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Compelling Benefit of Soluble Suppression of Tumorigenicity-2 in Post–Myocardial Infarction Estimation of Risk: The Time Is Right for Its Routine Use in the Clinic

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It is estimated that in the United States, each year, >780 000 people will experience an acute coronary syndrome. Approximately 70% of these people will have a non–ST-elevated myocardial infarction (NSTEMI), and the rest will have an ST-elevated myocardial infarction (STEMI).[1] Patients with NSTEMI typically have more comorbidities, both cardiac and noncardiac, than patients with STEMI.

In both STEMI and NSTEMI, risk estimation by current guidelines recommends the use of the TIMI (Thrombolysis in Myocardial Infarction) or GRACE (Global Registry of Acute Cardiac Events) risk scores. The TIMI risk score is composed of 7, 1-point risk indicators (≥65 years of age, ≥3 risk factors for coronary artery disease, prior coronary stenosis ≥50%, ST deviation on ECG, ≥2 anginal events in prior 24 hours, use of aspirin in prior 7 days, and elevated cardiac enzyme levels),[2] and it has been validated internally within the TIMI 11B trial and in 2 separate cohorts of patients from the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events) trial,[3] published 20 years ago. The TIMI risk score calculator is available at http://www.timi.org. The GRACE risk model predicts in-hospital and postdischarge mortality of MI.[4,5] The GRACE tool was developed from 11 389 patients in GRACE and validated in subsequent GRACE and GUSTO (Global Utilization of Streptokinase and TPA [Tissue Plasminogen Activator] for Occluded Arteries) IIb cohorts, also reported a couple of decades ago.[4,6] The GRACE clinical application tool is available at http://www.outcomes-umassmed.org/grace.

During the past 2 decades, since these scores were developed, several things have changed in the management of patients with STEMI and NSTEMI, as well as the phenotype of these patients, who are generally older and have more comorbidities. Remarkably, biomarkers have entered into the center stage in cardiovascular diseases. Among them, natriuretic peptides (NPs) have had a successful path from research studies to clinical guidelines and routine implementation, mainly to rule in and rule out heart failure (HF). Despite the versatility of NPs, other biomarkers have provided additional and complementary information. The soluble suppression of tumorigenicity-2 (sST2) protein is one such biomarker.[7] It is regarded as a 3-in-1 biomarker because of its comprehensive added value in cardiovascular pathological features.

In the setting of NSTEMI, higher sST2 levels are associated with an increased risk of adverse outcomes.[8] In a study of 577 patients with NSTEMI, predischarge sST2 levels provided independent prediction of 18-month risk of death, HF admission, or reinfarction.[9] Subsequently, a substudy from the larger MERLIN (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes)-TIMI 36 study of 4426 high-risk patients with NSTEMI found that sST2 levels were independently associated with increased risk of cardiovascular death or new/worsened HF at 30 days and 1 year.[10] In this study, sST2 levels remained predictive of risk, even after adjusting for NP and troponin levels.

In patients with STEMI, several studies have found that sST2 levels are independently associated with an increased risk of death or HF.[11,12] This risk appears to be additive to standard risk factors and NP levels.[11] ST2 levels in patients with STEMI also improved on short-term risk prediction using the GRACE score and NP levels, with significant improvement in risk discrimination when all 3 were combined.[12] Remarkably, in the setting of an acute MI with HF signs or symptoms, an sST2 level >35 ng/mL before discharge identified the

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. 2017;6:e007665 DOI: 10.1161/JAHA.117.007665.

subset of patients in whom eplerenone was likely to be especially beneficial in terms of preventing left ventricular adverse remodeling during follow-up.[13]

In the study by Gerber et al, published in the current issue of *JAHA*,[14] the authors are to be commended for a comprehensive analysis of patients with MI in a real-life setting: Olmsted County, Minnesota, from November 2002 to December 2012. In the current report, the authors examined the added value of sST2 on top of currently recommended TIMI and GRACE scores. Relative to the discriminatory performance of sST2, the authors found that sST2 markedly improved discrimination over GRACE (c-statistic from 0.78 to 0.84) and TIMI (c-statistic from 0.61 to 0.81). Indeed, these changes in c-statistic are impressive. As an example, in the setting of HF, a biomarker is considered of relevance for risk stratification if it has the ability to improve the c-statistic by 0.02.[15] In this report, in the setting of MI, the incremental benefit of sST2 on the c-statistic ranged between 0.06 for GRACE and 0.20 for TIMI. A further verification of the impact of sST2 was obtained by reclassification examination. Gerber et al[14] showed that addition of sST2 reclassified 44.9% of patients over TIMI and 39.7% of patients over GRACE. Present data support, confirm, and validate previous reports on the use of sST2 for post-MI risk stratification. The time is right to consider incorporation of sST2 in routine clinical decision making.

