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EDITORIAL COMMENT

Found in Translation

Soluble ST2 and Heart Disease*

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Translational research has delivered us with many proven or potential biomarkers for evaluation and management of the patient with heart disease, and unmistakably, biomarker testing has absolutely contributed to the basic understanding of many cardiovascular diseases. However—with rare exception—most novel biomarkers with potential cardiovascular applications have a long road to travel before they find clinical applicability.

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Indeed, over the past decade, among the plethora of novel biomarkers described to have potential value for use in cardiovascular disease states, most (although intellectually logical and with interesting biologic data to support their use) have been found to be "not ready for prime time," frequently with issues regarding the imperfect methods for their measurement, as well as uncertainty about their true value to the clinician. Thus, for new blood tests with potential cardiac applications, getting "lost in translation" during the bench-to-bedside journey is an obvious risk.

The bridging of biologic plausibility to clinical practicality is crucial for the survival of a biomarker during its bench-to-bedside translation; in addition to the obvious question as to whether a new marker is robust and easy to measure in the clinical arena, important questions to consider during this period include whether the test adds meaningful information to what we already have from other, more established biomarkers; whether the test truly adds to what we already know about the underlying biology of the patient in whom it is tested; and lastly, whether there is a potential therapeutic imperative associated with the results from testing. In other words, does the marker help us do a better job of caring for our patients?

Looking to biomarkers that have withstood this "test," as an example, clinicians are well versed with the value of cardiac troponin (cTn) in patients with acute myocardial infarction (AMI). Both cTnT and cTnI are superior to creatine kinase-myocardial band for the diagnosis of AMI, and biologically, patients with acute coronary syndromes and elevated cTn concentrations more often have intracoronary and microvascular thrombus or high-risk coronary anatomy and have worse outcomes. Lastly, just as would be predicted by the biology that leads to cTn release, patients with elevated values of these markers appear to have incremental benefit from intravenous antiplatelet drugs or early invasive management compared to patients without such elevations.

Thus, cardiac biomarkers can—and do—play a role in the way we clinicians approach our patients; yet, this does not change the fact that most novel markers get lost along the way from scientific discovery to clinical application, often because it is totally unclear where a new biomarker test truly fits in.

It is in this setting that, in this issue of the *Journal*, Weir et al. (1) add to the understanding of a novel biomarker called ST2. A peptide with a structural sequence that identifies it as an interleukin (IL)-receptor family member, ST2 exists both in membrane-bound form (ST2 ligand [ST2L]) as well as in a shed, truncated soluble form (soluble ST2 [sST2]) (2). Although described to play a role in inflammation and tolerance (mediating function of T-helper cells), ST2 clearly has a cardiovascular role elucidated with a classical "translational research" approach: in a model of myocyte stretch, the *ST2* gene transcript was found to be dramatically up-regulated (3); furthermore, in the context of left ventricular pressure and volume overload, interruption of the *ST2* gene (or infusion of large amounts of sST2) results in a deleterious phenotype marked by unchecked myocardial hypertrophy, dilation of ventricular chambers, and reduction in ejection fraction—essentially the human equivalent of remodeling after AMI or severe heart failure (HF) (4).

It is of note and of interest that the functional ligand for ST2 is IL-33, a cardiac fibroblast product, also produced in response to stretch. IL-33 is known to mediate the negative effects of pressure and volume overload on ventricular myocytes—infusion of this hormone prevents remodeling when the heart is acutely exposed to pressure overload, for example—and thus has a cardioprotective role in the setting of myocyte stretch and injury (4). The current theory is that sST2 plays a delicate role as a "decoy" receptor for IL-33; too much sST2 in the context of potential stretch-induced injury to the heart may therefore result in inadequate cardioprotection from IL-33, with a heightened risk for remodeling, ventricular dysfunction, or death.

Clinically, as might be expected from this biological background, among patients with HF, sST2 values appear to associate with more prevalent cardiac structural abnor-

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malities on echocardiography, including a more dilated and dysfunctional left and right ventricle, as well as elevated filling pressures (5). Furthermore, and strikingly, concentrations of sST2 are powerfully prognostic (and additive to natriuretic peptides for this purpose) among patients who have acutely destabilized HF, while in patients with AMI, sST2 concentrations are similarly additive to cTns or natriuretic peptides for predicting death or the development of future HF (5–11).

Despite these interesting observational results, mechanistically, it remained yet unclear just what biologic process in vivo sST2 might be predicting that so powerfully identified a risk for future cardiovascular events—events not necessarily predicted by our current biomarker armamentarium.

