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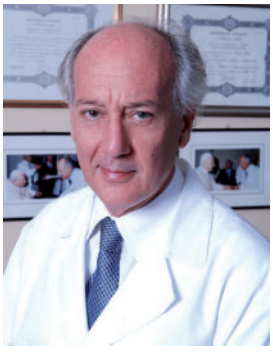
Addressing Residual Risk in Ischaemic Heart Disease with Anti-Inflammatory Drugs: Between Scylla and Charybdis



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This Issue opens with the Special Article '***European Heart Journal* quality standards**', authored by Fernando Alfonso from the Hospital Universitario de La Princesa in Madrid, Spain, and colleagues.[1] The authors note that the aim of the *European Heart Journal* (EHJ) is to attract innovative, methodologically sound, and clinically relevant research manuscripts able to change clinical practice and/or substantially advance knowledge on cardiovascular diseases. As the reference journal in cardiovascular medicine, the EHJ is committed to publishing only the best cardiovascular science adhering to the highest ethical principles. EHJ uses highly rigorous peer review, critical statistical review, and the highest quality editorial process to ensure the novelty, accuracy, quality, and relevance of all accepted manuscripts with the aim of inspiring the clinical practice of EHJ readers and reducing the global burden of cardiovascular diseases. This contribution summarizes the quality standards followed by the EHJ in pursuit of its mission.

The Issue continues with a Focus on ischaemic heart disease. The benefits of regular physical exercise on the human body are multiple and indisputable. The improvements in cardiovascular risk profile associated with exercise are partly secondary to its positive impact on atherosclerotic risk factors such as blood pressure, lipid profile, body mass index, and insulin resistance.[2,3] In sharp contrast, extreme strenuous and exhaustive exercise increases oxidative stress and can result in a systemic inflammatory response, although this is usually short-lived and resolves within a few hours. In a State of the Art Review entitled '**The heart of the ageing endurance athlete: the role of chronic coronary stress**', Gemma Parry-Williams from George's University of London in the UK and colleagues note that current guidelines recommend at least 150 min of moderate exercise or 75 min of vigorous exercise per week.[4] Endurance athletes perform exercise at a level that is 10- to 20-fold greater than these recommendations. These athletes reveal several structural and functional cardiac adaptations, including increased cardiac size, enhanced ventricular filling, and augmentation of stroke volume even at the highest heart rates. The long-term effects of endurance exercise on the heart are unknown. Endurance exercise is associated with a transient increase in serum concentrations of biomarkers of cardiac damage and ventricular dysfunction which improves within 72 h. Over the past decade, there have been emerging studies reporting attenuated mortality benefit amongst individuals who perform the highest volume of exercise. Studies in life-long male athletes aged above 40 years old show a higher prevalence of high coronary artery calcium scores (>300 Agatston units), a higher coronary plaque burden, and myocardial fibrosis compatible with subclinical myocardial infarction compared with relatively sedentary healthy controls, raising speculation that life-long intense exercise imposes chronic coronary stress on the heart (*Figure 1*). This review article provides a critical analysis of the existing data.

Colchicine is a unique, sophisticated anti-inflammatory agent that has been used for decades for the prevention of acute inflammatory flares in gout and familial Mediterranean fever, and in recent years trials have demonstrated its potential in a range of cardiovascular conditions.[5,6] In another State of the Art Review entitled '**Colchicine and the heart**', Massimo Imazio from the University Hospital 'Santa Maria della Misericordia' in Udine, Italy, and colleagues note that colchicine is avidly taken up by leucocytes, where its binding to tubulin interferes with microtubular function, affecting the expression of cytokines and interleukins as well as the ability of leucocytes to marginate, aggregate, express superoxide, release neutrophil extracellular traps (NETs), and interact with platelets.[7] In patients with acute and recurrent pericarditis, clinical trials in >1600 patients have

