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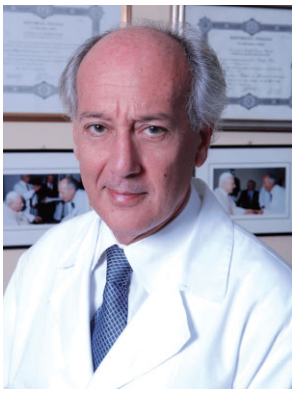
New therapeutic targets in the prevention of atherosclerotic cardiovascular disease



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This Focus Issue on vascular biology and medicine contains the State of the Art Review article '**Vascular repair and regeneration in cardiometabolic diseases**' authored by David Hess from the University of Toronto in Canada, and colleagues.[1] The authors present current strategies to assess the progression of provascular regenerative cell depletion in peripheral blood samples of individuals with type 2 diabetes mellitus (T2D) and obesity, and summarize novel clinical data showing that intervention using sodium–glucose co-transporter 2 inhibition or gastric bypass surgery can efficiently restore cell-mediated vascular repair mechanisms associated with profound cardiovascular benefits in recent outcome trials. Collectively, this thesis generates a compelling argument for early intervention using current pharmacological agents to prevent or restore imbalanced circulating progenitor content and maintain vascular regenerative cell trafficking to sites of ischaemic damage. This conceptual advancement may lead to the design of novel therapeutic approaches to prevent or reverse the devastating cardiovascular comorbidities currently associated with T2D and obesity.

Stroke is a leading cause of death and disability worldwide.[2–8] Women are disproportionately affected by stroke, exhibiting higher mortality and disability rates post-stroke than men. In a second State of the Art Review article entitled '**Importance of sex and gender in ischaemic stroke and carotid atherosclerotic disease**', Karina Gasbarrino from McGill University in Montreal, Canada, and colleagues note that clinical stroke research has historically included mostly men, and studies were not properly designed to perform sex- and gender-based analyses, leading to underappreciation of differences between men and women in stroke presentation, outcomes, and response to treatment.[9] Reasons for these differences are probably multifactorial; some are due to gender-related factors (i.e. decreased social support or lack of stroke awareness), yet others result from biological differences between sexes. Unlike men, women often present with 'atypical' stroke symptoms. Lack of awareness of 'atypical' presentation has led to delays in hospital arrival, diagnosis, and treatment of women. Differences also extend to carotid atherosclerotic disease, a cause of stroke, where plaques isolated from women are undeniably different in morphology/composition compared with men. As a result, women may require different treatment from men, as evidenced by the fact that they derive less benefit from carotid revascularization than men but benefit more from medical management. Despite this, women are less likely than men to receive medical therapy for cardiovascular risk factor management. This review focuses on the importance of sex and gender in ischaemic stroke and carotid atherosclerotic disease, summarizing the current evidence with respect to (i) stroke incidence, mortality, awareness, and outcomes; (ii) carotid plaque prevalence, morphology and composition, and gene connectivity; (iii) the role of sex hormones and sex chromosomes in atherosclerosis and ischaemic stroke risk; and (iv) carotid disease management.

Evidence suggests that overactivation of the mineralocorticoid receptor (MR) leads to inflammation and fibrosis in the heart, kidneys, and vasculature where the MR is extensively expressed, that can drive chronic kidney disease (CKD) and cardiovascular disease (CVD) progression.[10] Finerenone is a novel, selective, non-steroidal MR antagonist (MRA) that blocks MR-mediated sodium reabsorption and MR overactivation, and has demonstrated anti-inflammatory and antifibrotic effects in pre-clinical kidney disease and CVD models. In a Fast Track Clinical Research article entitled '**Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis**', Rajiv Agarwal from the Indiana University School of Medicine and Richard Roudebush VA Medical Center in Indianapolis, USA, and colleagues indicate

