European Heart Journal (2014) **35**, 1776–1778
doi:10.1093/eurheartj/ehu115

EDITORIAL

High-sensitivity C-reactive protein: still need for next-generation biomarkers for remote future cardiovascular events

Kimio Satoh and Hiroaki Shimokawa*

Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

Online publish-ahead-of-print 21 March 2014

This editorial refers to 'C-reactive protein and risk of cardiovascular and all-cause mortality in 268 803 East Asians'†, by K.-C. Sung *et al.*, on page 1809.

Inflammation in the vessel wall plays a crucial role in the pathophysiology of atherogenesis, progression of atherosclerosis, and plaque instability. Atherosclerosis is initiated by dysfunction of endothelial cells (ECs), leading to expression of adhesion molecules for inflammatory cells.[1,2] Vascular inflammation leads to an oxidizing environment due to activation of macrophages that secrete cytokines/chemokines as well as growth factors,[3] all of which contribute to the progression of atherosclerosis.[4] Therefore, the interactions among ECs, vascular smooth muscle cells (VSMCs), and inflammatory cells are substantially involved in the development of cardiovascular diseases.[5] ECs produce nitric oxide and prostacyclin, which protect against vascular remodelling.[5] Activated VSMCs produce proinflammatory cytokines and chemokines, which are stimulated by oxidative stress.[6–8]

C-reactive protein for prediction of cardiovascular events in the remote future

The study by Sung *et al.*[9] represents the largest cohort of Asian subjects to date that has been investigated for the association between high-sensitivity C-reactive protein (hsCRP) and cardiovascular outcomes and total mortality. After studying 268 803 Korean men and women, the authors demonstrated that hsCRP levels are much lower in this population than in Caucasians. Interestingly, they showed that the association with future cardiovascular events is stronger in men than in women. Accumulating evidence suggests that elevated hsCRP levels in apparently healthy subjects increase the risk for major adverse cardiovascular events.[10] The Hisayama study previously has also reported an association between elevated hsCRP levels and adverse cardiovascular outcomes in Japanese subjects.[12] These reports consistently demonstrate that hsCRP levels are much lower in Asians than in Western populations.[12] As Sung *et al.* mentiond in their Discussion, the ethnic differences in hsCRP levels cannot be simply due to differences in body mass index but are due rather to the composite effects of a number of factors.[10–12] More importantly, Sung *et al.* demonstrated that CRP levels are more predictive in men than in women in their study. However, it should be noted that this study has a huge number of subjects and carries the risk of overinflating small differences in terms of clinical application. Recommendations against its use as a practical biomarker have already been publised.[13]

No causality of C-reactive protein for the development of atherosclerosis

High-sensitivity C-reactive protein predicts cardiovascular events in the remote future.[10–12] However, this has been inappropriately conflated with causality of atherogenesis. Many of the known causative factors (e.g. circulating cytokines/chemokines and growth factors) for atherosclerosis induce CRP synthesis in the liver (*Figure 1*). However, genetic epidemiology studies have never supported a pathogenic role for CRP. Recently, Lane *et al.* investigated the effects of infusion of pure natural human CRP into healthy adult human volunteers.[14] They used comprehensively characterized, pharmaceutical grade, endotoxin-free, purified CRP, prepared to GMP (Good Manufacturing Practice) standard from pooled normal human donor plasma.[14] Importantly, the human CRP molecule itself did not exert any proinflammatory effects in the volunteers, suggesting that circulating CRP is not a proatherogenic factor but just a reflection of inflammation.[14] Similarly, many animal studies also revealed that CRP is not directly involved in atherogenesis.[15]

Biomarkers for existing cardiovascular diseases

High-sensitivity C-reactive protein is useful for prediction of cardiovascular events in the general population.[10–12] Currently, most

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.
† doi:10.1093/eurheartj/ehu059.

* Corresponding author. Tel: +81 22 717 7151, Fax: +81 22 717 7156, Email: shimo@cardio.med.tohoku.ac.jp

hospitals in the world are well equipped for the measurement of hsCRP. However, hsCRP is not a biomarker that is used daily for differential diagnosis of existing cardiovascular diseases. In the outpatient clinic, no specialist relies on the use of hsCRP for emergent assessment of patients with possible symptoms of coronary artery disease (CAD). This is because hsCRP has a limited ability to diagnose existing cardiovascular diseases (e.g. severe coronary artery stenosis or unstable plaque).

