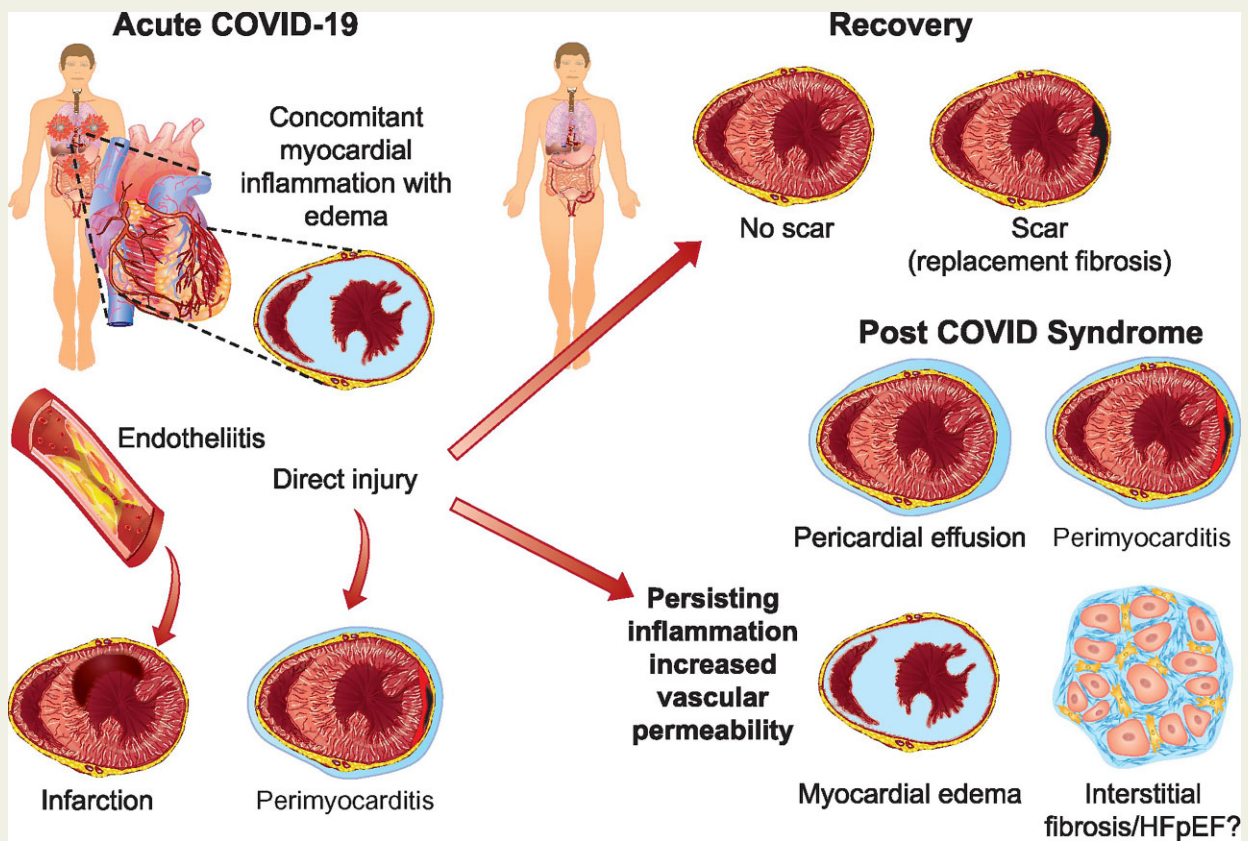


The year in cardiovascular medicine 2021: acute cardiovascular care and ischaemic heart disease

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Received 15 December 2021; accepted 23 December 2021; online publish-ahead-of-print 3 January 2022



Graphical Abstract Mechanisms and clinical phenotypes: the potential impact of acute COVID-19 on the heart and its longer-term sequelae. Reprinted with permission from: Friedrich MG, Cooper LT Jr. What we (don't) know about myocardial injury after COVID-19. *Eur Heart J* 2021;**42**:1879–1882.

