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ESC Congress 2021

EDITOR'S PICK

Association Between the Hospital Readmissions Reduction Program and Heart Failure Subtype Readmissions and Mortality in the USA

INTERVIEWS

EMJ spoke to Rebecca Dobson about her recent guideline publication, position as a Council Representative at the British Cardiovascular Society (BCS), and innovations in the field of cardiac imaging

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Spencer Gore, CEO

Editorial Board

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EMJ Cardiology 9.1

Welcome

Dear Readers,

I would like to welcome you to the latest issue of *EMJ Cardiology*. This eJournal is packed with the latest advancements in the field, including exclusive interviews with key opinion leaders, and an array of compelling peer-reviewed articles. It is also our pleasure to share with you an in-depth review of the European Society of Cardiology (ESC) Congress 2021, alongside exciting abstract summaries of a range of presented sessions.

In this issue, we are proud to present peer-reviewed articles on fascinating topics including COVID-19 and myocardial infarction, biomarker-based therapy for heart failure, and an interesting case report on ischaemic cardiomyopathy. This issue's Editor's Pick is an article titled 'Association between the Hospital Readmissions Reduction Program and Heart Failure Subtype Readmissions and Mortality in the USA'. This riveting study by Sheikh et al. evaluates the effectiveness of the Hospital Readmission Reduction Program through analysing national mortality datasets based on heart failure subtypes. We were delighted to interview Rebecca Dobson, Consultant Cardiologist at the Liverpool Heart and Chest Hospital, UK, and Women in Cardiology (WIC) Council Representative for the British Cardiovascular Society (BCS). Dobson shared insights into her career, her recently published works, and innovations in cardiac imaging.

A comprehensive review of the ESC Congress 2021 is included in this issue of *EMJ Cardiology*. The exciting 4-day event presented the latest insights and innovations in the field of cardiology, with sessions from leading experts in the discipline. The ESC emphasised interactivity with their unique scientific programme, ensuring a valuable learning experience for attendees, despite restrictions from the ongoing pandemic. Standout author-written summaries of several abstracts presented at the congress are also included in this journal, covering topics such as mitral valve myxomatosis, the impact of depression on cardiac autonomic activity, and much more.

Finally, I would like to take this opportunity to express my gratitude to the Editorial Board, authors, peer reviewers, and interviewees for their continued hard work in bringing this research to you. We hope that this issue of *EMJ Cardiology*, and future publications, will continue to encourage and present new research ideas that contribute to the ever-developing field of cardiology.

Spencer Gore

Chief Executive Officer, EMG-Health

Foreword

Dear Colleagues,

It is a great pleasure to introduce the latest issue of *EMJ* Cardiology. As with previous journals, you will find an immersive array of expertly written, peer-reviewed articles and case reports contained within these pages, which focus on the hot topics and most up-to-date advances from across the discipline.

My Editor's Pick for this publication is a fascinating and highly relevant study by Sheikh et al., which evaluates the efficacy of the Hospital Readmission Reduction Program (HRRP) in the USA by utilising large national datasets, and is the first to analyse based on heart failure subtypes. The authors report novel findings that advance our knowledge in the field of heart failure. Therefore, I am certain that this manuscript will be a stimulus for the EMJ readership.

For those who were unable to attend this year's European Society of Cardiology (ESC) Congress, or wish to relive the highlights, I highly recommend the Congress Review. This features late-breaking research news from the meeting on the long-term effects of carotid artery surgery and stenting on stroke, early coronary angiography in cardiac arrest without ST-segment elevation, and the possibility of personalising sudden cardiac death prevention after a myocardial infarction. Also included is a compelling in-house feature providing an overview of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure.

The abstract review summaries are another valued addition and not to be missed. These cover topics such the impact of depression on cardiac autonomic activity; premature alterations in arterial stiffness, endothelial integrity, and coronary and cardiac performance 4 months after COVID-19 infection; and echocardiographic parameters in patients with COVID-19 pneumonia in hospital and 3 months after discharge.

I would like to thank all the authors, contributors, Editorial Board members, and reviewers for their outstanding work in creating the 2021 issue of *EMJ Cardiology*. I hope that this journal will prove an inspiring read and a source of valuable information to assist in daily practice.

Çetin Erol

Ankara University, Turkey

Congress Review

Review of the European Society of Cardiology (ESC) Congress 2021

Location: ESC Congress 2021: The Digital Experience

Date: 27th–30th August 2021

Citation: EMJ Cardiol. 2021;9[1]:11-21. Congress Review.

THE EUROPEAN Society of Cardiology (ESC) Congress 2021 successfully brought together clinicians and researchers from across the globe, working to advance cardiovascular care and medicine and improve patient outcomes. This year, the online meeting attracted more than 39,000 healthcare practitioners from 169 countries. In comparison, the 2019 face-to-face event in Paris, France, was attended by 33,510 delegates from 151 countries. Clearly, the transition to a digital format allowed for greater accessibility, diversity, and inclusivity, enabling the ESC to "provide health professionals working in the field of cardiovascular disease and prevention with information intended to reduce the burden of cardiovascular disease."

Stephan Achenbach, ESC President, discussed the importance of this year's event, both directly on cardiologists and indirectly on patients: "Across four days we discovered the latest research findings that will impact cardiovascular practice and improve patient care in a scientific bonanza like no other."

The spotlight of the ESC Congress 2021 was sudden cardiac death, with presentations highlighting therapeutic interventions and risk of sudden cardiac death in structural heart disease, risk calculators to predict sudden cardiac death in cardiomyopathies, and alternatives to transvenous defibrillators for the prevention of sudden death. Beyond this overarching theme, topics encompassed the consequences of COVID-19 in heart failure, novel approaches to catheter ablation, recent advances in the diagnosis and treatment of hypertension, challenges of cardiovascular pharmacotherapy in the elderly, spiroergometry in clinical practice, insights into metabolic strategies to treat cardiovascular disease, and antithrombotic therapy after transcatheter aortic valve implantation.

Of note were the 'Guidelines in Practice' sessions, which examined the management of patients with asymptomatic chronic coronary syndrome, the management of atrial septal defects with pulmonary hypertension, and the ESC and European

Society of Hypertension (ESH) guidelines on the management of arterial hypertension in elderly patients.

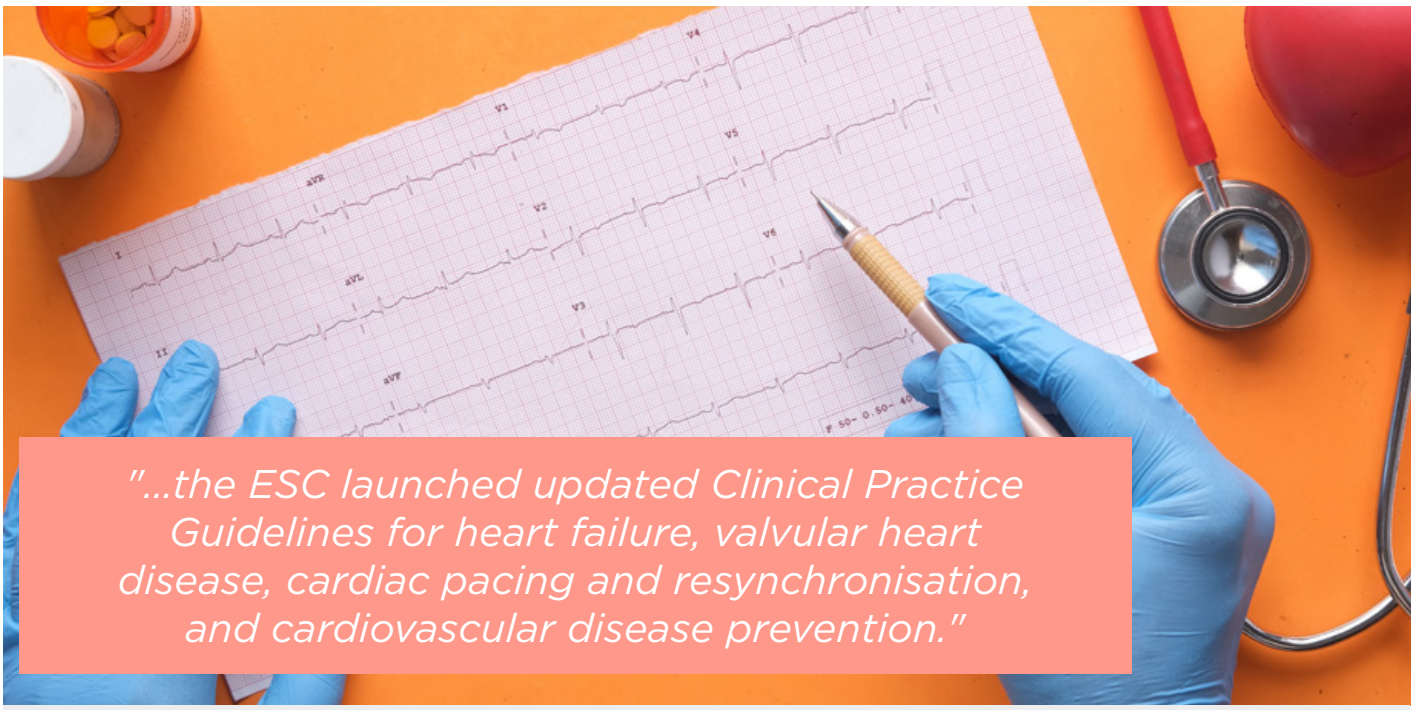
Stephan Windecker, Congress Programme Chair, stressed that "sessions were not just one-way presentations. There were plenty of opportunities for scientific exchange between delegates and expert faculty through the discussion chats and live Q&A [question and answer] sessions." As a result, this year's event was "a truly interactive congress connecting health professionals around the world."

Furthermore, almost 3,700 abstracts were presented over the course of the 4-day conference, providing insights across the various sub-disciplines of cardiology. Several standout abstracts have been summarised in this issue of *EMJ Cardiology*, covering highly relevant topics such as echocardiographic parameters of individuals with COVID-19 pneumonia in hospital and 3 months after discharge, the impact of depression on cardiac autonomic activity, and the effects of elevated circulating levels of TGF-β on the progression of valve myxomatosis and leaflets billowing.

In addition, the ESC launched updated Clinical Practice Guidelines for heart failure, valvular heart disease, cardiac pacing and resynchronisation, and cardiovascular disease prevention. Essential messages were "presented by task force chairs and a panel of experts exploring the implications for clinical practice," said Windecker. A compelling in-house feature outlining the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure has been included in our independent congress review.

An overview of hot-topic ESC press releases can also be found within these pages, including whether the influenza vaccination should be considered as part of standard hospital care following acute myocardial infarction, the use of ablation and biventricular pacing in people with severely symptomatic permanent atrial fibrillation, and the long-term effects of carotid artery surgery versus stenting on fatal or disabling stroke in patients with asymptomatic carotid stenosis. Each groundbreaking news story featured in this publication was based on research presented during the ESC Congress 2021.

EMJ looks forward to welcoming you all, hopefully in-person, to Barcelona, Spain, next year for the 2022 meeting of the world's largest cardiology conference. Until then, read on for our key scientific insights from the ESC Congress 2021. ■



"...the ESC launched updated Clinical Practice Guidelines for heart failure, valvular heart disease, cardiac pacing and resynchronisation, and cardiovascular disease prevention."

ESC 2021 REVIEWED →

Stenting and Carotid Artery Surgery Have Similar Effects on Chance of Stroke

"We have shown that, for patients with a severely narrowed carotid artery, stenting and surgery have similar effects on the chances of having a disabling or fatal stroke. The risk from each procedure is about 1%."

BREAKING research conducted on patients with asymptomatic severe carotid artery stenosis has discovered comparable long-term effects between stenting and surgery on fatal or disabling stroke, according to research presented during a Hot Line session at the ESC Congress 2021. Both carotid artery stenting (CAS) and carotid endarterectomy (CEA) surgery aim to restore patency and reduce risk of stroke, combatting elevated risk in patients with severe carotid stenosis. The importance of the current ACST-2 trial lies with the provision of comparative data, which is lacking, on the long-term protective effects of both procedures.

ACST-2 was the largest trial to compare CAS and CEA in asymptomatic patients with a severely narrowed carotid artery that had not yet resulted in an ischaemic event, enrolling 3,625 participants from 33 countries. These patients were randomly allocated to CAS or CEA and followed for an average of 5 years. Outcomes measured included procedural risks for both morbidity and mortality within a month of the procedure, as well as non-procedural stroke sub-divided by severity. One percent of patients in both groups had a disabling stroke or died within 30 days (15 allocated to CAS and 18 to CEA), meanwhile 2% had a non-disabling procedural stroke (48 allocated to CAS and 29 to CEA). Alison Halliday, the principal investigator from the University of Oxford, UK, summarised these findings: "We have shown that, for patients with a severely narrowed carotid artery, stenting and surgery have similar effects on the chances of having a disabling or fatal stroke. The risk from each procedure is about 1%. After that, however, the annual risk over the next 5 or more years is halved, from 1% down to 0.5% per year." This is clearly reflected in the main outcome, finding that 5-year fatal or disabling non-procedural stroke occurrence was 2.5% in patients of each group, with a rate ratio (RR) of CAS versus CEA of 0.98 (95% confidence interval [CI]: 0.64–1.48; p=0.91). Additionally, any non-procedural stroke occurred in 5.3% of the CAS group versus 4.5% of the CEA group (RR: 1.11; 95% CI: 0.86–1.57; p=0.33). A meta-analysis of this and all other major trials of a similar design yielded a matching non-significant result for any stroke (RR: 1.11; 95% CI: 0.91–1.32; p=0.21).

Evidence this trial brings forward will be esteemed in a field with existing knowledge gaps. Future studies will likely build upon this research to support treatment of the growing number of patients suffering from carotid artery stenosis. ■

Gum Disease Is Linked with an Elevated Likelihood of Cardiovascular Disease

INCREASED risk of heart disease has been associated with gum disease, according to a study in Sweden, which unravelled a directly proportionate relationship between periodontitis severity and risk of heart attack. Research results were presented during the ESC Congress 2021. Labelled PAROKRANK, the original version of this study presented periodontitis as significantly more common in first-time heart attack patients compared with healthy peers of the same age and sex in the same area. This long-term follow-up described an increased risk of new cardiovascular events over time, both in patients who have had heart attacks and their healthy peers, with the presence of gum disease.

"This long-term follow-up described an increased risk of new cardiovascular events over time, both in patients who have had heart attacks and their healthy peers, with the presence of gum disease."

Analysis included 1,587 participants with an average age of 62 years, who underwent a dental exam between 2010 and 2014: 985 were classified healthy, 489 with moderate periodontitis, and 113 with severe periodontitis. The occurrence of cardiovascular events and death were followed until the end of 2018, with the primary endpoint a composite of all-cause death, non-fatal heart attack or stroke, or severe heart failure. Over an average of 6.2 years, there were 205 primary endpoint events, whereby participants with periodontitis at baseline had 49% higher odds relative to those with healthy gums. In this way, the probability of primary endpoint rose with increasing severity of gum disease.

Giulia Ferrannini, one of the study authors, suggested action based on their findings: "Our study suggests that dental screening programmes, including regular check-ups and education on proper dental hygiene, may help to prevent first and subsequent heart events." This is of particular importance to patients who have experienced a heart attack in the past, where this association of study was discovered to be particularly evident. Ferrannini hypothesised a cause for their discovery: "We postulate that the damage of periodontal tissues in people with gum disease may facilitate the transfer of germs into the bloodstream. This could accelerate harmful changes to the blood vessels and/or enhance systemic inflammation that is harmful to the vessels." Clinicians will second Ferrannini's warning that "the quality of care in Sweden is high, as confirmed by the overall low number of total events during follow-up," and await confirmation or disagreement with contrasting demographics in subsequent studies of a similar design. ■

Improving and Personalising Prediction of Sudden Cardiac Death

THE LARGEST dataset ever analysed with the purpose of improving understandings of sudden cardiac death risk was presented at the ESC Congress 2021. This is the first phase of the PROFID consortium.

PROFID aims to personalise the prevention of sudden cardiac death after cardiac myocardial infarction. The first phase, presented at the ESC Congress, focused on developing a model to predict the risk of sudden cardiac death in individual post-infarction patients. Sudden cardiac death is the cause of approximately 20% of fatalities, usually resulting from myocardial infarction. Patients with a left ventricular ejection fraction (LVEF) of 35% or lower are recommended a prophylactic cardioverter defibrillator. However, sudden cardiac death occurs most frequently in those with an LVEF of 35% or higher.

The first phase of the PROFID project aimed to develop a model to predict the risk of sudden cardiac arrest in patients post myocardial infarction. Data was pooled for 19 datasets across Europe, Israel, and the USA. Datasets included information on demographics, clinical parameters, medication, ECG, biomarkers, echocardiography, and patient outcomes. Six of the datasets also included cardiac MRI information. In total, approximately 225,000 patients were analysed. Participants were drawn from a pool of patients who had previously suffered a myocardial infarction regardless of LVEF or ischaemic cardiomyopathy with LVEF below 50%.

Traditional analytical methods and artificial intelligence techniques were used to develop the four models. The models were subsequently tested for their accuracy at predicting primary patient outcomes. The accuracy of the predictions was compared to using LVEF as a predictor. The models were initially developed with the Cardiac MRI data excluded. Researchers found that none of these initial models showed substantial improvement in predicting sudden cardiac events over using LVEF. Researchers are currently in the process of updating the models to include Cardiac MRI data. The preliminary results from these models indicate an improved predictive performance. Nikolaos Dagres, Principal Investigator, explained the importance of these results: "These results contribute substantially to our approach to sudden cardiac death prediction. For the first time it has become obvious that relying on clinical variables alone, we will not be able to achieve significant improvement." ■

"For the first time it has become obvious that relying on clinical variables alone, we will not be able to achieve significant improvement."

Is Difficulty Breathing a More Accurate Predictor of Cardiac Arrest than Chest Pain?

BREATHING problems reported prior to cardiac arrest have been identified as an under-rated warning sign, with patients less likely to receive emergency medical help. According to research carried out at the North Zealand Hospital, Hillerod, Denmark, and presented on the 27th August at the ESC Congress 2021, difficulty breathing is the most common symptom before cardiac arrest. There is currently limited knowledge about the out-of-hospital early warning signs preceding a cardiac arrest. Increasing knowledge of these signs would improve assessment of cardiac event risk by medical professionals, enabling more effective prevention.

The study drew patients from the Danish Cardiac Arrest Registry and identified those who had contacted emergency services with symptoms 24 hours prior to cardiac arrest. The calls to emergency services were systematically evaluated to identify the symptoms reported by the caller. These patients were subsequently linked to nationwide databases to collect further information, such as survival.

Analysis identified 4,071 patients who had suffered an out-of-hospital cardiac arrest, 481 (11.8%) of whom had made pre-arrest calls. Breathing problems were the most frequently reported pre-arrest symptom, identified by 59.4% of patients, followed by confusion (23.0%), unconsciousness (20.2%), chest pain (19.5%), and paleness (19.1%). Notably, urgent medical response was dispatched to just 68.7% of calls reporting breathing problems compared with 83.0% who reported chest pain.

Furthermore, regarding survival rates, 81% of patients with breathing problems died within 30 days compared with 47% of those with chest pain.

Filip Gnesin, a research scholar at the North Zealand Hospital, explained the findings: "Breathing difficulty was the most common complaint and much more common than chest pain. Despite this, compared to chest pain, patients with breathing issues were less likely to receive emergency medical help and more likely to die within 30 days after arrest. These findings indicate that breathing problems are an under-rated warning sign of cardiac arrest". He further stated: "We hope our findings will stimulate further research to help emergency medical dispatchers distinguish between symptoms of a pre-arrest condition versus other medical issues." ■

"These findings indicate that breathing problems are an under-rated warning sign of cardiac arrest."

Early Coronary Angiography in Cardiac Arrest Found Not Superior to a Delayed Selective Approach

INVASIVE, immediate strategies towards out-of-hospital cardiac arrest (OHCA) have been classified as not superior to a delayed invasive strategy. The TOMAHAWK trial presented information to clarify this, relating to early coronary angiography for patients without ST-segment elevation. The trial delivers information in a field where the usefulness and timing of coronary angiography for OHCA survivors without ST-segment elevation are uncertain. This can be applied to diagnostic coronary angiography and can guide potential percutaneous interventions, offering a beneficial initiative, where one-third of patients experience acute myocardial infarction as a cause of cardiac arrest.

The randomised and open-label TOMAHAWK trial builds on previous guidelines set by the COACT trial, which examined whether immediate coronary angiography for treating or ruling out acute coronary events in OHCA survivors without ST-segment elevation is beneficial for all-cause mortality at 30 days, compared with intensive care unit assessment and delayed selective angiography. The current study enrolled 554 patients aged 30 years or over, all with successful resuscitation after OHCA and including both shockable and non-shockable rhythms, randomised at hospital admission to immediate coronary angiography or initial intensive care unit assessment with delayed angiography, if indicated. The primary endpoint was all-cause mortality at 30 days, occurring in 143 patients (54%) assigned to immediate coronary angiography and 122 patients (46%) in the delayed group. No differences were observed between groups in safety endpoints, including moderate or severe bleeding, stroke, and acute renal failure requiring renal replacement therapy. Other secondary endpoints such as length of intensive care unit stay, peak troponin release, myocardial infarction, or rehospitalisation for congestive heart failure also did not differ between groups. Secondary endpoint of all-cause death or severe neurological deficit at 30 days did occur more frequently in the immediate angiography group (relative risk: 1.16; 95% confidence interval: 1.002–1.340).

Steffen Desch, the Principal Investigator from the Heart Centre Leipzig, Germany, summarised the progress the study has made in the specialty of cardiology: "TOMAHAWK was the second and largest randomised trial addressing the question of early coronary angiography in OHCA

patients without ST-segment elevation. Like the COACT trial, we found that early angiography was not superior to a delayed or selective approach. COACT was restricted to patients with shockable rhythm and TOMAHAWK extends the findings to patients with non-shockable rhythm." Desch acknowledged limitations: "The higher rate of death or severe neurological deficit in the immediate angiography group is only hypothesis-generating." Even so, "the results of the trial suggest that patients without a significant coronary lesion as the trigger of cardiac arrest do not benefit form an invasive approach and might even be harmed." This study provides an infrastructure for upcoming investigations to take further, as well as useful guidance for the treatment of OHCA in patients without ST-segment elevation. ■

"Like the COACT trial, we found that early angiography was not superior to a delayed or selective approach. COACT was restricted to patients with shockable rhythm and TOMAHAWK extends the findings to patients with non-shockable rhythm."

Could the Influenza Vaccine Protect Heart Attack Sufferers?

FASCINATING evidence has emerged suggesting that the influenza vaccine may have protective effects combatting adverse cardiovascular events. Presented in a Hot Line Session at ESC Congress 2021 from research in the IAMI randomised trial, this information has prompted the recommendation for flu jabs to become a part of standard care for those who have suffered heart attacks.

During periods of influenza epidemic, there is an observed increase in deaths caused by adverse cardiovascular events, putting many at risk. Previous observational studies have indicated that the influenza vaccine may provide a protective effect against these events. This vaccine, although currently recommended for sufferers of heart disease, is not part of standard care following an acute myocardial infarction.

The IAMI trial aimed to analyse whether the effects improved outcomes in sufferers of myocardial infarction, or percutaneous coronary intervention in high-risk sufferers of coronary artery disease following vaccination. The trial, which is the largest of its kind to date, was carried out at 30 hospitals in 8 countries, over 4 influenza seasons.

"Our findings suggest that influenza vaccination should be considered as part of in-hospital treatment after myocardial infarction."

Each participant was randomly chosen to receive either the influenza vaccine or a placebo within 72 hours of invasive coronary surgery, or hospitalisation. The primary endpoint of the study was comprised of all-cause death, myocardial infarction, or stent thrombosis at 12 months; a hierarchical testing strategy was also used to assess the key secondary outcomes of these events.

The trial, although prematurely stopped due to the COVID-19 pandemic, enrolled 2,571 patients. The primary composite endpoint was observed in 5.3% of vaccinated patients, and 7.2% of the placebo group. The placebo group also experienced a higher incidence of secondary endpoints, with the exception of myocardial infarction rates which saw no disparity between the two groups.

The results of this study indicated that early administration of the influenza vaccine reduced the incidence of adverse events compared to the placebo group. Ole Fröbert, Örebo University, Sweden, the Principal Investigator of the study explained: "Our findings suggest that influenza vaccination should be considered as part of in-hospital treatment after myocardial infarction." ■

Salt Substitutes as an Affordable Method of Stroke Risk Mitigation

SALT substitutes offer a cheap and simple alternative that can lower risk of high blood pressure, stroke, and cardiovascular disease-caused mortality. These findings have been demonstrated in late-breaking research presented at the ESC Congress 2021.

The SSaSS compared the effect of reduced sodium salt substitutes, made of potassium chloride, against regular salt (sodium chloride). Elevated sodium intake and low potassium have both been previously associated with high blood pressure and an increased risk of cardiovascular disease and premature death. Salt substitutes have been shown to lower blood pressure; however, they have previously drawn concerns about causing hyperkalaemia in patients with chronic kidney disease and their effects on heart disease, stroke, and death have been uncertain. The SSaSS investigated whether reduced sodium salt affected blood pressure, risk of cardiovascular events, mortality, and hyperkalaemia.

The open, cluster-randomised trial enrolled a total of 20,995 patients between April 2014 and January 2015. Participants were adults who had either suffered a previous stroke or were aged 60 or older with poorly controlled blood pressure and were drawn from 600 villages in 5 rural provinces of China. Participants were cluster randomised by village in a 1:1 ratio of intervention salt substitute versus continued use of regular salt.

During the 5-year follow up, more than 3,000 participants had a stroke, over 4,000 died, and over 5,000 had a major cardiovascular event. The comparison found that the risk of stroke was reduced in the intervention salt substitute group compared with the regular group (29.14 versus 33.65 per 1,000 patient years, representing a significant reduction at 95% confidence interval as p=0.006). Furthermore, risk of major cardiac events was reduced and there was no increased risk of serious adverse events attributed to clinical hyperkalaemia associated with the salt substitute compared to regular salt.

"This study provides clear evidence about an intervention that could be taken up very quickly at very low cost."

Principle investigator Bruce Neal of the George Institute for Global Health, Sydney, Australia stated that: "This study provides clear evidence about an intervention that could be taken up very quickly at very low cost." He further highlighted the significance of the findings: "The trial result is particularly exciting because salt substitution is one of the few practical ways of achieving changes in the salt people eat." ■

Ablation and Biventricular Pacing Boosts Survival in Selected Atrial Fibrillation Patients

"The improvement in survival shown by the APAF-CRT trial supports ablation plus CRT as a first line therapy in patients with permanent AF, narrow QRS, and previous hospitalisation for heart failure."

REDUCED mortality rates have been observed in severely symptomatic permanent atrial fibrillation (AF), by the use of ablation plus cardiac resynchronisation therapy (CRT) compared to pharmacological therapy, states a new study presented at the ESC Congress on 28th August 2021. Research has previously demonstrated, by slowing and regularising the ventricular rate in patients diagnosed with AF, atrioventricular (AV) junction ablation, and right ventricular pacing has led to improved symptoms, quality of life, and cardiac function.

The APAF-CRT trial involved patients diagnosed with severely symptomatic permanent AF and a narrow QRS. Phase I of the study demonstrated that both AV junction ablation and CRT led to reduced hospitalisation compared to the pharmacological therapy. The results of the multicentre, international, prospective, randomised, Phase II trial were presented in the ESC Congress 2021. The criteria of the patients included were severely symptomatic permanent AF (over 6 months) considered unsuitable for AF ablation or in whom AF ablation had failed; narrow QRS (110 msec or below); and at least one hospitalisation for heart failure the previous year. A total of 133 patients were randomised were assigned in a 1:1 ratio to either optimal pharmacological rate control therapy (drug arm) or AV junction ablation and biventricular pacing (ablation+CRT arm). The participants were a mean age of 73 years, and 62 patients (47%) were female.

The primary endpoint of death occurred seven patients (11%) in the ablation+CRT arm and in 20 patients (29%) in the drug arm group (hazard ratio: 0.26; 95% confidence interval: 0.10–0.65; p=0.004). The estimated death rates at 4 years were 14% and 41% in the ablation+CRT and drug arms, respectively. Additionally, at 4 years, the relative and absolute risk reductions were 74% in the ablation+CRT arm and 27% in the drug arm group. Furthermore, AV junction ablation and CRT reduced combined risks of death from any cause or hospitalisation for heart failure by 60% (95% confidence interval: 0.22–0.73; p=0.002).

Principal Investigator Michele Brignole, Professor of the IRCCS Istituto Auxologico Italiano, San Luca Hospital, Milan, Italy, said: "We hypothesise that the observed benefit was due to the combination of the strict rate control and rate regularisation achieved by AV junction ablation, together with biventricular pacing, which counteracted the adverse effects of right ventricular pacing. The improvement in survival shown by the APAF-CRT trial supports ablation plus CRT as a first line therapy in patients with permanent AF, narrow QRS, and previous hospitalisation for heart failure." ■

2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure

Natasha Meunier-McVey
Editorial Assistant

Citation: EMJ Cardiol. 2021;9[1]:22-25.

An engaging session on the newly revised European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure (HF) was conducted on the first day of the 2021 ESC virtual congress. Chaired by Colin Baigent, Professor of Epidemiology, University of Oxford, UK, the session also explored the classification and management of HF, and addressed questions from the congress audience.

THE MANAGEMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION

Roy Gardner, Honorary Professor at the Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK, opened the session by exploring the management of HF with reduced ejection fraction (HFrEF). Gardner outlined the key changes to the HFrEF therapeutic algorithm, last revised in 2016, which include the recommendation of dapagliflozin and empagliflozin for the management of HFrEF. These SGLT2 inhibitors have been given a Class IA recommendation under the new ESC guidelines, following the emergence of data from the DAPA-HF trial linking their use to reduced hospitalisation and mortality in patients with HF. The new 2021 therapeutic algorithm emphasises the importance of commencing key drug therapies as quickly and safely as possible following diagnosis. These therapies include angiotensin-converting enzyme inhibitors, β-blockers, SGLT2 inhibitors, and mineralocorticoid receptor antagonists, and should be used in conjunction with a loop diuretic to relieve congestion.

"The new 2021 therapeutic algorithm emphasises the importance of commencing key drug therapies as quickly and safely as possible following diagnosis."

Gardner went on to explain the importance of tailored disease management in the 2021 HF guidelines. The new guidelines advise clinicians to take a more phenotypic approach to the management of HFrEF, in an aim to reduce mortality through tailoring treatment to each

patient. Aside from the disease-modifying therapies that can be prescribed, selected patients can also be offered device therapy, heart transplantation, or specific treatments for comorbidities. Device therapies for patients with advanced HF include mechanical circulatory support of various forms. Gardner also discussed methods to improve patient quality of life, such as exercise rehabilitation and multidisciplinary care.

DIAGNOSIS AND TREATMENT OF HEART FAILURE WITH MILDLY REDUCED EJECTION FRACTION AND HEART FAILURE WITH PRESERVED EJECTION FRACTION

Carolyn Lam, Professor of Duke-NUS Cardiovascular Academic Clinical Programme, Singapore, presented a session on the diagnosis and treatment of HF with mildly reduced ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF). Lam began by defining HF as "a clinical syndrome consisting of cardinal symptoms that may be accompanied by signs." The speaker then went on to explain the diagnostic algorithm of HF, which begins with the clinical assessment of these signs through ECG to determine underlying cardiac abnormalities. The left ventricular ejection fraction (LVEF) is then assessed for HF classification; an LVEF of ≤40% indicates HFrEF, 41–49% HFmrEF, and ≥50% HFpEF.

One of the most notable changes from the 2016 guidelines in this area of HF is the modification of the term 'HF with mid-range ejection fraction' to 'HF with mildly reduced ejection fraction'. This change was implemented following evidence demonstrating that patients with HFmrEF could benefit from similar therapies to those recommended for individuals with HFrEF. A table of recommendations for HFmrEF treatment has also been added to the guidelines, an area which was previously merged with HFpEF treatments.

Lam explained the challenges related to the diagnosis of HFpEF and outlined the guideline alterations implemented to improve this. The 2021 guidelines now outline a simplified approach to HF diagnosis, which focuses on the most widely

used and accessible diagnostic methods. Patients with HFrEF who experience an improvement in LVEF (≥50%) are now described as having 'recovered HFrEF', rather than HFpEF. Although some improvements have been observed in some cases, no treatments have yet reduced mortality or morbidity in patients with HFpEF. Treatments are under ongoing revisions, and recommendations such as reducing body weight in obese patients continue to be advised where appropriate.

NEW RECOMMENDATIONS FOR COMORBIDITIES

Marianna Adamo, Interventional Cardiologist at the ASST Civil Hospital of Brescia, Italy, discussed the 2021 ESC guidelines for comorbidities associated with HF. Adamo began by outlining the management of cardiovascular comorbidities in HFrEF, including atrial fibrillation. The revised guidelines recommend anticoagulation therapy, treatment of triggers, and optimisation of HF therapies in all patients with atrial fibrillation and HFrEF. Further treatment strategies were also recommended depending on the individual case and stability of the patient. Adamo then explored therapies for chronic coronary syndrome and valvular heart disease, before discussing non-cardiovascular comorbidities. In patients with Type 2 diabetes mellitus and HF, SGLT2 inhibitors have been recommended to reduce hospitalisations, adverse cardiovascular events, and death. Other common comorbidities discussed included iron deficiency and cancer. Adamo also presented the new algorithms for the management of myocarditis and amyloidosis.

