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Current opinion

The year in cardiovascular medicine 2022: the top 10 papers in acute cardiac care and ischaemic heart disease

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The papers discussed herein provide data that may influence future research and the management of ischaemic heart disease patients and those requiring acute cardiac care *(see Graphical Abstract).*

Redefining critical illness and new approaches to blinding and randomization of patients

The COVID-19 pandemic profoundly changed approaches to critical illness research. A paper (1) from global leaders in critical care suggests moving the research focus from the traditional syndrome-based framework towards understanding and addressing the underlying biology/pathophysiology of critical illness and embracing the concept of precision-medicine. Learning from oncology/cardiovascular medicine, the author's further highlight both that different insults can generate shared biological abnormalities and different patients may respond differently to injury. Moreover, the authors proposed the integration of biological characteristics (clinical, biomarkers, physiology, imaging, genomic, transcriptomic, proteomic, and metabolomics profiling) and the use of unsupervised machine learning for subtype discovery and supervised machine learning to identify additional potential biomarkers. Finally, the definition of a physiological state of interest and associated predictive biomarkers would constitute a 'treatable trait' which, after demonstration of efficacy in clinical trials, would be integrated into clinical pathways for the critically ill. These new concepts challenge the fundamentals upon which all previous research in the field has been based and forms the basis for a paradigm shift for the specialty.

Another challenging issue in critical care clinical research is double-blind randomization. The BOX trial (2) (Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest trial) provided a mechanism whereby future studies using measured physiological variables can be effectively randomized and blinded, which may represent a game-changer in the field. Using a 2-by-2 factorial design, the BOX trial investigators evaluated the effects of targeting a mean arterial blood pressure

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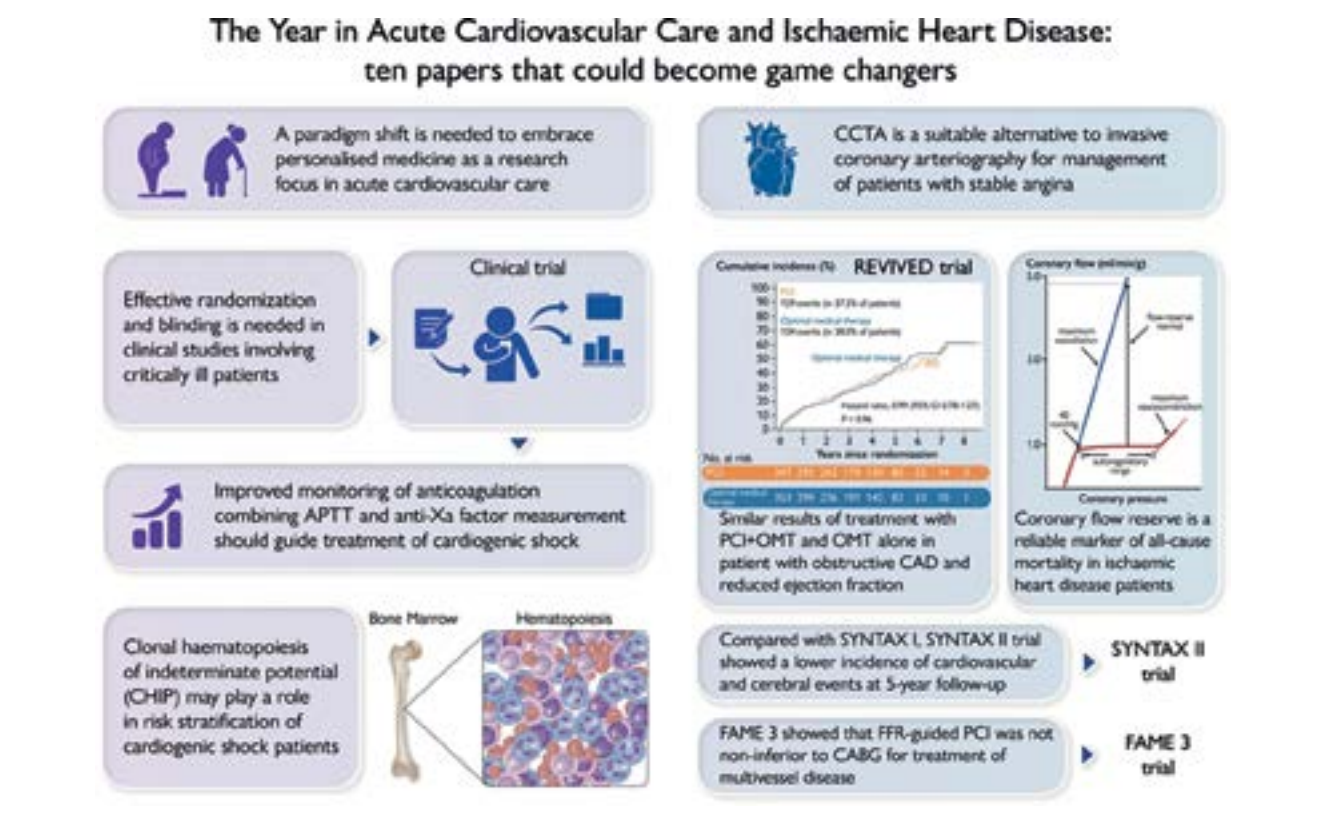