Keywords Acute cardiac care • Acute coronary syndromes • Ischaemic heart disease • Cardiogenic shock • COVID-19

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Preamble

In a year when COVID-19 continued to dominate healthcare, its impact on cardiovascular disease in the acute and emergency settings remained evident. The cardiovascular literature documented persistent disruption in healthcare delivery, with continued reduction in patients presenting with ST-segment elevation myocardial infarction (STEMI) and increased late presentations of STEMI, infarct size, and complications,^{1,2} delay in revascularization,³ reduction in admissions for acute heart failure (AHF), and an associated increased in-hospital AHF mortality.⁴ The extent, nature, and aetiology of COVID-19-related cardiac injury were the focus of numerous studies,^{5,6} PIMS-TS (paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2) became well recognized as a disease entity with potential significant cardiac involvement, and defined diagnostic criteria and treatment strategies.^{7,8} The important but rare side effect of mRNA vaccine-related myocarditis emerged,⁹ and the syndrome of thrombosis with thrombocytopenia after ChAdOx1 NcoV-19 vaccination¹⁰ prompted development of a novel score (FAPIC) to predict mortality.¹¹ Despite this immense disruption to healthcare, significant advances were nonetheless made in the fields of acute coronary syndromes (ACS), ischaemic heart disease, and acute cardiovascular care, with a number of important papers published in the *European Heart Journal* and elsewhere that significantly furthered our knowledge in these fields.

Pathophysiology

It is well recognized that not all patients with coronary artery atheroma develop an acute myocardial infarction (AMI), but the reasons why are less well understood. In this context, Hartiala and co-workers postulated that genetic factors for atherosclerosis might differ from those predisposing to plaque vulnerability, erosion, rupture or thrombosis.¹² Based on a meta-analysis of genome-wide association study (GWAS) data from the UK Biobank and CARDIoGRAMplusC4D consortium, they performed multiple independent replication analyses and functional approaches, to prioritize loci and evaluate candidate genes for MI. They established eight novel genetic risk loci for MI, with six

showing a stronger effect size for MI vs. atheroma. Additionally, a locus on chromosome 1p21.3 harbouring the choline-like transporter 3 gene (SLC44A3) was significantly associated with MI in those with coronary atheroma, but not with lifetime risk of coronary atherosclerosis. Further, the SLC44A3 locus was unrelated to cardiovascular risk factors, prothrombotic biomarkers, and a series of proatherosclerotic metabolites. It was, however, expressed in the aorta of carriers of the AMI risk allele at chromosome 1p21.3, increased in ischaemic coronary arteries, and associated with smooth muscle cell migration *in vitro*, thus potentially implicating SLC44A3 in the pathophysiology of vulnerable plaques (Figure 1).

New clues regarding plaque erosion emerged from the prospective, multicentre study OPTICO-ACS.¹³ Here Leistner and colleagues analysed the microenvironment of culprit plaques in 170 ACS patients integrating *in vivo* high-resolution optical coherence tomography (OCT) imaging and the local immune response (Figure 2). Intact fibrous cap (IFC) was characterized by lower lipid content, less calcification, and localization near a coronary bifurcation when compared with ruptured fibrous cap (RFC-ACS). The microenvironment of IFC-ACS lesions showed selective enrichment in T lymphocytes (predominantly CD8+) and higher T-cell-associated extracellular circulating microvesicle levels. Further, significantly higher numbers of CD8+ T lymphocytes were detectable in thrombi aspirated from IFC-culprit sites and higher levels of soluble cytotoxic effector mediators. Finally, co-culture demonstrated the proapoptotic effect of CD8+ T cells and their cytotoxic effector molecules on endothelial cells, and *in vivo* experiments showed enhanced adhesion of CD8+ T cells to endothelial cells subjected to culture in disturbed (vs. laminar) flow conditions. Whether T-cell activation is a key step in the sequence leading to plaque erosion and thrombus formation, or an epiphenomenon, remains to be determined.

Appreciation of inflammation in cardiovascular disease has prompted the search for additional mechanisms, including those where remote events may worsen/accelerate plaque formation. Kyaw and co-workers used an apolipoprotein-E-deficient (ApoE^{-/-}) mouse model of MI-accelerated atherosclerosis to assess the importance of B cells in accelerated plaque formation.¹⁴ Here, 1-week post-MI B cells were depleted using an anti-CD20 antibody, resulting in attenuation of IgG accumulation in plaques and