ADVANCED AND ACUTE HEART FAILURE

In the final presentation, Ovidiu Choincel, Professor at the Iliescu Institute for Emergency Cardiovascular Diseases, Bucharest, Romania, explored the guidelines for advanced and acute HF. A new definition for advanced HF was provided, which is now described as a "distinct clinical entity in the progression of heart failure." The revised ESC guidelines also outline specific criteria that must be met in order for a condition to be classed as advanced HF, and provide new recommendations for device therapies and heart transplants. For the first time, organisational issues related to patient referral in advanced HF centres have been addressed, and the criteria for referral defined. End-of-life care was also considered, with an emphasis on ensuring the best quality of life for patients.

"One of the most notable changes from the 2016 guidelines in this area of HF is the modification of the term 'HF with mid-range ejection fraction' to 'HF with mildly reduced ejection fraction.'"

Acute HF has consistently been defined as a 'rapid onset' condition by past guidelines. Choincel explained how research has now identified that worsening symptoms may also appear gradually, causing a shift in definition of the disease. He went on to identify acute HF as a multi-event disease and presented a revised definition that characterises acute HF as "the rapid or gradual onset of symptoms of HF, severe enough to seek urgent medical attention and leading to an unplanned hospital admission or an emergency department visit." Results from clinical trials GALACTIC-HF and ELISABETH showed no benefit from early sustained vasodilation for those with HF, which led to a decrease in guideline classification for vasodilators. Although the classification for vasoconstrictors has remained the same, the revised guidelines have removed the recommendation of epinephrine following the OptimaCC trial, which presented an increase in refractory cardiogenic shock in patients treated with this drug.

CONCLUDING REMARKS

These updated ESC guidelines will undoubtedly further help physicians in clinical decision-making and will contribute to optimising patient care. Ongoing research and clinical trials are essential for ensuring a continuous improvement of clinical guidelines leading to better disease outcomes.

New Therapies for Patients Following a Worsening Heart Failure Event? What's Next for Your Patients Following a Worsening Heart Failure Event?

These virtual symposia took place on the 28th and 29thAugust 2021, as part of the European Society of Cardiology (ESC) 2021 annual congress

Co-chairs: Carolyn Lam,[1] Paul Armstrong,[2] Faiez Zannad[3]

Speakers: Carolyn Lam, Paul Armstrong, Michele Senni,[4] Burkert Pieske,[5] Faiez Zannad, Javed Butler,[6] Ewa Jankowska[7]

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Meeting Summary

Despite the use of guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (HFrEF), significant unmet need exists in patients with worsening HF who remain at high-risk of recurrent events. During these two symposia, leading cardiology experts explored therapeutic advances for patients with symptomatic chronic HF following a worsening HF event, focusing on the new soluble guanylate cyclase stimulator vericiguat. Key outcomes data from the VICTORIA trial show that vericiguat affords significant clinical benefits in this patient population and has an important role to play in the future treatment landscape for worsening HF.

SYMPOSIUM 1

New Therapies for Patients Following a Worsening Heart Failure Event

Patients with HF embark on a vicious cycle characterised by progressive worsening over time, recurrent hospitalisations associated with deteriorating cardiac function, and eventual death.[1,2] This worsening HF is a component now recognised as increasingly prevalent, noted Armstrong, but has "not yet achieved the clinical attention it deserves." Despite the use of best evidence-based GDMT, patients with HFrEF continue to remain at significant residual risk of both cardiovascular (CV) death and HF hospitalisation (HFH).[3-7]

Unlike existing therapies that target established activated disease pathways in HF, vericiguat represents a new therapeutic approach that stimulates soluble guanylate cyclase (sGC) to restore the impaired nitric oxide (NO)-sGC-cyclic guanosine monophosphate (cGMP) pathway (Figure 1).[1,8-14] Armstrong explained that it is the "conspiracy" between endothelial dysfunction and oxidative stress that leads to intracellular NO deficiency, thereby impairing the cell's inability to generate cGMP and protein kinase G (PKG). Vericiguat is a direct sGC stimulator and also recruits residual NO in the cell, thereby accentuating this novel pathway and restoring the heart and the vasculature to a more normal state.[8,15-18]

Therapeutic Advances: A New sGC Stimulator for Patients Following a Worsening Heart Failure Event

Pieske introduced the VICTORIA study, a state-of-the-art, international, randomised, parallel-group, placebo-controlled, double-blind, event-driven Phase III trial, whose objective was to evaluate the effect of vericiguat in patients with symptomatic chronic HF following a worsening HF event.[16,19] Eligibility criteria included HFrEF with a left ventricular ejection fraction (LVEF) <45%, New York Heart Association (NYHA) Class II–IV, and elevated natriuretic peptides (stratified by the presence of atrial fibrillation [AF] or sinus rhythm). Renal dysfunction was permitted down to a "very low" estimated glomerular filtration rate (eGFR) cut-off of 15 mL/min/1.73m^2, remarked Pieske. In order to qualify for the VICTORIA study, patients were required to have experienced HFH within 6 months or undergone intravenous (IV) diuretic treatment for HF within 3 months. In total, 5,050 patients were randomised 1:1 to vericiguat or placebo, and uptitrated to a target dose of 10 mg once daily (achieved in approximately 90% of patients in both arms after 12 months). The primary endpoint was time to first occurrence of the composite of CV death and HFH.[16,19]

Pieske described key baseline characteristics of VICTORIA patients: mean age was 67 years, approximately one-quarter were female, and two-thirds were white.[19] Importantly, two-thirds of participants (66.9%) had been hospitalised for decompensated HF within the past 3 months, 17.2% within the past 3–6 months, and 15.9% had received IV diuretics for a worsening HF event within the prior 3 months. Around 40% of patients had an NYHA Class III or IV at baseline, illustrating that patients were more advanced in their HF disease journey, added Pieske. Overall, 10% of the total patient population had eGFR <30 mL/min/1.73m^2 and median N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) was 2,816 pg/mL. Around 60% were already receiving triple therapy for HF.[19]

In the VICTORIA trial, vericiguat significantly reduced the annualised absolute rate of time to

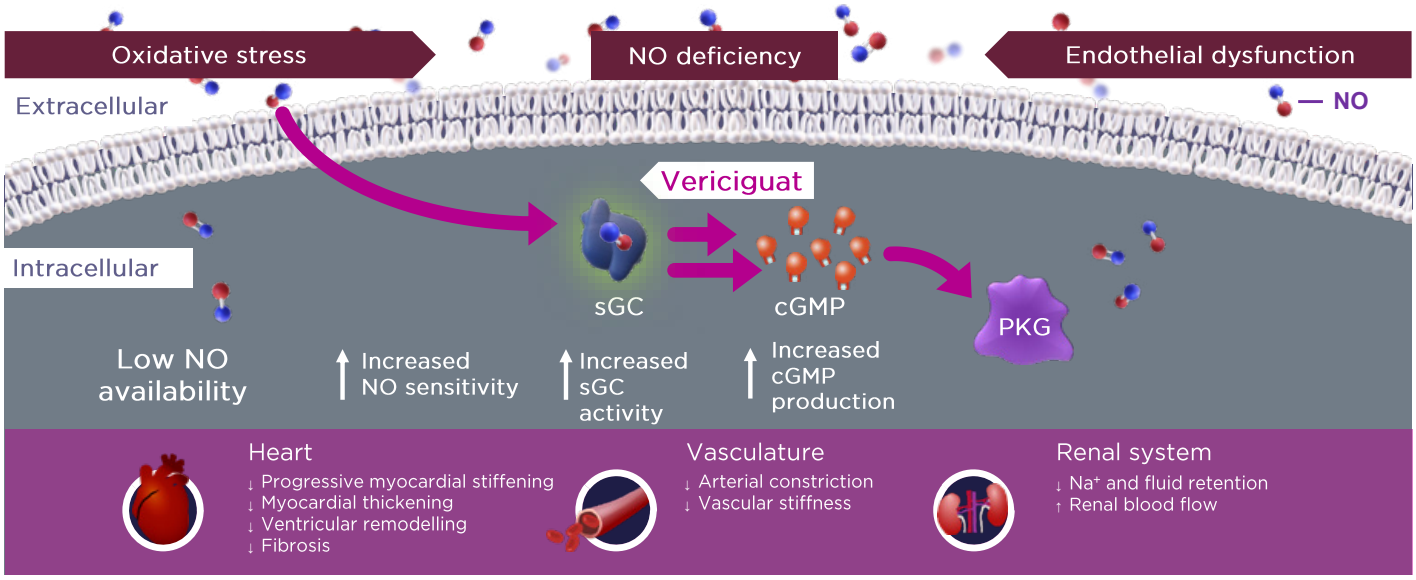


Figure 1: Vericiguat increases soluble guanylate cyclase activity to improve myocardial and vascular function.[1,8,12-14]

cGMP: cyclic guanosine monophosphate; Na^+: sodium ion; NO: nitric oxide; PKG: protein kinase G; sGC: soluble guanylate cyclase.

HFH or CV death, meeting the study's primary endpoint (Figure 2).[19] The annual event rate was 37.8 events per 100 patient-years in the placebo arm. Pieske described this as "very high," with over 35% of patients experiencing a primary event of CV death or first HFH after 1 year. In contrast, patients treated with vericiguat achieved a significant reduction in the primary endpoint (hazard ratio [HR]: 0.90; 95% confidence interval [CI]: 0.82–0.98; p=0.02), translating to an absolute rate reduction (ARR) of 4.2 events per 100 patient-years and a number needed to treat (NNT) of 24.[19] These data are comparable to ARR outcomes from other recent HFrEF trials, remarked Pieske.

Secondary outcomes were in line with the primary endpoint, with vericiguat achieving a significant reduction in total HFH (p=0.02; HR: 0.91; 95% CI: 0.84–0.99) and the composite of first HFH or all-cause mortality (p=0.02; HR: 0.90; 95% CI: 0.83–0.98) compared to placebo.[19] Analysis of primary composite endpoint outcomes showed a consistent benefit of vericiguat across a range of prespecified patient subgroups, with no impact of pretreatment with sacubitril/valsartan or baseline eGFR on vericiguat efficacy. There was, however, a significant interaction of NT-pro-BNP levels at baseline, with patients in the lowest three quartiles deriving most benefit from vericiguat treatment.[19]

Pieske described the safety of vericiguat in the VICTORIA trial as "excellent," with both the overall adverse event (AE) profile and the incidence of serious AEs proving very similar to placebo. In terms of key AEs of interest, symptomatic hypotension (9% versus 8%) and syncope rates (4% versus 3%) were slightly higher with vericiguat versus placebo; however, no significant differences were noted between the study arms.[19]

Top Tips for Practical Patient Management

Top tips for the practical management of worsening HF with vericiguat were provided by Senni, who focused on three key phenotypes that commonly present in clinical practice: patients at risk of hypotension, patients with renal impairment, and patients with hyperkalaemia.

Looking at hypotension, data from the VICTORIA trial showed only very small differences in mean systolic blood pressure (SBP) values between patients treated with vericiguat and placebo.[19] These decreases in SBP occurred very early in the titration phase and then remained stable throughout the rest of the study, with no further

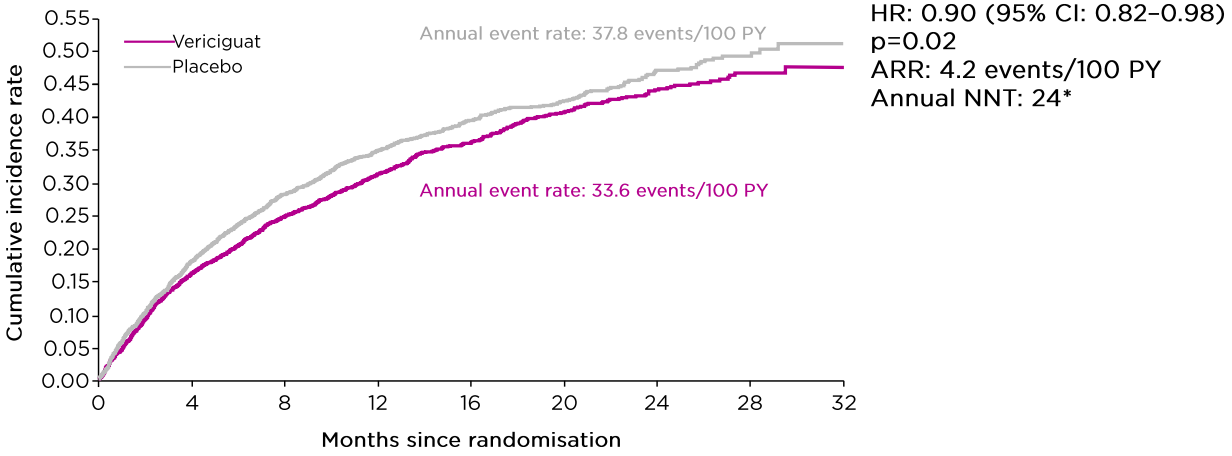


Figure 2: Primary efficacy endpoint from the VICTORIA trial.[19]

Time to CV death or first HFH. Median treatment duration for primary endpoint: 10.8 months.

CI: confidence interval; CV: cardiovascular; HFH: heart failure hospitalisation; HR: hazard ratio.

clinically relevant reductions in BP observed.[19] No excessive BP reductions were seen with vericiguat in patient groups in VICTORIA at elevated risk of hypotension such as elderly patients (>75 years of age), those with SBP <110 mmHg, or those taking sacubitril/valsartan, noted Senni.[20] Moreover, the benefit of vericiguat versus placebo on the primary endpoint was similar across the spectrum of baseline SBP.[20]

Considering the issue of renal impairment, the impact of vericiguat on renal function trajectories in VICTORIA was found to be similar to that of placebo based on changes in both eGFR and creatinine levels over time.[21] Vericiguat also provided a benefit in clinical outcomes of HFH or CV death, HFH or all-cause death, and CV death in patients across all eGFR categories (≤30, >30–≤60, and >60 mL/min/1.73m^2).[21]

For the third and final phenotype, the incidence of hyperkalaemia in VICTORIA was found to be similar between treatment arms, even in patients with low renal function (eGFR ≤30 mL/min/1.73m^2), where 8.0% of vericiguat-treated patients experienced hyperkalaemia compared to 10.2% on placebo. Compared to placebo, vericiguat also showed no impact on sodium or potassium levels over time.[21]

Overall, these data from VICTORIA indicate that vericiguat can be used in clinical practice for the management of worsening HF in patients at risk of hypotension, patients with renal impairment, and patients with hyperkalaemia, Senni concluded.

Questions and Answers

Lam opened the panel discussion segment of the symposium by highlighting important recent changes to European Society of Cardiology (ESC) guidelines, which now recognise worsening HF for the first time and recommend a sGC stimulator as a new treatment option on top of GDMT.[22] Vericiguat received a Class IIb recommendation from the ESC and may be considered for patients in NYHA Class II–IV who have had worsening HF, despite treatment with an angiotensin-converting enzyme inhibitor (or angiotensin receptor-neprilysin inhibitor), a β-blocker, and a mineralocorticoid receptor antagonist to reduce the risk of CV mortality or HFH.[22] This marks a "huge milestone," said Lam, with the addition of vericiguat providing an important opportunity to optimise therapy for patients with worsening HF.

Against the backdrop of new ESC guidelines, Pieske outlined how he would manage a patient with chronic worsening HF. The guidelines now acknowledge the entity of worsening HF, where HFrEF patients experience recurrent events despite good background therapy. For these patients, clinicians are "mandated" to provide optimal therapy with the addition of

vericiguat, Pieske pointed out. The safety profile is favourable and vericiguat is now approved by both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory bodies, so cardiologists will soon have it "at hand" for this important, high-risk patient population, he added.

In the setting of the HF outpatient clinic, Senni was asked where he saw the window of opportunity for vericiguat and any particular circumstances that might dictate prescribing. He outlined practical considerations for starting vericiguat after HFH, which include the need for stable background medical therapy, BP >100 mmHg, and a stable condition in terms of congestive signs and symptoms (making it essential to evaluate patients' fluid status first). Treatment should be uptitrated from 2.5 mg every 2 weeks to reach the target maintenance dose of 10 mg/day. In the event of development of hypotension, concomitant medications such as calcium blockers, nitrates, or α-blockers may be stopped, and consideration given to reducing diuretic therapy. These steps can allow you to move forward with a successful uptitration of vericiguat, explained Senni. On the issue of comorbidities, data show that the clinical benefits of vericiguat endure irrespective of AF or anaemia status, worsening renal function, or hypotension risk.

Armstrong gave his perspectives on how the VICTORIA study has helped to advance the field of HFrEF management. He described the entity of worsening HF as "extraordinarily important, increasingly common, and imposing a high burden of morbidity and mortality." Yet it has not been well studied previously in dedicated clinical trials. The discovery of vericiguat has opened up NO-sGC-cGMP as a new therapeutic pathway, explained Armstrong, and by targeting that pathway we have seen a "remarkable," absolute reduction in CV death and HFH events comparable to the well-known foundational therapies. Vericiguat is an easy-to-use, well tolerated, once-daily medication that can be used without laboratory monitoring for renal function or hyperkalaemia. It represents "a new arrow in our quiver," said Armstrong, and an important option for patients that are either unable to tolerate standard-of-care therapy or have broken through with new symptoms.

Lam drew the first symposium to a close by reiterating the urgent, unmet need that exists in patients with worsening chronic HFrEF, who have failed GDMT and require intensification of their HF treatment. Now that the regulatory approvals for vericiguat have been granted and ESC guidelines recommendations received, it is time to start thinking about implementation in clinical practice, she concluded.

SYMPOSIUM 2

What Is Next for Your Patients Following a Worsening Heart Failure Event?

This follow-up symposium provided a practical perspective on identifying patients with worsening HF in the clinic and intervening with vericiguat to optimise therapy and improve outcomes.

When managing worsening HF, it is important to recognise what part of the HF trajectory patients are on, explained Lam. The phase of worsening HF despite optimal medical and device therapy is where "we can really make a difference," she stressed, before patients progress to advanced HF risk, which is refractory to GDMT. Worsening HF events are characterised by progressive signs and symptoms of HF, for which medical treatment is warranted despite the use of GDMT. Events can manifest as either HFH, the requirement for IV diuretics (regardless of setting), or the need for an urgent outpatient HF visit.[23-25] These events are very high-risk and characterised by a progressive reduction in median survival with each hospitalisation.[26] Increased mortality risk is evident regardless of care location, seen equally in worsening HF events that occur outside the hospital setting.[23]

Worsening HF is both a common and prognostically important condition, continued Lam. The PINNACLE Registry® of over 11,000 adults with newly diagnosed symptomatic chronic HF found that 17% developed symptomatic chronic HF following a worsening HF event.[24] Hospitalisations were also shown to accumulate for patients with worsening HF. Overall, 56% of patients were re-hospitalised within 30 days of their worsening HF event and the number of HFHs increased with time.[24] One

in five patients died within 2 years of the event.[24]

Residual risk, therefore, remains in patients with HFrEF despite the use of existing medications, underscoring the need for new therapies. If patients are manifesting worsening HF "we really need to act," insisted Lam. "It's not just a matter of optimising diuretics, it's about changing patients' foundational therapies by adding new therapies that work."

VICTORIA in Context: Deep Dive into the Latest Data

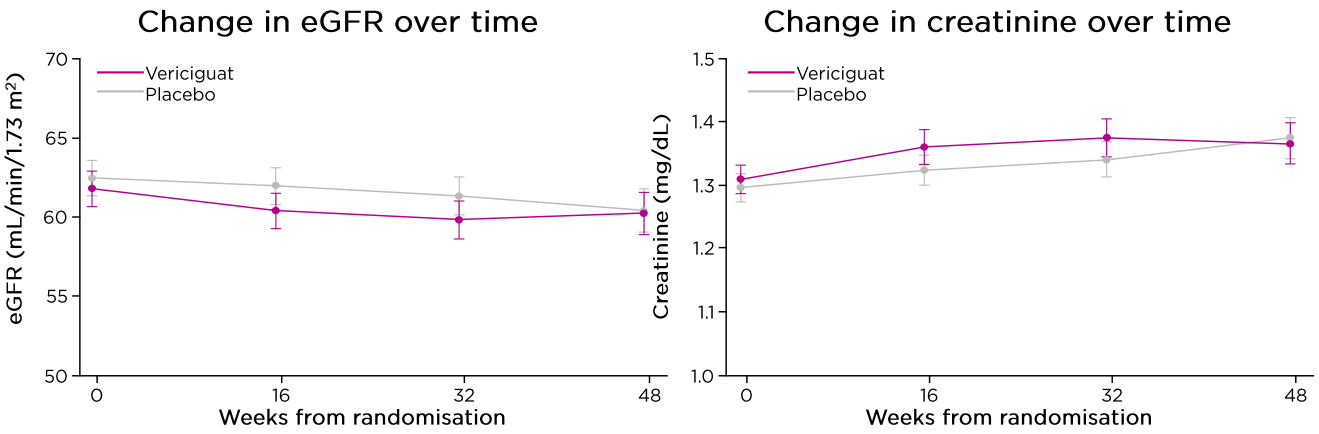
Taking a deep dive into the VICTORIA trial, Butler contextualised the clinical outcomes with a focus on the impact of key patient comorbidities such as chronic kidney disease. He explained that the VICTORIA trial exclusively targeted a population of patients with worsening HF, thereby differentiating it from other trials in the HFrEF space.[19] Other elements of the trial design were also different. While most other HFrEF studies have stipulated that patients must have an eGFR >30 mL/min/1.73m^2, VICTORIA included patients with renal function as low as eGFR >15 mL/min/1.73m^2.[19] VICTORIA also enrolled a wider group of patients in terms of left ventricular ejection fraction inclusion criteria: <45% versus ≤40% for comparator HFrEF studies.[6,7,19,27-33]

Overall, this trial design yielded a different patient population compared to contemporary HFrEF trials, said Butler.[6,7,19,27-33] Natriuretic peptide levels, a key marker of high risk, were substantially greater in the VICTORIA trial (median: 2,816 pg/mL) and the proportion of patients with NYHA Class III or IV symptoms (41%) was higher than in most other studies. Over one-half of the patients in VICTORIA trial (53%) had an eGFR <60 mL/min/1.73m^2, indicative of chronic kidney disease (a higher rate of renal dysfunction than all other comparator studies). Overall, these clinical characteristics translated into a substantially higher risk patient population, explained Butler. This was evidenced by the fact VICTORIA had the shortest median follow-up time of all recent trials in HFrEF (10.8 months) because patients were so high risk that events were accrued quickly. Similarly, the primary endpoint event rate of first HFH or CV death in the control arm was "extraordinarily high" in VICTORIA, remarked Butler, and substantially greater than in most contemporary studies. Events per 100 patient-years were 37.8 in VICTORIA, compared to 13.2 in PARADIGM-HF (sacubitril/valsartan), 15.6 in DAPA-HF (dapagliflozin), 21.0 in EMPEROR-Reduced (empagliflozin), and 26.3 in GALATIC-HF (omecamtiv mecarbil).[6,7,19,27-33]

Butler emphasised that although the relative risk of the primary composite endpoint of CV death/HFH was only reduced by 10% in VICTORIA, because of the very high-risk nature of the population, this equated to a "substantial ARR of 4.2%."[19] Significant reductions in total HFH and the composite of all-cause mortality or HFH were also seen with vericiguat, and there was a directional benefit in the outcomes of CV death, HFH, and all-cause mortality.[19] Although direct head-to-head comparisons between different agents have not been conducted, the ARR in VICTORIA, which Butler described as a "measure that is very important to our patients," was similar or numerically better than other recent trials in HFrEF. ARR for the primary endpoint was 4.2 in VICTORIA compared to 2.7 in PARADIGM-HF, 4.0 in DAPA-HF, and 5.2 in EMPEROR-Reduced.[33]

The clinical benefit of vericiguat was seen across all prespecified subgroups defined by the index event, including hospitalised patients, indicating a generally consistent treatment effect.[19] The primary composite endpoint outcomes were also directionally consistent irrespective of sacubitril/valsartan use at baseline. This is important because an increasing proportion of HFrEF patients are on this background therapy, explained Butler.[19]

Regardless of patients' baseline renal function, vericiguat provided benefit in clinical outcomes of HFH or CV death and HFH or all-cause death, with a trend towards reduced CV death also seen across all eGFR categories.[21] The association between worsening renal function (WRF) and subsequent clinical outcomes was also explored in the VICTORIA trial and the benefit of vericiguat proved consistent even in subjects who developed WRF, with similar effects on the primary endpoint (interaction; p=0.76).[21] Patients treated with vericiguat showed a stable pattern in terms of changes in eGFR and creatinine over time, with little fluctuation in renal function trajectories (Figure 3). This confirms not only the efficacy but also the safety profile of vericiguat in terms of renal function, noted Butler, and is



Patients	Baseline	Week 16	Week 32	Week 48
Placebo	2,237	2,181	1,991	1,559
Vericiguat	2,196	2,155	1,971	1,553

Figure 3: Impact of vericiguat on renal function trajectories was similar to placebo.[21]

eGFR: estimated glomerular filtration rate.

important because cardiologists are particularly cognisant of changes in renal function, which can preclude optimisation of medical therapy, especially with renin-angiotensin-aldosterone system inhibitors (RAASi).

Panel Discussion: Managing the Patient After a Worsening Heart Failure Event

Patients with worsening HF are commonly encountered in everyday clinical practice and constitute a cohort with significant unmet medical need. Jankowska reiterated that these patients are at very high risk; recurrent HFH events cannot be prevented despite life-saving foundational therapies, meaning additional treatment interventions are required. Overall, the panel agreed that discharge provides a "critical window" to maximise disease-modifying therapies for previously hospitalised patients with worsening HF and alter their disease natural history. Zannad suggested that the early 1–2-week post-discharge visit, recommended in the updated ESC guidelines, could also prove an opportune time to implement add-on therapy with vericiguat.

On the subject of comorbidities, Butler acknowledged that this is a complex and multidirectional issue in HFrEF. Renal function is particularly relevant because patients with worsening HF are at increased risk of WRF. VICTORIA was the first trial to enrol patients with an eGFR as low as 15 mL/min/1.73m^2 and, with over 5,000 patients recruited, provided the power to look at several different subgroups. With vericiguat, the clinical benefit was accrued across the complete spectrum of eGFR at baseline, with negative p interaction values for all outcomes, explained Butler. The data on renal function trajectories with vericiguat also remained stable over time, even in these subjects with very low eGFR. Similarly, the overall number of patients who developed WRF was balanced between the two study arms and did not predict any lowering of vericiguat benefit. Results from VICTORIA also confirmed that the clinical benefits of vericiguat were retained across other key comorbidities including coronary disease with ischaemic and non-ischaemic aetiology and AF. Comorbidities are so common in patients with HFrEF that to have the signal for safety and efficacy with vericiguat "is very important," Butler concluded.

The panel then discussed what constitutes optimised GDMT. Butler emphasised the importance of exploring underlying reasons that may have precluded optimisation of a patient's foundational therapies such as intolerance. VICTORIA shows that the clinical benefit of vericiguat is maintained "on top of optimised

GDMT," he added, as study participants were very well-treated at baseline (>90% RAASi and β-blocker use, 70%+ mineralocorticoid receptor antagonist use, and 60% on triple therapy). Vericiguat also boasts a further advantage, noted Butler. Of the four most common reasons why patients are unable to tolerate optimal medical therapy (increased heart rate, hyperkalaemia, hypotension, and increased creatine), none apply to vericiguat.

On the issue of safety, Lam emphasised that vericiguat was very well tolerated in the VICTORIA trial, with almost 90% of patients successfully uptitrated to the full 10 mg/day target dose. Mean BP was only a few mmHg lower in patients receiving vericiguat versus placebo and this effect manifested early, resolving within 4 months. VICTORIA also looked specifically at patients vulnerable to hypotension such as the elderly, those with lower baseline BP, and patients receiving angiotensin receptor-neprilysin inhibitors. In all these subgroups, there were no further increases in symptomatic hypotension or syncope episodes with vericiguat treatment.

The panel agreed that, based on resoundingly positive results from the large-scale VICTORIA trial, it was now time to focus on the clinical practice implementation of vericiguat. Zannad noted that this should be "very straightforward," based on the robust comorbidity data and good safety profile. The EMA label specifies that patients must be stabilised before starting vericiguat and, in this context, Lam suggested stability would mean ensuring patients are decongested and ready to be discharged. Butler also added that ongoing clinical monitoring requirements for vericiguat should prove "easy" as there are no creatinine, potassium, or heart rate issues and only routine BP monitoring is recommended.

Summarising the key messages from the symposium, Zannad reiterated that patients with HFrEF remain at high risk of recurrent HFH and death after discharge. For these patients with worsening HF, the VICTORIA trial has shown the clear benefit of vericiguat in significantly reducing time to CV death or HFH, with an ARR in the range of contemporary HFrEF trials recently conducted. Vericiguat, therefore, marks an important new addition to the HFrEF armamentarium, concluded Zannad. Its implementation in clinical practice will help to optimise management and reduce the "enormous risk" faced by patients with worsening HF.

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Abstract Reviews

Sharing insights and updates from a selection of abstracts presented at the European Society of Cardiology (ESC) Congress 2021, renowned clinicians and researchers have provided these summaries of their fascinating and highly relevant studies.

Endothelial Glycocalyx Integrity and Microvascular Perfusion Are Associated with Novel Echocardiographic Markers and Carotid Intima–Media Thickness in Patients with Psoriasis

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Carotid intima–media thickness, coronary flow reserve, endothelial glycocalyx, myocardial deformation, psoriasis.

Citation: EMJ Cardiol. 2021;9[1]:35-36. Abstract Review No. AR1.

BACKGROUND AND AIMS

Psoriasis has been associated with vascular and myocardial dysfunction through mechanisms of inflammation and oxidative stress.[1,2]

The authors' aim was to evaluate sublingual microvascular perfusion and glycocalyx barrier properties in patients with psoriasis, as well as their correlation with coronary microcirculatory function and markers of myocardial deformation and atherosclerosis (carotid intima-media thickness [cIMT]).

MATERIALS AND METHODS

The authors examined 297 patients with psoriasis and 150 controls, adjusted for age, sex, and atherosclerotic risk factors. Perfusion boundary region (PBR), a marker of glycocalyx barrier function, was measured non-invasively in sublingual microvessels, with a diameter ranging from 5 µm to 25 µm, using a dedicated camera (Sidestream Dark Field imaging, Microscan, GlycoCheck). An increased PBR indicates reduced glycocalyx thickness. Indexes of microvascular perfusion including red blood cell (RBC) filling percentage and functional microvascular density were also calculated.[3] The authors measured coronary flow reserve, cIMT, and myocardial deformation markers by speckle tracking imaging, utilising echocardiography (peak twisting; the percentage changes between peak twisting and untwisting at mitral valve opening [%dpTw-Utw_{MVO}], at peak [%dpTw-Utw_{PEF}], and at the end of early left ventricular diastolic filling [%dpTw-Utw_{EDF}]).

RESULTS

Patients with psoriasis had higher PBR_{5-25} compared to controls (2.13±0.29 versus 1.78±0.25 µm; $p<0.05$). There was an inverse association of PBR_{5-25}, with perfused microvascular density ($r=-0.42$; $p<0.001$) and RBC fraction ($r=-0.80$; $p<0.001$). In the population of people with psoriasis, PBR_{5-25} was inversely correlated to coronary flow reserve ($r=-0.30$; $p=0.045$). Increased values of PBR_{5-9} were associated with reduced untwisting at the end of the mitral inflow E wave ($r=-0.24$; $p=0.006$) and reduced %dpTw-Utw_{MVO} ($r=-0.35$; $p<0.001$). Furthermore, the decreased RBC filling percentage and perfused microvascular density were related to worse left ventricular longitudinal strain and increased cIMT ($p<0.05$). Finally, a positive correlation between perfused microvascular density and %dpTw-Utw_{MVO} was observed in patients with psoriasis ($p<0.05$).

CONCLUSION

Endothelial glycocalyx thickness is reduced in patients with psoriasis and is associated with impaired coronary and myocardial function and vascular atherosclerosis. ■

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Circulating TGF-β1 and Progression of the Mitral Valve Myxomatosis and Leaflets Billowing: A 15-Year Follow-Up

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Mitral regurgitation, mitral valve myxomatosis, mitral valve prolapse (MVP), TGF-β1.

Citation: EMJ Cardiol. 2021;9[1]:37-38. Abstract Review No. AR2.

BACKGROUND AND AIMS

TGF-β1 is a crucial regulatory cytokine that contributes to the development of the mitral valve. Under normal conditions, TGF-β regulates extracellular matrix protein synthesis in valvular interstitial cells.[1] Growing evidence supports the role of TGF-β as a mediator of the myxomatous changes in syndromic and non-syndromic mitral valve prolapse (MVP).[2,3] Upon changes in the TGF-β expression, valvular interstitial cells acquire features of activated myofibroblasts, proliferate, and produce increased amounts of collagens, proteoglycans, and metalloproteases, which are responsible for the remodelling of collagen and elastic fibres in mitral leaflets.[4] To evaluate the effect of elevated circulating TGF-β level on the progression of the valve myxomatosis and leaflets billowing at long-term follow-up, the authors conducted an observational, prospective, single-centre study.

