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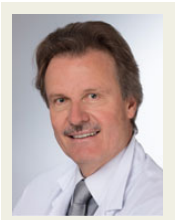
Neglected cardiovascular risk factors



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Obesity and the metabolic syndrome are highly prevalent conditions. The metabolic syndrome not only precedes cardiovascular conditions, and hence represents an important cluster of risk factors,[1,2] but also remains relevant in patients with established coronary artery disease and heart failure and other cardiovascular conditions.[3] It is still unclear, if—in the setting of cardiac dysfunction—it represents an adverse risk factor for clinical outcomes. The obesity paradox complicates the definition of its role in these patients.[4–6] The epidemiological implications of metabolic syndrome in heart failure have been studied intensely, as many of its components contribute to the incidence and severity of heart failure. In particular, insulin resistance, diabetes mellitus, and lipid abnormalities represent the main components that contribute to disease progression. Yet, other components of the metabolic syndrome, i.e. overweight and obesity as well as high blood pressure, are favourably associated with outcome in heart failure. This complex interaction of risk factors is extensively discussed in a timely *Clinical Review* entitled '**The role of metabolic syndrome in heart failure**' by Pasquale Perrone-Filardi from the Federico II University of Naples in Italy.[7]

Proper identification of subjects at increased risk for cardiovascular events plays a central role in our efforts to improve the prevention and management of cardiovascular disease and to decrease the related costs. Despite their high predictive value on a population level, traditional risk factors fail to predict individual risk fully. Thus, the discovery of novel risk markers remains an unmet need. In the second *Clinical Review* '**Novel methodologies for biomarker discovery in atherosclerosis**',[8] Imo Hoefer from UMC Utrecht in The Netherlands provides a summary of current vascular biomarkers other than the traditional risk factors, with a special focus on the emerging -omics technologies which may provide even better markers in the future. First, the limitations of current biomarkers such as high sensitivity C-reactive protein and N-terminal pro-brain natriuretic peptide, as well as those of other circulating plasma biomarkers such as HDL are discussed. Based on the failure of recent trials,[9–11] and basic science findings,[12] the authors emphasize the conceptual shift from HDL-cholesterol levels to HDL composition and function for cardiovascular risk assessment and future interventions. Promising novel sources for plasma-derived markers include microparticles, microvesicles, and exosomes,[13] and their use for current omics-based analytics. For the search for novel biomarkers, circulating microRNAs,[14–16] short RNA sequences regulating gene expression, have attracted growing attention. Also, mass spectrometry and nuclear magnetic resonance spectroscopy have become key complementary technologies in the search for new biomarkers, such as proteomic searches or identification and quantification of small metabolites including lipids (metabolomics and lipidomics).[17] Furthermore, based on the view that atherosclerosis represents a chronic inflammatory disease,[18] proinflammatory lipid metabolites have gained much interest in the cardiovascular field. The authors conclude that the discovery of novel biomarkers reflecting hitherto unrecognized disease mechanisms may improve individual cardiovascular risk prediction and in turn disease management.