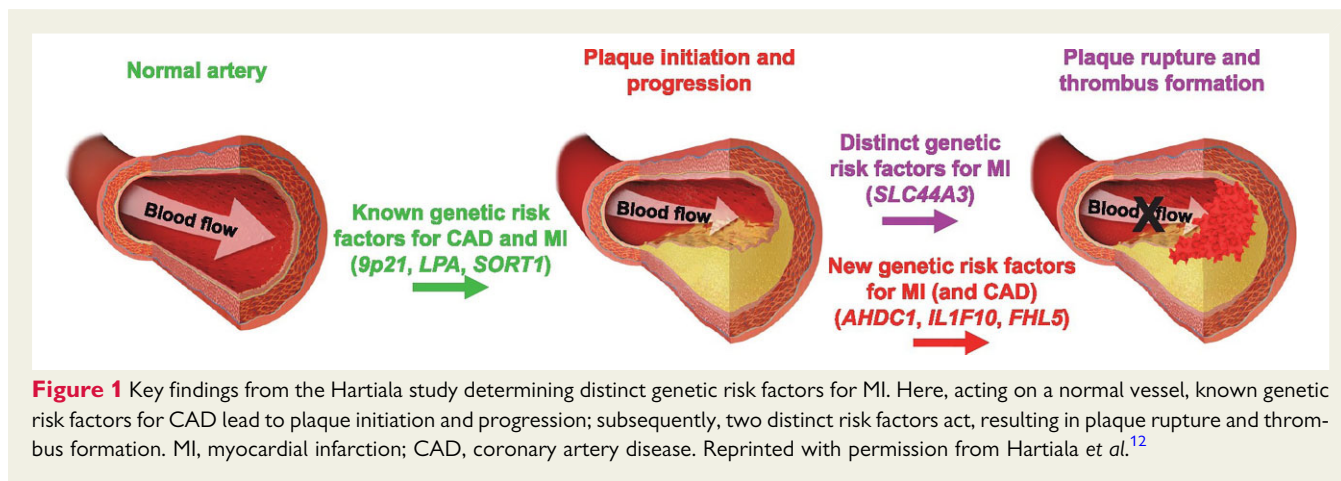


Figure 1 Key findings from the Hartiala study determining distinct genetic risk factors for MI. Here, acting on a normal vessel, known genetic risk factors for CAD lead to plaque initiation and progression; subsequently, two distinct risk factors act, resulting in plaque rupture and thrombus formation. MI, myocardial infarction; CAD, coronary artery disease. Reprinted with permission from Hartiala et al.¹²

