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Editorial

suPAR: A Cardiac Biomarker With a Future?

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See article by Hodges et al., pages 1293-1302 of this issue.

Conventional risk factors have been shown to be moderately effective in predicting outcomes in patients with cardiovascular disease. However, up to 20% of patients who present with cardiovascular disease have no traditional risk factors.[1] Substantial efforts to improve our ability to recognize patients with cardiovascular disease at earlier stages have included identification of "biomarkers."

These biomarkers, usually in the form of a blood test, represent objective measurements of a particular biologic process considered important in the pathogenesis of the disease of interest. Thus, cardiac biomarkers are used to predict or prognosticate the presence or severity of a cardiac condition, and have been proposed to supplement conventional risk factors. Several biomarkers have been incorporated into well known risk scores and provide improved prognostication into higher and lower risk groups.[2,3] The most well known biomarkers include: high-sensitivity C-reactive protein (hs-CRP)—a marker of inflammation; albuminuria—a marker of renal dysfunction; troponin—a marker of cardiac damage; brain natriuretic protein (BNP)—volume overload; and fibrinogen—a marker of the coagulation cascade. An ideal biomarker should be inexpensive, easy to measure, stable in plasma, serum, and blood samples, accurately differentiate patient outcomes, and help guide the treatment of a specific patient.

Several new cardiac biomarkers have been identified in recent years, including some in widespread use (eg, inflammation, volume overload, oxidative stress, apoptosis). Some have gained widespread use (eg, BNP and albuminuria). However, even common biomarkers such as hs-CRP and endothelial function markers have not gained general acceptance because of cost issues, logistic concerns, or lack of studies that show effects on hard clinical end points. Recently, multimarker strategies in studies that incorporate several biomarkers have been shown to improve their ability to predict future major cardiac events.[4,5]

In this issue of the *Canadian Journal of Cardiology*, Hodges and colleagues present a comprehensive review on a relatively unknown, new cardiovascular biomarker, soluble urokinase plasminogen activator receptor (suPAR).[6] suPAR has been linked to endothelium dysfunction, damaged cardiac microcirculation, increased vascular stiffness, and finally, more extensive atherosclerosis. It is part of the inflammation and/or endothelial system. suPAR was initially identified in the 1990s and early 2000s as a predictor of mortality in patients with various cancers, including hematopoietic, ovarian, and colorectal.[7-10] Because it regulates fibrin as part of the coagulation system,[11] it was later evaluated as a biomarker for an expanding list of diverse cardiovascular diseases,[12] including stroke, myocardial infarction, heart failure, abdominal aortic aneurysms, coronary restenosis,[13] and advanced atherosclerosis.[6]

suPAR levels are associated with lifestyle factors, such as smoking, alcohol intake, and sedentary lifestyle, but interestingly, not obesity. Levels are also noted to be higher in women. Unlike other inflammatory biomarkers, suPAR appears to be related to chronic low grade inflammation and does not respond as an acute phase reactant, unlike hs-CRP. The stability of blood levels, even in the setting of acute vascular events, such as acute myocardial infarction or bypass surgery, alleviates concerns about the timing of sample collection and should facilitate interpretation of the levels.

Currently, there does not seem to be adequate clinical justification for measurement of suPAR levels in routine clinical practice. First, in contrast to other biomarkers (eg, low-density lipoprotein, albuminuria, hs-CRP, BNP, troponin), the cutoff levels have not been sufficiently clinically validated. Second, there are significant gaps in our understanding of the factors that regulate suPAR levels. It is not clear why women have higher levels and why suPAR is not linked with obesity. Is the risk linear according to the level or is there a "safe" level? Do "abnormal" cutoffs vary according to sex or race? Additional studies are required to determine values in various subgroups with risk profiles different from the Northern European patients who predominate in published studies, such as high-risk South Asian populations.[14] Moreover, more extensive data on hard cardiovascular end points

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(eg, mortality, acute myocardial infarction) in large population studies would be of much more value than surrogate end points (eg, albuminuria, arterial stiffness, pulse wave velocity, carotid plaque size) currently available from smaller studies.

Third, there are no currently recognized therapies to consistently decrease suPAR levels, and the clinical benefits of decreasing suPAR levels are not known. CRP has been shown to be reduced by multiple interventions, including statin treatment and weight loss.[15] Albuminuria can be reduced by angiotensin converting enzyme inhibitors and angiotensin blockers with beneficial clinical effects.[16] suPAR levels have not been yet shown to be altered by any of these therapies. The potential clinical benefits of measuring suPAR levels will have to be balanced against the additional costs of the test to the health care system. Finally, we do not currently understand whether suPAR is just a marker, or an actual participant in the pathogenesis of the cardiac disease pathological process.