MATERIALS AND METHODS

Seventy-eight asymptomatic young subjects (mean age: 19.7±1.6 years; 72% male) with MVP were consecutively enrolled in the authors' observational, prospective, single-centre study. MVP was diagnosed by billowing one or both mitral leaflets >2 mm above the mitral annulus in the long-axis parasternal view. Concentration of TGF-β1 in serum was determined by ELISA using test system Human Platinum ELISA (Thermo Fisher Scientific, Waltham, Massachusetts, USA).

RESULTS

During 1,170 person-years of follow-up (median: 14.5 years), no deaths or MVP-related events occurred. Posterior leaflet's thickening (from 3.9±1.4–4.4±1.7 mm [diameter (D): +0.5 mm]; p<0.01) and increase of the billowing (progression in maximal prolapse depth from 3.5±2.4–4.8±2.8 mm [D: +1.3 mm]; p<0.001) leads to the mitral regurgitation progression (vena contracta: 2.3±0.4 mm versus 3.5±0.4 mm [D: +1.2 mm]; p<0.0001) over 15 years of follow-up.

TGF-β1 serum level was increased (15.2±12.3 ng/mL) and strongly correlated with the thickening of the posterior leaflet (effective size estimate: 0.72; p=<0.0001 [Figure 1]). In multivariate Cox analysis, the TGF-β1 level was the independent predictor of the posterior leaflet's thickening (2.07; 95% confidence interval [CI]: 1.34–3.29; p=0.001) and progression of the billowing (2.89; 95% CI: 1.61–4.37; p=0.0001).

TGF-β1 >7.0 ng/mL was a strong predictor (area under the receiver operating characteristic curve: 0.84; 95% CI: 0.7–0.9; sensitivity: 82%; specificity: 95% [Figure 1]) for progression of MVP (maximal prolapse depth increase: D+1.9±1.2 mm [TGF-β1: >7.0 ng/mL] versus 0.7±0.6 mm [TGF-β1: <7.0 ng/mL]; p<0.0001) and mitral regurgitation (vena contracta increase: D+1.5±0.5 mm [TGF-β1: >7.0 ng/mL] versus 0.5±0.4 mm [TGF-β1: <7.0 ng/mL]; p<0.0001).

CONCLUSION

Despite the overall benign prognosis, the authors found the obvious echocardiographic progression of the valve myxomatosis and leaflets billowing in a long-term follow-up in young people. Elevated above 7.0 ng/mL, TGF-β1 serum level might serve as a prognostic biomarker and identify patients with increased risk of the MVP progression. ■

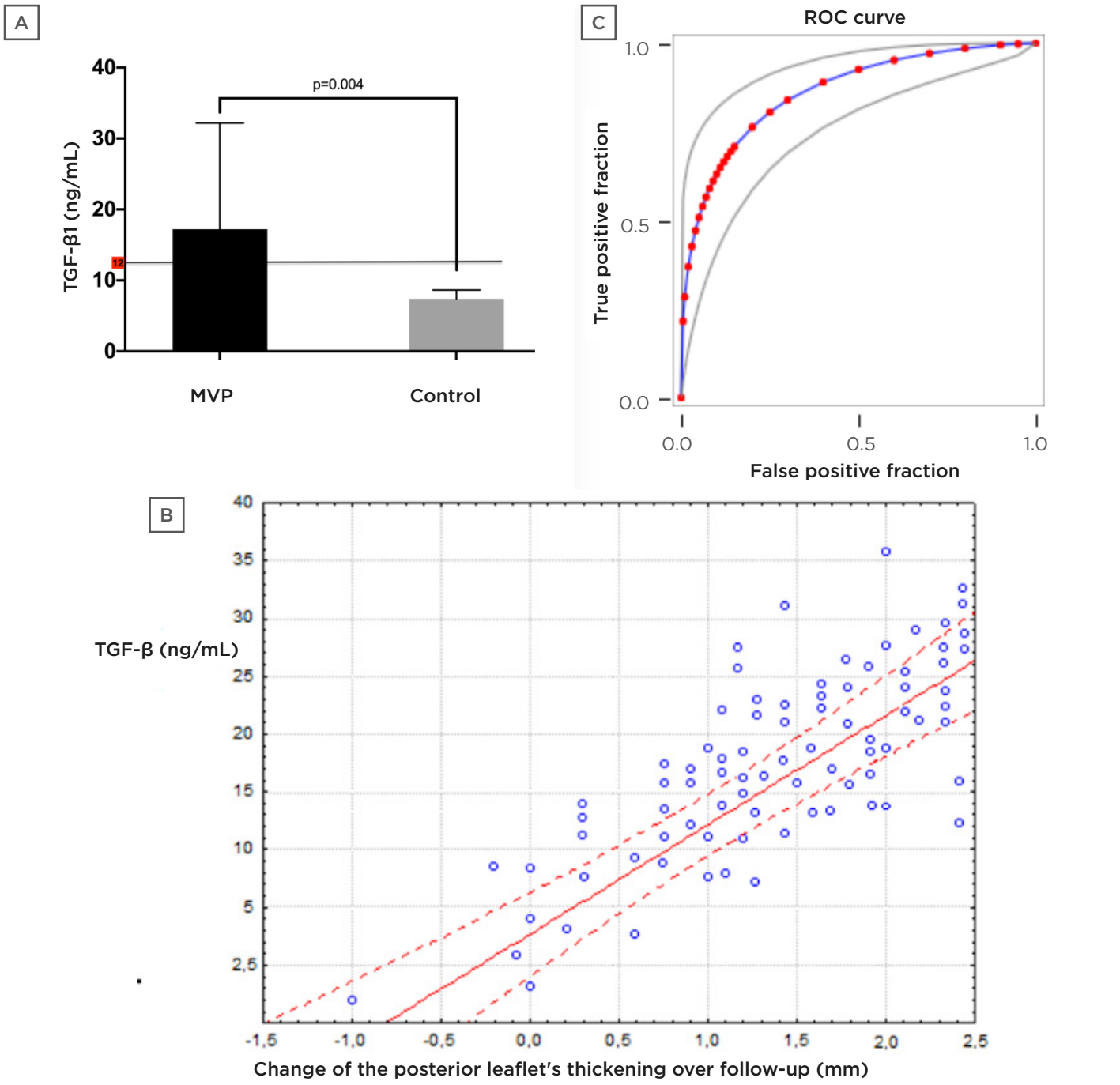

Figure 1: Increasing plasma TGF-β1 in patients with MVP.

Plasma TGF-β1 level increased in patients with MVP when compared to controls (A). Regressions showing the correlation between plasma TGF-β1 concentrations and the thickening of the posterior leaflet during the follow-up (B). Graphical representation of the ROC analysis (C).

MVP: mitral valve prolapse; ROC: receiver operating characteristic.

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Emotional and Cardiovascular Health: The Impact of Depression on Cardiac Autonomic Activity

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Autonomic dysfunction, depression, corrected QT interval (QTc) duration, ventricular repolarisation.

Citation: EMJ Cardiol. 2021;9[1]:39-41. Abstract Review No. AR3.

BACKGROUND

Depression is a frequent comorbidity in patients with cardiovascular diseases, with a prevalence ranging from 35% to 74%.[1-3] It is believed that the presence of a major depressive disorder may be an independent predictor of adverse cardiovascular outcomes.[4] A possible explanation could be the dysregulated autonomic nervous system,[5] leading to a higher incidence of malignant ventricular arrhythmias and, ultimately, sudden cardiac death.

The surface electrocardiogram can provide important information, with the heart rate-corrected QT interval being a non-invasive, easily accessible, and indirect measure of parasympathetic nervous system activity.[6] With regards to the interplay between depressive disorders and QT interval, limited data are available in the existing literature to the authors' knowledge.

MATERIALS AND METHODS

In the setting of the cross-sectional Corinthia study, the authors analysed participants aged 40 years or older who were not taking any QT-prolonging medication, such as antiarrhythmic drugs, antibiotics, antidepressants, or antipsychotics. The participants underwent clinical evaluation as well as self-assessment of depression through the Zung Self-Rating Depression Scale (SDS) for subjects below 65 years and the Geriatric Depression Scale (GDS) for older subjects. These two questionnaires were selected for their superior performance as self-rating scales. The presence of depression was considered in younger individuals with a Zung SDS score of ≥50 and in elderly with a GDS score of ≥5. Participants that did not complete the questionnaire were excluded from the analysis.

A resting 12-lead ECG with 10 sec duration was performed, with smart ECG measurement and interpretation programmes being used for automated measurement and interpretation of amplitudes and duration of ECG waves in each of the 12 leads. QT interval measurements were extracted from each individual lead after correction for heart rate (QTc) using Bazett's formula. A QTc greater than 440 msec was defined as abnormal.

RESULTS

From the entire study population, 1,637 individuals (980 female and 657 male) were included in the final analysis. The younger age population with depression was predominantly female and had a higher prevalence of coronary artery disease. Interestingly, those classified as having depression had a longer QTc duration and percentage of abnormal QTc. No differences were noted in the other examined parameters. On the other hand, elderly individuals had similar values of QTc and percentage of abnormal QTc irrespective of depression status.

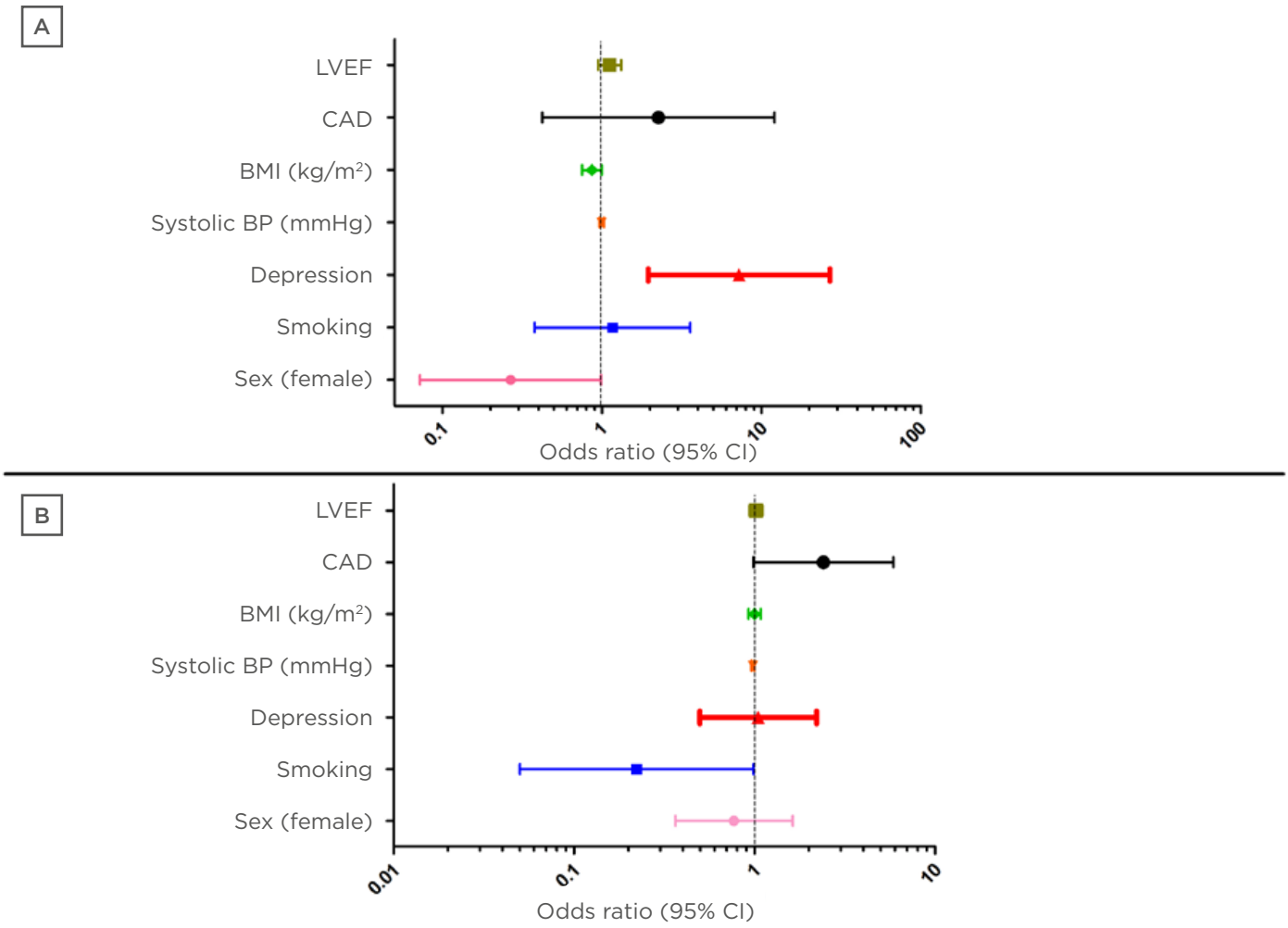

Figure 1: Logistic regression analysis concerning the impact of depression on abnormal corrected QT interval duration in A) younger and B) elderly individuals after adjustment for various factors implicated in QT prolongation.

BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; CI: confidence interval; LVEF: left ventricular ejection fraction.

To test the impact of depression status on the duration of QTc interval, the authors performed a linear regression analysis according to age groups, adjusting for factors associated with QT prolongation. Importantly, the presence of depression was associated with increased QTc duration (by approximately 10.8 msec), independently from the confounders and only in the younger age subgroup. Similarly, depression was associated with approximately seven-fold higher prevalence of abnormal QTc in younger individuals, a finding that was not observed in the elderly participants (Figure 1).

CONCLUSIONS

As the authors' findings indicate, even though elderly individuals had increased QTc and a higher prevalence of abnormal QTc compared with younger participants, the presence of depression was associated with longer QTc only in the younger age subgroup, even after adjustment for known QT-prolonging factors. Moreover, the authors detected a greater prevalence of prolonged QTc in younger participants with depression, while in the elderly individuals no differences were noted concerning this parameter. The authors' findings highlight the inter-relationship between emotional and cardiovascular health and the potential role of depression as a cardiovascular risk factor. ■

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Comparison of Echocardiographic Parameters of Patients with COVID-19 Pneumonia in Hospital and 3 Months After Discharge

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Cardiovascular disease, COVID-19 pneumonia, echocardiography, right heart.

Citation: EMJ Cardiol. 2021;9[1]:41-43. Abstract Review No. AR4.

BACKGROUND AND AIMS

COVID-19 primarily affects the respiratory system of patients; however, the cardiovascular system is also damaged. To study the impact of a novel coronavirus infection on the cardiovascular system, in particular on echocardiographic parameters after severe acute respiratory syndrome coronavirus-2, is therefore very important.

The aim of this study was to compare echocardiographic parameters in patients with COVID-19 pneumonia in hospital and 3 months after hospital discharge.

MATERIALS AND METHODS

The patients were identified according to the data of the medical information system of the monohospital from April to July 2020, within the framework of the 'One-year Cardiac Follow-up of Patients With COVID-19 Pneumonia' trial,[1] 3 months±2 weeks after discharge. The inclusion criteria were a documented diagnosis of COVID-19-associated pneumonia, age ≥18 years, and the patient's desire to participate in follow-up. The authors did not include patients with chronic diseases in the acute stage, heart defects, HIV, chronic hepatitis, cancer under 5 years, tuberculosis, and other diseases accompanied by pulmonary fibrosis. The exclusion criteria were a refusal to participate, pregnancy, and unsatisfactory visualisation by echocardiography. Eight patients were excluded: two due to departure in another region, three due to pregnancy, and three due to refusal to undergo dynamic CT lung screening. A total of 106 men and women were included. Mean age was 47 years (standard deviation: ±16 years; range: 19–84 years), mean BMI was 28.2 kg/m^2 (standard deviation: ±5.7 kg/m^2), and 49% were

Table 1: Dynamics of echocardiographic parameters in patients survived COVID-19 pneumonia (n=106).

Parameters		Hospitalisation	Three months after discharge	p
LV end-diastolic diameter	mm, M±SD	49.3±4.1	47.9±3.4	0.003
LV end-diastolic volume	mL, M±SD	113.8±26.8	93.5±29.4	<0.001
LV end-systolic volume	mL, M±SD	37.7±13.0	31.3±14.2	<0.001
LV stroke volume	mL, M±SD	77.2±17.8	62.2±18.7	<0.001
LV ejection fraction (2D Simpson)	%, M±SD	67.4±6.2	66.8±6.3	0.453
LA anterior-posterior dimension	mm, Me (Q1–Q3)	36.0 (33.0–40.0)	36.0 (32.0–38.0)	0.657
Maximum LA volume	mL, Me (Q1–Q3)	49.5 (42.0–58.0)	46.0 (37.8–62.3)	0.274
Maximal RA volume	mL, Me (Q1–Q3)	42.0 (37.0–50.0)	31.0 (22.0–36.5)	<0.001
Maximal RA length	mm, M±SD	46.7±6.8	48.6±7.1	0.021
Maximal RA width	mm, M±SD	36.1±4.6	34.5±6.5	0.023
RVOT proximal diameter	mm, Me (Q1–Q3)	26.0 (24.0–29.3)	25.0 (23.0–27.0)	0.004
Pulmonary trunk diameter	mm, M±SD	21.8±3.6	18.7±2.5	<0.001
Tricuspid regurgitation ≥Grade 2	n (%)	2.0 (2.4)	2.0 (2.4)	1.000
PAPs	mmHg, Me (Q1–Q3)	28.0 (25.0–32.3)	21.5 (17.0–25.0)	<0.001
PAPs >36 mmHg	n (%)	13.0 (15.9)	4.0 (4.9)	0.012
Pericardial effusion	n (%)	5.0 (6.1)	1.0 (1.2)	0.125

LA: left atrium; LV: left ventricular; M: mean; Me: median; n: portion of patients; PAPs: systolic pulmonary artery pressure; Q1: quartile 1; Q3: quartile 3; RA: right atrium; RVOT: right ventricular outflow tract (parasternal view, long axis); SD: standard deviation.

female. During hospitalisation, chest CT detected mild lesions in 29.2%, moderate lesions in 31.1%, severe lesions in 27.4%, and critical lesions in 5.7% of patients.

RESULTS

Cardiovascular diseases were detected in 52% of patients. Three months after discharge, complaints persisted in the majority of patients (86%). Three months after discharge, significant decreases in left ventricular (LV) end-diastolic, end-systolic, and stroke volumes were noted (Table 1). A tendency to decrease the systolic volume of the left atrium was found. There were no dynamics from the linear left atrium parameters and LV ejection fraction. The frequency of significant tricuspid regurgitation in hospital was 2.4%, and it did not change within 3 months. End-diastolic right ventricular outflow tract diameter and pulmonary artery trunk diameter became significantly lower, as well as average systolic pulmonary artery pressure. As for the right atrium, its average volume and width decreased, and its length increased. Three months after discharge, the rate of right ventricular dilatation in the authors' patients was 2.9% and the rate of tricuspid annular plane systolic excursion decrease was 9.5%.

DISCUSSION

To date, three European research groups have published the results of observation 3 months after hospitalisation with COVID-19.[2-4] Echocardiographic data was studied only by the Austrian group.[4] According to the observation of 145 Austrian patients, the LV ejection fraction was reduced in four out of 133.[4] In the authors' work, it was reduced in two out of 106. The frequency of pulmonary hypertension and a decrease in LV ejection fraction in the Austrian cohort did not change over 3 months after discharge. Additionally, the number of patients with pericardial effusion decreased.[4] In the present study, the number of patients with echo signs of pulmonary hypertension significantly decreased. Furthermore, the number of patients with pericardial effusion also decreased; however, these differences did not reach significance.

CONCLUSIONS

In patients after COVID-19 pneumonia, echocardiography showed decrease of the load, predominantly on the right heart 3 months after discharge. In 86.0% of patients, complaints persisted. Cardiovascular diseases were detected in 52.0% of the patients, including arterial hypertension in 48.1% and coronary artery disease in 15.1%. ■

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Patients with COVID-19 Present Impaired Endothelial Glycocalyx, Vascular Dysfunction, and Myocardial Deformation Resembling Those Observed in Patients with Hypertension 4 Months After Infection

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Arterial stiffness, COVID-19, endothelial function, inflammation, oxidative stress, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

Citation: EMJ Cardiol. 2021;9[1]:43-45. Abstract Review No. AR5.

BACKGROUND AND AIMS

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has been associated with deregulations in vascular, endothelial, and myocardial function.[1-7] Inflammation and oxidative stress have been suggested as possible pathophysiological mechanisms that lead to these impairments after COVID-19 infection.[1-3] The aim of this study was to investigate premature alterations in arterial stiffness, in endothelial integrity, and in coronary and cardiac performance 4 months after COVID-19 infection.

MATERIALS AND METHODS

In this prospective observational case-control study, the authors consecutively recruited 70 patients 4 months after a confirmed infection by SARS-CoV-2, 70 age- and sex-matched patients with untreated hypertension (positive control), and 70 healthy individuals. The authors evaluated:

- perfused boundary region (PBR) of the sublingual arterial microvessels (increased PBR indicates reduced endothelial glycocalyx thickness);
- coronary flow reserve (CFR) by Doppler echocardiography;
- flow-mediated dilation (FMD);
- pulse wave velocity and central systolic blood pressure;
- left ventricular global longitudinal strain; and
- malondialdehyde (MDA), an oxidative stress marker.

RESULTS

Patients diagnosed with COVID-19 and patients with untreated hypertension displayed similar FMD and CFR, while both groups had lower FMD and CFR values than controls. Patients diagnosed with COVID-19 had similar PBR values with patients with untreated hypertension but both groups had greater PBR values compared to control group. Patients diagnosed with COVID-19 and patients with untreated hypertension had higher pulse wave velocity carotid-femoral and central aortic systolic blood pressure values compared with control group. Patients diagnosed with COVID-19 had similar left ventricular global longitudinal strain values with hypertensives but significantly different (less negative) from control group. Patients diagnosed with COVID-19 displayed much higher MDA levels than both patients with untreated hypertension and healthy individuals (Table 1).

CONCLUSION

SARS-CoV-2 infection may cause endothelial and vascular dysfunction, which are linked to impaired longitudinal myocardial deformation 4 months after COVID-19 infection. The 10-fold increase of MDA in patients diagnosed with COVID-19 relative to patients with untreated hypertension and normal control indicate oxidative stress as a possible pathophysiological mechanism contributing to vascular, endothelial, and myocardial deregulations. ■

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Table 1: Markers of cardiac and vascular function.

	All participants (n=210)	COVID-19 group (n=70)	Hypertensives (n=70)	Control group (n=70)	F-value	p value
CFR	2.82±0.64	2.48±0.41	2.58±0.58	3.42±0.65	7.82	0.001
FMD (%)	6.90±2.54	5.86±2.82	5.80±2.07	9.06±2.11	8.71	0.000
LVGLS (%)	-20.42±2.24	-19.55±2.56	-19.23±2.67	21.98±1.51	5.14	0.006
PBR5-25 (µm)	2.01±0.21	2.07±0.15	2.07±0.26	1.89±0.17	7.70	0.001
PWVc-f (m/sec)	11.35±2.52	12.09±2.50	11.92±2.94	10.04±1.80	4.23	0.04
SBP-central (mmHg)	126.91±18.85	128.43±17.39	135.17±16.83	117.89±18.85	6.20	0.003
MDA (nm/L)	4.48±1.18	10.67±2.75	1.76±0.30	1.01±0.50	9.60	0.001

CFR: coronary flow reserve; FMD: flow mediated dilatation; LVGLS: left ventricular global longitudinal strain; MDA: malondialdehyde; PBR5-25: perfused boundary region of the sublingual vessels with diameter 5-25 µm; PWVc-f: pulse wave velocity carotid to femoral; SBP-central: central (aortic) systolic blood pressure.

Paroxysmal Supraventricular Tachycardia: Highlighting Unmet Needs in Emergency Care

Interviewees: John Camm,[1] Felix Sogade[2]

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2. Georgia Arrhythmia Consultants, Macon, Georgia, USA

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Interview Summary

The clinical syndrome of paroxysmal supraventricular tachycardia (PSVT) is characterised by recurrent, acute episodes of rapid heart rate. PSVT is a common condition, affecting patients' daily lives through the unpredictable onset of symptoms such as palpitations, breathlessness, chest pain, and associated anxiety. However, its transient nature can impede diagnosis and the acute management of PSVT episodes often requires emergency hospital care. During interviews conducted with the EMJ in July 2021, two leading cardiologists specialising in the treatment of arrhythmias, John Camm, St George's University Hospitals NHS Foundation Trust, London, UK, and Felix Sogade, Georgia Arrhythmia Consultants, Macon, Georgia, USA, discussed PSVT, focusing on current unmet needs in emergency care. Topics covered included the challenges of diagnosis and key concerns around both the acute and long-term management of PSVT attacks. The burden PSVT presents to patients and the healthcare system was also examined, with consideration of how the emergence of home-based approaches and improved patient and caregiver education may help to address current unmet needs.

INTRODUCTION

Paroxysmal Supraventricular Tachycardia: Prevalence and Patient Impact

Supraventricular tachycardias (SVTs) are a group of conditions that produce elevated heart rates of >100 bpm at rest due to altered electrical activity in or above the His bundle.[1,2] As a subgroup of SVT, PSVTs are characterised by sporadic episodes of regular tachycardia that start and stop abruptly. The most common types of PSVT are atrioventricular nodal re-entrant tachycardia and atrioventricular reciprocating tachycardia, which are both linked to the abnormal re-entry of propagating impulses. Focal atrial tachycardias are less common PSVTs caused by abnormalities in the automaticity of the heart.[3,4]

Camm explained that overall prevalence estimates for PSVT vary depending on source and means of data collection. Epidemiological studies are limited, but the estimated prevalence of SVT in the general USA population is cited

as 2.25 per 1,000 persons, with an incidence of 35 per 100,000 person-years.[2,5] This estimate from the 1990s reflects the acute burden of PSVT in the healthcare setting, given patients were required to have documented PSVT on ECG during the specific encounter.[5] The study likely underestimates PSVT prevalence due to the episodic nature of the disease, variability in duration of SVT episodes, and the fact that the majority of SVT episodes are experienced outside of the healthcare setting.[4] A 2021 study used a longitudinal claims-based approach and estimated PSVT prevalence to be 2–3 times larger than prior estimates (1.2–2.1 million treated prevalence). Regardless of epidemiologic approach, the risk of PSVT is higher in females and in those aged ≥65 years.[2] Reflecting on his experience in the USA, Sogade noted: "PSVT is a very prevalent disorder, but it is often under-diagnosed or misdiagnosed. We know that approximately 1–2 million people per year suffer from this condition in the USA alone, and one can only project that this is a disease of significant impact both in the USA and globally."

From case to case, PSVT differs in terms of the frequency of episodes (weekly, monthly, or yearly) and symptom severity or impact. However, the experts agreed that the patient experience of PSVT mainly centres on the effects of a rapid heart rate and associated anxiety. "The majority of patients sense PSVT immediately because of a rapid thumping in the chest, usually between 140 and 240 bpm," said Camm. "That, of course, can provoke other symptoms like breathlessness, chest pain, light-headedness, and particularly anxiety. For patients who are suffering their first attack, for example, anxiety is a very prominent feature because they think they're having a heart attack and want to seek help immediately." Sogade further described the association between anxiety and PSVT: "Because the palpitations cause a level of discomfort and restlessness, PSVT also results in social anxiety whereby people are afraid to travel on vacation, or are afraid to go out." According to Camm, the overall impact of PSVT depends very much on the frequency of the attacks. "Obviously the more frequently it happens, and the more unpredictable, the more the patients' quality of life will be disturbed by the arrhythmia," he concluded.

Diagnosis of Paroxysmal Supraventricular Tachycardia

The unpredictable, transient nature of PSVT means that the condition is frequently diagnosed when the patient seeks help for acute attacks, and an ECG is pivotal to this diagnosis. As outlined by Sogade: "Clinical history is very important for the diagnosis of PSVT, whereby the patient presents with palpitations and other symptoms, but the most important factor is the ECG." Camm reinforced this point: "In order to make a definitive diagnosis of PSVT, you must see it on an ECG and be capable of interpreting the ECG, or accessing an expert opinion about an ECG if you are in the emergency room (ER), for example. Many patients will go to their general practitioner, who can also make the diagnosis if they have the means to record and interpret an ECG."

However, diagnosis may be impeded for reasons other than ECG interpretation. "Most episodes of PSVT are self-terminating, so by the time somebody seeks medical attention the episode may have ended, and the healthcare provider observes a normal heart rate," said Sogade. He also described how, for this reason, females tend to be misdiagnosed with anxiety disorder on clinical presentation of PSVT.[6] Camm noted that there may still be clues on an apparently normal-looking ECG such as the classical pattern of Wolff-Parkinson-White ventricular pre-excitation but accepted that "in most instances, you have to try to document the arrhythmia when it happens." To this end, the use of Holter or event monitors or wearable devices was discussed. According to Camm: "If the arrhythmia occurs every few days, you can use a Holter ambulatory monitor with chest electrodes attached to a solid-state recorder to pick up an attack. Even in people who think they only have rare attacks, over 24 or 48 hours you may be able to make a diagnosis based on a very brief asymptomatic event on a Holter ECG. If, however, the patient is having attacks every 6–9 months, then you have to think about event recorders. Nowadays, smartphones and watches allow ready acquisition of an ECG, and patients can be trained in their use. It's a quick way of finding out about the rhythm disturbance, and is a very good system that I often suggest to patients." Sogade shared this view: "I find the wearable devices that are currently entering the

market very interesting. Patients are coming in with their own ECG rhythm strips documenting their episode, and I think that is going to lead to a larger population of diagnosed patients who we will be able to treat," he said. "There are a number of reasons why people may complain of palpitations that may be mistaken for PSVT, e.g., a quickening of the pulse if they are fearful or worried, but misdiagnosis doesn't usually occur once there is an ECG," concluded Camm.

Unmet Needs in the Diagnosis of Paroxysmal Supraventricular Tachycardia

Summarising unmet needs in the diagnosis of PSVT, Sogade re-emphasised that the emergence of mobile monitoring is beginning to address the problem of under-diagnosis. In addition, Camm noted the potential benefits of advanced techniques and the increased use of invasive cardiac electrophysiology studies to pinpoint diagnoses: "By putting catheters with electrodes into the heart you can identify abnormal pathways, which allows you to make a very accurate diagnosis and in practical terms allows you to actually destroy the abnormal part of the heart so that the palpitations will not continue." However, at the opposite end of the spectrum Sogade raised the issue of access to any form of care as a notable unmet need: "I live in the USA, and while it's easier if you live near to medical resources, imagine living in a place that is far away from medical facilities. Some patients, a mixed bag of diagnosed and non-diagnosed, have had PSVT for 40 years with no specific treatment. Furthermore, access to care during the COVID-19 pandemic has been very restricted, and these patients have fallen into a lower priority for ER treatment," he stressed.

TREATMENT OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Acute Treatment

In terms of acute treatment, it was discussed how, at present, there are limited home-based therapies for PSVT and no approved pharmacological options for patients to self-administer. According to Camm, the initial advice given to a patient who experiences an attack at home is to sit or lie down and relax. "They can also do a vagal manoeuvre, aiming to intensify the activity of the vagus nerve to act as a brake and literally stop the tachycardia. This can be done in a variety of ways, for example, by massaging the carotid sinus in the neck, but this is very uncomfortable. It also has some dangers as it could dislodge plaques from the carotid artery and cause strokes. Alternative methods include the Valsalva manoeuvre (activating the vagal nerve by increasing pressure in the chest) or employing the diving reflex to slow the heart rate (covering the nose with water to activate the autonomic vagal nervous system). However, if these don't work and you're at home, there's nothing much else you can do but rest and wait or take yourself to the doctor," said Camm.

"Once in the ER, the standard of care is intravenous adenosine for classically recognised PSVT," said Sogade. "This results in termination of the episode, but requires you to obtain an intravenous line, connect the patient to a monitor, and have trained medical personnel available. In addition, medical personnel may be uncomfortable/anxious giving intravenous adenosine because of the sudden or awful effect it can create in the patient," he cautioned. Camm explained further: "A quick and simple injection of a few milligrams of adenosine breaks the tachycardia within seconds, but during these few seconds the patient often feels as though they are going to die, although this sensation doesn't last for more than a few moments." Verapamil and diltiazem (non-dihydropyridine calcium antagonists [calcium-channel blockers]) or β-blockers like bisoprolol or esmolol were cited as other intravenous treatment options, although both experts highlighted adenosine as the classical approach to the acute treatment of PSVT. Yet Camm also pointed out that these treatment options are not appropriate for all PSVTs: "Atrial tachycardias, which have a relatively small occurrence compared to the other forms of PSVT, don't respond in the same way to a Valsalva manoeuvre or to drugs such as adenosine, but do respond well to ion channel inhibitors like fast sodium channel blockers etc.," he said.