The use of biomarkers, such as cardiac troponin T, enables us to diagnose patients with myocardial infarction. However, even with these biomarkers, it is difficult to diagnose patients with severe CAD or unstable atherosclerotic plaque, which will cause myocardial infarction in the near future. In the actual clinical settings, what we really need is a practical biomarker that enables us to identify patients at risk before cardiovascular events occur. Therefore, the development of a biomarker for existing CAD or cardiovascular diseases is required.[16]

Novel biomarkers for the diagnosis of coronary artery disease

There are several reports on the role of circulating biomarkers for prediction of existing CAD.[17,18] Circulating CRP is produced mainly by the liver and reflects the elevated cytokines/chemokines caused by inflammation (*Figure 1*). In contrast, pentraxin 3 (PTX3) is produced at the site of vascular inflammation by various cell types, including macrophages, ECs, and VSMCs.[17] The role of circulating PTX3 for the diagnosis of patients with CAD has recently been demonstrated.[17] Additionally, we also have recently demonstrated that plasma cyclophilin A (CyPA) is a novel biomarker for CAD (*Figure 1*).[18] Multivariable analysis demonstrated that in addition to the established risk factors (e.g. age, sex, smoking, hypertension, and diabetes), CyPA at >15 ng/mL was significantly correlated with CAD.[18] Importantly, excluding patients with high hsCRP did not significantly change the results. In patients with hsCRP values of < 1000 mg/L, the adjusted odds ratio for CAD in the fourth quartile of CyPA, as compared with the first quartile, was 13.2 ($P < 0.001$). Our analysis revealed that the number of stenotic coronary arteries was slightly increased in the fourth quartile of hsCRP.[18] However, the *P*-value for the trend was small ($P = 0.107$) as compared with the quartiles of CyPA ($P < 0.001$).[18] Moreover, quartiles of hsCRP did not show any significant correlation with the requirement for cardiovascular intervention.[18] Importantly, there was no significant difference in the angiographic findings or the requirement for cardiovascular intervention between high and low hsCRP groups. In contrast, in both the subgroups with low and high hsCRP, CyPA levels were significantly higher in patients with severe CAD than in those without it.[18]

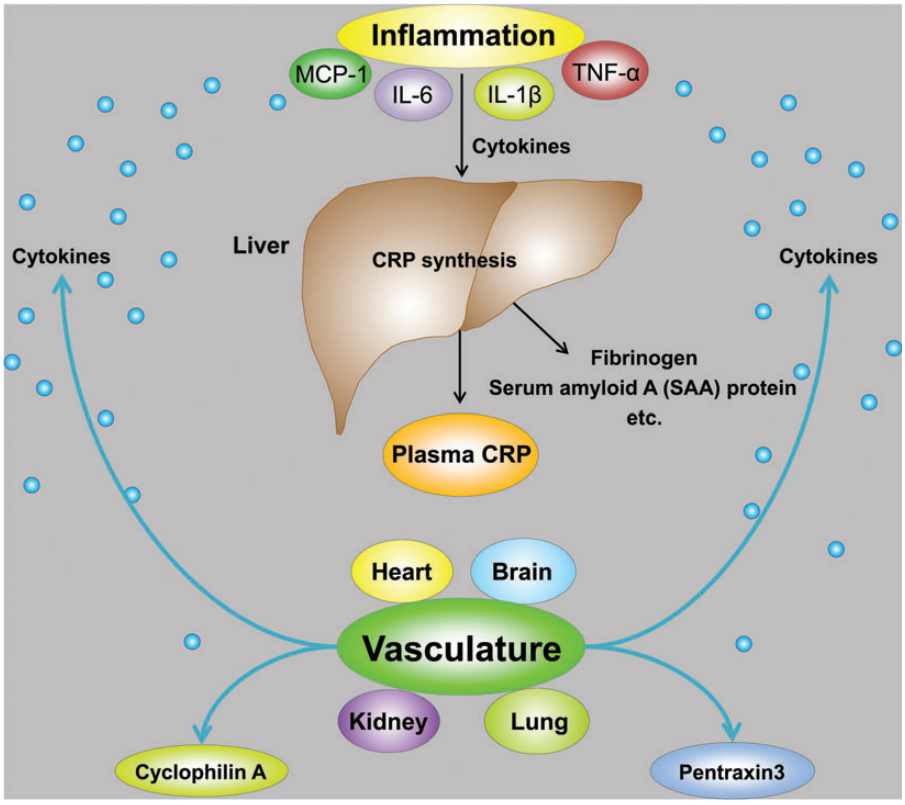

Figure 1 C-reactive protein (CRP): a reflection of elevated circulating cytokines. Plasma CRP is a biomarker for the assessment of remote future cardiovascular events. The synthesis of CRP in the liver is increased by circulating inflammatory cytokines [e.g. interleukin-6, interleukin-1β (IL-1β), IL-6, monocyte chemoattractant protein-1 (MCP-1), or tumour necrosis factor-α (TNF-α)].

