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Role for Cystatin C–Based Risk Stratification for Patients After Acute Coronary Syndrome in the Era of High Sensitivity Cardiac Troponin Assays

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Renal dysfunction plays a fundamental role in the physiopathological characteristics of cardiovascular diseases. Impaired renal function in heart failure and coronary heart disease correlates independently with higher risk of death and hospitalization.[1] Renal function evaluation is a primary feature when studying comorbidities in a cardiovascular disease population. In patients with coronary heart disease and especially in a population with acute coronary syndrome (ACS), even mild stages of renal dysfunction are associated with an increased risk of death and other cardiovascular events independent of other risk factors.[2] To assess renal function, estimated glomerular filtration rate (eGFR), generally a serum creatinine (SCr)–based, formula is recommended unless there are circumstances that may affect the accuracy of the eGFR with creatinine. In such instances, the measurement of eGFR with a cystatin C–based equation may be more accurate.[3]

Cystatin C is a low-molecular-weight protein (a member of the family of papainlike cysteine proteinase inhibitors) expressed in all nucleated cells, with essentially a constant quantity produced over time. It is filtered by the glomerular basement membrane, almost completely reabsorbed in the proximal tubular ducts, and then catabolized.[4] Cystatin C concentration versus SCr is less affected by demographic features (age and sex) and cardiovascular comorbidities and medical conditions (except for thyroid illness). In practice, cystatin C has been identified during the past 15 years as a valuable estimator of GFR, comparable to SCr in the population at large and slightly superior to SCr eGFR calculations in the population with mildly impaired GFR.[3] For these reasons, there has been an interest to determine if a cystatin C–based eGFR would be more accurate for prognostication in patients with coronary heart disease. Multiple studies spanning from "at-risk" individuals, such as older adults, to those presenting with ACS have demonstrated that cystatin C is strongly associated with all-cause mortality, independent of SCr levels.[5–7] Cystatin C is also an independent predictor of major adverse cardiovascular events, in addition to the natriuretic peptides, in studies of patients with ACS[8] and in those with stable coronary heart disease.[9] Furthermore, cystatin C–based eGFR calculations may have particular prognostic advantages when substituted for SCr-based eGFR in the well-established GRACE (Global Registry of Acute Coronary Events) score.[10] The Table is a summary of ACS studies using cystatin C as a prognosticator for major adverse cardiovascular events that typically include in their multivariate models conventional cardiac troponin (cTn) assay results and natriuretic peptides when available.[6,11–14]

Unlike conventional or sensitive cTn results, cTn measured by a high sensitivity assay is measurable in most of a healthy population. High sensitive cTn assays have been evaluated in clinical trials for >10 years, are commonly used in clinical practice throughout the world, and were recently approved by the US Food and Drug Administration for use in the United States. B-type natriuretic peptide and NT-proBNP (N-terminal pro-B-type natriuretic peptide) are also 2 nearly ubiquitously available cardiac-specific biomarkers in clinical practice; although predominantly used to diagnose and prognosticate heart failure, they have been shown to be independent prognosticators in patients with ACS.[15] Therefore, the SOLID-TIMI 52 (Stabilization of plaques usIng Darapladib-Thrombolysis in Myocardial Infarction) substudy by Correa et al in this issue of the *Journal of the American Heart Association (JAHA)*, inclusive of 4965 (predefined biomarker subset) from a total 13 026 patients enrolled with ACS within 30 days, who had cystatin C and both an hs-cTnI and NT-proBNP measured, represents an important update to contemporary practice to the studies noted

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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J Am Heart Assoc. 2018;7:e010589. DOI: 10.1161/JAHA.118.010589.

Table. Cystatin C as a Predictor of Adverse Events in ACS: Major Studies

ACS Study	Year of Publication	Size Sample	End Points	Results
Plasma cystatin C for prediction of 1-y cardiac events in Mediterranean patients with non–ST-segment elevation ACS: SIESTA[6]	2010	525	Composite of cardiovascular death, nonfatal MI, and unstable angina requiring admission during 1 y of follow-up	Multivariable analysis HR, 1.08 (95% CI, 0.75–1.56) for cystatin C as a continuous variable
Cystatin C as a predictor for adverse outcome in patients with ST-segment–elevation and non–ST-segment–elevation ACS in the PLATO study[11]	2012	16 402	Risk of cardiovascular death or MI during 1 y of follow-up	Multivariable-adjusted HR per SD, 1.10 (95% CI, 1.03–1.17; P=0.0488); not statistically different than $eGFR_{Cr}$ in risk stratification
Cystatin C is a novel predictor of outcome in suspected or confirmed non–ST-segment –elevation ACS[12]	2004	726	Mortality and recurrent MI	In multivariable-adjusted models, cystatin C level was independently associated with mortality but not with the risk of subsequent MI; cystatin C was superior to SCr for mortality prognostication
Cystatin C for enhancement of risk stratification in patients with non–ST-segment–elevation ACS with an increased troponin T[13]	2009	1128	Mortality and recurrent MI	Third vs first tertile, adjusted HR for mortality, 2.04 (95% CI, 1.02–4.10; P=0.04); and for MI, 1.95 (95% CI, 1.05–3.63); not evaluated vs SCr or $eGFR_{Cr}$
Comparison of the long-term prognostic value of cystatin C to other indicators of renal function among patients with ACS[14]	2009	160	MACE (cardiac death, nonfatal MI, or unstable angina) within 12 mo of follow-up	Adjusted RR (per log), 9.43 (95% CI, 4.0–21.8; P<0.001); cystatin C discrimination by C-statistic superior to SCr