What are the next steps required before considering suPAR as part of current guidelines for routine clinical practice?[17] We will need to understand the biology better, particularly the effects of current cardiac medical therapies (eg, statins) on suPAR levels. Moreover, if suPAR levels can in fact be modified, we need to show better outcomes in properly designed, prospective studies. The potential additive clinical benefits of measuring suPAR levels will then need to be balanced against the additional costs of the test to the health care system. Importantly, the article by Hodges et al. also informs clinicians on the complex statistical methods used in these type of risk prediction studies.[6] It is clear that to critically assess the literature, readers need to become acquainted with a broader range of statistics, including c-statistics for model assessment, and net reclassification index, rather than to rely on more conventional tests, such as hazard ratios.

In summary, the current review on suPAR indicates an interesting new cardiovascular biomarker. However, significant work is required to better understand the biology and to show measurable incremental improvements beyond existing tests for it to ultimately be of clinical use.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003;290:898-904.
2. Cook NR, Paynter NP, Eaton CB, et al. Comparison of the Framingham and Reynolds Risk scores for global cardiovascular risk prediction in the multiethnic Women's Health Initiative. Circulation 2012;125:1748-56. S1-11.
3. Goliasch G, Kleber ME, Richter B, et al. Routinely available biomarkers improve prediction of long-term mortality in stable coronary artery disease: the Vienna and Ludwigshafen Coronary Artery Disease (VILCAD) risk score. Eur Heart J 2012;33:2282-9.
4. Velagaleti RS, Gona P, Larson MG, et al. Multimarker approach for the prediction of heart failure incidence in the community. Circulation 2010;122:1700-6.
5. Lieb W, Larson MG, Benjamin EJ, et al. Multimarker approach to evaluate correlates of vascular stiffness: the Framingham Heart Study. Circulation 2009;119:37-43.
6. Hodges GW, Bang CN, Wachtell K, Eugen-Olsen J, Jeppesen JL. suPAR: a new biomarker for cardiovascular disease? Can J Cardiol 2015;31:1293-302.
7. Mustjoki S, Alitalo R, Stephens RW, Vaheri A. Blast cell-surface and plasma soluble urokinase receptor in acute leukemia patients: relationship to classification and response to therapy. Thromb Haemost 1999;81:705-10.
8. Sier CF, Stephens R, Bizik J, et al. The level of urokinase-type plasminogen activator receptor is increased in serum of ovarian cancer patients. Cancer Res 1998;58:1843-9.
9. Stephens RW, Nielsen HJ, Christensen IJ, et al. Plasma urokinase receptor levels in patients with colorectal cancer: relationship to prognosis. J Natl Cancer Inst 1999;91:869-74.
10. Rigolin GM, Tieghi A, Ciccone M, et al. Soluble urokinase-type plasminogen activator receptor (suPAR) as an independent factor predicting worse prognosis and extra-bone marrow involvement in multiple myeloma patients. Br J Haematol 2003;120:953-9.
11. Higazi AA, Ajawi F, Akkawi S, et al. Regulation of the single-chain urokinase-urokinase receptor complex activity by plasminogen and fibrin: novel mechanism of fibrin specificity. Blood 2005;105:1021-8.
12. Pawlak K, Pawlak D, Mysliwiec M. Urokinase-type plasminogen activator and metalloproteinase-2 are independently related to the carotid atherosclerosis in haemodialysis patients. Thromb Res 2008;121:543-8.
13. Strauss BH, Lau HK, Bowman KA, et al. Plasma urokinase antigen and plasminogen activator inhibitor-1 antigen levels predict angiographic coronary restenosis. Circulation 1999;100:1616-22.
14. Chiu M, Maclagan LC, Tu JV, Shah BR. Temporal trends in cardiovascular disease risk factors among white, South Asian, Chinese and black groups in Ontario, Canada, 2001 to 2012: a population-based study. BMJ Open 2015;5:e007232.
15. Rude J, Azimova K, Dominguez C, et al. Depression as a predictor of length of stay in patients admitted to the cardiovascular intensive care unit at a university medical center. Angiology 2014;65:580-4.
16. Haller H, Ito S, Izzo JL Jr, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907-17.
17. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889-934.