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The spectrum of chronic coronary syndromes: genetics, imaging, and management after PCI and CABG

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Coronary artery disease (CAD) has many aspects: it may be chronic or present acutely, and it may be due to structural or functional changes of the coronary circulation; thus, the new expression 'chronic coronary syndromes' for what we formerly called stable CAD appears appropriate, as it refers to the many faces of the disease and is complementary to acute coronary syndromes. The causes of acute and chronic coronary syndromes are also varied, but genetics may be an important underlying cause. Indeed, recent genome-wide association studies have identified >100 gene variants associated with CAD,[1,2] and sudden cardiac death,[3] among them the *JCAD* locus. However, the mechanisms whereby *JCAD* confers risk remain unclear. Zheng Gen Jin and colleagues from the University of Rochester Medical Center in Rochester, USA addressed this issue in their article entitled '**The novel coronary artery disease risk gene *JCAD/KIAA1462* promotes endothelial dysfunction and atherosclerosis**'.[4] By mining data in the Genotype-Tissue Expression database, they found that CAD-associated risk variants at the *JCAD* locus are linked to increased *JCAD* gene expression in human arteries. In global and endothelial cell-specific *JCAD*$^{-/-}$ mice, diet-induced endothelium-dependent relaxation was improved and atherosclerosis reduced. Genome-wide transcriptional profiling of *JCAD*-depleted human coronary artery endothelial cells showed that this inhibited the YAP/TAZ pathway (*Figure 1*) and the expression of downstream pro-atherogenic genes, including *CTGF*[3] and *Cyr61*.[5] As a result, *JCAD*-deficient endothelial cells attracted fewer monocytes in response to lipopolysaccharide stimulation. Moreover, *JCAD* expression in endothelial cells was decreased under unidirectional laminar flow *in vitro* and *in vivo*. Proteomics studies suggest that JCAD regulates YAP/TAZ activation by interacting with actin-binding protein TRIOBP, thereby stabilizing stress fibre formation. Finally, endothelial *JCAD* expression was increased in mouse and human atherosclerotic plaques (*Figure 1*).

Thus, the CAD risk gene, *JCAD*, identified by genome-wide association studies promotes endothelial dysfunction and atherosclerosis, thus highlighting the possibility of new therapeutic strategies for CAD by targeting *JCAD*. These promising novel findings are put into context in an **Editorial** by Sokrates Stein from the Center for Molecular Cardiology in Zurich, Switzerland.[6]

Genetic disposition and lifestyle factors are understood as independent components underlying the risk of multiple diseases. However, genes associated with educational attainment may importantly affect compliance with lifestyle and medical prescriptions,[7,8] and, in turn, clinical outcome. In their article entitled '**Genetically modulated educational attainment and coronary disease risk**', Heribert Schunkert and colleagues from the Deutsches Herzzentrum München and DZHK in Germany investigated the interplay between genetics, educational attainment, and coronary risk.[2] Based on the effect sizes of 74 genetic variants associated with educational attainment, they calculated a 'genetic education score' in 13 080 cases and 14 471 controls, and observed an inverse correlation between it and coronary artery risk (*Figure 2*). Importantly, they replicated their findings in 146 514 individuals of the UK Biobank.

Mendelian randomization analyses using 1271 variants affecting educational attainment further strengthened these findings. Thus, genetic variants known to affect educational attainment may have implications for a health-conscious lifestyle later in life and subsequently affect the risk of CAD.

In patients undergoing coronary angiography prior to percutaneous coronary intervention (PCI) or bypass surgery, cardiologists traditionally based their decisions on visual estimation of the degree of coronary artery stenosis. However, numerous studies have shown that this may be erroneous and that intracoronary pressure measurements are much more reliable.[9,10] However, while fractional flow reserve (FFR) is used to guide PCI, this has not been widely used prior to bypass surgery, with the exception of computed tomography (CT)-based FFR.[11] In their article '**Impact of pre-operative fractional flow reserve on arterial bypass graft anastomotic**

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function: the IMPAG trial', David Glineur and colleagues from the University of Ottawa Heart Institute in Ontario, Canada investigated whether pre-operative invasive FFR measurement of coronary lesions would be associated with graft function 6 months after surgery in a double blind study of 67 patients and 199 lesions.[12] Pre-operative FFR was significantly associated with 6 months anastomotic function for all conduits and for all targets. An FFR of ≤0.78 was associated with an anastomotic occlusion rate of 3%. Thus, the association between pre-operative FFR of the target vessel and anastomotic functionality at 6 months, with a cut-off of 0.78, should be integrated into the pre-operative diagnostic workup before bypass surgery, a conclusion that is further discussed in an **Editorial** by Morton Kern from the University of California in the USA.[13]