Long-Term Treatment

The experts went on to describe the treatments available for PSVT beyond acute care. "Going forward, there are a number of drugs to

prevent the recurrence of PSVT. There are also electrophysiology studies followed by ablation where you can identify and essentially destroy the critical areas and interrupt these tachycardias. Ablation in particular is very effective, but anti-arrhythmic drugs can also be effective," said Camm. Sogade agreed that ablation was an effective treatment, although noted that the technique is "costly, and not widely available" in the USA. Sogade also outlined some of the disadvantages of long-term medical therapy: "Most of the long-term management of PSVT involves the patient being prescribed medications, β-blockers, and calcium-channel blockers to reduce the heart rate and the frequency of PSVT. The most common side effects with β-blockers are a sense of fatigue, weight gain, insomnia, and poor sleep. The alternative, calcium-channel blockers, cause constipation and can also lower blood pressure too far." Furthermore, Sogade stressed that taking medication every day to help prevent these attacks is a considerable undertaking across a lifetime, especially if diagnosis is in the teenage years.

Unmet Needs in the Treatment of Paroxysmal Supraventricular Tachycardia

After considering the current treatment situation in PSVT, alternative options for patient self-administration at home was the chief unmet need identified by both Camm and Sogade. "If, eventually, we have a home therapy by which patients use their medication only during an attack, it would be another item in our armamentarium, and this is an area that I believe is going to be revolutionary," said Sogade. Camm agreed: "It would be of value if the patient could do something more at home, and this is where new developments come in." The experts described the study drug etripamil (Milestone Pharmaceuticals, Montreal, Canada), a rapidly acting, non-dihydropyridine calcium-channel blocker in the same class as verapamil, that is being developed as an intra-nasal spray for patient self-administration.[7] Described by Sogade as "the first of its kind," the nasal administration was said to allow rapid absorption of the drug and so terminate the tachycardia within a few minutes.[7] Camm explained that a self-administered treatment such as this would benefit both patients and the healthcare system by reducing the number of patient visits to the ER with mild attacks of PSVT. "Generally, emergency physicians want to reassure patients and tell them how to deal with PSVT at home as far as possible," commented Camm.

HEALTHCARE BURDEN

Treating patients with PSVT is associated with a notable healthcare burden that, as discussed above, predominantly centres on the provision of care in a hospital setting. Moreover, this burden alters markedly at the point of diagnosis. "We know there is definitely a doubling or tripling of the cost of healthcare resource utilisation when the patient is diagnosed with PSVT,"[8,9] said Sogade. "Pre-diagnosis, the patient has been utilising medical care and going to the ER during an episode, and there is a cost related to that. Yet once patients are diagnosed, they are on medical therapy, visiting for check-ups with their healthcare provider, and they may also be offered invasive therapy with catheter ablation," he said. Camm noted that the burden of PSVT depends on the treatment received, and that if the patient is in a healthcare system in which ablation is readily available then the problem may be solved quite rapidly with no further needs. Sogade agreed that a successful ablation procedure is considered curative for most PSVTs. However, although it is associated with a high success rate (>90%), and the risks of recurrence (2.0–8.0%) and complications (0.3–1.5%) are relatively low in atrioventricular nodal re-entrant tachycardia or atrioventricular reciprocating tachycardia.[2,10] Sogade observed that any recurrence with a need for repeat ablation, or complications requiring hospitalisation or additional procedures, would notably increase treatment costs. "You always have to balance the risks and benefits," he added. Further to this, Camm explained that while the true cost of an ablation procedure is not considerable, health insurance considerations mean that in some countries it costs a lot more due to it being an interventional approach requiring hospital admission. "For the average person, in the USA, the cost would be 5,000 USD before diagnosis and this would jump to a range of around 10,000–40,000 USD after diagnosis," said Sogade.

The experts also discussed how PSVTs and associated healthcare resource use vary by gender due to the combined influence of differences in prevalence, diagnosis, and treatment. "PSVTs are more common in females than in males,"[4,11] said Camm. "Data [from a USA medical care survey] show that female patients aged <65 years account for the largest percentage of ER visits for PSVT, although the annual visit rate is higher in those aged ≥65 years. Overall, the annual visit rate per 100,000 individuals was 26 for females and only 11 for males,"[4,12] he stated. "As in most aspects of cardiovascular medicine, we see the issue of gender difference in terms of PSVT diagnosis and treatment," said Sogade. "Definitely there are more females who are diagnosed with PSVT; two-thirds of patients are female.[13] Perhaps more female patients seek healthcare or engage the healthcare system when they experience symptoms. However, when it comes to therapy, females are not offered invasive options as often as males."[13] Camm agreed that ablation is less often applied to females than to males: "I think it's a general rule that compared to males, females have fewer major interventional approaches offered to them in any setting. Otherwise, males and females respond to ablation and drugs in a very similar fashion." As would be expected, the gender differences in diagnosis and treatment are reflected in healthcare resource use and expenditure.[13] Sogade suggested that increased awareness from both healthcare providers and patients is key to addressing this sex disparity and overcoming any issues in care provision.

Addressing the Healthcare Burden in Paroxysmal Supraventricular Tachycardia

The experts moved on to discuss how addressing unmet needs in diagnosis and treatment could help reduce the healthcare burden of PSVT. Home monitoring was seen as an advance that could bring marked patient and health economic benefits by facilitating the diagnosis of PSVT. "There are so many self-monitoring devices that are accurate in terms of recording an event when it's happening," commented Sogade. The experts concurred that greater supply and use of home monitoring devices would give patients the ability to record and share ECGs with their healthcare provider, and so help to accelerate an accurate diagnosis.

Regarding treatment, improved technology and home-based approaches were described as pivotal to the future of PSVT management. According to Camm: "Better ablation technology will mean we are able to do these procedures more quickly and more safely, which will be an advantage. In addition, new drug targets will be identified and there are options for developing brand new medications. As already discussed, there are also different formulations being developed so that patients can administer drugs to themselves when appropriate." Sogade underscored the value of a home therapy option. "If people don't want to take medications every day and they don't/can't have an ablation, then the ability to treat themselves at home with an agent that can terminate the episode would, I think, be useful."

In addition, Sogade reiterated the message of better education around PSVT to expedite both diagnosis and treatment. "I think the biggest unmet need is in the education of the public and we have to find a way of delivering information, maybe online or using the different social media platforms. We need to raise awareness of the PSVT conditions, how they present symptoms, the different means of diagnosis, and all the therapeutic alternatives that are available, especially the agent under investigation, etripamil, as an alternative option for intermittent therapy. We don't want patients to make decisions on their own, but do want them to have sufficient information to enable the best healthcare decisions," he concluded.

SUMMARY

Camm and Sogade discussed the impact of PSVT as a common arrhythmia that presents a notable burden to patients and to providers of emergency healthcare. The nature of PSVT with its unpredictable, transient episodes was said to present challenges in diagnosis, and greater use of patient home monitoring devices to facilitate diagnosis was endorsed. The experts were encouraged by the ongoing development of self-administered drug formulations to enable patients to treat

mild attacks at home. As well as bringing meaningful benefits to patients, it was predicted that home-delivered treatments would also lessen the impact of PSVT on healthcare resources by reducing the burden on the ER and giving an alternative to long-term, preventive medication use. Prioritising patient and physician education to generate greater awareness of PSVT, its diagnosis, and treatment, was also highlighted as valuable.

Biographies

John Camm

St George's University Hospitals NHS Foundation Trust, London, UK

John Camm is emeritus Professor of Clinical Cardiology at St George's Hospital Medical School, University of London, UK. He graduated from Guy's Hospital, London, UK, and pursued a career in cardiology at St Bartholomew's Hospital, London, UK, before moving to St George's as British Heart Foundation Professor of Clinical Cardiology in 1986. Camm is a Fellow of many professional societies, including the European Society of Cardiology (ESC). He is President and Trustee of the Arrhythmia Alliance (AA), and founder of the Atrial Fibrillation Association (AFA), past Editor-in-chief of *EP Europace*, current Editor-in-chief of *European Heart Journal – Case Reports* and Editor of the *European Society of Cardiology Textbook of Cardiovascular Medicine* and its digital version *ESC CardioMed*. He has been involved in the production of numerous guidelines, including the ESC Guidelines for the management of atrial fibrillation. Camm was awarded the ESC Gold Medal in 2005 and the British Cardiovascular Society Mackenzie Medal in 2008. He has authored or co-authored over 1,250 papers and 35 books.

Felix Sogade

Georgia Arrhythmia Consultants, Macon, Georgia, USA

Founding physician of Georgia Arrhythmia Consultants (GACRI), Felix Sogade completed his Cardiac Electrophysiology Fellowship at Duke University, Durham, North Carolina, USA; Cardiology Fellowship at the State University of New York (SUNY) at Stony Brook, New York, USA; and MBBS at the University of Ibadan, College of Medicine, Ibadan, Nigeria. He is an Associate Professor at Mercer University School of Medicine, Macon, Georgia, USA, and Director of Cardiac Electrophysiology at Atrium Health Navicent, Macon, Georgia, USA. He serves as an editor for *Circulation: Arrhythmia and Electrophysiology*. He is a Fellow of the American College of Cardiology (ACC) and the Heart Rhythm Society (HRS). He serves as an HRS Ambassador to Africa and helped create the Africa Heart Rhythm Association (AFHRA). He was former Board Chairman of the Association of Black Cardiologists.

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Interview

Rebecca Dobson

Consultant Cardiologist, Imaging and Cardio-Oncology, Liverpool Heart and Chest Hospital NHS Foundation Trust; Women in Cardiology (WIC) Council Representative, British Cardiovascular Society

Q1

Was there a particular event or person that encouraged you to pursue a career in cardiology and, more specifically, cardio-oncology and echocardiography imaging?

One of my first 'house jobs' was in cardiology, in a District General Hospital, with two great Consultants, one male and one female, who both encouraged me to pursue my interest within the specialty. I think good role models are vital to encourage and support young doctors to become cardiologists. As part of my post-graduate degree, I spent time echoing patients at my local oncology specialist trust and, whilst I was there, there were always many questions from oncologists about cardiology issues and the need for a cardio-oncology service was clear to me. I therefore combined this with my love for echocardiography and have set up a regional cardio-oncology programme.

Q2

Do you think there are any misconceptions about your speciality?

Yes! Many medical students and junior doctors believe that cardiology is not family-friendly or it's not possible to work part-time or flexibly, and I believe this puts off a significant number of talented doctors from ever applying to the specialty. Many seemingly well-meaning consultants told me when I was a junior: "Don't be a cardiologist if you want to have a life outside of work." I'm so glad I ignored them as I have a great job and work-life balance. Part of my role as Women in Cardiology (WIC) rep for the British Cardiovascular Society (BCS) is to engage with medical students and junior doctors to dispel these misconceptions. I firmly believe that we can't be what we don't see and so having highly visible role models is crucial to this initiative.

Q3

In the guideline you co-authored last year, entitled 'British Society of Echocardiography and British Cardio-Oncology Society Guideline for transthoracic echocardiographic assessment of adult cancer patients receiving anthracyclines and/or trastuzumab', what was the key message you were trying to deliver?

This guideline was aimed at all involved in the assessment of cancer patients receiving anthracyclines and/or human epidermal growth factor receptor 2 directed therapy. It provides a framework and echocardiographic protocol to shape the assessment of this group of patients, with an emphasis on high quality, accurate, and reproducible scans and analysis. The key

"I think good role models are vital to encourage and support young doctors to become cardiologists"

message is that, in order to achieve this, 3D volume assessment and the measurement of global longitudinal strain are required as this decreases inter-observer variability and improves reproducibility. The guideline also provides definitions of anthracycline/trastuzumab-induced cardiotoxicity and touches upon other issues such as who to refer to a cardio-oncology service.

Q4

Over the years that you have been practicing within cardio-oncology, how have you seen the field change?

The world of cardio-oncology is expanding rapidly. The incidence of cancer is increasing but, happily, more and more people are surviving their cancer. This has resulted in more and more people being exposed to potentially cardio-toxic therapy and also patients who previously would have died of their cancer are now surviving and living with the late-effects of chemotherapy and radiotherapy and also concomitant cardiovascular disease. Immunotherapy is a perfect example of a type of drug which has revolutionised prognosis for patients with particular types of cancer, such as malignant melanoma, but comes with the cost of potential cardiotoxicity. These patients need to be screened and monitored for cardiovascular complications as the consequences of immunotherapy-induced cardiotoxicity can be fatal.

Q5

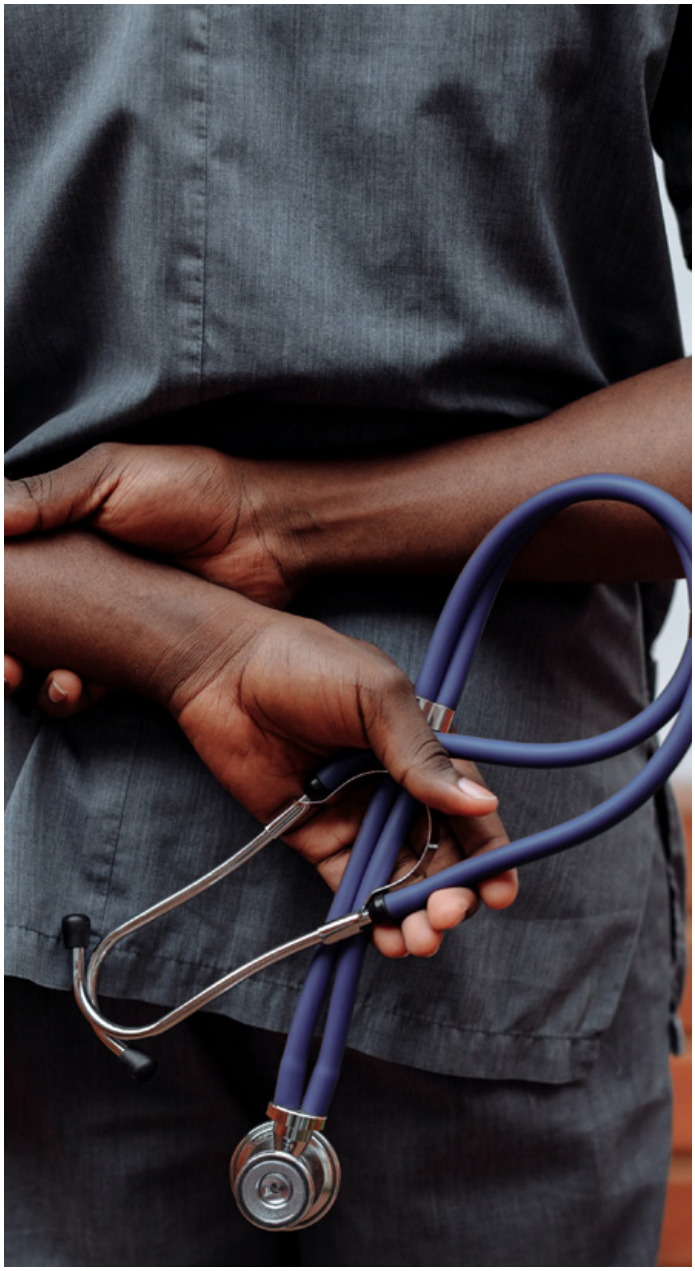
Since your appointment as a Council Representative with the BCS, what has been your proudest achievement?

Since becoming a BCS WIC rep, I have joined forces to form a BCS WIC group with four other female cardiologists who are all passionate about promoting and supporting women in cardiology. We're also all keen to engage with medical students and junior doctors who are considering a career in the field. Through the combined efforts of this group, we have secured funding from the BCS for a dedicated WIC administrator, who will facilitate our planned projects and initiatives; that is my proudest achievement to date, although I must say it wouldn't have been possible without the invaluable input from the BCS WIC group.

Q6

Are there any innovations on the horizon in the field of cardiac imaging that you think are particularly noteworthy?

I think that artificial intelligence will become increasingly important in the field of cardiac imaging. We know that computers are generally better than humans at a whole multitude of things and I suspect the same is true for interpretation of cardiac imaging.



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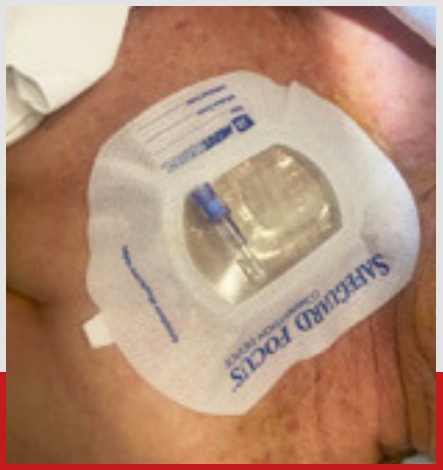

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Association Between the Hospital Readmissions Reduction Program and Heart Failure Subtype Readmissions and Mortality in the USA

EDITOR'S PICK

The Hospital Readmission Reduction Program (HRRP) in the USA sought to penalise hospitals with readmissions above the national average, and heart failure (HF) has been a leading contributor to these HRRP penalties. However, the effectiveness of this strategy has recently been questioned. Therefore, my choice for the Editor's Pick in this issue is the fascinating and timely study by Sheikh et al., which examines the effect of the HRRP on HF mortality and readmissions over time using large national datasets and is the first to analyse based on HF subtypes. This article reports novel findings that advance our understanding of HF and is a valuable addition to the literature.

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Abstract

Background: The Hospital Readmission Reduction Program (HRRP) sought to reduce readmissions by penalising centres with readmissions above the national average, and heart failure (HF) is the leading driver of the readmission penalty. Recent Medicare analyses question the effectiveness of this strategy. This study evaluated the efficacy of HRRP by utilising large national datasets and is the first to analyse based on heart failure subtypes.

Methods: Aggregate data was used from the National Inpatient Sample (NIS) to study mortality and the National Readmissions Database (NRD) to study readmissions. Both included all payer-types and were stratified by heart failure subtype and time (pre- and post-HRRP implementation).

Results: Patients with HF with preserved ejection fraction (HFpEF) tended to be older females with a higher proportion of comorbidities compared to patients with HF with reduced ejection fraction (HFrEF). In the post-HRRP period, readmission rates decreased for HFrEF (21.4% versus 22.3%, p<0.001) and HFpEF (21.2% versus 22.4%, p<0.001); readmission rates for the two subtypes were not statistically different compared to the other. Post-HRRP, inpatient mortality was consistent for HFrEF (2.8% versus 2.8%, p=0.087), but decreased for HFpEF (2.4% versus 2.5%, p=0.029). There were no significant differences noted in average length of stay. Patients with HFrEF were more frequently discharged to short-term hospitals or home with home healthcare, and patients with HFpEF were discharged to skilled nursing facilities more often. Estimated inpatient costs decreased in both subtypes post-HRRP, but readmission costs were higher for HFrEF.

Conclusions: This study suggests that HRRP was associated with minimal change in readmission and inpatient mortality.

INTRODUCTION

The Hospital Readmissions Reduction Program (HRRP) was designed to penalise hospitals for excess readmission ratios in six categories, including heart failure (HF).[1] HF has been a major contributor to these HRRP penalties.[2-4] While initial data have indicated a decline in readmission rates following initiation of the HRRP in 2012,[5,6] Medicare data suggest that the 30-day post-discharge mortality following HF hospitalisations has increased.[7,8] These findings suggest that an inverse relationship exists between readmission rates and mortality.[9-11]

Most studies relating the HRRP to HF readmission and mortality rates make no distinction between HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) subtypes, despite the fact that HFpEF represents nearly half of all heart failure admissions.[12-16] However, it is clear that the HF subtypes affect distinctly different populations, with HFpEF occurring predominantly in older females and patients with more comorbidities.[17,18] Due to the different populations and fundamental pathophysiology, outcomes should differ between the HF subtypes. This study sought to examine the effect of HRRP implementation on HF mortality and readmissions over time using the National Readmissions Database (NRD) and the National Inpatient Sample (NIS), stratified by HF subtype and time period, and divided into pre- and post-HRRP implementation.

METHODS

Data Source

This study was deemed exempt by the Institutional Review Board at Rhode Island Hospital, Providence, Rhode Island, USA. Data were obtained from two data sets: the NRD and the NIS. The NRD is a publicly accessible database that collects clinical, non-clinical, and procedural data for roughly 36 million yearly discharges, tracking both payers and the uninsured. The data are drawn from state-specific inpatient databases in order to generate approximations of national readmissions. The NRD database was created from 27 geographically dispersed states with verifiable patient linkage numbers, which were subsequently utilised to track patients across hospitals within a state while maintaining privacy through de-identification of patient information. The NIS is the largest publicly available, all-payer, inpatient healthcare database in the USA, sampled from all inpatient data contributed to the federally funded Healthcare Cost and Utilization Project (HCUP), approximating a 20% stratified sample of all discharges from community hospitals in the USA.

Study Population

A total of 4,483,987 patient records were identified using the NIS and 2,790,873 patient records were identified using the NRD.

Sample weights were applied in the analysis to estimate the overall national cohort. Of the patient records identified through the NIS, 2,596,442 were pre-HRRP, of which 1,409,597 were identified as HFrEF and 1,186,845 as HFpEF; and 1,887,595 were post-HRRP, of which 1,012,430 were identified as HFrEF and 875,115 as HFpEF. Similarly, of the patients identified through the NRD, 1,271,532 were pre-HRRP, of which 713,796 were identified as HFrEF and 557,736 as HFpEF; and 1,519,341 were post-HRRP, of which 802,254 were identified as HFrEF and 717,087 as HFpEF. The International Classification of Diseases 9th Revision (ICD-9) codes utilised in the analysis are as follows: 438.20, systolic HF, unspecified; 428.21, acute systolic HF; 428.22, chronic systolic HF, 428.23, acute-on-chronic systolic HF; 428.30, diastolic HF, unspecified; 428.31, acute diastolic HF; 428.32, chronic diastolic HF; and 428.33, acute-on-chronic diastolic HF.

Table 1: Demographic, clinical, and hospital characteristics by heart failure subtype pre- and post-Hospital Readmissions Reduction Program (HRRP) in the Nationwide Readmissions Database (NRD).

NRD	Pre-HRRP		Post-HRRP		p value
	HFrEF	HFpEF	HFrEF	HFpEF	
	n=713,796	n=557,736	n=802,254	n=717,087	
Age of admission (years)	70.6±14.6	75.6±12.6	70.1±14.6	75.5±12.7	<0.001 0.038
Proportion of females	40.1%	64.2%	38.8%	62.4%	<0.001 <0.001
Expected payor					
Medicare	72.7%	82.8%	71.6%	83.2%	<0.001 <0.001
Private insurance	12.3%	8.7%	11.8%	8.1%	<0.001 <0.001
Medicaid	9.0%	5.5%	10.5%	5.7%	<0.001 <0.001
Total proportion of cases					
Government hospitals	12.5%	10.6%	11.6%	9.5%	<0.001 <0.001
Non-profit private hospitals	73.9%	75.1%	73.6%	76.6%	<0.001 <0.001
For-profit hospitals	13.6%	14.4%	14.2%	14.0%	<0.001 <0.001
Metropolitan non-teaching hospitals	40.2%	43.3%	31.9%	34.2%	<0.001 <0.001
Metropolitan teaching hospitals	47.5%	44.7%	56.7%	54.1%	<0.001 <0.001
Non-metropolitan hospitals	12.2%	12.0%	11.4%	11.8%	<0.001 <0.001
Chronic conditions					
Peripheral vascular disorders	11.8%	12.2%	12.2%	12.8%	<0.001 <0.001
Chronic pulmonary disease	33.5%	40.6%	34.8%	42.3%	<0.001 <0.001

Table 1 continued.

Diabetes with complications	9.1%	12.2%	10.0%	13.1%	<0.001 <0.001
Liver disease	2.6%	2.6%	3.2%	3.1%	<0.001 <0.001
Obesity	14.2%	21.2%	17.8%	26.9%	<0.001 <0.001
Renal failure	39.2%	42.3%	40.7%	44.6%	<0.001 <0.001
Hypertension	72.8%	78.8%	75.7%	81.1%	<0.001 <0.001
Readmission rate	21.8%	22.1%	21.0%	21.0%	<0.001 <0.001
Length of stay (days)	5.4±6.1	5.4±5.3	5.5±6.3	5.3±5.0	0.811 <0.001
Cost of readmission (USD)	14,434±25,809	14,111±21,037	15,086±29,233	13,935±21,350	<0.001 0.365
Cost of index admission (USD)	7,489	7,418	7,469	7,454	0.216 <0.001
Median time to readmission (days)	5–20	5–20	6–20	6–20	<0.001 <0.001

HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HRRP: Hospital Readmissions Reduction Program; NRD: Nationwide Readmissions Database.

Statistical Analysis

Data were retrospectively reviewed from all heart failure hospitalisations in the NIS to study mortality and in the NRD to study readmissions, stratified by time. The population was divided into two cohorts: pre- and post-HRRP. The NIS 'pre-HRRP' included 1st January 2005 until 30th September 2012, and 'post-HRRP' included 1st October 2012 until 30th September 2015. Similarly, the NRD was divided into 'pre-HRRP', from 1st January 2010 until 30th September 2012, and 'post-HRRP', from 1st October 2012 until 30th September 2015. Associated comorbid conditions, demographic data, disposition, and hospital type were also extrapolated and shown as mean±standard deviation for continuous and n (%) for categorical data. For unadjusted comparisons, pre- and post-HRRP variables were compared using Student's t-test and chi-square test, as appropriate. Risk-standardised mortality and readmission rates along with 95% confidence intervals were generated using SAS® 9.4 (SAS; Cary, North Carolina, USA) for all analyses. A p value of 0.05 indicated statistical significance.

RESULTS

Nationwide Readmissions Database

Heart failure with reduced ejection fraction

The total sample size for the pre- and post-HRRP periods were 713,796 and 802,254, respectively. Demographic, clinical, and hospital data from the NRD stratified by HF subtype and the pre- and post-HRRP periods are shown in Table 1. The post-HRRP period saw an increase in the number of chronic conditions (2.8±1.2 versus 2.9±1.2, p<0.001).

The post-HRRP period saw a reduction in readmission rate (21.8% versus 21.0%, p<0.001). The cost of the index admission was not statistically different between both time periods; however, the readmission cost was statistically higher in the post-HRRP period (14,434±25,809 versus 15,086±29,233 USD, p<0.001). The median time to readmission was slightly higher in the post-HRRP group (5–20 days versus 6–20 days, p<0.001).

Heart failure with preserved ejection fraction

The total sample size for the pre- and post-HRRP periods were 557,736 and 717,087, respectively. There was a statistically significant decrease in the proportion of female HFpEF cases (64.2% versus 62.4%, p<0.001).

The readmission rate in the post-HRRP period was lower compared to pre-HRRP (22.1% versus 21.0%, p<0.001). The readmission length of stay was slightly lower in the post-HRRP period (5.4±5.3 versus 5.3±5.0 days, p<0.001). The cost of the index admission was higher in the post-HRRP period (7,418 versus 7,454 USD, p<0.001).

Heart failure with reduced ejection fraction versus heart failure with preserved ejection fraction: pre-Hospital Readmissions Reduction Program

On average, patients in the HFpEF group tended to be older (p<0.001), and were more likely to be female (p<0.001). The HFpEF group was more likely to have Medicare as the expected payor, whereas Medicaid and Private insurance were more likely to be the payor for patients with HFrEF. Patients with HFpEF were more likely to be either at private non-profit or private for-profit hospitals, while patients with HFrEF were more likely to be in government-owned hospitals (p<0.001). Of the Elixhauser comorbidities, patients with HFpEF tended to have a higher likelihood of having chronic lung disease, diabetes with chronic complications, renal failure, obesity, and hypertension.

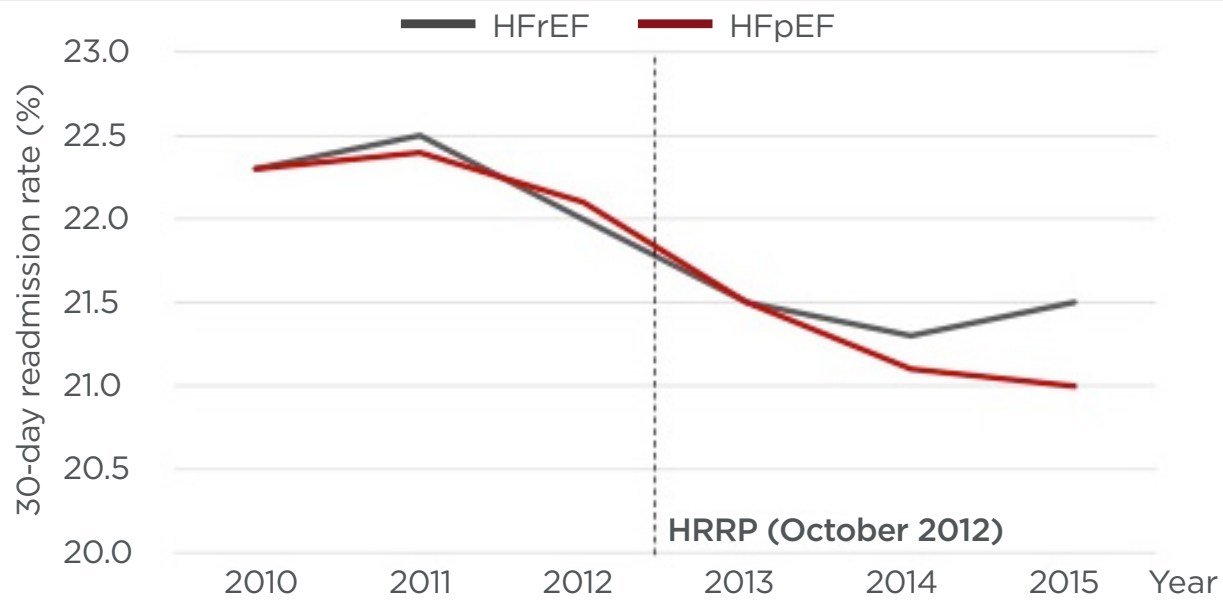

Figure 1: Thirty-day readmission rates before and after implementation of the Hospital Readmissions Reduction Program (HRRP).

HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HRRP: Hospital Readmissions Reduction Program.

The readmission rate pre-HRRP between HFpEF and HFrEF were not statistically different (p=0.831). The cost of readmission and index admission was higher for patients with HFrEF (p<0.001); however, the length of stay for patients with HFpEF was higher (p=0.01).

Table 2: Demographic, clinical, and hospital characteristics by heart failure subtype pre- and post-Hospital Readmissions Reduction Program (HRRP) in the National Inpatient Sample (NIS).

NIS	Pre-HRRP		Post-HRRP		p value
	HFrEF	HFpEF	HFrEF	HFpEF	
	n=713,796	n=557,736	n=802,254	n=717,087	
Age of admission (years)	70.9	75.68±13.14	69.9	75.34±12.76	<0.001 <0.001
Proportion of females	40.1%	64.8%	38.1%	62.8%	<0.001 <0.001
Expected payor					
Medicare	10.8%	80.7%	8.7%	81.5%	<0.001 <0.001
Medicaid	8.7%	5.6%	10.8%	6.1%	<0.001 <0.001
Private payer	13.5%	10.3%	12.9%	9.4%	<0.001 <0.001
Proportion of cases by race					
Caucasian	67.2%	72.6%	65.1%	73.9%	<0.001 <0.001
African American	21.5%	6.7%	22.5%	6.5%	<0.001 <0.001
Hispanic	1.4%	1.6%	1.9%	1.8%	<0.001 <0.001
Total proportion of cases					
Rural non-teaching hospitals	12.0%	11.9%	10.9%	11.6%	<0.001 <0.001
Urban non-teaching hospitals	40.9%	43.6%	32.0%	33.8%	<0.001 <0.001
Teaching hospitals	47.1%	44.6%	57.1%	54.6%	<0.001 <0.001
Chronic conditions					
Iron deficiency anaemia	24.6%	33.3%	26.5%	36.5%	<0.001 <0.001
Chronic pulmonary disease	33.6%	40.5%	35.8%	43.5%	<0.001 <0.001
Uncomplicated diabetes	33.1%	33.7%	35.0%	34.8%	<0.001 <0.001
Hypertension	69.1%	75.8%	75.9%	81.6%	<0.001 <0.001
Liver disease	2.5%	2.4%	3.5%	3.3%	<0.001 <0.001
Obesity	12.5%	19.1%	17.6%	26.9%	<0.001 <0.001
Peripheral vascular disease	11.6%	11.6%	12.9%	13.0%	<0.001 <0.001
Renal failure	38.1%	40.2%	41.6%	45.3%	<0.001 <0.001

Readmission disposition	55.0%	47.1%	53.4%	44.2%	<0.001 <0.001
Transfer to SNF	16.9%	24.2%	16.7%	24.7%	<0.001 <0.001
Transfer to short-term hospital	2.9%	1.83%	3.2%	1.84%	<0.001 <0.001
Transfer to HHC	21.3%	23.9%	22.6%	26.1%	<0.001 <0.001
Length of stay (days)	5.43±5.87	5.37±5.09	5.41±6.31	5.23±4.93	0.305 <0.001
Estimated inpatient cost (USD)	13,094±21,879	10,657±13,221	12,897±25,979	10,251±13,099	<0.001 <0.001
Inpatient mortality	2.8%	2.5%	2.8%	2.4%	0.087 <0.001

HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HHC: home healthcare; HRRP: Hospital Readmissions Reduction Program; NIS: National Inpatient Sample; SNF: skilled nursing facility.

