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EDITORIAL COMMENT

Corin Levels in Patients With Acute MI

Do We Need More Tools for Risk Stratification?*

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Two decades ago, Lee et al. (1) identified the major predictors of mortality within 30 days after acute ST-segment elevation myocardial infarction (STEMI) treated with 1 of 4 fibrinolysis regimens in the GUSTO-I (Global Utilization of Streptokinase To Open Occluded Arteries) trial. Among 41,021 patients, increasing age, lower systolic blood pressure, higher Killip class on admission, higher heart rate, and anterior location of the infarct were each associated with a higher mortality. Interestingly, these 5 variables explained approximately 90% of the variability in mortality (age alone accounted for 50% of that). The c-statistic of the model was 0.84, indicating excellent discrimination, and there was near perfect correlation when comparing expected versus observed mortality among deciles of risk. Other significant variables, with much less contribution to the model, were previous myocardial infarction (MI), time to treatment, height and weight, diabetes, current smoking, choice of lytic agent, prior coronary artery bypass surgery, and hypertension.

CAN WE DO BETTER THAN THAT?

The GRACE (Global Registry of Acute Coronary Events) registry provided risk estimation for patients with STEMI and non-STEMI, treated frequently with revascularization (2). The GRACE risk score (version 2.0, c-statistic 0.81 for death at 6 months) (3), validated in more than 100,000 patients enrolled at ~250 centers, predicts risk for death and death or MI during the hospital stay, at 6 months and at 1 and 3 years. The score is based on easy-to-obtain variables: age, heart rate, systolic blood pressure, creatinine level, Killip class, ST-segment deviation, cardiac arrest on admission, and elevation of markers of myonecrosis. The first version also included lack of revascularization during the initial hospitalization. When tested in a Canadian population of >12,000 acute MI (AMI) patients, it had excellent discrimination (c-statistic 0.84) for in-hospital mortality (4).

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In this issue of *Journal*, Zhou et al. (5) evaluate the role of corin as a predictor of outcome in 1,382 patients with AMI treated with state-of-the-art medical and interventional therapy, and followed for about 3 years. Corin is secreted as a zymogen and activated by proprotein convertase subtilisin/kexin 6 (PCSK6). It is a transmembrane type II serine protease from the trypsin superfamily responsible for the activation of inert precursors of atrial natriuretic protein (ANP) and brain natriuretic protein (BNP), secreted from the atria and ventricles of the human heart. These proteins are responsible for homeostasis of water and sodium, and for vasodilation and maintenance of optimal blood pressure (6). It appears that the bioassay for corin takes at least 4 h.

More than one-half of the cohort had STEMI and the rest had non-STEMI. Nearly three-quarters of the patients were treated with percutaneous coronary intervention. Guideline-recommended therapy with beta-blockers, antiplatelet agents, statins, and inhibitors of the renin-angiotensin system was very prevalent. None of the patients were lost to follow-up.

Multivariable Cox regression models were built to estimate the relationship between the level of corin (above and below median, logarithmic transformation) and major cardiac events (MACE)

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as a combined endpoint of all-cause mortality, readmission for heart failure, or reinfarction. The multivariable model included many, but not all, of the parameters used in the GUSTO trial, and added mechanical or surgical reperfusion, estimated glomerular filtration rate, medications received during hospital stay—statins, beta-blockers, renin-angiotensin system blockers, aspirin—as well as laboratory measurements—troponin I, N-terminal pro-BNP (NT-proBNP), and corin.

The authors identified 3 correlates of low level of corin at enrollment: female sex, presence of decompensated heart failure, and hypertension. Patients with lower levels of corin had a significantly higher mortality and MACE rate than those with corin levels above the median. Most of the MACE and deaths occurred as expected in the first 12 months after the MI. The absolute rate of events is not clearly displayed but appears in line with other large registries: mortality of ~7% to 8% and MACE of ~15% at 1 year for the entire cohort. Multivariable regression analysis confirmed the significance of low corin levels in predicting MACE and mortality (hazard ratios of 0.61 and 0.65, respectively, $p = 0.03$ for both). The discrimination capability of the model for MACE increased modestly from 0.75 to 0.80 ($p < 0.001$)—still lower than in the GUSTO trial—with the addition of corin to the other variables, resulting in greater integrated discrimination improvement. The authors found an interaction between type of MI and the impact of corin ($p = 0.043$), suggesting it may not be predictive of MACE in non-STEMI patients. This interaction is of borderline significance and is quantitative only, making it less likely to be clinically meaningful, particularly in the absence of obvious biological plausibility. More importantly, higher corin levels on admission predicted lower rate of death and rehospitalization for heart failure, but not lower rates of reinfarction. Pro-BNP levels were significantly related to death and hospitalization for heart failure, but not to reinfarction. The authors concluded that corin is a valuable prognostic marker of MACE in patients with AMI, independent of other established risk factors.

Prima facie, it would seem indeed that Zhou et al. (5) were able to identify a relatively novel marker that improves risk stratification in patients with AMI. It appears they could improve on an already excellent and simple predictive tool derived from a 30-fold larger population. But closer inspection requires that some caveats be highlighted.

First, corin may be related (inversely) to adverse events, but this association is not independent of other variables. In fact, the authors themselves show a high correlation between corin and female sex, hypertension, and decompensated heart failure—Killip class >1. The first 2 variables were markedly different in patients with and without MACE by univariable analysis and became insignificant in the multivariable model. Decompensated heart failure remained highly correlated with MACE in both univariable and multivariable analyses. Second, the model itself does not include the key hemodynamic measurements used in other risk scores, such as systolic blood pressure and heart rate. It is very possible that these 2 variables would have altered the results of the multivariable analysis.

Third, and most interesting caveat, though, has to do with the fact that corin levels below median coexist with higher, rather than lower levels of proBNP. The metabolism and processing of proBNP is quite complex. ProBNP 1-108 is converted by 2 convertases—corin and furin—into the inactive NT-proBNP 1-76 and the active BNP 1-32, which we can measure clinically. Both components are elevated in heart failure patients because of the lack of specificity of the assays used (7). Corin levels would be expected to correlate directly, not inversely as in this report, with the levels of these compounds if it were the sole convertase responsible for natriuretic peptides processing. In a mouse model of progressive cardiomyopathy, there was marked dyssynchrony between levels of corin and natriuretic peptides. Corin transcription and plasma levels declined early in the development of heart failure (stage B) and remained low through stages C (structural heart disease with prior or current heart failure) and D (refractory heart failure). By contrast, increases in levels of ANP and BNP were noted in stages C and D only, despite persistently low levels of corin (8). This dissociation requires further investigation and raises the possibility that mechanisms other than corin are responsible for the secretion and activation of natriuretic peptides.

Other authors found that corin levels are depressed in non-STEMI patients as well and are associated with MACE (9). The area under the curve for the multivariable model was 0.79, similar to that reported in Zhou et al.'s paper (5).

In conclusion, it is important to identify new mechanisms of disease and quantify relationships that can potentially predict risk and suggest new therapies.

Yet, to paraphrase Albert Einstein, "…not everything that can be measured counts, and not everything that counts can be measured.…"

I doubt that measuring levels of corin in patients with acute coronary syndromes will make its way into clinical practice because of the time and

expense associated with the assay, because there are additional mechanisms that can convert natriuretic peptides, and because it does not seem to surpass in its risk stratification capability the currently, readily available clinical parameters we routinely collect.

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