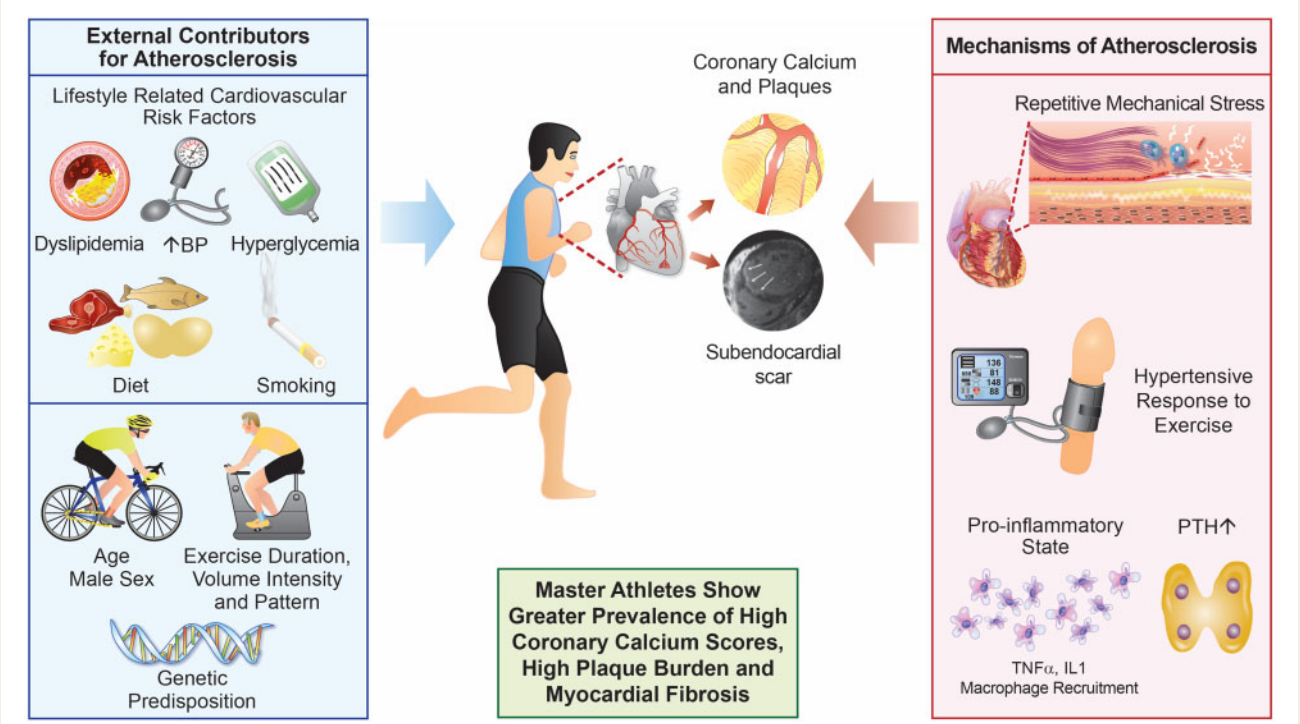

Figure 1 Graphical Abstract (from Parry-Williams G, Gati S, Sharma S. The heart of the ageing endurance athlete: the role of chronic coronary stress. See pages 2737–2744).

consistently demonstrated that colchicine halves the risk of recurrence. In patients with acute and chronic coronary syndromes, multicentre randomized controlled trials in >11 000 patients followed for up to 5 years demonstrate that it may reduce the risk of cardiiovascular death, myocardial infarction, ischaemic stroke, and ischaemia-driven revascularization by >30%. Use of colchicine at doses of 0.5–1.0 mg daily in cardiovascular trials has proved safe. Early gastrointestinal intolerance limits its use in ∼10% of patients; however, ∼90% of patients tolerate it well over the long term. Despite isolated case reports, clinically relevant drug interactions with moderate to strong CYP3A4 inhibitors/competitors or P-glycoprotein inhibitors/competitors are rare, when colchicine is used at these doses, in the absence of advanced renal or liver disease. This review summarizes the contemporary data supporting the efficacy and safety of colchicine in patients with cardiovascular disease.