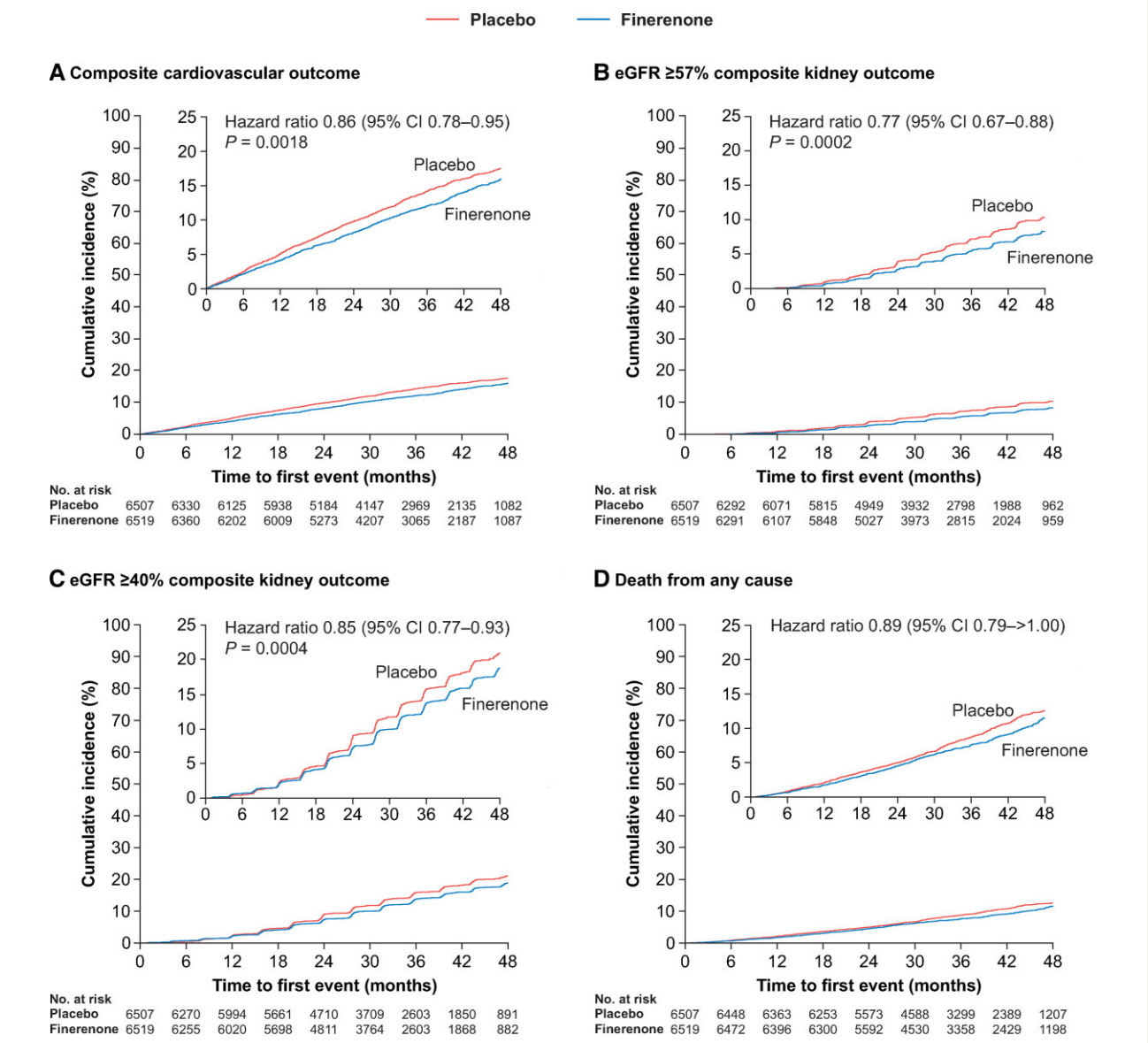

Figure 1 Time to efficacy outcomes. (*A*) The composite cardiovascular outcome defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure (Aalen–Johansen curve). (*B*) The composite kidney outcome defined as kidney failure, sustained ≥57% decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death (Aalen–Johansen curve). (*C*) The composite kidney outcome defined as kidney failure, sustained ≥40% decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death (Aalen–Johansen curve). (*D*) All-cause mortality (Kaplan–Meier curve). Outcomes were assessed in time-to-event analyses.[11]

