EMJ CARDIOLOGY

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+ ESC CONGRESS 2020

Reviewed

+ EDITOR'S PICK

Artificial Intelligence in Patients with Congenital Heart Disease: Where Do We Stand?

+ INTERVIEWS

In a round table interview, past and present ESC board members share insights from their careers, and a cardiology surgeon discusses the importance of clinical trials.

+ ABSTRACT REVIEWS

Reviews of fascinating abstract summaries of research presented at ESC Congress 2020.

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"Bringing you matters topical this autumn, we present EMJ Cardiology 8.1, an issue with one purpose: to bring to our readers the very latest updates and exciting findings in the specialty."

Spencer Gore, CEO

+ INTERVIEWS

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Editorial Board

VIEW IN FULL ←

Aims and Scope

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EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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EMJ Cardiology 8.1

Welcome

Dear Readers,

Bringing you matters topical this autumn, we present *EMJ Cardiology 8.1*, an issue with one purpose: to bring to our readers the very latest updates and exciting findings in the specialty.

Cardiology has had its fair share of the medical spotlight this year, with the management of cardiovascular disease in patients with coronavirus disease (COVID-19) becoming a priority for frontline healthcare workers, as well as consideration of the implications of long COVID and its possible effects on the heart. The European Society of Cardiology (ESC) Congress 2020 proved to be an unmissable event in this regard, as the scientific programme committee organised a meeting focussed on guidelines, real-world practice, and the latest clinical developments to keep cardiologists up to date while we are adapting to new virtual collaboration. Our Congress Review focusses on the hottest topics presented at the meeting, with our exclusive session review of the new guidelines on 'Sports Cardiology and Exercise in Patients with Cardiovascular Disease.'

As always, readers will find a variety of reviews and case reports enclosed within this eJournal. Our Editor's Pick for this publication is the cutting-edge review by Pool et al. 'Artificial Intelligence in Patients with Congenital Heart Disease: Where Do We Stand?' In this article, the authors make the case for using data science to spur the development of decision support systems that could aid physicians in predicting clinical deterioration and in managing patients with congenital heart disease.

Worthy of note within *EMJ Cardiology 8.1* are the exclusive interviews with professors Dan Atar, Stephan Achenbach, and Jose Zamorano, all past and present members of the ESC Board, who spoke with our editorial team about their roles in the society and their ambitions for the organisation. We also had the pleasure of interviewing Dr Rasha Al-Lamee of the National Heart & Lung Institute, London, UK, who spoke to us about the challenges the current pandemic has thrown at cardiologists, as well as how to be a successful clinical triallist.

It only remains for me to thank all of our contributors to this blockbuster issue, as well as all of our staff at EMJ. I hope the following pages provide education and stimulation, and encourage discussion in the sphere of cardiology.

Spencer Gore

Chief Executive Officer, EMG-Health

Foreword

Dear Readers and Colleagues,

It is my great pleasure to introduce the latest edition of *EMJ Cardiology*, which I truly hope finds you in good health. This issue contains interviews with various members of the ESC Board and an ESC congress review, which, for the first time, was held as an online congress free of charge because of the ongoing coronarvirus disease (COVID-19) pandemic. In addition to this, *EMJ Cardiology 8.1* features a collection of expertly written, peer-reviewed articles including comprehensive review articles summarising hot topics in cardiology as well as fascinating case reports.

To give you a glimpse of what to expect in the following pages, Pool et al. discuss the fascinating opportunities of artificial intelligence to aid in clinical decision making. However, they highlight the hurdles of implementing it into clinical practice for patients with congenital heart disease. These obstacles associated with the translatability of new and innovative research are, in this case, mainly attributed to the current lack of large datasets that are required for efficient learning algorithms. Other important diagnostic and prognostic tools for clinical decision-making are reliable cardiac biomarkers. Whyte et al. summarise the remarkable evolution of cardiac biomarkers over the last half century and critically discuss their future prospects. Another comprehensive article by Boyle et al. reviews the complex interplay between ventricular arrhythmias and heart failure. They provide an excellent overview of the underlying pathophysiology and current strategies to manage the disease. Finally, Nicholls and co-workers discuss the potential cardioprotective role of high-density lipoproteins (HDL). Specifically, they highlight a paradigm shift of HDL targeting strategies now focussed on enhancing HDL quality rather than increasing its quantity.

My personal pick, as well as a highlight particularly relevant for cardiac surgeons, is the case of a patient who had received a left-sided pneumectomy 13 years prior to cardiac surgery. Mohammad and colleagues describe how they dealt with the main challenges arising in such cases which may include altered anaesthesia protocols, left displacement of the heart, and the absence of left pulmonary veins.

Taken together, I am very confident that you will share in my excitement and enjoy *EMJ Cardiology 8.1.* With these final remarks, I would like to end by sincerely thanking all contributors.

With warm regards,

Dr Christian Bär

Dr Christian Bär

Hannover Medical School, Hannover, Germany

Congress Review

Review of the European Society of Cardiology (ESC) Congress 2020

Location: ESC Congress 2020: The Digital Experience

Date: 28th August–1st September

Citation: EMJ Cardiol. 2020;8[1]:10-22. Congress Review.

FOUNDATIONS comprising more than a million poles, each of which is rooted 12 metres into the ground, support the historic city of Amsterdam, which was set to house this year's European Society of Cardiology (ESC) Congress before the coronavirus disease (COVID-19) pandemic architectured its transition to a digital experience. Capital of the Netherlands and blue printed with over 1,200 bridges, the metropolis was the perfect backdrop as it provided the framework for the archway between keynote speakers and medical professionals in their *huizen* all over the world.

"Welcome to virtual Amsterdam": Prof Barbara Casadei, President of the ESC, delivered the inaugural session with a green-screen backdrop featuring iconic landmarks of the city: canals, windmills, and cobbled streets, mixed with the city's 17th century UNESCO status buildings. Welcoming delegates to 'The Digital Experience', Prof Casadei addressed the elephant in the room: the impacts of COVID-19 on the ESC community: "Periodically we are challenged by natural catastrophes. We have had our well-oiled and highly sophisticated systems, and our way of living, shaken by a fragment of RNA."

A record-breaking event, the online meeting attracted 116,000 healthcare professionals from 211 countries. Considering 33,510 delegates from 150 countries attended in 2019, the suggestion is that the transition to a virtual event allowed for greater global participation, which will be key to the long-term future of medicine, as well as in the short-term to overcome the current challenges facing the medical community. "Patient care in the COVID-19 outbreak has not been 21st century medicine," said Prof Casadei. She continued: "It was not what we trained for, not what our trainees were aspiring to do." Without knowing if treatments would bring benefit or harm, clinicians have had

"Periodically we are challenged by natural catastrophes. We have had our well-oiled and highly sophisticated systems, and our way of living, shaken by a fragment of RNA."

to make life-influencing decisions. Prof Casadei summarised this: "We have had to base our practice on anecdotes."

By coming together virtually, it was the hope of the ESC President that informed patient care would prevail over the confusing matters surrounding the disease, such as small studies, or those with inadequate design, which had been published in respected journals, before having to be retracted on the grounds of inaccuracies. However, she reminded everyone that: "At times such as this, what we have in common counts so much more than our differences."

Beyond COVID-19-related content, 'Spotlight 2020: The Cutting Edge of Cardiology' was the overarching theme of the ESC Congress 2020, with sessions highlighting applications of the latest technology in clinical cardiology, including: the use of advanced therapies, involving stem cells and genes, moving towards personalised medicine; big data, artificial intelligence and wearable technology to reshape the delivery of medical care; and robotics to introduce remote care and remote interventional cardiology to patients worldwide.

In what was the biggest online gathering of cardiovascular professionals the world has ever seen, more than 4,000 abstracts were presented, alongside 70 late-breaking science studies reported across the 4-day event. As is tradition, ESC launched several of their Clinical Practice Guidelines at the congress, with live presentations combined with interactive panel discussions on updated clinical practice for atrial fibrillation, adult congenital heart disease, non-ST-segment elevation acute coronary syndromes, and sports cardiology and physical activity in patients with cardiovascular disease, the latter of which has been included in our Congress Review.

Late-breaking abstracts of the congress have also been summarised in *EMJ Cardiology,* covering topics such as smoking cessation reducing stroke risk in atrial fibrillation, long naps increasing the risk of cardiovascular disease, and why not all vegetarian diets are linked to improved cardiovascular health.

More than 400 topics covering the entire spectrum of cardiology were offered by the ESC Congress 2020, all with the mission of ESC in mind: to reduce the burden of cardiovascular disease. All attendees of the inaugural session were left feeling inspired by Prof Casadei and her commitment to the ESC mission, who left delegates with the words: "The effort and ingenuity of our community will ensure progress in the care of our patients with cardiovascular disease and prosperity for our society."

EMJ looks forward to welcoming you all, hopefully for a face-to-face meeting, to London, UK next year for the 2021 meeting of the world's largest cardiology congress.

ESC 2020 REVIEWED →

Gut Dysbiosis May Be Associated with High Blood Pressure

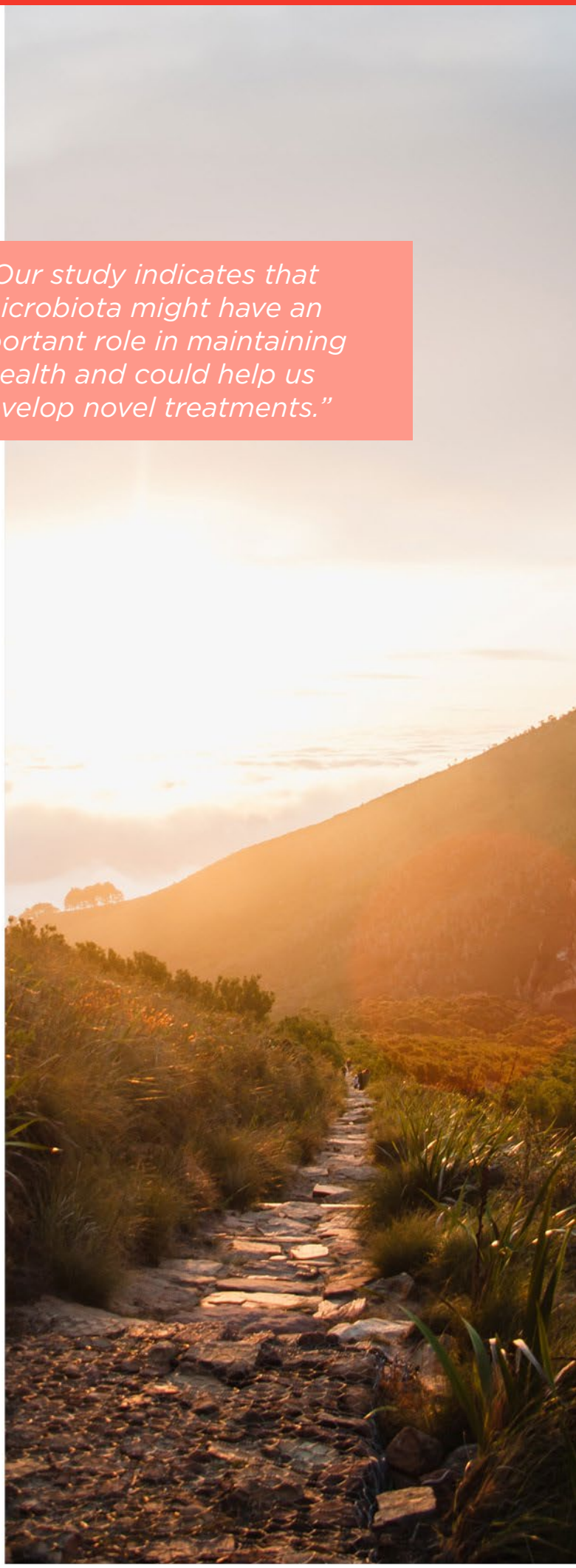
MICROBIOTA in the digestive tract are associated with numerous health conditions, including those outside of the gut. A study presented at ESC Congress 2020 and in a press release dated 27th August 2020 found that bacteria and other microorganisms in the digestive tract are linked to conditions such heightened blood pressure, blood lipids, and BMI.

"Our study indicates that microbiota might have an important role in maintaining health and could help us develop novel treatments."

While small-scale studies have been conducted and have shown an association between the gut microbiome and single diseases, for the first time the researchers investigated numerous diseases within a single cohort. Further explaining the rationale behind the study, study author Dr Hilde Groot of University Medical Centre Groningen, Groningen, the Netherlands, noted: "Previous research has shown that the human gut microbiome composition could be partially explained by genetic variants. So, instead of directly measuring the make-up of the microbiome, we used genetic alterations to estimate its composition." The UK Biobank was used as the source of data, from which 422,417 unrelated individuals (average age: 57 years; 54% female) who had undergone genotyping were sourced, including information such as diseases, BMI, and blood pressure of the individuals.

Increases in 11 bacteria were associated with 28 health and disease outcomes, including chronic obstructive pulmonary disease and high blood pressure, blood lipids, and BMI. One particular example is the relationship between bacteria of the *Ruminococcus* genus and blood pressure, in which higher levels of *Ruminococcus* bacteria were linked to increased blood pressure.

"Our study indicates that microbiota might have an important role in maintaining health and could help us develop novel treatments," said Dr Groot. While these results are a step in the right direction to characterising the impact of dysbiosis in the gut microbiome on human health, the researchers acknowledged the need for follow-up studies to validate these findings.



Association Between Depression and Anxiety in Young Males and Myocardial Infarction Risk

ADOLESCENTS who have experienced mental health conditions such as depression and anxiety have been linked to an increased risk of myocardial infarction in mid-life, according to a new study presented at ESC Congress 2020 and in a press release dated the 26th August 2020.

With indications suggesting that the mental well-being of young people is declining, the researchers aimed to investigate what impact this may have on the health of the individuals later in their life. Males who were born between 1952 and 1956 who had undergone extensive medical examinations as part of assessments in compulsory military service were included in the study (N=238,013). The medical examinations comprised assessments from physicians and psychologists for both medical and psychiatric means, and took place when the males were 18 or 19 years of age, through to middle age (up to 58 years). Non-psychotic mental health disorders, such as depression or anxiety, were diagnosed in 34,503 males at conscription. Using psychologist interviews and questionnaires, as well as familial, social, medical, behavioural, and personality characteristics, the ability to cope with stress in day-to-day life (also known as stress resilience) was also assessed.

Through the use of hospital records, the investigators found that experiencing a mental health condition during adolescence was associated with a 20% higher risk of having a myocardial infarction by middle age. The influence of stress resilience on this outcome was then assessed, for which it partially described the link. Study author Dr Cecilia Bergh Örebro University, Örebro, Sweden, highlighted that: "Better fitness in adolescence is likely to help protect against later heart disease, particularly if people stay fit as they age. Physical activity may also alleviate some of the negative consequences of stress. This is relevant to all adolescents, but those with poorer wellbeing could benefit from additional support to encourage exercise and to develop strategies to deal with stress."

"Experiencing a mental health condition during adolescence was associated with a 20% higher risk of having a myocardial infarction by middle age."

Smoking Cessation Reduces Stroke Risk in Atrial Fibrillation

QUITTING smoking can reduce risk of stroke in atrial fibrillation (AF). While smoking is known to increase risk of developing AF, a Korean study has examined the impact of smoking cessation on later risk of stroke and death, as described in a press release from the ESC Congress 2020 dated 25th August 2020.

AF will develop in one in four adults in Europe and the USA, and is projected to affect 17 million people in the European Union by 2030. AF increases risk of stroke by five times, and increases risk of death following stroke by two-fold in females and 1.5-fold in males.

"Regardless of how much you smoke, kicking the habit is good for health."

The study examined the influence of smoking cessation following new AF diagnosis on risk of stroke and all-cause death by comparing national health check-up data from the Korean National Health Insurance Service and National Health Screening databases from 2010 to 2016. In this period, 523,174 patients were newly diagnosed with AF; researchers examined the outcomes for the 97,637 patients who had a national health check-up <2 years prior to this new diagnosis and a second check-up within 2 years following the new diagnosis.

The researchers classified these patients by smoking status: never smokers (51.2%), ex-smokers (quit prior to diagnosis; 27.3%), quitters (quit following diagnosis; 6.9%), and current smokers (14.6%). Over the median 3-year follow-up, there were 3,109 strokes and 4,882 all-cause deaths. Quitters had a 30% lower likelihood of stroke compared to current smokers, and a 16% lower risk of all-cause death, even after considering other factors including age, sex, blood pressure, BMI, and physical activity. Quitters remained at a higher risk compared to never smokers, although this association was noted only in males. New smokers (commencing following diagnosis) had the highest increase in stroke risk, with an 84% increase in probability compared to those who had never smoked.

The study message for clinicians and patients was highlighted by Dr So-Ryoung Lee, Seoul National University Hospital, Seoul, Korea: "If you don't smoke, don't start. If you do, it's never too late to quit. Regardless of how much you smoke, kicking the habit is good for health."

Long Naps Increase Risk of Cardiovascular Disease

ONE hour or longer naps (long naps) have been identified as a risk factor for all-cause death and a higher likelihood of cardiovascular disease (CVD), according to results published by authors from Guangzhou Medical University, Guangzhou, China and reported in a press release dated 26th August 2020 at the ESC Congress 2020.

"The results suggest that shorter naps (especially those less than 30 to 45 minutes) might improve heart health in people who sleep insufficiently at night."

An association between lengthy naps and CVD and all-cause mortality has long been suggested, but the evidence is controversial. The study authors therefore took it upon themselves to undertake a systematic review and dose-response meta-analysis of the relationship. This study included 313,651 participants from >20 countries, of whom 39% took naps.

Long naps were found to increase risk of all-cause death by 30% in both males and females. In a subgroup analysis of participants who took long naps and were also female and aged >65 years, there was a significantly higher risk of CVD compared to those who did not nap. In the population of those aged >65 years, naps of any length increased risk of death by 17% overall, which rose to 22% in the female population. The reasons for this are still unclear, though previous studies have linked the association to high blood pressure, diabetes, higher levels of inflammation, and poorer overall physical health.

In comparison, naps for <60 minutes showed no significance in increasing risk of cardiovascular disease. First author Dr Zhe Pan summarised these comparative findings: "The results suggest that shorter naps (especially those less than 30 to 45 minutes) might improve heart health in people who sleep insufficiently at night."

He concluded: "If you want to take a siesta, our study indicates it's safest to keep it under an hour. For those of us not in the habit of a daytime slumber, there is no convincing evidence to start."

Results of 14-year Study Show Benefits of Deep Chest Compressions

DEEP chest compressions for cardiopulmonary resuscitation (CPR) can crack ribs, but can reduce brain damage during cardiac arrest. This is according to the results of a new study presented as part of a press release dated 24th August at the ESC Congress 2020.

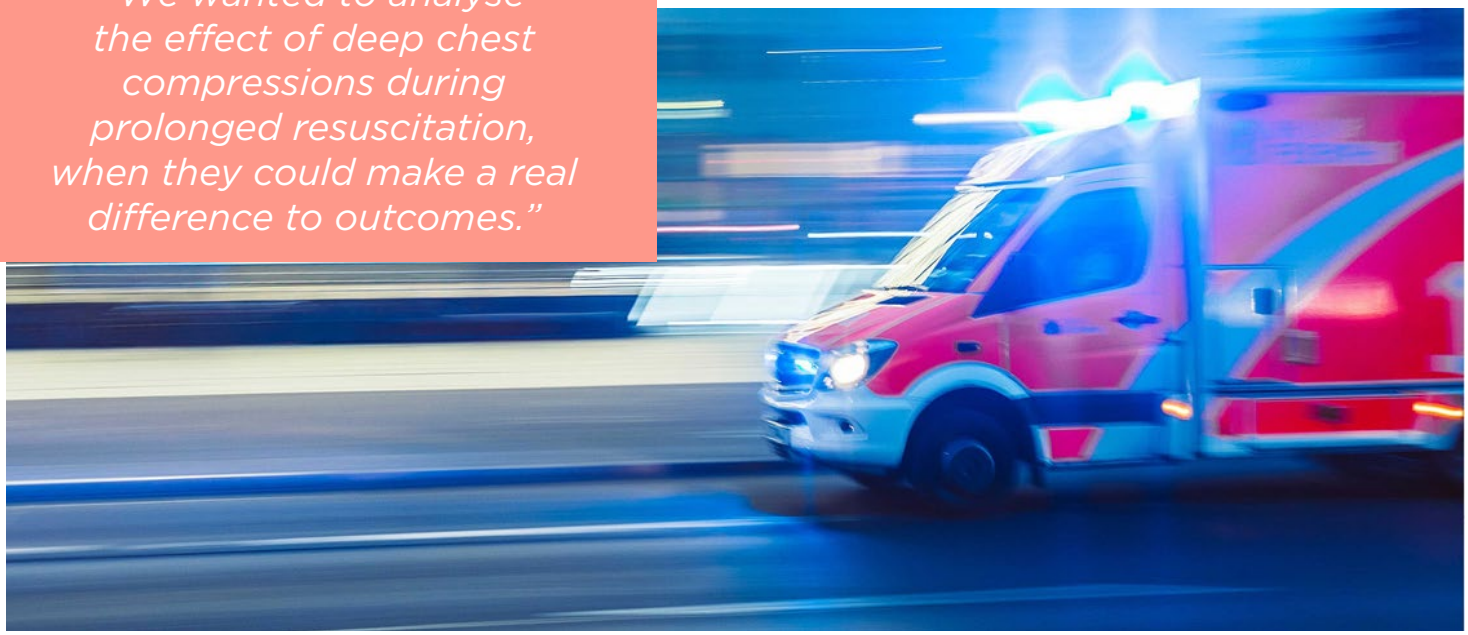
Every 5 years, guidelines to aid healthcare professionals and the public to perform CPR are updated. The recommendation for deeper chest compressions introduced in 2010 garnered concerns for the increased risk of CPR-related injuries, such as cracked ribs. A study conducted by researchers from University Hospital La Paz, Madrid, Spain, examined the effect of deeper chest compressions on neurological outcomes, and the rate of CPR-related injuries, and their association with prognosis, in people who had cardiac arrest.

The study included 510 patients who survived cardiac arrest and were admitted to hospital while unconscious between 2006 and 2020. The patients, with an average age of 63 years and of whom 81% were male, were designated into groups for CPR guideline updates: 2006–2010, 2011–2015, and 2016–2020.

Those who would have received prolonged resuscitation and were now comatose survivors were included in the study whereas individuals who had regained consciousness after the cardiac arrest are likely to have received an immediate electric shock and only brief chest compressions to restore circulation. "We wanted to analyse the effect of deep chest compressions during prolonged resuscitation, when they could make a real difference to outcomes," said Dr Irene Marco Clement, study author.

After 2010, the researchers found a higher proportion of CPR-related injuries: 12.7% in 2006–2010, 23.5% in 2011–2015, and 22.7% in 2016–2020. Brain performance at 3 months significantly increased over the course of the study (in the later years) and patients with CPR-related injuries were more likely to have better brain performance. Almost two-thirds (65.1%) of patients with injuries had high brain function compared to 43.2% without injuries, the most common of which were rib or sternal fractures. CPR by the public and the use of automated external defibrillators observably increased throughout the study and more than half of the patients survived and were discharged from the hospital. Marco Clement confirmed the results of the study: "Survival and neurological outcome improved significantly during the 14-year study. Injuries from CPR rose, but these patients were less likely to have brain damage."

"We wanted to analyse the effect of deep chest compressions during prolonged resuscitation, when they could make a real difference to outcomes."



Influenza and Pneumonia Vaccinations Contribute to Decreased In-Hospital Morbidity in Patients with Heart Failure

"Our study provides further impetus for annual immunisations in patients with heart failure."

RESPIRATORY infections such as influenza and pneumonia increase the severity of heart failure, an already debilitating disease resulting in fluid build-up in the lungs, shortness of breath, and coughing. According to a recent study presented at ESC Congress 2020 in a press release on 28th August, influenza and pneumonia vaccinations are associated with fewer hospital deaths in patients with heart failure.

It is estimated that 26 million people are affected by heart failure worldwide and that one in five will develop heart failure during their lifetime. Study author, Dr Karthik Gonuguntla of the University of Connecticut, Storrs, Connecticut, USA, noted that: "The COVID-19 pandemic has shone the spotlight on the importance of vaccination to prevent respiratory infections, particularly for people with diseases like heart failure," prompting the conduct of this study. While it is known that infections exacerbate heart failure, and that inoculations protect against respiratory infections, not many studies have investigated the outcomes of vaccinations in heart failure patients.

The study utilised data from the National Inpatient Sample (NIS), covering >95% of the USA population, and included 2,912,137 patients with heart failure who were admitted to hospital between 2010 and 2014. Analysis showed that 1.4% of the patients were inoculated against the flu and 1.4% against pneumonia. To assess the correlation between vaccination and morbidity, the researchers compared in-hospital death rates between heart failure patients who had received flu and pneumonia vaccinations that year to those that were not vaccinated.

Results showed that the rates of in-hospital mortality were significantly lower in patients who received the flu vaccine compared to those that did not (1.3% versus 3.6%, respectively). Equally, patients inoculated against pneumonia had lower rates (1.2%) compared to those who were not inoculated (3.6%). In conclusion Dr Gonuguntla stated: "Our study provides further impetus for annual immunisations in patients with heart failure. Despite advice to do so, uptake remains low." He further suggested that: "Pneumonia and flu vaccines are vital to preventing these respiratory infections and protecting patients with heart failure. Although many people have rejected common and safe vaccines before COVID-19, I am optimistic that the pandemic has changed perceptions about the role of immunisations in safeguarding our health."

Not All Vegetarian Diets are Linked to Improved Cardiovascular Health

PLANT-BASED foods have been shown to improve health status, but a recent study by authors from Harokopio University, Athens, Greece have found that not all diets that limit animal-based products are linked to better heart health. These findings were reported in a press release from the ESC Congress 2020, dated 27th August 2020.

The prospective study, which ran between 2001–2012, analysed 1,528 females and 1,514 males who were free of cardiovascular disease and metabolically healthy obese. The participants were divided into two groups; those who ate a 'healthful' diet which incorporated an increased consumption of fruits/vegetables, whole grains, nuts, legumes, oils, and tea/coffee, compared to those who ate an 'unhealthful' diet of juices, sweetened beverages, refined grains, potatoes, and sweets.

At 10-year follow-up, 54% of females and 45% of males who were previously metabolically healthy participants were regarded as metabolically unhealthily obese. Indices of the plant-based diet quality found that those who adhered to the healthful plant-based diet had a higher retention of their metabolically healthy status, with a greater significance observed in females. Unhealthier plant-based food choices were linked to developing higher blood pressure, blood lipids, and blood sugar, again with a greater association seen in females.

"Eating less meat is beneficial for heart health, particularly when it is replaced with nutritious plant foods such as whole grains, fruits, vegetables, nuts, and olive oil."

Dr Matina Kouvari, first author of the study, suggested that the reason for the increased association in females is because they are more likely to eat less animal products than males. She also noted that participants were classified as obese and so these results should not be extrapolated to include other weight categories.

Dr Kouvari concluded that: "Eating less meat is beneficial for heart health, particularly when it is replaced with nutritious plant foods such as whole grains, fruits, vegetables, nuts, and olive oil."

Could Saliva Diagnose a Heart Attack?

RAPID diagnosis of heart attack by using saliva to detect troponin released by myocardial injury may soon be a clinical reality, following research presented in an abstract at the ESC Congress 2020 and in a press release dated 26th August 2020.

Diagnosis of heart attack is usually dependent on symptomology, electrocardiogram (ECG) evidence, and raised troponin levels upon blood testing, which can take up to an hour for a laboratory to confirm. Researchers from Soroka University Medical Centre, Beer Sheva, Israel, studied the ability for adapted commercially available tests to detect elevated troponin in the saliva of patients at the time of myocardial injury.