Heart failure with reduced ejection failure versus heart failure with preserved ejection fraction: post-Hospital Readmissions Reduction Program

Post-HRRP was similar to pre-HRRP, except post-HRRP saw a higher proportion of HFrEF cases in government-owned and private for-profit hospitals, whereas HFpEF had a higher proportion of private non-profit in the post-HRRP period. In the post-HRRP period, patients with HFpEF were more likely to be in metropolitan non-teaching and non-metropolitan hospitals compared to patients with HFrEF, who tended to be in metropolitan teaching hospitals. In the post-HRRP period, patients with HFpEF tended to have an increase in the same comorbidities as pre-HRRP, plus iron deficiency anaemia.

The readmission cost was higher for HFrEF (p<0.001), as was the cost of the index admission (p<0.001). Figure 1 displays the year-by-year trend of readmission for both subtypes.

National Inpatient Sample

Heart failure with reduced ejection fraction

The total sample size for pre-HRRP was 1,409,597 and 1,012,430 for post-HRRP. Demographic, clinical, and hospital data from the NIS stratified by HF subtype and the pre- and post-HRRP periods are shown in Table 2. Nearly all of the Elixhauser comorbidity measures were increased in the post-HRRP cohort.

The post-HRRP saw a decrease in routine disposition (55.0–53.4%, p<0.001) and transfers to skilled nursing facilities (SNF) (16.9–16.7%, p<0.001), but saw increases in transfers to short-term hospitals (2.9–3.2%, p<0.001) and HHC (21.3–22.6%, p<0.001). The estimated inpatient cost for HfrEF decreased in the post-HRRP period (13,094±21,879–12,897±25,980 USD, p=0.004).

Heart failure with preserved ejection fraction

The total sample size was 1,186,845 for the pre-HRRP period and 875,115 for the post-HRRP period. The post-HRRP period had a statistically significant annual increase of HfpEF cases. Nearly all of the Agency for Healthcare Research and Quality (AHRQ) comorbidity measures were increased in the post-HRRP cohort.

There was a slightly shorter length of stay post-HRRP for patients with HfpEF (5.37±5.09–5.23±4.93 days, p<0.001). The post-HRRP period saw decreases in routine disposition (47.1–44.2%, p<0.001) but increases in transfers

to SNFs (24.2–24.7%, p<0.001) and a slight increase in transfers to short-term hospitals (1.83–1.84, p<0.001). The inpatient mortality for HfpEF had a statistically significant decrease in the post-HRRP period (2.5–2.4%, p=0.029). Overall, the average cost of hospitalisation for HFpEF decreased (10,657±13,222–10,252±13,099 USD, p<0.001).

Heart failure with reduced ejection fraction versus heart failure with preserved ejection fraction: pre-Hospital Readmissions Reduction Program

Comparatively, HFrEF had a higher yearly proportion of cases during the pre-HRRP period. The average age at admission for HFpEF was higher compared to HFrEF (75.68±13.14 versus 70.89±14.70, p<0.001). Overall, HFpEF was higher in Caucasian patients (72.67% versus 67.2%, p<0.001), while African American and Hispanic patients had higher HFrEF rates (21.5% versus 16.5%, p<0.001; 7.0 versus 6.7%, p<0.001, respectively). Overall, HFpEF had a higher proportion of Medicare as the primary expected payor (80.7% versus 71.9%, p<0.001), while Medicaid and private insurance had higher proportions of HFrEF cases (8.7% versus 5.6%, p<0.001; 13.5% versus 10.3%, p<0.001, respectively).

Proportions of Elixhauser comorbidities were different between both groups, with HFpEF having a higher proportion of deficiency anaemias, chronic pulmonary disease, diabetes, obesity, and renal failure.

There was a slightly higher length of stay for patients with HFrEF (5.43±5.87 versus 5.37±5.09 days, p<0.001), and a higher overall cost for patients with HFrEF. HFrEF had a higher tendency for routine disposition and short-term hospitalisations, whereas patients with HFpEF were more likely to be transferred to a SNF or HHC. The inpatient mortality rate was higher for HFrEF than HFpEF (2.8% versus 2.5%, p<0.001).

Heart failure with reduced ejection fraction versus heart failure with preserved ejection fraction: post-Hospital Readmissions Reduction Program

During 2014–15, HFpEF had higher representation in the inpatient sample compared to HFrEF.

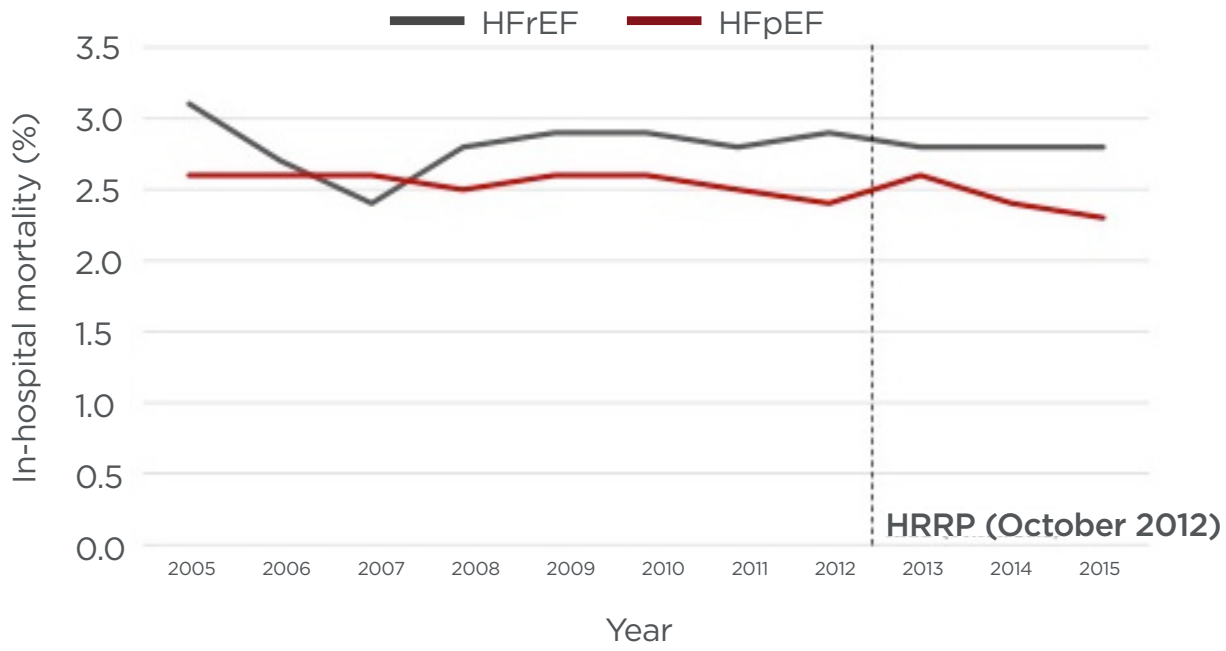

Figure 2: In-hospital mortality before and after implementation of the Hospital Readmissions Reduction Program (HRRP).

HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HRRP: Hospital Readmissions Reduction Program.

Average age, female proportion, and proportion of Elixhauser comorbidities, as stated previously, were still higher in the HFpEF sample. HFrEF continued to have a higher mortality rate, higher cost, and higher length of stay. Figure 2 displays the inpatient mortality trends on a year-by-year basis.

DISCUSSION

The HRRP was billed as a unifying policy targeting the reduction of excess readmissions, determined by a ratio of expected risk-adjusted 30-day readmission rates (excess reductions ratio: >1), in six major categories including heart failure. Subsequent analyses reinforce the notion that real-world HRRP execution has reduced readmissions by negligible amounts.[19,20] More critical studies posit that HRRP has been a net loss with regard to the societal cost of enforcement, given that 'safety net' hospitals are disproportionately penalised and resources that could have potentially been funnelled into programmes aimed at improving outcomes such as mortality have instead been redirected into efforts to reduce readmissions and avoid penalisation.[21,22]

The results support prior observations that any reduction in readmissions for HF has been minimal. Although mortality rates derived from NIS data are inherently limited to inpatient deaths, trends in inpatient mortality can serve as loose and indirect measures of the evolution of disease severity as hospitals are incentivised to reduce admissions and treat healthier patients in the emergency department or observation units, reserving inpatient status for patients who are sicker.[9,23] This analysis did not reveal a difference in mortality for patients with HFrEF. Notably, mortality for patients with HFpEF declined in a statistically significant manner following HRRP implementation.

Prior studies have attempted to delineate trends in mortality and readmissions in HF as a global entity after HRRP implementation but, to date, no analysis exists for the HF subtypes. Overall, readmissions decreased slightly after HRRP implementation for both subtypes (HFrEF: 22.3–21.2%; HFpEF: 22.4–21.2%). HFpEF mortality rates decreased (2.5–2.4%), while HFrEF inpatient mortality rates remained static (2.8%). For both time periods, HFrEF exhibited higher inpatient mortality rates when compared with HFpEF.

Following HRRP, patients with HFrEF were discharged to short-term hospitals or home with HHC more frequently, while patients with HFpEF were discharged to SNF more often. The readmission cost for HFrEF increased post-HRRP, relative to the cost pre-HRRP. Compared to HFpEF, HFrEF admissions and readmissions were more expensive both before and after HRRP implementation. There was also a shift in the proportion of patients to teaching hospitals in the post-HRRP era in both HF subtypes.

The increased utilisation of short-term hospitals, HHC, and SNF perhaps represents efforts to decrease readmissions via transitory healthcare institutions. It is not immediately clear if these efforts have translated into lower readmission rates, but studies evaluating differences in discharge disposition trends between high and low readmission centres have not demonstrated any significant correlation.[10] This suggests that, given the higher costs, hospitals could aim to target HFrEF readmissions.

Among the elderly, HF remains the most common cause for both hospitalisations and readmissions.[24] When compared with the other disease targets of HRRP, HF is the leading driver of the readmissions penalty, highlighting the potential impact of and necessity of strategies aimed at improving quality care for patients with HF.[2] In the first year of HRRP alone (fiscal year 2013), 64% of participating centres were penalised to the tune of 290 million USD, prompting hospitals to invest resources into reducing readmissions.[10] An analysis found that the steepest decline in readmission rates following the passage of the HRRP coincided with changes in the electronic transaction standards used by hospitals to submit Medicare claims, allowing an increase from 9–10 to 25 diagnosis codes, resulting in increased patient risk scores and subsequently 'lower' risk-adjusted readmission rates.[19] A similar study utilised the NRD to replicate risk-adjusted readmission rates and found readmission rates decreased following the implementation of HRRP. The decline was much more modest than that reported by Centers for Medicare & Medicaid Services (CMS),

likely due to the change in electronic transaction standards, and readmission rates of Medicaid patients were consistently higher than those of Medicare beneficiaries.[25-27]

The overall lack of HF readmissions reduction cannot be blamed on HRRP or policy alone, as this is a well-documented problem. A meta-analysis identified multiple effective strategies (e.g., post-discharge communications, supervised exercise programmes, and dietary interventions) were marginally beneficial individually, but combinations of interventions doubled the probability of avoiding readmission.[4] A cross-sectional study evaluating the effects of readmission reduction strategies in patients with HF at 599 hospitals enrolled in nationwide readmission reduction programmes identified six effective interventions, though <30% of hospitals employed the measures and only 7% of hospitals enacted all six strategies.[28] Though evidence-guided strategies to reduce HF readmissions exist, they are often hampered by either minimal efficacy or inconsistent application on the part of the patient.

Similarly, multiple investigations have found that the transition from inpatient to outpatient care can cause problems, as more than half of patients are unaware of medication changes at discharge, with nearly 25% of these changes likely made in error, due to incomplete medication reconciliation.[29] With results suggesting a shift in eventual disposition, proper reconciliation may be critical for successful patient outcomes. The multi-centre HF-ACTION trial, consisting of 2,331 patients across 82 centres, found that patient adherence to prescribed home exercise programmes over a median of 30 months was approximately 30%.[30] Attendance at outpatient cardiac rehabilitation programmes seems to be particularly poor among the Medicare population.[31] This combination of patient and hospital factors resisting adoption of the limited number of proven methods to reduce HF readmissions forms a barrier to progress that no single policy can remedy. Regardless, the results underscore the notion that the HRRP, despite and perhaps partly due to the aforementioned challenges in its place, has been unsuccessful in reducing readmissions for the HF population.

Further studies stratifying by payor may prove enlightening. Using the entirety of Medicare inpatient claims from 2009, Gu et al.[32] created a sample population using Medicare's inclusion and exclusion criteria for readmission measures, and using dual Medicare and Medicaid eligibility as a surrogate for low socioeconomic status, they found that readmission rates for dual-eligible patients were significantly higher across the conditions targeted by the HRRP when compared with Medicare beneficiaries alone, with a HF readmission rate of 27.2% in dual-eligible patients versus 23.9% in non-dual-eligible patients. Applying this same methodology to both mortality and readmissions may uncover disparities with regard to downstream consequences of a push away from admitting patients.

LIMITATIONS

This analysis has several limitations. Namely, this is a retrospective and observational analysis. Additionally, this study utilised two databases, the NRD and NIS, and extracted data from both using ICD-9 codes, raising the possibility of inadequate capture of patients and potential misclassification of patients. These databases do not contain clinical variables, so it was not possible to objectively confirm whether patients had true systolic versus diastolic dysfunction. All insurance types were included in this analysis, though the HRRP targets Medicare recipients aged 65 years or older. However, the inclusion of all payors allowed for a more robust commentary regarding the efficacy of the programme in achieving its underlying intent to reduce readmission rates at large.

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Biomarker-Based Guideline-Directed Medical Therapy of Heart Failure: The Gap Between Guidelines and Clinical Practice

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Abstract

Current clinical recommendations provided by the 2016 European Society of Cardiology (ESC) and 2017 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) are substantially distinguished in the use of circulating biomarkers in the management of heart failure (HF). To date, natriuretic peptides continue being the universal biomarkers used in diagnosis, risk stratification, and prediction of cardiovascular death, all-cause mortality, and HF-related outcomes for patients with both phenotypes of HF. However, biomarkers of fibrosis and inflammation, including soluble suppressor of tumourgenicity 2 and galectin-3, were able to increase predictive ability of natriuretic peptides in HF patients regardless of cardiovascular risk-factor presentation and HF phenotypes. Therefore, there are many various biomarkers describing several pathophysiological processes such as fibrosis, inflammation, oxidative stress, neurohumoral activation, extracellular matrix turnover, and vascular reparation, that play a pivotal role in the natural evolution of HF. This review discusses whether multiple biomarker models are more effective than a single biomarker in improving risk stratification strategies in patients with HF. It emphasises how in routine clinical practice, the multiple biomarker approach to elicit response to therapy of HF and predict clinical outcomes is rare, probably because of the relatively high cost, low affordability, lack of clear recommendations for clinical implementation, and significant disagreements in the interpretation of the data obtained.

INTRODUCTION

The prevalence of heart failure (HF) worldwide is 64.34 million cases, and almost 10 million years have been lost due to HF-related disability.[1] The global trend prevalence of HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) over the last decade has shown an increase in HFpEF and tendency to stabilisation of newly diagnosed cases of HFrEF.[2] However, the prevalence of HFrEF in developed countries is decreasing, whereas in developing countries it demonstrated steady growth.[3] In fact, by the year 2030, in low-to-middle income regions, the prevalence of HF is estimated to rise

by over 50%, while high-income countries will have a declined rate of up to 27%.[4] Mortality is considerable variable in different regions, i.e., from 34% in Africa to 7% in China, with the overall mortality rate being 16.5%.[5] This high variability of HF prevalence and mortality in distinct regions is linked to substantial difference in cardiovascular (CV) risk-factor distribution, affordability of novel technologies in therapy of CV diseases, structure of public health systems, and other factors.[5]

In addition, the presenting clinical syndromes in HFpEF and HFrEF are not distinguishable from one another, but mortality and co-existing comorbidities substantially differ. In this context, the profile of biomarkers that could be used for diagnosis and prognosis of HFpEF would not resemble their signature in HFrEF. Indeed, predictive ability of natriuretic peptides (NPs) in HFrEF was found as higher than in HFpEF. In contrast, soluble suppressor of tumourgenicity 2 (sST2) and galectin-3 when being added to NPs sufficiently improved final discriminative potency of the model in patients with HFpEF.[6]

However, there is no agreement in biomarker profile between the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC).[6,7] A contemporary conceptual framework for the diagnosis and management of HFrEF and HFpEF provided by the AHA (2017) includes the first generation of biomarkers such as NPs, sST2, highly sensitive troponin (hs-Tn), and galectin-3.[6] Current 2016 ESC HF guidelines indicate the priority of HF having the highest level of evidence before other biomarkers; the discriminative potency of them requires thorough elucidation.[7]

Reflecting the varying stages of evolving HF, biomarkers can predict its clinical course, short- and long-term prognosis, and risks of all-cause mortality and hospital admission.[8] An abundant number of new biomarkers, i.e., mid-regional pro-adrenomedullin, cystatin-C, IL-6, growth differential factor-15 (GDF-15), matrix metalloproteinases, collagen turnover biomarkers, osteonectin, and others, are now clinically available, and continuous monitoring of their levels in peripheral blood is promising in the context of receiving additional prognostic and diagnostic information, which can improve guiding treatment strategies of different phenotypes of HF.[8]

The aim of this narrative review is to summarise knowledge about prospective potencies of circulating cardiac biomarkers in HF patients that could be useful for routine clinical practice.

METHODS AND METHODOLOGY

The bibliographic database of life science and biomedical information MEDLINE, EMBASE, Medline (PubMed), the Web of Science, and the Cochrane Central were searched for English publications satisfying the keywords of this study. The authors used the following keywords: "heart failure," "heart failure with reduced ejection fraction," "heart failure with preserved ejection fraction," "cardiac cachexia," "cardiac myopathy," "cardiovascular risk," "cardiovascular risk factors," "cardiac biomarkers," "circulating biomarkers," "secretomics," and "prognosis". Both authors independently evaluated the quality of the articles, correspondence to the main idea of the study, and constructed the final list of the references.

BIOMARKERS FOR HEART FAILURE

As HF is a multiply complex disease with sophisticated pathogenesis, which is substantially different for HFrEF and HFpEF, there are many biomarkers proposed to determine stages and severity of the disease, predict occurrence, clinical course and outcomes of HFrEF/HFpEF, a risk of CV and HF-related mortality, and a response to treatment (Table 1). Previously, there were suggestions that pro-inflammatory conditions, adipose-tissue dysfunction, oxidative stress and fibrosis predominantly underlie the pathophysiology of HFpEF, whereas neurohumoral activation, cardiac injury, and biomechanical stress much better describe the adverse cardiac remodelling and natural evolution of HFrEF than HFpEF.[9,10] This view has been disregarded more recently because biomarkers of biomechanical stress, such as NPs, exhibited their high potency to exclude HFpEF and predict outcomes in both HFrEF and HFpEF, and biomarkers of fibrosis and inflammation, including sST2, galectin-3, increased predictive ability of NPs in HF patients, regardless of CV risk-factor presentation and HF phenotypes.[11,12]

Table 1. 2016 European Society of Cardiology (ESC) and 2017 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) clinical practice guideline recommendations for the use of biomarkers in the management of heart failure.

Strategy for use	Biomarkers	ESC; 2016			ACC/AHA/HFSA; 2017		
		COR	LOE	Phenotype of HF	COR	LOE	Phenotype of HF
Diagnosis	BNP/NT-proBNP/MR-proANP*	I	A	AHF, HFpEF, HFmrEF	I	A	AHF, CHF
Risk of in-hospital death	BNP/NT-proBNP	I	C	AHF	I	A	AHF, CHF
	hs- TnT/I	I	C	AHF	I	A	AHF, CHF
Risk of recurrent hospital admission	BNP/NT-proBNP	NA			I	A	AHF, CHF
Risk of post-discharged death	BNP/NT-proBNP	I	A	AHF, CHF	I	A	AHF, CHF
	hs- TnT/I	I	C	AHF, CHF	I	IIa	AHF, CHF
	Galectin-3	NA			IIb	B	AHF, CHF
	sST2	NA			IIb	B	AHF, CHF
Prevention of HF onset	BNP/NT-proBNP	NA			IIa	B	AHF, CHF
Guided therapy	BNP/NT-proBNP	NA			I	A	HFrEF/HFpEF

*Provided for 2016 ESC recommendation only.

ACC: American College of Cardiology; AHA: American Heart Association; AHF: acute heart failure; BNP: B-type natriuretic peptide; CHF: chronic heart failure; COR: class of recommendation; ESC: European Society of Cardiology; HF: heart failure; HFmrEF: heart failure mid-range ejection fraction; HFpEF: heart failure preserved ejection fraction; HFrEF: heart failure reduced ejection fraction; HFSA: Heart Failure Society of America; hs-TnT : high sensitivity troponin; LOE: level of evidence; MR-proANP: mid-regional pro A-type natriuretic peptide; NA: not applicable; NT-proBNP: N-terminal pro-B-type natriuretic peptide; sST2: soluble suppressor of tumourgenicity 2.

However, NPs remain universal biomarkers that represent diagnosis, risk stratification and prediction of CV death, all-cause mortality and HF-related outcomes for patients with both phenotypes of HF.[13,14] There are recommendations for use of the levels of B-type NP (BNP) >35 pg/mL and N-terminal pro-BNP (NT-proBNP) >125 pg/mL to exclude HF in the acute settings. Higher values of these markers (BNP >100 pg/mL, NT-proBNP >300 pg/mL, and mid-regional pro A-type NP [MR-proANP] >120 pmol/L) are approved for use in diagnosis of chronic HF.[6,7] These diagnostic cut-off points are applied strictly, similar to HFrEF and HFpEF, but circulating levels of BNP/NT-proBNP and MR-proANP are frequently lower for patients having HFpEF when compared with those who have HFrEF. A peak value of NT-proBNP >5,000

pg/mL predicts an adverse outcome in HFrEF in-patients, whereas poor prognosis for stable outpatients having HFrEF was suspected when NT-proBNP levels were >1,000 pg/mL. The trend for reducing the levels of NT-proBNP >1,000 pg/mL is now considered a concise indicator of adequate therapy of HFrEF patients, while stability of soaring NT-proBNP levels predicts poor clinical outcomes of the disease.[14] Overall, high levels of NT-proBNP provided similar predictive information in patients with HFpEF as in those with HF mid-range EF (HFmrEF) and HFrEF; other biomarkers, including sST2, galectin-3, and high-sensitivity C-reactive protein (hs-CRP), have demonstrated controversial evidence regarding their ability to be carefully tailored to HF phenotypes and comorbidities.[15,16] However, negative diagnostic and predictive values of NPs were found to be higher than positive values for prognostication. This implies that single or serial measures of NPs are not enough to completely predict HF evolution, especially among older patients and those who have various CV diseases and comorbidities. These facts are extremely important because there is no descriptive clinical model that can independently predict the clinical endpoint in HFpEF.[17]

Previous clinical studies have shown that the levels of sST2, galectin-3, and hs-CRP were significantly higher in HFrEF patients when compared with HFpEF individuals.[18-21] Although peak levels of sST2, high sensitivity troponin (hs-TnT)/I, galectin-3, and hs-CRP, and their dynamic changes substantially improved predictive potency of NPs among patients with HF, there are serious economic concerns regarding the increased number of biomarkers involved in the multiple diagnostic models.[22-27] In addition, there are sustentative disagreements in justifying whether these biomarkers can be adequately discriminative, and have certain calibration, abilities for reclassification, and likelihood analyses in various cohorts of HF individuals, depending on conventional CV risk factors (sex, age, ischaemic versus non-ischaemic aetiology, left-ventricular EF, estimated glomerular filtration rate, hypertension, and dyslipidaemia), comorbidities (diabetes mellitus, abdominal obesity), New York Heart Association (NYHA) functional class, HF medical therapy, and NT-proBNP levels.[28] In fact, sST2 and galectin-3 not only predicted all-cause and CV death and HF hospitalisation in both HFrEF and HFpEF, with good performance in Kaplan–Meier analysis in face-to-face comparisons with NT-proBNP and hs-TnT/I, but they yielded significant improvement of comparator models (NT-proBNP and hs-TnT/I) adding prognostic information.[29-31] Consequently, sST2 and galectin-3 have been considered as part of a multiple biomarker panel together with NT-proBNP and hs-TnT for most population HF subgroups independently of comorbidity status and CV risk.

CURRENT CLINICAL RECOMMENDATIONS FOR BIOMARKER UTILITY IN HEART FAILURE

Current clinical recommendations provided by ESC (2016) and ACC/AHA/Heart Failure Society of America (HFSA; 2017) are substantially distinguished in the use of circulating biomarkers in the management of HF (Table 1). Both clinical guidelines agreed with the diagnostic strategy of acute and chronic HF based on a measure of circulating levels of NPs additionally to clinical signs and symptoms assay, echocardiographic parameter evaluation and analysis of ECG findings. Therefore, the risk of in-hospital death can also be predicted with NT-proBNP peak level at admission and based on a trend of NT-proBNP level change. However, other utilities of NPs, such as guided therapy and assay of the risk of recurrent hospital admission, were approved in the 2017 ACC/AHA/HFSA clinical guideline, but not in the 2016 ESC HF recommendation. Moreover, sST2 and galectin-3 as alternative biomarkers for additional risk stratification were recommended by the only 2017 ACC/AHA/HFSA clinical guideline, while the evidence for sST2 and galectin-3 remains very weak, as shown by the low grade of evidence, which currently discourages translation to clinical practice.

Thus, the 2017 ACC/AHA/HFSA clinical practice guideline recommends more extensive biomarker strategy for HF management than the 2016 ESC HF recommendation, while there is a gap of evidence regarding use of biomarkers to predict occurrence of different phenotypes of HF, and limited data for risk stratification depending on CV diseases and comorbidities.

BIOMARKER PROFILE AND HEART FAILURE STATUS

There are numerous investigations focusing on the inter-relation between specific biomarkers of fibrosis, inflammation, oxidative stress, neurohumoral activation, extracellular matrix turnover, vascular reparation, and HF status (HFrEF versus HFpEF).[32-38] Usually, authors executed univariable and multivariable interactions of baseline biomarker levels and outcomes in HF patients with further correction for the COACH risk engine that included variable anthropometric data, CV diseases (atrial fibrillation, peripheral artery disease, coronary artery disease, dilated cardiomyopathy) and comorbidities (diabetes mellitus, abdominal obesity), estimated glomerular filtration rate, and network analysis. As a result of these investigations, the profile of biomarkers that fitted into HF status for the best was received.[37,38] The profile of biomarkers might look like this (Figure 1).

Indeed, various circulating biomarkers in key pathophysiological domains are predictive of outcomes in HFpEF and HFrEF, while their circulating levels were substantially different in patients having distinct HF status. For instance, patients with HFrEF had higher median levels of GDF-15, hs-TnT, heart-type fatty-acid-binding protein, and NT-proBNP, but not sST2, galectin-3, hs-CRP, procollagen peptides, and other abundant biomarkers of extracellular turnover, than those who have HFpEF.[21,30,31,39] In contrast, most biomarkers of fibrosis, inflammation and extracellular matrix remodelling have demonstrated higher levels in HFpEF than HFrEF.[21,26,30-33,38] A novel paradigm for HFpEF has been described in close connection with CV risk factors and comorbidities, which drive microvascular inflammation, endothelial dysfunction, altered vascular repair, adverse cardiac remodelling, and dysfunction of skeletal muscles and adipose tissue.[40] In fact, the presentation and number of risk factors contributing to HFpEF distinguish from those that correspond with HFrEF and demonstrate strong association with age, sex, genetic predisposition, ethnicity, level of education, and region.[41,42] In this context, dominant biomarker clusters are required to thoroughly identify individuals at risk of HF occurrence and mortality due to cardiac dysfunction. Consequently, multiple biomarker models appear to be more prognostic than single biomarkers in risk stratification strategies in patients at high risk of HFpEF and those who have overt HFpEF. Obviously, the optimal choice of biomarker combination is strongly needed for effective multiple biomarker strategy to improve HF patient management and outcomes. However, there are limited data to conclude whether multiple biomarker models are better in HFpEF when compared with HFrEF to predict HF-related outcomes and death.[38,39]

MULTIPLE BIOMARKER MODELS

The panel of biomarkers, which measures diverse biological processes and can be a prognostic tool in HFrEF, was investigated by Ky B et al.[43] In a multicentre cohort of 1,513 patients with HFrEF, the levels of several biomarkers such as hs-CRP, myeloperoxidase, BNP, soluble FMS-like tyrosine-kinase receptor-1, Tn-1, soluble toll-like receptor-2, creatinine, and uric acid were measured. Authors created multiple biomarker scores and assessed their performance for prediction of the risk of death, cardiac transplantation, or as a ventricular-assistant device in comparison with conventional clinical risk scores (the Seattle Heart Failure Model [SHFM]) for 2.5 years. Investigators found that patients with HFrEF have the highest tertile of the multiple biomarker score had a 13.7-fold increased risk of adverse clinical outcomes when compared with those who had the lowest tertile (95% confidence interval [CI]: 8.75–21.50). Moreover, these effects were independent of the SHFM and adding the multiple biomarker score to the SHFM markedly improved its discriminative potency.

To characterise HF status, and evaluate a possible relationship between HF status and the risk of all-cause death or HF-related hospital admissions, Chirinos et al.[44] used 49 plasma biomarkers received from patients withn HFpEF (n=379) enrolled in the TOPCAT trial. The authors constructed several clusters, which included biomarkers of fibrosis/tissue remodelling (sST2), inflammation (TNF-α, soluble TNF-receptor 1, and IL-6), renal injury/dysfunction (cystatin-C), liver fibrosis (YKL-40), neurohormonal regulators of mineral metabolism/calcification (FGF-23 and osteoprotegerin), intermediary metabolism/adipose-tissue dysfunction (fatty-acid-

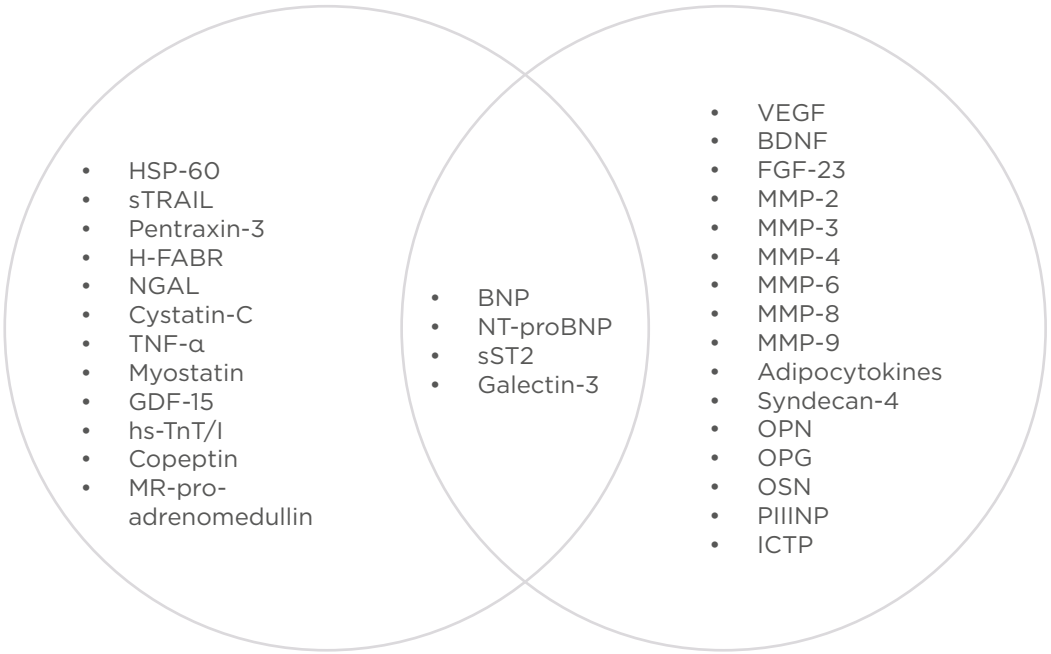

Figure 1: Corresponding biomarker profiles with heart failure status.

BDNF: Brain-derived neurotrophic factor; BNP: B-type natriuretic peptide; FGF-23: fibroblast growth-factor-23; GDF-15: growth differential factor-15; H-FABP: heart-type fatty-acid-binding protein; ICTP: collagen type I carboxy-terminal telopeptide; MMP: matrix metalloproteinase; MR-proANP: mid-regional pro A-type natriuretic peptide; NGAL: neutrophil gelatinase-associated lipocalin; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PIIINP: procollagen type III N-terminal propeptide; sST2: soluble suppressor of tumourgenicity 2; VEGF: vascular endothelial growth factor.

binding protein-4 and GDF-15), angiogenesis (angiopoietin-2), biomarkers of myocardial injury (hs-TnT), extracellular matrix remodelling (MMP-7), and biomechanical stress (NT-proBNP). Using a machine-learning-derived model, the authors found that a combination of biomarkers was strongly predictive of the risk of HF-related hospital admission and sufficiently improved the risk prediction when added to the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score.[44] In addition, the model markedly predicted the risk of admission due to HF progression (hazard ratio: 2.74; 95% CI: 1.93–3.90; p<0.0001), which was also independent of the MAGGIC risk score.[44]

Using a random algorithm Yuan et al.[46] found that the combination of creatine kinase-MB, BNP, galectin-3, and sST2 were useful for prediction of HFpEF/HFrEF occurrence.[45] In contrast, Zhang et al.[46] reported that discriminative ability of sST2 and NT-proBNP for 1-year all-cause death in patients with acute HF was similar and remained significant between patients having ischaemic and non-ischaemic aetiology of HF.