that the purpose of the FIDELITY analysis was to perform an individual patient-level pre-specified pooled efficacy and safety analysis across a broad spectrum of CKD to provide more robust estimates of safety and efficacy of finerenone compared with placebo.[11] For this pre-specified analysis, two phase III, multicentre, double-blind trials (FIDELIO-DKD and FIGARO-DKD) involving patients with CKD and T2D, randomized 1:1 to finerenone or placebo, were combined. Main time-to-event efficacy outcomes were a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure, and a composite of kidney failure, a sustained ≥57% decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death. Among 13 026 patients with a median follow-up of 3.0 years, the composite cardiovascular outcome occurred in 825 (12.7%) patients receiving finerenone and in 939 (14.4%) receiving placebo [hazard ratio (HR) 0.86; $P = 0.0018$]. The composite kidney outcome occurred in 360 (5.5%) patients receiving finerenone and in 465 (7.1%) receiving placebo (HR 0.77; $P = 0.0002$). Overall safety outcomes were generally similar between treatment arms. Hyperkalaemia leading to permanent treatment

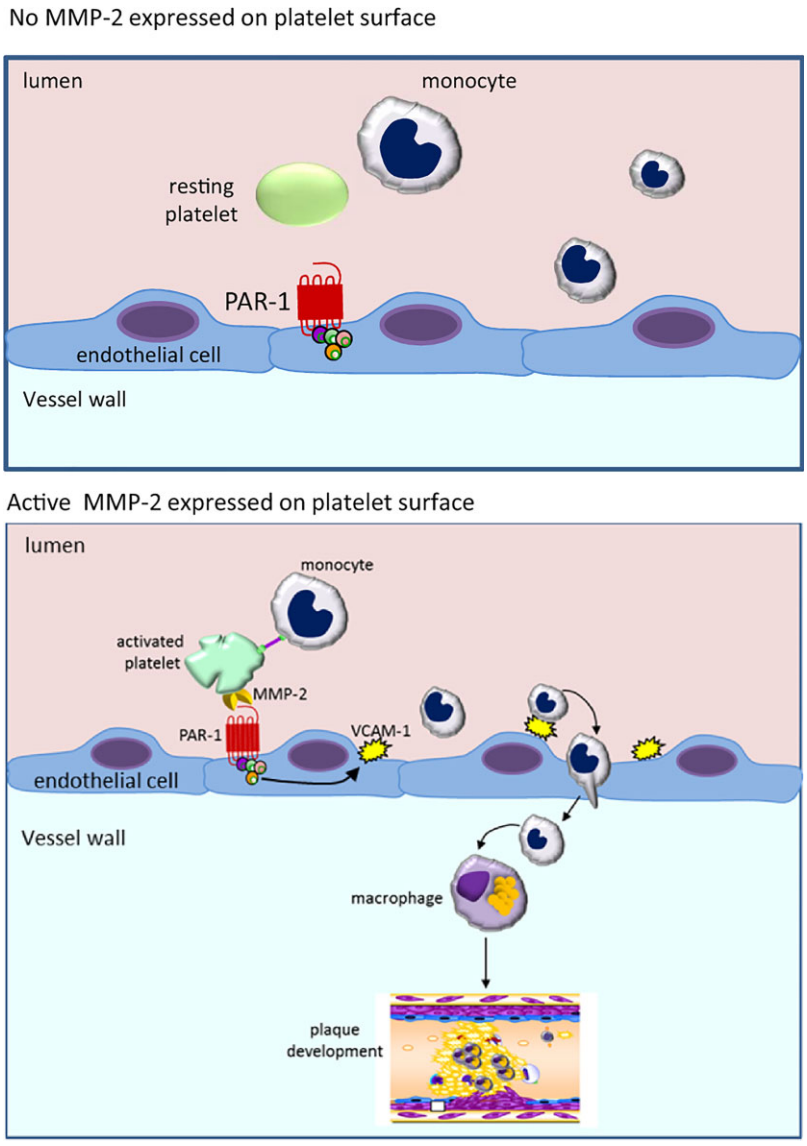

Figure 2 The study demonstrates that platelet-derived MMP-2 plays a pivotal role in the very early phases of atherogenesis in hypercholesterolaemic mice. Circulating activated platelets expressing MMP-2 on their surface interact with PAR-1 of endothelial cells, triggering signal transduction and activation with the consequent exposure of adhesion molecules (i.e. VCAM-1), the latter in turn facilitate the adhesion and transmigration of monocytes through the endothelial monolayer ultimately leading to atheroma formation. The interaction between MMP-2 expressed by activated platelets and endothelial cell PAR-1 may represent a novel therapeutic target for the prevention of atherosclerosis.[18]

discontinuation occurred more frequently in patients receiving finerenone (1.7%) than in those receiving placebo (0.6%).

