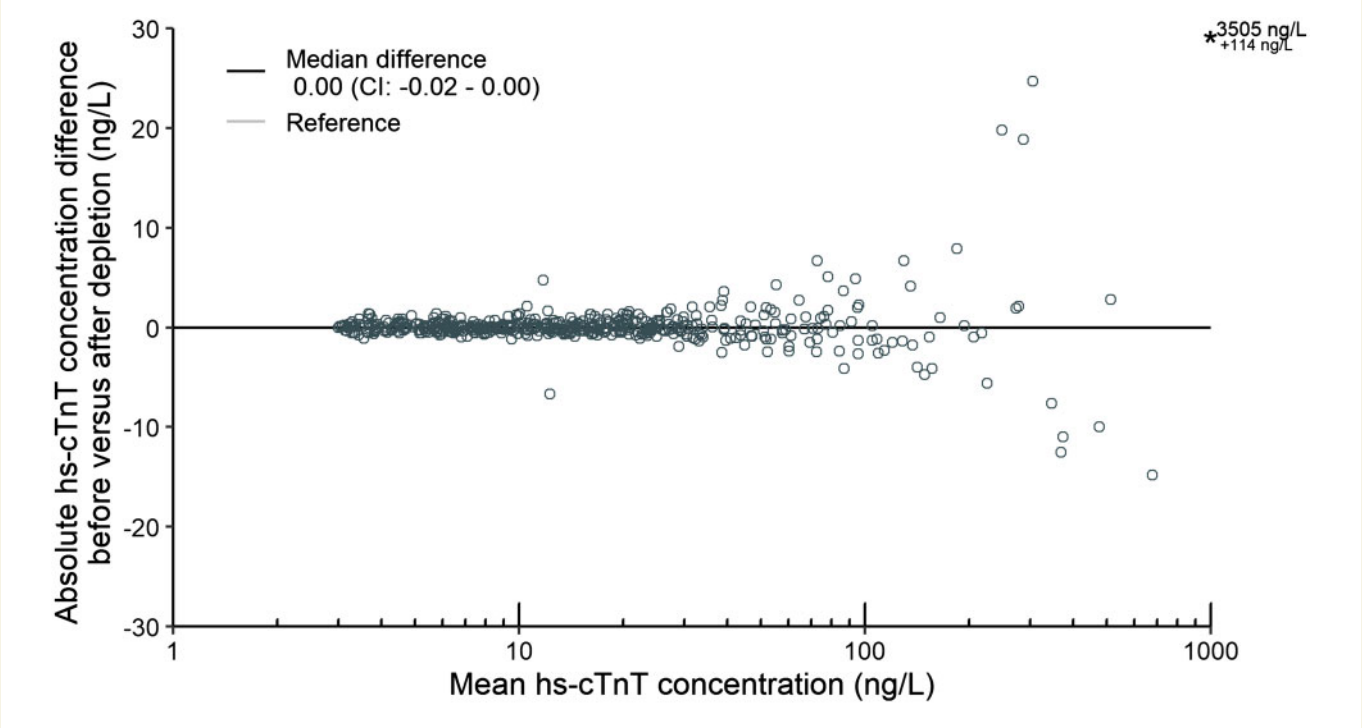

Figure 1 Bland–Altman plot of absolute hs-cTnT concentration differences before and after biotin depletion in 572 patients. The open dots are individual data points. The black line represents the median difference (0.00, 95% CI: -0.02 to 0.00) and the grey line is the reference line.

therefore, we cannot extrapolate these results to assays from other manufacturers employing the biotin–streptavidin detection system. Further research is needed to ensure that the impact of biotin interference is similarly negligible for these assays. In light of these limitations, the recent hs-cTnT immunoassay adjustments to abolish the risk of biotin interference is an important improvement to further minimize risk and maximize the diagnostic accuracy of this pivotal AMI biomarker.

Conflict of interest: none declared.

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