Dual antiplatelet therapy is the gold standard for patients undergoing PCI.[13] Its use and duration have been heavily discussed because of the risk of bleeding that may be reduced by proton pump inhibitors,[14] but remains a concern nonetheless.[15] However, while its use in patients undergoing PCI has been extensively investigated,[16] the antiplatelet treatment strategy providing optimal balance between thrombotic and bleeding risks in those undergoing coronary artery bypass grafting (CABG) is unclear. In their FAST TRACK '**Randomized trial of ticagrelor vs. aspirin in patients after coronary artery bypass grafting: the TiCAB trial**',[17] Heribert Schunkert and colleagues from the German Heart Centre Munich in Germany randomly assigned in double-blind fashion patients scheduled for CABG to ticagrelor 90 mg b.i.d. or 100 mg aspirin once daily. Twelve months after CABG, of 1859 out of the 3850 planned patients, major adverse cardiovascular events (MACE) occurred in 9.7% in the ticagrelor group and in 8.2% in the aspirin group, which did not differ statistically. All-cause mortality was also similar, with 2.5% with ticagrelor and 2.6% with aspirin (hazard ratio 0.96, 95% confidence interval 0.53–1.72, $P = 0.89$), as was cardiovascular death (ticagrelor 1.2% vs. aspirin 1.4%), and myocardial infarction and stroke. The main safety endpoint of bleeding was also not different between groups. Thus, in this prematurely terminated and thus underpowered randomized trial of ticagrelor vs. aspirin in patients after CABG no significant differences in MACE were found. In an **Editorial** by Paul A. Gurbel from the Inova Heart and Vascular Institute in Baltimore, Maryland (USA) the value of these findings for everyday practice are further discussed.[18]

Non-invasive imaging techniques in patients with CAD have been introduced to avoid unnecessary angiographies.[19] Today, technologies providing insight into coronary structure are able to document ischaemia such as CT[20], stress echocardiography, magnetic resonance imaging,[21] and nuclear scans,[22] and are widely used. The strengths and weaknesses of these imaging modalities and their place in the evaluation of different clinical conditions are reviewed in the article '**Non-invasive imaging of the coronary arteries**'. David E. Newby and colleagues from the Royal Infirmary in Edinburgh, UK note that non-invasive imaging of the coronary arteries is an enterprise in rapid development.[23]

Although PCI is a very successful technique today, with restoration of coronary flow in the vast majority of the patients,[24] up to 20–40% complain of recurrent angina at 1-year follow-up even with FFR-guided PCI and drug-eluting stents and in the presence of an angiographically documented good result of the procedure.[25] This puzzling issue is discussed in a review article '**Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization**' by Filippo Crea and colleagues from the Universita Cattolica del Sacro Cuore in Rome, Italy.[26] Importantly, persistent or recurrent angina post-PCI is associated with a significant economic burden, with almost two-fold higher healthcare costs in such patients. However, guideline recommendations regarding the management of angina post-PCI are not very helpful, as there are gaps in evidence for the mechanisms of post-PCI angina. This review discusses potential mechanisms of this phenomenon including microvascular dysfunction[27] and side branch occlusion, among others, proposes a practical diagnostic algorithm, and summarizes current knowledge gaps.

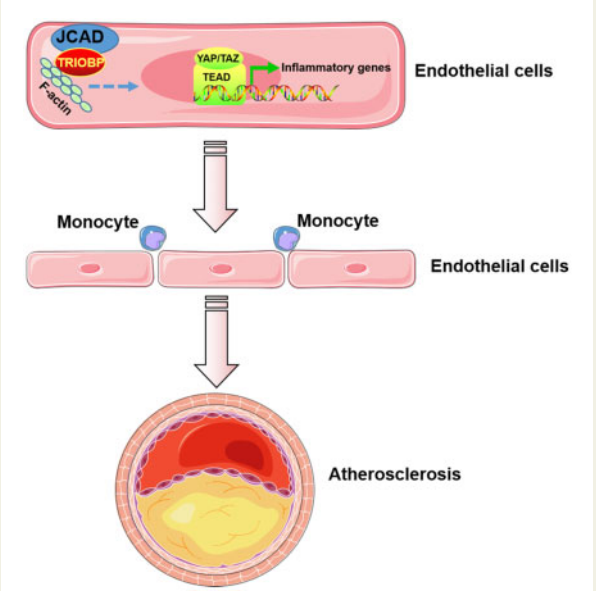

Figure 1 JCAD promotes endothelial dysfunction and atherosclerosis. Junctional protein JCAD promotes the activation of YAP/TAZ/TEAD by interacting with TRIOBP and thus stabilizing F-actin stress fibres. By doing so, JCAD triggers the expression of inflammatory genes in endothelial cells, driving an inflammatory process via the recruitment of monocytes and resulting in the formation of atherosclerotic plaques. (from Xu S, Xu Y, Liu P, Zhang S, Liu H, Slavin S, Kumar S, Koroleva M, Luo J, Wu X, Rahman A, Pelisek J, Jo H, Si S, Miller CL, Jin ZG. The novel coronary artery disease risk gene *JCAD/KIAA1462* promotes endothelial dysfunction and atherosclerosis. See pages 2398–2408).