ACS indicates acute coronary syndrome; CI, confidence interval; $eGFR_{Cr}$, estimated glomerular filtration rate calculated with creatinine; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; PLATO, Platelet Inhibition and Patient Outcomes study; RR, risk ratio; SCr, serum creatinine; SIESTA, Systemic Inflammation Evaluation in patients with NSTE-ACS.

in the table with the inclusion of hs-cTn.[16] The primary end point for this analysis was a composite outcome of cardiovascular death or hospitalization for heart failure. The objective was to assess whether cystatin C remained an independent prognosticator in this contemporary cohort after incorporating the cardiac-specific assays hs-cTnI and B-type natriuretic peptide as well as an additional prognostic renal biomarker, fibroblast growth factor-23. Correa et al[16] found that despite the expected strong correlation between cystatin C and SCr concentrations (r=0.60, P<0.0001), cystatin C was a superior prognosticator to SCr. For example, in a fully adjusted model including the cardiac biomarkers, cystatin C remained a significant prognosticator for cardiovascular death and heart failure hospitalization (adjusted hazard ratio for quartile 4: quartile 1–quartile 3, 1.34; 95% confidence interval, 1.01–1.77; P=0.04). In contrast, eGFR calculated with SCr was not a predictor of this combined end point. Furthermore, using the C-statistic to measure improvement in model discrimination for this combined end point, a rigorous and recommended measure when assessing prognosis with a novel biomarker,[17] cystatin C added significantly, all be it modestly, to the area under the curve when included in an otherwise fully adjusted model, but eGFR calculated with SCr did not. The results from SOLID-TIMI 52 add important incremental knowledge about the independent prognostic information associated with cystatin C in a contemporary ACS cohort, but a couple questions remain. First, the authors evaluated other biomarkers in their multivariate model as dichotomous, and not as continuous variables. A biomarker such as hs-cTn has prognostic information contained throughout a spectrum of concentrations, even near the limit of detection.[18] This choice of dichotomization of the other biomarkers for statistical modeling could have overestimated the prognostic value of cystatin C in the risk assessment of the population when including these other powerful prognostic biomarkers. In contrast, in an earlier publication evaluating fibroblast growth factor-23 within the same cohort, cystatin C, hs-cTnI, hs-C-reactive protein, and B-type natriuretic peptide were evaluated as log-transformed continuous variables.[19] For comparing the relative merits of these 2 different renal biomarkers, it would be potentially ideal to maintain consistency when modelling the biomarkers. Second, although cystatin C demonstrates a potentially important role in renal function evaluation,[20] its adaptation as a prognostic factor after an ACS event, a domain with well-established prognostic biomarkers, will ultimately be driven by finding a novel role when used in isolation or at least when combined with other biomarkers to guide therapy to improve outcomes.

In conclusion, measurement of cystatin C provides an accurate blood-based measurement to estimate GFR. The findings from SOLID-TIMI 52 using a contemporary post-ACS cohort and incorporating hs-cTn results represents an important update and suggest that, although cystatin C could

provide incremental prognostic information compared with eGFR calculated with SCr, this appears to have only a marginal usefulness in stratifying risk for patients with ACS. Further work will need to be done to determine if cystatin C could ultimately better classify patients with ACS versus SCr when incorporated into composite risk scores, such as the GRACE score in the era of hs-cTn, but for now cystatin C has not yet found its place on the front lines of ACS patient management.

Disclosures

deFilippi has research grants through Inova, his employer, from Siemens Healthcare Diagnostics, Roche Diagnostics, Abbott Diagnostics, Ortho Diagnostics, and FujiRebio. He also directly receives consulting/honorarium/end point committee/royalty payments from Siemens Healthcare Diagnostics, Alere/Abbott Diagnostics, FujiRebio, Radiometer, Roche Diagnostics, Ortho Diagnostics, Metabolomics, Quintiles, WebMD, and UpToDate. Latta has no disclosures to report.

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Key Words: Editorials • cystatin C • myocardial infarction • renal function • troponin