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- Counterpoint -

Detection of Myocardial Infarction—Is It All Troponin? Role of New Markers

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It has become good scientific practice to mention potential conflicts at the beginning of the presentation. My main conflict related to this topic is that I love cardiac troponin, for the very reasons listed by Giannitsis and Katus *(1)*. Cardiac troponin is beyond a doubt the most important biomarker in cardiovascular medicine, even more so after the clinical introduction of sensitive assays *(1–6)*. For the detection of acute myocardial infarction (AMI),[2] the room for additional biomarkers, if any, seems to be small and restricted to add-on applications to be used in conjunction with cardiac troponin, clinical assessment, and the 12-lead electrocardiogram. Clinical settings in which there are still unmet needs include: (*a*) the early diagnosis of AMI, (*b*) differentiation of type I and type II AMI, and (*c*) risk stratification for death or recurrent AMI.

Cardiac troponins are structural proteins. Their detection in peripheral blood indicates cardiomyocyte damage and likely cell death *(1–7)*. Invariably, there is some time delay between the onset of AMI (coronary plaque rupture and coronary occlusion) and the appearance of cardiac troponin in the peripheral circulation. Because cardiac troponin signals cardiomyocyte damage regardless of the underlying cause, multiple nonischemic conditions can challenge the interpretation of increases in cardiac troponin, particularly mild ones *(1, 7)*. Thus, we could benefit from information provided by additional biomarkers that (*a*) reflect myocardial ischemia (not necrosis), (*b*) indicate plaque rupture or other signals present at the very onset of AMI (e.g., endogenous stress), or (*c*) are associated with a specific pathobiology present in only a subset of AMI patients, thereby allowing more personalized and targeted patient management. Recent evidence suggests that markers fulfilling at least some of these properties might soon become clinically available.

Copeptin, the C-terminal part of the vasopressin prohormone, is secreted stoichiometrically with arginine-vasopressin from the neurohypophysis. The fact that copeptin is a stable analyte eliminates some previous limitations and difficulties in assessing the arginine-vasopressin system. Copeptin concentrations seem to quantify the individual endogenous stress level in multiple medical conditions, including AMI *(8–10)*. Given that endogenous stress is present at the very onset of AMI, we and others have hypothesized that the combination of a marker of cardiomyocyte damage such as cardiac troponin with a pathophysiologically different biomarker reflecting acute endogenous stress, such as copeptin, might allow a means to rapidly and accurately rule out AMI at initial presentation without serial blood sampling and thereby overcome the sensitivity deficit of cardiac troponin. Support for this hypothesis was obtained independently in 2 multicenter studies *(9, 10)*. In the first study, copeptin was significantly higher in AMI patients than in patients with other diagnoses (median, 20.8 pmol/L vs 6.0 pmol/L; $P < 0.001$). The combination of cardiac troponin T (cTnT) (fourth-generation assay) and copeptin at initial presentation produced an area under the ROC curve of 0.97 (95% CI, 0.95–0.98), which was significantly higher than the 0.86 value (95% CI, 0.80–0.92) for cTnT alone ($P < 0.001$) *(9)*. In the second study, the area under the ROC curve based on measurements taken at presentation was 0.84 for cTnT alone and 0.93 for the combination of cTnT and copeptin ($P < 0.001$) *(10)*. Copeptin also provided incremental value when combined with cTnI measured with the Siemens Ultra assay ($P < 0.05$). The negative predictive value at presentation of the combination of cardiac troponin and copeptin with 14 pmol/L used as the cutoff was 95%–99% and allowed the rapid rule out of AMI in two thirds of consecutive patients. The negative predictive value of the dual-marker approach could be further improved by using lower cutoff values for copeptin (e.g., 9 pmol/L), which, of course, also would reduce the percentage of patients that could be ruled out at the time of presentation. It is important to stress that the accuracy of the dual-marker concept will be even

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[2] Nonstandard abbreviations: AMI, acute myocardial infarction; cTnT, cardiac troponin T; Flt-1, fms-like tyrosine kinase; PlGF, placental growth factor; sFlt-1, soluble Flt-1; hs-cTnT, high-sensitivity cTnT (assay); NT-proBNP, N-terminal pro–B-type natriuretic peptide; H-FABP, heart-type fatty acid–binding protein.