The authors conclude that finerenone reduces the risk of clinically important cardiovascular and kidney outcomes vs. placebo across the spectrum of CKD in patients with T2D. The contribution is accompanied by an **Editorial** by Pardeep Jhund and Carly Adamson from the University of Glasgow in Scotland, UK.[12] They highlight that there is one important finding for the cardiologist from FIDELITY: it offers insight into which patients may benefit from finerenone in the future. In an analysis of the components of the cardiovascular outcomes, the biggest relative risk reduction (22%) was in hospitalizations for heart failure. Heart failure has suffered from issues of artificial cut-offs for ejection fraction which have only recently begun to be disentangled by guidelines. While MRAs hold a class 1A recommendation for the treatment of heart failure with reduced ejection fraction, trials of MRAs in heart failure with preserved ejection fraction have not been so conclusive. Finerenone is being tested in the FINEARTS-HF trial (NCT04435626) in a population with heart failure with preserved ejection fraction (≥40%) to determine if this non-steroidal MRA

can improve outcomes in the spectrum of ejection fraction not covered by current guideline recommendations for MRAs. The authors conclude that we should continue to define diseases, and risk, by cut-offs in a measure of renal or cardiac function until trial design advances to accommodate the blurry nature of these definitions. Until then, FIDELITY serves as yet another reminder that combining populations will continue to yield important insights into the efficacy of treatments in wider populations.

Endothelial dysfunction plays an important role in CVDs.[13] In a Translational Research article entitled '**Tubulin-folding cofactor E deficiency promotes vascular dysfunction by increased endoplasmic reticulum stress**', Panagiotis Efentakis from the University Medical Center Mainz in Germany, and colleagues aimed to evaluate novel markers of flow-mediated dilation (FMD) at the population level.[14] In order to identify novel targets that were negatively correlated with FMD and investigate their contribution to vascular function, the authors performed a genome-wide association study (GWAS) of 4175 participants of the population-based Gutenberg Health Study. Subsequently, conditional knockout mouse models deleting the gene of interest were generated and characterized. GWAS analysis revealed that single nucleotide polymorphisms (SNPs) in the tubulin-folding cofactor E (TBCE) gene were negatively correlated with endothelial function and TBCE expression. Vascular smooth muscle cell (VSMC)-targeted TBCE deficiency was associated with endothelial dysfunction, aortic wall hypertrophy, and endoplasmic reticulum (ER) stress-mediated VSMC hyperproliferation in mice, paralleled by calnexin up-regulation and exacerbated by the blood pressure hormone angiotensin II. Treating SMMHC-ERT2-Cre$^{+/-}$TBCE$^{fl/fl}$ mice with the ER stress modulator tauroursodeoxycholic acid (TUDCA) amplified Raptor/Beclin-1-dependent autophagy and reversed vascular dysfunction.

Efentakis and colleagues conclude that TBCE and tubulin homeostasis seem to be novel predictors of vascular function and offer a new drug target to ameliorate ER stress-dependent vascular dysfunction. This manuscript is accompanied by an **Editorial** by Tohru Minamino and Hiroshi Iwata from the Juntendo University Graduate School of Medicine in Tokyo, Japan.[15] They conclude that precision medicine with TBCE genotyping would be desirable to examine the individual effects of treatment of these ER stress-related diseases, including CVD. It would also be of interest to examine whether TBCE genotypes contribute to the residual CVD risk after lowering LDL cholesterol and explore the potential of the additional treatment with TUDCA for atherosclerotic diseases.