Comparing 32 patients with serum evidence of raised troponin to 13 healthy volunteer controls, the researchers collected saliva samples by asking participants to spit into a tube. Half of each sample was tested unprocessed while the other half was processed prior to testing. The findings supported a strong association between the processed saliva samples and serum troponin. For those patients with raised serum troponin, 84% of the processed samples tested positive for troponin, compared to 6% of the unprocessed samples. None of the samples, both processed and unprocessed, tested positive for troponin among the healthy volunteer participants.

Dr Roi Westreich, Soroka University Medical Centre, discussed the future research plans for the saliva testing: "Further research is needed to determine how long troponin stays in the saliva after a heart attack. In addition, we need to know how many patients would erroneously be diagnosed with heart attack and how many cases would be missed." Dr Westreich is optimistic about the future value of this rapid testing strategy and prototype testing of specialised tests for detecting troponin in saliva: "It will be calibrated to show positive results when saliva troponin levels are higher than a certain threshold and show a yes/no result like a pregnancy test."

"The findings supported a strong association between the processed saliva samples and serum troponin."

People with 'Sudden' Cardiac Arrest Show Increased Contact with Doctors

LETHAL 'sudden' cardiac arrest, the third leading cause of death worldwide, is said to have been reported by more than half of patients during the 2 weeks before the event. This is according to the results of a new study presented as part of a press release dated 25th August at the ESC Congress 2020.

On average, less than 10% of people survive from sudden cardiac arrest if left untreated and it is very important to identify who may be at risk. "This is very challenging since these are considered sudden and unexpected events. But our study indicates that patients felt unwell in the days leading up to the cardiac arrest," said study author Dr Nertila Zylyftari, Copenhagen University Hospital Herlev and Gentofte, Hellerup, Denmark.

The novel study investigated contact with general practitioners (GP) and hospitals in the 1 year prior to cardiac arrest, studying each week to assess contact variation. The Danish Cardiac Arrest Registry was used to identify a total of 28,955 people who had an out-of-hospital cardiac arrest between 2001 and 2014, of which 67% were male and the average age was 72 years. There was relative consistency between patient–GP contact during the year until 2 weeks before the event when contact reached 54%, showing an increase of 28% compared to previous weeks. Compared to patients, just 14% of the overall population in Denmark, who patients were matched to by age and sex, contacted their GP in that year. The researchers found that contact by patients with hospitals also peaked at 2 weeks before cardiac arrest.

This study showed that proportionally, patients contacted their GP more every week for a year before cardiac arrest compared to the matched population in the same year. The researchers did not assess the reasons why cardiac arrest patients sought medical advice. Zylyftari commented on the direction needed following this study: "More data and research are needed on the reasons for these interactions, for example symptoms, to identify warning signs of those at imminent danger so that future cardiac arrests can be prevented."

"On average, less than 10% of people survive from sudden cardiac arrest if left untreated and it is very important to identify who may be at risk."

Can Yoga Reduce the Burden and Symptoms of Atrial Fibrillation?

YOGA and breathing have been linked with improved symptoms in patients with atrial fibrillation (AF), according to research presented in a press release dated 24th August 2020 at ESC Congress 2020.

AF, the most common heart rhythm disorder, causes 20–30% of all strokes and increases the risk of morbidity 1.5-fold in males and 2.0-fold in females. Its development has a prevalence of one in four in middle-aged adults in Europe and the USA. It also greatly diminishes the quality of life in patients and 10–40% of these patients are hospitalised each year. "The symptoms of AF can be distressing. They come and go, causing many patients to feel anxious and limiting their ability to live a normal life," stated study author Dr Naresh Sen, HG SMS Hospital, Jaipur, India. Symptoms include palpitations, racing or irregular pulse, shortness of breath, tiredness, chest pain, and dizziness.

"These results validate the ability of yoga practice to reduce patient-reported AF symptoms and statistically impact quality of life, physical function, depression, and anxiety devoid of side effects from medication or cardiac ablation."

In their study, Dr Sen and his team investigated whether yoga would improve symptoms in patients with AF and therefore recruited 538 volunteers in 2012 to 2017. For 12 weeks the patients did no yoga and then for 16 weeks attended 30-minute yoga sessions every other day and therefore served as their own controls. During the yoga period, patients were also encouraged to practice the learned movement and breathing techniques daily at home. Symptoms and episodes of AF were recorded in a diary, heart rate and blood pressure were measured, and some patients wore heart monitors to verify AF episodes. Anxiety and depression surveys and questionnaires assessing the patient's energy levels and mood and the ability to socialise and conduct everyday activities were also completed by each patient.

After comparing the outcomes between the yoga and non-yoga period, the results highlighted that during the 16-week yoga period, patients experienced significant improvements in all areas compared to the 12-week non-yoga period. This was exemplified by the fact that during the yoga period patients experienced an average of eight symptomatic AF episodes compared to 15 in the non-yoga period. Additionally, the average blood pressure was 11/6 mmHg lower after yoga training. These results validate the ability of yoga practice to reduce patient-reported AF symptoms and statistically impact quality of life, physical function, depression, and anxiety devoid of side effects from medication or cardiac ablation.

2020 ESC Guidelines on Sports Cardiology and Exercise in Patients with Cardiovascular Disease

Anaya Malik
Editorial Assistant

Citation: EMJ Cardiol. 2020;8[1]:23-25.

ADVISING individuals with diseases of the heart on what types and intensities of sport to participate in is not a practice cardiologists typically have official guidelines on. A taskforce from ESC has now come together and created guidelines, the first of their kind, on exercise and sports participation in patients with cardiovascular disease. The guidelines were presented at the ESC Congress 2020 in a session chaired by Prof Antonio Pelliccia, Scientific Director of the Institute of Sports Medicine & Science from Rome, Italy.

Pelliccia was joined by Prof Martin Halle, President of the European Association of Preventive Cardiology (EAPC), Munich, Germany, and Prof Matthias Wilhem, Head of the Centre for Preventive Cardiology, Sports Medicine, Department of Cardiology at the Inselspital, University Hospital of Bern, Switzerland. The guidelines derived from the need to assist patients who had experienced cardiovascular events and were questioning their limits of sports participation. Prof Halle commented on his experience in the taskforce: "The level of evidence is rather low, so it is very much the personal perspective and the experience of the experts which made us come to that one conclusion in the guidelines. It is something that should be developed in years to come."

A series of videos were shown, presented by specialists who were invited to discuss some of the most relevant topics of the guidelines.

EXERCISE AND SPORT FOR RISK MANAGEMENT OF CARDIOVASCULAR DISEASE

Prof Halle addressed the risk assessment and exercise recommendations for healthy individuals, patients who may be at risk of cardiovascular disease, and the elderly. According to the guidelines, healthy individuals are advised to perform at least 150 minutes of endurance exercise weekly at moderate intensity, or 75 minutes at vigorous intensity, preferably

"The level of evidence is rather low, so it is very much the personal perspective and the experience of the experts which made us come to that one conclusion in the guidelines. It is something that should be developed in years to come."

exercising daily. Individuals who are obese or with well-controlled hypertension are advised to take part in moderate exercise most days of the week, with variations in exercise intensity based on the management of hypertension. In the ageing population, exercise is recommended, and physical activity to improve balance and co-ordination is encouraged. Moderate intensity should be the primary choice for this group and those >65 years of age who wish to participate in high intensity activity should undergo a full clinical assessment.

EXERCISE AND SPORT IN SUBJECTS WITH CORONARY HEART DISEASE

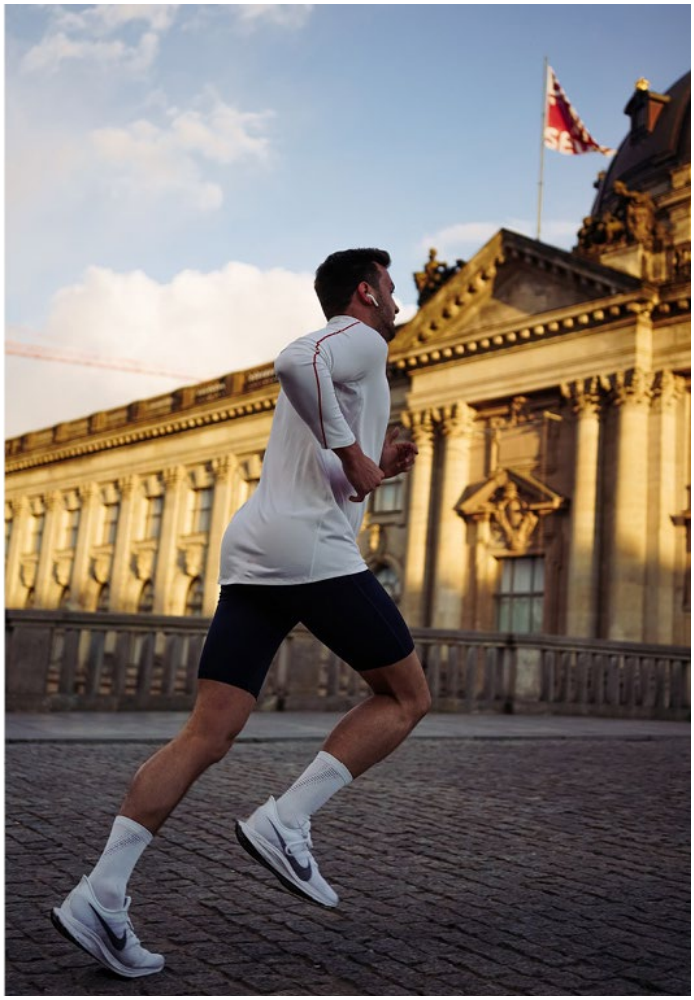
Prof Mats Börjesson, taskforce member and Head of Center for Health and Performance (CHP), University of Gothenburg, Gothenburg, Sweden discussed the guidelines for individuals at risk of atherosclerotic coronary artery disease and asymptomatic individuals in whom coronary artery disease is detected upon screening. The clinical evaluation of these patients should include an assessment of cardiovascular disease risk, consideration of the intended exercise programme intensity, clinical evaluation and a maximal exercise stress test, and further diagnostic testing in selected individuals. Further investigation is also a possibility and may allow some to perform competitive sports.

The guidelines list high-risk features for those with established chronic coronary syndrome. Recommendations include risk stratification, regular follow-up, and consideration for competitive or leisurely sport for those at low risk of exercise-induced events.

EXERCISE IN HEART FAILURE

Prof Massimo Piepoli, Head of the Heart Failure and Cardiomyopathy Unit at Guglielmo da Saliceto Hospital, Piacenza, Italy, discussed exercise in individuals with heart failure. Piepoli explained that exercise interventions should only be started in clinically stable individuals.

In summary, the recommendations for exercise prescription in patients with heart failure include: regular discussions about exercise participation and individualised exercise prescriptions with motivational and psychological support; cardiac rehabilitation to improve exercise capacity, quality of life, and reduced frequency of hospital readmission; and clinical reassessment when exercise intensity is increased.



EXERCISE IN VALVULAR HEART DISEASE

The guidelines for exercise and sports recommendations in individuals with valvular heart disease were introduced in the form of short key messages by Dr Sabiha Gati, Royal Brompton and Harefield Hospitals, London, UK:

1. It is recommended that all individuals with valvular heart disease do some form of exercise given the multiple benefits of physical activity.
2. Asymptomatic individuals with mild valvular abnormalities can participate in all recreational and competitive sports. Individuals with severe valvular abnormalities should not participate in intensive exercise.
3. The management of individuals with valvular heart disease requires assessment of their symptomatic status with clinical history, ECG looking for strain patterns, echocardiography with a focus on the valve morphology and function, and exercise stress testing.
4. It is unclear whether exercise accelerates aortic dilation in bicuspid aortic valves in the long term; therefore, a cautious approach to sports participation is recommended.
5. Mitral valve prolapse has a benign nature meaning asymptomatic individuals with mild-to-moderate regurgitation can participate in all competitive and recreational sports.

EXERCISE IN PATIENTS AT RISK OF ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

Prof Hein Heidbuchel, Professor and Chair of Cardiology at Antwerp University, Antwerp, Belgium, was the last expert to present the new guidelines, giving an overview of arrhythmias and channelopathies. He explained that the recommendations in the guidelines for athletes with arrhythmias are based on three main considerations: the risk of sudden cardiac death during sports, sports performance limited by symptoms, and the impact of the sport on arrhythmogenic condition progression. Prof Heidbuchel noted that research and data are limited in this field, therefore shared decision making and discussion with the patient are vital.

CONCLUDING REMARKS

In the last part of the presentation, Prof Pelliccia led a live question and answer session with questions from experts viewing the discussion from all over the world. Prof Pelliccia then ended the session by inviting his colleagues to read the novel guidelines which contain more topics than those covered in the live session. He shared his ambition to provide a referral document for all cardiologists and examining physicians for patients who ask about exercise, before reflecting on the goals the taskforce set to achieve in creating the guidelines: “We tried to provide the instruments and knowledge for assessing the clinical status of the patient and to give him or her the best advice to approach exercise and sport.” As a stimulus for additional research in a field with limited trial data, the comprehensive guidelines presented at ESC for sports cardiology and exercise in patients with cardiovascular disease are sure to aid in closing the research gap.

Therapeutic Advances in Patients with Heart Failure with Reduced Ejection Fraction Who Have Had a Previous Worsening Heart Failure Event

This virtual symposium took place on the 29th August 2020, as part of the European Society of Cardiology (ESC) Congress 2020

Chairperson: Carolyn Lam[1]

Speakers: Carolyn Lam,[1] Burkert Pieske,[2] Justin Ezekowitz,[3] Javed Butler[4]

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Meeting Summary

Despite clinical advances in the management of heart failure with reduced ejection fraction (HFrEF), new treatment strategies are still urgently needed for patients with symptomatic chronic HF who have experienced a previous worsening HF event. These patients remain at risk of recurrent worsening HF events despite optimal, guideline-directed medical and device therapy. During this symposium, leading cardiology experts explored therapeutic advances in patients with HFrEF who have had a previous worsening HF event, focussing on the novel cyclic guanosine monophosphate (cGMP) pathway stimulator vericiguat, as well as results from the landmark VICTORIA trial.

Introduction from the Chair

Professor Carolyn Lam

European and USA treatment guidelines are aligned in their standard recommendation of therapies for symptomatic HFrEF.[1,2] First-line treatment is centred on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers plus β-blockers, with diuretics as needed. Next steps in the treatment pathway include adding mineralocorticoid receptor antagonists, replacing an angiotensin-converting enzyme inhibitor with an angiotensin receptor neprilysin inhibitor, or adding ivabradine in patients with sinus rhythm (heart rate ≥70 beats per minute).[1,2] However, Prof Lam stressed that an important residual risk remains in many patients with HFrEF despite the guidelines-directed use of these available HF medications.

Landmark trials have highlighted the successes that have been achieved with the current armoury of HFrEF therapies.[3-7] Yet even in the most recent of these studies, DAPA-HF, residual risk of cardiovascular (CV) death remained at 10% in the treated arm over 18 months' follow-up.[7] This risk is accentuated following a HF event. Real-world data from the PINNACLE registry showed that 56% of patients were rehospitalised within 30 days of a worsening HF event, and the number of HF-related hospitalisations increased over time.[8]

Therefore, although baseline risk in patients with HFrEF can be successfully lowered with standard guideline-directed therapies, it is important to recognise that a worsening HF event or hospitalisation is a key sign of increasing risk. These patients typically follow a worsening disease trajectory, with risk of further hospitalisations eventually culminating in advanced HF.[9] Prof Lam posed the important clinical question: can we bend this curve in worsening HF, delay the progression of worsening HF events, and improve outcomes for patients with HFrEF?

Stimulating sGC: VICTORIA Trial Reveals Improved Outcomes in Patients with HFrEF

Professor Burkert Pieske

HFrEF is a complex systemic disorder in which a number of abnormal and dysregulated pathways interact, leading to progressive cardiac remodelling and repeat decompensations. Although a number of these pathways are already medically addressed with existing treatment modalities, important therapeutic targets remain, including the nitric oxide (NO)–soluble guanylate cyclase (sGC)–cGMP pathway.[1,10-18]

In HFrEF, increased oxidative stress reduces NO bioavailability, which in turn leads to reduced activity of the important enzyme sGC and lower levels of cGMP. Vericiguat is a once-daily oral therapy that stimulates sGC, thereby restoring intracellular cGMP levels and leading to improved myocardial and vascular function in HF (Figure 1).[12,15,19-24]

VICTORIA was an international, Phase III, randomised, parallel-group, placebo-controlled, double-blind, event-driven, outcome trial of vericiguat in patients with symptomatic chronic HF who had a previous worsening HF event despite currently available HF therapies.[22,25] A total of 5,050 patients were randomised 1:1 to vericiguat or placebo, with the target dose of 10 mg once daily achieved in 89.2% and 91.4% of patients, respectively, after 12 months. The primary endpoint was time to first occurrence of the composite of CV death and first HF hospitalisation.[22,25]

Eligibility criteria for VICTORIA included symptomatic chronic HF, New York Heart Association (NYHA) Class II–IV, and left ventricular ejection fraction (LVEF) <45% on optimal background HF therapies plus a worsening HF event, defined as recent HF decompensation (HF hospitalisation or intravenous [IV] diuretic use) and elevated natriuretic peptides.[22,25] Prof Pieske described VICTORIA patients as 'high risk', with 84% having experienced an index HF hospitalisation within 6 months. Otherwise, VICTORIA included a typical advanced HFrEF patient population: elderly (mean age 67 years) and predominantly male (76%).

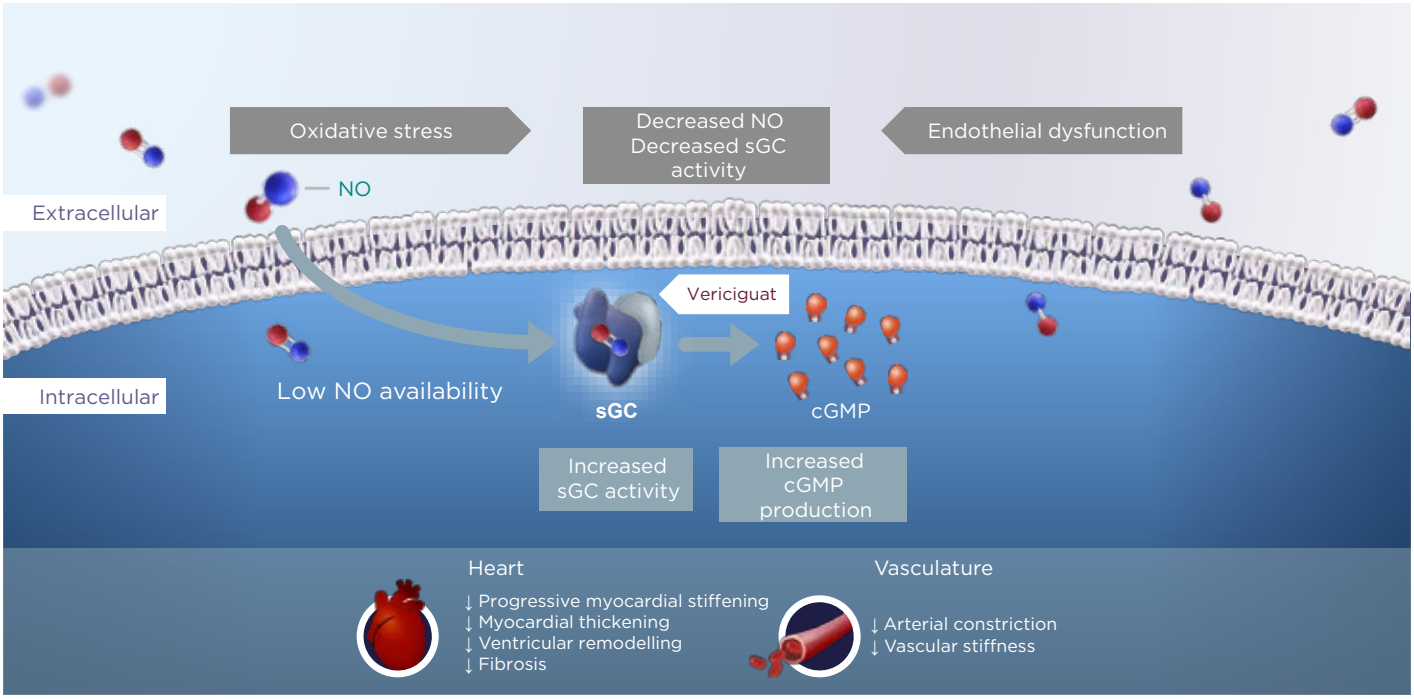


Figure 1: Vericiguat increases soluble guanylate cyclase activity to improve myocardial and vascular function.[12,15,19-24]

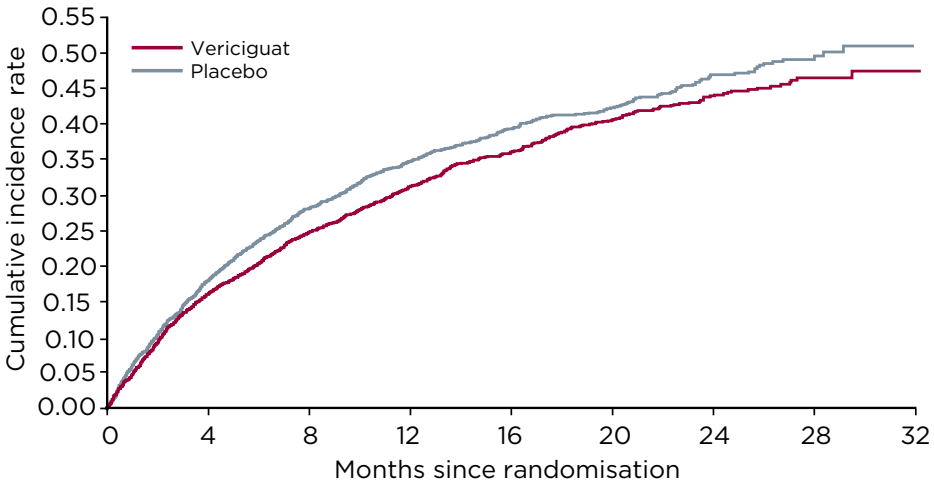
cGMP: cyclic guanosine monophosphate; NO: nitric oxide; sGC: soluble guanylate cyclase.

Patients were overtly symptomatic (NYHA Class II: approximately 60%; Class III: 40%), with mean LVEF of 29% at screening.[25] Around 60% of patients were on three baseline standard of care therapies, including approximately 15% on sacubitril/valsartan.[25]

After 10.8 months' follow-up, vericiguat significantly reduced the cumulative incidence rate of time to CV death or first HF hospitalisation versus placebo (p=0.02; hazard ratio [HR]: 0.90; 95% confidence interval [CI]: 0.82–0.98), meeting VICTORIA's primary endpoint (Figure 2).[25] The absolute risk reduction with vericiguat was 4.2% per year, translating to an annual number needed to treat of 24.[25] For the individual components of the primary endpoint, vericiguat achieved a 7% relative risk reduction in time to CV death and 10% reduction in time to HF hospitalisation, confirming its beneficial impact in this high-risk patient population.[25,26]

In terms of secondary outcom-s, vericiguat significantly reduced total HF hospitalisations (p=0.02; HR: 0.91; CI: 0.84–0.99) and significantly lowered the composite of first HF hospitalisations and all-cause mortality (p=0.02; HR: 0.90; CI: 0.83–0.98) compared to placebo.[25] Prespecified subgroup analysis of the primary endpoint showed a consistent benefit of vericiguat treatment across the majority of subgroups.[25] Younger patients tended to benefit slightly more from vericiguat therapy than older subjects in the study.[25] Prof Pieske also highlighted the impact of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels at baseline as an interesting signal requiring further evaluation. Patients with baseline NT-proBNP levels in the lower three quartiles showed a more pronounced benefit from vericiguat compared to the highest quartile (>5,314 pg/mL).[25]

Overall, vericiguat proved to be well tolerated in the VICTORIA trial, with an overall adverse event (AE) profile and incidence of serious AE comparable to that of placebo.[25] Patients on vericiguat were slightly more likely to develop mild anaemia versus placebo (7.6% versus 5.7%), but there was no interaction with electrolyte balance.[25] Looking at AE of clinical interest, there were no significant differences in the rates of symptomatic hypotension or syncope between vericiguat and placebo.[25]



Number of subjects at risk									
Vericiguat	2,526	2,099	1,621	1,154	826	577	348	125	1
Placebo	2,524	2,053	1,555	1,097	772	559	324	110	0

Figure 2: VICTORIA trial primary endpoint: time to cardiovascular death or first heart failure hospitalisation.[25]

Although minor declines in systolic blood pressure were noted early in the uptitration phase, no further clinically relevant reductions in blood pressure were observed throughout the remainder of the study.[25] There were no decreases in estimated glomerular filtration rate (eGFR) with vericiguat therapy, despite use in patients with baseline eGFR as low as 15 mL/min/1.73 m^2.[25]

In summary, vericiguat marks a potential advance in the treatment of HFrHF, enhancing the cGMP pathway to improve both myocardial and vascular function. Prof Pieske described efficacy findings from the VICTORIA trial as 'clinically relevant', with vericiguat significantly reducing the annualised risk of the VICTORIA composite outcome of time to HF hospitalisation or CV death by 4.2%.[25]

New Insights from a Deep Dive into VICTORIA Data and Its Potential Impacts

Professor Justin Ezekowitz

In the VICTORIA trial, treatment heterogeneity was observed in baseline NT-proBNP levels (which were prespecified into quartiles); hence, continuous analysis was carried out to further explore the relationship between NT-proBNP and HF event outcomes. Results from this analysis were discussed in a deep dive by Prof Ezekowitz. Overall, the treatment effect of vericiguat on the primary outcome proved consistent across most of the 13 prespecified subgroups analysed in the VICTORIA trial, with a clear benefit favouring vericiguat over placebo irrespective of sex, geographical region, index event, sacubitril/valsartan use, NYHA class, renal function, or ejection fraction.[25] A weak interaction with age was identified that requires further interaction.[25]

Despite the overall homogeneity of the VICTORIA trial findings, an interaction was observed between treatment and the primary outcome according to NT-proBNP levels.[25] NT-proBNP is known to be a strong marker of prognosis in patients with HFrEF.[27,28] Data from the Swedish registry have highlighted the clear link between higher NT-proBNP levels and an increasing risk of CV events in patients with HFrEF.[28] NT-proBNF is also used as an inclusion criteria for clinical trials and is linked to treatment efficacy, with evidence of an association between treatment-related changes in natriuretic peptides and clinical effects such as HF hospitalisation.[27]

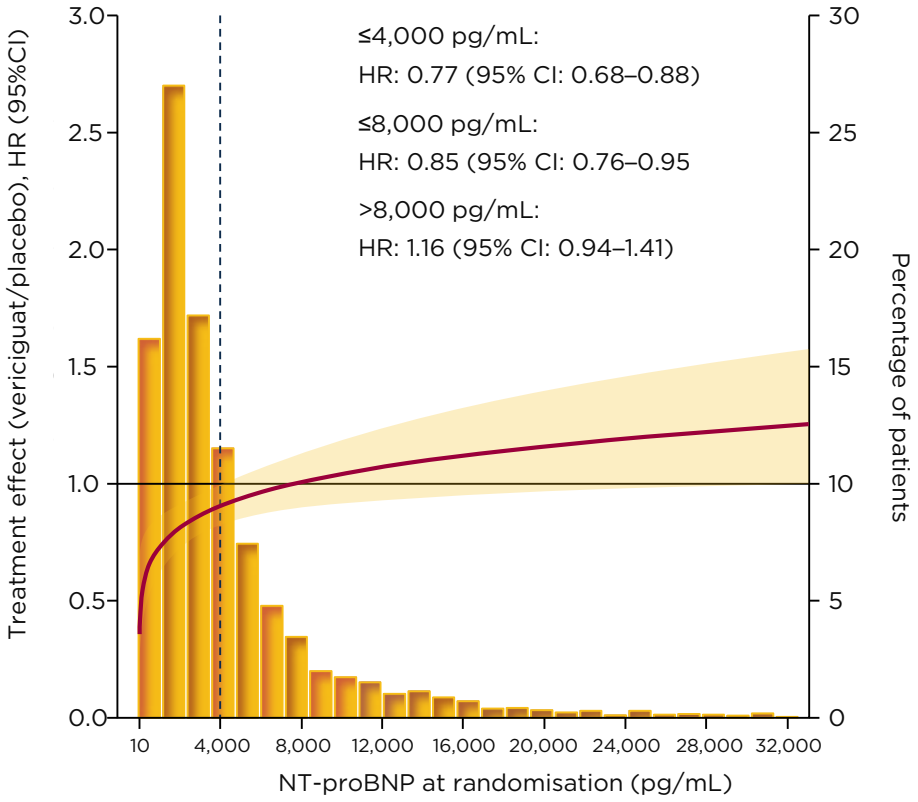


Figure 3: VICTORIA primary composite outcome: clinical outcomes by N-terminal pro-brain natriuretic peptide at randomisation.[29]

CI: confidence interval; HR: hazard ratio; NT-proBNP: N-terminal pro-brain natriuretic peptide.