In a provocative Viewpoint article entitled '**Coronary artery disease: "gout" in the artery?**', Timo E. Strandberg from the University of Helsinki in Finland, and colleagues note that in a 'system biology perspective', inflammation and its potential triggers are unifying factors in the pathophysiology of both gout and atherosclerotic cardiovascular diseases (ASCVD).[8–10] Furthermore, therapies to diminish the crystal-induced inflammation with canakinumab or colchicine have been shown to prevent the respective clinical presentations, especially the acute ones.[11] A final common similarity is that the root causes—hyperuricaemia in gout and hypercholesterolaemia in ASCVD—must be effectively addressed to attain the best results for patients in the long term.

Recent randomized trials demonstrated a benefit of low-dose colchicine added to guideline-based treatment in patients with ASCVD.[12,13] In a clinical research article entitled '**Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials**', Aernoud Fiolet from the University Medical Centre Utrecht in the Netherlands, and colleagues performed a systematic review and meta-analysis to obtain best estimates of the effects of colchicine on major adverse cardiovascular events (MACE).[14] The authors searched the literature for randomized clinical trials of long-term colchicine in patients with atherosclerosis published up to 1 September 2020. The primary efficacy endpoint was MACE, the composite of myocardial infarction, stroke, or cardiovascular death. The authors combined the results of five trials that included 11 816 patients. The primary endpoint occurred in 578 patients. Colchicine reduced the risk for the primary endpoint by 25% [relative risk (RR) 0.75; $P = 0.005$], myocardial infarction by 22% (RR 0.78, $P = 0.010$), stroke by 46% (RR 0.54; $P = 0.009$), and coronary revascularization by 23% (RR 0.77; $P < 0.001$). They observed no difference in all-cause death [RR 1.08, 95% confidence interval (CI) 0.71–1.62; $P = 0.73$], with a lower incidence of cardiovascular death (RR 0.82, 95% CI 0.55–1.23; $P = 0.34$) counterbalanced by a higher incidence of non-cardiovascular death (RR 1.38, 95% CI 0.99–1.92; $P = 0.060$) (*Figure 2*).

The authors conclude that their meta-analysis indicates that low-dose colchicine reduces the risk of MACE as well as that of myocardial infarction and stroke, and the need for coronary