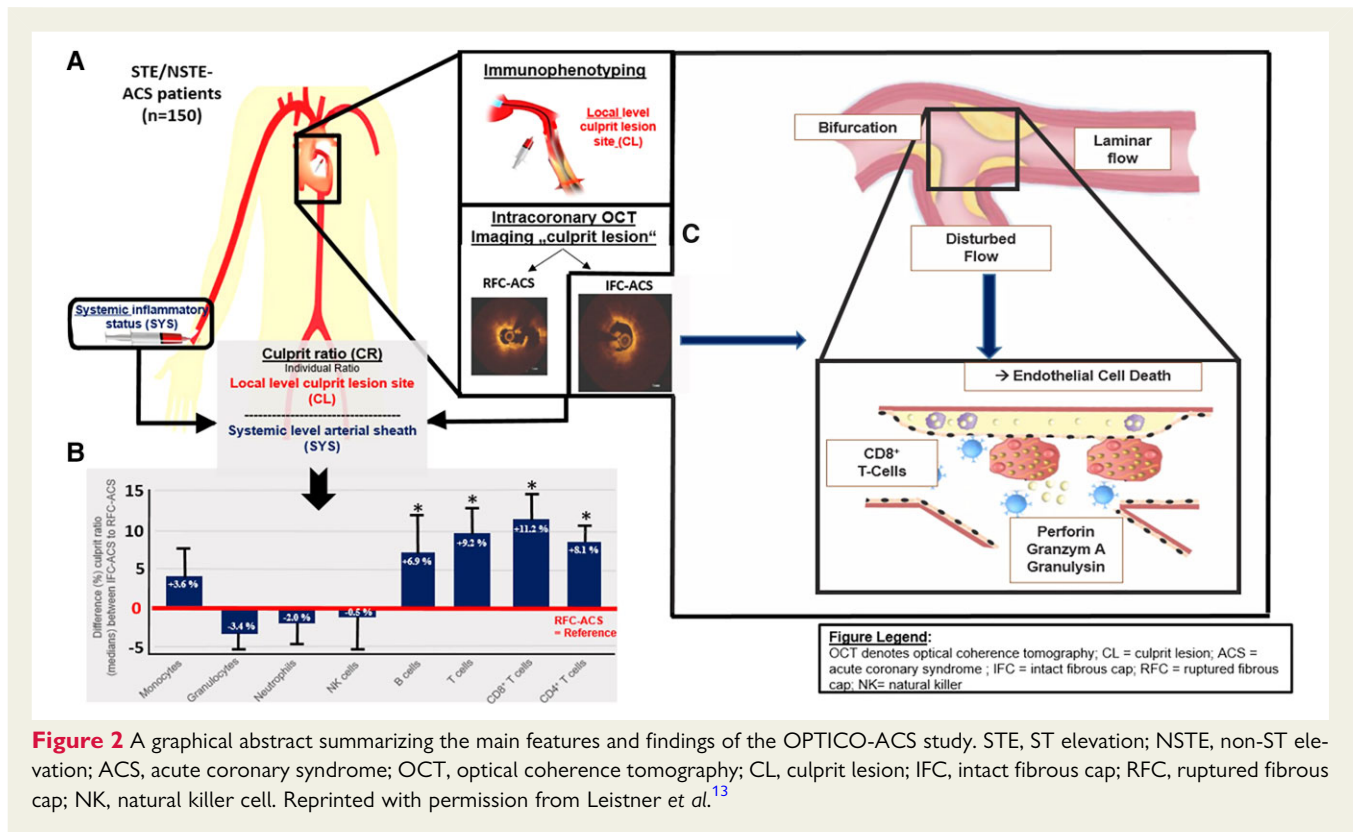


Figure 2 A graphical abstract summarizing the main features and findings of the OPTICO-ACS study. STE, ST elevation; NSTE, non-ST elevation; ACS, acute coronary syndrome; OCT, optical coherence tomography; CL, culprit lesion; IFC, intact fibrous cap; RFC, ruptured fibrous cap; NK, natural killer cell. Reprinted with permission from Leistner et al.¹³

MI-induced accelerated atherosclerosis. Further, adoptive transfer of reactive B cells into atherosclerotic ApoE^{-/-} mice without MI increased IgG accumulation in plaque, and accelerated atherosclerosis. These findings suggest that B cells are key for lesion enhancement, and suggest that MI could potentially worsen atheroma via the development of autoimmunity against the vessel wall through autoreactive B-cell memory. If these findings transfer to humans, the implications for secondary prevention strategies are significant.

Recognition of the potential role of white blood cell subtypes has resulted in numerous studies evaluating their role in the mechanism and risk prediction in cardiovascular disease. Adamstein and co-workers performed an analysis of the neutrophil-lymphocyte ratio (NLR) from five major randomized controlled trials (RCTs).¹⁵ Collecting baseline and on-treatment NLRs in ~60 000 participants, they aimed to determine whether the NLR predicts incident major adverse cardiovascular events and is modified by anti-inflammatory therapy. They demonstrated that baseline NLR consistently and independently predicted cardiovascular events and death, and although lipid-lowering agents had no significant impact, NLR decreased during canakinumab therapy. This readily available biomarker could in future be used for risk stratification and potentially to guide anti-inflammatory treatment; however, the biological basis for these findings, and their potential effects on outcomes, demand further evaluation.

Cardiovascular risk and biomarkers

A pre-specified analysis of the SWEDEHEART registry revealed that STEMI patients without standard modifiable cardiovascular

risk factors (SMuRFs) have significantly increased risk of early all-cause mortality (females, 17.6%; males, 9.6%) compared with patients with ≥ 1 SMuRF (females, 11.1%; males, 6.3%; $P < 0.0001$).¹⁶ After correction for confounders, this difference persisted, but disappeared after inclusion of guideline-recommended pharmacotherapy at discharge. The authors concluded that evidence-based optimal pharmacotherapy at discharge should be given to 'low-risk' patients to reduce mortality.

To identify predictors of future type 1 and type 2 MI within 1-year follow-up, the High-STEACS investigators conducted a secondary analysis of a trial population of >48 000 consecutive patients presenting with suspected ACS.¹⁷ Risk factors for recurrent MI included age, diabetes, hyperlipidaemia, known coronary artery disease, and renal dysfunction ($P < 0.05$).