In the VICTORIA trial, continuous analysis across the spectrum of NT-proBNP demonstrated that the treatment effect of vericiguat was maintained at levels up to 8,000 pg/mL, representing 86% of the study population (Figure 3).[29] Prof Ezekowitz explained that NT-proBNP levels >10,000 pg/mL are uncommon in both clinical practice and the clinical trial setting. The HR for vericiguat versus placebo for the primary composite endpoint was 0.85 in patients with NT-proBNP levels ≤8,000 pg/mL.[29] This treatment effect of vericiguat was further amplified in patients with NT-proBNP levels ≤4,000 pg/mL, accounting for 65% of the VICTORIA population, with a HR for the primary composite outcome of 0.77.[29] Looking at the individual components of the primary endpoint, the treatment effect of vericiguat in patients with NT-proBNP levels ≤8,000 pg/mL was found to extend to both CV death and HF hospitalisation, with similar HR for both.[29]

When carrying out post hoc analysis such as this, it is important to employ robust statistical methods and consider potential unmeasured confounders. Prof Ezekowitz explained that values from this NT-proBNP subgroup analysis were adjusted with the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score and also proved consistent when validated with an internally-derived risk score from the VICTORIA trial, indicating a 'robust' data set.[29]

Putting the VICTORIA Trial into Perspective with Contemporary HFrEF Clinical Trials

Professor Javed Butler

The important question of how to compare different HFrEF clinical trials to make therapeutic decisions based on data was discussed by

Prof Butler. Although similar in size, scope, and primary endpoint, VICTORIA was fundamentally different to contemporary HFrEF trials in its patient population. In addition to minor differences in parameters such as blood pressure and NT-proBNP, VICTORIA enrolled a broader population in terms of ejection fraction (<45%) compared to DAPA-HF (≤40%) and PARDIGM-HF (≤35%), and importantly included patients with an eGFR cut-off as low as 15 mL/min/1.73 m^2.[6,7,22,25,30,31] Prof Butler noted that there is a clinical need to gather more data in this often overlooked renally-impaired patient population.

The VICTORIA trial stood out against other HFrEF trials because of its requirement, by design, for patients not only to have chronic symptomatic HF but also a worsening HF event.[22,32,33] The rationale for selecting such patients was to focus on a population with substantial unmet need who require new treatment strategies. Prof Butler emphasised that patients with worsening HF despite optimal use of guideline-directed medical therapy are at substantially increased risk of poor prognosis. Aggressive treatment, both with known therapies if there are gaps and novel therapies if available, is therefore vital to move these patients back to the 'residual' risk category and prevent progression to advanced HF. Evidence indicates that within 1.5 years of a new HFrEF diagnosis, around 17% of patients will develop worsening HF.[8] The 2-year mortality rate currently stands at approximately 23% in patients with symptomatic chronic HF who have experienced a previous worsening HF event.[8]

Examining study characteristics for the contemporary HFrEF trials at baseline reveals that inclusion of the 'worsening HF event' criteria in VICTORIA had a significant impact on the resulting patient population. Median NT-proBNP levels were substantially higher in VICTORIA patients (2,816 pg/mL) compared to both DAPA-HF (1,437 pg/mL) and PARADIGM-HF (1,608 pg/mL).[6,7,25,30,34,35] VICTORIA also enrolled a greater proportion of patients with NYHA Class III/IV at baseline: 41% versus 32% and 25%, respectively. Compared to a minority of the patients in DAPA-HF (16%) and PARADIGM-HF (31%), the vast majority of VICTORIA patients (84%) had experienced HF hospitalisation within 6 months.[6,7,25,30,34,35] The remaining 16% of VICTORIA patients had previously undergone IV diuretic treatment, equating to an overall study population of whom 100% had experienced a recent HF event.[25]

However, the conclusive evidence came from the outcomes, explained Prof Butler. In VICTORIA, the event rate for the primary endpoint in the comparator arm was 37.8 per 100 patient-years (PY), which was more than double that of the other two trials (DAPA-HF: 15.6 per 100 PY; PARADIGM_HF: 13.2 per 100 PY).[6,7,22,25,26,30,34,35] Similarly, event rates for HF hospitalisation in the comparator arm were more than three times higher in VICTORIA (29.1 per 100 PY) compared to DAPA-HF (9.8 per 100 PY) and PARADIGM-HF (7.7 per 100 PY), and event rates for CV death were doubled (13.9 per 100 PY versus 7.9 per 100 PY and 7.5 per 100 PY, respectively).[6,7,22,25,26,30,34,35]

Understanding the high-risk nature of the VICTORIA patients helps to put the trial results into clinical perspective. Relative risk reduction for the primary endpoint in the VICTORIA trial was approximately 10%, but because of the high-risk nature of the patient population, the absolute risk reduction was 4.2%; this translated to an annual number needed to treat of only 24 to achieve the composite endpoint benefit.[25,26] This reflects the high event rate for the primary endpoint and its components in the comparator arm despite guidelines-directed medical therapy. All events for the primary endpoint were collected within just 10 months of follow-up.[25,26]

Other ongoing trials in the HFrEF arena include the EMPEROR-Reduced study of empagliflozin (the results from this study were not available at the time the symposium took place) and the GALACTIC-HF trial of omecamtiv mecarbil.[36-39] These are large trials with primary endpoints comparable to VICTORIA. However, VICTORIA enrolled a wider group of patients in terms of LVEF inclusion criteria (<45%) than both EMPEROR-Reduced (≤40%) and GALACTIC-HF (≤35%).[22,25,31,36-39] While EMPEROR-Reduced and GALACTIC-HF employed lower eGFR cut-offs (≥20 mL/min/1.73 m^2) compared to previous HFrEF trials, VICTORIA remains the lowest for renal function requirements at >15 mL/min/1.73 m^2.[22,25,31,36-39] In terms of prior HF events, EMPEROR-Reduced inclusion criteria included chronic HF for ≥3 months with no current acute decompensated HF requiring IV diuretics, vasodilators, inotropic agents, or mechanical

support within 1 week of screening nor during the screening period prior to randomisation.[36,37] GALACTIC-HF patients were required to have chronic HF with current HF hospitalisation or ≤1 year of screening.[38,39]

Prof Butler concluded that, although EMPEROR-Reduced and GALACTIC-HF include some high-risk patients, VICTORIA remains the only trial to focus primarily on the high-risk group of patients with HFrEF with a previous worsening HF and is the first study to show therapeutic benefit in this important population.

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New Insights into Icosapent Ethyl for Patients with Residual Cardiovascular Risk

These oral and poster presentations took place from 29th August to 1st September 2020, as part of the European Society of Cardiology (ESC) Congress 2020

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Meeting Summary

In this article, the authors share and discuss data reported in four posters at the European Society of Cardiology (ESC) Congress 2020, held from 29th August to 1st September 2020. These data come from, or are related to, the REDUCE-IT trial, a double-blind, randomised controlled trial of icosapent ethyl, a purified ester of eicosapentaenoic acid, versus placebo. A total of 8,179 patients who had been prescribed statin therapy but continued to have elevated triglycerides (TG) were enrolled.

The first poster considers icosapent ethyl for cardiovascular (CV) risk reduction in a subgroup of the UK Biobank population that fit REDUCE-IT patient inclusion criteria. The second poster presents an accumulation of data, from prespecified interim analyses to final analyses. The third poster reports a reduction in total ischaemic events across the full range of baseline low-density lipoprotein cholesterol (LDL-C) and other key subgroups. The final poster presents the outcomes by baseline statin type and statin category (i.e., lipophilic versus lipophobic).

Introduction

REDUCE-IT was a Phase IIIb, double-blind, placebo-controlled trial that randomised 8,179 patients to receive icosapent ethyl (4 g/day) or placebo.[1,2] Icosapent ethyl (Vascepa®, Amarin Pharma, Inc., Bridgewater, New Jersey, USA) is a novel formulation of highly purified eicosapentaenoic acid. Patients were on stable statin therapy and had either established CV disease (CVD) or diabetes, plus additional CV risk factors, elevated TG levels between 1.7 and 5.6 mmol/L, and LDL-C between 1.0 and 2.6 mmol/L. Patients were followed for a median of 4.9 years and a maximum of 6.2 years.

The primary endpoint was a composite of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularisation, or unstable angina requiring hospitalisation, and the key secondary endpoint was a composite of CV death, MI, or stroke.[1-3] Time to first event analysis showed a relative risk reduction of 24.8% (hazard ratio [HR]: 0.75; 95% confidence interval [CI]: 0.68–0.83; p<0.001) for the primary endpoint and 26.5% (HR: 0.74; 95% CI: 0.65–0.83; p<0.001) for the key secondary endpoint, with an absolute risk reduction of 4.8% and 3.6%, respectively.[2-4] Icosapent ethyl was associated with marked reductions in primary composite and key secondary endpoints, with a number needed to treat of 21 (95% CI: 15–33) for the primary and 28 (95% CI: 20–47) for key secondary endpoints, over a median of 4.9 years.

The following posters present the results of modelling to assess the use of icosapent ethyl in a subgroup of the UK Biobank that fits REDUCE-IT inclusion criteria, and further analyses using REDUCE-IT data to assess the benefit of icosapent ethyl in patients with residual CV risk.

The Effect of Elevated Triglycerides and Purified Eicosapentaenoic Acid for Cardiovascular Risk Reduction in the UK Biobank Population

Doctor Dina Radenkovic

Elevated plasma TG are associated with insulin resistance, metabolic syndrome, and major adverse CV events (MACE). In REDUCE-IT, an absolute risk reduction in MACE of 4.8% was observed with icosapent ethyl compared to placebo, reflecting a 25% relative risk reduction and a number needed to treat of 21.[2] Consequently, in 2019, the U.S. Food and Drug Administration (FDA) approved icosapent ethyl for CV risk reduction in select statin-treated patients with elevated TG.[5]

Dr Radenkovic and colleagues modelled the REDUCE-IT inclusion criteria, utilising data from the UK Biobank to evaluate the effects of icosapent ethyl administration on risk reduction of MACE in the UK population. The UK Biobank is a panomic resource that holds data on 500,000 participants who have been followed-up for at least 10 years.[6] Age- and sex-adjusted rates of CVD in the UK Biobank participants are representative of the general UK population.

Patients with plasma TG between >2.94 and ≤11.28 (10th decile), compared to those with plasma TG between >0.23 and ≤0.77 mmol/L (baseline), had a greater risk (HR: 5.44) of combined CV outcomes (stroke, coronary heart disease, and atherosclerosis). Risk was correlated with increasing plasma cholesterol and TG levels, and survival was inversely correlated with increasing TG. Data from >200,000 UK Biobank participants were used to train the relevant models (i.e., Cox proportional-hazards and DeepSurvival).

Of UK Biobank participants, 3,563 matched with the REDUCE-IT inclusion criteria. Assuming icosapent ethyl had the same effect on the UK Biobank population as in REDUCE-IT, 29% of participants given icosapent ethyl would have suffered an adverse outcome within the UK Biobank during follow-up, compared to the 37% not taking icosapent ethyl. Thus, MACE would have decreased from 1,318 to 1,037, a reduction of 281 individuals, and 13 patients would need to be treated to prevent one from experiencing an event over a median follow-up of 4.9 years.

Dr Radenkovic's analysis concluded that elevated TG increased risk of CV events in the UK Biobank population, and that icosapent ethyl may reduce CV morbidity in this database. As icosapent ethyl has been shown to be safe and well tolerated, it should become an important tool for CV risk reduction. Dr Radenkovic emphasised the applicability of the methodology, which could be used for modelling other treatments and diseases among the UK Biobank population. Additionally, the use of icosapent ethyl may be extended because of its vast pleiotropic effects, including suppression of proinflammatory pathways, stimulation of phagocytosis of macrophages and other immune cells, association with better lung gas exchange in intensive care units, and antithrombotic properties.[7,8]

REDUCE-IT: Accumulation of Data Across Prespecified Interim Analyses to Final Results

Doctor Brian Olshansky

REDUCE-IT, an event-driven trial, randomised 8,179 statin-treated patients with elevated TG and increased CV risk to icosapent ethyl or placebo.[1] In REDUCE-IT, 1,612 primary endpoint events (CV death, nonfatal MI, nonfatal stroke, coronary revascularisation, or hospitalisation for unstable angina) were targeted for a projected 90% power to detect a 15% relative-risk reduction. Two interim analyses were performed by an independent, unblinded data and safety monitoring committee (DMC). The sponsor, steering committee, and clinical endpoint committee were blinded to the final database lock. Dr Olshansky and colleagues considered the efficacy and safety of icosapent ethyl at two prespecified interim and final analyses.[9]

The first interim analysis, performed after approximately 60% of the targeted number of primary endpoint events (n=953), occurred with a median follow-up of 2.9 years, and the second interim analysis was conducted at approximately 80% of accrued events (n=1,218) with a median follow-up of 3.7 years. The final analysis, including 1,606 events, was conducted at a median follow-up of 4.9 years.

Before decisions were made about study continuation at each interim analysis, the DMC discussed the need for a mature dataset to support robustness and consistency of the final efficacy and safety findings. Decisions to continue the study were guided by an analysis plan and prespecified decision-making processes that included assessments of safety, efficacy, primary composite endpoint formal analyses, and informal robustness analyses, with no futility stopping requirements.

Dr Olshansky reported that, compared to placebo, icosapent ethyl reduced the primary composite endpoint by 23% in the first (HR: 0.77; 95% CI: 0.68–0.87; p=0.00005) and second (HR: 0.77; 95% CI: 0.69–0.87; p=0.0000008) interim analyses, and by 25% (HR: 0.75; 95% CI: 0.68–0.83; p=0.00000001) in the final analysis. Similarly, compared to placebo, icosapent ethyl

reduced key secondary endpoint events by 29% (HR: 0.71; 95% CI: 0.60–0.83; p=0.00005) in the first interim analysis, 28% (HR: 0.72; 95% CI: 0.62–0.83; p=0.000009) in the second interim analysis, and 26% (HR: 0.74; 95% CI: 0.65–0.83; p=0.0000006) in the final analysis.

Thus, compared to placebo, icosapent ethyl improved primary and key secondary composite endpoints in both interim analyses; the significance persisted until the final analysis. The benefit of icosapent ethyl versus placebo remained consistent, with similar robustness across individual endpoint components. The clarity of findings in both the study as a whole and in patient subgroups improved steadily across endpoints with a greater number of events.

Data from a continuous landmark analysis of the primary composite endpoint showed consistent, statistically significant benefits of icosapent ethyl versus placebo, starting at 21 months postrandomisation. Similarly, a continuous landmark analysis of key secondary endpoints showed consistent, statistically significant benefits of icosapent ethyl versus placebo, starting at 25 months postrandomisation.

The DMC discussed stopping the trial because of the overwhelming efficacy at each interim analysis. They considered historical examples of failed CV outcome studies for TG-lowering and mixed omega-3 therapies. They reflected on overestimations of the final demonstrated benefit when incomplete datasets are used and weighed societal impacts of fuller datasets before recommending continuation of the trial beyond each interim analyses.

Dr Olshansky and colleagues concluded that consistent, potent efficacy of icosapent ethyl emerged early, within a few months of treatment, and persisted across two prespecified interim analyses until the final analyses. The mature dataset demonstrated highly statistically significant reductions in primary and key secondary endpoints, allowing robust analyses to support overall efficacy and safety conclusions. By allowing the REDUCE-IT dataset to mature fully, physicians and patients were provided with consistent and reliable efficacy and safety data. This provided a basis for clinical decisions regarding icosapent ethyl in CV risk reduction for many of the important subsets of patients included in REDUCE-IT.

REDUCE-IT: Total Ischaemic Events Reduced Across the Full Range of Baseline LDL-C and Other Key Subgroups

Doctor Deepak Bhatt

As previously mentioned, icosapent ethyl reduced time to first primary endpoint ischaemic events by 25% compared to placebo in REDUCE-IT.[2,3] In addition to reducing first events, icosapent ethyl also significantly reduced second (HR: 0.68; 95% CI: 0.60–0.77), third (HR: 0.70; 95% CI: 0.59–0.83), and fourth or more (rate ratio [RR]: 0.46; 95% CI: 0.36–0.60) events.[10,11] Overall, icosapent ethyl was associated with a 31% (RR: 0.69; 95% CI: 0.61–0.77; p<0.001) reduction in total (i.e., first and subsequent) primary endpoint ischaemic events compared to placebo.[10,11] Similar reductions in both first and total key secondary endpoint ischaemic events were observed. Dr Bhatt and colleagues further explored the extent to which icosapent ethyl reduced total primary and key secondary events across prespecified baseline biomarker subgroups (TG, LDL-C, and high-sensitivity C-reactive protein [CRP]).

Total events analyses of prespecified biomarker subgroups demonstrated robust and generally consistent findings for the primary and key secondary composite endpoints. Dr Bhatt reported significant reductions in total primary (range: 24% [RR: 0.76; 95% CI: 0.63–0.91] to 39% [RR: 0.61; 95% CI: 0.48–0.76]) and secondary (range: 24% [RR: 0.76; 95% CI: 0.61–0.96] to 37% [RR: 0.63; 95% CI: 0.48–0.83]) endpoint event rates across all different cut-points of included baseline biomarkers.

The highest reductions in both primary and key secondary total events were in patients with high TG (≥2.3 mmol/L) and low high-density lipoprotein-cholesterol (HDL-C; <0.9 mmol/L), a subgroup of patients who have been of interest in prior and ongoing trials. Icosapent ethyl reduced the total primary and secondary

endpoint event rate in this group by 39% (RR: 0.61; 95% CI: 0.48–0.76) and 37% (RR: 0.63; 95% CI: 0.48–0.83), respectively. Median baseline LDL-C levels in ascending tertiles (≤1.7, >1.7–2.2, >2.2 mmol/L) were 1.5, 2.0, and 2.5 mmol/L, respectively. There were large, significant relative reductions in total primary endpoint events with icosapent ethyl across LDL-C tertiles (35% [RR: 0.65; 95% CI: 0.53–0.79], 28% [RR: 0.72; 95% CI: 0.59–0.87], and 27% [RR: 0.73; 95% CI: 0.60–0.89], respectively; interaction p=0.62), with parallel substantial absolute risk reductions. Similarly, significant relative reductions in total key secondary endpoint events of 33% (RR: 0.67; 95% CI: 0.53–0.87), 28% (RR: 0.72; 95% CI: 0.57–0.90), and 24% (RR: 0.76; 95% CI: 0.61–0.96) across ascending LDL-C tertiles were observed (interaction p=0.77), along with substantial absolute risk reductions. Large, significant total event reductions in both primary and key secondary endpoints were also reported for patients with baseline high sensitivity CRP, both above (primary [RR: 0.76; 95% CI: 0.65–0.88]; secondary [RR: 0.75; 95% CI: 0.63–0.89]) and below (primary [RR: 0.62; 95% CI: 0.52–0.73]; secondary [RR: 0.67; 95% CI: 0.55–0.82]) 2 mg/L.

Dr Bhatt concluded that icosapent ethyl (dosed at 2 g twice daily) significantly reduced total ischaemic events in statin-treated patients with elevated TG and well-controlled LDL-C (<2.6 mmol/L). In the first-event analysis, reductions in total events were observed across a variety of biomarker subgroups, including all baseline levels of TG, LDL-C, and high sensitivity CRP. In addition, a substantial reduction across already low LDL-C tertiles, and in the subgroups with or without low HDL-C but with elevated TG, was evident. Icosapent ethyl is an important option to reduce the high burden of total atherosclerotic events beyond statins and other modern therapies.

REDUCE-IT: Outcomes by Baseline Statin Type

Doctor Deepak Bhatt

Patients with elevated TG have high residual atherosclerotic CVD (ASCVD) risk despite LDL-C control with statin therapy.[12-14] In REDUCE-IT, icosapent ethyl significantly reduced time to first occurrence of the primary composite endpoint and the key secondary endpoint events versus placebo. There were also substantial reductions in lipid parameters associated with TG (-19.7%; p<0.001) and non-HDL-C (-13.1%; p<0.001) with icosapent ethyl versus placebo, as well as modest reductions in LDL-C (-6.6%; p<0.001) and apolipoprotein B (ApoB; -9.7%; p<0.001).[2] However, the mechanisms for the ASCVD benefit of icosapent ethyl are not fully understood.[2,15]

Dr Bhatt and colleagues analysed data from REDUCE-IT to explore the impact of baseline and concomitant statin types and lipophilic versus lipophobic statin categories on ASCVD outcomes and on LDL-C and ApoB levels, and to further consider the relevance of LDL-C pathways in the observed benefit of icosapent ethyl on ASCVD. Of the 8,179 participants enrolled in REDUCE-IT, the largest proportion took atorvastatin (n=3,265; 39.9%) at baseline, followed by simvastatin (n=2,461; 30.1%), rosuvastatin (n=1,755; 21.5%), pravastatin (n=617; 7.5%), lovastatin (n=129; 1.6%), fluvastatin (n=23; 0.3%), and pitavastatin (n=21; 0.3%). Approximately 70% (n=5,683; 69.5%) and 30% (n=2,368; 29.0%) took a lipophilic (hydrophobic: atorvastatin, simvastatin) or lipophobic (hydrophilic: rosuvastatin, pravastatin) statin, respectively, at baseline. For concomitant use (while on study), the largest proportion of patients enrolled in REDUCE-IT used atorvastatin (n=4,048; 49.5%), followed by simvastatin (n=2,576; 31.5%), rosuvastatin (n=2,170; 26.5%), pravastatin (n=739; 9.0%), lovastatin (n=160; 2.0%), fluvastatin (n=31; 0.4%), and pitavastatin (n=33; 0.4%). Almost three-quarters (n=6,068; 74.2%) took a lipophilic statin and one-third (n=2,836; 34.7%) took a lipophobic statin concomitantly. The distribution of baseline and concomitant statin use in each arm was similar to the overall cohort.

Use of atorvastatin, rosuvastatin, simvastatin, or pravastatin as single agents accounted for 96.1% of REDUCE-IT patients. Patients on one of these four statins at baseline were included in a Cox proportional-hazards regression model, which showed a similar benefit of icosapent ethyl on primary and key secondary endpoints across baseline statin types (interaction primary p=0.61; key secondary p=0.49). A similar benefit was also seen across lipophilic/lipophobic statin categories (interaction primary p=0.46; key

secondary p=0.66). Individual baseline statin type (interaction p=0.98) and lipophilic/lipophobic category (interaction p=1.00) had no meaningful impact on the modest median LDL-C changes from baseline to 1 year (range: -5.8 to -8.4%), observed with icosapent ethyl versus placebo. Similarly, baseline statin type (interaction p=0.96) and lipophilic/lipophobic category (interaction p=0.98) did not impact ApoB changes from baseline to 2 years (range: -8.7 to -11.7) observed with icosapent ethyl versus placebo. Results were similar for primary and key secondary composite endpoint outcomes and for changes in LDL-C and ApoB by concomitant statin use.

Dr Bhatt concluded that there were no meaningful treatment differences in primary or key secondary endpoints across individual statin types or lipophilic/lipophobic groups. A similar lack of treatment difference was observed in LDL-C changes from baseline to 1 year. Therefore, LDL-C and ApoB changes and ASCVD risk reduction observed in REDUCE-IT appear to be independent of the type or lipophilicity of concomitant statin therapy, and of LDL-C levels.[2] These data provide clinicians with additional insight regarding concomitant statin therapy considerations when prescribing icosapent ethyl, and suggest there are important mechanisms of action for the substantial ASCVD risk reduction observed with icosapent ethyl that are distinct from the LDL receptor pathway.

Summary

These posters provide further support for icosapent ethyl as an important tool in CV risk reduction. Modelling data presented by Dr Radenkovic suggest that icosapent ethyl may reduce CV morbidity in the UK in patients who meet REDUCE-IT inclusion criteria with implications for wider potential use. Further analyses of REDUCE-IT data provide additional evidence for a beneficial effect of icosapent ethyl in statin-treated patients with elevated TG and well-controlled LDL-C. Dr Olshansky confirmed that allowing the REDUCE-IT dataset to mature fully, despite icosapent ethyl efficacy emerging early, provided physicians and patients with robust, consistent, and reliable efficacy and safety data upon which to base clinical decisions for icosapent ethyl in CV risk reduction. Dr Bhatt showed that, in addition to reducing time to first events, icosapent ethyl significantly reduced total ischaemic events across a variety of biomarker subgroups, highlighting its potential role as a further treatment option to reduce the high burden of total atherosclerotic events. Dr Bhatt also reported no meaningful treatment differences in primary or key secondary endpoints across individual statin types or lipophilic/lipophobic groups. He concluded that these data provide clinicians with additional insight regarding concomitant statin therapy considerations when prescribing icosapent ethyl, and suggest other mechanisms of action apart from the LDL receptor pathway, which might explain the substantial reduction in ASCVD risk observed with icosapent ethyl.

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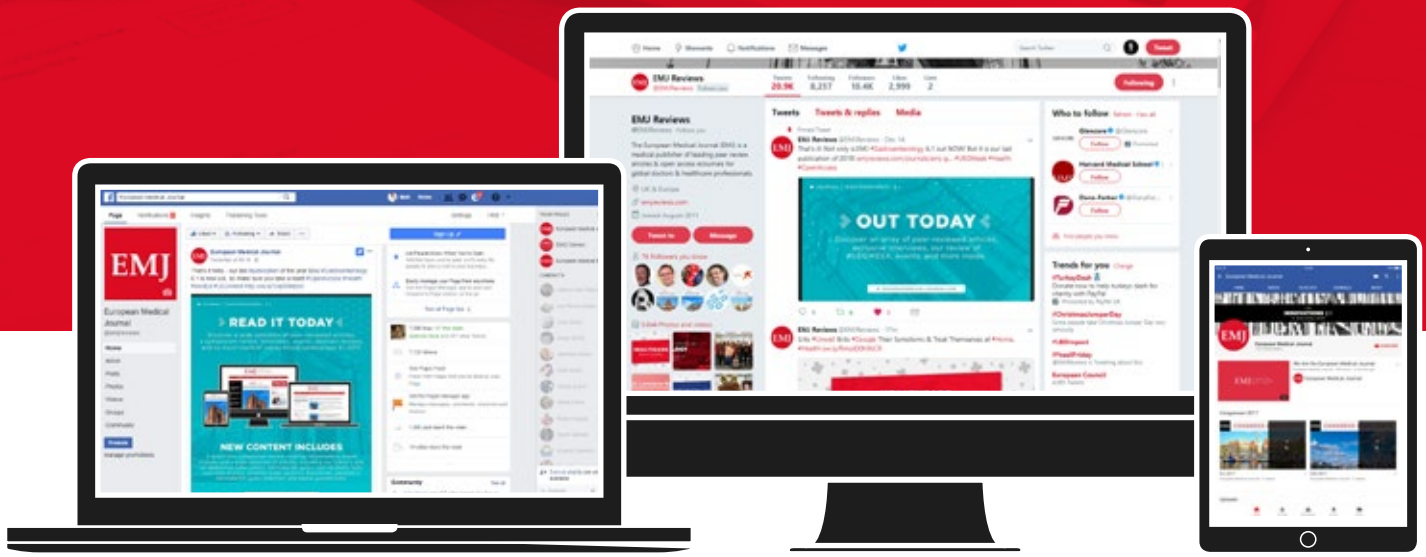

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First Clinical Validation of the 0-Hour/1-Hour Algorithm Using High-Sensitivity Cardiac Troponin I for the Diagnosis of Acute Myocardial Infarction in Japanese Patients

This poster presentation took place between 29th August and 1st September 2020, as part of the European Society of Cardiology (ESC) Congress 2020

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Meeting Summary

Acute myocardial infarction (AMI) is a common and life-threating condition. Approximately 10% of all emergency department (ED) consultations are for suspected AMI, which places a large burden on healthcare systems. Because of the high levels of morbidity and mortality, rapid diagnosis and treatment is crucial.[1-4] The European Society of Cardiology (ESC) suggests the use of the 0-hour/1-hour algorithm for rapid 'rule-out' and 'rule-in' of non-ST-segment-elevation myocardial infarction (NSTEMI) by adopting high-sensitivity cardiac troponin I (hsTnI) assays.[2,5] However, there are limited data regarding the use of this algorithm in Asian populations.

