Letters

RESEARCH LETTER

Use of High-Sensitivity Cardiac Troponin in Patients With Kidney Impairment: A Randomized Clinical Trial

High-sensitivity cardiac troponin (hs-cTn) assays have improved the diagnosis of myocardial infarction in patients with healthy kidney function and are now widely used in clinical practice. However, in patients with kidney impairment, long-term elevations in troponin levels are common, and interpretation can be more challenging. As such, the effect of implementing hs-cTn testing on the diagnosis and outcomes of patients with kidney impairment is uncertain.

Methods | High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome (High-STEACS) was a stepped-wedge, cluster-randomized clinical trial that evaluated the use of a hs-cTn assay in consecutive patients with suspected acute coronary syndrome across 10 hospitals (NCT01852123) (Supplement 1; eAppendix in Supplement 2). The trial was conducted in accordance with the Declaration of Helsinki and with the approval of the Scotland Research Ethics Committee, the Public Benefit and Privacy Panel for Health and Social Care, and each National Health Service Health Board. As randomization was at the hospital level, individual patient consent was not sought. Throughout the trial, cTnI was measured using contemporary and high-sensitivity assays (ARCHITECT STAT; Abbott Laboratories). Before use, results from the hs-cTnI assay were suppressed, and the contemporary assay (single threshold based on the coefficient of variation) guided care. Sites were then randomly assigned to early or late use of hs-cTnI testing, for which results from the contemporary assay were suppressed and care was guided by the hs-cTnI assay with sex-specific 99th percentile diagnostic thresholds.

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Kidney impairment was defined as an eGFR of less than 60 mL/min/1.73 m². In this prespecified secondary analysis, the primary outcome of subsequent type I or 4b myocardial infarction following the index presentation or cardiovascular death within 1 year was compared before and after implementation of the hs-cTnI assay in all patients with elevated hs-cTnI concentrations and in the subgroup of patients reclassified by hs-cTnI testing with normal contemporary troponin concentrations, as stratified by eGFR (<60/≥60 mL/min/1.73 m²) using Cox models that were adjusted for age, sex, phase, hospital site (random effect), seasonality, presentation date, diabetes, ischemic heart disease or cerebrovascular disease, hs-cTnI concentrations, and deprivation status. Statistical analysis was performed in R, version 3.6.1 (R Foundation). A 2-sided P value of less than .05 was considered to indicate statistical significance.

Results | Across both phases, hs-cTnI concentrations were elevated in 10,111 of 46,927 patients (22%; mean [SD] age, 71 [15] years; 48,533 women [48%]), of whom 42,20 (42%) had kidney impairment. The proportion of patients with elevated hs-cTnI concentrations increased as kidney function declined, from 10% (1,911 of 19,763) at an eGFR of 90 or greater to 66% (1,171 of 1,766) at an eGFR of less than 30 mL/min/1.73 m² (P < .001) (Figure, A). In contrast, the proportion of patients with type 1 myocardial infarction decreased from 74% (1,261 of 1,709) to 35% (328 of 934) (P < .001) (Figure, B).

Following the use of hs-cTnI testing, the proportion of patients with an elevated troponin increased from 37% (1,386 of 3,721) to 47% (2,503 of 5,359) and from 13% (1,918 of 14,686) to...

Figure. Myocardial Injury and Myocardial Infarction (MI) in Patients With Kidney Impairment

A, Number of patients with high-sensitivity cardiac troponin concentrations above and below the sex-specific 99th percentile across the entire study population (n = 46,927) according to estimated glomerular filtration rate (eGFR). B, Frequency of adjudicated diagnoses in patients with high-sensitivity cardiac troponin concentrations above the sex-specific 99th percentile (n = 10,111), according to eGFR.
While the frequency of elevated hs-cTnI concentrations increased 6-fold as kidney function declined from an eGFR of 90 or greater to less than 30 mL/min/1.73 m², the proportion attributable to type 1 myocardial infarction halved. Although hs-cTnI is effective at enabling the early rule out of myocardial infarction in patients with kidney impairment, its use did not improve outcomes in patients with elevated levels whether they had kidney impairment or not. The reasons for this are complex. Two-thirds of patients with kidney impairment and elevated hs-cTnI concentrations had a diagnosis other than type 1 myocardial infarction. In the absence of evidence from randomized trials, there is little guidance to inform clinical decisions for this heterogeneous group. Moreover, for those with kidney impairment and type 1 myocardial infarction, the available evidence is largely extrapolated from clinical trials in patients with broadly normal kidney function. Further research is therefore needed to convince clinicians of the safety and efficacy of these treatments in patients with kidney impairment. A limitation of this study is that it was not possible to discriminate between acute and chronic kidney injury. While both are associated with cardiovascular risk, these conditions are distinct. Following the use of hs-cTnI testing in clinical practice, 1 in 2 patients with kidney impairment had an elevated troponin concentration, but these were less likely due to myocardial infarction, and outcomes did not improve.