The range of biomarkers to enhance diagnosis in the emergency setting is increasing. Neumann and colleagues investigated the discriminative value of 29 biomarkers in the emergency room to differentiate type 1 and type 2 MI, and myocardial injury.¹⁸ By multivariate analysis, N-terminal probrain natriuretic protein (NT-proBNP), copeptin, apolipoprotein AII, and cardiac troponin I (cTnI) remained significant discriminators between type 1 and type 2 MI. For discrimination between MI and myocardial injury, adiponectin, NT-proBNP, cTnI, copeptin, transthyretin, and pulmonary and activation-regulated chemokine were selected. In both discriminations, internal validation showed an area under the curve >0.8. In contrast, the utility of some older biomarkers is increasingly questioned. Last year (2021) may signal the end of the use of CK-MB (creatin kinase myocardial band), with reasons proposed including its lower sensitivity in detecting myocardial injury/infarction compared with cardiac troponin, lack of additional value for risk

stratification in suspected MI, temporal appearance, and poor performance in re-infarction/peri-procedural myocardial injury.¹⁹

Clinical outcomes

Even in the acute setting, long-term outcomes are important. A study compared long-term all-cause and cardiovascular mortality among 3829 adults (median age 44 years; 30% women) presenting with type 1 MI (55%), type 2 MI (32%), or myocardial injury (13%).²⁰ Long-term mortality (>10 years) was lowest for type 1 MI (12%), followed by type 2 MI (34.2%) and myocardial injury (45.6%) ($P < 0.001$). Those with myocardial injury/type 2 MI were younger, had fewer classical cardiovascular risk factors, but increased non-cardiovascular co-morbidities. Accordingly, their all-cause mortality was significantly higher [hazard ratio (HR) 1.8; 95% confidence interval (CI) 1.2–2.7; $P \leq 0.004$]. Cardiovascular mortality was also higher in this group (HR 2.7; 95% CI 1.4–5.1; $P = 0.003$); however, many had suboptimal therapy at discharge.

There is little information regarding long-term outcomes in patients with late-presentation STEMI (12–48 h after symptom onset). In a nationwide prospective Korean registry, Hoon and colleagues investigated 624 late-presenting STEMI patients compared with early presenters (<12 h of symptom onset; $n = 5202$) for 180-day and 3-year mortality.²¹ As expected, late presenters had a significantly higher all-cause mortality after 180 days (10.7 vs. 6.8%; $P < 0.001$) and 3 years (16.2 vs. 10.6%; $P < 0.001$) attributed in part to fewer percutaneous coronary intervention (PCI) procedures (acute and total) in late presenters. Future studies should determine those late presenters that might benefit from intervention.

Therapeutic strategies

Two studies addressed the role of inflammation in cardiovascular disease. In AMI, Broch *et al.* performed a randomized trial of tocilizumab ($n = 101$) vs. placebo ($n = 98$) in patients with STEMI within 6 h of symptom onset in order to evaluate its effect on myocardial salvage.²² They reported a significantly larger myocardial salvage index in tocilizumab-treated patients compared with placebo (adjusted difference 5.6%; 95% CI 0.2–11.3; $P < 0.04$). To date, the clinical significance remains uncertain, and larger studies are required to investigate the effects on clinical endpoints. A number of RCTs have demonstrated a benefit of the addition of low-dose colchicine to guideline-based treatment in patients with recent MI or chronic coronary disease. Fiolet and colleagues performed a systematic review and meta-analysis of five trials comprising 11 816 patients with the aim to determine major adverse cardiac events (MACE; composite of MI, stroke, or cardiovascular death).²³ Their findings showed that colchicine reduced the risk for the primary endpoint by 25% [relative risk (RR) 0.75; 95% CI 0.61–0.92] (Figure 3).

Optimal transfusion thresholds in AMI remain uncertain. The French REALTY (Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction) investigators aimed to determine whether a restrictive transfusion strategy (haemoglobin trigger ≥ 8 g/dL) was non-inferior to a liberal strategy

(haemoglobin trigger ≥ 10 g/dL) in AMI.²⁴ The restrictive strategy (11%; 95% CI –8.4 to 2.4%) fulfilled the non-inferiority criterion vs. the liberal strategy (14%; 95% CI 10.0–17.9%) for the composite outcome of all-cause death, stroke, recurrent MI, or emergency revascularization at 30 days.