The issue is further complemented by two Discussion Forum contributions. In the first contribution '**Transient ST-segment elevation and coronary flow**' Ruben Coronel and colleagues from the Academic Medical Center in Amsterdam, The Netherlands comment on the article '**Timing of revascularization in patients with transient ST-segment elevation myocardial infarction: a randomized clinical trial**'.[28,29] Niels van Royen and colleagues from the Radboud University Medical Center in Nijmegen, The Netherlands, who authored the article in question, respond to the comments of Ruben Coronel and colleagues in their own contribution.[30]

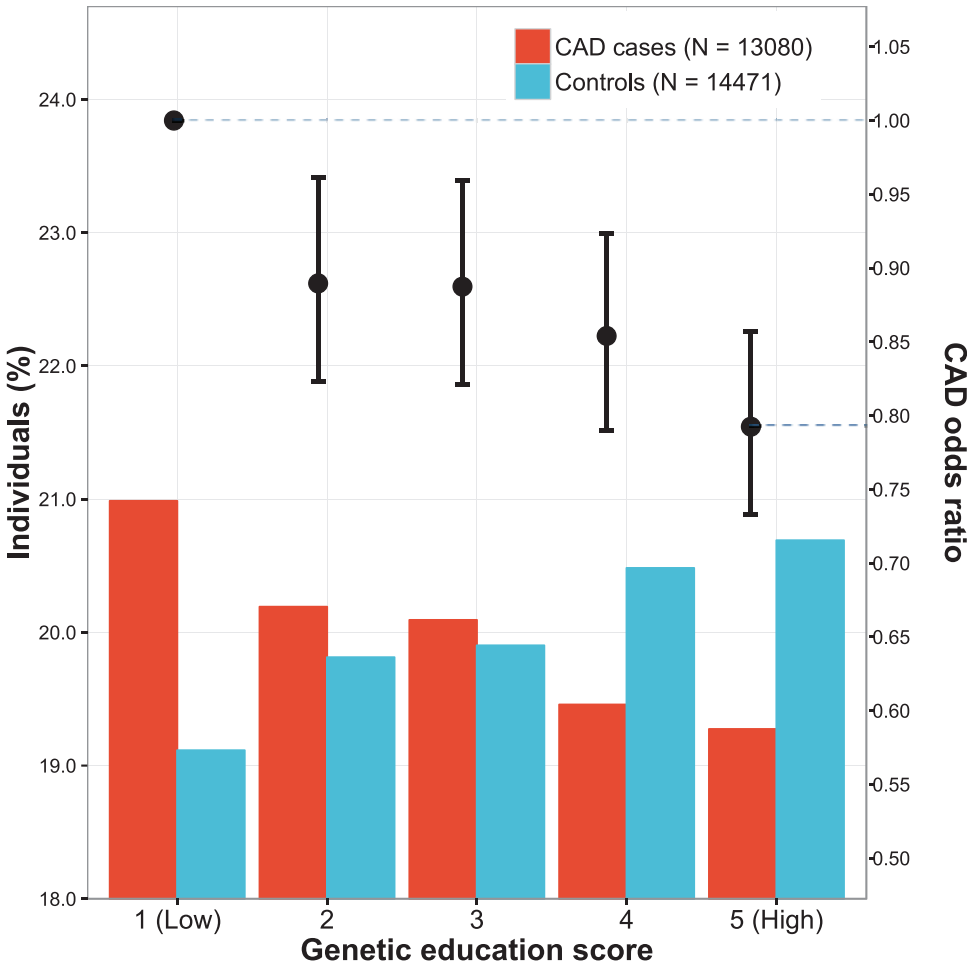

Figure 2 Inverse relationship of genetically determined educational attainment and risk of coronary artery disease (CAD). Individuals from each of the nine studies were grouped into quintiles based on their weighted genetic risk score for school attainment, with quintile 1 indicating the lowest genetic score and quintile 5 the highest. Odds ratios, shown with 95% confidence intervals, for CAD were 20.8% lower in the quintile with the highest genetically determined educational attainment as compared with those with the lowest 'genetic education score'. The distribution of all cases (red bars) with CAD is decreasing with an increasing 'genetic education score', while that of all controls (blue bars) has an opposite trend. *P*-value = 7.66×10^{-9} was obtained from Cochran–Armitage trend test. (from Zeng L, Ntalla I, Kessler T, Kastrati A, Erdmann J, The UK Biobank CardioMetabolic Consortium CHD Working Group, Danesh J, Watkins H, Samani NJ, Deloukas P, Schunkert H. Genetically modulated educational attainment and coronary disease risk. See pages 2413–2420).

The editors hope that readers of this issue of the *European Heart Journal* will find it of interest.

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