Acute and stable coronary heart disease: different risk factors

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This editorial refers to ‘Contribution of novel biomarkers to incident stable angina and acute coronary syndrome: the PRIME Study’† by J.-P. Empana et al., on page 1966

Coronary heart disease (CHD) continues to be a worldwide leading cause of death for both men and women. When coronary atherosclerosis progresses, there is deposition of plaque external to the lumen of the artery, thus the plaque may extend eccentrically and outward without compromising the lumen initially. As atherosclerosis worsens the plaque mass may later on bulge into the lumen and may therefore result in a haemodynamic obstruction and angina pectoris symptoms. Typically, angina pectoris develops when an atherosclerotic plaque obstructs at least 70% of the arterial lumen. Thus, stable angina pectoris is a condition in which there is regional myocardial ischaemia caused by inadequate coronary perfusion and is usually induced by increases in myocardial oxygen requirements. Chest pain that can be characterized as chronic stable angina typically is produced with physical exertion and relieved by rest and/or nitroglycerin. In contrast, chest pain that occurs at rest usually is indicative of unstable disease, such as acute coronary syndrome (ACS) that usually is caused by a coronary plaque rupture and subsequent intracoronary thrombosis formation.

Same disease or two different diseases?

Prognosis of patients with stable angina is in general very good, with an incidence of death or non-fatal myocardial infarction not exceeding 2% per year.1 On the other hand, patients with an ACS without ST elevation [non-ST-segment elevation myocardial infarction (NSTEMI)] have a much worse prognosis since 10–15% experience death or non-fatal myocardial infarction within 1 year after admission.2

Despite a similar anatomical background, there are differences between stable angina pectoris and ACS. Thus, vulnerable plaques are typically defined by a large lipid pool, and a high percentage of inflammatory cells, as well as a thin fibrous cap separating the lipid core from the blood pool. In contrast to collagen-rich hard plaques, which may progress in severity and result in stable angina pectoris, the vulnerable soft plaque is more prone to acute rupture and exposure of the potentially thrombogenic core to the blood pool, with resultant intracoronary thrombosis and an ACS.3 Furthermore, when studying coronary angiograms, it has been shown that patients with ACS generally have fewer diseased vessels, fewer stenoses and occlusions, and a lower atherosclerosis extent index than those with stable angina pectoris.4 These differences in plaque vulnerability and extent of atherosclerosis between patients with stable angina pectoris and ACS may suggest that the two presentations of CHD, at least in part, may develop in different ways and the vulnerability of the plaque rather than the extent of coronary atherosclerosis is likely to be the determinant of ACS. The rate of progression of atherosclerotic lesions is variable and hard to predict. angiographically, small coronary lesions may be associated with acute progression to severe stenosis or total occlusion, and may eventually account for the majority of the patients who develop unstable angina or other ACS.5 However, there is no plaque rupture in all patients with ACS, but rather a superficial erosion of a plaque.

What makes the atherosclerotic disease progress to either a stable angina pectoris or an unstable coronary disease?

Classical cardiovascular risk factors

It is possible that stable angina pectoris and ACS do not share the same cardiovascular risk factor profile. There are some data suggesting that, however the results are heterogeneous.6–7

Inflammation

Inflammation is known to have an important role in the progression of atherosclerotic disease and is considered to be a promoter of the disease. Elevated levels of high-sensitivity C-reactive protein (hs-CRP) have prognostic value with respect to cardiovascular events in patients from several different populations.8–10 In
the study by Empana et al.\textsuperscript{11} higher systemic levels of hs-CRP, interleukin-6 (IL-6), IL-18 and intercellular adhesion molecule-1 (ICAM-1) were equally predictive of stable angina pectoris and ACS. Thus, the possible plaque rupture-triggering effect of inflammation was not specific to unstable disease in this study. Whether CRP reflects the inflammatory component of atherosclerotic plaques or of the circulating blood, and whether it is a surrogate marker or a biologically active element in plaque development of thrombus formation at the site of the atherosclerotic vessel is still under debate.

**The endothelium**

The endothelium, the inner layer of blood vessels, is a dynamic autocrine and paracrine organ. It regulates contractile, secretory, and mitogenic activities in the vessel wall, as well as blood thrombogenicity, by producing several locally active substances. The endothelium is involved in the control of vasomotion through production of vasodilators, such as nitric oxide, and vasoconstrictors, such as endothelin-1, and in the haemostasis system of the vessels by production of factors involved in the coagulation and fibrinolysis system. von Willebrand factor (vWF) is almost exclusively produced by endothelial cells and has several important functions in the process of thrombus formation. vWF is produced and released by vascular endothelial cells in response to a variety of stimuli associated with acute ischaemic syndromes, including hypoxia, inflammatory cytokines, thrombin, and adrenaline.\textsuperscript{12}