GRAPHICAL ABSTRACT. Several papers in 2022 have provided data that are likely to influence future research, as well as the diagnosis and treatment of ischaemic heart disease patients and those requiring acute cardiac care. APTT, activated partial thromboplastin time; CABG, coronary artery by-pass grafting; CAD, coronary artery disease; CCTA, computed coronary tomography angiography; FFR, fractional flow reserve; OMT, optimal medical treatment; PCI, percutaneous coronary intervention

of 63 vs. 77 mmHg in 789 comatose adults resuscitated after out-of-hospital cardiac arrest. Irrespective of the study results, i.e. no difference in death from any cause or hospital discharge with a cerebral performance category of 3/4 within 90 days, between the two groups, the practical importance of this study relates to the ingenious mechanism by which the treating teams were blinded to the blood pressure targets. Here, the blood pressure monitoring devices were randomly offset to display ±10% of the target (70 mmHg). Where equipoise exists, effective blinding is a key to avoid bias.

Anticoagulation strategies in acute mechanical circulatory support

Increasingly, patients with cardiogenic shock (CS) are managed with acute mechanical circulatory support (MCS), with high risk of lethal bleeding/thrombosis. In a state-of-the-art review, *Vandenbriele et al.* (3) provide an in-depth discussion on anticoagulation strategies in acute MCS, including acute myocardial infarction-induced–CS requiring additional dual antiplatelet therapy and disadvantages of relying solely on activated partial thromboplastin time (APTT). The authors provide a practical algorithm of optimal anticoagulation monitoring and treatment guidance, based on combined measurements of APTT and anti-Xa, and discuss management of bleeding complications.

The role of clonal haematopoiesis of indeterminate potential as a risk factor in cardiogenic shock

CS remains one of the most lethal manifestations of cardiovascular disease. Studies showing a high prevalence of clonal haematopoiesis of indeterminate potential (CHIP) in CS patients and an association with impaired clinical outcomes suggest a potential role for this marker in CS risk stratification. CHIP describes a relatively common phenomenon in elderly individuals where mutations in haematopoietic stem cells lead to selective clonal expansion (allele frequency ≥0.02). Further to its role as a risk factor for haematologic malignancies and for atherosclerosis, two studies described a potential role for CHIP in CS (4, 5). In CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock trial)

(446 CS patients), CHIP variants were described in 29% of cases, who were older, sicker, and had marked inflammatory activation (4). Importantly, CHIP was associated with worse clinical outcomes. A second study, involving 686 patients with heart failure (HF) (n = 345) or CS (n = 341), demonstrated a higher CHIP prevalence in CS patients, which was associated with reduced survival (5). Additional research is needed to explore whether these findings offer novel targets for treatment.

Advances in diagnosis and management of chronic coronary syndromes

Increasingly, non-invasive computed coronary tomography angiography (CCTA) has either rivaled or supplanted invasive coronary angiography (ICA) to identify flow-limiting coronary stenoses. Recently, the DISCHARGE Trial (The Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease trial) compared CCTA with ICA as an initial diagnostic imaging strategy in 3561 patients with stable angina and an intermediate pre-test probability of obstructive coronary artery disease (CAD) (6). No significant difference between CCTA and ICA was found in the composite primary endpoint of cardiovascular death, non-fatal myocardial infarction, or nonfatal stroke during a median 3.5-year follow-up, while the frequency of major procedure-related complications was lower with an initial CCTA strategy. Thus, the DISCHARGE trial results confirm that CCTA is a suitable alternative to ICA for management of stable angina CAD patients.