From a biological perspective, the ST2 protein is a member of the Toll-like/interleukin (IL)-1 receptor superfamily, encoded by the IL-1 receptor like 1 (*IL1RL1*) gene that has 2 primary isoforms regulated by different promoters.[16] The transmembrane ST2 isoform (ST2L) is a membrane-bound isoform; sST2 is a circulating isoform, which lacks the transmembrane and intracellular domains. IL-33 has been identified as an extracellular ligand for ST2L.[16] IL-33/ST2L signaling has emerged as a pathway with a central role in processes of the immune response, homeostasis, and tissue injury/repair.[17] Several lines of experimental evidence suggest that sST2 acts as a decoy receptor, attenuating the cellular and tissue effects of the IL-33/ST2L axis.[16,17]

At the cardiac level, both ST2L and sST2 are transcriptionally induced by mechanical strain in rat cardiomyocytes and cardiac fibroblasts.[18,19] In cardiomyocytes and cardiac fibroblasts, IL-33 was transcriptionally induced by mechanical stretch, angiotensin II, and phorbol ester,[19] as well as by the proinflammatory cytokines tumor necrosis factor-α, interferon-γ, and IL-1β.[20] IL-33 markedly blocked angiotensin II– and phenylephrine-induced nuclear factor-κB activation and hypertrophy in cardiomyocytes.[19] Interestingly, IL-33 prevents cardiomyocyte apoptosis and improves cardiac function and survival after MI in rats through ST2L signaling.[21] After pressure overload by transverse aortic constriction, ST2$^{-/-}$ mice had more left ventricular hypertrophy, myocardial fibrosis, and chamber dilation, and decreased fractional shortening and survival, compared with wild-type littermates.[19] Furthermore, recombinant IL-33 treatment reduced hypertrophy and fibrosis and improved survival after transverse aortic constriction in wild-type mice, but not in ST2$^{-/-}$ littermates. Treatment with sST2 antagonizes the ability of IL-33 to block angiotensin II– and phenylephrine-induced hypertrophy in cardiomyocytes,[19] suggesting that sST2 functions in the myocardium as a soluble decoy receptor and introducing the possibility that an excess of sST2 could reduce IL-33/ST2L-mediated cardioprotective signaling.

From an analytical perspective, in the current study, measurement of sST2 was accomplished via the Presage assay. Three different ELISA assays can be used for sST2: one produced by MBL International, Inc (Woburn, MA), one produced by R&D Systems (Minneapolis, MN), and one produced by Critical Diagnostics (San Diego, CA; the Presage assay). Of these assays, the first 2 are research assays only, whereas the Presage assay is Food and Drug Administration approved and Conformité Européene (CE) marked as an aid in risk stratification of patients with HF or MI. More important, a recent method comparison study found that sST2 results obtained with the 3 different assays are not equal to each other; thus, results obtained using one method are not directly comparable to the other methods.[22] The lack of agreement between the 3 assays is likely because of different antibodies (which may be detecting different epitopes), different purification processes for the standards, and possibly different reagents and buffers as well.[22] The Presage assay has good precision (coefficient of variation, <5%), even at low analyte concentrations, and high in vitro stability.[23] sST2 levels appear to be stable over the long-term in frozen samples. Levels of sST2 are not significantly associated with body mass index and have a weak association with age and renal insufficiency compared with NP.[7,24]

The recommended clinical cut point for sST2 is 35 ng/mL, and between 90% and 95% of normal individuals have levels lower than this threshold. A recent study evaluating the biological variation of sST2 and other cardiovascular biomarkers found that the long-term intraindividual variation for sST2 was only 11%, considerably lower than that of NP (33%–50%).[25] The low biological variation suggests that sST2 may be a useful biomarker to follow serially to guide therapy.

The roadmap for precision and personalized medicine after MI advocates the incorporation of biomarkers to refine and improve current risk stratification based on clinical and imaging techniques. Pathophysiological, clinical research, and analytical data on sST2 during the past years are robust and consistent. The study by Gerber et al[14] suggests that sST2 may emerge as a bona fide and precise tool to estimate long-term risk in patients after MI on a day-to-day basis. Additional research about the impact of treatment-induced longitudinal changes in sST2 levels over time on clinical outcomes after MI

is ongoing. Furthermore, sST2 has inhibited the release of proinflammatory cytokines by human immune cells.[26] This property could be advantageous, taking into account that immune activation and increased production of proinflammatory cytokines play an important role in both myocardial repair and clinical outcome after MI.[27]