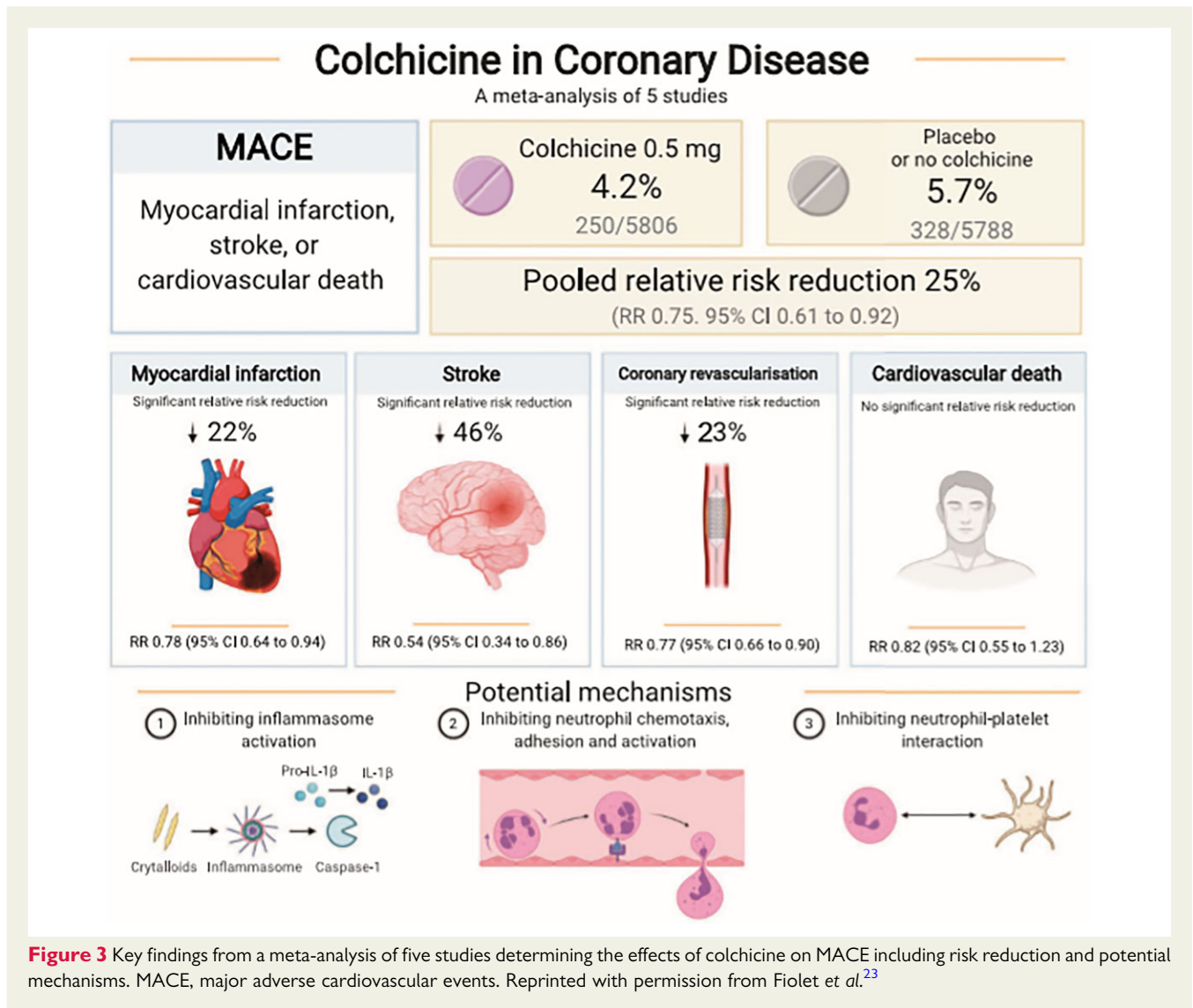
Debate concerning antithrombotic therapy post-PCI continues. Two post-hoc analyses of the TWILIGHT trial, comparing short (3-month) dual antiplatelet therapy (DAPT) with aspirin and ticagrelor followed by ticagrelor monotherapy up to 12 months vs. 12-month DAPT in high- and very high-risk patients undergoing PCI and stent implantation, were recently published. The TWILIGHT-CKD trial studied the impact of chronic kidney disease, demonstrating that ticagrelor monotherapy when started early significantly reduced the risk of bleeding without significantly increasing thrombo-isaemic endpoints (combination of death, MI, stroke; all-cause death; MI; stent thrombosis).²⁵ Comparable results were demonstrated in the TWILIGHT-HBR study where patients with high bleeding risk (HBR) with 3 months DAPT (aspirin plus ticagrelor followed by ticagrelor monotherapy) vs. 12 months DAPT exhibited significantly reduced bleeding without an increase in ischaemic events.²⁶ In a meta-analysis of patients with HBR after revascularization receiving short (1 month) vs. longer (3–6 month) DAPT (aspirin + different P2Y₁₂ inhibitors, followed by P2Y₁₂ inhibitor monotherapy), Valgimigli *et al.* reported that early P2Y₁₂ inhibitor monotherapy showed comparable risk of death, MI, or stroke but significantly lower bleeding risk compared with prolonged DAPT.²⁷ It seems therefore that shortening of DAPT in patients undergoing PCI is associated with significantly less bleeding and no increase in risk of thrombo-isaemic events.