Peter J. Gallacher, MD
Eve Miller-Hodges, MD
Anoop S.V. Shah, MD
Atul Anand, MD
Neeraj Dhaun, MD
Nicholas L. Mills, MD
for the High-STEACS Investigators

Author Affiliations: BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, Scotland (Gallacher, Miller-Hodges, Shah, Anand, Dhaun, Mills); Department of Renal Medicine, Royal Infirmary of Edinburgh, Edinburgh, Scotland (Miller-Hodges, Dhaun); London School of Hygiene and Tropical Medicine, London, England (Shah); Usher Institute, University of Edinburgh, Edinburgh, Scotland (Mills).

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Corresponding Author: Nicholas L. Mills, MD, BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh EH16 4SA, United Kingdom (nick.mills@ed.ac.uk).

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Concept and design: All authors.

| Characteristic | No. (%) | Overall | Overall | Overall | Overall | Overall |
|----------------|---------|---------|---------|---------|---------|---------|
|                | eGFR, mL/min/1.73 m² | Before Use | Use | After Use | Use | Overall |
| No. of participants | 4220 | 1717 | 2503 | 5891 | 2281 | 3610 | 10 111 |
| Primary outcome | | | | | | | |
| MI or cardiovascular death | 1016 (24) | 426 (25) | 590 (24) | 686 (12) | 293 (13) | 393 (11) | 1702 (17) |
| Secondary outcomes | | | | | | | |
| MI | 313 (7) | 129 (8) | 184 (7) | 357 (6) | 168 (7) | 189 (5) | 670 (7) |
| Unplanned revascularization | 116 (3) | 44 (3) | 72 (3) | 283 (5) | 114 (5) | 169 (5) | 399 (4) |
| All-cause death | 1500 (36) | 662 (39) | 838 (34) | 808 (14) | 353 (16) | 455 (13) | 2308 (23) |
| Death of cardiovascular causes | 785 (19) | 330 (19) | 455 (18) | 367 (6) | 143 (6) | 224 (6) | 1152 (11) |
| Death of cardiac causes | 630 (15) | 261 (15) | 369 (15) | 294 (5) | 113 (5) | 181 (5) | 924 (9) |
| Hospital admission for heart failure | 601 (14) | 250 (15) | 351 (14) | 396 (7) | 195 (9) | 201 (6) | 997 (10) |
| Ischemic stroke | 95 (2) | 47 (3) | 48 (2) | 100 (2) | 50 (2) | 50 (1) | 195 (2) |
| Safety end points | | | | | | | |
| Major hemorrhage | 43 (1) | 21 (1) | 22 (1) | 57 (1) | 22 (1) | 35 (1) | 100 (1) |
| Unplanned hospital admission at 30 d | 1158 (27) | 537 (31) | 621 (25) | 1805 (31) | 820 (36) | 985 (27) | 2963 (29) |
| Noncardiovascular death | 715 (17) | 332 (19) | 383 (15) | 440 (8) | 210 (9) | 230 (6) | 1155 (11) |

Abbreviations: eGFR, estimated glomerular filtration rate; hs-cTnI, high-sensitivity cardiac troponin; MI, myocardial infarction.

a Subsequent type 1 or type 4b MI.

b Defined as urgent or emergency percutaneous coronary intervention or coronary artery bypass grafting from discharge to 1 year later.

c Bleeding Academic Research Consortium type 3 or type 5.

d Excludes type 1 or type 4b MI.
Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Gallacher, Miller-Hodges, Dhaun, Mills.

Critical revision of the manuscript for important intellectual content: Shah, Anand, Dhaun, Mills.

Statistical analysis: Gallacher, Dhaun.

Obtained funding: Mills.

Administrative, technical, or material support: Miller-Hodges, Anand, Mills.