Prospective Validation of 0-Hour/1-Hour Algorithm Using High-Sensitivity Cardiac Troponin I in Japanese Patients Presenting to the Emergency Department

In 2015, the ESC recommended the use of the 0-hour/1-hour algorithm as an alternative to the 0-hour/3-hour algorithm, to rule-in or rule-out AMI based on hsTnI assays for patients presenting with suspected non-ST-elevation acute coronary syndromes in the emergency room. Several studies demonstrated that hsTnI at presentation and after 1 hour had similar diagnostic accuracy compared to the 3-hour algorithm. It was suggested that using the hsTnI 0-hour/1-hour algorithm may improve the time to diagnosis and treatment. Furthermore, the use of this algorithm may also reduce the length of stay in the ED for patients in whom NSTEMI has been excluded. Multiple assays measuring hsTnI exist. Each assay varies in diagnostic accuracy and cut-off levels. Furthermore, limited data are available that have validated the 0-hour/1-hour algorithm using hsTnI in Asian populations.

This single-centre, prospective study validated the 0-hour/1-hour algorithm using hsTnI in Japanese patients (median age: >20 years) presenting to the ED.[6] The hsTnI concentration was measured using the ADVIA Centaur® High-Sensitivity Troponin I Assay (Siemens Healthineers, Erlangen, Germany) at presentation and after 1 hour. Patients were divided into three groups according to the algorithm:

- Rule-out (low risk) group: hsTnI <3 ng/L if chest pain onset was >3 hours or <6 ng/L and Δ1 hour <3 ng/L.
- Rule-in (high risk) group: hsTnI ≥120 ng/L or Δ1 hour ≥12 ng/L.
- 'Observe' group: all other patients.

Based on the fourth universal definition of myocardial infarction,[7] the final diagnosis was adjudicated by two independent cardiologists using all available information, including coronary angiography, coronary CT, and follow-up data. The safety of rule-out was determined by the negative predictive value for NSTEMI. The accuracy of rule-in was determined by the positive predictive value. The overall efficacy of the 0-hour/1-hour algorithm and the ADVIA Centaur High-Sensitivity Troponin I Assay was defined as the proportion of patients triaged towards rule-out or rule-in within 1 hour.

A total of 754 Japanese patients (mean age: 71.1 years; male: n=395), with symptoms suggestive of NSTEMI with serial hsTnI testing, were included in this investigation. The most common comorbidities were hypertension (59%), followed by dyslipidaemia (33%) and diabetes (24%). For the patients with AMI (n=69), the 0-hour median hsTnI was 116 pg/mL (interquartile range [IQR]: 24.2–1,111.0) and 1-hour hsTnI was 362 pg/mL (IQR: 87.5–2,129.0). For the patients without AMI (n=858), the 0-hour hsTnI was 13.0 pg/mL (IQR: 5.0–48.0) and 1-hour hsTnI was 13.5 pg/mL (IQR: 5.4–56.1).

The prevalence of NSTEMI was 7.4% (Figure 1). The safety (negative predictive value) of the 0-hour/1-hour algorithm using hsTnI was 100%, and 28% of patients could be ruled-out.

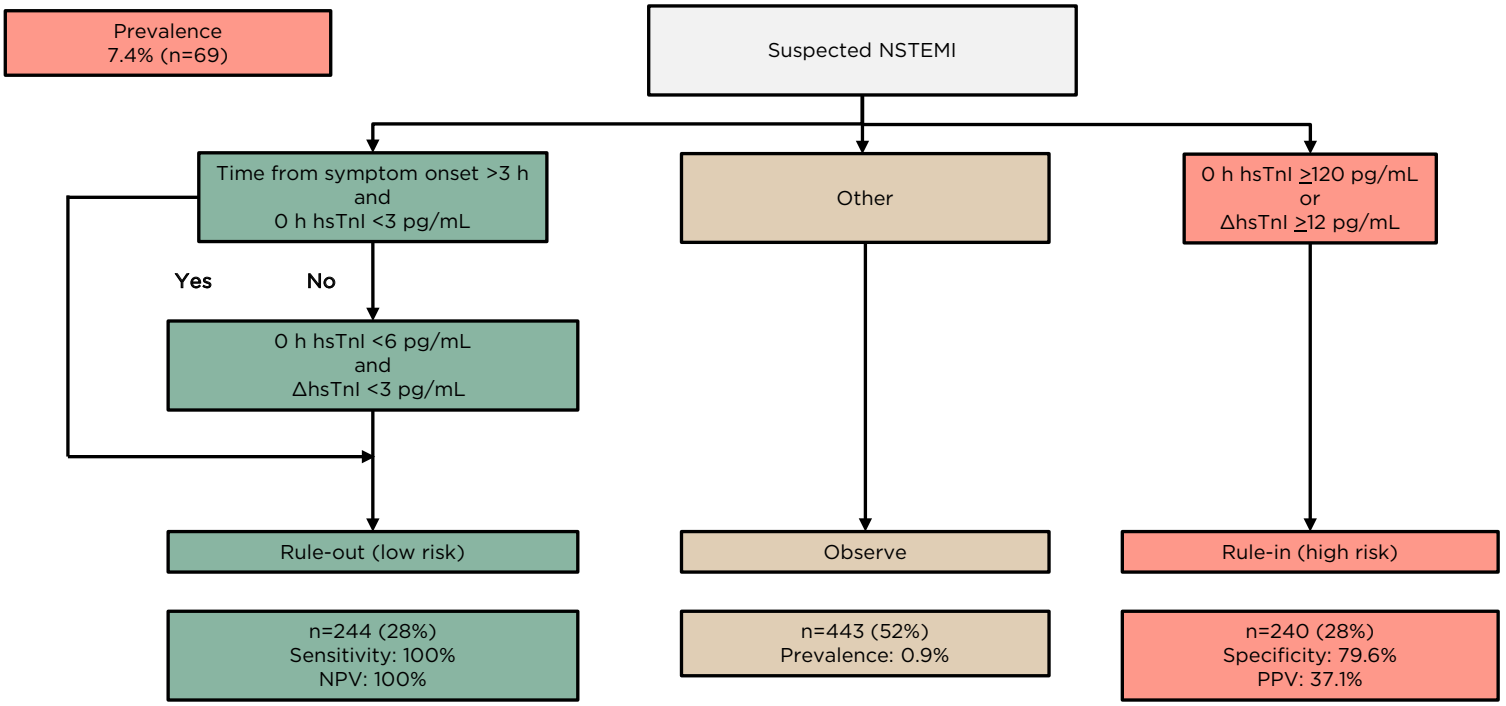

Figure 1: Findings of the first clinical validation of the of 0-hour/1-hour algorithm using high-sensitivity cardiac troponin I in Japanese patients presenting to the emergency department.

ED: emergency department; h: hours; hsTnI: high-sensitivity cardiac troponin I; NPV: negative predictive value; NSTEMI: non-ST-segment-elevation myocardial infarction; PPV: positive predictive value.

Adapted with permission from Ohtake et al.[6]

First presented during ESC Congress 2020 - The Digital Experience

The proportion of patients who could be ruled in was 28%. The accuracy for the rule-in group, determined by the positive predictive value, was 37.1% and the specificity was 79.6%. These data show that the 0-hour/1-hour algorithm using the ADVIA Centaur High-Sensitivity Troponin I Assay is a safe and effective tool for triaging Japanese patients presenting to the ED with suspected NSTEMI. The diagnostic accuracy and sensitivity of the 0-hour/1-hour algorithm using this assay is high and comparable with other well-established methods.[1] The use of this algorithm and assay supports the triage of patients within 1 hour of ED presentation for the majority of individuals, reducing the time to treatment initiation and the length of stay in the ED.

During the ESC Congress 2020, new non-ST-segment-elevation acute coronary syndrome guidelines were introduced.[5] Validation of the 0-hour/1-hour algorithm with a Japanese population aligns with the latest guidelines and confirms the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) algorithm validation published in 2018.[1]

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Abstract Reviews

Read on for summaries of abstracts presented at the ESC Congress 2020, covering topics such as psychosocial factors in Type 2 diabetes mellitus and hospital readmissions after catheter ablation among patients with heart failure.

Hospital Readmissions After Catheter Ablation for Atrial Fibrillation Among Patients with Heart Failure in the USA

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Atrial fibrillation (AF), catheter ablation, heart failure, hospital readmissions.

Citation: EMJ Cardiol. 2020;8[1]:45-46. Abstract Review No. AR1.

BACKGROUND AND AIMS

Atrial fibrillation (AF) and congestive heart failure coexist frequently,[1] and ablation is increasingly utilised as a safe and effective treatment modality for achieving sinus rhythm in patients with heart failure.[2,3] While other studies have examined risk factors for post-ablation readmission, rates of hospital readmission after catheter ablation for AF among patients with an established diagnosis of heart failure is still largely unknown.[4] In this study, the authors aimed to assess the causes and rates of 30-day readmission among patients with heart failure undergoing catheter ablation, compared to medical therapy for AF in the USA.

MATERIALS AND METHODS

The authors utilised the 2016 Nationwide Readmissions Database (NRD) to screen patients with a diagnosis of heart failure and AF using the 10th Revision of International Classification of Disease (ICD-10) codes. Index admission was defined as hospital admission for management of either heart failure or AF.

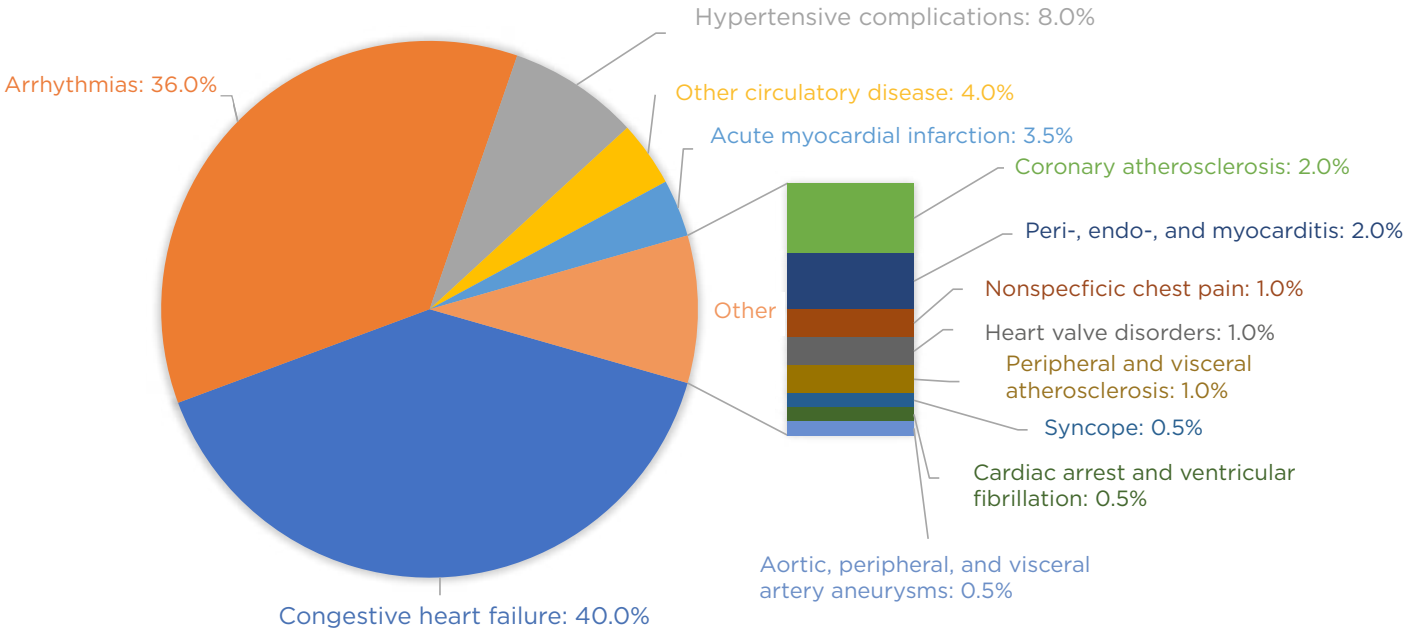

Figure 1: Cardiac causes of 30-day hospital readmission in patients with heart failure and atrial fibrillation that underwent catheter ablation.

Patients who subsequently underwent catheter ablation for AF were grouped separately from those treated medically for AF. Patients who died during the 30 days following discharge, those who were admitted for heart failure or AF management prior to the index admission, and those who had a prior admission for any reason within 30 days of index admission, were all excluded. Thirty-day readmissions were assessed for both the ablation and medical therapy only groups.

RESULTS

The 2016 NRD was screened for all admissions with a diagnosis of heart failure and AF. The final analytic cohort included 749,776 patients (national estimate of 1,421,673) with heart failure and AF. In total, 2,204 patients underwent catheter ablation, compared to 747,572 patients who underwent medical therapy. Patients treated with catheter ablation had lower 30-day readmissions compared to the medical therapy group (16.8% versus 20.1%; p<0.001). In the catheter ablation cohort, 55% of all readmissions were related to cardiac events. Among this group, heart failure (40%) and arrhythmia (36%) were the most common cardiac causes for readmission (Figure 1).

CONCLUSION

In a contemporary nationwide analysis of patients with heart failure and AF, patients treated with catheter ablation for AF compared to medical therapy had fewer 30-day readmissions after discharge from index hospitalisation. Among patients treated with catheter ablation, the most common causes for readmissions were congestive heart failure exacerbation and arrhythmia.

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Usefulness of the Coronary Artery Calcium Score for Statin Prescription in Primary Prevention: Results in Over 16,000 Assessments

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Calcium-scoring, CT scan, lipids, primary prevention, statins.

Citation: EMJ Cardiol. 2020;8[1]:47-48. Abstract Review No. AR2.

BACKGROUND

The latest American Heart Association (AHA)/American College of Cardiology (ACC) cholesterol guidelines on primary prevention of coronary artery disease recommend the use of the absolute coronary artery calcium (CAC)-score to help decision making for using statins. If the CAC-score is 0, it is reasonable to withhold statin therapy if more severe conditions are absent. If the CAC-score is 1–99, it is reasonable to initiate statin therapy for patients ≥55 years of age. If the CAC-score is ≥100, initiation of statin therapy is recommended. In this present analysis, the authors assessed the impact of these guidelines in everyday cardiology practice.

PATIENTS AND LIMITATIONS

- 16,083 people (males: 11,271; females: 4,812).
- If individuals had several CT scans, only the first scan was included.
- Data were prospectively collected in a dedicated data base (FileMaker Pro [Claris International Inc., Santa Clara, California, USA]).
- Only people for primary prevention were analysed.
- Patients had no or very atypical chest pain.
- Patients with exercise-dependent chest pain or shortness of breath were excluded.
- Individuals with cardiac catheterisation were excluded.
- Limitations included: lack of calculation of the many recommended risk scores for atherosclerotic cardiovascular disease, there was no data on low-density lipoprotein cholesterol, and patients with diabetes were included.

RESULTS

In the middle-age group, approximately one-third of males and two-thirds of females would not need a statin, whereas one-third of males and 10% of females would need a statin. Thus, the coronary calcium score has shown it could be valuable in individualised medicine. Please see Table 1.

SUMMARY AND CONCLUSIONS

1. In patients between 40 and 75 years of age, without diabetes, low-density lipoprotein cholesterol <190 mg/dL (<4.9 mmol/L), and a 10-year risk in the middle range (5.0–19.9%), the use of statins is uncertain.
2. The decision for statins should be taken very seriously because it is for life and comprises side effects.
3. The only 'risk enhancer' with a practical instruction for decision making in individual cases is the CAC-score. This recommendation is based on the absolute value of the calcium score.
4. This new form of recommendation makes the interpretation of the calcium score faster, easier, and more reliable than it is according to percentile distribution.
5. Considering the limitations mentioned for this analysis, in the authors' cardiology practice the use of calcium score in 'middle-aged persons':

- Could avoid statin prescription in approximately 30% of male and approximately 60% of females.

- On the other hand, the use of statins is reasonable in approximately two-thirds of higher aged males and one-third of higher aged females for primary prevention in individuals who otherwise would not receive it.

6. Besides this, the CAC-score enables direct visualisation of the disease and, therefore, increases adherence to the therapy with statins and other cardiovascular drugs.

Table 1: Calcium scores according to sex and age groups.

Age (years)	40-44	45-49	50-54	55-59	60-64	65-69	70-75
Calcium scores males: (n=11,271)							
0 Withhold statin	59%	46%	34%	24%	16%	11%	4%
>0 to <100 reasonable if ≥55 years	34%	40%	44%	43%	40%	35%	29%
≥100 statin recommended	7%	14%	22%	33%	44%	54%	67%
Calcium scores females: (n=4,812)							
0 Withhold statin	81%	79%	67%	58%	49%	35%	24%
>0 to <100 reasonable if ≥55 years	17%	17%	25%	33%	35%	42%	40%
≥100 statin recommended	2%	4%	8%	9%	16%	23%	36%

Spontaneous Coronary Artery Dissection: Contemporary Management and Outcome of a National Cohort

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: This study was supported by the Swedish Heart-Lung Foundation.

Keywords: Acute coronary syndrome (ACS), outcome, prognosis, spontaneous coronary artery dissection (SCAD).

Citation: EMJ Cardiol. 2020;8[1]:49-50. Abstract Review No. AR3.

BACKGROUND AND AIMS

Spontaneous coronary artery dissection (SCAD) is an important cause of acute coronary syndrome (ACS) in predominantly young females. Treatment guidelines advocate conservative treatment of SCAD.[1] The aim of this study was to conduct a first description of Swedish SCAD patients regarding the prevalence of risk factors, treatment, and prognosis.

MATERIALS AND METHODS

All patients with acute myocardial infarction (MI) registered in the Swedish Coronary Angiography and Angioplasty Register (SCAAR) from December 2015 until December 2017 were included. The index angiographies of the SCAD patients were re-evaluated by an independent angiographer at each centre. Patients with non-SCAD MI (n=31,670) were used for comparison.

RESULTS

SCAD was identified in 147 patients with MI (111 females; 36 males). The SCAD population was younger than the non-SCAD population, with a mean age of 52.9 (95% confidence interval [CI]: 51.0–54.9) years versus 68.5 (95% CI: 68.4–68.6) years, more often female (75.5% versus 31.9%), and presented with less risk factors (diabetes: 3.0% versus 21.4%; hypertension: 26.5% versus 59.4%; smoking: 38.1% versus 58.1%; statin therapy: 12.2% versus 39.1%; and previous MI: 10.9% versus 21.1%; p<0.001 for all comparisons). SCAD patients less frequently underwent percutaneous coronary intervention (40.1% versus 70.9%; p<0.001). SCAD patients who did undergo percutaneous coronary intervention received coronary stenting to a lesser extent compared to controls (30.6% versus 65.8%; p<0.001). There was no significant difference regarding treatment with aspirin (93.0% versus 89.7%; p=0.45) or double antiplatelet therapy (86.7% versus 84.2%; p=0.43) at discharge. SCAD patients did, however, receive less statin treatment (78.9% versus 91.5%; p<0.001). Analysis of composite outcome consisting of death, MI, and acute re-angiography showed no significant difference between the two groups in December 2017. Interestingly, data showed a higher rate of acute coronary re-angiography in SCAD patients in December 2018 (9.5% versus 4.5%; p<0.001). However, a composite outcome of death and reinfarction in December 2017 showed in the SCAD population was 5.4% versus 13.1% in controls (p=0.018).

CONCLUSION

With a current prevalence of 0.45% of all Swedish MI, data strongly suggest SCAD being an underdiagnosed condition with a prognosis resembling that of non-SCAD MI. Swedish SCAD patients are, as previous studies indicate, younger and harbour less cardiovascular risk factors than patients with traditional MI. The majority of SCAD patients were conservatively

treated in contrast to patients with Type 1 MI. Nevertheless, 40% underwent coronary intervention, indicating overtreatment of SCAD during this time period.

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Incremental Prognostic Value of Tricuspid Annular Dilatation Over the Society of Thoracic Surgeons (STS) Score

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Disclosure: Prof Mehilli has received an institutional research grant from Boston Scientific; lecture fees from Edwards Lifesciences, Medtronic, Biotronik, Terumo, Boston Scientific, BMS, and AstraZeneca. Prof Hausleiter has received speaker honoraria, research support, and serves on the advisory board for Abbott Vascular and Edwards Lifesciences. Dr Braun has received speaker honoraria from Abbott Vascular. The remaining authors report no conflicts of interest.

Keywords: Aortic stenosis, aortic valve intervention, Society of Thoracic Surgeons (STS) score, transcatheter aortic valve replacement (TAVR), tricuspid annular dilatation (TAD).

Citation: EMJ Cardiol. 2020;8[1]:50-51. Abstract Review No. AR4.

BACKGROUND AND AIMS

Transcatheter aortic valve replacement (TAVR) is the treatment of choice in many patients with severe aortic stenosis. The Society of Thoracic Surgeons (STS) score is a well-established risk score to estimate morbidity, mortality, and procedural risks of patients undergoing TAVR. However, tricuspid annular dilatation (TAD), which is an increasingly recognised pathology associated with increased mortality, is not implemented in the STS score. The purpose of this analysis was to investigate the incremental prognostic value of TAD over the STS score.

MATERIALS AND METHODS

The maximal septal-lateral diameter of the tricuspid annulus was measured in 923 patients on three-dimensional multidetector CT datasets. A cut-off of 23 mm/m^2 body-surface area was revealed by receiver-operating curve statistics and used to define TAD in a previous analysis (data accepted for publication). Incremental prognostic information was tested with C-index statistics and continuous net reclassification improvement. Patients were followed for 2 years and all-cause mortality was defined as the study endpoint.

RESULTS

Of the 923 patients included in this analysis, TAD was found in 370 patients (40%). Patients with TAD had a significantly higher mortality (hazard ratio: 2.18; 95% confidence interval [CI]: 1.71–2.78; p<0.001).

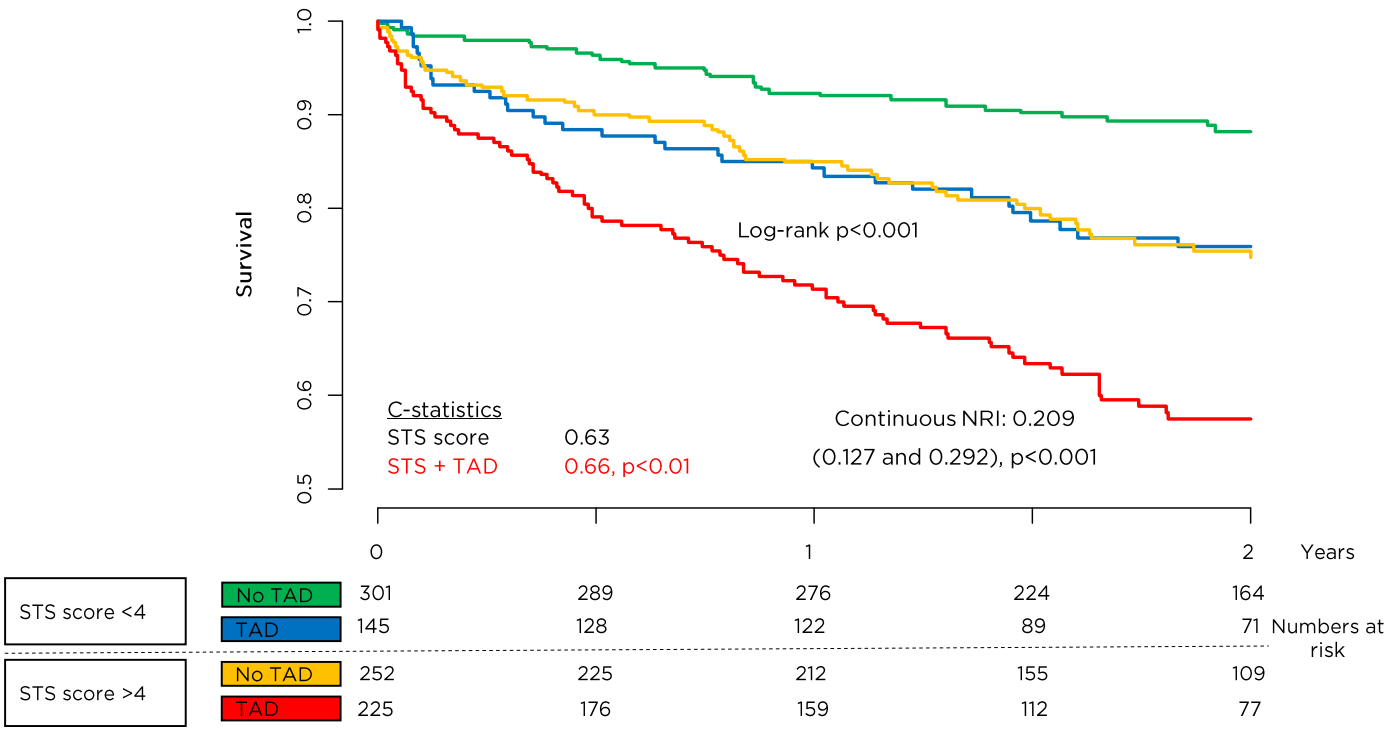

Figure 1: Survival stratified of tricuspid dilation and Society of Thoracic Surgeons (STS) score.

The survival of patients after a transcatheter aortic valve replacement procedure, stratified for Society of Thoracic Surgeons (STS) score using a cut-off of 4 and tricuspid annular dilatation.

NRI: net reclassification improvement; STS: Society of Thoracic Surgeons; TAD: tricuspid annular dilatation.

The mean STS score in the investigated patient cohort was 5.6±5.0. TAD provided incremental prognostic information over the STS score when assessed with C-index statistics (a rise from 0.63 to 0.66; p<0.01) or continuous net reclassification improvement (0.209; 95% CI: 0.127–0.292; p<0.001). Estimated survival rates at 2 years were 88.2% (95% CI: 84.5–92.1) in patients with a low STS score (<4) and no TAD and 57.5% (95% CI: 51.1–64.7) in patients with a high STS score (>4) and TAD. Estimated survival rates in patients with a low STS score and TAD and patients with a high STS score and no TAD were similar (75.8%; 95% CI: 68.9–83.5; versus 74.8%; 95% CI: 69.2–80.7, respectively). Kaplan–Meier curves are shown in Figure 1.

CONCLUSION

TAD is a common entity in patients undergoing TAVR for severe aortic stenosis. It is associated with significantly higher mortality and provides incremental prognostic information over the STS score.