Platelets participate in CVD with mechanisms not yet fully clarified.[16,17] Vascular wall matrix metalloproteinase-2 (MMP-2) is involved in the arterial remodelling accompanying atherosclerosis. In a Translational Research article entitled '**Matrix metalloproteinase-2 on activated platelets triggers endothelial PAR-1 initiating atherosclerosis**', Stefania Momi from the University of Perugia in Italy, and colleagues point out that platelets contain and release MMP-2 but no information is available on its role in atherosclerotic lesion formation.[18] The authors generated double knockout mice lacking the LDL receptor (LDLR) and MMP-2 only in circulating blood cells, showing that they develop significantly less femoral intima thickening after photochemical-induced arterial damage and atherosclerotic lesions in the aorta, measured by the *en face* method, after 4 months of atherogenic diet as compared with LDLR$^{-/-}$ mice. Moreover, repeated transfusions of autologous-activated platelets in LDLR$^{-/-}$ mice on an atherogenic diet significantly enhanced the extension of aortic atherosclerotic lesions while transfusion of activated platelets from MMP-2$^{-/-}$ mice did not. *In vitro* co-incubation studies showed that platelet-derived MMP-2 plays a pivotal role in the development and progression of atherosclerosis through a complex cross-talk between activated platelets, monocyte/macrophages, and endothelial cells. Translational studies in patients with coronary artery disease and chronic HIV infection showed that platelet surface expression of MMP-2 highly significantly correlated with the degree of carotid artery stenosis.

The authors conclude that they demonstrate a previously unknown mechanism of the pathway through which platelets expressing MMP-2 trigger the initial phases of atherosclerosis and provide a mechanism showing that they activate endothelial PAR-1, triggering endothelial p38MAPK signalling and the expression of adhesion molecules. Thus, the development of drugs selectively blocking platelet MMP-2 or its expression may represent a new approach to the prevention of atherosclerosis. This contribution is accompanied by an **Editorial** by Judith Cosemans from Maastricht University in the Netherlands.[19] Cosemans concludes that making use of the diversity in signalling downstream of PAR-1 upon its activation by MMP-1 and -2 vs. thrombin may provide a promising avenue to selectively target the proinflammatory activity of PAR-1.

Atherosclerotic cardiovascular disease (ACVD) is a major cause of mortality and morbidity worldwide, and increased LDLs play a critical role in development and progression of atherosclerosis.[20–23] In a Translational Research article entitled '**Propionate attenuates atherosclerosis by immune-dependent regulation of intestinal cholesterol metabolism**', Arash Haghikia from the Charité–Universitätsmedizin Berlin in Germany, and colleagues examined for the first time gut immunomodulatory effects of the microbiota-derived metabolite propionic acid (PA) on intestinal cholesterol metabolism.[24] In apolipoprotein E−/− (*Apoe*$^{-/-}$) mice fed a high-fat diet (HFD), PA reduced intestinal cholesterol absorption and aortic atherosclerotic lesion area. Further, PA increased regulatory T-cell numbers and interleukin (IL)-10 levels in the intestinal microenvironment, which in turn suppressed the expression of Niemann–Pick C1-like 1 (Npc1l1), a major intestinal cholesterol transporter. Blockade of IL-10 receptor signalling attenuated the PA-related reduction in total and LDL cholesterol and augmented atherosclerotic lesion severity. To translate these pre-clinical findings to humans, the authors conducted a randomized, double-blind, placebo-controlled human study (clinical trial no. NCT03590496). Oral supplementation with 500 mg of PA twice daily over the course of 8 weeks significantly reduced LDL (−15.9 vs. −1.6 mg/dL, $P = 0.016$), and non-HDL cholesterol levels (−18.9 vs. −0.6 mg/dL, $P = 0.002$) in subjects with elevated baseline LDL cholesterol levels.

Haghikia *et al.* conclude that their findings reveal a novel immune-mediated pathway linking the gut microbiota-derived metabolite PA with intestinal Npc1l1 expression and cholesterol

homeostasis. The results highlight the gut immune system as a potential therapeutic target to control dyslipidaemia that may introduce a new avenue for prevention of ACVDs. The manuscript is accompanied by an **Editorial** by Elena Osto from the University and University Hospital Zurich in Switzerland, and colleagues.[25] Osto concludes that to prove beyond doubt whether and how changes in the gut microbiota are causally associated with CVD, are influenced by CVD, or are simple bystanders represents the most difficult challenge to be faced within the next decade to make sure that the microbiome might become an integral part of clinical cardiovascular medicine.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled '**How to identify which patients should not have a systolic blood pressure target of <120 mmHg**', J. David Spence from Western University, London, Ontario, Canada, and colleagues comment on the recent publication '**On cerebrotoxicity of antihypertensive therapy and risk factor cosmetics**' by Franz H. Messerli from the University of Bern in Switzerland.[26,27] Messerli *et al.* respond in a separate comment.[28]

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

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