However, galectin-3 did not increase prognostic ability of sST2 and NT-proBNP when added to this combination in patients with ischaemic HFrEF, but not in individuals with non-ischaemic HF regardless of its phenotype. In a cohort of adult patients with HF due to congenital heart disease, a multiple biomarker model constructed from neurohormones (angiotensin II, endothelin-1, norepinephrine, aldosterone, and plasma renin activity), inflammatory biomarkers (hs-CRP, hs-TNF, soluble TNF receptor Types I and II, and IL-6), and BNP, predicted HF mortality.[47] Thus, aetiology of acute HF should be considered when an optimal panel of biomarkers has been validated.

Jackson et al.[48] measured the levels of biomarkers received from 628 inpatients with acutely decompensated HF. The authors noticed that patients did not always have markedly increased circulating levels of mid-regional pro-adrenomedullin, MR-proANP, copeptin, hs-cTnT, sST2, galectin-3, cystatin-C, combined free light chains, and hs-CRP. Consequently, authors undertook a dichotomisation into low (up to

two elevated biomarkers) or high (at least three and more elevated biomarkers) risk groups. It was found that patients with HF from the high-risk group provided much more incremental prognostic value than individuals from the low-risk group (hazard ratio: 2.20; 95% CI: 1.37–3.54; p=0.001). Finally, elevated circulating levels of five biomarkers demonstrated the highest predictive ability for the risk of death.[48]

Interestingly, in the patient population with HF (n=1,497) enrolled in the CORONA study, a multiple biomarker approach using two panels of biomarkers, which included model 1 (endostatin, IL-8, sST2, TnT, galectin-3, and C-C motif ligand 21) and model 2 (TnT, sST2, galectin-3, pentraxin-3, and soluble TNF-receptor-2), in addition to hs-CRP and NT-proBNP, demonstrated limited attributive potency of inflammatory biomarker panels for identifying the risk of adverse clinical outcomes.[49] Therefore, in the PLATO study, elevated baseline levels of NT-proBNP and GDF-15 were strong predictors for all-cause death based on their associations with HF-related death, as well as arrhythmia and sudden cardiac death among patients with acute coronary syndrome.[50] Unfortunately, in routine clinical practice, a multiple biomarker approach to elicit response to HF therapy and predict clinical outcomes is very rare, probably due to the relatively high cost, low affordability, lack of clear recommendations for clinical implementation, and significant disagreements in the interpretation of data obtained.

GUIDED THERAPY OF HEART FAILURE

While the current data on using biomarkers to guide HF management remain mixed, more research is necessary to better understand how to utilise biomarkers to improve HF management.[51] Guided therapy in clinical practice is mostly based on serial changes of NPs, while other biomarkers such as sST2 and galectin-3 have been considered as a component of this strategy.[52] Previous proof-of-concept studies have reported controversial results for biomarker-guided strategies in HF.[53] The GUIDE-IT study did not find benefit from biomarker-guided therapy versus usual care in improving the primary endpoints of HF hospital admission or CV mortality in patients with overt HF.[54] However, HFrEF patients whose NT-proBNP levels decreased to ≤1,000 pg/mL over 90 days of HF therapy had better outcomes and significantly better quality of life than those who had no reduced levels of the biomarker.[55] These findings urge us to reassume whether guide therapy is a powerful tool for the entire population of HF patients. However, the role of a multiple-biomarker strategy in guided therapy is not certain, and well-designed, largescale, multi-centre, randomised clinical trials are definitively required to shed light on these approaches to HF management.

COST/BENEFIT TO USE OF BIOMARKERS

Implementation of biomarker strategies in routine clinical practice corresponds to substantial cost for patients and the health system. Consequently, biomarker-guided decisions should desirably yield economic benefit in HF administration and a better allocation of financial resources. Indeed, the REACH-HF trial has shown that home-based facilitated intervention (with inclusion of predominantly NP biomarkers) for HFrEF was clinically superior in disease-specific 1-year quality of life and, thereby, offers an affordable alternative to traditional centre-based programmes for HFrEF.[56] In addition, the risk stratification of elderly patients with HF, based on multiparametric approach, ensured cost benefit in quality of life.[57] However, the 2016 ESC and 2017 AHA/ACC guidelines did not concisely emphasise which patients with HF might especially benefit from the biomarker approach. It is reasonable to consider the administration of NPs in patients with HFrEF/HFpEF , while other biomarkers (cardiac Tns, sST2, galectin-3) could have a significant economic impact in predicting all-cause mortality, identifying new patients with HF requiring hospitalisation, optimising treatment, and consequently preserving hospital budget.[39,58-60] In fact, uncertain cost/benefit ratio is still one of the unsolved problems for a non-NP biomarker strategy for an unselected real-world population. This is the reason most biomarker models currently cannot be applied in routine clinical practice.

PROSPECTIVES

Several underlying pathophysiological processes (extracellular matrix structural constituents,

proteinaceous extracellular matrix) and signalling pathways (regulation of apoptotic process and integrin signalling pathway) involved in the pathogenesis of HFrEF/HFpEF can be described by the signature of non-coding RNAs. Indeed, transcriptome analysis offers great potential in identifying HF biomarkers. Among 1,139 differentially expressed messenger RNAs, He et al.[61] identified clusters constructed from nine long non-coding RNAs, three micro-RNAs, and 25 messenger RNAs that were closely associated with progression and outcomes of HF. However, the predictive value of the RNA signature requires elucidation in large clinical trials.[62] However, metabolomic and lipidomic phenotyping of patients having HFrEF/HFpEF to indicate a profile of oxidative stress, lactic acidosis, and metabolic syndrome, coupled with mitochondria dysfunction, is a promising approach to stratify them at high risk of poor outcomes.[63]

CONCLUSION

In conclusion, cardiac biomarkers such as NPs are a promising tool for individualising care in patients with HF, whereas alternative biomarkers (sST2, hs-TnT/I, galectin-3) having weaker clinical evidence than NPs and require more investigation to easily identify the target population in which they would have most cost benefit. A multiple biomarker approach is probably more optimistic for HF-risk stratification and predicting HF-related outcomes than a single biomarker approach, especially in patients with older age, HFpEF, and those having comorbidities. Optimal choice of biomarkers for panels requires in-depth evaluation of economic burden, and not only their discriminative probability for all-cause and CV mortality, HF occurrence, and HF incidence. New biomarkers of the inflammatory axis, matrix remodelling, fibrosis, metabolic axis, and oxidative stress demonstrate uncertainty in their potential therapeutic interventions and are under follow-up investigation. Large clinical trials are required to better understand the role of a multiple-biomarker strategy in HF care to decrease morbidity and mortality, improve quality of life, and propose an easy-to-execute approach for routine clinical practice.

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A Case Series of Eight Coronary Artery Perforations and a Review of the Up-to-Date Literature

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Abstract

Percutaneous coronary intervention has become a fundamental diagnostic and treatment strategy in coronary artery disease. Much like any procedure, it is not without risk; in fact, a rare but life-threatening complication as a result of percutaneous coronary intervention is coronary artery perforations (CAP). The risk of CAPs correspondingly rises in relation to the difficulty of the procedure, location of lesion, and complexity of anatomy. It follows then that early recognition and instigation of an appropriate treatment strategy is key in reducing the mortality and morbidity associated with CAPs. The authors present eight case reports of varying difficulties, their analogous management, and a literature review of management approaches in treating CAPs in order to provide a review of management strategies and to highlight the importance of immediate recognition of a potentially fatal complication.

INTRODUCTION

Percutaneous coronary intervention (PCI) has become a mainstay treatment of coronary artery disease, being performed at a rate of 1,548 per million population in the UK alone.[1] An infrequent complication contributing to a five-fold rise in 30-day mortality is iatrogenic coronary artery perforation (CAP), noticed more commonly in females and older patients.[2,3] Often presenting with an acute and sharp chest pain when the stent is deployed or during balloon inflation, the average incidence of CAP is approximately 0.5% but can rise to approximately 3.0% in chronic total occlusion (CTO) PCIs.[2-5] It follows then that the risk of CAP is proportional to the difficulty of the procedures, compounded by complex coronary anatomy and the use of instrumentation that confers a higher risk of perforation.[4]

Further assessment with a repeat echocardiogram within 24 hours should be performed after high-risk cases such as CTO PCI to rule out a late cardiac tamponade, where there have been any concerns.[6] CAP has typically been classified using the Ellis classification (Table 1) to determine the risk of complications based on angiographic severity assessment.[2,6] The location and severity of CAPs determine the need for further action; whereby, proximal or larger vessel lesions may require covered stents or surgical repair and distal lesions may be more amenable to treatment with embolisation techniques.[2]

PERFORATION CASE SERIES

Here, the authors present a series of eight cases of coronary perforation in their centre over a period of 1 year, with a total PCI case load of

1,600 cases (Table 2). The management strategy for each case varies depending on the clinical need for intervention and anatomy.

Case 1

The first case involved a 72-year-old female who attended for a staged elective PCI to her right coronary artery (RCA) CTO following elective PCI to her left anterior descending artery (LAD) for stable angina and inducible inferior and apical ischaemia on myocardial perfusion scanning, on a background of hypertension, hypercholesterolaemia, and positive family history of ischaemic heart disease. She underwent PCI to her mid- and distal-RCA, with overlapping Resolute Onyx drug-eluting stents (DES; Medtronic, Dublin, Ireland). Following on from PCI, she unfortunately developed pericardial tamponade from an Ellis Grade 3 perforation following stent balloon inflation, which required drainage, and was treated successfully with covered stent insertion (Figure 1A; Case 1). She remained an inpatient for 5 days, with a repeat echocardiogram 48 hours post-drain removal showing normal left ventricle (LV) function and no significant pericardial effusion.

Table 1: Ellis classification for coronary artery perforation.[6]

Perforation classification	
Grade 1	Extraluminal crater without extravasation
Grade 2	Pericardial or myocardial blush without contrast jet extravasation
Grade 3	Extravasation through frank (≥1 mm) perforation
Grade 4 (cavity spilling)	Perforation into an anatomic cavity chamber, coronary sinus, etc.

Table 2: Summary of cases.

Case number	Age (years)	Sex	Lesion	Ellis grade	Therapy
1	72	Female	CTO RCA	3	Covered stent
2	72	Female	Proximal RCA stenosis	2 (distal wire)	Balloon tamponade
3	77	Male	Proximal LAD stenosis	1	Conservative
4	53	Male	Calcified proximal LAD stenosis	3	Covered stent
5	60	Male	Acute-on-chronic RCA occlusion	2	Balloon tamponade
6	70	Male	Proximal RCA stenosis	2 (wire perforation)	Covered stent
7	58	Male	Mid-LAD ISR	1	DES implantation
8	58	Male	Mid-LAD fibrocalcific lesion	3	Covered stent

CTO: chronic total occlusion; DES: drug-eluting stent; ISR: in-stent restenosis; LAD: left anterior descending artery; RCA: right coronary artery.

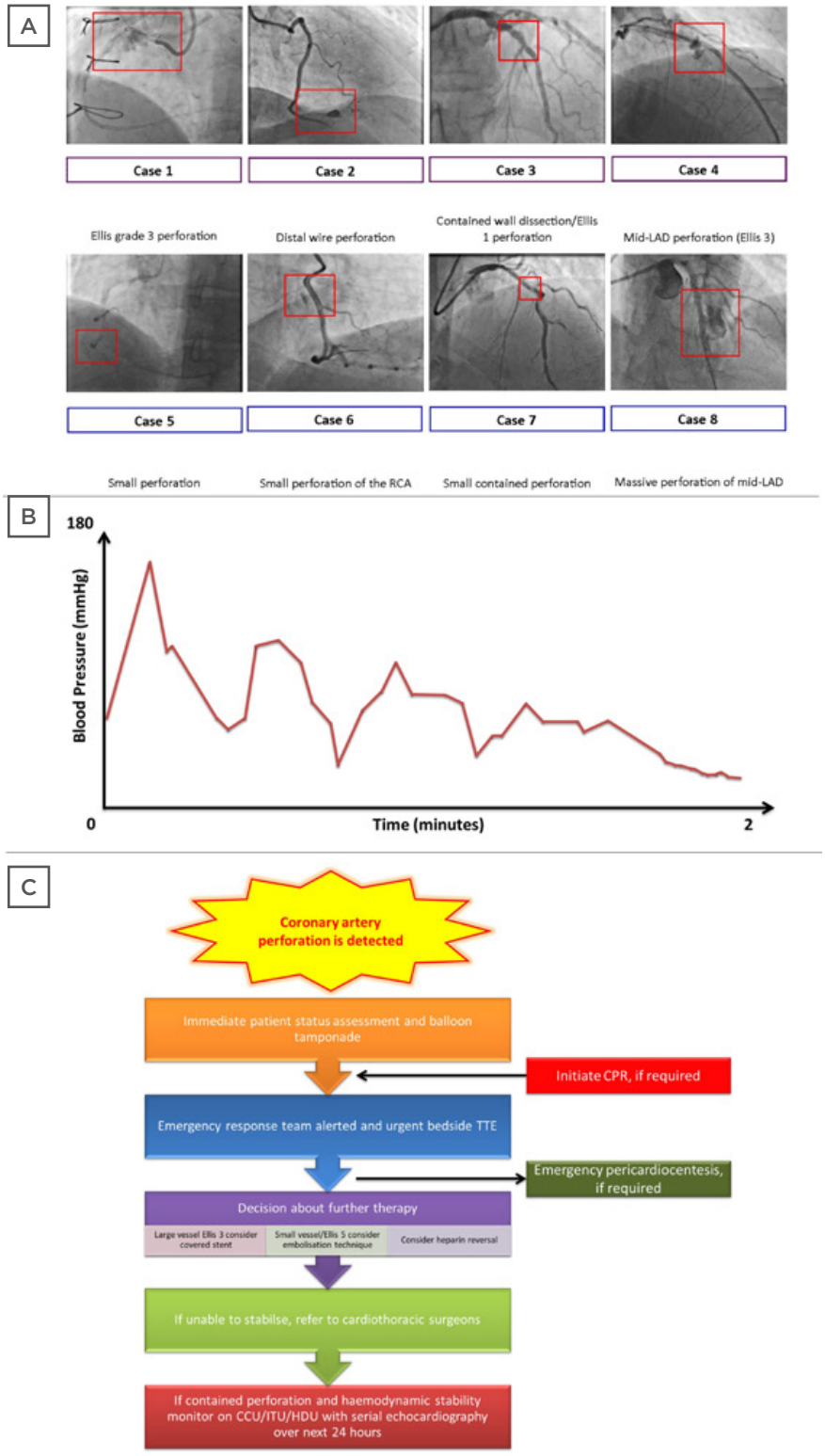

Figure 1: A) Key angiogram findings. Case 1: Ellis Grade 3 perforation; Case 2: distal wire perforation; Case 3: contained wall dissection/Ellis 1 perforation; Case 4: mid-LAD perforation (Ellis 3); Case 5: small perforation; Case 6: perforation; Case 7: small, contained perforation; Case 8: perforation. The red box in each case highlights the site of perforation and is not to scale. In general, a guide catheter of 2 mm (6 Fr) is the reference to guide the size of the vessel/perforation. **B)** Illustrative example of a pressure trace that requires urgent attention given the possibility of coronary artery perforation. **C)** Emergency management of a cardiac tamponade in the cardiac catheterisation laboratory.

CCU: coronary care unit; CPR: cardiopulmonary resuscitation; HDU: high-dependency unit; ITU: intensive treatment unit; LAD: left anterior descending artery; TTE transthoracic echocardiogram.

Case 2

A 72-year-old female attended for elective angiography due to symptoms of stable angina on a background of pre-diabetes, hypertension, and hypercholesterolaemia. Her angiogram had demonstrated a severe proximal RCA stenosis with a mid-vessel occlusion that was treated with 2.75x38.00 mm and 3.00x22.00 mm overlapping DESs, with pre-dilatation and 6 Fr Guidezilla™ support (Boston Scientific, Marlborough, Massachusetts, USA). There was a distal wire perforation (Figure 1A; Case 2) caused by wiring with a Pilot 200 (Abbott Vascular, Santa Clara, California, USA) that was managed conservatively with prolonged balloon inflation. She stayed in hospital for 3 days, with repeat echocardiograms showing a minimal effusion. Three months post-procedure her echocardiogram reported no pericardial effusion.

Case 3

A 77-year-old male with a history of chronic kidney disease, osteoarthritis, deep vein thrombosis, and ulcerative colitis presented with unstable angina-type symptoms. He had severe RCA disease at angiography, which was treated with PCI with an excellent final result but was also noted to have bystander LAD disease. Whilst an inpatient, he developed acute chest pain with new anterior ST-elevation and thus was taken for a repeat angiogram. His LAD was visualised to be severely diseased in the proximal and mid-vessel segments and therefore PCI was performed. His electrocardiogram normalised soon after pre-dilatation. PCI was performed with a 2.75x22.00 mm Resolute Onyx to the mid-vessel and post-dilated with 3.0x15.0 mm non-compliant (NC) balloon. The proximal lesion was significantly calcified but yielded with a 3.0 mm NC. Consequently, he was stented with a 3.0x18.0 mm Resolute Onyx and optimised with 3.0 NC distally and 3.5x9.0 NC proximally. Unfortunately, a contained wall dissection/Ellis 1 perforation (Figure 1A; Case 3) behind the proximal stent was noted (no pericardial effusion on echocardiogram). Repeat angiography with optical coherence tomography confirmed Ellis 1 contained perforation within the stented segment. This was managed conservatively because a covered stent would lead to the loss of a large septal branch and the defect was noted to be healing. Repeat echocardiograms showed no effusion. However, he did require a pacemaker for prolonged pauses captured on cardiac monitoring. He was discharged after 8 days of admission.

Case 4

The fourth case is of a 53-year-old male who presented with angina. He was hypertensive, an ex-smoker, had previously had a left thalamic infarct, and had a very strong family history of coronary artery disease. He presented for elective LAD PCI, given that his previous optical coherence tomography study of the LAD showed proximally a long segment of severe (500 µm) circumferential calcified plaque with a minimal lumen area of 2 cm^2. His LAD was wired with RotaWire Floppy (Boston Scientific), and a 1.75 mm burr was used for rotational atherectomy to his LAD. Post-dilation, there was a mid-LAD perforation (Ellis 3) due to the calcium (Figure 1A; Case 4). This was covered with Papyrus covered stent (BIOTRONIK, Inc., Lake Oswego, Oregon, USA) with no residual extravasation. Post-PCI echocardiography did not show any pericardial effusion. The patient was discharged after 24 hours following observation, and a bedside echocardiogram reported no evidence of an effusion.

Case 5

A 60-year-old male was admitted with severe chest pain with an electrocardiogram showing ST-elevation in the inferior leads on a background of intermittent angina ongoing for 3 weeks prior to this. Angiography showed an ectatic left coronary artery with mild-to-moderate diffuse, calcified atheroma but Thrombolysis in Myocardial Infarction (TIMI) 3 flow, and no occlusion. The RCA was also ectatic and proximally occluded, with appearances of an organised clot and some early collaterals to the distal RCA from the left side (TIMI 0 flow). An attempt to cross the mid-RCA with a Sion Blue wire (Asahi Intecc, Aichi, Japan) and subsequently Pilot 50 (Abbott Vascular) were unsuccessful; however, a Fielder XT-A wire (Asahi Intecc) with fine-cross support succeeded but there was no flow. Sequential ballooning with 1.5 mm and 2.5 mm semi-compliant (SC) balloons did not yield good flow either. Therefore, a 3.0x15.0 mm NC at high pressure was used to balloon, which led to the balloon rupturing

and a small perforation (Figure 1A; Case 5). A balloon tamponade was then performed with the 2.5 mm SC balloon. The patient remained asymptomatic and haemodynamically stable, with an echocardiogram showing a small pericardial effusion. Unfortunately, the patient suffered a retroperitoneal bleed resulting from the removal of a 4 Fr femoral access, which was managed conservatively and remained stable. Flow to the RCA could not be fully established. A cardiovascular MRI showed a sub-endocardial myocardial infarction in the RCA territory, but all segments appeared viable. As such, a multi-disciplinary team discussion suggested treating the patient conservatively.

Case 6

A hypertensive 70-year-old male presented with stable angina symptoms, demonstrated moderate RCA disease, and the derived fractional flow reserve-CT was positive in the proximal and mid-RCA on CT coronary angiography. Thus, he had angiography, which revealed moderate-to-severe RCA disease in the proximal segment. A right coronary 3D guide was used; however, it was not possible to advance a pressure wire beyond the proximal portion. A repeat wiring with Sion Blue showed likely perforation due to the pressure wire, which had a balloon tamponade with 2.0 mm and 2.5 mm SC balloon, then stented with a DES to the proximal to mid-portion (3.0x22.0 mm) and the proximal portion was post-dilated with a 3.5 mm NC balloon.

The perforation (Figure 1A; Case 6) was treated with this and two further covered stents (3.0x15.0 mm) with Guidezilla supports; however, the perforation persisted. The distal portion was covered with a 3.0x26.0 mm covered stent and overlapped the existing stents. Following post-dilation, the perforation ceased. Echocardiogram during and immediately after the procedure showed no pericardial effusion. Further echocardiogram prior to discharge confirmed that there was no cardiac effusion, LV and right ventricle systolic function were normal, and there was no valvular pathology.

Case 7

A 58-year-old male patient with complex coronary anatomy had a CTO of the circumflex artery. He previously had an angioplasty to the LAD and RCA. He represented with troponin-negative chest pain and was found to have severe in-stent restenosis in the LAD at angiography. He had PCI to mid LAD with 2.75x26.0 mm and 2.75x22.00 mm Onyx DES. However, this was complicated by a small, contained perforation (no pericardial effusion) due to LAD dissection and loss of the second diagonal artery (Figure 1A; Case 7).

With significant difficulty and a Guidezilla guide extension, an overlapping stent was placed between his previous proximal and mid-vessel stent with a 2.75x22.00 mm Onyx and optimised with 3.25 mm NC. There was no pericardial effusion on the table and on subsequent repeat echocardiography.

Case 8

The final case is that of another 58-year-old male with hyperlipidaemia, pre-diabetes, and an episode of syncope who was admitted with breathlessness and stable angina. His CT coronary angiography showed a tight lesion in the LAD just after the first diagonal with disease to the mid-LAD (coronary CT fractional flow reserve <0.7). On the table, he had pre-dilation with a 2x20 mm SC balloon, insertion of a 3.5x48.0 mm Synergy DES (Boston Scientific) and post-dilated with a 4 mm NC balloon. However, there was residual non-expansion of the stent at the mid-zone. A repeat dilation with a 4 mm balloon at 18 atm resulted in a perforation (Figure 1A; Case 8).

The balloon was re-inflated, after which a covered stent was inserted. The patient became unstable and required intravenous fluids, atropine, and catecholamines to maintain haemodynamic stability. On the table, echocardiography showed a modest effusion. It was felt that there was a residual leak and, therefore, a second covered stent was inserted. The patient became more haemodynamically unstable and his blood pressure dropped. Repeated attempts at a pericardial drain yielded minimal fluid and one was not inserted. A repeat echocardiogram on the table showed stable effusion. The CT of his abdomen and chest showed a small pericardial effusion. A departmental echo showed pericardial effusion seen against the right ventricular free wall, LV apex, and LV anterolateral wall in subcostal and apical views. Unfortunately, this patient became more unwell later that evening. Repeat angiography showed

a patent LAD. The patient had acute cardiac tamponade and thus a pericardial drain was inserted under fluoroscopic and echo guidance; 180 mL of fluid was drained with immediate normalisation of haemodynamics. There was a significant reduction in the size of the pericardial effusion following the pericardiocentesis procedure, with no significant effusion visible in the images obtained post-procedure. A repeat echocardiogram 4 days later showed normal LV function and a very small pericardial effusion not haemodynamically significant, and thus the patient was discharged.

OUTCOMES

The authors performed a follow-up with this patient set to assess for adverse outcomes, including death or myocardial infarction, with a maximum follow-up period of 12 months. There were no events detected.

TREATMENT APPROACH

Based on the aforementioned cases, the authors highlight the possible treatment approach in the management of CAPs. Predominantly, it is the urgent recognition (by monitoring haemodynamics during a PCI procedure; Figure 1B) of CAP that consequents CAP therapy. Although the Ellis classification is useful in grading perforation severity, treatment cannot be standardised or generalised based purely on the Ellis grade and depends on the response to initial therapy, operator skill, and experience.

In general, the treatment approach for perforation is dependent on the vessel size and location.[2] Universal initial therapy involves balloon inflation proximal to the site of perforation to occlude flow preventing further extravasation, and provides time whilst intravenous anticoagulation is discontinued and clotting is corrected.[2] This relatively conservative approach is often sufficient to manage Ellis Grade 1 and 2 CAPs and distal perforations to regain haemostasis.[2] However, in the majority of cases, this is a temporary measure whilst further therapy can be delivered.

If the site of perforation is an epicardial coronary artery >2 mm in diameter, a covered stent can be deployed to seal the vessel tear.[2,7] However, in their application, covered stents could occlude side branches, which has been known to increase thrombogenicity in some cases.[8-10] Small branch or distal vessel perforations that are unamenable to the insertion of a covered stent can be managed with coils delivered through guide catheters. This approach, though, is limited by the mismatch between the size of the coil and the vessel size.[11] Additionally, clot-forming methodologies of thrombin injection, autologous blood clots, and fat embolisation provide a local and precise sealant for distal perforation.[12-14] A poorly studied technique for sealing CAPs is microspheres, which has the capacity to embolise most vessels owing to their wide range of sizes.[2] This is an area of research interest where further safety and efficacy data is needed to conclusively use microspheres in routine practice, notwithstanding their cost.

These therapies can be either delivered via the guide system in use for balloon tamponade by rapidly deflating the balloon and exchanging for the desired device or alternatively using a 'ping-pong' system. This involves acquiring a second point of access and utilising a second guide catheter and guidewire system with a pre-loaded therapy device that can be rapidly delivered following deflation of the balloon tamponade and withdrawal of the primary device. Confirmation of sealing of the perforation can then be achieved with angiography to decide if further therapy is required.

An urgent bedside echocardiogram should be performed to consider the need for pericardiocentesis (along with clinical state and haemodynamic parameters) in the event of a cardiac tamponade (Figure 1C). Serial echocardiograms over the next few hours are then advised to ensure there is no late accumulation of pericardial effusion from a persisting leak not visualised at angiography, along with close monitoring of the patient in an appropriate setting.

CONCLUSION

Though CAPs are an infrequent complication of PCI, they pose a significant morbidity and mortality for the patient. The incidence of CAP in the authors' population (which included chronic total occlusion as well as acute and elective

cases) was 0.5%, which is in accordance with large contemporary registries, with no documented deaths or emergency surgery within 12 months. The authors have highlighted two key points:

- To consider CAP as a potential complication of all PCI cases, thus ensuring early recognition and subsequent treatment in a timely manner.
- The importance of having an individualised and trust-specific protocol for the management of cardiac tamponade.

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A Case Report on Ischaemic Cardiomyopathy with Severe Left Ventricular Dysfunction

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Abstract

Ischaemic cardiomyopathy is a condition that arises when heart muscle is weakened because of coronary artery disease or a heart attack. Left ventricular (LV) dysfunction occurs when the left ventricle is either defective or damaged, thus disrupting healthy function. Normal LV function can be perturbed because of several causes. Some cardiac defects such as valvular malformations or conditions block the passage of blood into the body. Effective and cost-effective treatment is available for such patients that can reduce both morbidity and mortality. Herein, the authors present the case of a 69-year-old male who was brought to the emergency department with a history of hypertension on medication. Later, the patient was transferred to the cardiology department. The patient was brought to the hospital after midnight and had bleeding gums, and experienced bleeding from the site of needle puncture. Earlier reports showed that the international normalised ratio was >6.0, and the 2D echocardiogram showed large LV blood clots, mild LV dysfunction, mild mitral regurgitation, and aortic valve stenosis. Finally, the patient was diagnosed with ischaemic cardiomyopathy associated with LV dysfunction. During discharge, the patient and patient's representative were counselled in layman's language about the conditions and prognosis of the disease, the use and adherence to medications, lifestyle modifications, and were advised to review back to the cardiologist.

INTRODUCTION

Cardiomyopathy is a group of diseases that affect the heart muscle. Early on, there may be few or no symptoms. As the disease worsens, shortness of breath, feeling tired, and swelling of the legs may occur, due to the onset of heart failure (HF). An irregular heartbeat and fainting may occur.[1] Those affected are at an increased risk of sudden cardiac death.[1]

In 2015, cardiomyopathy and myocarditis affected 2.5 million people.[2] Hypertrophic cardiomyopathy affected approximately one in 500 people while dilated cardiomyopathy affected one in 2,500;[1,3] these conditions resulted in 354,000 deaths, increased from 294,000 in 1990.[2,4]

Types of cardiomyopathy include hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular dysplasia, and Takotsubo cardiomyopathy (broken heart syndrome).[1]

Dilated cardiomyopathy is a condition in which the heart becomes enlarged and cannot pump blood effectively.[1] Symptoms vary from none to feeling tired, leg swelling, and shortness of breath.[1] It may also result in chest pain or fainting.[1] Complications can include HF, valvular heart disease, or an irregular heartbeat.[1]

Approximately one in 2,500 people are affected by cardiomyopathy.[5] It occurs more frequently in males than females.[1] Onset is most often in middle age.[6] The 5-year survival rate is approximately 50%.[5] Although in many cases no cause is apparent, dilated cardiomyopathy is probably the result of damage to the myocardium produced by a variety of toxic, metabolic, or infectious agents.[7] It can also occur in children and is the most common type of cardiomyopathy in this age group.[5] It may be because of fibrous change to the myocardium from a previous myocardial infarction. Or it may be the late sequelae of acute viral myocarditis, such as with Coxsackie B virus and other enteroviruses,[8] possibly mediated through an immunologic mechanism.[7]

Ischaemic cardiomyopathy (ICM) is the most common type of dilated cardiomyopathy. In ICM, the ability of the heart to pump blood is decreased because the heart's main pumping chamber, the left ventricle, is enlarged, dilated, and weak. This is caused by ischaemia: a lack of blood supply to the heart muscle caused by coronary artery disease and heart attacks.

Causes include genetics, alcohol, cocaine, certain toxins, complications of pregnancy, and certain infections.[1,5] Coronary artery disease and high blood pressure may play a role, but are not the primary cause.[6,7] In many cases, the cause remains unclear.[1] It is a type of cardiomyopathy, a group of diseases that primarily affects the heart muscle.[1] The diagnosis may be supported by an ECG, chest X-ray, or echocardiogram.[5]

Symptoms may include shortness of breath; swelling of the legs and feet (oedema); weight gain, cough, and congestion related to fluid retention; dizziness or lightheadedness; fatigue, inability to exercise, or carry out activities as usual; palpitations or fluttering in the chest because of arrhythmia; and fainting caused by irregular heart rhythms and abnormal responses of the blood vessels during exercise. Angina that occurs with exercise, physical activity, rest, or after meals is a less common symptom.[1]

Major risk factors of heart disease, such as family history, high blood pressure, smoking, diabetes, high blood cholesterol, and obesity can also place individuals at increased risk for cardiovascular disease and ICM.

In those with HF, treatment may include medications in the angiotensin-converting enzyme inhibitor, β-blocker, and diuretic families.[5] A low-salt diet may also be helpful.[6] In those with certain types of irregular heartbeat, blood thinners or an implantable cardioverter defibrillator (ICD) may be recommended.[5] If other measures are not effective, a heart transplant may be an option in some.[5]

The progression of HF is associated with left ventricular (LV) remodelling, which manifests as gradual increases in LV end-diastolic and end-systolic volumes, wall thinning, and a change in chamber geometry to a more spherical, less elongated shape. This process is usually associated with a continuous decline in ejection fraction. The concept of cardiac remodelling was initially developed to describe changes that occur in the days and months following myocardial infarction.[9]

CASE REPORT

A 69-year-old male presented to a tertiary care hospital with a large LV clot and on warfarin 5 mg oral anticoagulant, which had induced bleeding. The patient's chief complaints were of bleeding from the gums and bleeding at the site of needle puncture for 1 day. At presentation, patient reports showed an international normalised ratio (INR) >6.0. In addition, 2D echocardiography also detected abnormalities, including a large clot in the LV apex, mild LV dysfunction, mild mitral regurgitation (MR), and aortic valve stenosis. The patient had a history of hypertension and was on medication. His vitals on 4 consecutive days are shown in Table 1.

Personal medical history revealed that the patient was a non-alcoholic and non-smoker, appetite was normal, sleep was adequate, and bowel and bladder functions were regular. The patient did not have any other comorbidities and no significant family history was noted.

Table 1: The patient's vitals on 4 consecutive days.