A Comparison of In-Hospital Outcomes Between the Use of Microaxial Left Ventricular Assist Device and Intra-Aortic Balloon Pump in Revascularised Acute Myocardial Infarction Complicated by Cardiogenic Shock

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Cardiogenic shock, in-hospital outcomes, intra-aortic balloon pump (IABP), microaxial left ventricular assist device (MLVAD).

Citation: EMJ Cardiol. 2020;8[1]:52-53. Abstract Review No. AR5.

BACKGROUND AND AIMS

Acute myocardial infarction (AMI) complicated by cardiogenic shock is associated with significant morbidity and mortality. Mechanical circulatory supporting devices, including microaxial left ventricular assist devices (MLVAD; Impella®, Abiomed, Danvers, Massachusetts, USA, and TandemHeart®, LivaNova, London, UK) and intra-aortic balloon pumps (IABP), have increased treatment options in addition to pharmacotherapy. IABP consist of a cylindrical balloon placed in the aorta and work via 'counterpulsation' with balloon inflation in diastole and deflation in early systole; however, the IABP-SHOCK II trial showed inferior survival and more complications compared with optimal medical treatment.[1] On the other hand, MLVAD are positioned across the aortic valve via a peripheral artery and create continuous forward blood flow from the left ventricle into the aorta at a constant rate by a rotary pump. Despite that, all randomised clinical trials, including PROTECT II, ISAR-SHOCK, IMPELLA-STIC, and IMPRESS in Severe Shock, were not able to discern survival benefit over IABP.[2,3] There is limited knowledge of the in-patient complications of these devices.

Purpose

To compare the outcomes of patients with AMI who underwent percutaneous coronary intervention (PCI) complicated by cardiogenic shock treated with IABP versus MLVAD.

MATERIALS AND METHODS

The Nationwide Inpatient Sample (NIS) database is the largest inpatient registry in the USA. The authors used NIS data from 2009–2014 to identify adult patients admitted for AMI who received PCI complicated by cardiogenic shock. Based on the use of IABP or MLVAD, the study population was divided into two groups. To reduce selection bias, propensity score matching was performed using the Kernel method. Patient characteristics, hospital characteristics, and comorbidities were matched. Logistic regression was used for categorical variables including in-hospital mortality, requirement for blood transfusion, sepsis, cardiac arrest, and cardiac complications (including iatrogenic complications, haemopericardium, and cardiac tamponade). Poisson regression was used for continuous variables, including length of stay and total cost.

RESULTS

A total of 49,837 patients were identified. With propensity score matching, 34,132 patients in the IABP group were matched to 1,430 patients in the MLVAD group. Compared with the MLVAD group, the IABP group had lower in-hospital mortality rates (28.29% versus 40.36%; odds ratio [OR]: 0.58 [0.42–0.81]; p=0.002), lower rates of blood transfusion (9.63% versus 11.50%; OR: 0.49 [0.27–0.88]; p=0.017), and lower costs

($47,167 versus $70,429 USD; p<0.001). The IABP and MLVAD groups had similar lengths of stay (8.9 versus 9.3 days; p=0.882), rates of cardiac complications (6.50% versus 7.24%; OR: 0.56 [0.26–1.19]; p=0.134), rates of sepsis (9.30% versus 14.98%; OR: 0.66 [0.38–1.14]; p=0.133), and rates of cardiac arrest (37.84% versus 41.05%; OR: 0.70 [0.45–1.10]; p=0.123). (Table 1)

Table 1: Propensity score-matching outcomes.

In-hospital outcomes	Adjusted odds ratio	p value
Mortality	0.58 (0.41–0.82)	0.002
Length of stay (coefficient)	-0.01 (-0.16–0.14)	0.882
Total cost (coefficient)	-0.32 (-0.40– -0.23)	<0.001
Cardiac complication	0.56 (0.26–1.19)	0.134
Blood transfusion	0.49 (0.27–0.88)	0.017
Sepsis	0.66 (0.38–1.14)	0.133
Cardiac arrest	0.70 (0.45–1.10)	0.123

CONCLUSION

In patients with AMI who underwent PCI complicated by cardiogenic shock, MLVAD compared with IABP was associated with higher risk of in-hospital mortality; greater requirement for blood transfusion, indicating the presence of major bleeding complications; and higher cost, although study interpretation is limited by the retrospective observational design. Further research is warranted to elucidate the optimal mechanical circulatory supporting devices in these patients.

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Psychosocial Factors Predicting Mastery in Type 2 Diabetes Mellitus

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Depression, diabetes distress, mastery, moderation, Type 2 diabetes mellitus (T2D).

Citation: EMJ Cardiol. 2020;8[1]:54-55. Abstract Review No: AR6.

BACKGROUND

Type 2 diabetes mellitus (T2D), like many other chronic conditions including cardiovascular disease, requires effective self-management to ensure optimal outcomes and reduce associated complications.[1] Mastery is a recognised health protective factor among those with chronic conditions, with higher levels of mastery associated with better control of chronic conditions, treatment adherence, and improved health behaviours.[2,3]

The literature generally highlights the individual impact of psychosocial factors on effective self-management of chronic conditions. Depression is associated with poorer clinical outcomes, medication adherence, and motivation impacting negatively on self-management.[4] Disempowerment is associated with poorer outcomes.[5] Diabetes distress is negatively associated with self-management, glycaemic control, and adherence.[5] However, little is known about how these psychosocial factors impact mastery.

METHODS

This study used baseline data drawn from a randomised controlled trial (RCT) of a structured diabetes education intervention. The sample comprised 131 participants with T2D aged 39–85 years (median: 62.3; standard deviation: 8.8), of whom 59.5% were male. Participants were assessed using: Problem Areas in Diabetes (PAID) scale, measuring diabetes related distress;[6] Pearlin Mastery (PM) scale;[7] Hospital Anxiety and Depression Scale (HADS);[8] and the Diabetes Empowerment Scale-Short Form (DES-SF).[9]

The purpose of this study was to evaluate the moderating role of diabetes empowerment and depression in the relationship between diabetes distress and mastery. To test this, a moderated model was specified and tested in SPSS using PROCESS, a "logistic regression-based path analytical framework for estimating direct and indirect effects in simple and multiple moderation models."[10]

RESULTS

All variables were statistically significant predictors of mastery. Diabetes distress (b: -0.249; t(5,112): -3.71; p<0.005) and depression (b: -0.980; t(5,112): -5.73; p<.005) were negatively associated with mastery; with diabetes empowerment (b: 0.280; t(5,112): 3.02; p<.005) positively associated. A significant interaction between diabetes-specific distress and depression was found, (b: 0.024; t(112): 3.79; p<.005), indicating that the magnitude of the diabetes distress effect on mastery depends on the level of depression. There was a significant increase in the variance in mastery explained because of the diabetes distress and depression interaction (F[1,112]: 14.40; p<.005; coefficient of determination [ΔR^2]: 0.06). A further increase in the mastery variance explained was found when the interaction was expanded to involve both moderators (F[2,112]: 16.88; p<.005; ΔR^2: 0.14). The results highlight, at low levels of empowerment, increasing depression in the presence of increasing levels of distress predicted lower levels of mastery. This held true at both moderate and high levels of empowerment.

CONCLUSIONS

The significant interaction between diabetes distress and depression highlights how the negative impact of diabetes distress on mastery is heightened by increasing levels of depression, with this interaction creating greater reduction in mastery. Additionally, it appears that any positive effect of diabetes empowerment on mastery is eroded in the presence of diabetes distress and depression. The evidence suggests that the psychosocial interventions likely to have greatest impact on mastery are those that do not only focus on condition-specific distress, but also recognise and target key moderators, particularly depression.

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Congress Interviews

In this round table interview, we gather the opinions and perspectives of Professors Atar, Achenbach, and Zamorano, who have all served on the ESC Board, discussing why they entered the field of cardiology and their roles within the ESC.

Prof Stephan Achenbach

University of Erlangen, Erlangen, Germany; President of the ESC

Prof Dan Atar

University of Oslo, Oslo, Norway; Past Secretary/Treasurer of the ESC

Prof Jose Zamorano

University Complutense, Madrid, Spain; Past Vice President of the ESC

Q1 What fascinates you the most about cardiology, and why did you decide to have a career in this field?

Prof Atar: We cardiologists are proud to have chosen one of the most dynamic and innovative fields of medicine. Few disciplines have encountered similar progresses in disease detection and in therapies, both pharmacology-based and interventional alike. During the past 40 years, our field has gone through achievements that have revolutionised medicine to a great extent.

"I love being a doctor and feeling that we can help many people; this happens in our profession daily and we feel privileged."

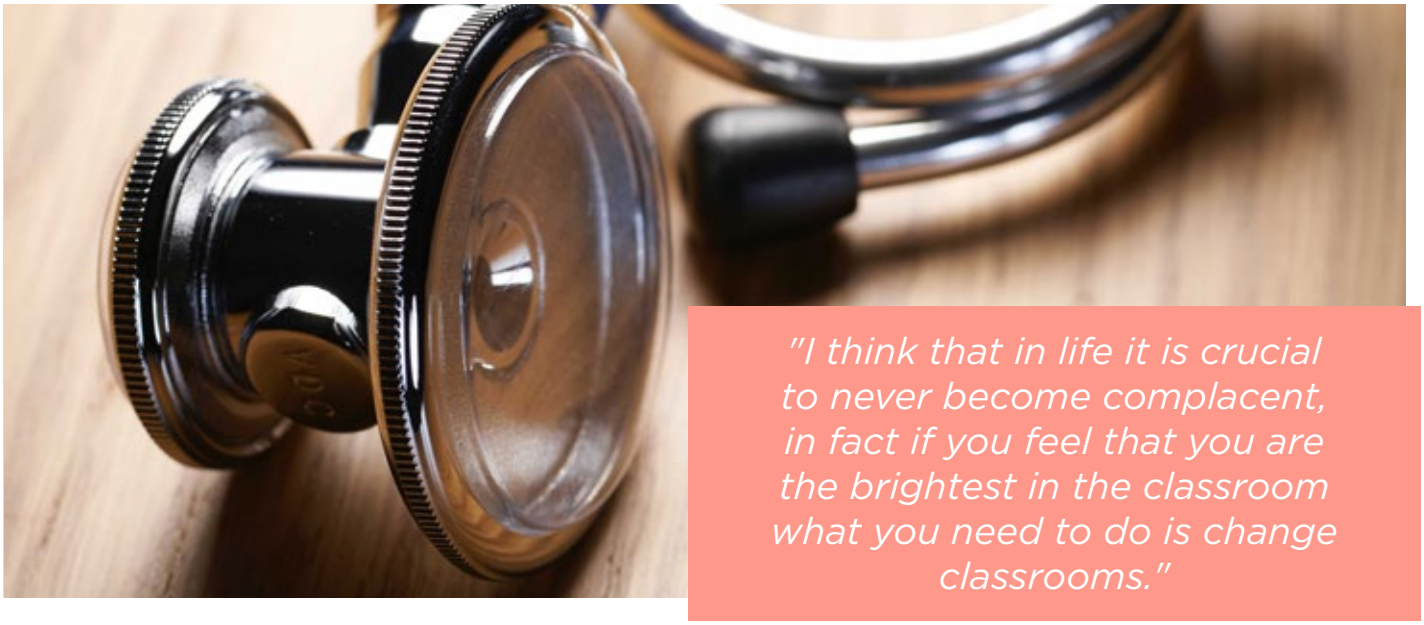
Prof Achenbach: First of all, cardiology is extremely interesting from a physiology perspective. We have an organ that is constantly moving, with a complex interplay of muscle, valves, vessels, blood supply, and electrical currents. In addition, we can help not all, but many patients very rapidly and effectively, and get them to move on and continue leading a normal life. As an interventionalist who also practices imaging and general cardiology, I like the balance of manual work and 'intellectual' challenges; but please do not get me wrong, there is a lot of intellect in interventional work also.

Prof Zamorano: I am not the typical example of a person that was thinking of becoming a doctor since childhood. I was much simpler and wanted to become a football player. But after finishing school, I decided to enter medical school and become the first doctor in my family. Once I entered medical school, the heart became the most fascinating organ for me. From physiology to pathology, it is was all really intriguing, and still makes me happy whenever I research, diagnose, or treat a patient. Moreover, it is a privilege that we as doctors are able to help other people every day. In simple words, being a doctor is simply not the same as working as a doctor. I love being a doctor and feeling that we can help many people; this happens in our profession daily and we feel privileged.

Q2 Could you tell us about your most recently published paper, and the impact you hope the conclusions to have on the cardiology community?

Prof Atar: In my most recent publication, the title says it all: "The Myth of Stable Coronary Heart Disease." The article explains that the term stable is a misconception, and it should be named 'chronic' instead, to reflect the progressive nature of disease. Shortly after this publication, the European Society of Cardiology (ESC) guidelines used the same terminology.

Prof Achenbach: At the moment, we are publishing mainly around 1) risk stratification by cardiac CT, helping to avoid individuals getting



"I think that in life it is crucial to never become complacent, in fact if you feel that you are the brightest in the classroom what you need to do is change classrooms."

a myocardial infarction and 2) the use of non-invasive imaging to make interventional procedures more effective and safer. This will help patients who undergo procedures such as percutaneous coronary intervention (PCI) or transcatheter aortic valve implantation (TAVI) to get better results at lower risk. Our contributions may be small, but overall, everyone who contributes helps to move the field further.

Prof Zamorano: My research life has been committed to improving diagnostic methods in cardiology and managing cardiovascular risk factors. My last contribution related to the new classification of tricuspid regurgitation (including the 'massive' and 'torrential' concept). Indeed, this implies not only a more accurate diagnosis but also aims to improve the prognosis of such patients. The new percutaneous approaches to valve diseases in cardiology implies a more accurate diagnosis and also aims to establish the optimal timing for treatment. I do believe that a more accurate diagnosis followed by earlier treatment will benefit our patients.

Q3 What does your role on the European Society of Cardiology (ESC) Board entail, and what have you achieved so far in this position?

Prof Atar: I have served our society in a variety of elected positions and have enjoyed the various aspects to interact with colleagues. My role as Vice-President for National Affairs took me to 43 different national congresses and so-called leadership meetings, where we had a chance to discuss the future input of that particular national society to the ESC as an overarching multinational organisation, and I then delivered the specific wishes from the national leaders back to the ESC. In my current role as Treasurer/Secretary of the society, I had the opportunity to monitor the growing activities across various constituent scientific bodies. All of these tasks were extremely rewarding and provided a lot of personal learning.

Prof Achenbach: I am currently the president-elect and, as of September, I will be the president of the ESC for a period of two years. It will be both a challenge and a privilege to be at the front of such a distinguished group of colleagues and staff members.

In previous roles, among other things, I chaired the programme committee for the ESC Congresses 2017 in Barcelona and 2018 in Munich, and I had responsibilities for ESC global affairs, the website, and a rebranding programme.

Prof Zamorano: After reading this question, I realised that ESC has been quite relevant in my personal life, my family, and my career.

"During the last few years, we have discussed digital cardiology many times and now COVID-19 has, in an abrupt way, moved all of us towards digital medicine."

I started as a member of the Scientific Committee of the European Association of Echocardiography (EAE) with Prof Fausto Pinto (2001–2004), Member of the Accreditation Committee of the EAE (2003), Member of the Guidelines Committee chaired by Prof Silvia Priori (2004–2008), elected Councillor of the ESC with Prof Kim Fox (2006–2008), elected President-elect of the EAE (2006–2008), Secretary/Treasurer of the ESC with Prof Roberto Ferrari (2008–2010), President of the EAE (2008–2010), Chair of the ESC Guidelines Committee (2012–2016), Chair of the ESC Global Affairs Committee (2016–2018), and I currently am Vice-president of the ESC. A lot of time and effort has been committed. I could list personal contributions but will refrain from it as I never seek recognition for teamwork. I do not recall any sad memories in my ESC history, they were all good moments. I only remember having excellent and brilliant cardiologists around me driving me to improve. I think that in life it is crucial to never become complacent, in fact if you feel that you are the brightest in the classroom what you need to do is change classrooms. This feeling never happened to me at ESC, I was always surrounded by brilliant, committed and hardworking people. I found some friends at ESC, cardiologists and staff, and I feel that ESC will always be a part of my life. Even if I did mange some great projects, new ideas, books etc., I have the feeling that I always received much more than what I gave and I am forever grateful.

Q4 It has been decided to move the ESC Congress 2020 into a virtual meeting this year. What do you believe to be the advantages of an online congress?

Prof Atar: There was undoubtedly a disappointment in the ESC Board when we had to take this decision. Nothing can replace the buzz of a face-to-face meeting. There are a few advantages in substituting a live congress with a virtual event, and we shall make the best of it. However, I would say that the excitement of meeting colleagues face-to-face and performing live scientific discussions is never the same in a virtual meeting.

Prof Achenbach: It will allow more individuals to connect and participate, from all around the world, so that is a major benefit. We can reach further but it is also necessary that we adapt our programme and content to that new situation. The ESC team has been performing marvellous work to achieve that.

Prof Zamorano: Life is digital. The world is not changing, is has already changed. Learning and education goes hand in hand in a different way nowadays. There is no doubt that we need to move towards this new concept. What should not be done is simply replicating the usual ESC Congress to an electronic format. I am happy to see that this is not the spirit of the ESC Congress 2020. We should also not expect attendees to sit in front of their computers for 3 days and learn. Again, this is not the spirit of the meeting. Therefore, ESC will again be leading a new trend of education and I am sure it will be a great meeting and boast a new way of teaching.

Q5 'Spotlight 2020: The Cutting Edge of Cardiology' will be the overarching theme of the ESC Congress. How have recent advancements in technology helped research and patient care?

Prof Atar: New developments in therapy are constantly evolving, and hence the title of this year's spotlight. We will be proud to feature some of the breakthrough findings in cardiovascular science.

Prof Achenbach: There are so many developments, reaching from small interfering RNA to catheter-based treatment techniques of valve disease and smart watches to follow the heart rhythm. We constantly have new opportunities to diagnose and treat, and need to carefully evaluate what is good, useful, and has a benefit in the long run.

Prof Zamorano: Cardiology as a specialty has always been in nexus with technology. New diagnostic methods, innovations in therapy, or research are part of the DNA of cardiologists, it is something that attracts our professionals. Therefore, the topic is quite pertinent, especially nowadays with all the changes that suddenly appeared in our medical profession as a result of the COVID-19 pandemic. During the last few years, we have discussed digital cardiology manny times and now COVID-19 has, in an abrupt way, moved all of us towards digital medicine.

Q6 The mission of the ESC is: "To reduce the burden of cardiovascular disease." In your opinion, what areas of cardiology need the most support at this time?

Prof Atar: Cardiology encompasses all sub disciplines, each of which has an enormous impact on health, and I therefore would not emphasise one of those areas in preference of the others. The spectrum goes from prevention, to diagnosis, to therapy.

Prof Achenbach: We need to address inequalities and make sure that, if in any way possible, all individuals and patients in Europe and beyond get access to those diagnostic and therapeutic measures that will reduce mortality and morbidity. Singling out a certain area of cardiology that needs particular attention, whether intervention, arrhythmias, heart failure, or other, would not be adequate since there are constant improvements in all of these areas that need to be made known and implemented. However, the ESC also has a particular role in trying to influence health policies towards healthier behaviour, and to make sure that funding for cardiovascular research does not fall even more behind that of other diseases such as cancer. Cardiovascular disease remains the most frequent cause of death and efforts to fight cardiovascular disease must not decline.

Prof Zamorano: It is difficult to state a specific area. Obviously, all areas, but if you ask me what I did in my own department in the last months, I can answer that we changed many things.

"It is very important that the 'usual care' for heart patients is not interrupted and remains available at a low threshold, even during times of this or other pandemics..."

We have invested a lot into digital technology and into changing our approach to treat and control our patients. We have a new outpatient approach; we created the digital platform ECardio where we receive all our new patients and distribute them to the proper path from that platform. We are now also creating a digital cardiology department, akin to a virtual hospital. We also incorporated a new format of teaching courses where the speakers do not use any slides and the attendees are the real relevant people. Teaching today is simply answering what the attendees want to know, not what the teacher wants to show. Now the attendees ask their topic-based questions via chat and all that the faculty need to bring to the session is their brain. We have video chats (attended virtually from America to Australia) and soon we will host our Valve Fest in October, again with this new modality of virtual teaching.

Q7 The ESC produced a guidance document for clinicians to follow to provide expert care for patients with cardiovascular disease during the COVID-19 pandemic. Could you summarise the key recommendations?

Prof Atar: One of our greatest concerns is the delay of cardiac patients in access to healthcare during the COVID-19 pandemic. Cardiovascular disease manifestations often require immediate attention, a fact that must not be forgotten in the midst of the challenge of infection risk.

Prof Achenbach: It is very important that the 'usual care' for heart patients is not interrupted and remains available at a low threshold, even during times of this or other pandemics; certainly a lesson we have learned for the future. Media of all sorts have led to a substantial amount of fear in the nonaffected population that going to a hospital will put them at risk of contracting COVID-19. We have seen too many patients presenting too late with severe heart conditions.

Prof Zamorano: Well I was not involved in the production of the document so I cannot comment on that specifically, but again the consensus here is that from the beginning ESC wanted to help. We were heavily involved in treating these patients at our hospital. More than 3,000 patients were admitted and at the peak we had more than 800 patients coming in daily to the Hospital. No doubt this was a horrible situation, but also included many benefits. I saw many people come together with incredible solidarity trying to help and acting as a true team. There was no personalism, in the stock market, the decreasing values included personal recognition and those increasing were group motivation, inclusiveness, discovering new values and talented people, and demonstrating that leaders reflect the example that they show and that behavioural example legitimatises them as true leaders. This is also something that was shown to me from the ESC in all activities; no personalism, it is about teamwork and growing together.

Q8 Guanylate cyclase stimulators are increasingly being seen as the future of heart failure treatment; what potential do you believe they truly have?

Prof Atar: As a rational and truly innovative mechanism to ameliorate heart failure, there is a great potential in pharmacological guanylate cyclase stimulation. The newest results support this notion, based on randomised experience against contemporary state-of-the-art heart failure therapies.

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Key Findings from the EXPLORER-HCM Study of Mavacamten in Obstructive Hypertrophic Cardiomyopathy: Insights From the Principal Investigator

Interviewee: Iacopo Olivotto

Florence Referral Center for Cardiomyopathies, Careggi University Hospital, Florence, Italy

Disclosure: Dr Olivotto has received grants and/or fees from MyoKardia, Amicus, Sanofi Genzyme, Shire Takeda, and Cytokinetics.

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Interview Summary

Hypertrophic cardiomyopathy (HCM) is a progressive myocardial disease that impacts function and quality of life. Patients with HCM may have shortness of breath (dyspnoea), effort intolerance, chest pain (angina), palpitations, and syncope,[1-3] and have increased risk of atrial fibrillation, stroke, heart failure (HF), and sudden cardiac arrest or death.[2-5] Community-based studies indicate the prevalence of HCM is 1 in 500, with many individuals remaining undiagnosed throughout life. HCM can affect people of any age, race, or sex.[1,5-7]

Obstructive HCM (oHCM) is characterised by unexplained left ventricular (LV) hypertrophy, which is associated with dynamic LV outflow tract (LVOT) obstruction, and is defined by the presence of either a resting or provoked LVOT peak gradient ≥30 mmHg.[8] Current pharmacological treatments for oHCM are nonspecific, cause side effects, or have limited efficacy in relieving symptoms;[1,2,8] hence, there is a significant unmet need for targeted treatment of this disease.

Mavacamten (MyoKardia, Brisbane, California, USA) is a first-in-class, targeted inhibitor of cardiac myosin that reduced LVOT obstruction, improved exercise capacity, and relieved symptoms of oHCM in the PIONEER-HCM Phase II study.[9,10] The EXPLORER-HCM Phase III was a pivotal, randomised, double-blind, placebo-controlled study,[11] conducted to investigate the efficacy and safety of mavacamten in treating symptomatic oHCM.[8,12]

For this article, EMJ conducted an interview on 9th September 2020 with the principal investigator of EXPLORER-HCM Dr Iacopo Olivotto, who has a wealth of experience and expertise in managing oHCM, to gain his perspectives on the study and its importance in the field.

TREATMENT OF OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY AND THE NEED FOR EXPLORER-HCM

Dynamic LVOT obstruction was recognised from the earliest clinical descriptions of HCM >60 years ago,[13,14] and is arguably the most visible and well-known pathophysiological component of this heterogeneous disease.[15] Dr Olivotto described how patients with oHCM have been treated to manage symptoms for >40 years with drugs developed for other cardiac conditions; however, these treatments act downstream and do not target the core molecular abnormalities of the disease. Furthermore, alcohol septal ablation or surgical removal of the obstruction is invasive, has inherent risk, requires expertise that is not widely available, and does not alter the long-term progression of myocardial dysfunction. Dr Olivotto reflected that there is much known about oHCM, including molecular mechanisms, genetics, risk, and natural history. From the time of diagnosis, there is a span of 20–30 years before the disease progresses to HF; therefore, this is an unexploited opportunity to interfere with the disease and halt disease progression.

EXPLORER-HCM was the first Phase III study to assess targeted, disease-specific treatment for oHCM, and comprised 251 mildly to moderately symptomatic patients (New York Heart Association [NYHA] functional Class II–III symptoms: 123 on mavacamten; 128 on placebo) at 68 centres in 13 countries.[8,12]

Dr Olivotto outlined: "oHCM is a neglected disease that affects millions of people worldwide and for which there is no licensed drug. We see the disease progressing and we have nothing to counter it. The need for EXPLORER-HCM reflects the need for a proper treatment for this disease. Interfering with the basic mechanism of disease is really what we need to do and EXPLORER-HCM is just the beginning."

OBJECTIVE AND KEY ENDPOINTS OF EXPLORER-HCM

EXPLORER-HCM was conducted to test a first-in-class, targeted strategy of myosin inhibition to improve LVOT obstruction and haemodynamic status, biomarker status, symptom burden, exercise capacity, and key aspects of quality of life.[8,12] The primary composite functional endpoint of EXPLORER-HCM was clinical response at Week 30 of treatment with mavacamten versus placebo compared to baseline, defined as either an increase in peak oxygen consumption (pVO_2) ≥1.5 mL/kg/min and reduction of ≥1 NYHA functional class, or an increase of ≥3.0 mL/kg/min in pVO_2 with no worsening of NYHA class.[8] Secondary endpoints included change in post-exercise LVOT gradient, NYHA class, pVO_2, and patient-reported outcomes assessed by the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ CSS) and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB). Safety endpoints included the incidence of major adverse cardiac events (death, stroke, acute myocardial infarction) and ventricular tachyarrhythmias. Exploratory endpoints were to characterise the effect of mavacamten on multiple aspects of oHCM pathophysiology.[8]

KEY FINDINGS FROM EXPLORER-HCM

All primary and secondary endpoints in EXPLORER-HCM achieved statistically and clinically significant differences compared to placebo ($p<0.001$ for all differences from placebo). The primary endpoint of EXPLORER-HCM was achieved by more than twice as many patients treated with mavacamten compared to placebo: 45/123 (37%) patients on mavacamten versus 22/128 (17%) on placebo, which was statistically significant (95% confidence interval [CI]: 8.7–30.1; $p=0.0005$).[12] Secondary endpoint results were as follows: patients on mavacamten compared to those on placebo had greater reductions in post-exercise LVOT gradient (36 mmHg; 95% CI: -43.2 to -28.1; $p<0.0001$); greater increase in pVO_2 (+1.4 mL/kg/min; 95% CI: 0.6–2.1; $p=0.0006$); and improved symptom scores (KCCQ-CSS: +9.1, 95% CI: 5.5–12.7; HCMSQ-SoB: -1.8, 95% CI: 2.4–1.2; $p<0.0001$).[10] Improvement of ≥1 NYHA class was reported in 80/123 (65%) and 40/128 (31%) patients in the mavacamten and placebo groups, respectively (+34%; 95% CI: 22.2–45.4; $p<0.0001$).[10]

Dr Olivotto noted: "To show such a benefit in mildly to moderately symptomatic patients is quite impressive." Safety and tolerability

of mavacamten were similar to placebo. Treatment-emergent adverse events were generally mild. One patient died (sudden death) in the placebo group.