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Invited Commentary

High-Sensitivity Cardiac Troponin Assay in Patients With Kidney Impairment: A Challenge to Clinical Implementation

High-sensitivity cardiac troponin (hs-cTn) assay was approved by the US Food and Drug Administration in 2017, and its appropriate use is currently being investigated. In this issue of JAMA Internal Medicine, Gallacher et al examine the use of hs-cTn assays in patients with kidney impairment in a prespecified secondary analysis of a randomized clinical trial of patients with suspected acute coronary syndrome (ACS). Their major finding is that while the frequency of elevated levels of hs-cTn increases as kidney function deteriorates, two-thirds of patients with kidney impairment and elevated hs-cTn concentrations do not have a type 1 myocardial infarction (MI related to coronary thrombosis). Despite the discovery of more patients with elevated troponin levels by hs-cTn assays, 1-year rates of a type 1 MI or type 4B MI (occurring ≤48 hours after percutaneous coronary intervention) or cardiovascular death were unchanged before and after implementation of hs-cTn testing in patients with and without kidney impairment.

The scale of the challenge of hs-cTn testing implementation, combined with the challenge of interpreting elevated hs-cTn values in patients with conditions that may produce an elevated hs-cTn value not directly related to acute myocardial injury (such as kidney impairment), is difficult to overstated. Acute coronary syndrome is the leading cause of worldwide mortality and morbidity, and chest pain—a symptom that often triggers an ACS workup—is the second most frequent reason for all US emergency department (ED) visits. Although a minority of chest pain ED visits are related to ACS, the rate of missed ACS after an ED evaluation is 2% to 4% and is associated with doubled mortality. Perhaps unsurprisingly, missed ACS remains the top reason for malpractice claims against ED physicians. Thus, there are enormously high stakes, both clinically and medicolegally, for appropriate evaluation of patients with chest pain and use of hs-cTn testing to improve efficiency of diagnosis and treatment without increasing unnecessary testing and admissions.

This analysis by Gallacher et al highlights the need for thoughtful use of hs-cTn testing, particularly in patients with kidney impairment. While hs-cTn testing has acceptable sensitivity as part of a workup to rule out MI, kidney impair-
ment poses a particular challenge. Decreased kidney clearance of troponin often results in elevated serum levels that do not reflect true myocardial injury. However, patients with kidney disease are at elevated risk for cardiovascular disease, and kidney disease is often comorbid with conditions that are cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes. Thus, there is a need to accurately detect myocardial injury in this high-risk population, but the lower specificity of hs-cTn testing compared with conventional troponin assays for all populations has the potential to trigger unnecessary stress tests, angiorgrams, coronary revascularization procedures, and admissions for all patients, and this potential is particularly high in the population with kidney impairment. Despite these challenges, it is not operationally feasible to use different troponin assays (conventional vs high sensitivity) for different patient populations; therefore, this topic is pressing.

The hope for hs-cTn assays was both to enable earlier diagnosis of acute MI (type 1) than by conventional troponin assays and to reduce costs and improve efficiency by allowing more rapid discharge of low-risk patients, thereby helping to relieve strained ED and hospital capacity by safely reducing the number of patients with suspected ACS who are admitted or observed for serial troponin measurements and provocative cardiac testing. Many EDs have adopted protocols to expedite diagnostics, such as laboratory or radiographic testing. These protocol-driven evaluations, such as standing nurse-driven chest pain triage protocols or physician-in-triage models, have led to overuse of troponin assays in patients with low pretest probability of ACS. Adoption of hs-cTn testing means that more patients—most who do not have ACS—will have a falsely positive troponin result and undergo protocol-driven but unnecessary additional testing or observation, particularly patients with kidney impairment, as shown by Gallacher et al. Thus, adoption of hs-cTn assays may increase resource utilization, including admission or observation, stress testing, and cardiology consultation, without benefit to patient outcomes.

While much of the analysis on this topic centers on an outcome of type 1 MI, the problem of elevated hs-cTn values in patients with kidney impairment poses another challenge for the ED physician: the diagnosis of type 2 MI (associated with mismatches in myocardial oxygen supply and demand, rather than coronary thrombosis) in patients with kidney impairment and, in particular, when to treat patients with myocardial oxygen supply-and-demand mismatch with heparin. While this same problem existed prior to use of hs-cTn assays, the relative increase in the proportion of patients with kidney impairment who have elevated cardiac troponin values increases with hs-cTn testing compared with conventional troponin testing, meaning that the scale of this question is greater. Does the clinician obtain serial values to determine the delta, in which case the patient is at risk for further myocardial damage during this interval? Or does the clinician initiate anticoagulation, and all the risks entailed therein, in a patient whose diagnosis is not yet clear? There is little established guidance on these questions. While serial measurements will be crucial in patients with kidney impairment to determine the delta (or lack thereof) between the first and second troponin measurements and therefore help to rule in or rule out MI, the question of whether to make a diagnosis of type 2 MI after a single hs-cTn measurement in a patient with kidney impairment presenting with chest pain currently has no clear answer. Clinicians will have to rely on the pretest probability of myocardial injury, incorporating risk factors, medical history, and clinical gestalt, in making these early diagnostic and treatment decisions.