A sedentary lifestyle is an important risk factor for cardiovascular disease.[19] Accordingly, all prevention guidelines recommend exercise programmes.[20] However, such programmes are often difficult to implement in the real-world setting. It is unknown whether standing is a suitable replacement activity for sitting or whether ambulatory movement is required. In the first clinical research paper, '**Replacing sitting by standing or stepping: associations with cardio-metabolic risk biomarkers**', Genevieve N. Healy from the University of Queensland in Australia,[19] modelled—using isotemporal substitution analyses—cross-sectional associations of biomarkers of cardio-metabolic risk with the reallocation of time (2 h/day) from sitting to standing or stepping. To that end, a subsample of 698 participants from the Australian Diabetes, Obesity and Lifestyle Study wore the posture-based activPAL3 monitor. Associations of activPAL3-derived mean daily time spent sitting or lying analysed together or standing and stepping with body mass index (BMI), waist circumference, blood pressure, glycated haemoglobin (HbA_{1c}), fasting glucose, and lipids such as HDL- and LDL-cholesterol, the total/HDL-cholesterol ratio, and triglycerides as well as 2-h plasma glucose plasma levels were examined. Adjusted for relevant confounders, sitting to standing reallocations for 2 h per day were associated with a 2% lower fasting plasma glucose, 11% lower triglycerides, 6% lower total/HDL-cholesterol ratio, and 0.06 mmol/L higher HDL-cholesterol. Sitting to stepping reallocations per 2 h per day were associated with ~11% lower BMI, 7.5 cm lower waist circumference, 11% lower 2-h plasma glucose, 14% lower triglycerides, and 0.10 mmol/L higher HDL-cholesterol; while standing to stepping reallocations were associated with ~10% lower BMI, 7 cm lower waist circumference, and 11% lower 2-h plasma glucose. The authors' findings therefore suggest that sitting reduction strategies targeting increased standing, stepping, or both, may benefit cardio-metabolic health. Standing is a simple

alternative to sitting, and requires further examination in prospective and intervention studies. This paper is accompanied by an **Editorial** by Francisco Lopez-Jimenez from the Mayo Clinic in Rochester, Minnesota, USA.[21]

Environmental noise is an increasingly recognized cardiovascular risk factor, particularly for individuals living in urban areas.[22] In the second paper, '**Road traffic noise is associated with increased cardiovascular morbidity and mortality, and all-cause mortality in London**', Jaana I. Halonen and colleagues from the Finnish Institute of Occupational Health in Kuopio, Finland[23] hypothesized that road traffic noise may be associated with hypertension and clinical outcome. To that end, the authors examined the effects of long-term exposure to road traffic noise on hospital admissions and mortality in 8.6 million inhabitants of London. They assessed small area-level associations of daytime and night-time road traffic noise with cardiovascular hospital admissions and all-cause and cardiovascular mortality in all adults and the elderly through Poisson regression models. The models were adjusted for age, sex, area-level socio-economic deprivation, ethnicity, smoking, air pollution, and neighbourhood spatial structure. Median daytime exposure to road traffic noise was 55.6 dB. Daytime road traffic noise increased the risk of hospital admission for stroke, with a relative risk of 1.05 in the elderly in areas above 60 dB as compared with those exposed to $<$55 dB. Night-time noise was associated with stroke admissions only among the elderly. Daytime noise was associated with all-cause mortality in adults, with a relative risk of 1.04 in areas $>$60 dB as compared with those exposed to $<$55 dB. Positive but non-significant associations were seen with mortality for cardiovascular and ischaemic heart disease, and stroke. The authors conclude that long-term exposure to road traffic noise was associated with small, but measurable increases in risks of all-cause mortality and cardiovascular mortality and morbidity in the general population, particularly for stroke in the elderly.

The issue closes with a *Brief Communication* '**Cholesterol efflux capacity in humans with psoriasis inversely relates to non-calcified burden of coronary atherosclerosis**'[24] by Nehal Mehta and colleagues from the National Institute of Health in Bethesda, Maryland, USA. Cholesterol efflux capacity plays an important role in lipid metabolism,[21,25] and might predict future cardiovascular events.[26] As with many inflammatory diseases, psoriasis increases cardiovascular risk[27] and also impairs HDL efflux capacity. However, whether having poor cholesterol efflux capacity increases coronary plaque burden is currently unknown. Total burden and non-calcified burden plaque indices were assessed in 101 psoriasis patients using quantitative software, while HDL efflux was quantified using a cell-based *ex vivo* assay measuring the ability of apoB-depleted plasma to mobilize cholesterol from lipid-loaded macrophages. As HDL efflux increased, non-calcified burden decreased, which persisted after adjustment for cardiovascular risk factors, HDL levels, and apoA1 levels. Furthermore, a significant gender interaction was noted, whereby women with low efflux had higher non-calcified burden compared with men. Thus, HDL efflux is negatively associated with coronary plaque burden measured by quantitative coronary computed tomography (CT) angiography. Low HDL efflux may therefore be a strong biomarker for subclinical coronary atherosclerosis in psoriasis.