EXPLORER-HCM Highlights the Benefits of Disease-Specific Treatment for Obstructive Hypertrophic Cardiomyopathy

Treatment with mavacamten in EXPLORER-HCM improved exercise capacity, LVOT obstruction, NYHA functional class, and health status in patients with oHCM.[12] In contrast to the broad intervention approach usually used in cardiology, the favourable results of this pivotal study highlight the benefits of disease-specific treatment for this condition.[12] Controlling obstruction and other structural aspects effectively in a noninvasive manner may postpone or avoid the need for surgery; this is currently being tested in a Phase III study, VALOR HCM.[16]

Dr Olivotto concluded: "EXPLORER-HCM shows that targeting aetiology with a precision medicine approach really pays off."

HOW DOES MAVACAMTEN DIFFER FROM CURRENT PHARMACOLOGICAL OPTIONS?

Dr Olivotto explained that established cardiac drugs, such as β-blockers, calcium antagonists, and anticoagulants, when used correctly, can be helpful in oHCM; however, rather than targeting the cause of disease, these therapies can help to manage symptoms, such as shortness of breath, palpitations, and chest pain, or complications, such as atrial fibrillation.

Dr Olivotto stated: "Mavacamten is a targeted drug that specifically inhibits cardiac myosin and is the closest possible treatment to gene therapy. It does not mend the gene, but it corrects the immediate consequences and pathophysiological cause of the disease. The beauty of this drug compared with other drugs available is the clean, precise action, with no effect on blood pressure and heart rate."

WHAT DOES THE TARGETED DRUG, MAVACAMTEN, MEAN FOR PATIENTS?

Dr Olivotto emphasised that the general well-being objectives of patients with chronic diseases sometimes differ greatly from those of physicians. Drug-related issues, such as poor digestion, prostate problems, and nocturnal palpitations, add up to a burden of disease that is hard to quantify in clinical practice and may be dismissed by physicians as not severe enough to be of concern or as not treatable.

Dr Olivotto highlighted: "Clearly, issues that are hard to quantify in clinical practice are core concerns for patients with chronic diseases such as oHCM. Patients wish to feel 100% well, rather than settling for 'just OK', and are looking for a drug that achieves this goal." Dr Olivotto's direct experience with mavacamten has been "quite rewarding" in this respect.

FUTURE PROSPECTS

The next steps for mavacamten in oHCM, outlined by Dr Olivotto, are to accrue long-term safety and efficacy data; establish the effects of the drug as monotherapy, which may be explored in an ongoing, long-term, safety extension study;[17] demonstrate the effects on natural history and outcome; and assess the impact on advanced disease.

Future research in other areas includes expanding understanding of how mavacamten works in nonobstructive disease and investigating whether this drug is useful in selected patients with HF with preserved ejection fraction, which accounts for approximately 50% of patients with HF,[18,19] for whom treatment is limited.[20]

Dr Olivotto concluded: "EXPLORER-HCM marks the first targeted drug for oHCM in Phase III and is the beginning of a new era. This study sets the stage for further studies looking at disease progression and early upstream treatment to prevent disease complications and change the natural history of the disease."

Biography

Dr Iacopo Olivotto

Staff Physician, Florence Referral Center for Cardiomyopathies, Careggi University Hospital, Florence, Italy

Dr Iacopo Olivotto trained in Florence, Italy, and London, UK, and pursued a career firstly in emergency medicine and subsequently in cardiology at the Careggi University Hospital in Florence, Italy, where he currently serves as a staff physician. Dr Olivotto is the clinical co-ordinator of the Florence Referral Center for Cardiomyopathies.

Over the last two decades, Dr Olivotto's main clinical and research interests have included various aspects of cardiomyopathies, with special focus on HCM, ranging from clinical predictors of disease progression and outcome, arrhythmias, characterisation of the end-stage phase, medical and surgical management, imaging studies of coronary flow reserve with PET, functional and prognostic relevance of magnetic resonance studies, echocardiographic screening and early HCM diagnosis, studies of prehypertrophic phenotype, genetic studies addressing the prevalence and characterisation of HCM-causing mutations, genotype–phenotype correlations, family studies, developmental aspects of HCM, molecular studies of myofilament contractility, and correlation of *in vitro* findings with clinical and echocardiographic variables. These lines of research are being carried out in co-operation with a rapidly growing multidisciplinary team in Florence, as well as several distinguished institutions in Europe and the USA.

Dr Olivotto has been among the first in promoting randomised trials in cardiomyopathies based on translational approaches to the core pathophysiological mechanisms of disease. He has co-authored over 200 papers in peer-reviewed journals and serves as a reviewer for the main international cardiovascular journals. He is a founding member of the international Sarcomeric Human Cardiomyopathy Registry.

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Interview

Dr Rasha Al-Lamee

Faculty of Medicine, National Heart & Lung Institute, London, UK

Q1 What do you find most interesting about complex coronary intervention and coronary physiology?

I went into cardiology to combine the science of medicine and the practical skills of surgery. I enjoy finding a problem and doing my best to fix it. Complex intervention presents continual challenges and stepwise, logical problem solving that keeps my job interesting. No two cases or 2 days in the catheterisation laboratory (cath lab) are the same. You never know what you will get and that keeps you on your toes! Coronary physiology adds more accuracy to what we do. It helps me to plan my procedures and make me feel surer of the result. I use physiology and intravascular imaging in the vast majority of my cases because I hate guesswork; I like to feel as certain as can be as I perform intervention.

Q2 In light of the global COVID-19 pandemic, what do you believe are the biggest challenges currently facing the clinical interventional cardiology community?

I think the greatest challenge we will have ahead of us is dealing with the collateral damage from COVID-19. The pandemic and lockdown have really had an impact on patient care. Many patients were dissuaded from seeking medical attention when they needed it. We are now seeing the knock-on effects from that as we recover and pick up the pieces. I also worry about the effect on cardiovascular morbidity and mortality because access to primary and secondary prevention was limited for some. I am concerned for the impact it has had on clinical research and clinical training. These are unprecedented times. I hope that we can get back on track as soon as we possibly can.

Q3 What motivated you to become a clinical triallist and what was the goal you set out to achieve when you embarked on this path?

In my mind one of the best aspects of cardiology is its strong evidence base. I love that from the beginning of our training we are taught to think about the science behind what we do. For me the most natural way to combine cardiology and academia was to design and conduct clinical trials. At an early stage in my training I was involved in recruitment and collecting data for studies in the UK. My interventional fellowship in Milan, Italy, taught me the importance of international collaboration and how clinical trials have shaped all the major

I love that from the beginning of our training we are taught to think about the science behind what we do.

developments in cardiology. I knew then that I wanted to start designing trials to answer my own clinical questions and it was the next natural step to embark upon a clinical trial for my PhD.

Q4

You conducted and led the Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA) trial. Could you elucidate the key findings?

The results of ORBITA were as surprising to me as they were to the many interventional cardiologists worldwide! This was the first placebo-controlled trial of angioplasty. The primary analysis showed a smaller than expected effect of angioplasty on treadmill exercise time and symptoms compared to placebo. The subsequent analyses showed even more interesting data: we found that one in five more patients reported being free from angina in the percutaneous coronary intervention (PCI) arm in a non-prespecified analysis. We also found that, when we stratified patients based on their pre-randomisation invasive physiology, the lower the fractional flow reserve (FFR) and the instantaneous wave-free ratio (iFR) index, the greater the placebo-controlled efficacy of PCI on improving stress echocardiography ischaemia. Also, the higher the pre-randomisation stress echocardiography score, the greater the improvement of frequency of angina with placebo-controlled PCI.

Q5

In your expert opinion, what key attributes are required for a successful clinical triallist, and what would be your advice to young scientists considering this career?

You need to find questions that truly need answering and design trials that will be clinically relevant and interesting. Completing any study is hard work and extremely challenging so, at the end of it, you should know it's something people will want to read about. Ideally the results of your trial will change practice but often that's very difficult, so you need to feel that your work will, at the very least, provide new data that add to the totality of our knowledge and will help us to make incremental steps towards the final answer.

Q6

As an advocate for rigorous testing of clinical practice and the use of evidence-based medicine in all phases of medical care, do you believe these standards are currently being upheld?

Yes, I do! I think we try very hard to uphold standards in medical care and use the evidence-base to inform what we do. Some teams are better than others at doing this, but in general I think cardiologists do a pretty good job at keeping up to date.

"You need to find questions that truly need answering and design trials that will be clinically relevant and interesting."

Q7

Overall, you have more than 70 publications and are actively involved in the development and recruitment for various multicentre clinical trials. What are you working on next?

My next big trial is ORBITA-2 which is currently in the recruitment phase. This will build on the work of ORBITA. It is the next placebo-controlled trial of angioplasty and will test whether PCI improves symptoms in a wider range of patients than those included in the first trial. My main focus at the moment is continuing to understand the link between stenosis, ischaemia, and symptoms in patients with stable coronary artery disease. I have three PhD students working on really interesting studies that will help us to know much more.

Q8 As a result of COVID-19, multiple new options for disseminating scientific developments have arisen. By what means do you stay up to date with the latest cutting-edge advancements in cardiology?

I think the challenging last few months have taught us that it is possible to connect globally and to keep learning even without our traditional face-to-face conferences and meetings. The organisers of scientific congresses have worked so hard to find new platforms and new ways to present information digitally. Social media has been an invaluable resource; it means we can have real time interactions with our peers which has certainly improved a stressful experience. Some of this new experience has been fantastic and has allowed us to juggle conference attendance with busy day jobs and our home lives; however, I really miss the old times. Nothing can really replace the ability to chat face-to-face and I am looking forward to the return of the conventional meeting! But I am thankful that we have all been able to support each other across the world; I think that seeing each other again will be all the more precious given what we've all been through.

Q9 Within the 14 years of your clinical cardiology career, you have presented at multiple international cardiology conferences worldwide; why do you consider presenting at events to be of importance?

The dissemination of science is absolutely vital to our ability to advance knowledge and change practice. I have presented in all sorts of formats all over the world. Sometimes my audience has been interested in the results and other times they have been less happy to listen. Whatever the situation, I enjoy the challenge of explaining my work to others and the collaborations and future research that creates.

Artificial Intelligence in Patients with Congenital Heart Disease: Where Do We Stand?

EDITOR'S PICK

The authors have performed a literature search of how state-of-the-art imaging diagnoses for congenital heart disease are taking place with the help of artificial intelligence (AI). There is a clinical unmet need for the use of AI in congenital heart disease, and a joint effort is needed to spread AI knowledge and applications in the medical field to improve diagnosis, treatment, and outcomes for patients. This review gives an overview of AI usage in diagnostic imaging, electrocardiograms, and clinical diagnosis in patients with congenital heart disease.

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Abstract

Life expectancy of patients with congenital heart disease (CHD) has increased in recent decades; however, late complications remain frequent and difficult to predict. Progress in data science has spurred the development of decision support systems and could aid physicians in predicting clinical deterioration and in the management of CHD patients. Newly developed artificial intelligence (AI) algorithms have shown performances comparable to humans in clinical diagnostics using statistical and computational algorithms and are expected to partly surpass human intelligence in the near future. Although much research on AI has been performed in patients with acquired heart disease, little data is available with respect to research on AI in patients with CHD. Learning algorithms in patients with CHD have shown to be promising in the interpretation of ECG, cardiac imaging, and the prediction of surgical outcome. However, current learning algorithms are not accurate enough to be implemented into daily clinical practice. Data on AI possibilities remain scarce in patients with CHD, and studies on large data sets are warranted to increase sensitivity, specificity, accuracy, and clinical relevance of these algorithms.

INTRODUCTION

Improved medical treatment and surgical techniques has caused the life expectancy of patients with congenital heart disease (CHD) to be significantly prolonged.[1-3] As these patients reach adulthood, late complications such as arrhythmias and congestive heart failure occur,[1] resulting in reduced quality of life and life expectancy.[4] Furthermore, these complications often result in unscheduled hospital visits or even emergency admissions.[3,5-7] Although visits to the outpatient clinic are frequent, it remains difficult to predict and prevent clinical deterioration.

With the introduction of the electronic medical record and the ability to digitally store data for diagnostic modalities, such as ECG and echocardiography, large amounts of patient data have been generated over the past few decades. Using machine learning (ML) or deep learning (DL) for the analysis of these data has been a topic of interest for some years. Progress in data science has spurred the development of decision support systems which can aid physicians in the management of CHD patients and therapeutic decision making.[4,8,9] Newly developed algorithms perform as well as humans in clinical diagnostics using statistical and computational algorithms to perform recognition, classification, and learning tasks, and are expected to outperform humans in the near future.[10,11]

Used in this context, artificial intelligence (AI) is an umbrella term for the use of computers to model intelligent behaviour. The terms 'neural networks,' DL, and ML are technical concepts that fall under this umbrella but are confusingly used interchangeably with the term AI in the literature. This review will focus on ML and DL. Learning algorithms learn from data given as an input, also called the training dataset. The algorithm then gets tested on a so-called test or validation dataset, which contains new unseen data. ML, specifically, refers to algorithms that can 'learn' patterns from training data and then use the learned patterns to classify previously unseen data.[12] DL algorithms have an extra hidden layer, which allows them to automatically detect important features from the data, while in ML algorithms, the features need to be provided manually.[4,13]

Although several AI studies have been performed in patients with CHD over the past few years, data are limited compared to data in patients with acquired heart disease.[4,8,9,13-16] Considering the propensity of CHD patients for developing arrhythmias and heart failure, the predictive abilities of the AI algorithms could prove to be lifesaving. Therefore, the aim of this review is to provide an overview of studies investigating the potential of AI algorithms with respect to the various imaging modalities in patients with CHD.

METHODS

Literature Search

Medline® (Northfield, Illinois, USA) and EMBASE (Elsevier, Amsterdam, the Netherlands) were used to search for studies published up to 9th August 2019. The search was developed iteratively for synonyms of 'congenital heart disease,' ML, DL, and AI, both controlled vocabulary (Medical Subject Headings [MeSH]) and free-text words. Nonhuman studies, case reports, biomarker studies, and reviews were excluded. The reference list and cited articles were checked for additional references.

Selection of Studies

Studies were included if they applied AI algorithms for diagnostics (heart sound, echocardiography, MRI, CT, electrocardiogram analysis, and classification/prediction models, for example) in CHD patients. Since the terms AI, DL, and ML are used interchangeably, all three terms were included in this review. All potential articles were read in full by two authors (Ms Marinka D. Oudkerk Pool and Mr Dirkjan Kauw). Disagreements concerning eligibility were resolved by discussion.

Extraction of Data

The extracted data from each paper were author, publication year, total number of patients (both training and test set), patient population, data used for analysis (input data in the algorithm), primary outcome (goal of the study), the used AI algorithm, and accuracy of the proposed AI algorithm. For comparison between the different techniques the sensitivity (SE), specificity (SP), and accuracy were used.

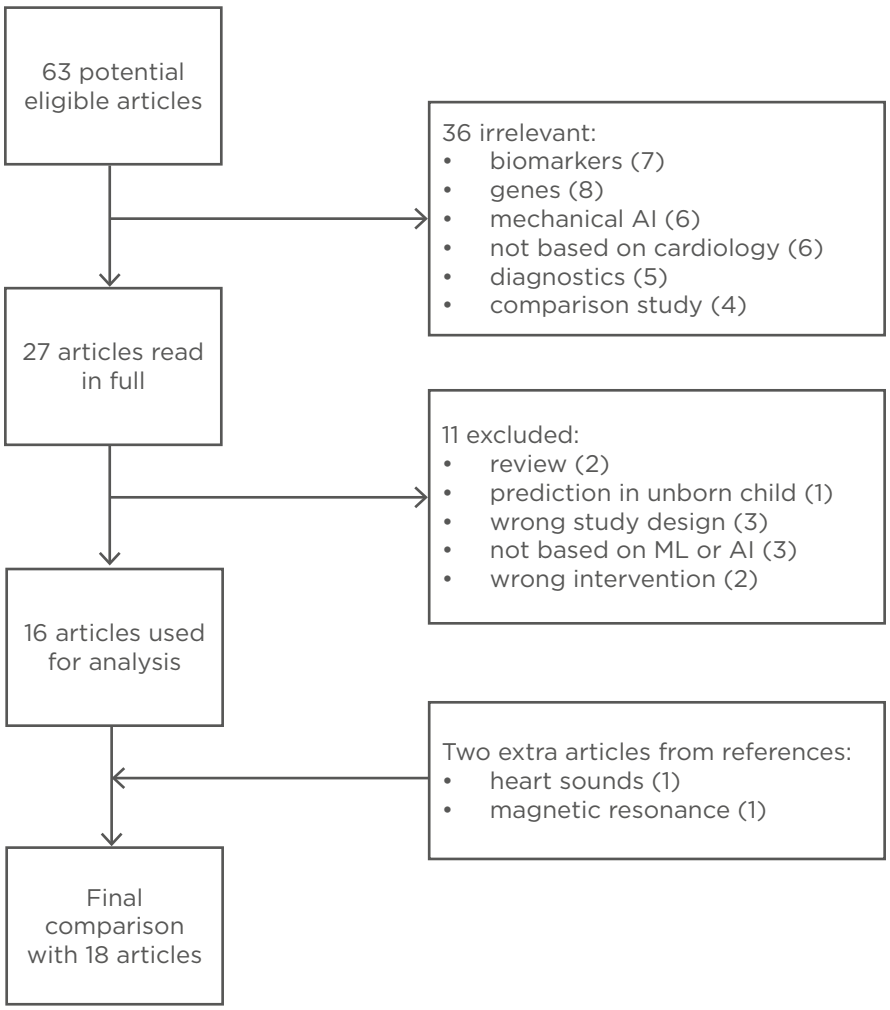

Figure 1: Flow diagram of search query.

AI: artificial intelligence; ML: machine learning.

Accuracy is defined as the number of correctly classified results compared to the 'true' value (either positive or negative), as assessed by the gold standard technique.

True positive (TP) is the proportion of actual positives that are correctly identified as such. True negative (TN) is the proportion of actual negatives correctly identified as such. False positive (FP) is a negative value identified as a positive value, and false negative (FN) is a positive value identified as a negative value. SE, SP, and accuracy can be defined using equations:[17-20]

$$SE = 100 \times \frac{TP}{TP + FN}$$

$$SE = 100 \times \frac{TP}{TN + FP}$$

$$\text{accuracy} = 100 \times \frac{TP + TN}{TP+TN+FP+FN}$$

RESULTS

In total, 63 articles were potentially eligible for this review after removing duplicates. Forty-eight articles were considered irrelevant because they focussed on biomarkers, genes, mechanical AI, were not based on cardiology (either neurology or mechanical ventilation), diagnostics (over the phone or medication), or comparison study in which two or more imaging modalities were compared. Twenty-seven articles were read in full, after which an additional 11 articles were excluded. Two additional articles were selected by going through the references. The final analysis consisted of 18 articles (Figure 1).

Topics of these studies included analyses of cardiac imaging modalities (echocardiography, MRI), ECG, and clinical prediction models using AI algorithms.

Table 1: Selected articles.

First author (year)	n (training set)	n (test set)	Patient population	Category for analysis	Data used for analysis	Primary outcome	Learning algorithm	Accuracy (%)
Elgendi et al.[21] (2015)	27. Unclear how data has been split.		Patients who were undergoing right heart catheterisation	Heart sound	Heart sounds measured with 3M™ Littmann® 3200 Electronic Stethoscope*	Recorded heart sounds to distinguish subjects with PAH	Linear discriminant analysis	SE: 92.86 SP: 92.31
Gharehbaghi et al.[22] (2015)	50. Unclear how data has been split.		Twenty-eight healthy children and 22 children with BAV	Heart sound	Heart sounds measured with Meditron Electronic Stethoscope†	Develop algorithm for detecting BAV in children	Support vector machine	72.9 Practitioner: 71.60
Gharehbaghi et al.[9] (2017)	90. Unclear how data has been split.		Fifty-five healthy children and 35 children with BAV	Heart sound	Heart sounds measured with Meditron Electronic Stethoscope	Detecting BAV, healthy, or MR from heart sound	Combination of hidden Markolov model and support vector machine	86.4
Elgendi et al.[23] (2018)	60. Unclear how data has been split.		Patients who were undergoing right heart catheterisation	Heart sound	Heart sounds measured with 33M Littmann 3200 Electronic Stethoscope	Recorded heart sounds to distinguish subjects with PAH	Linear discriminant analysis	SE: 84.00 SP: 88.57
DeGroff et al.[24] (2001)	69 used for both training and validation		Paediatric patients	Heart sound	Heart sounds measured with Cambridge Heart Sound Microphone	Distinguish between innocent and pathological	Artificial neural network	SE: 100.00 SP: 100.00
Sepehri et al.[25] (2009)	60	60	Heart sounds from database (both healthy and with CHD)	Heart sound	Phonocardiogram and electrocardiogram	Identifying children with congenital heart disease	Artificial neural network	93.6
Thompson et al.[26] (2018)	603. Unclear how data has been split.		Heart sounds from database (John Hopkins Outpatient Center, Baltimore, Maryland)	Heart sound	Heart sounds recorded with an electronic stethoscope with corresponding ECG	Distinguish between innocent and pathological	Not specified	88
Bhatikar et al.[27] (2004)	241. Unclear how data has been split.		Heart sounds from database (The Children's Hospital, Denver, Colorado)	Heart sound	Heart sounds from a microphone optimised for low frequencies	Diagnosis of heart murmurs in paediatrics	Artificial neural network	SE: 83.00 SP: 90.00

Table 1 continued

First author (year)	n (training set)	n (test set)	Patient population	Category for analysis	Data used for analysis	Primary outcome	Learning algorithm	Accuracy (%)
Sepehri et al.[28] (2016)	134	129	Children referred to the hospital	Heart sound	Phonocardiogram and electrocardiogram	Identifying children with congenital heart disease	Arash-Band	87.45
Diller et al.[4] (2018)	159	40	Patients undergoing routine transthoracic examinations	Ultrasound	Echocardiographic data	Discriminate between patients with TGA after atrial switch operation, patients with ccTGA and normal controls	Convolution neural network	98
Pereira et al.[16] (2017)	163	91	Boston Children's Hospital database	Ultrasound	Echocardiographic data	Detecting CoA in newborns via ultrasound	Support vector machine	Not mentioned
Neukamm et al.[29] (2013)	30. Unclear about split between sets.		Patients with Tetralogy of Fallot after pulmonary valve replacement	Ultrasound	End-diastolic volume, end-systolic volume, and ejection fraction	Volumetric assessment compared to gold standard MRI	Knowledge-based	EDV; SE: 100.00, SP: 86.00 ESV; SE: 78.00, SP: 86.00 EF; SE: 75.00, SP: 43.00
Nyns et al.[30] (2016)	17. Unclear about split between sets.		Children and adolescents	MRI	Ventricular volumetry, using a short-axis cine stack	Evaluate feasibility, accuracy and labour intensity compared to conventional Simpson's method	Knowledge-based	EDV: 82.00 ESV: 93.00 EF: 73.00
Yang et al.[13] (2002)	106 used for both training and testing.		ECG from database (Nagoya University Hospital, Nagoya, Japan)	ECG	ECG features: waveforms, and voltages of upright and negative deflections	Differentiate between ASD and non-ASD	Artificial neural network	ACC: 91.50 SE: 91.40 SP: 91.70
Ruiz-Fernandez et al.[8] (2015)	2432 used for both training and testing.		Children heart disease database	Classification model	Presurgical and postsurgical data	Classifying the risk of paediatric cardiac surgery	Multilayer Perceptron; Radial Basis Function; Self-organising Map; Decision Tree	99.87; 95.60; 81.79; 80.09

Table 1 continued

First author (year)	n (training set)	n (test set)	Patient population	Category for analysis	Data used for analysis	Primary outcome	Learning algorithm	Accuracy (%)
Ruiz et al.[14] (2019)	93 patients. Unclear about split between sets.		Infants with single-ventricle physiology	Prediction model	Inpatient data	Predict critical events early and accurately	Naïve Bayes	SE: 84.00 SP: 81.00
Diller et al.[15] (2018)	8.015	2.004	Adult patients under active follow-up in Royal Brompton Hospital, London, UK	Classification model	Patient data, including diagnosis, clinical status, and medication	Categorise patients in diagnostic and disease complexity subgroups	Deep Learning	90.20
Chiogna et al.[31] (1996)	457	114	Neonates	Classification model	21 questions based on clinical presentation, blood gasses, and imaging modalities	27 congenital heart disease classes	Decision tree	59.00

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†Welch Allyn®, Skaneateles Falls, New York, USA.

ACC: accuracy; ASD: atrial septal defect; BAV: bicuspid aortic valve; ccTGA: congenitally-corrected transposition of great arteries; CHD: congenital heart disease; CoA: coarctatio aortae; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; MR: mitral regurgitation; PAH: pulmonary artery hypertension; SE: sensitivity; SP: specificity; TGA: transposition of great arteries.

Table 1 shows an overview of each selected article found in this search. No articles on CT in CHD patients were found during this search.[4,8,9,13-16,21-31]

Patient Population

In total, 15,244 patients were analysed: 10,354 adults (35% male; 33% female; 32% no gender described; mean age of 33.30 ±13.00 years), 1,858 children (>2 years old; mean age of 9.22 ±1.09 years [42% of patients]; 58% no age described), and 4,099 were infants (<2 years old; age not described). Diagnoses of CHD of varying complexity were made in 14,532 (95.33%) patients and 712 (4.67%) patients were included as a healthy control group.

Learning Algorithms

In the 18 analysed articles, 15 different AI algorithms were used. The most used technique was the artificial neural network (ANN) in four of the articles (22%). Table 2 gives an overview of all techniques used in this review. Nine out of 18 articles analysed the use of ML in heart sounds (50%). The other articles analysed echocardiography (n=3, 17%), MRI (n=1, 6%), ECG (n=1, 6%), as well as prediction or classification models (n=4, 22%).

Heart Sound Analysis

Nine articles aimed to distinguish between pathological or innocent murmurs using ML on sound recordings from an electronic stethoscope.

The study by DeGroff et al.[24] aimed to determine pathological from innocent murmurs using spectral resolution and frequency range as input. Using an ANN, they found high SP and SE (both >90.0%). Sepehri et al.[25] also found high accuracy (93.6%) using an ANN based on spectral and timing properties of the sound recordings of heart sounds of murmurs. The algorithm was trained on 60 normal and 60 pathological heart sound recordings.

Table 2: Overview of artificial intelligence algorithms used in the review.