The pressing question seems not to be how to interpret a single hs-cTn value in a patient with kidney disease suspected to have ACS, but rather to selectively order troponin testing in patients with higher pretest likelihood of ACS and how to integrate hs-cTn testing into the broader workup of such patients. These questions include whether and at what interval to obtain serial hs-cTn values, how to interpret the change in value when obtaining serial hs-cTn measurements, and how to weigh clinical factors, such as the patient’s age, comorbidities, prior history of cardiovascular or cerebrovascular disease, history and physical examination findings, and electrocardiogram changes.

While the optimal strategy for management of myocardial injury without ACS is unknown, it is clear that elevated troponin levels are strongly related to increased long-term mortality. Without a clearer understanding of elevated hs-cTn values in patients with kidney impairment and alternative risk stratification tools that are easily implemented in the ED environment, such as a modified HEART score adapted to this population, the clinical and medicolegal risks associated with missed myocardial injury still favor a conservative approach of increased testing and closer monitoring for those with elevated hs-cTn results.

Gallacher et al highlight the challenges that accompany determining the appropriate use of hs-cTn assays. Further research focused on the performance characteristics of comprehensive strategies to rule in and rule out suspected MI in patients with kidney impairment, with an emphasis on composite cardiac outcomes, is necessary to guide clinical implementation.

Keith C. Hemmert, MD
Benjamin C. Sun, MD, MPP

Author Affiliations: Department of Emergency Medicine, University of Pennsylvania, Philadelphia (Hemmert); Department of Emergency Medicine and the Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia (Sun).

Corresponding Author: Benjamin C. Sun, MD, MPP, Department of Emergency Medicine and the Leonard Davis Institute of Health Economics, University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104 (benjamin.sun@pennmedicine.upenn.edu).

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**Effectiveness of Tocilizumab in Patients Hospitalized With COVID-19: A Follow-up of the CORIMUNO-TOCI-1 Randomized Clinical Trial**

Eight randomized clinical trials of tocilizumab for treating patients with COVID-19 have reported heterogeneous results. Although 4 of them achieved their primary end point, improved 28-day survival was demonstrated only in the 2 largest studies and those with the highest mortality, RECOVERY and REMAP-CAP. Moreover, only RECOVERY enrolled only patients with elevated C-reactive protein (CRP) levels. The RECOVERY and REMAP-CAP trials involved a high rate of patients using dexamethasone (>80% of the patients in both treatment arms). Differences in trial outcomes may be associated with differences in power, populations, design, management, or length of follow-up.

We previously published a trial of tocilizumab in hospitalized patients who were receiving oxygen (rate, ≥3 L/min) but did not require high-flow or mechanical ventilation. The study met its primary composite end point, which was the proportion of patients who required noninvasive ventilation or intubation or who died at day 14, but found no survival difference at day 28. In this follow-up article, we extended follow-up to 90 days and examined whether survival varied with baseline CRP levels.

**Methods** The details of the trial have been previously reported (Supplement 1 and Supplement 2). Institutional review board approval was provided by Comités de Protection des Personnes Île-de-France VI, and written informed consent was gained. In this follow-up article, we compared survival at 3 months using random-effects Cox models that were adjusted for age at randomization and center. We performed a post-hoc analysis that was stratified by CRP. Statistical analyses were conducted using R, version 3.6.4 (R Foundation).

**Results** By day 90, death had occurred in 7 of 63 (11%) and 11 of 67 patients (18%) in the tocilizumab and usual care arms, respectively (adjusted hazard ratio [HR], 0.64; 95% CI, 0.25-1.65) (Figure). When outcomes were analyzed according to CRP levels, we found a statistical interaction between CRP levels and the primary composite end point at day 14 and survival at day 90, with a benefit of tocilizumab in patients if their CRP levels were greater than 15.0 mg/dL (to convert to mg/L, multiply by 10), but not if CRP levels were 15.0 mg/dL or less. In patients with CRP levels greater than 15.0 mg/dL, the chance of achieving the primary end point (the percentage of pa-