Vitals	Day 1	Day 2	Day 3	Day 4	Units
Blood pressure	160/70	130/90	110/60	130/60	mmHg
Heart rate	68	90	92	88	Beats/min
Respiratory rate	40	20	22	23	Breaths/min
Cardiovascular system	S1S2+	S1S2+	S1S2+	S1S2+	N/A
Per abdomen	Soft, non-tender	Soft, non-tender	Soft, non-tender	Soft, non-tender	N/A

N/A: not applicable.

Physical examination showed that the patient was conscious, co-operative, and responding properly. The patient was feeling weak, with a blood pressure of 160/70 mmHg on medication.

On cardiac auscultation, there was a regular heartbeat with no murmur heard and a heart rate of 89 beats/min was recorded. Respiratory auscultation revealed symmetrical breath sounds and normal bronchial airway entry with a respiratory rate of 20 breaths/min. The patient's abdomen was soft, regular, and non-tender.

Initial laboratory investigation showed that prothrombin time (PT) and activated partial thromboplastin time were >1 min, and high-sensitivity troponin-I levels were 36 ng/L. Furthermore, 2D colour Doppler echocardiography revealed notable features of the patient's heart muscle structure and function, such as dilated LV; regional wall motion abnormality; hypokinesia of lateral wall, apex, and anteroseptal wall; mild LV dysfunction; mild MR; mild tricuspid regurgitation (TR); moderate aortic regurgitation; mild pulmonary arterial hypertension; and no pulmonary embolism, clot, or vegetations. Electrocardiography revealed sinus bradycardia with first-degree atrioventricular block, left ventricular hypertrophy with repolarisation abnormality, and an abnormal ECG. Other lab investigations such as complete blood picture, lipid profile, liver function test, and serum electrolytes were normal.

The patient was given an intravenous injection of tranexamic acid (40 mg), an injection of pantoprazole (40 mg once daily [qd]), an injection of ondansetron (4 mg twice daily), and an intramuscular qd injection of vitamin K. Furosemide plus amiloride tablets (40 mg qd), digoxin tablets (0.25 mg qd), telmisartan plus hydrochlorothiazide tablets (40 mg/12.5 mg qd), metoprolol succinate tablets (25 mg qd), and rosuvastatin tablets (10 mg nightly) were also administered.

PT and INR were addressed on the day of admission. On Day 2, the patient had no further episodes of bleeding and was advised to continue the same treatment. The patient was also advised to have PT and INR tested daily. On Day 3, the patient had no fresh complaints; he was conscious, coherent, and co-operative, and INR was found to be 3.9. The patient was discharged on the fifth day with the following medications: pantoprazole 40 mg qd; furosemide plus amiloride 40 mg/5 mg qd; digoxin 0.25 mg qd; telmisartan plus hydrochlorothiazide 40 mg/12.5 mg qd; rosuvastatin 10 mg nightly; and metoprolol succinate 25 mg qd.

DISCUSSION

The INR is a calculation based on results of PT and is used to monitor individuals who are being treated with the blood-thinning

medication (anticoagulant) warfarin. The PT and INR are used to monitor the effectiveness of the anticoagulant warfarin.

HF due to ischaemic or dilated cardiomyopathy is associated with a significant increase in the risk of thromboembolism. Unless there are contraindications, anticoagulant treatment is mandatory for patients with HF and atrial fibrillation. HF is an independent risk factor for over-anticoagulation. Therefore, patients with HF should be closely monitored to prevent potential bleeding complications; anticoagulants have to be adjusted accordingly.[10]

Elevated pulmonary arterial pressure has been established as a predictor of death in patients with HF with both ischaemic and non-ischaemic cardiomyopathy.[11]

MR can be found in a sizeable percentage of patients with chronic congestive HF and systolic LV dysfunction despite a structurally normal valve. This functional or secondary regurgitation results from a dysbalance between closing and opening forces on the mitral leaflets because of reduced LV contractility, geometric distortion of the sub-valvular apparatus, and global dilatation of the left ventricle and the mitral annulus. MR in LV dysfunction has a negative impact on both symptoms and prognosis. MR is common and independently predicts mortality in patients with LV systolic dysfunction. Its management remains challenging because of the complexity and variety of potential mechanisms implicated.[12,13]

TR aetiologies are currently divided into primary and secondary TR. Intrinsic abnormalities of the tricuspid valve leading to significant TR (primary) are rare and are seen in approximately 8–10% of patients with severe TR.[14,15] In contrast, secondary TR is the most frequent form of TR requiring surgical intervention. Secondary TR occurs mainly from tricuspid annular dilatation and increased tricuspid leaflet tethering because of right ventricular enlargement, which is often secondary to left HF from myocardial or valvular causes.[16,17]

Aortic stenosis (AS) is one of the most common and serious valve disease problems. AS is a narrowing of the aortic valve opening, which restricts the blood flow from the left ventricle to the aorta and may also affect the pressure in the left atrium. The correlation between the severity of AS and onset of symptoms is poor and depends largely on the hypertrophic response of the left ventricle to the pressure overload.[18]

LV hypertrophy is a compensatory mechanism to restore wall stress and maintain cardiac output under increasing pressure afterload caused by the stenotic valve. However, progressive cardiomyocyte death and consequent fibrosis that accompanies LV hypertrophy may lead to the development of LV dysfunction and HF symptoms. In addition, the frequent association of AS and MR can also complicate the aetiological contributors to HF. However, the coexistence of severe AS, reduced LVEF, and HF is complex and poses diagnostic and clinical decision-making dilemmas.[18,19]

Mitral annulus calcification (MAC) is a chronic, degenerative process of the fibrous support of the mitral valve.[20,21] MAC is usually visualised on echocardiography as an echo-dense, shelf-like structure with an irregular, lumpy appearance involving the mitral valve annulus, with associated acoustic shadowing.[22] MAC generally has little or no impact on LV inflow haemodynamics or mitral valve function.[23] There are limited data suggesting that MAC may exacerbate MR. Patients with MAC have a higher prevalence of atrioventricular block, bundle branch block, intraventricular conduction delay, and atrial fibrillation.[24]

Among patients with HF, first-degree atrioventricular block is present in anywhere between 15% and 51%. Data from cardiac resynchronisation therapy studies have shown that first-degree atrioventricular block is associated with an increased risk of mortality and HF hospitalisation.[25]

Troponin T (TnT) is the best laboratory parameter in the diagnosis of myocardial injury. Because the cytoplasm of cardiomyocytes contains a small amount of free TnT, even small damage to the cell membrane causes their release and the possibility of detection in the blood sample under investigation. Therefore, TnT detected in plasma is a highly specific marker of myocardial injury.[26,27]

DRUG–DRUG INTERACTIONS

Major Interactions

Digoxin and hydrochlorothiazide

Onset is delayed and documentation is excellent. Concurrent use of digitalis glycosides and thiazide diuretics can result in digitalis toxicity (nausea, vomiting, and arrhythmias). It is hypothesised that this is because diuretic-induced hypokalaemia and hypomagnesaemia enhance Na+/K+-ATPase inhibition by cardiac glycosides.

Patients given diuretics with digitalis should be told to add rich sources of potassium to their diet or they should be given potassium supplements, even though their serum potassium level is normal. The use of potassium-sparing diuretics in combination with potassium-depleting diuretics is also a rational approach. Patients may want to include some extra potassium in their diet.

Digoxin and telmisartan

Onset is not specified and documentation is excellent. Concurrent use of digoxin and telmisartan may result in an increased risk of digoxin toxicity (nausea, vomiting, and arrhythmias). The probable mechanism is unknown.

Co-administration of digoxin and telmisartan may increase digoxin plasma concentrations to 50%.[28,29]

Measure digoxin concentrations prior to initiation of concurrent use. Reduce the digoxin dose (by approximately 15–30% for oral) or modify the dosing frequency. Continue monitoring digoxin plasma concentration.[28]

Moderate Interactions

Amiloride hydrochloride and digoxin

Onset is delayed and documentation is fair. Concurrent use of digoxin and amiloride may result in decreased digoxin effectiveness. The probable mechanism is unknown.

Clinical management should focus on monitoring patients for reduced therapeutic effect of digoxin.

Amiloride hydrochloride and telmisartan

Onset is not specified and documentation is fair. Concurrent use of telmisartan and potassium-sparing diuretics may result in an increased risk of hyperkalaemia. The probable mechanism is additive hyperkalaemia.

Hyperkalaemia may occur with concomitant use of potassium-sparing diuretics and telmisartan, with an increased risk of hyperkalaemia in patients with advanced renal impairment, HF, and those receiving renal replacement therapy, potassium supplements, salt substitutes, or other drugs that may increase potassium levels. Periodic electrolyte monitoring should be considered to detect possible electrolyte imbalances.[29]

Digoxin and furosemide

Onset is delayed and documentation is fair. Concurrent use of digoxin and loop diuretics may result in increased risk of digoxin toxicity (nausea, vomiting, and cardiac arrhythmias). This is because potassium and magnesium loss may enhance the effect of digoxin.

Frequent monitoring of potassium and possibly magnesium with appropriate replacement is recommended. Clinicians should educate patients about the importance of maintaining an adequate intake of dietary potassium and potassium supplements.

Digoxin and metoprolol succinate

Onset is not specified and documentation is good. Concurrent use of β-adrenergic blockers and digitalis glycosides may result in increased risk of bradycardia and possible digitalis glycoside toxicity. This is because of the additive effects on atrioventricular node conduction.

Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate, and concurrent use can increase the risk of bradycardia. If these drugs are co-administered, monitor heart rate and PR interval[30] and use with caution.

DRUG–DISEASE INTERACTIONS

Severe Potential Hazard

Ondansetron and QT-interval prolongation

ECG changes including QT interval prolongation have been observed in patients receiving ondansetron. Additionally, there have been some post-marketing reports of Torsade de Pointes cases. The use of ondansetron should be avoided in patients with congenital long QT syndrome. ECG monitoring is recommended in patients with electrolyte abnormalities such as hypokalaemia or hypomagnesaemia; patients with congestive HF or bradyarrhythmia; and patients taking other medicines that could lead to QT prolongation.

Digoxin and preserved left ventricular ejection

Patients with HF associated with preserved LV systolic function, such as in restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale may be particularly susceptible to the toxicity of digoxin. Therapy with digoxin should be considered and administered cautiously in such patients. In hypertrophic cardiomyopathy (idiopathic hypertrophic subaortic stenosis), the inotropic effects of digoxin may worsen the outflow obstruction.

TREATMENT OPTIONS

Medical Therapy

Drug therapy can slow down progression and, in some cases, improve the heart condition. Standard therapy may include salt restriction, angiotensin-converting enzyme inhibitors, diuretics, and β-blockers.[31] Anticoagulants may also be used for antithrombotic therapy. There is some evidence for the benefits of coenzyme Q10 in treating HF.[32-34]

Electrical Treatment

Artificial pacemakers may be used in patients with intraventricular conduction delay and ICD in those at risk of arrhythmia. These forms of treatment have been shown to prevent sudden cardiac death, improve symptoms, and reduce hospitalisation in patients with systolic HF.[35]

Surgical Treatment

In patients with advanced disease who are refractory to medical therapy, heart transplantation may be considered. For these individuals, 1-year survival approaches 90% and over 50% survive for more than 20 years.[35]

CONCLUSION

By considering this case report, patients with HF associated with preserved LV systolic function such as in restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale may be particularly susceptible to the toxicity of digoxin because of the various drug–drug interactions mentioned above. In ICM, the inotropic effects of digoxin may worsen the outflow obstruction. Therapy with digoxin should be considered and administered cautiously in such patients.

Elevated INR to more than 6.0 and bleeding complications occurred after warfarin was added to the patient's regimen. The PT and INR are used to monitor the effectiveness of the anticoagulant warfarin. HF due to ischaemic or dilated cardiomyopathy is associated with a significant increase in the risk of thromboembolism. Unless there are contraindications, anticoagulant treatment is mandatory for patients with HF and atrial fibrillation. HF is an independent risk factor for over-anticoagulation.

Therefore, patients with HF should be closely monitored to prevent potential bleeding complications. And thus, the anticoagulants must be adjusted accordingly. For patients treated with warfarin, healthcare professionals should play a key role in monitoring possible interactions with other drugs, foods, herbs, and dietary supplements.

HF is one of the most damaging clinical outcomes for ICM patients. Heart transplantation is still the main method of long-term treatment, which can convey the protective effect of preventing heart death and improving the survival rate in the later stages of cardiac ICM. ICM causes an imbalance between myocardial oxygen demand and supply, leading to myocyte loss, myocardial scarring, and ventricular failure.

The prevalence of ICM is not completely understood, mainly because of the lack of a standardised and universally acceptable terminology. Clinical management methods are lifestyle modifications, medical therapy, device therapy (ICD or cardiac resynchronisation therapy), revascularisation, and cardiac transplantation.

ICM is a well-recognised disease entity; however, the current classification systems of cardiomyopathy exclude cardiomyopathies secondary to ischaemia. Moreover, research on ICM is extensively fragmented, which has undermined both research consensus and comprehensive understanding.

Therefore, the purpose of the present review is to accumulate research on ICM to produce a comprehensive understanding of its clinical status, diagnosis, clinical management, and ultimately improve survival.

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Hydroxychloroquine- and Azithromycin-Induced Transient Left-Bundle Branch Block in a Patient with COVID-19

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Abstract

Background: COVID-19 has emerged and rapidly spread worldwide due to the high infectivity of the novel coronavirus. A new regimen consisting of a combination of hydroxychloroquine and azithromycin has been under evaluation for efficacy and side effects, especially cardiotoxicity.

Case summary: A 58-year-old man was admitted to the hospital for COVID-19 pneumonia. His initial ECG showed sinus tachycardia. He was started on combination therapy of azithromycin and hydroxychloroquine. After the second dose of hydroxychloroquine and initial dose of azithromycin, his ECG showed complete left-bundle branch block (LBBB). The treatment was stopped, and the patient had no cardiac symptoms. On Day 8 of admission, his repeat ECG showed an absence of LBBB.

Discussion: The cumulative dose of hydroxychloroquine observed in patients treated for malaria or systemic diseases is cardiotoxic, and few cases of LBBB, have been reported. It is, however, not known whether the use of azithromycin in association with a small dose of hydroxychloroquine induces transient LBBB.

INTRODUCTION

Since the emergence of the novel coronavirus (referred to as severe acute respiratory syndrome coronavirus 2 [SARS-Cov-2]) in December 2019 in Wuhan City, China, and up until now, several studies and trials have been conducted to manage infected patients. Over the last few weeks, the focus moved from fear to hope in the form of the recently approved regimen (the

combination of hydroxychloroquine [HCQ] and azithromycin [AZT])[1]. This treatment, however, has its own limitations and cardiac adverse effects including arrhythmias, QT prolongation, and Torsade de Pointes (TdP).[1]

The authors report here the case of a male patient diagnosed with COVID-19 pneumonia, who was started on this regimen and developed transient complete left-bundle branch block (LBBB) as a consequence.

TIMELINE

Day 0: A 58-year-old man was admitted with possible COVID-19 pneumonia.

Day 1: Real-time (RT)-PCR was positive. His baseline ECG showed sinus tachycardia. He was started late that day on HCQ and AZT.

Day 2: He received a second HCQ dose. Repeat ECG showed complete LBBB. Combination therapy was stopped. Daily ECG was performed and LBBB persisted.

Day 8: The ECG reverted spontaneously normal.

CASE PRESENTATION

A 58-year-old man, non-smoker, with a medical history significant for hypertension, who recently came back from Liberia to Lebanon, presented to hospital on 16th April 2020 with a productive cough and pleuritic chest pain. He denied fever or dyspnoea. His symptoms started a couple of days following his return from travel. Upon presentation, he was anxious but clinically stable. His oxygen saturation was 98% on ambient air, his heart rate 95 beats per minute, blood pressure 180/90 mmHg, and had a temperature of 36.1 °C. Chest auscultation was unremarkable; heart sounds were regular without murmurs. He had no peripheral oedema.

A nasopharyngeal swab for RT-PCR COVID-19 was sent the same day of presentation and he was admitted to the COVID-19 unit. Laboratory workup of admission, including a complete blood-cell count, blood urea nitrogen, creatinine, electrolytes, magnesium, liver function tests, and cardiac enzymes were unremarkable. His ECG on admission showed sinus tachycardia with occasional premature ventricular complexes. PR interval was 200 ms, QT 320 ms, QTc 356 ms, by Bazett Formula (Figure 1).

A CT scan of the chest without intravenous contrast administration showed a faint focal ground-glass patch in the posterior segment of the left lower lobe, which was related to early COVID-19 pneumonia. The heart was normal in size. There were no significant abnormalities otherwise.

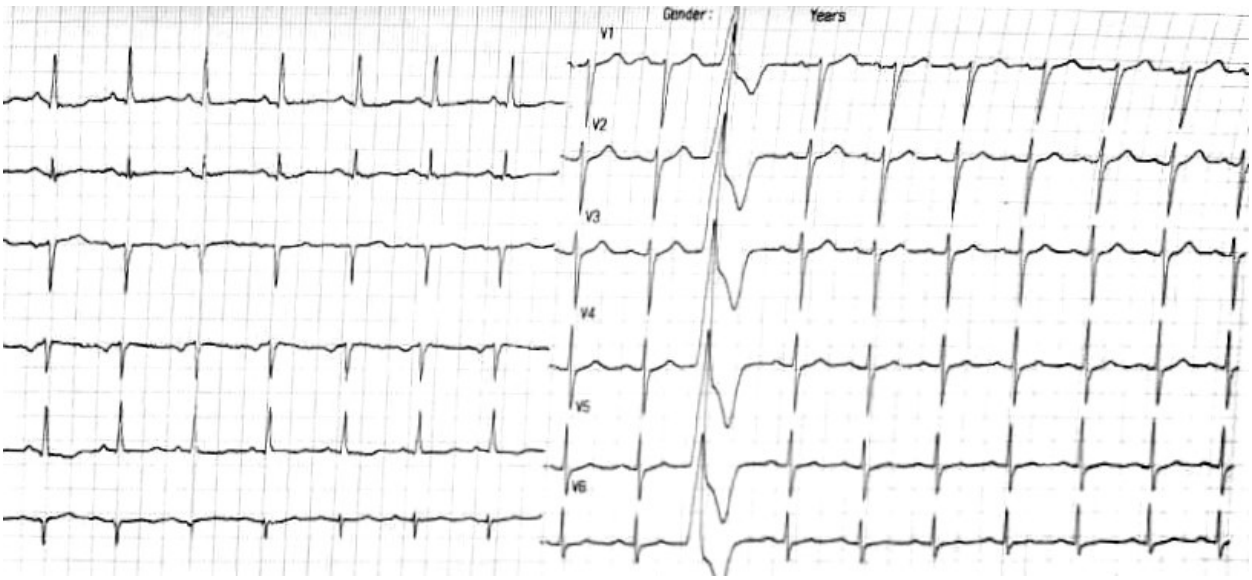

Figure 1: Initial ECG done prior to initiation of hydroxychloroquine and azithromycin.

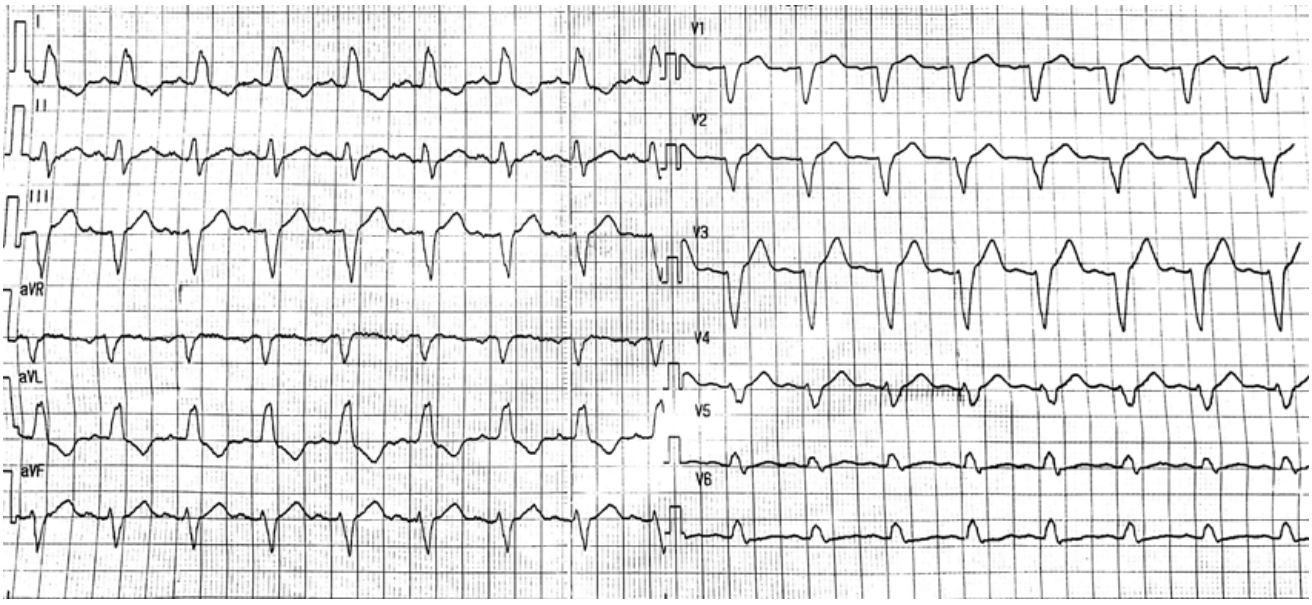

Figure 2: The ECG that was done after second dose of hydroxychloroquine and showed left-bundle branch block.

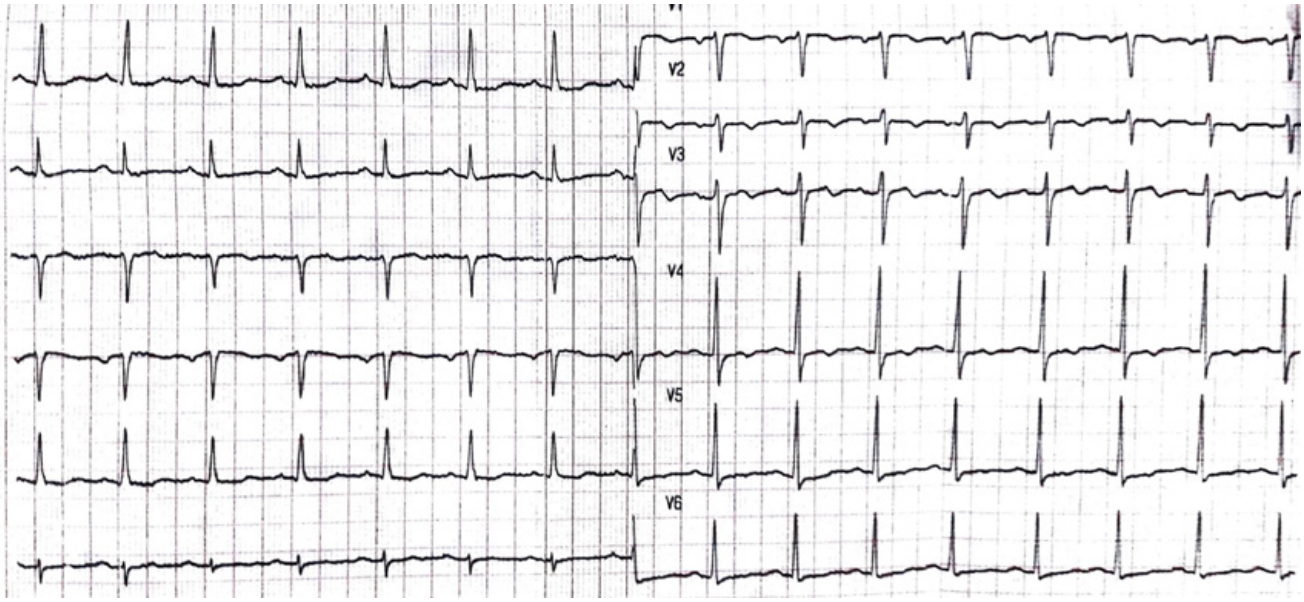

Figure 3: The ECG that was done on Day 6 after stopping the treatment that showed no left-bundle branch block.

The RT-PCR COVID-19 came back positive (cycle threshold: 16.38) and after discussing therapeutic options currently available with the patient, the decision was made to start HCQ 200 mg orally every 8 hours for 10 days in combination with AZT 500 mg orally, once as an initial dose, then to continue 250 mg orally daily for 4 days.

Cardiac clearance was obtained prior to initiation of this regimen as there were no contraindications, no QT prolongation on ECG, no association with other pro-arrhythmic drugs, and no electrolytes or liver function test disturbances. A repeat ECG 2–3 hours after the second dose of HCQ and 12 hours after loading of AZT showed sinus tachycardia and complete LBBB (Figure 2).

The patient remained completely asymptomatic and was clinically and haemodynamically stable, with no signs of fluid overload, jugular venous distension, or peripheral oedema.

Blood workup was repeated, including cardiac enzymes, D-dimers, and pro-brain natriuretic peptide, and was always negative. Arterial blood gas readings were within normal. The regimen was aborted, and the patient was kept on telemetry and symptomatic treatment. Repeat ECG 24 hours after stopping the treatment showed persistent LBBB. During the 5 days following the cessation of the regimen, his daily ECG showed LBBB, and on the Day 6, his ECG reverted to normal without LBBB (Figure 3). A complete transthoracic echocardiography was performed showed no significant findings.

DISCUSSION

HCQ and chloroquine (CQ) have been used to treat malaria infection and connective tissue disorders such as systemic lupus erythematosus. A high incidence of cardiac conduction disorders and atrioventricular block has been observed with CQ.[2] Severe cardiac toxicities were also observed with acute and chronic use of HCQ, such as TdP, QT prolongation, decreased resting heart rate, and refractory ventricular arrhythmias.[3,4] On the other hand, the widely used antibiotic AZT is increasingly recognised as a rare cause of QT prolongation, serious arrhythmias, and increased risk for sudden death, especially in advanced age and the female sex. Interestingly, azithromycin can also provoke non-pause-dependent polymorphic ventricular tachycardia. The U.S. Food and Drug Administration (FDA) perspective supported the observations that AZT administration leaves the patient vulnerable to QTc interval prolongation and TdP.[1]

In December 2019, China reported a cluster of pneumonia cases that were identified as SARS-CoV-2. Patients with COVID-19 frequently present with fever, cough and shortness of breath within 2-14 days of exposure.[5]

Direct myocardial injury occurs via the binding of the virus to angiotensin-converting enzyme 2, a membrane-bound aminopeptidase that is highly expressed in heart, leading to alteration of the angiotensin-converting enzyme 2 signalling pathway.[6] Increased cardiometabolic demand, associated with systemic infection, coupled with hypoxia caused by acute respiratory illness, can impair the myocardial oxygen demand–supply relationship and additionally lead to acute myocardial injury.[7]

HCQ is a cationic, weak amphiphilic base that crosses cell membranes and binds to phospholipids, accumulates in lysosomes, and causes direct inhibition of phospholipases.[8] Immunohistochemistry has revealed the accumulation of the autophagic markers, LC3 and p62, suggesting a potential role of autophagy in the pathophysiology of HCQ-induced cardiomyopathy.[9] The accumulation of these metabolic products leads to the development of cellular hypertrophy of cardiac myocytes and myocardial fibrosis.[8] Ultimately, these changes result in a cardiomyopathy with concentric hypertrophy and restrictive features, along with conduction abnormalities.[8]

AZT is a semi-synthetic macrolide antibiotic thought to prolong the QT interval through a blockade of the rapid component, IKr, of the delayed rectifier potassium current IK, which is encoded by the *human ether-a-go-go-related gene 1* (*hERG1*), leading to intracellular accumulation of potassium and ventricular repolarisation.[10]

Drug–drug interaction may explain a prolonged QT interval. When AZTs are used with other QT-prolonging drugs such as HCQ, they may inhibit CYP enzymes and reduce the metabolism of other drugs by forming an inactive CYP complex.[11]

In an ongoing study on patients included in a single-arm protocol from early March to 16th March, HCQ treatment has been significantly associated with viral load reduction/disappearance in patients with COVID-19 and its effect is reinforced by AZT.[12] Consequently, given their potential risk for arrhythmias and QT prolongation, published data reported the impact of the association of both drugs in treating infected patients, and thereby recommendations to prevent cardiotoxicity.[13]

Transient bundle branch block is defined as an intraventricular conduction defect, that, if only temporarily, subsequently returns to normal conduction.[14] It has been associated with several conditions such as bradycardia, tachycardia, anaesthesia, acute pulmonary

embolism, changes in intrathoracic pressure, chest trauma, cardiac interventional procedures, and other clinical conditions.[14] Apart from coronary artery disease, other causes of LBBB include valvular heart disease, cardiomyopathies (dilated, infiltrative, hypertensive) congenital heart disease, degenerative-conduction heart disease, myocarditis, infective endocarditis, heart trauma/surgery, hyperkalaemia, myxoedema, and systemic sclerosis.[14]

The authors' patient was known to be previously hypertensive, is 58-years old, and had no previously known history of heart failure or myocardial infarction. He was not septic, off diuretics, and had normal QTc on baseline ECG and normal electrolytes. His Tisdale Score was 3. Therefore, he had no contraindications for receiving the regimen.

In a study on 85 unselected outpatients (79 females and 6 males) routinely followed up for 1 year after January 2003, all treated with HCQ for lupus erythematosus, only one patient developed complete LBBB.[2] The authors' patient had no associated signs or symptoms of myocardial infarction or new onset of heart failure, given his clinical and haemodynamic stability and the normal series of blood biomarkers. His vital signs remained stable without change in heart rate throughout his stay. His ECG findings including left ventricular function, regional wall motions, valves, and pressures were all within normal.

Although acute ECG changes such as T-wave inversion occur in response to administration of CQ/HCQ, major conduction abnormalities in the acute setting are much less common than chronic CQ toxicity.

Nevertheless, while all biomarkers and ECG were normal, one cannot exclude a low-level myocarditis, which could be present in the absence of any positive biomarkers. Cardiac MRI was not available for confirmation as myocarditis might have been picked up as a hyperintense signal on T2-weighted images, suggestive of myocardial oedema without significant fibrosis. Hence, one cannot fully exclude COVID-19 myocarditis, which might also show a similar time course. Because of that limitation, one cannot ascribe the ECG changes to the drugs with 100% certainty.

In conclusion, it is known that the chronic use of HCQ, when previously prescribed for malaria or lupus, is associated with an increase in cardiac toxicity, cardiomyopathies, and arrhythmia, secondary to its cumulative effect, and especially when combined with another cardiotoxic agent. However, new-onset LBBB after only the second dose of HCQ is interestingly debatable, especially when this drug is associated with another arrhythmogenic agent such as AZT.

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COVID-19 Infection and Myocardial Infarction Pathophysiology and Therapy

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Abstract

The relationship between COVID-19 and cardiovascular disease has been of interest since the beginning of the pandemic, with the focus more recently shifting towards thrombotic complications, including myocardial infarction (MI). While the inflammatory burden of infection has previously been implicated in the pathogenesis of MI, at least early in the pandemic, many hospitals were seeing fewer ST-elevation MI admissions and the delivery of acute coronary syndrome care was disrupted in multiple ways. Furthermore, patients presenting with both COVID-19 infection and MI have been noted in small studies to have unique characteristics that pose clinical challenges, and there is reason to believe that standard therapy for both the prevention and treatment of all thrombotic events, including MI, may not be adequate. The aim of this article is to review the data regarding MI and other thrombotic events during the pandemic, to explore the link between inflammation and thrombosis, and to suggest possible novel therapeutic options for the treatment and prevention of thrombosis in patients with COVID-19.

INTRODUCTION

There have been a number of concerns from the early stages of the COVID-19 pandemic regarding its implications in cardiovascular disease. Early on in the pandemic, standard acute coronary syndrome (ACS) care had been disrupted in several ways, and of particular interest in the recent literature was the relationship of COVID-19 to coronary artery disease and acute myocardial infarction (MI). This paper reviews the pandemic's effects on ACS care; discusses the overlapping pathophysiology between COVID-19 infection, MI, and mimics of MI; and explores potential therapeutic strategies for treating and preventing thrombotic complications in patients with COVID-19.

The interplay between infection and MI has been previously well-described, namely in the setting of influenza and bacterial pneumonias.[1] The prothrombotic and procoagulant state that is associated with acute infection further increases the risk of thrombosis, and this phenomenon has indeed been noted in the setting of advanced COVID-19 infection. A retrospective study of >3,000 hospitalised patients with COVID-19 in New York City, New York, USA, found an incidence of ≥1 thrombotic event in 16% of patients, most of whom were on prophylactic-dose anticoagulation (6.2% had venous thromboembolism and 11.1% had arterial,

with 1.6% of those being ischaemic stroke and 8.9% being MI);[2] however, the definition of MI was not specified in that report. Likewise, in a large registry from Boston, Massachusetts, USA, of >1,100 patients with COVID-19, arterial and venous thromboembolism occurred with high frequency in patients in the intensive care unit (ICU) (35.3%), despite a high utilisation of thromboprophylaxis (>85%). Symptomatic venous thromboembolism accounted for 27% of these events in the ICU. MI occurred in 7.7%, all of which were non-ST-elevation MI (NSTEMI) and possibly all Type 2. In hospitalised, non-ICU patients, the incidence of arterial and venous thromboembolism was 2.6%.[3]

TRENDS IN MYOCARDIAL INFARCTION DURING THE PANDEMIC

As COVID-19 spread across the world, disturbing trends were noted early on in ST-elevation MI (STEMI) presentations and outcomes in some hospitals, and many oddities were noted in patients presenting with STEMI.