**von Willebrand factor**

There are several prospective epidemiological studies showing that plasma measures of different haemostatic factors may predict the future onset of atherothrombotic events in different populations.\textsuperscript{10,12} However, elevated plasma levels of vWF are also associated with several established cardiovascular risk factors and, after adjustments for these traditional risk factors, the significant associations between vWF and future cardiovascular events have been lost in some studies. The risk ratios have varied a lot when individuals with plasma vWF levels in the highest quartile have been compared with those in the lowest quartile. In the large Reykjavik study, consisting of almost 20 000 previously healthy subjects, an odds ratio of 1.23 for the highest vs. the lowest quartile of vWF was reported, and the increased risk of the fourth quartile became insignificant after adjustment for other cardiovascular risk factors.\textsuperscript{13} Morange \textit{et al.} have previously reported a 3-fold increased risk for myocardial infarction in individuals with plasma vWF levels in the highest quartile compared with those in the lowest quartile in the PRIME study.\textsuperscript{14} Also in patients with cardiovascular disease vWF appears to predict the disease, and the association between vWF levels and cardiovascular events seems to be stronger in patients with previous cardiovascular disease than in a healthy population.\textsuperscript{12}

**Interpretation of the study**

In the study of Empana \textit{et al.},\textsuperscript{11} higher levels of vWF were significantly more predictive of acute coronary disease than stable angina pectoris. How could that be explained? vWF has been detected in coronary thrombi rich in platelets and fibrin in acute myocardial infarction,\textsuperscript{15} and during an acute myocardial infarction vWF is elevated, with a peak 2–3 days after the index event. This vWF increase has also been shown to be an independent predictor of short-term adverse clinical outcome in patients with acute CHD.\textsuperscript{12} Thus vWF is involved in the acute setting of a myocardial infarction. In subjects without any known clinical cardiovascular disease it is possible that an elevated level of vWF mirrors an activated coagulation system and/or an endothelial dysfunction, and therefore a subject with an elevated vWF level is more likely to suffer from ACS in the future. In most studies of healthy subjects, the association between vWF levels and coronary events has been rather weak and there is a considerable overlap in vWF levels between subjects who remain healthy and those suffering from an acute coronary event. Therefore, despite a very interesting pathophysiological observation in the present study, the clinical value of vWF measurements in a healthy population is probably limited. We know that ACS is also a heterogeneous condition that may be divided into unstable angina pectoris, NSTEMI, and ST-segment elevation myocardial infarction (STEMI). When diagnosing NSTEMI, we assume that a thrombus incompletely or intermittently occludes a coronary artery, causing non-transmural or short-lasting transmural myocardial ischaemia. The patient will not benefit from thrombolysis and does not need urgent revascularization, but rather stabilizing pharmacological treatment such as antplatelet and antithrombotic drugs. In STEMI, a thrombus completely and permanently occludes a coronary artery, causing transmural myocardial ischaemia, and the thrombus will benefit from an acute percutaneous coronary intervention or thrombolysis. Thus, NSTEMI and STEMI patients have different characteristics and prognosis, and the treatment is different. In the study of Empana \textit{et al.}, discharge diagnoses rather than admission diagnoses were given, and therefore the prognostic value of inflammatory and haemostatic biomarkers may not be the same for the risk of developing STEMI and NSTEMI.

In summary, vWF is a weak predictor of future cardiovascular disease in a healthy population, and an elevated level of vWF may mirror an activated coagulation system and/or an endothelial dysfunction, and therefore a subject with an elevated vWF level might be more likely to suffer from a future ACS.

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**References**


A rare cause of cardiac tumour: an Erdheim–Chester disease with cardiac involvement co-existing with an intracerebral Langerhans cell histiocytosis

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A 65-year-old man, who was diagnosed few weeks ago an intracerebral Langherans cell histiocytosis (CD68+, CDA1+) (Panel A), was admitted for check up of extracerebral localization. CT scan showed lung fibrosis, retroperitoneal fibrosis, and moderate intra-pericardial and pleural effusion. Transthoracic echocardiography revealed a cardiac tumour developed in the interatrial septum and right atrial wall. Transoesophageal echography and MRI confirmed the diagnosis (Panels B and C). An echo-guided biopsy was performed (Panel C). Histology of the cardiac tumour fragments showed histiocytes proliferation, as well as lung and retroperitoneal fragments, but with a different immunohistochemical profile than intracerebral localization (CD68+, CDA1−), typical of those encountered in Erdheim–Chester disease (Panel D).

Erdheim–Chester disease is a systemic, non-Langerhans cell histiocytosis, with various clinical manifestations. The most frequent abnormality is symmetric long tubular bone involvement, but lung or retroperitoneal fibrosis and perirenal or periarotic infiltration can be seen. Infrequently, pericardial or cardiac involvements have been described.

This is the first case of co-existing Langerhans and non-Langerhans cells histiocytosis with cardiac involvement.

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