Lessons to be learnt

The development of biomarkers has contributed to medical progress in the world. However, we still do not have a biomarker that is truly useful to identify patients at risk before cardiovascular events. Although hsCRP may be useful for the prediction of cardiovascular events in the distant future, we should focus on the development of next-generation biomarkers for existing CAD or cardiovascular diseases with a high accuracy and simplicity.

Funding

This work was supported in part by a grant-in-aid for Tohoku University Global COE for Conquest of Signal Transduction Diseases with Network Medicine and those for Scientific Research (21790698, 23659408, and 24390193), all of which are from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Tokyo, Japan; and a grant-in-aid for Scientific Research from the Japanese Ministry of Health, Labour, and Welfare, Tokyo, Japan (10102895).

Conflict of interest: none declared.

References

1. Shimokawa H, Tomoike H, Nabeyama S, Yamamoto H, Araki H, Nakamura M, Ishii Y, Tanaka K. Coronary artery spasm induced in atherosclerotic miniature swine. *Science* 1983;**221**:560–562.
2. Berk BC. Atheroprotective signaling mechanisms activated by steady laminar flow in endothelial cells. *Circulation* 2008;**117**:1082–1089.
3. Nigro P, Satoh K, O'Dell MR, Soe NN, Cui Z, Mohan A, Abe J, Alexis JD, Sparks JD, Berk BC. Cyclophilin A is an inflammatory mediator that promotes atherosclerosis in apolipoprotein E-deficient mice. *J Exp Med* 2011;**208**:53–66.
4. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;**352**:1685–1695.
5. Shimokawa H. Primary endothelial dysfunction: atherosclerosis. *J Mol Cell Cardiol* 1999;**31**:23–37.
6. Berk BC. Vascular smooth muscle growth: autocrine growth mechanisms. *Physiol Rev* 2001;**81**:999–1030.
7. Satoh K, Matoba T, Suzuki J, O'Dell MR, Nigro P, Cui Z, Mohan A, Pan S, Li L, Jin ZG, Yan C, Abe J, Berk BC. Cyclophilin A mediates vascular remodeling by promoting inflammation and vascular smooth muscle cell proliferation. *Circulation* 2008;**117**:3088–3098.
8. Satoh K, Nigro P, Matoba T, O'Dell MR, Cui Z, Shi X, Mohan A, Yan C, Abe J, Illig KA, Berk BC. Cyclophilin A enhances vascular oxidative stress and the development of angiotensin II-induced aortic aneurysms. *Nat Med* 2009;**15**:649–656.
9. Sung K-C, Ryu S, Chang Y, Byrne CD, Kim SH. C-reactive protein and risk of cardiovascular and all-cause mortality in 268 803 East Asians. *Eur Heart J* 2014;**35**:1809–1816.
10. Ridker PM. High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. *Am Heart J* 2004;**148**:S19–S26.
11. Arima H, Kubo M, Yonemoto K, Doi Y, Ninomiya T, Tanizaki Y, Hata J, Matsumura K, Iida M, Kiyohara Y. High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama study. *Arterioscler Thromb Vasc Biol* 2008;**28**:1385–1391.
12. Albert MA, Glynn RJ, Buring J, Ridker PM. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). *Am J Cardiol* 2004;**93**:1238–1242.
13. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;**350**:1387–1397.
14. Lane T, Wassef NL, Poole S, Mistry Y, Lachmann H, Gillmore J, Hawkins PN, Pepys MB. Infusion of pharmaceutical grade natural human C reactive protein is not pro inflammatory in healthy adult human volunteers. *Circ Res* 2014;**114**:672–676.
15. Kovacs A, Tornvall P, Nilsson R, Tegner J, Hamsten A, Bjorkegren J. Human C-reactive protein slows atherosclerosis development in a mouse model with human-like hypercholesterolemia. *Proc Natl Acad Sci USA* 2007;**104**:13768–13773.
16. Hamm CW, Crea F. The year in cardiology 2013: acute coronary syndromes. *Eur Heart J* 2014;**35**:349–352.
17. Kotooka N, Inoue T, Aoki S, Anan M, Komoda H, Node K. Prognostic value of pentraxin 3 in patients with chronic heart failure. *Int J Cardiol* 2008;**130**:19–22.
18. Satoh K, Fukumoto Y, Sugimura K, Miura Y, Aoki T, Nochioka K, Tatebe S, Miyamichi-Yamamoto S, Shimizu T, Osaki S, Takagi Y, Tsuburaya R, Ito Y, Matsumoto Y, Nakayama M, Takeda M, Takahashi J, Ito K, Yasuda S, Shimokawa H. Plasma cyclophilin A is a novel biomarker for coronary artery disease. *Circ J* 2013;**77**:447–455.