Invasive vs. conservative management of patients with obstructive CAD and left ventricular dysfunction

Revascularization strategies, added to optimal medical therapy (OMT), have been proposed to reverse left ventricular (LV) remodeling and improve clinical outcomes. Two main trials have addressed this population using either coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI), namely Surgical Treatment for Ischaemic Heart Failure (STICH) and, this year, Revascularization for Ischaemic Ventricular Dysfunction (REVIVED) (7). Both trials included patients with LV ejection fraction (EF) <35% and obstructive CAD. In REVIVED, extensive CAD and myocardial viability in at least four segments were required in all subjects to maximize the benefit of PCI on outcomes. The primary outcome in REVIVED was a composite of all-cause mortality or hospitalization for HF and required that revascularization be centred on functional recovery. Both trials employed high rates of OMT with ≥90% adherence. The overall primary event rate in REVIVED was 38% with an annualized 11.1% incidence of death or HF, similar to the 11.6%/year rate in STICH. CABG + OMT did not reduce overall mortality compared to OMT alone at 5 years in STICH but did so at 10 years. In REVIVED, there were no differences between PCI + OMT and OMT alone in either the primary composite outcome or secondary outcomes. Despite a high prevalence of multi-vessel CAD subtending viable myocardium and successful stenting of all stenoses in 71% of subjects, PCI did not result in a significant reduction of cardiac events. The median follow-up in REVIVED is only 41 months, and whether an extended follow-up may show a late mortality benefit (as in STICH) must await future analysis.

Assessment of prognosis in ischaemic heart disease and beyond – role of coronary flow reserve

Despite being a non-specific marker of abnormalities in blood flow regulation, coronary flow reserve (CFR) has emerged as a prognostic marker of cardiovascular risk. Indeed, a meta-analysis involving 79 studies (59 740 patients) by *Kelshiker et al.* (8) showed that a reduced

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CFR (≤2) was associated with increased risk of death or major adverse coronary events. The study included a wide range of patient groups; 19% (n = 10 848) had no obstructive or flow-limiting CAD and no history of cardiomyopathy, heart transplantation, or aortic stenosis. Despite its limitations, i.e. high study heterogeneity and different methodologies used for CFR measurement, the results are important, namely that CFR is a marker of all-cause mortality and adverse cardiovascular outcomes. For the field to move forward, however, CFR or equivalent measurements should be tested in large prospective clinical trials. CFR alone or added to other established risk markers may be important for patient risk stratification and personalized therapeutic interventions.

Invasive coronary physiology to guide myocardial revascularization

The SYNTAX II study (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery II trial) investigators hypothesized that improved patient selection (SYNTAX score II) and use of current best practice PCI would improve clinical outcomes in patients with three-vessel disease when compared to the SYNTAX I trial. This open-label, single-arm trial using SYNTAX score II in 454 patients with potential equipoise between PCI and CABG, 5-year follow-up data (98% of patients) showed significantly lower major cardiovascular and cerebral events compared with the SYNTAX I results (9) including a lower rate of all cause death (mainly cardiac death), with lower rates of MI, revascularization, and stent thrombosis. Importantly, there was no difference in outcomes when the SYNTAX II cohort was compared to the SYNTAX I pre-specified equipoise-selected CABG cohort. While the results are important, it must be emphasized that this was a non-randomized study, with a historical control group. Another important study, the randomized controlled Fractional Flow Reserve vs. Angiography for Multivessel Evaluation (FAME) 3 trial assessed whether FFR-guided PCI treatment in patients with three-vessel disease would be non-inferior to CABG for the primary composite endpoint of death, MI, stroke, or repeat revascularization at 1 year (10). One thousand five hundred patients were randomized at 48 sites to FFR-guided PCI vs. CABG. Main findings were that FFR-guided PCI was not non-inferior to CABG. This was a surprising result for many, particularly in view of the SYNTAX II trial findings. Could the discrepancy between the two trials be explained by the fact that most patients in FAME 3 had intermediate or high SYNTAX scores and intravascular imaging for which PCI was only used in 12% of patients in FAME 3 vs. 84% in SYNTAX II? Differences in operators' skills, operative techniques, and the effectiveness of medical treatment have been also suggested. Or was it that the SYNTAX II trial unfairly compared modern PCI practice with outdated CABG practice, or none of the above? Time will tell if FAME 3 can influence the guidelines and change practice.

Data availability

No new data were generated or analysed in support of this research.

Conflict of interest

S.P., W.E.B., and J.N.K. have no conflict of interest to declare. K.H. has received speaker fees from Bayer, Bristol Myers Squibb/Pfizer, Boehringer-Ingelheim, Daiichi Sankyo, Sanofi, and Aventis. R.A.-L. received speaker honoraria from Philips Volcano, Menarini Farmaceutica SRL and Servier and has participated as advisory board member for Janssen Pharmaceuticals. J.C.K. received speaker fees from Menarini Farmaceutica SRL. K.K. has received honoraria for lectures from Amgen, Novartis, and Sanofi.

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