Resuscitation science

Out-of-hospital cardiac arrest (OHCA) remains a major public health challenge with a global incidence of 55/100 000 person-years and poor survival. There is ongoing discussion regarding management priorities, in particular in post-resuscitation care.

Aiming to determine whether routine immediate coronary angiography potentially followed by revascularization is superior to a deferred/selective approach, the TOMAHAWK investigators examined all-cause 30-day mortality in 558 patients with haemodynamically stable resuscitated OHCA without STEMI.²⁸ Outcomes were not significantly different between patient groups, suggesting that—if stable—it is appropriate to prioritize immediate post-resuscitation care over angiography.

The ARREST study (Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation) aimed to determine whether implementation of early extracorporeal membrane oxidation (ECMO)-facilitated resuscitation vs. standard resuscitation improved survival.²⁹ This phase II single-centre open-label adaptive safety and efficacy RCT included adults with OHCA and refractory ventricular fibrillation with a primary outcome of survival to hospital discharge. The trial was terminated at the first pre-planned interim analysis after enrolling only 30 patients because the posterior probability of ECMO superiority exceeded the pre-specified monitoring boundary (survival in 1 of 15 patients with standard resuscitation vs. 6 of



14 with early ECMO; risk difference 36.2%, 3.7–59.2; posterior probability of ECMO superiority 0.9861). The results of further randomized trials are awaited.

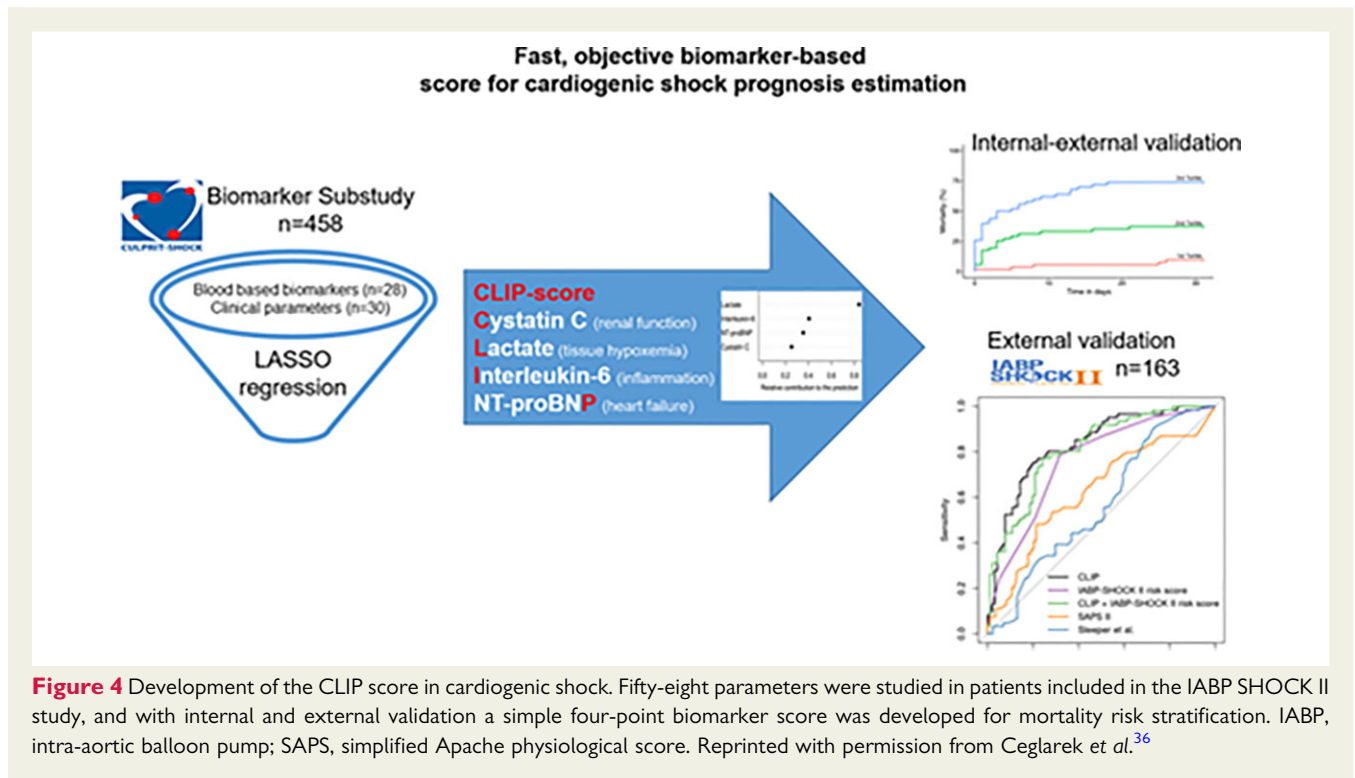
Two studies added to our understanding of targeted temperature management (TTM) post-arrest. First, in an open-label trial, 1900 adults with coma post-OHCA were randomized to TTM (33°C) or normothermia ($\geq 37.8^\circ\text{C}$).³⁰ The primary outcome of 6-month all-cause mortality was no different between the groups. In the CAPITA-CHILL study (single-centre, double-blind randomized clinical superiority trial), 389 patients with OHCA were randomly assigned to 31°C (193 patients) vs. 24°C (196 patients) for 24 h.³¹ Primary outcome was 180-day all-cause mortality/poor neurological outcome with no difference between the groups. These findings support recommendations in current resuscitation guidelines.