In the work by Weir et al. (1), further important answers about sST2 have been gained. In this relatively small but important study of 100 subjects randomly assigned to receive eplerenone or placebo after AMI, sST2 values were correlated with multiple measures from cardiac magnetic resonance imaging, including left ventricular ejection fraction and left ventricular chamber size as well as MI volumes; in addition, sST2 values were compared with other biomarkers, including measures of neurohormonal activation. The authors found that sST2 values at enrollment strongly correlated with greater infarct severity as well as the presence of microvascular obstruction, 2 very important predictors of future adverse outcome for patients with MI. In addition, concentrations of sST2 correlated with both levels of norepinephrine and aldosterone, but not with N-terminal pro-brain natriuretic peptide (NT-proBNP). Importantly, as each subject had serial magnetic resonance imaging scans, the authors were also able to connect the fact that sST2 concentrations at the time of enrollment were strongly predictive of future infarct remodeling.

An interesting finding in the study by Weir et al. (1) was the post hoc observation that the antiremodeling benefits of eplerenone were mainly restricted to patients with a high sST2 concentration at the time of enrollment. These findings are additive to those of Iraqi et al. (12), who found that treatment with eplerenone suppressed post-AMI collagen turnover. Taken together, these findings imply the potential opportunity to use biomarkers to identify patients at highest risk for remodeling—the very patients most likely to respond favorably to antiremodeling therapies, such as aldosterone receptor blockade.

The importance of a biomarker to predict remodeling is not insignificant: remodeling after AMI or in chronic HF is a pivotal step leading to worsened ventricular function and heightened risk for death. Remodeling has no symptoms, the timing of its occurrence is difficult to predict, and remodeling cannot be detected without imaging techniques such as magnetic resonance imaging or echocardiography. Given these facts and the fact that remodeling is not necessarily a universal process among patients at risk for it, it is attractive to consider the possibility of seeking remodeling in patients using markers of the biological processes that underlie it. In this regard, several biomarkers have been examined for this application, including matrix metalloproteinases, natriuretic peptides, and inflammatory markers (Table 1), to name a few. We can now add sST2 to this list; to one degree or another, these markers appear to provide unique information about the presence and significance of remodeling and potentially provide a therapeutic target for remodeling—at a pivotal step in HF development or progression

Table 1 Selected Biomarkers Associated With Ventricular Remodeling*

Natriuretic peptides
Troponins
Matrix metalloproteinases
Collagen turnover markers: type I collagen telopeptide
Tenascin C
Inflammatory markers: tumor necrosis factor receptors, C-reactive protein, cardiotrophin-1
Fibrosis markers: osteopontin, soluble ST2
Neurohormonal markers: aldosterone, aldosterone/renin ratio, angiotensin II
Others: tissue plasminogen activator

*List abbreviated for brevity.

Although a small study and not designed a priori to examine the value of sST2 in remodeling, the study by Weir et al. (1) does add some important mechanistic data to an increasingly interesting story about sST2 in cardiac disease. Tempering our enthusiasm for the results in the present study, both NT-proBNP and, particularly, aldosterone appeared to be associated with changes in ventricular structure and function over time, so it remains unclear whether sST2 was superior (or at least additive) to these markers for predicting remodeling; given the absence of correlation between sST2 and NT-proBNP, and the relative lack of change in aldosterone concentration over time, it is tempting to think that sST2 measurement provided unique information that was not reflected by either other marker.

Although excellent basic scientific data existed to support the candidacy of sST2 measurement in patients, mechanistic data were lacking in patients. Clinically, the data of Weir et al. (1) help us to understand why sST2 measurement appears to convey important prognostic information (that is additive to markers such as natriuretic peptides) across American Heart Association stages B, C, and D; given the importance of remodeling on the early development of HF, it would also obviously be tempting to speculate on the value of sST2 for predicting future HF in patients at risk for it (so-called stage A HF). With the recent development of a highly sensitive sST2 assay (able to detect the protein in very small quantities among apparently-normal patients), such studies may now be performed.

As more studies are done to examine the role of sST2 in heart disease onset, progression, and complication, this marker seems increasingly important, and the journey of sST2, "found in translation," continues onward. The prognostic value of sST2 is already established. If, as the study by Weir et al. (1) suggests, a therapeutic imperative could be found to reduce the risk for development or progression of

HF associated with elevated sST2 values, that would be a considerable advance.

Along these lines, we should consider, generally speaking, where things are heading for the field of cardiac biomarker testing: as we slowly move further toward a biologically-guided era of management of our patients with heart disease, biomarkers in cardiology must go from being something "nice to have" to something that we "need to have." Rather than using markers to confirm something we already know about our patients (or to identify a bad prognosis we can do nothing about), measuring concentrations of a biomarker such as sST2 should not only tell us something that we would not have otherwise known at the bedside, but also identify an opportunity to better treat our patients as a consequence.

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Key Words: ST2 ■ cardiac magnetic resonance ■ myocardial infarction ■ remodeling ■ aldosterone.