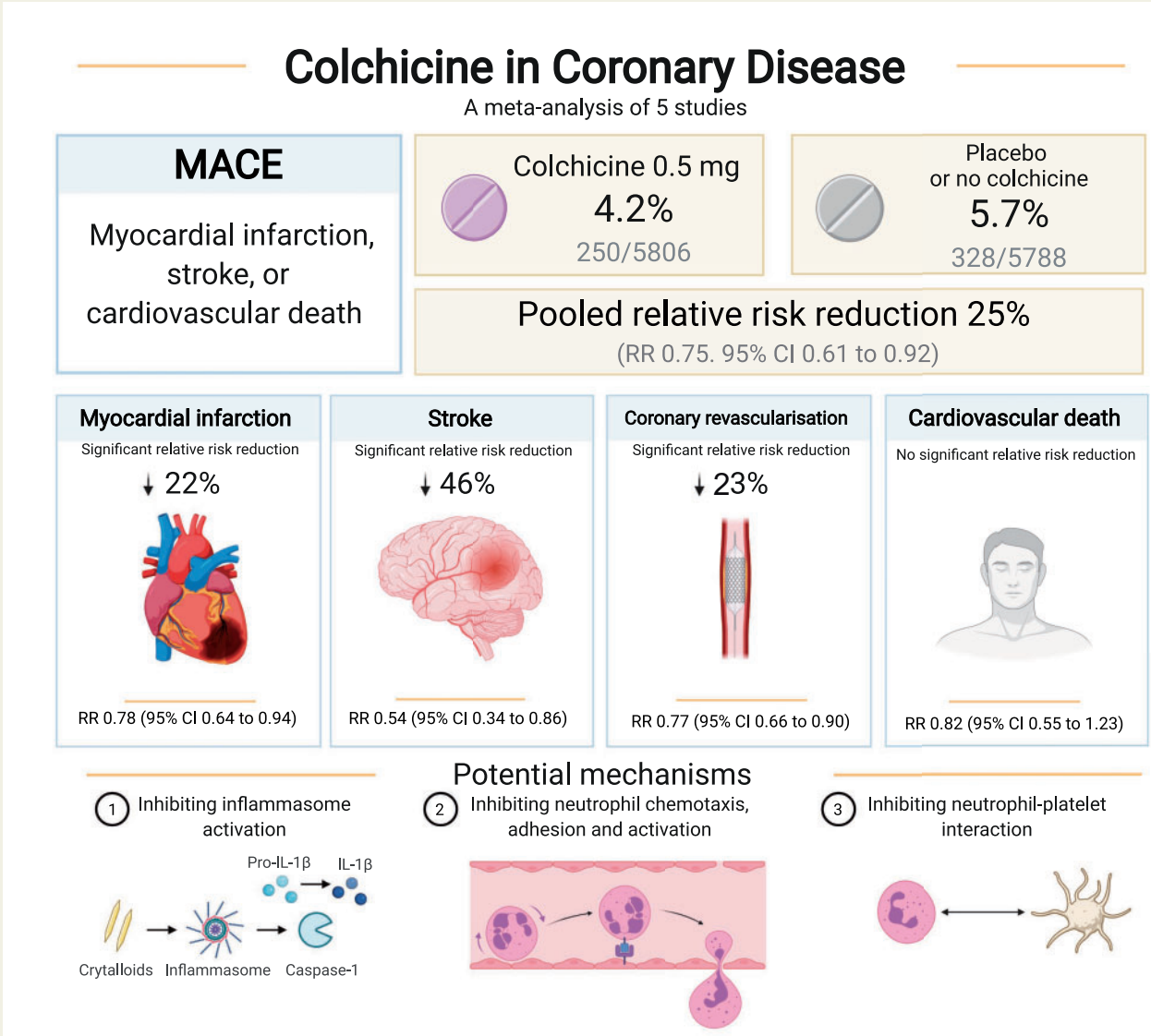

Figure 2 Main findings and potential mechanisms of action of colchicine in coronary disease. CI, confidence interval; MACE, major adverse cardiovascular events; RR, relative risk (from Fiolet ATL, Opstal TSJ, Mosterd A, Eikelboom JW, Jolly SS, Keech AC, Kelly P, Tong DC, Layland J, Nidorf SM, Thompson PL, Budgeon C, Tijssen JGP, Cornel JH; on behalf of the Colchicine Cardiovascular Trialists Collaboration. Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials. See pages 2765–2775).

revascularization in a broad spectrum of patients with coronary disease. There was no difference in all-cause mortality, and fewer cardiovascular deaths were counterbalanced by more non-cardiovascular deaths. The manuscript is accompanied by an **Editorial** by Aruna Das Pradhan from the Brigham and Women's Hospital Department of Medicine in Boston, MA, USA.[15] Pradhan concludes that the meta-analysis by Fiolet *et al.* is a clear presentation of aggregate data from carefully selected cardiovascular outcomes trials. The data demonstrate strong evidence for substantial cardiovascular benefit from anti-inflammatory therapies, but the authors do not minimize the finding of excess non-cardiovascular mortality in these trials, and rightly so. This early signal of benefit and possible signal of harm require further scrutiny from forthcoming controlled clinical trials expected to enrol >12 000 participants, a doubling of exposed individuals, that will permit safety analysis in diverse clinical settings. The results of CONVINCE (ClinicalTrials.gov NCT02898610) and CLEAR-SYNERGY (ClinicalTrials.gov NCT03048825), two large, long-term studies in secondary prevention, are needed to convince critics and clear up unresolved issues with respect to non-cardiovascular mortality and, importantly, to gather data in female and minority patients before the use of colchicine is more broadly endorsed. Until those studies are completed, further efforts to identify population segments at potentially elevated risk and those potentially deriving greater drug-derived benefit would add to the body of evidence available for risk–benefit profiling.