Support vector machine (SVM)	The SVM searches for the best separation line or decision boundary (also called the maximum margin hyperplane) between two groups of data. The maximum margin is the equidistance between the closest vectors of both groups. These two vectors are called the support vectors. The maximum margin hyperplane is determined by the training dataset. Any new vector from the testing or validation dataset will fall on one side of the hyperplane or the other; based on this, the vector is sorted into the correct class.[9,25]
Decision tree (DT)	In a DT, the algorithm is dividing the data into different groups. During each separation, the algorithm tries to maximise the number of vectors from a certain category. Rules for separation are generated by following the path from branch to leaf; however, since a lot of paths are possible, it can reach a considerable size. DT are not very powerful on their own but can be used in other methods that leverage their simplicity.[8]
Knowledge-based	The knowledge-based algorithm tries to reconstruct shapes of the heart based on anatomical landmarks. The database already contains information of reconstructed 3D surface models of the preferred anatomy. The algorithm will reconstruct the requested anatomy from a new patient based on data out of the database.[30]
Arash-band method	Every heart disease has a discriminative frequency band, named the Arash-Band. The Arash-Band is defined as the spectral energy band that provides maximum discrimination with respect to the normal condition. The Arash-Band is calculated during the training phase, using statistical techniques as the discriminating tools for the band selection.[28]
Linear discriminant analysis (LDA)	The LDA tries to find a linear combination of features to separate between two or more classes. The LDA has continuous independent variables (the features) and the class label as a continuous dependent variable.[21]
Hidden Markov model (HMM)	A Markov model can be used to calculate a probability for an observable event, an HMM also looks at hidden events, such as part-of-speech tags. In an HMM there is a hidden Markov layer, which contains a Markov chain. A Markov chain is a model that calculates the probabilities of sequences of random variables. A Markov chain only takes into account the current state and does not account for any previous state.[9]
Self-organising map (SOM)	This algorithm represents competitive learning, all neurons compete to be the closest to the input value. The Euclidian distance is used to measure similarities between the input value and each neurons' weight in order to choose the winning neuron. Afterwards, the weight of the winner and its neighbours is updated for the next input value.[8]
Naïve Bayes (NB)	The NB assumes that every feature is independent of the value of any other feature. The classifier is based on Bayes theorem, meaning the probability of A happening, given B has occurred is equal to the probability of B happening, given A has occurred times the probability of A, divided by the probability of B. The NB is an oversimplification of assumptions but tends to work quite well in complex problems.[14]
Deep learning (DL)	Deep Learning refers to every algorithm with multiple layers, making it deep. In the article by Diller et al.[15] it is referred to a combination of convolutional network and a dense network. A dense network is a network in which the number of links between nodes is close to the maximal number of nodes.[15]
Artificial neural network (ANN)	The neural networks are made to mimic the neural networks in the brain. The neural network usually consists of an input layer, one or more hidden layers, and an output layer. The input values represent the dendrites going to a neuron, which then ends in the output signal, representing the axon. The neuron determines if the sum of the input values is important and if they get passed along to the output value. The neuron is represented by the so-called activation function. The weighted sum of the input values is applied in the activation function (most common functions are the threshold, sigmoid, rectifier, or hyperbolic tangent function). Every activation function has a different method to determine how it will be activated. If the weighted sum is high enough, the signal will be passed onto the output value. Every input value is connected to every hidden layer neuron, from which one value is passed to the output layer neuron, after which one value is the output value. The output value can be binary, categorical, or continuous. The predicted output value is compared to the actual output value. Using a cost-function, the error between the output values is compared, this error is fed back to the neuron, and the weights of the input are updated (this is called backpropagation). This process is repeated for all the values of the training dataset. After which the final weights are applied to the test or validation dataset.[24,27]

Table 2 continued

Convolutional neural network (CNN)	CNN have a similar algorithm to the ANN, however the input for a CNN is an image as to a value in the ANN. The image gets down sampled by a feature detector (also known by kernel or filter), which results in a feature map. The size of the feature detector determines the size of the feature map. The bigger the feature detector, the smaller the feature map will be and the bigger the down-sampling of the original image. Many feature maps will be created to obtain the first convolutional layer, using different feature detectors. Trough training the algorithm determines how the feature detectors should look to preserve important features from the original image. After the convolutional layer, a rectified linear unit function is applied to remove all linearity since images themselves are highly nonlinear. When making the feature maps, linearity can occur due to the down sampling. Then a pooling layer has been applied. The pooling layer makes the image recognisable even if the image has been tilted or shifted and makes overfitting less possible by reducing the size of the convolutional layer. Lastly, a flattening layer conducts a similar function as the activation function in the ANN. After the flattening layer, the output of this process will be used as an input for an algorithm that is similar to the ANN. In the backpropagation not only are the weights adjusted, but also the feature detectors, creating a more accurate down-sampling of the image.[4]
Radial basis function networks (RBF)	RBF is a type of ANN. The input layer and the hidden layer do not have associated weights. Each neuron in the hidden layer represents an RBF. The neurons compute the Euclidean distance between the synaptic weights vector and the input values. Over this distance the RBF is applied, which most often is the Gaussian function.[8]
Multi-layer perceptron (MLP)	The MLP is an example of feedforward ANN. In general, it refers to multiple layers of perceptrons with threshold activation.[8,25]

To evaluate the algorithm, it was tested with 60 either innocent or pathological murmurs to correctly identify first and second heart sounds. Other articles used multiple algorithms to distinguish between a pathological or innocent murmur, namely linear discriminant analysis, support vector machine, a combination between hidden Markov model and support vector machine, ANN, and the Arash-band. ANN was the most frequently used algorithm (n=3, 33%), and yielded the highest accuracy, SE, and SP.

Echocardiographic Analysis

AI algorithms were used on echocardiographic data to distinguish between structurally normal or pathological hearts, or to determine cardiac cavity volumes and function. The algorithm can be trained to detect change in echogenicity in the collected data, which can be seen in the wall of the heart. In this manner, Diller et al.[4] found accuracy of 98% in distinguishing between transposition of the great arteries (TGA) after an atrial switch operation, congenitally corrected-TGA, and normal controls using a convolutional neural network (CNN) algorithm. The endocardial border was marked by two researchers and compared to the border marked by a CNN algorithm. A knowledge-based article written by Neukamm et al.[29] only looked at SE and SP and found that making a 3D model out of the 2D echocardiogram data is feasible in 97% of cases; however, results for assessing the ejection fraction (EF) were unsatisfactory and MRI remains the method of choice.

MRI

In one of the articles by Nyns et al.,[30] MRI was used as an input for knowledge-based reconstruction of the volume of the right ventricle after atrial switch operation in patients with a TGA. In a knowledge-based reconstruction, the input is compared to a database that contains information on the 3D model of the place of interest and tries to reconstruct based on this database.[30] The knowledge-based reconstruction was compared to the gold standard, which is the Simpson's method. The Simpson's method is a geometric model in which the right ventricle is calculated based on the sum of a cylinder (base of the heart to the tricuspid valve).[32] The accuracy of the end-diastolic volume (82%), end-systolic volume (93%), and EF (73%) were compared. Knowledge-based reconstruction is a feasible, accurate, and fast method compared to the gold standard for measuring right ventricle volumes in patients after arterial switch operation.[30]

Electrocardiogram Analysis

One article was found using ML on ECG of patients with CHD. In this article by Yang et al.,[13] the authors aimed to distinguish atrial septum defect from patients with nonatrial septum defect and healthy controls' ECG. The QRS and T wave measurements from lead I, lead II, and all precordial leads were used as input. A SE of 91.4% and SP of 91.7% was found, with an accuracy of 91.5% using an ANN.

Classification Model

In the classification and prediction models, the ML algorithms were used to predict clinical deterioration, to classify surgical risk, or to classify the heart disease using patient characteristics. If the output of the network is categorical, it will make a prediction model. If the output has discrete values, the algorithm will do a classification of the data.[33] Ruiz-Fernandez et al.[8] found an accuracy of 99.9% in classifying the risk of mortality in paediatric surgery using the multilayer perceptron algorithm. The goal of this study was to develop a clinical decision support system to help cardiologists decide whether surgery was indicated. Ruiz et al.[14] investigated early prediction of critical events in infants using a naïve Bayesian model. Thirty-four routinely collected data points, such as heart rate, CO_2, and lactate, were used as input for the models. The model was able to detect future events up to 1 hour away with a SE of 84.0% and a SP of 81.0%. Diller et al.[15] used DL techniques (statistical learning which extracts features from raw data) to categorise diagnostic group, disease complexity, and New York Heart Association (NYHA) class, with an accuracy of 90.2%. In addition, they also estimated prognosis of the disease of adults with all types of CHD and to decide if patients needed to be discussed in the multidisciplinary team. Lastly, Chiogna et al.[31] used a decision tree algorithm to classify neonates with CHD into 27 disease classes, compared to an expert opinion. Input data consisted of routinely clinical data acquired at birth, such as ECG data, pO_2, heart size based on the chest X-ray, partial pressure of CO_2, and oligemic lung fields. Accuracy of 59.0% was achieved.

Discussion

This review provides an overview of the possibilities of AI for patients with CHD. Although AI algorithms have been used for patients since 2001, relatively few articles have been published on this subject. However, AI algorithms are gaining popularity in healthcare and especially in cardiology.[24] This is also demonstrated in this review since most articles are of relatively recent date (earliest dated 2015). In this review the authors found high SE and SP in most categories (echocardiographic data, ECG data, and in prediction/classification models), which means AI algorithms have great potential as an additional diagnostic tool in patients with CHD. However, the SE, SP, and accuracy are not yet high enough to be able to implement these algorithms safely in daily practice.

Most of the articles used ML on heart sounds, with high SP and SE. The highest accuracy (94%) was found using the ANN algorithm. Heart sound analysis is noninvasive, inexpensive to perform, and remains an important diagnostic tool in both adults and children. Overall, the techniques that were used distinguished between healthy and pathological sounds only, which might be useful as a primary screening tool. Heart sound analysis in patients with acquired heart disease also showed high SE, SP, and accuracy.[34] Ari et al.[35] managed to distinguish between aortic insufficiency, aortic stenosis, atrial septal defect, mitral regurgitation, mitral stenosis, or normal heart sound with an accuracy of 92%. These techniques can establish a diagnosis but do not yet determine the severity of the valve lesion. However, one could argue that heart sound analysis using ML should not be the main objective, as other noninvasive methods (echocardiography and cardiovascular MRI) are likely to be more informative if interpreted by ML techniques. The technique could be used as a screening tool by general practitioners to distinguish who should be sent to the hospital for further check-up.

Learning algorithms on noninvasive cardiac imaging (echocardiographic and MRI) shows a high accuracy when using a CNN algorithm, especially in the assessment of cardiac volumes.[4] AI algorithms have been used for echocardiographic imaging since 2006, but only started gaining popularity since 2012. Asch

et al.[36] trained a ML algorithm to automatically estimate the left ventricular EF on a database of >50 echocardiographic studies, including the apical 2- and 4-chamber views, and were compared to the left ventricular EF as assessed by the echocardiographist or cardiologist. The ML algorithm proved less sensitive (90% versus 93%), but more specific (92% versus 87%), and accurate (92% versus 89%), which makes the algorithms highly feasible in daily practice. However, patients with CHD tend to develop problems in their right ventricle. Genovese et al.[37] analysed 3D quantification of the right ventricle size and function in 56 patients receiving both cardiac magnetic resonance and 3D echocardiography exam on the same day. Echocardiographic volumes were analysed with a ML technique and compared with the cardiac MRI using the Bland-Altman and linear regression analyses. The automated ML analysis was correct in 18 patients (32%) but needed corrections in the remaining 38 patients. Although an intraclass correlation coefficient of 97% could be reached for the end-diastolic volume, 98% for the end-systolic volume, and 95% for the EF, the accuracy of a ML algorithm remains strongly correlated with the image quality. It seems likely that with increasing image quality, ML algorithms for its interpretation will become more reliable.

As with the echocardiography, cardiac MRI combined with ML has been gaining popularity and is already being used in daily practice. Ruijsink et al.[38] tried to analyse the cardiac magnetic resonance imaging using DL algorithms to automate ventricular function assessment for both ventricles, and reached SE of 95%, SP of 83%, and an accuracy of 89%. In the technique described by Nyns et al.,[30] the right ventricle was automatically analysed, but the key anatomical landmarks needed to be selected beforehand. More research is needed to evaluate if the DL algorithm could also make this process quicker with comparable SE, SP, and accuracy.

Remarkably, the sole article on ECG in CHD patients dates from 2002, although a lot of ML is conducted on ECG data in the general cardiac population[33,39-43]. Adult patients with CHD of 10 experience arrhythmias, which makes them a suitable group to use ML techniques with to predict events.[44] However, the baseline ECG recordings of these patients often already has an abnormal appearance and differs between patients with the same congenital heart defect, further complicating the analysis of the ECG. In patients with acquired heart disease, the most analysed arrhythmia is atrial fibrillation. Using ML, ECG characteristics during sinus rhythm can be determined to establish the presence of an atrial fibrillation signature during sinus rhythm, with high SE (79%), SP (80%), and accuracy of (79%).[20] This algorithm could be used in patients with CHD as it seems suitable in left and right bundle branch block, premature ventricular contraction, atrial premature beat, and paced beat. Further research on ML ECG interpretation in patients with CHD is warranted and seems feasible.

ML can also be used to make prediction or classification models, which are used to determine in which group a specific outcome would fit. In patients with acquired heart disease the prediction models are mostly used to determine an outcome after surgery or to make a definitive risk model; however, these models perform poorly in predicting outcomes.[45,46] The model by Ruiz et al.[14] in 2016 gave a low accuracy when classifying different diagnoses of congenital heart defects based on a questionnaire. The model made by Ruiz-Fernandez et al.[8] in 2019 could be used in clinical practice because of the high accuracy, but no SE or SP is given. If the SE, SP, or accuracy is low, more research must be carried out or alternative endpoints must be chosen. A solution could be found by comparing the results to human analysis; if it is better than the current gold standard, it could be implemented in clinical practice. However, an accuracy, SE, and SP above 95% should be pursued before implementation is preferred.

The use of AI algorithms in cardiology has gained enormous interest in recent years and is predicted to grow even more in the upcoming years. In patients with acquired heart disease, ML and DL is already being used for imaging modalities and outcome prediction. In patients with CHD, on the other hand, the authors found only 18 articles on learning algorithms. These algorithms have high potential in the population of patients with CHD. Cardiac evaluation in the hospital with ECG and imaging techniques are frequent and a great amount of data is generated from these patients. Moreover, patients with CHD are vulnerable to cardiac morbidity and mortality and often experience complications. Prediction of deterioration in these patients could save lives.

There are a lot of different AI algorithms, with none being superior over the others for their specific task. The authors found that most techniques gave comparable SE, SP, and accuracy. It is more important to choose the right patient features or input data and perform preprocessing of the data to be used.[47-49] Because a large number of different algorithms were used, it was difficult to compare them. It is important avoid deviation in the different algorithms to keep track of the focus: implementation in the clinical setting. In an ideal situation, the authors would like to have an algorithm that would be able to calculate the same values (in case of calculating ventricle volumes) as an imaging physician would. Bigger and more diverse datasets are needed to train the algorithms better and to be applicable to every patient in clinic. A limitation of current algorithms is that even though the accuracy, SE, and SP can be high, mistakes can still occur. This raises questions regarding the extent to which physicians should trust the algorithm and what safeguards are in place if the conclusion of the algorithm is incorrect. However, these questions are beyond the scope of the current review.

CONCLUSION

AI algorithms are increasingly applied in healthcare and draw a lot of attention given the large potential the technology promises. Results of recent studies on AI algorithms in patients with CHD indeed show promising results, as the algorithms aid analysis of ECG, cardiac imaging, and helps to predict outcomes. However, current data on AI algorithms in patients with CHD is still limited and larger scale studies are warranted to provide algorithms that could assist physicians better in the future with high SE, SP, and accuracy.

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Sex Differences in Heart Failure with Preserved Ejection Fraction Therapy: Potential Mechanisms and Clinical Implications

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Abstract

Heart failure (HF) with a preserved ejection fraction (HFpEF) is now the predominant HF subtype in Europe. It manifests as reduced cardiac output and/or increased left ventricular filling pressures at rest and/or during exercise, caused by left ventricular diastolic dysfunction. HFpEF is proposed to occur as a result of systemic microvascular endothelial inflammation associated with various comorbidities such as hypertension, obesity, and diabetes. However, nearly two-thirds of those with HFpEF are females, which points to sex-specific driving factors such as differences in cardiac structure and physiology, and in systemic and pulmonary circulation; oestrogenic influence on physiology and molecular mechanisms; and pregnancy-related hypertensive disorders. Pharmacotherapy for HFpEF is lagging behind that for HF with reduced ejection fraction, and no treatment has yet been convincingly shown to reduce morbidity or mortality. Current treatment strategies target symptom alleviation and comorbidities. No trials have specifically examined the difference between sexes in response to HFpEF treatment; however, post hoc analyses have revealed differing effects of some treatments according to sex, such as spironolactone or sacubitril/valsartan, which may be of more use in females with HFpEF than in males. Further studies are needed to confirm if better outcomes were because of specific female physiology and HFpEF pathophysiology, and whether the outcome measures can be more tailored to address the goals

of female participants. This paper highlights some key differences between females and males with HFpEF, discusses clinical trials assessing treatments, and proposes what is needed to target HFpEF care according to sex.

INTRODUCTION

Heart failure (HF) represents a major public health issue, with prevalence approaching 2% in most European countries and considerable associated morbidity, mortality, and healthcare expenditure.[1] The European Society of Cardiology (ESC) proposed a classification of HF subtypes according to left ventricular ejection fraction (LVEF): 'HF with preserved ejection fraction' (HFpEF) when ≥50%, 'HF with reduced ejection fraction' (HFrEF) when <40%, and 'HF with mid-range ejection fraction' when between 40% and 50%.[2] While HF symptoms and/or signs with reduced LVEF define HFrEF, diagnostic criteria for HFpEF/HF with mid-range ejection fraction are more complex, requiring elevated natriuretic peptide levels and at least one additional criterion of structural heart disease and/or left ventricular (LV) diastolic dysfunction.[2] Two more refined diagnostic approaches of HFpEF using scores that take into account multiple clinical, biological, echocardiographic, or invasive haemodynamic parameters have been proposed, but still need confirmation in clinical practice before being adopted.[3,4]

In the last 20 years, the proportion of people with HFpEF has increased relative to those with HFrEF, resulting in HFpEF being the predominant HF subtype in Western countries, representing >50% of those with HF.[1,5] In Europe, an estimated 4.9% of the general population aged ≥60 years have HFpEF.[6] Demographic and clinical characteristics of people with HFpEF clearly differ from those with HFrEF. For instance, the former are on average 6 years older and approximately 63% are females, as opposed to 43% with HFrEF.[5] In addition, several cardiovascular (CV) and non-CV comorbidities, such as hypertension, chronic kidney disease, atrial fibrillation, and diabetes, are more frequent in HFpEF,[1,5] and play a role in its pathogenesis.[1] Regarding clinical outcomes, while CV mortality is lower, non-CV mortality is slightly higher in people with HFpEF compared to HFrEF.[5] However, several studies have reported similar outcomes regarding hospitalisation rates and quality of life (QoL) regardless of HF diagnosis.[7,8]

Until now, no treatment has proven effective in reducing morbidity and mortality in HFpEF. This is particularly relevant for females, who are over-represented in this HF category. A recent HFpEF trial indicated that females may have different responses to therapy compared with males;[9,10] therefore, a sex-specific approach to HFpEF assessment and treatment could result in improved treatment efficacy. This review explores sex differences with regard to HFpEF pathophysiology, outcomes, and pharmacotherapy. Potential underlying mechanisms and clinical implications are also discussed.

PATHOPHYSIOLOGY OF HEART FAILURE WITH A PRESERVED EJECTION FRACTION AND RELATIONSHIP WITH SEX

The central pathophysiological alteration in HFpEF is LV diastolic dysfunction (impaired relaxation and increased diastolic stiffness) leading to abnormal haemodynamics, namely reduced cardiac output and/or increased LV filling pressures at rest and/or during exercise. HFpEF was previously termed 'diastolic HF', but this nomenclature was abandoned as a certain degree of LV diastolic and systolic dysfunction coexists in all HF subtypes and nondiastolic and noncardiac mechanisms are involved in HFpEF. Traditionally, LV diastolic dysfunction is associated with a concentric pattern of LV remodelling, characterised by normal end-diastolic LV volume and increased LV wall thickness, frequently secondary to systemic arterial hypertension.[11] However, many with HFpEF exhibit normal chamber structure without remodelling.

A pathophysiological concept is proposed in which comorbid conditions, such as hypertension, overweight/obesity, diabetes, chronic obstructive pulmonary disease, sedentary lifestyle, or iron deficiency, create a systemic microvascular endothelial inflammation.

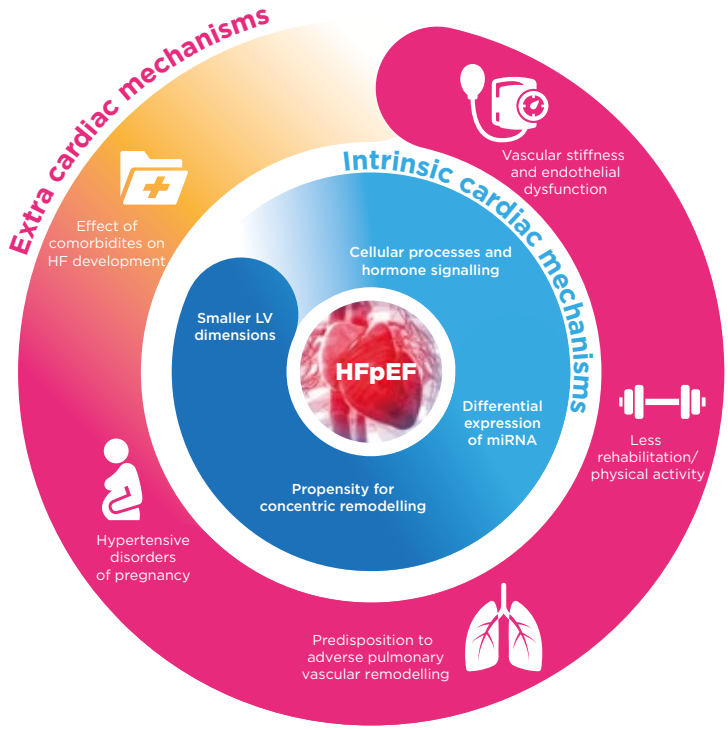

Figure 1: Potential mechanisms behind the pathophysiology of heart failure with a preserved ejection fraction in females.

HF: heart failure; HFpEF: heart failure with preserved ejection fraction; LV: left ventricular; miRNA: micro RNA.

These lead to microscopic myocardial inflammation and fibrosis, increased oxidative stress, and alterations in cardiomyocyte signalling pathways, causing cardiomyocyte remodelling and dysfunction.[12] Myocardial blood flow is reduced in HFpEF patients without obstructive coronary disease, further emphasising the role of the microcirculation in HFpEF development.[13] Furthermore, there are important roles for subtle abnormalities in systolic function,[14-16] arrhythmias (particularly atrial fibrillation),[16,17] pulmonary vascular and right ventricular function,[19,20] stiffness and dysfunction of large and small arteries,[21-23] and skeletal muscle.[24,25]

Females are predisposed to develop HFpEF and exhibit differences in disease phenotype. Female sex is associated with 2.8-times greater odds of having HFpEF compared with HFrEF.[26] Sex differences in HFpEF pathophysiology include structural and functional cardiac/noncardiac factors and comorbidities (Figure 1).[27]

Compared with males, females have smaller LV dimensions and lower stroke volumes, even accounting for body size; as such, heart rate needs to more greatly increase during exercise in females, which is exacerbated with ageing.[27] Females are also more prone to increased LV wall thickness, concentric remodelling, and diastolic dysfunction, particularly when accompanied by hypertension.[28,29] Additionally, LVEF is on average higher and increases more with age in females, though they develop a greater reduction in systolic long-axis contraction velocity.[30,31] Also with increasing age, males tend to lose myocardium and LV chamber size increases whereas for females, LV mass and chamber size can remain fairly stable, rendering females more at risk from chronotropic incompetence and systolic/diastolic impairment seen in HFpEF, particularly on exertion.[27,32]

The underlying molecular and cellular mechanisms predisposing females to LV diastolic dysfunction remain largely unexplained, though many different, primarily hormonally-mediated, hypotheses have been proposed.[27] For instance, oestrogen is involved in downregulation of protein kinase A, which

modulates phosphorylation of the sarcomeric structural protein titin/connectin involved in cardiomyocyte stiffness.[33] Somewhat greater LV concentric hypertrophy is also associated with oestrogen, attributed to growth factor modulation.[34] Oestrogen levels also control transcription and processing of some microRNA, which affect post-transcriptional cellular processes, with several microRNA known to escape X-chromosome inactivation more expressed in particular female cell types. These microRNA can notably influence response to metabolic stress and vascular inflammation of endothelial cells, vascular smooth muscle cells, and cardiomyocytes. They may promote endothelial dysfunction, smooth muscle cell proliferation, and cardiac hypertrophy, among other mechanisms involved in HFpEF.[35]

Sex differences in systemic and pulmonary circulation may play a role in HFpEF development. For instance, increased vascular stiffness and endothelial dysfunction predominantly affect females.[32,36] Depending on artery size and localisation, pathophysiological consequences include increased wave reflection with greater increase of ventricular elastance, abnormal ventricular–arterial coupling, and coronary microvascular dysfunction.[27] Pulmonary vascular reactivity and remodelling can vary between sexes. For example, females are more affected by idiopathic pulmonary arterial hypertension.[37] In HFpEF studies, many more females are noted in cohorts with pulmonary hypertension (82%) compared to those without (58%).[38] Lastly, HFpEF comorbidities are also important, particularly because of their contribution to systemic inflammation. Many are more prevalent in females, including iron deficiency, obesity, or autoimmune disease; more frequently associated with HF, such as hypertension and diabetes; or present uniquely, as in pregnancy-related hypertensive disorders.[27]

Several studies have highlighted sex differences in HFpEF phenotype. The largest echocardiographic study found females with HFpEF were more likely to have concentric LV remodelling with smaller LV diameters and higher LVEF.[39] In one haemodynamics study (n=161), compared to males, females with HFpEF had a higher pulmonary capillary wedge pressure (PCWP) indexed to peak exercise workload and a smaller rise in stroke volume index with exercise, indicating poorer diastolic reserve. Systemic and pulmonary compliance levels were also lower in females at rest and during exercise.[36] In another study, adding cardiopulmonary exercise testing during right heart catheterisation with repeated measures of PCWP and cardiac output found a steeper PCWP/cardiac output slope during exercise in females, indicating greater diastolic reserve impairment.[40] In addition, females exhibited poorer peripheral oxygen extraction and worse right ventricular and LV systolic reserve during exercise.

IS THERE A DIFFERENCE IN RESPONSE TO THERAPY BETWEEN MALES AND FEMALES?

Therapies attempted in HFpEF generally mirror those with efficacy in HFrEF, such as angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, angiotensin receptor neprilysin inhibitors, mineralocorticoid receptor antagonists, and β-blockers. However, no treatment has yet been convincingly shown to reduce morbidity/mortality associated with HFpEF.[2,9] Current therapeutic strategies in HFpEF comprise first alleviating congestion with diuretics, then treating comorbidities. A combined endurance/resistance rehabilitation training programme should also be proposed to improve exercise capacity and QoL.[2]

No trials have specifically examined sex differences in response to HFpEF treatments; however, post hoc analyses of five HFpEF trials have reported such differences in baseline characteristics and clinical outcomes or in response to therapy (Table 1).[10,41-44]

In the primary DIG trial[45,46] (LVEF >45%; n=988), digoxin use was not associated with any effect on mortality or hospitalisations with HFpEF and no significant heterogeneity in treatment effect between sexes were reported. However, subanalysis of baseline characteristics of 719 patients with a LVEF ≥50% (n=341 females)[41] did reveal differences prior to therapy. Females were on average 3 years older, had higher blood pressure (BP) and LVEF, and had more symptoms and signs of advanced HF, but less coronary artery disease (CAD) and chronic kidney disease. After adjustment for baseline differences, female sex was an independent

predictor of lower mortality (hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.43–0.82), although HF hospitalisation rates were similar between sexes (HR: 1.06; 95% CI: 0.75–1.51).[41]

Another secondary analysis confirmed better survival in females compared to males for both HFrEF and HFpEF. Hospitalisation rates were similar for HFpEF, but greater in males with HFrEF.[47]

Table 1: Sex-related differences in trials of heart failure with a preserved ejection fraction.