Reductions in STEMI Incidence

It is presently unclear whether STEMI is increased due to COVID-19 infection. To the contrary, some data have shown a reduction in STEMI presentations during the first months of the pandemic. Data compiled from 1,372 chest pain centres in China found a 26% reduction in STEMI presentations after the China Chest Pain Center's modified STEMI protocol was introduced on 23rd January 2020 (that protocol being one that prioritised thrombolysis over primary percutaneous coronary intervention [PCI]).[4] A similar trend was seen in some Italian and North American centres when COVID-19 was surging in those areas.[5,6]

Presentation and Treatment Delays

Along with this apparent decrease, delays in ACS care were frequently noted in registry data. From China, there was a numerical but insignificant increase in symptom-to-first-medical-contact time during the initial COVID-19 surge across their chest pain centre network of approximately 1 hour, on average.[4] In Italy, the time from symptom onset to coronary angiography increased by 39.2% during the COVID-19 surge.[5] Data from 75 hospitals in Spain noted similar findings.[7]

Worsening Outcomes

These trends are very concerning given the increased morbidity and mortality associated with STEMI treatment delays, and observational data have indeed noted increases in both during the pandemic. In China, in-hospital mortality increased from 4.6% to 7.3% and in-hospital heart failure increased from 14.2% to 18.4% during the outbreak period.[4] In Italy, STEMI case fatality rates were more dramatically increased, at 13.7% versus the 4.1% registered in 2019, and major complications were registered in 18.8% of cases in 2020 versus 10.4% in 2019. About 10% of patients in that registry were COVID-19-positive, and the case fatality rate among COVID-19-positive STEMIs was substantially higher (28.6%) compared with all other STEMI patients registered during the same week in 2020 (11.9%).[5] In the USA, the Providence St. Joseph Health system noted an observed-to-expected mortality ratio of 1.96 for patients with STEMI during the early stages of the pandemic.[8]

Increased Incidence of Out-of-Hospital Cardiac Arrest

The aforementioned observations beg the question: where have the STEMIs gone? It seems unlikely that MIs dramatically decreased during the pandemic, and various explanations have been offered, including patient avoidance of healthcare settings and misdiagnosis by providers in a time of crisis. Given the perceived hesitation of patients to present to healthcare settings during the pandemic, there is a deadlier possibility for this decrease. Delaying presentation with STEMI might increase out-of-hospital cardiac arrest due to unstable ventricular dysrhythmias. Global trends in out-of-hospital cardiac arrest support this hypothesis, with Italy seeing a 58% increase during their surge[9] and New York seeing a 5-fold increase. Furthermore, the proportion of those found dead on scene doubled compared to the same time period in 2019.[10]

It is presently unclear to what extent these aberrations in ACS presentations and care persist as the pandemic continues unabated and how the recent surges in COVID-19 infections seen worldwide will subsequently affect admission rates. Furthermore, it also remains unknown how pervasive these aberrations existed worldwide, even during the first months of the pandemic,

as articles showing abnormalities were more likely published. However, a recent retrospective registry from 77 European centres assessing STEMI admissions early in the pandemic noted significant reductions in only 39% of centres, which was unrelated to COVID-19 incidence.[11]

STEMI IN PATIENTS WITH COVID-19 INFECTION

Absence of Culprit Lesions

STEMI care during the pandemic was further complicated by the phenomenon of STEMI mimics identified in small studies. An early registry from Italy of 28 patients with COVID-19, all of whom met guideline definitions of STEMI at presentation, underwent coronary angiography, with 11/28 found to not have a culprit lesion. Seven of these 11 had regional wall motion abnormalities on echocardiography. In patients without a culprit lesion, the investigators were unable to determine the aetiology of their clinical presentation.[12]

In another series from New York of 18 patients with COVID-19 who had ST-segment elevation (only one-third with a documented complaint of chest pain), a total of nine patients (50%) underwent coronary angiography and only six of these patients (67%) were noted to have obstructive disease.[13] Since this publication, it has become apparent that myocarditis, cytokine-mediated myocardial injury, stress-induced cardiomyopathy, pulmonary embolism, and microvascular thrombosis are all clinical possibilities in patients with COVID-19 presenting with ischaemic symptoms and ST-elevations on ECG, with numerous case reports and series detailing cardiovascular magnetic resonance and autopsy findings of patients with similar presentations.[14,15]

There are differing opinions in the available literature regarding the incidence of myocarditis in patients with COVID-19. While there are a number of reports detailing cardiac MRI findings of late gadolinium enhancement suggestive of myocarditis,[16] pathology data thus far have not suggested that viral infiltration of the myocardium is associated with myocyte necrosis and therefore have not corroborated these imaging findings.[17,18] Rather than myocarditis as the primary entity, pathologic findings indicated microvascular thrombosis with resulting focal myocyte necrosis, which might explain the MRI findings.[18] A list of the potential causes of MI and ACS-like presentations (with reference to the fourth universal definition of MI) in patients who tested positive for COVID-19 is contained in Figure 1.[19]

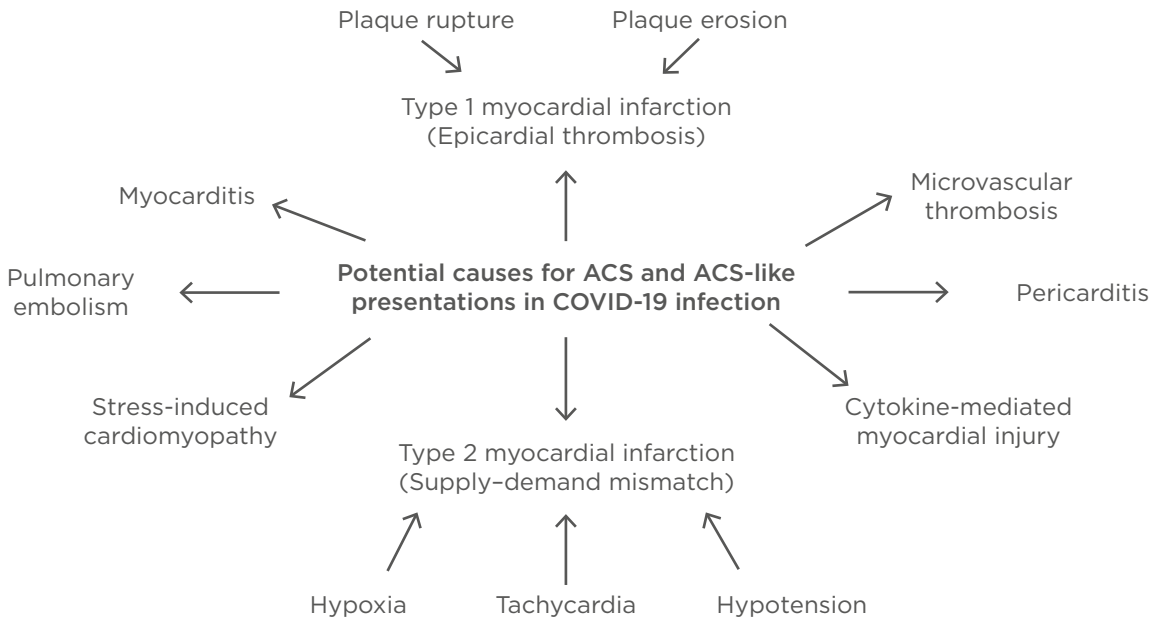

Figure 1: Potential causes for acute coronary syndrome and acute coronary syndrome-like presentations in COVID-19 infection.

ACS: acute coronary syndrome.

Unique Features of Culprit Lesions

In patients with COVID-19 and STEMI with confirmed obstructive disease, Choudry et al.[20] assessed angiographic characteristics of patients who tested positive for COVID-19 versus patients who tested negative for COVID-19 during the same time period. This was a single-centre, observational study of 115 consecutive patients, and 39 (33.9%) were diagnosed with concurrent COVID-19 infection. In those who were COVID-19 positive, there were significantly higher rates of multi-vessel thrombosis, stent thrombosis, and a higher thrombus burden with consequently higher use of GP IIb/IIIa inhibitors and thrombus aspiration versus COVID-19-negative STEMIs. Higher heparin doses to achieve therapeutic activated clotting times were also noted, and myocardial blush grade and left ventricular function were significantly lower with higher in-hospital mortality.[20] These observations support the hypothesis that COVID-19 may increase arterial thrombosis in epicardial coronary vessels and, with STEMI, a thrombotic burden that might be challenging to overcome with current therapies.

COVID-19 INFECTION, NSTEMI, MYOCARDIAL INFARCTION TYPES 1 AND 2, AND MYOCARDIAL INJURY

Data regarding COVID-19 and Type 1 NSTEMI are more difficult to dissect given the overlap with Type 2 MI and myocardial injury alone without MI. As in STEMI, it is unknown if NSTEMI (Types 1 and 2) occurrence is increased with COVID-19 infection or if its incidence is greater than that seen with other viruses. Myocardial injury (elevated troponin levels) is common in patients with COVID-19, with increasing frequency noted with increased disease severity, and up to 100% prevalence in small studies of those critically ill.[21] Non-COVID-19 studies have demonstrated that myocardial injury is more likely to occur in critically ill, older patients and in those with comorbidities,[20] with similar data reported in those infected with COVID-19.[21] Furthermore, myocardial injury with concomitant echocardiographic abnormalities including left ventricular, right ventricular, and pericardial abnormalities portended a poorer prognosis than elevated troponin levels alone, suggesting echocardiography as a potential prognostic tool in evaluating the significance of myocardial injury in patients with COVID-19.[22]

The responses to acute infection, including the release of cytokines and catecholamines, as well as hypoxia, acidosis, tachycardia, and/or hypotension, are associated with Type 2 NSTEMI. While there appears to be a large proportion of patients with COVID-19 presenting with acute myocardial injury, NSTEMI rates have mirrored STEMI in their decline during the pandemic,[5-7] raising the question of how many NSTEMIs (particularly Type 2 MIs) are being labelled as troponin elevation only (acute myocardial injury). Unfortunately, the criteria for diagnosis of Type 2 MI are not specific and are variably interpreted, even in the absence of infection, making any Type 2 data difficult to interpret.[23]

PATHOGENESIS OF THROMBOSIS IN THE SETTING OF COVID-19 INFECTION

The interplay between endothelial injury, inflammation, and thrombosis has been long-recognised, and COVID-19 infection is implicated in these processes. Increases in proinflammatory cytokines such as IL-1 and TNF-α lead to an imbalance that promotes thrombosis in various vascular beds. An amplification loop in cytokine production (cytokine storm) promotes a prothrombotic milieu potentially leading to venous, microvascular, as well as large-vessel thrombosis causing MI and stroke. The endothelial cell lining of all vascular beds is a prime target of the virus, and viral penetration into the endothelium along with proinflammatory cytokines and other molecules change the normally protective antithrombotic, anti-inflammatory, vasodilatory endothelium into an altered proinflammatory, prothrombotic, and vasoconstrictor substrate.[24-26] Certain conditions such as diabetes, obesity, and the metabolic syndrome can further potentiate these processes, and the presence of angiotensin-converting enzyme 2 receptors on adipose tissue may provide additional reason for poorer prognosis in patients with these conditions.[27,28] In patients with underlying coronary artery disease, the proinflammatory, prothrombotic milieu of COVID-19 infection may promote destabilisation of lipid-rich plaques leading to rupture and thrombus, the usual substrate for

STEMI. Acute phase reactants such as fibrinogen, plasminogen activator inhibitor-1, and C-reactive protein potentiate this prothrombotic and proinflammatory state and serve as biomarkers of inflammation in COVID-19 infections.

This prothrombotic milieu is also associated with the observation that the fibrin degradation product D-dimer appears to be a strong prognostic marker associated with high mortality in patients with COVID-19, with an early study from China noting that D-dimer level of >2.14 mg/L predicted in-hospital mortality with a sensitivity of 88.2% and specificity of 71.3% in a series of 250 patients.[29] More recent observational studies of larger patient populations have also noted the strength of this association, further suggesting that D-dimer serves as a reliable marker of prognosis.[30] In the observational data from New York that found high thrombosis rates in patients hospitalised with COVID-19, all-cause mortality was notably higher in those with thrombotic events, at 43.2% versus 21.0% without thrombosis.[2]

Disseminated intravascular coagulopathy (DIC) or a DIC-like picture is common in patients critically ill and dying from COVID-19.[31] However, in the latter, it is hypothesised that some patients develop organ failure caused by thrombi in micro-vessels with some features of DIC. Unlike classic DIC, however, there are findings of elevated fibrinogen levels, only moderately low platelets, and little evidence of a bleeding diathesis. This picture is more consistent with an immune-triggered, complement-mediated thrombotic microangiopathy,[32] which would require different therapies than classic DIC. As alluded to earlier, pathology data also noted that microvascular thrombi found at autopsy in patients who died of COVID-19 infection contained higher concentrations of fibrin and complement components than in COVID-19-negative controls.[18] This phenomenon of fibrin-rich microvascular thrombi may be an example of this thrombotic microangiopathy and could also contribute to elevated D-dimer levels in patients critically ill with COVID-19 without evidence of large-vessel thrombosis. These microvascular thrombi might also explain the patchy late gadolinium enhancement found on cardiac MRI.

POTENTIAL THERAPEUTIC APPROACHES

Given the mortality associated with thrombotic complications, preventing and treating inflammation-driven thrombosis is paramount. The remainder of this paper discusses potential therapeutic approaches that warrant further investigation.

Patients with COVID-19 Presenting with Acute Coronary Syndrome

Controversy remains surrounding ACS care since the pandemic onset, starting with the Chinese Chest Pain Center network prioritising thrombolysis in STEMI as the preferred treatment strategy. However, morbidity and mortality increased in patients with STEMI after protocol introduction.[4]

The joint statement of the Society for Cardiovascular Angiography and Interventions (SCAI), American College of Cardiology (ACC), and American College of Emergency Physicians (ACEP) stressed that primary PCI is still the standard reperfusion strategy in patients with STEMI with suspected COVID-19 infection, particularly in those with high-risk features. Their algorithm allows for bedside echocardiography to confirm regional wall motion abnormalities prior to cardiac catheterisation laboratory activation, especially if there are equivocal features in presentation.[33] Coronary CT may be preferable initially to invasive angiography in equivocal cases to limit hospital staff exposure.[34] In cases of patients with suspected COVID-19 and STEMI presenting to non-PCI centres with low likelihood of immediate transfer for PCI, thrombolytic therapy could be considered as long as high-risk features are absent.[35] However, as noted earlier, some COVID-positive STEMI-like presentations, even with regional wall motion abnormalities on echocardiography, do not have angiographic culprit lesions. This calls into question the utility of thrombolytic therapy even with prior echocardiography. A proposed approach is outlined in Figure 2.

New recommendations for pharmacotherapy in patients with COVID-19 and STEMI have not been made. Patients with COVID-19 and STEMI are unique and may have a large thrombotic burden and worse outcomes.[12,20] Is standard dual

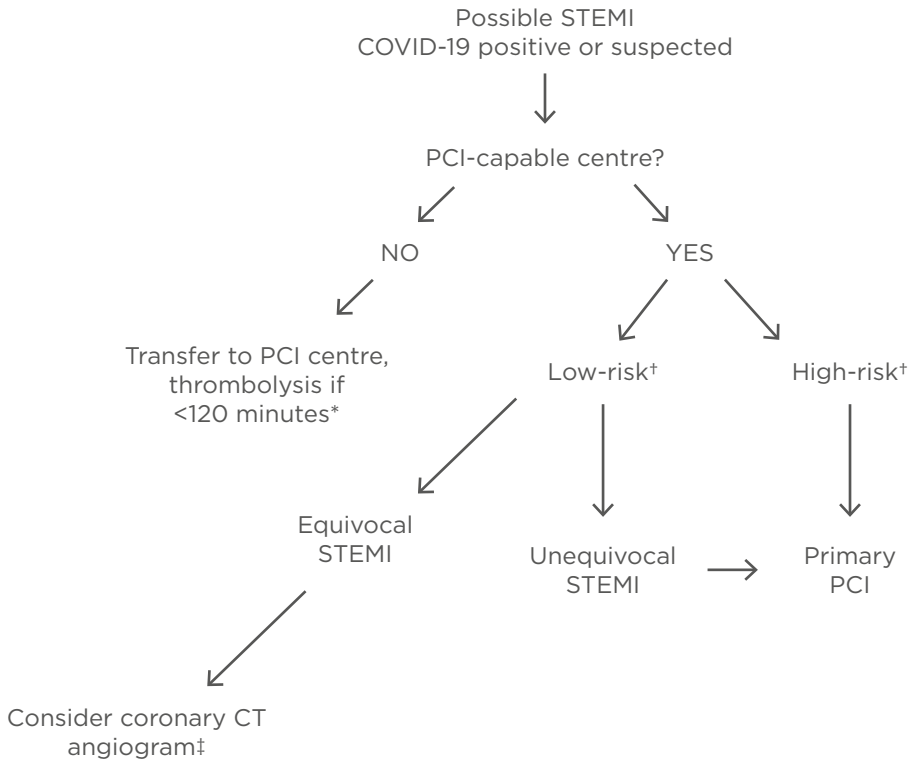

Figure 2: Potential ST-elevation myocardial infarction treatment algorithm.

*Time from presentation at non-PCI hospital to estimated balloon time at PCI centre. Thrombolytic therapy to be administered only if unequivocal STEMI.
†Risk assessment per Killip class, infarct-related artery, presence or absence of haemodynamic or electrical instability, timing of presentation.
‡To define presence of infarct-related lesion amenable to PCI.
PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction.

antiplatelet therapy and systemic anticoagulation enough? This approach may need to be tailored, especially in those critically ill with seemingly insurmountable inflammation-born thrombosis. Higher doses of heparin were required in the London, UK, registry to achieve therapeutic activated clotting times.[20] Given the outcomes for those in the COVID-19 STEMI group, as noted previously, a more aggressive pharmacotherapy may be warranted; however, at the present time, the optimal approach remains unclear.

What about COVID-19 patients with STEMI/NSTEMI-like presentations without culprit lesions? The differential includes stress-induced cardiomyopathy, pulmonary embolism, microvascular thrombosis, and myocarditis. In NSTEMI, the current recommendation is for early/urgent angiography only with high-risk clinical features, haemodynamic instability, or a Global Registry of Acute Coronary Events (GRACE) score exceeding 140.[33] NSTEMI care in patients who test positive for COVID-19 is confounded by observer variability regarding the diagnosis of Type 1 versus Type 2 NSTEMI or myocardial injury. Therefore, astute clinical diagnosis is needed prior to committing to a treatment plan. It appears that most NSTEMI are Type 2, which appears similar to what is found in patients who are seriously ill without COVID-19 in an ICU setting and is usually managed by treating the underlying condition.

Preventing Thrombosis in COVID-19 Infection

Can thrombotic complications in advanced COVID-19 infection be prevented, and who should receive these additional therapies? Breakthrough thrombotic events are common in patients hospitalised with COVID-19 who are receiving prophylactic anticoagulation, and are associated with poorer outcomes as mentioned earlier. A mortality benefit in patients receiving full-dose

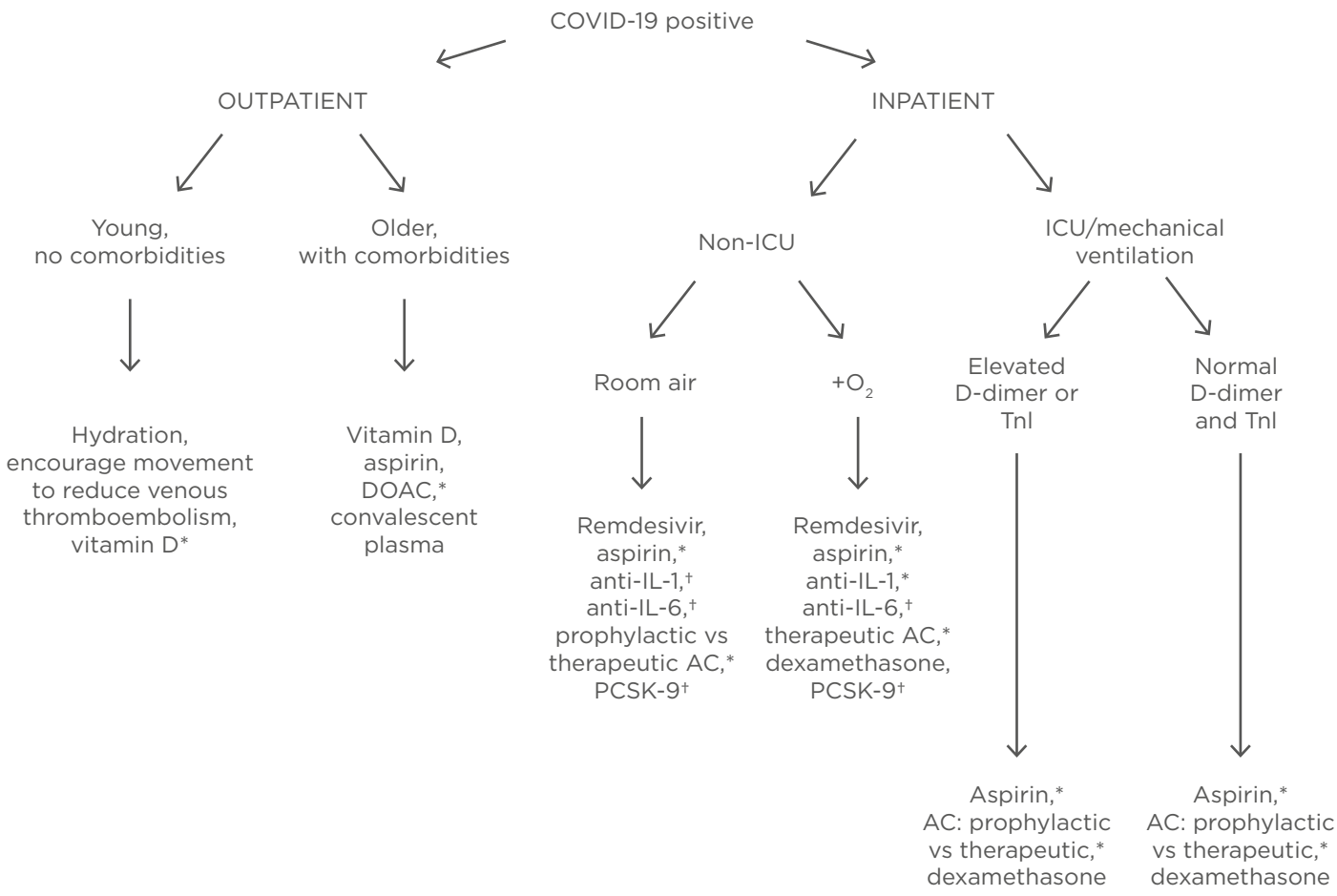

Figure 3: Potential thrombosis prevention algorithm.
*Potential options, pending outcomes of ongoing randomised controlled trials.
†Hypothesised therapies warranting further investigation.
AC: anticoagulation; DOAC: direct oral anticoagulants; ICU: intensive care unit; PCSK-9: proprotein convertase subtilisin/kexin type 9; TnI: troponin; vs: versus.

anticoagulation was noted by a retrospective observational study of 2,773 hospitalised patients with COVID-19.[36] In those requiring mechanical ventilation, there was a significant mortality benefit with full-dose anticoagulation, with an in-hospital mortality of 29.1% versus 62.7% in those not receiving treatment-dose anticoagulation, suggesting that thrombotic phenomena are more likely to occur with advanced illness. Bleeding rates were naturally increased in the anticoagulation group. These observational data suggested that an approach of increased anticoagulation dosing with increased disease severity may be reasonable, but more data are needed.

Since initial publication, three collaborative randomised controlled trials investigating anticoagulation in patients hospitalised with COVID-19 (REMAP-CAP, ACTIV-4, and ATTACC) have halted enrolment of critically ill patients, as full-dose anticoagulation appeared to be futile in these patients and heightened bleeding complications. However, preliminary, unpublished data thus far have reportedly found benefits in moderately ill hospitalised patients, suggesting early initiation of therapy may be of importance.[37] Other questions currently being explored are the utility of anticoagulation after discharge from the ICU, and whether oral anticoagulants at reduced doses have a role in patients with moderate illness severity.

What about patients with COVID-19 who have not been admitted to the hospital? As their symptoms are mild, do they need additional

therapies to reduce thrombotic events? In the Boston study quoted earlier,[3] there were no arterial or venous thromboembolic events in the 715 non-hospitalised patients. However, this was a younger population with fewer risk factors than those hospitalised. It is presently unknown whether some older patients not hospitalised with more comorbidities require a more aggressive antithrombotic strategy and, at the present time, no randomised data regarding this question have been published.

Beyond anticoagulation, can the current understanding of pharmacotherapy for the prevention and treatment of thrombotic events, including STEMI or Type 1 NSTEMI, be applied to mitigate these effects in severe COVID-19 infection? Inflammation can beget local thrombosis, and thrombosis can amplify inflammation.[25] Is there a role for the prophylactic use of aspirin, an agent with both anti-inflammatory and antithrombotic properties? Aspirin therapy in the setting of sepsis and acute respiratory distress syndrome has suggested a mortality benefit in observational studies.[38] Several outpatient COVID-19-positive trials are presently underway, such as the PEAC trial and the LEAD COVID-19 trial, as well as an inpatient study lead by the RECOVERY group. However, no results of these studies are presently available.

Statins have been of interest given their pleiotropic effects, with initial reports suggesting lower mortality in patients with COVID-19 on statin therapy. However, these were observational reports with a likely selection bias for non-critically ill patients. Although statin use may decrease cytokine production in the setting of sepsis,[39] previous trials and meta analyses in sepsis and ventilator-associated pneumonias have not shown a mortality benefit.[40,41] Proprotein convertase subtilisin/kexin type 9 inhibitors are also of potential interest (no randomised data as of yet) given that experimental models have suggested that their effects are not limited to only lowering cholesterol (which itself may confer protection against viral entry in human cells), but also can improve endothelial function, reduce oxidative stress and platelet adhesion, increase stability of atherosclerotic plaques, and increase interferon-β production.[42]

IL-1 inhibition with anakinra has been investigated in two small European studies,[43,44] with findings of less frequent need for ICU transfer, decreased inflammatory markers, and improved mortality. Thrombotic outcomes were, however, not reported in these studies, and bacteraemia was predictably higher in those receiving immunosuppressive therapy. Tocilizumab, an IL-6 inhibitor, has recently been investigated in patients hospitalised with COVID-19. While no mortality benefit was noted in a randomised trial, subgroup analysis of non-critically ill patients initiated on this therapy were less frequently transferred to the ICU level of care than those in the placebo group, suggesting a possible benefit if initiated in the setting of non-severe illness.[45]

Colchicine is readily available, inexpensive, and has potent anti-inflammatory effects, with an already promising role in the treatment of coronary artery disease.[46] A randomised and currently unpublished trial investigating the role for low-dose colchicine in treating COVID-19 infection reportedly did not suggest a significant clinical benefit in non-hospitalised patients,[47] and the RECOVERY trial halted randomisation of inpatients to colchicine therapy due to an apparent lack of efficacy.

Dexamethasone therapy has become standard therapy in COVID-19 infection as it has demonstrated mortality benefit in patients requiring supplemental oxygen. However, the early results of the dexamethasone trial have not, as of yet, reported the incidence of thrombosis or markers of inflammation and thrombosis,[48] and prior data on glucocorticoid administration and thrombosis are conflicting. Steroid administration has been implicated in thromboembolic events,[49] yet, in inflammatory states, steroid administration reduces fibrinogen and von Willebrand factor, and increases plasminogen activator inhibitor-1.[50] As decreasing the inflammatory burden of COVID-19 infection should decrease thrombotic complications and thrombotic events, this should be assessed in the thousands now receiving dexamethasone.

Vitamin D deficiency has been associated with venous thrombosis and MI, and approximately 60% of Americans are deficient.[51] However, the strength and mechanism of this association remains vague. In patients who are non-obese and vitamin D deficient without cardiovascular disease, supplementation with high-dose calcifediol reduced *in vitro* thrombin generation

and clot density.[52] A Spanish study randomised patients admitted with COVID-19 infection to high-dose calcifediol plus standard care versus standard care alone and found a significant reduction in the need for ICU care with calcifediol.[53] However, at this time, data are mostly observational and uncontrolled. It remains unclear if vitamin D supplementation in COVID-19 could potentially reduce thrombotic complications such as MI. See Figure 3 for a proposed algorithm for the prevention of thrombosis in COVID-19 infection.

CONCLUSIONS

COVID-19 infection can result in thrombosis in various vascular beds. While most thrombotic events are venous in origin, MI is one of its manifestations and can manifest as STEMI or NSTEMI. While it is presently unclear if MIs related to thrombotic events in the epicardial coronary arteries are necessarily increased with COVID-19 infection, troponin elevations are common. The astute clinician must diagnose with all the available information whether the clinical syndrome represents either STEMI, NSTEMI Type 1, Type 2 MI, acute myocardial injury, one of the other MI mimics, or pulmonary embolism, and treat accordingly.

The authors believe that a bigger challenge is in the prevention of thrombotic complications in COVID-19 infection. While this paper has reviewed the data and offered some suggestions, further study is required; the data are rapidly evolving, with multiple new studies published weekly. Ongoing and future randomised trials or registries should provide important answers to some of these questions that could hopefully improve future outcomes. The ultimate solution to thrombosis is, of course, effective vaccines to prevent COVID-19 infection.

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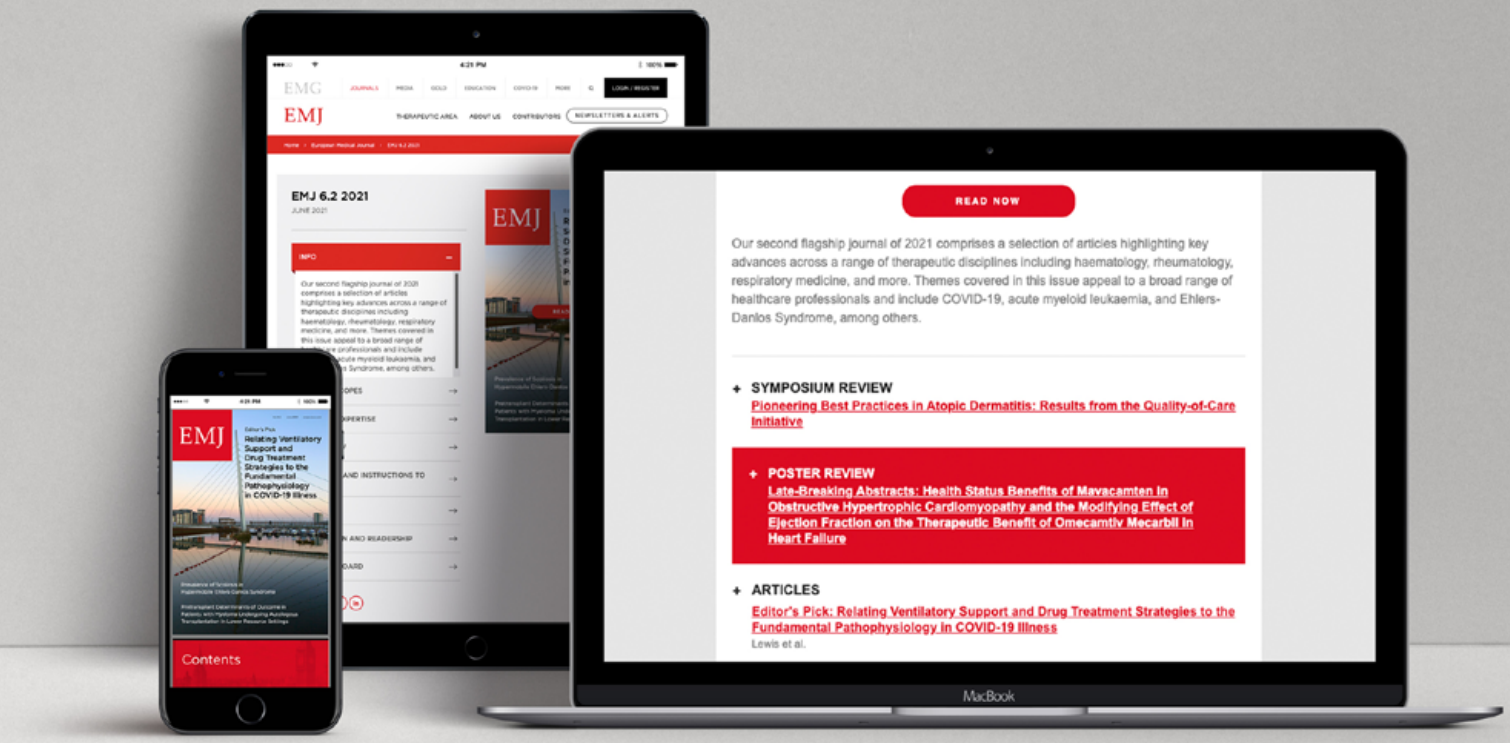

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