Systemic inflammation is a major component of the post-resuscitation syndrome. In a double-blinded placebo-controlled trial aiming to determine the efficacy of interleukin-6 (IL-6) inhibition to reduce systemic inflammation post-OHCA, 80 patients were randomized to an infusion of tocilizumab vs. placebo in

addition to standard care.³² The primary endpoint was C-reactive protein reduction from baseline, and secondary endpoints included markers of inflammation, and myocardial and brain injury. Here tocilizumab resulted in a significant reduction in inflammatory markers and myocardial injury. Whether this will translate into improved outcomes remains to be evaluated.

Cardiogenic shock

The landscape for cardiogenic shock (CS) is shifting. In a nationwide registry, changes in epidemiology, interventions, and outcomes were studied in 14 363 patients, comparing 2005 and 2017.³³ ACS as the underlying cause decreased (37.1% 2005 vs. 21.4% 2017), as did heart failure (16.3% vs. 12.0%) and arrhythmia (13.0% vs. 10.9%); however, CS complicating cardiac arrest increased significantly (11.3% vs. 2.5%). In parallel, the use of mechanical circulatory support (MCS) increased significantly, and although overall 30-day and 1-year mortality were relatively stable, there were significant decreases in those with ACS and



arrhythmias. Recognizing evidence from the last 5 years, key changes regarding CS in the latest ESC guidelines included modification of the definition to increase the focus on hypoperfusion rather than hypotension, removing adrenaline as a recommended inotrope, and upgrading recommendations for acute MCS.³⁴

The heterogeneity of the CS population means that accurate risk stratification for individual patients and populations within clinical trials remains challenging.³⁵ Using data from the CULPRIT-SHOCK trial, a biomarker-based risk score for 30-day mortality was developed from 458 patients with CS complicating AMI. Of 58 candidate variables, the four strongest predictors for mortality were cystatin C, lactate, IL-6, and NT-proBNP (CLIP, *Figure 4*).³⁶ The score outperformed the SAPS II and IABP-SHOCK II risk scores (0.83 vs. 0.62 and 0.83 vs. 0.76, respectively) and may contribute to early decision-making in CS after AMI; however, as with all biomarker-related scores in the acute/emergency setting, point-of-care testing and turn around times remain problematic.

Data guiding choice of inotropic agent in CS are limited. The expanding evidence base suggesting potential harm from adrenaline has increased focus on other drugs. In the DOREMI (Dobutamine Compared with Milrinone) trial, 192 patients with CS were randomly assigned to receive milrinone or dobutamine in a double-blind fashion.³⁷ Here, there was no difference in the primary composite outcome (in-hospital death from any cause, resuscitated cardiac arrest, receipt of cardiac transplant or MCS, non-fatal MI, transient ischaemic attack or stroke, or initiation of renal replacement therapy) between the groups, and in-hospital mortality remained disappointingly high. Whether these findings would be replicated across all phenotypes, aetiologies, and severity of CS remains to be determined.

Conclusions

Significant advances in understanding the underlying pathological mechanisms, the role of inflammation and the immune system, and in risk stratification of our most acute and critically ill cardiac patients continue to be made. The increasing collaboration between basic and clinical science, cardiology, critical care, and acute medicine continues to drive our knowledge base further, providing the evidence that will surely underpin best practice in these most challenging areas of cardiology in the future.

Conflict of interest: none declared.

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