Extracellular vesicles (EVs) are lipid bilayer-delimited, non-replicating particles released from different subcellular compartments. They can be classified on the basis of a physical characteristic, such as density or size or the cell/condition of origin—for example, platelet EVs, hypoxic EVs, or apoptotic bodies.[16,17] Moreover, because EVs originate from various cell types, they acquire specific antigens expressed by the cell of origin, in addition to negatively charged phospholipids and membrane-associated glycoproteins. Therefore, they can also be classified on the basis of their biochemical composition. EVs play a role in the intercellular communication pathways occurring among cells of the same as well as of different cell types. EVs, together with proteins, peptides, lipids, and non-coding RNAs, are part of the cellular secretome. Once released, EVs influence the surrounding environment through their cargo of active biomolecules, such as proteins, mRNAs, microRNAs, and lipids. Increased shedding of EVs has been associated with atherosclerosis, but whether this is true for myocardial diseases is still poorly known. In a translational research article entitled '**Myocardial hypoxic stress mediates functional cardiac extracellular vesicle release**', Achille Anselmo from the IRCCS-Humanitas Research Hospital in Rozzano, Italy, and colleagues used the surface antigen CD172a as a specific marker of cardiomyocyte (CM)-derived EVs; the CM origin of CD172a+ EVs was supported by their content of cardiac-specific proteins and heart-enriched microRNAs.[18] The authors found that patients with aortic stenosis, ischaemic heart disease, or cardiomyopathy had higher circulating CD172a+ cardiac EV counts than did healthy subjects. Cellular stress was a major determinant of EV release from CMs, with hypoxia increasing shedding in *in vitro* and *in vivo* experiments. At the functional level, EVs isolated from the supernatant of CMs derived from human induced pluripotent stem cells (iPSCs) and cultured in a hypoxic atmosphere elicited a positive inotropic response in unstressed CMs, an effect the authors found to be dependent on an increase in the number of EVs expressing ceramide on their surface. Of potential clinical relevance, aortic stenosis patients with the highest counts of circulating cardiac CD172a+ EVs had a more favourable prognosis for transcatheter aortic valve replacement than those with lower counts.

Anselmo *et al.* conclude that they identify circulating CD172a+ EVs as cardiac derived, showing their release and function, and providing evidence for their prognostic potential in aortic stenosis patients. The manuscript is accompanied by an **Editorial** by Chantal Boulanger from the Université de Paris, and colleagues.[19] The authors conclude that future pre-clinical animal models allowing EV tracking *in vivo* are much needed to finally demonstrate how the diseased part of the myocardium sends specific messages to the healthy part of the muscle in order to boost its contractile function. Certainly, the study by Anselmo *et al.* highlights EVs released from the myocardium as previously unsuspected 'spurs for a tired horse'.

The issue is also complemented by various Discussion Forum contributions. In a commentary entitled '**Colchicine and coronary artery disease: a virtuous adoption**', Filippo Angelini and colleagues from the University of Turin in Italy comment on the recent publication '**Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)**' by Nadia Bouabdallaoui from the Montreal Heart Institute and Université de Montreal in Canada.[12,20] Bouabdallaoui *et al.* respond in a separate comment.[6]

In another contribution entitled '**Colchicine administered early in acute myocardial infarction: ready, set … go?**', Dimitrios A. Vrachatis from the University of Athens in Greece, and colleagues also discuss the article by Bouabdallaoui *et al.*[12,13] Bouabdallaoui *et al.* also respond to this contribution.[5]

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

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