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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CARDIOVASCULAR FLASHLIGHT

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Successful stenting of left pulmonary veins stenosis resulting from fibrosing mediastinitis

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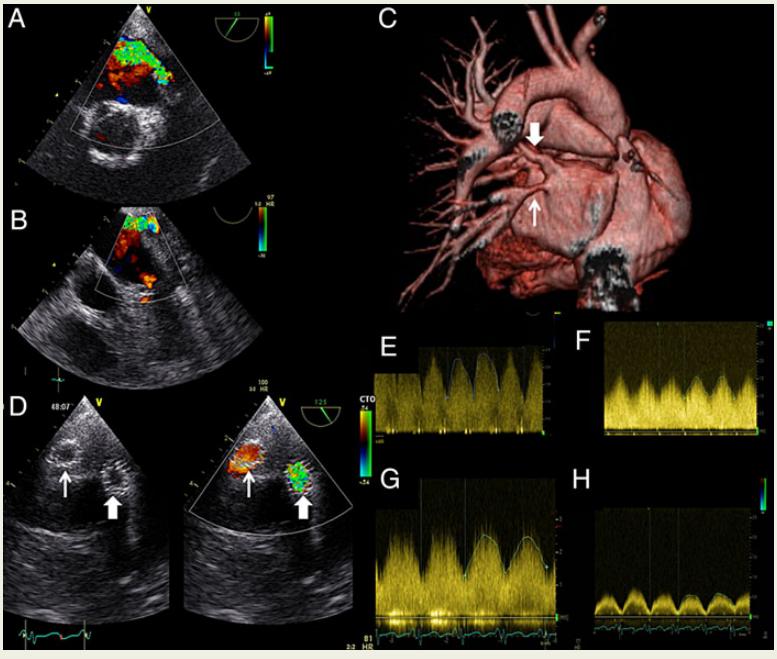

A 36-year-old woman presented with increasing dyspnoea and cough on minimal exertion and at rest. She presented a 7-year history of idiopathic fibrosing mediastinitis with asymptomatic superior vena cava obstruction. Echocardiography was consistent with pulmonary hypertension and right ventricular dysfunction (estimated pulmonary arterial systolic pressure 70 mmHg). Turbulent flows were identified within the left atrium. Transesophageal echocardiography was consistent with left upper (LU, 35° plane, *Panel A*) and lower (LL, 10° plane, *Panel B*) pulmonary veins (PVs) stenosis. On thoracic computed tomographic imaging, left PVs stenosis were confirmed (left posterior view, *Panel C*; LL and LU PV, thin and large arrows, respectively), and left lung pulmonary oedema was noted. Bare metal stents (Boston Scientific) were implanted in the LL and the LU PV (15 × 8 and 20 × 8 mm, respectively), through a transeptal approach (*Panel D*). The procedure allowed the velocities of the LU and LL PV to decrease from 1.97 to 1.29 m/s (*Panels E* and *F*) and from 2.05 to 0.43 m/s (*Panels G* and *H*), respectively. The patient was discharged with a lifelong aspirin 80 mg and a 1-month clopidogrel 75 mg regimen. She reported immediate marked symptomatic improvement, allowing her to resume activities of daily living.

Fibrosing mediastinitis is an extremely infrequent long-term sequella of fungal and mycobacterial infections. It is associated with substantial morbidity and mortality related to progressive narrowing of mediastinal structures. Only limited therapeutic options exist. Percutaneous stenting of PV is feasible and is associated with substantial haemodynamic and symptomatic improvement in selected patients.

Supplementary Material is available at *European Heart Journal* online.