## RESEARCH LETTER

# Kidney Function Specific Reference Limits for N-terminal Pro Brain Natriuretic Peptide and High Sensitivity Troponin T: The Systolic Blood Pressure Intervention Trial

*To the Editor:*

Cardiac-specific biomarkers N-terminal pro brain natriuretic peptide (NT-proBNP) and high sensitivity cardiac troponin T (hsTnT) are widely used for the diagnosis of acute heart failure and myocardial infarction.[1,2] Upper reference limits for NT-proBNP and hsTnT are applied to determine probability of disease and are often derived from the manufacturer's reported 99th percentile upper reference limit or from data reflecting the negative predictive value from select populations.[3,4] The current upper reference limit for hsTnT is 14 ng/L and for NT-proBNP is 125 pg/mL.

Reduced estimated glomerular filtration rate (eGFR) contributes, in part, to elevations in hsTnT and NT-proBNP because of reduced kidney excretion as well as structural heart disease commonly seen in chronic kidney disease (CKD). Elevations in these biomarkers are often discounted as a consequence of reduced eGFR rather than acute heart failure or myocardial infarction, despite the high risk of the latter. While evaluating the Chronic Renal Insufficiency Cohort (CRIC), a CKD population without baseline cardiovascular disease, we found that 40%-88% of participants had concentrations of NT-proBNP and hsTnT above conventional upper reference limits, with greater proportions above the upper reference limit in those in lower eGFR strata.[5] We proposed eGFR-specific thresholds for hsTnT and NT-proBNP using the 95th and 99th percentiles in CRIC.[5] Replicating these thresholds in other CKD populations is necessary to ensure their generalizability. Here, among participants with CKD in the Systolic Blood Pressure Intervention Trial (SPRINT), we determined the proportion of participants who were above the 95th and 99th percentile thresholds developed in CRIC, overall and across eGFR strata.

SPRINT randomized 9,361 hypertensive individuals at increased risk of cardiovascular disease to intensive versus standard systolic blood pressure lowering.[6] Diabetes, proteinuria >1 g/day, eGFR <20 mL/min/1.73 $m^2$, and acute heart failure or known reduced ejection fraction were exclusion criteria. For this analysis, we excluded those with missing NT-proBNP and hsTnT (n = 533), eGFR >60 mL/min/1.73 $m^2$ (n = 6,380), prevalent cardiovascular disease (n = 608) or heart failure (n = 72) at enrollment, leaving an analytic sample size of 1,768 individuals with CKD. NT-proBNP and hsTnT were measured from stored specimens collected at enrollment (using the Roche COBAS 6000 platform).[7] We determined the proportion of SPRINT participants who were above the 95th and 99th percentile thresholds developed in CRIC, overall and across strata by eGFR category.[5] In secondary analyses, we described these proportions across strata of sex, race, and age.[8,9]

Among 1,768 SPRINT participants with CKD, the mean (standard deviation) age was 73 (9) years and mean (standard deviation) eGFR was 46 (10) mL/min/1.73 $m^2$ (Table S1). The distributions of NT-proBNP and hsTnT were higher in lower categories of eGFR (Figure 1). Using a single cut-point for all CKD, the 95th percentile (1,039 pg/mL) and 99th percentile (3,592 pg/mL) CRIC thresholds for NT-proBNP were similar in SPRINT, with 5% and 0.7% of SPRINT participants above these upper reference limits, respectively (Table 1). The CRIC 95th and 99th percentile eGFR-specific thresholds for NT-proBNP were also replicated in SPRINT. In contrast, for hsTnT, the CRIC 95th (58 ng/L) and 99th (126 ng/L) percentile

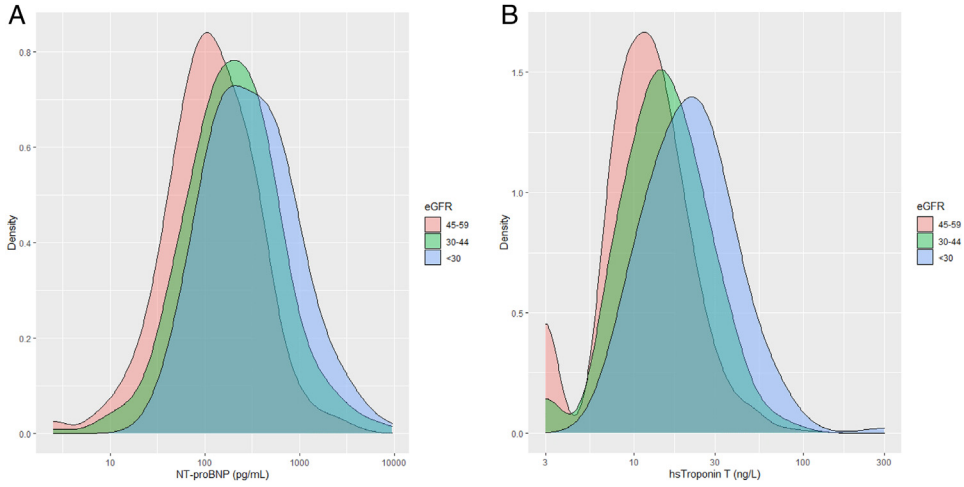


**Figure 1.** Density plots of distribution of (A) NT-proBNP and (B) hsTnT across eGFR strata (mL/min/1.73 $m^2$). Abbreviations: hsTnT; high sensitivity Troponin T; NT-proBNP, N-terminal pro brain natriuretic peptide.