Disclosures

Bayes-Genis received board membership fees and travel expenses from Novartis and Roche Diagnostics and reports a relationship with Critical Diagnostics. Díez has no disclosures to report.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6–e245.
2. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284:835–842.
3. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KA, Premmereur J, Bigonzi F; Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med*. 1997;337:447–452.
4. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163:2345–2353.
5. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA; GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;291:2727–2733.
6. Giugliano RP, Braunwald E. The year in non-ST segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2005;46:906–919.
7. Daniels LB, Bayes-Genis A. Using ST2 in cardiovascular patients: a review. *Future Cardiol*. 2014;10:525–539.
8. Eggers KM, Armstrong PW, Califf RM, Simoons ML, Venge P, Wallentin L, James SK. ST2 and mortality in non-ST-segment elevation acute coronary syndrome. *Am Heart J*. 2010;159:788–794.
9. Dhillon OS, Narayan HK, Quinn PA, Squire IB, Davies JE, Ng LL. Interleukin 33 and ST2 in non-ST-elevation myocardial infarction: comparison with Global Registry of Acute Coronary Events Risk Scoring and NTproBNP. *Am Heart J*. 2011;161:1163–1170.
10. Kohli P, Bonaca MP, Kakkar R, Kudinova AY, Scirica BM, Sabatine MS, Murphy SA, Braunwald E, Lee RT, Morrow DA. Role of ST2 in non-ST-elevation acute coronary syndrome in the MERLIN-TIMI 36 trial. *Clin Chem*. 2012;58:257–266.
11. Shimpo M, Morrow DA, Weinberg EO, Sabatine MS, Murphy SA, Antman EM, Lee RT. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. *Circulation*. 2004;109:2186–2190.
12. Sabatine MS, Morrow DA, Higgins LJ, MacGillivray C, Guo W, Bode C, Rifai N, Cannon CP, Gerszten RE, Lee RT. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. *Circulation*. 2008;117:1936–1944.
13. Weir RA, Miller AM, Murphy GE, Clements S, Steedman T, Connell JM, McInnes IB, Dargie HJ, McMurray JJ. Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. *J Am Coll Cardiol*. 2010;55:243–250.
14. Gerber Y, Weston SA, Enriquez-Sarano M, Jaffe AS, Manemann SM, Jiang R, Roger VL. Contemporary risk stratification after myocardial infarction in the community: performance of scores and incremental value of soluble suppression of tumorigenicity-2. *J Am Heart Assoc*. 2017;6:e005958. DOI: 10.1161/JAHA.117.005958.
15. Levy WC, Anand IS. Heart failure risk prediction models: what have we learned? *JACC Heart Fail*. 2014;2:437–439.
16. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. *Nat Rev Drug Discov*. 2008;7:827–840.
17. De la Fuente M, MacDonald TT, Hermoso MA. The IL-33/ST2 axis: role in health and disease. *Cytokine Growth Factor Rev*. 2015;26:615–623.
18. Weinberg EO, Shimpo M, De Keulenaer GW, MacGillivray C, Tominaga S, Solomon SD, Rouleau JL, Lee RT. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. *Circulation*. 2002;106:2961–2966.
19. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. *J Clin Invest*. 2007;117:1538–1549.
20. Demyanets S, Kaun C, Pentz R, Krychtiuk KA, Rauscher S, Pfaffenberger S, Zuckermann A, Aliabadi A, Gröger M, Maurer G, Huber K, Wojta J. Components of the interleukin-33/ST2 system are differentially expressed and regulated in human cardiac cells and in cells of the cardiac vasculature. *J Mol Cell Cardiol*. 2013;60:16–26.
21. Seki K, Sanada S, Kudinova AY, Steinhauser ML, Handa V, Gannon J, Lee RT. Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. *Circ Heart Fail*. 2009;2:684–691.
22. Mueller T, Zimmermann M, Dieplinger B, Ankersmit HJ, Haltmayer M. Comparison of plasma concentrations of soluble ST2 measured by three different commercially available assays: the MBL ST2 assay, the Presage ST2 assay, and the R&D ST2 assay. *Clin Chim Acta*. 2012;413:1493–1494.
23. Dieplinger B, Januzzi JL Jr, Steinmair M, Gabriel C, Poelz W, Haltmayer M, Mueller T. Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma: the Presage ST2 assay. *Clin Chim Acta*. 2009;409:33–40.
24. Bayes-Genis A, Zamora E, de Antonio M, Galán A, Vila J, Urrutia A, Díez C, Coll R, Altimir S, Lupón J. Soluble ST2 serum concentration and renal function in heart failure. *J Card Fail*. 2013;19:768–775.
25. Wu AH, Wians F, Jaffe A. Biological variation of galectin-3 and soluble ST2 for chronic heart failure: implication on interpretation of test results. *Am Heart J*. 2013;165:995–999.
26. Leung BP, Xu D, Culshaw S, McInnes IB, Liew FY. A novel therapy of murine collagen-induced arthritis with soluble T1/ST2. *J Immunol*. 2004;173:145–150.
27. Montecucco F, Liberale L, Bonaventura A, Vecchiè A, Dallegri F, Carbone F. The role of inflammation in cardiovascular outcome. *Curr Atheroscler Rep*. 2017;19:11.

Key Words: Editorials • biomarker • myocardial infarction • non–ST-segment elevation acute coronary syndrome • risk stratification • ST-segment elevation myocardial infarction