**Table 1.** Proportion of SPRINT CKD Participants Above CRIC 95th and 99th percentiles for NT-proBNP and hsTnT

| | | NT-proBNP | | | | hsTnT | | | |
|---|---|---|---|---|---|---|---|---|---|
| Category | N | CRIC 95th percentile threshold (pg/mL) | n (%) >95th percentile in SPRINT | CRIC 99th percentile threshold (pg/mL) | n (%) >99th percentile in SPRINT | CRIC 95th percentile threshold (ng/L) | n (%) with >95th percentile in SPRINT | CRIC 99th percentile threshold (ng/L) | n (%) with >99th percentile in SPRINT |
| Overall | 1,768 | 1,039 | 81 (5%) | 3,592 | 12 (0.7%) | 58 | 23 (1%) | 126 | 1 (0.1%) |
| eGFR (mL/min/1.73 $m^2$) | | | | | | | | | |
| <30 | 157 | 2,523 | 6 (4%) | 8,402 | 1 (0.6%) | 93 | 2 (1%) | 219 | 1 (0.6%) |
| 30-44 | 529 | 1,130 | 35 (7%) | 2,921 | 8 (1.5%) | 59 | 6 (1%) | 127 | 0 (0%) |
| 45-59 | 1082 | 682 | 50 (5%) | 1,887 | 12 (1.1%) | 43 | 23 (2%) | 97 | 1 (0.1%) |

Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; hsTnT, high sensitivity Troponin T; NT-proBNP, N-terminal pro brain natriuretic peptide; SPRINT, Systolic Blood Pressure Intervention Trial.

thresholds identified 1% and 0.1% of SPRINT participants above the upper reference limits, respectively (Table 1). Findings were similar using the CRIC eGFR stratum-specific thresholds. Findings were similar by sex, race, and age (Table S2).

We applied the 95th and 99th percentile thresholds for NT-proBNP and hsTnT developed in a relatively healthy ambulatory CKD cohort measured at a time of clinical stability to the SPRINT CKD population and found similar proportions above these thresholds for NT-proBNP. The proposed thresholds for hsTnT did not replicate, perhaps because of differences in the study populations (SPRINT participants were older, had higher systolic blood pressure, and did not have diabetes). There remains uncertainty on how to best apply the current upper reference limits of NT-proBNP and hsTnT for the diagnosis of acute cardiac disease in CKD, despite associations of elevated NT-proBNP and hsTnT with outcomes in CKD.[10] These data may inform development of eGFR-specific thresholds for cardiac biomarkers to identify acute heart failure or myocardial infarction in patients with a broad range of eGFRs presenting with acute symptoms.

Strengths of this study include use of a well-characterized clinical trial population and standardized measurement of cardiac biomarkers. The limitations include a small number of participants in specific eGFR strata. The Roche platforms used to measure the biomarkers were different in SPRINT relative to CRIC; however, this would not substantially influence results at the 95th and 99th percentiles. We studied a population with hypertension and without diabetes, which may explain some of the differences observed with the hsTnT thresholds. Both CRIC and SPRINT excluded persons with eGFR <20 mL/min/1.73 $m^2$.

In conclusion, the 95th and 99th percentile thresholds for NT-proBNP developed in CRIC across eGFR strata were similar in SPRINT participants with CKD. However, the CRIC hsTnT thresholds did not replicate, and larger studies are needed to identify eGFR-specific hsTnT thresholds. Further work is needed to validate eGFR-specific thresholds for cardiac biomarkers in patients presenting with acute symptoms to evaluate their accuracy for the diagnosis of acute heart failure and myocardial infarction in patients with a broad range of eGFRs.

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## SUPPLEMENTARY MATERIAL

**Supplementary File (PDF)**

**Table S1:** Baseline Characteristics of SPRINT Participants With CKD by Baseline eGFR Categories (mL/min/1.73 $m^2$)

**Table S2:** Proportion of SPRINT CKD Participants Above CRIC 95th and 99th Percentiles for NT-proBNP and Troponin T, Across Strata of Sex, Race, and Age

## ARTICLE INFORMATION

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**Support:** This work was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK103612 to Dr Bansal and R01DK098234 to Drs Ix and Shlipak) and National Heart Lung and Blood Institute (R01HL144122 to Dr Berry), as well as an unrestricted fund from the Northwest Kidney Centers. Roche provided in-kind support of materials for biomarker assays for this study. The funders of this study did not have a role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

**Financial Disclosure:** The authors declare that they have no relevant financial interests.

**Peer Review:** Peer Review: Received April 4, 2022 as a submission to the expedited consideration track with 3 external peer reviews. Direct editorial input from the Statistical Editor and the Editor-in-Chief. Accepted in revised form May 22, 2022.

 Published online July 7, 2022 with doi 10.1016/j.xkme.2022.100517

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