Study/sex difference subanalysis	DIG-PEF[41,42]	CHARM-Preserve[43]	I-PRESERVE[44]	TOPCAT (Americas)[42]	PARAGON-HF[10]
Number of patients	719	3,023	4,128	1,767	4,796
Females (%)	47	40	60	50	52
LVEF inclusion criteria (%)	≥50	>40	≥45	≥45	≥45
Baseline characteristics (females vs males)					
Age	↑	NA	↑	↑	↑
BMI	↔	NA	↑	↑	↑
LVEF	59.0 vs 55.5	NA	61.0 vs 58.0	59.8 vs 56.6	58.9 vs 56.0
Diabetes	↑	NA	↔	↓	↓
Hypertension	↑	NA	↑	↑	↑
CKD	↑	NA	↑	↑	↓
Atrial fibrillation	NA	NA	↓	↓	↓
CAD	↓	NA	↓	↓	↓
Event rates per 100 patient-years (females vs males)					
				Placebo arm	Valsartan arm
All-cause mortality	7.88 vs 8.07	5.68 vs 5.30	4.32 vs 6.72	3.64 vs 4.15	4.40 vs 5.80
CV mortality	5.96 vs 5.62	3.83 vs 3.87	2.51 vs 4.21	2.15 vs 2.68	2.50 vs 3.70
Non-CV mortality	1.84 vs 1.59	1.84 vs 1.43	1.26 vs 2.14	0.93 vs 1.20	1.57 vs 1.92
CV hospitalisation	15.20 vs 17.00	20.40 vs 20.40	17.00 vs 21.80	6.34 vs 6.80	15.47 vs 15.79
HF hospitalisation	5.26 vs 8.53	7.32 vs 5.75	7.10 vs 7.80	3.79 vs 4.43	12.20 vs 10.90
Non-CV hospitalisation	15.30 vs 13.10	19.30 vs 14.90	14.10 vs 17.50	6.91 vs 7.42	16.38 vs 16.60
Sex differences in response to therapy	No	Not investigated	Not investigated	Lower all-cause mortality in females with spironolactone vs placebo (HR: 0.66; 95% CI: 0.48–0.90; p=0.01) but not males (HR: 1.06; 95% CI: 0.81–1.39; p=0.68); significant interaction for sex (p=0.024).	Reduction of primary outcome (CV death + HF hospitalisation) in females with sacubitril/valsartan vs valsartan (ARR: 0.73; 95% CI: 0.60–0.90); significant interaction for sex (p=0.0225).

↑: statistically significantly higher in females

↓: statistically significantly lower in females

↔ : no statistically significant difference

ARR: Adjusted rate ratio; CAD: coronary artery disease; CI: confidence interval; CKD: chronic kidney disease; CV: cardiovascular; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; NA: not analysed.

Candesartan versus placebo was investigated in the CHARM-Preserved programme (LVEF >40%; n=3,023; 40% females).[48] In general, candesartan had neutral effects on mortality but a modest reduction in HF hospitalisations. Further analysis found females had better outcomes for mortality and HF hospitalisations compared with males, regardless of baseline LVEF.[42] More specifically, adjusted HR for all-cause mortality in females versus males was 0.77 (95% CI: 0.69–0.86; p<0.001) and 0.83 (95% CI: 0.76–0.91; p<0.001) for CV death or HF hospitalisation.[43]

The I-PRESERVE trial[49] compared irbesartan to placebo (LVEF ≥45%; n=4,128; 60% females; ≥60 years). Irbesartan did not improve the primary outcome (death from any cause or hospitalisation for a CV cause) or other prespecified outcomes, and no sex differences were observed. A subanalysis found that at baseline, females were on average 1 year older and more likely to be obese and have chronic kidney disease and hypertension, but were less likely to have ischaemic heart disease, atrial fibrillation, or chronic obstructive pulmonary disease.[43] During a mean follow-up of 49.5 months, the primary outcome unadjusted HR was 25% lower in females than males (HR: 0.75; 95% CI: 0.68–0.83; p<0.001) and remained significant after adjusting for baseline covariates (adjusted HR: 0.81; 95% CI: 0.72–0.92; p=0.001). Four baseline characteristics seemed to particularly mitigate this finding: atrial fibrillation, renal dysfunction, stable angina pectoris, or advanced New York Heart Association (NYHA) Class symptoms.[43]

In the TOPCAT trial[44] (LVEF ≥45%; n=3,445; 52% females),[50] spironolactone did not significantly reduce incidence of the primary composite outcome (CV death, aborted cardiac arrest, or HF hospitalisation) compared to placebo. Subgroup analysis did not show heterogeneity in treatment effects according to sex. However, in a secondary analysis, sex differences in outcomes and responses to spironolactone in 1,767 patients (50% females) found females were older and had higher LVEF, BP, and BMI, with fewer comorbidities.[44] There were no significant differences in outcomes between sexes in the placebo group. Spironolactone use was associated with reduction in all-cause mortality in females but not in males, with a significant sex-treatment interaction (Table 1).[44] These findings indicate a possible sex-specific benefit of spironolactone in females, but require confirmation.

Using individual patient data from the CHARM-Preserved, I-PRESERVE, and TOPCAT trials, a meta-analysis (4,458 females, 4,010 males; LVEF ≥45%) found that females were older and more were classed as obese and hypertensive, but were less likely to have CAD or atrial fibrillation.[51] Primary outcome risk (composite of HF hospitalisation or CV death) was lower in females compared with males (HR: 0.80; 95% CI: 0.73–0.88), with a similar risk of HF hospitalisation but a lower risk of sudden cardiac death.[51]

Finally, the PARAGON-HF trial[9] compared the angiotensin receptor neprilysin inhibitor sacubitril/valsartan to valsartan alone (n=4,822; mean age: 73 years; 52% female; mean LVEF: 58%). Primary outcome occurrence rate (composite of total hospitalisations for HF and death from CV causes) was slightly, but not significantly, reduced in the sacubitril/valsartan group versus the valsartan group (rate ratio: 0.87; 95% CI: 0.75–1.01; p=0.06). Prespecified subgroup analysis of the primary outcome indicated heterogeneity of treatment, with possible benefits of sacubitril/valsartan in patients with lower LVEF (≤57%) and in females. Dedicated analysis found that compared with males, females in the PARAGON-HF trial were on average 2 years older, had higher LVEF, lower N-terminal pro B-type natriuretic peptide (NT-proBNP), less CAD, and less atrial fibrillation. Compared to valsartan, the unadjusted rate ratio for the primary outcome with sacubitril/valsartan versus placebo was 0.73 (95% CI: 0.59–0.90) in females and 1.03 (95% CI: 0.84–1.25) in males (p interaction: 0.017), results that persisted after adjustment for sex differences in baseline covariates and that were exclusively driven by a reduction in HF hospitalisation (Table 1).[10]

POTENTIAL UNDERLYING MECHANISMS OF SEX DIFFERENCES IN CLINICAL OUTCOMES AND RESPONSE TO THERAPY

It is largely unknown why females with HFpEF have better mortality outcomes even after adjustment for potential confounders, though several hypotheses have been proposed. Most importantly, females in all trials were invariably

less affected by CAD and therefore at lower risk for sudden cardiac death, the main driver of mortality in the pooled clinical trial cohort.[51] Even if analyses were adjusted for CAD, some, predominantly males, with silent disease may not have been diagnosed.

The sex differences in response to spironolactone and sacubitril/valsartan observed in the secondary analyses of TOPCAT and PARAGON-HF may be due to chance, but several other mechanisms may be postulated (Figure 2).

Females with HFpEF may be better responders because their HFpEF pathophysiology is different. As previously mentioned, females in general, and specifically with HFpEF, have on average higher LVEF than males. This implies that in females even a preserved LVEF of 55% may be associated with mild alterations of other indices of systolic function, which were not considered in the above-mentioned analyses. As both spironolactone and sacubitril/valsartan have clear beneficial effects in HFrEF, they may also be more effective in females with HF and higher ranges of LVEF compared with males.[10]

A greater biological activity of spironolactone in females may be another explanation. In the active group of TOPCAT, greater increases in creatinine and potassium were observed, without any significant difference in the remaining medications. This indicates a more potent renal effect of spironolactone in females compared with males.[44] Animal studies have also shown a greater impact of mineralocorticoid receptor antagonists on cardiac remodelling in females versus males.[51] It could be that there is a greater myocardial profibrotic effect of aldosterone in females, though this has not yet been demonstrated. In PARAGON-HF, while there was no biological signal indicating a greater effect of sacubitril/valsartan in females as decreases in BP or NT-proBNP were similar in both sexes, other signals may not have been detected. Recent data from the BIOSTAT-CHF registry in HFrEF indicated that females achieve the lowest risk of death or hospitalisation from HF pharmacotherapy at 50% of the recommended doses with no further benefits at higher doses, whereas males have the best outcomes at 100% of the recommended dose.[52]

In TOPCAT and PARAGON-HF, it may be postulated that spironolactone was more effective because it was used at a relatively higher dosage for females compared to males, even if the absolute dose was not different.

In PARAGON-HF, natriuretic peptide levels were lower in females despite more advanced HF signs and symptoms, partly because they had more visceral obesity compared with males. This natriuretic peptide deficit in females may explain why they benefit more from sacubitril/valsartan which, by the action of sacubitrilat, the active metabolite of sacubitril, inhibits neprilysin and thus increases natriuretic peptides.

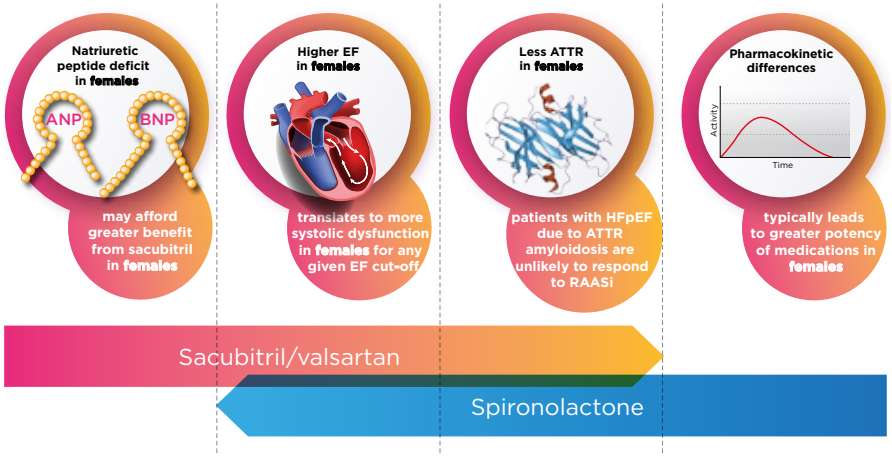

Figure 2: Possible mechanisms behind sex differences in response to sacubitril/valsartan and spironolactone.

ANP: atrial natriuretic peptide; ATTR: transthyretin amyloidosis; BNP: B-type natriuretic peptide; EF: ejection fraction; HFpEF: heart failure with preserved ejection fraction; RAASi: renin–angiotensin–aldosterone system inhibitors.

Neprilysin is an endopeptidase that degrades dozens of different vasoactive peptides. Females may have a different panel of these peptides and therefore a different response to sacubitril/valsartan. For instance, females are more prone to develop angioedema with neprilysin inhibition, which is mediated by bradykinin.[10]

Finally, wild-type transthyretin cardiac amyloidosis is increasingly shown as an important cause of HFpEF and may affect 13% of those hospitalised for this category of HF.[53] As there is a clear male predisposition to this condition (>90% of cases),[54] a significant proportion of males may have been affected in TOPCAT and PARAGON-HF by unrecognised wild-type transthyretin cardiac amyloidosis, which is known not to respond to renin–angiotensin–aldosterone inhibition and to have a poor prognosis.[53,54]

AREAS FOR FURTHER EXPLORATION AND FUTURE DIRECTIONS

Theoretically, sex differences observed in subgroup analyses of the TOPCAT and PARAGON-HF trials are hypothesis-generating only and should be confirmed in new trials conducted specifically in females. There is also significant scope to further explore underlying pathophysiologic and phenotypic differences in HFpEF between the sexes, particularly given that the heterogeneous nature of HFpEF has been postulated to be a significant contributor to the neutral outcome of multiple HFpEF trials.[55] Trials targeting underlying mechanisms behind HFpEF that are particularly problematic in females, such as pulmonary vascular dysfunction, greater pulsatile afterload and greater LV filling pressures, and lower stroke volume recruitment with exercise,[56] may be more effective than the application of existing treatments for HFrEF, which less commonly affects females.

Current trials of new therapies for HFpEF are underway that may address underlying mechanisms of HFpEF that are particularly relevant to females. First of all, the transcatheter InterAtrial Shunt Device (Corvia Medical, Inc., Tewksbury, Massachusetts, USA) has shown promising results in the REDUCE LAP-HF trial by reducing PCWP with exercise,[57] which could be of greater utility in females. Pulmonary vascular dysfunction is a key component of exercise intolerance in females with HFpEF.[36] As such, a trial investigating a specific pulmonary vasodilator, macitentan, in people with HFpEF and pulmonary vascular disease is underway (SERENADE).[58] Finally, two other HFrEF therapeutic strategies currently being tested in HFpEF, sodium glucose cotransporter inhibitors (EMPEROR-PRESERVED;[59] DELIVER[60]) and oral soluble guanylate cyclase activators (Vitality-HFpEF),[61] could be of particular interest to females in whom diabetes and arterial stiffness play an important role in HFpEF.

Another important consideration is the outcome measure used in trials of HFpEF, particularly in females. The marked sex difference in mortality outcomes described above highlights that studies with a CV mortality primary endpoint are of less relevance to the female HFpEF population. Rather, a focus on improving symptoms and QoL, along with hospitalisations, may be more meaningful as females with HF consistently report lower QoL and greater rates of anxiety and depression.[7] Treatments with a greater focus on symptomatic improvement and exercise tolerance warrant further exploration and may involve great investment in nonpharmacological therapeutic options, such as exercise regimens and weight loss, particularly given that this is underutilised among females.[62]

Finally, sex differences in key risk factors that predispose to HFpEF development require attention. For example, aggressively targeting systemic hypertension in females is a key component to HFpEF prevention; however, despite a greater prevalence of hypertension than males, particularly after menopause,[63] females have a lower rate of control when treated pharmacologically.[64] The development of hypertension following menopause is driven by the reduction in oestrogen causing both increased vascular resistance through a reduction in vasodilatory and anti-inflammatory pathways and a rise in sympathetic nervous system activity.[65] While hormone replacement therapy has proven ineffective in CV disease prevention in large studies, targeted oestrogen modulation could be investigated, particularly for the treatment of hypertension and HFpEF in women. Sex-specific preventative strategies for HFpEF should also address obesity, which affects more females than males globally.[27]

Similarly, there are a number of risk factors specific to females (e.g., hypertensive disorders of pregnancy) or that disproportionately affect females (e.g., autoimmune disorders) that may play a significant role in HFpEF development and for which there is very little framework at present to minimise future CV risk.[27]

CONCLUSION

In the context of increasingly recognised sex dimorphisms in the pathophysiology and phenotypes of HFpEF, it is unsurprising that responses to therapy differ. Although trials of pharmacologic therapies for HFpEF have been neutral, they have highlighted important differences in outcomes between the sexes, along with some signals for sex differences in the response to spironolactone and sacubitril/valsartan for HFpEF. This requires further exploration with dedicated trials, along with studies investigating therapies targeting the key pathophysiologic pathways and phenotypic features seen in females. Furthermore, trials of therapies for HF in females with broader outcomes encompassing QoL, rather than focussing on mortality, may be more relevant to the female population.

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Acute Severe Mitral Regurgitation Secondary to *Haemophilus parainfluenzae* Infective Endocarditis

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Abstract

Haemophilus parainfluenzae is an exceedingly rare cause of infective endocarditis, with only a few case reports describing its potential invasiveness. This case reports on a 25-year-old female who was admitted with a fever and was subsequently found to have *H. parainfluenzae* endocarditis. She was managed with intravenous antibiotics and mitral valve replacement.

INTRODUCTION

Haemophilus parainfluenzae has established itself as an important, albeit uncommon, cause of infective endocarditis (IE). In a multinational cohort study conducted in 2013 on patients hospitalised with definite or possible infective endocarditis, only 1.4% of cases were caused by a *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, or *Kingella* species (the HACEK group of bacteria).[1]

Historically, *H. parainfluenzae* endocarditis has been characterised as having a subacute course and usually inflicts disease in those with poor dentition and a history of pre-existing valve disease.[2] However, after reviewing the literature, a different tale of its pathogenicity has unfolded over the years; it can lead to an invasive disease with a mortality ranging from 10–35% in patients without any apparent risk factors.[3,4] Reports of large, destructive vegetations that most often affect the mitral valve have been described.[3] Additionally, they are frequently complicated by embolic phenomena such as cerebral emboli and splenic infarcts.[4]

The authors present the case of a 25-year-old female with no relevant medical history who was admitted for fever and was found to have acute native valve endocarditis secondary to *H. parainfluenzae*. She underwent successful replacement of the mitral valve. To the best of the authors' knowledge, this is one of the few cases demonstrating *H. parainfluenzae* endocarditis manifesting as acute severe mitral regurgitation (MR).[3,4]

CASE PRESENTATION

A previously healthy 25-year-old female was evaluated in the University of North Carolina Hospitals Emergency Department, Chapel Hill, North Carolina, USA. She presented with 1 week of fever, headache, and neck stiffness; she described the headache as "excruciating." Additional symptoms included nausea, anorexia, and an intermittent aching sensation across her precordium that worsened on inspiration. She denied having any rashes, lower extremity swelling, or dyspnoea, and she was without additional gastrointestinal or genitourinary complaints.

The patient had no past medical history. She was up to date on her immunisation schedule and denied intravenous drug use. She also denied recent dental procedures or having come into contact with anyone sick, but did have an 8-year-old son. However, she had not been living with him prior to the onset of her symptoms. She denied any recent travel and had been practicing social distancing as part of the recommended guidelines for the coronavirus disease 2019 (COVID-19) pandemic.

On physical examination, her temperature was 39.4 °C; blood pressure: 94/64 mm Hg; heart rate: 163 beats per minute; and oxygen saturation: 94% while breathing ambient air. A physical exam was notable for photophobia, meningismus, and a hyperdynamic precordium with a 3/6 holosystolic murmur, loudest at the apex, radiating to the axilla. There were no embolic phenomena or focal neurologic deficits. Examination of the oropharynx and skin, including the palms, soles, and nails, were normal.

The blood level of haemoglobin was 11.2 g/dL; white-cell count: 5.8 x10^9/L (reference range: 4.0–10.0 x10^9/L) with lymphopenia; platelet count: 74,000/mm^3; troponin: 0.062 ng/mL; pro-brain natriuretic peptide: 2490 pg/mL; C-reactive protein: 328.7 mg/dL; venous lactate: 2.6 mmol/L; sodium: 133 mmol/L, potassium: 3.4 mmol/L; chloride: 95 mmol/L; bicarbonate: 22 mmol/L; urea nitrogen: 14 mg/dL; creatinine: 0.64 mg/dL; glucose: 112 mg/dL; total protein: 5.8 g/dL; albumin: 3.1 g/dL; total bilirubin: 0.8 mg/dL; aspartate aminotransferase: 30 U/L; alanine aminotransferase: 36 U/L; and alkaline phosphatase: 183 U/L.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) PCR testing was negative, in addition to a respiratory pathogen panel and HIV screening. CT and MRI of the brain were both unremarkable. A lumbar puncture revealed a mild neutrophilic pleocytosis with 39 nucleated cells/mm^3; 75% neutrophils; 2 red blood cell count/mm^3; protein: 41 mg/dL; and glucose: 58 mg/dL. The opening pressure was 17 cm H_2O. Electrocardiography showed sinus tachycardia with normal intervals and no evidence of ST segment changes. A chest X-ray showed clear lung fields.

Given her neurologic complaints and elevated cardiac biomarkers, the patient was admitted to the hospital with a working diagnosis of viral aseptic meningitis with myocarditis. Volume rescucitation was administered, in addition to empiric antimicrobial coverage with intravenous vancomycin, cefepime, and acyclovir. Upon examination, the cardiac murmur could not be reconciled with the working diagnosis and the patient denied a previous history of a cardiac murmur. Therefore, a transthoracic echocardiogram was performed, which revealed moderate MR with possible mitral valve vegetation.

Later that night, both of the peripheral blood cultures collected on admission became positive; they were reported as gram-negative rods in the electronic medical record, but re-review of the gram stain revealed them to be coccobacillary gram-negative organisms in chains and clusters, suspicious for *Haemophilus spp*. The following day, the blood cultures speciated *H. parainfluenzae* using the BD Bactec™ (Becton, Dickinson, and Company, Franklin Lakes, New Jersey, USA) continuous blood culture monitoring system. Her antibiotic regimen was subsequently narrowed to ceftriaxone monotherapy. No susceptibility testing was performed.

Two days later, the patient developed respiratory distress and her cardiac murmur dynamically changed. On auscultation, there was a harsh holosystolic murmur heard at the apex with radiation to the left lower sternal border and axilla. A repeat transthoracic echocardiogram showed severe MR and a likely perforation of the anterior (A_3) versus posterior (P_3) leaflet (Figure 1).

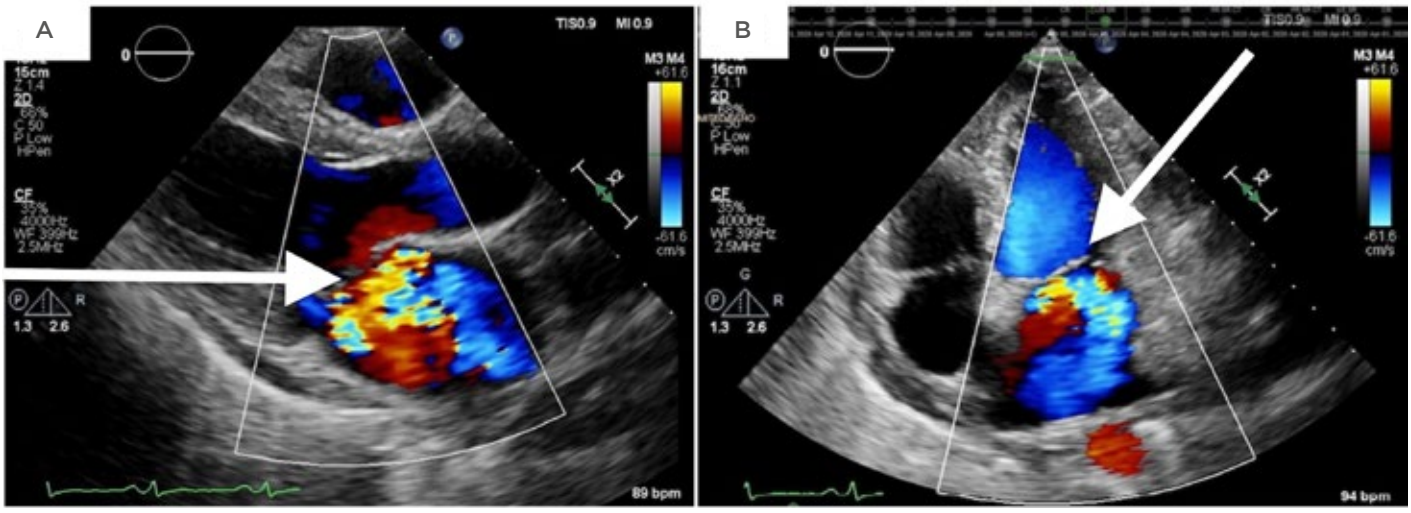

Figure 1: A repeat transthoracic echocardiogram revealing severe mitral regurgitation in the parasternal long-axis view **(A)** and an apical four-chamber view **(B).**

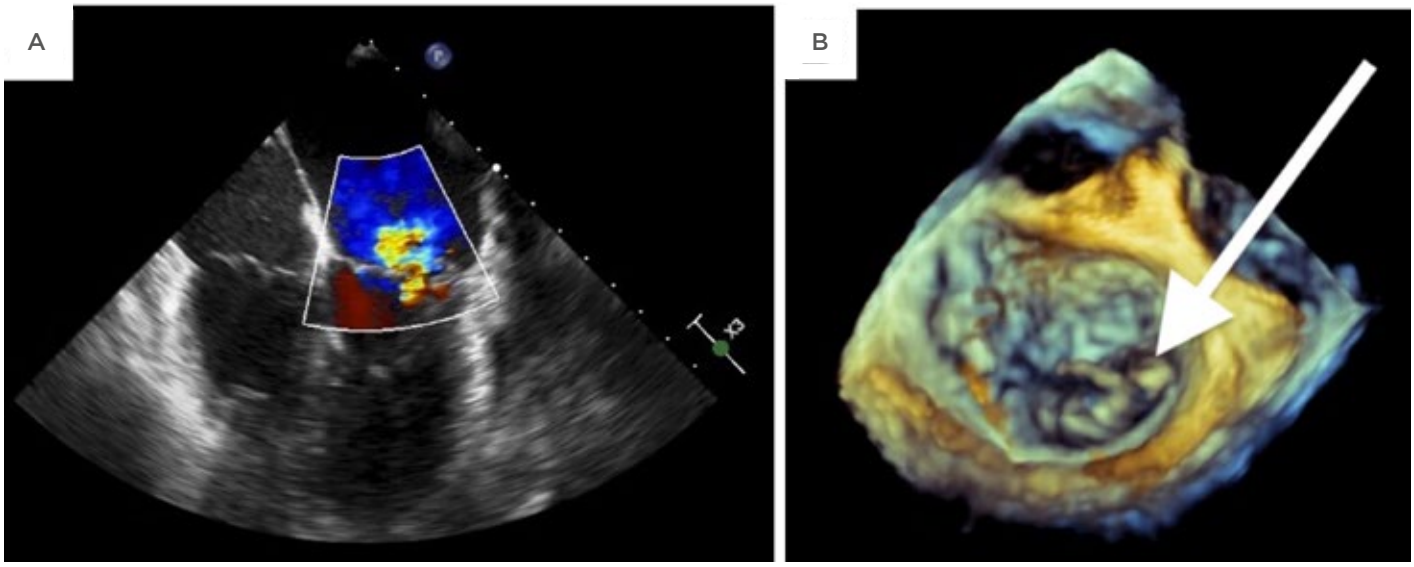

Figure 2: An intraoperative transesophageal echocardiogram demonstrating mitral regurgitation on midesophageal four-chamber view **(A)** as well as a 3-dimensional transthoracic echocardiogram showing a flail posterior leaflet **(B).**

Cardiothoracic surgery was considered. Although transesophageal echocardiography was desired for further surgical planning, it was ultimately not pursued because of the risk of periprocedural haemodynamic collapse. She was moved to the cardiac intensive care unit for closer monitoring until she underwent valve replacement. Although her presenting symptoms had mostly resolved, she continued to have sinus tachycardia with intermittent episodes of headache and fever leading up to the date of surgery.

Intraoperative findings included a perforated A_2 leaflet, a flail P_1 leaflet, and vegetations involving P_1, P_3, and the annulus (Figure 2). The involved leaflets, subvalvular apparatus, annulus, and a portion of the ventricle were resected and replaced with a mechanical mitral valve. The majority of its chordae tendineae were retained.

Although bacterial, fungal, and acid-fast bacilli cultures of the surgical specimens were negative, 16S rRNA sequencing of the valvular tissue revealed *H. parainfluenzae*. Repeat blood

cultures throughout the rest of her admission remained negative. The patient was started on warfarin with a goal international normalised ratio of 2.5–3.5. She completed 4 weeks of intravenous ceftriaxone with an adjunctive 10 days of gentamicin (5 days) followed by levofloxacin (5 days). Her post-discharge course was complicated by postoperative pericarditis treated with colchicine and transient neutropenia in the last week of ceftriaxone which recovered after completion of therapy.

DISCUSSION

The patient presented with multiple systemic complaints, namely fever, which is seen in 80% of cases of IE.[5] Her symptoms of headache, meningismus, and fever led the authors to initially consider meningitis. The prominent murmur and elevated cardiac biomarkers, in combination with echocardiography and blood cultures, were the clues that she did not fit the working diagnosis of aseptic meningitis and ultimately led to the correct diagnosis of IE secondary to *H. parainfluenzae*. However, it should be noted that meningitis can occur as a complication in 3.5% of IE cases.[6] The patient was successfully managed with surgical replacement of the mitral valve and intravenous antibiotics. Although not recommended under current American Heart Association (AHA) guidelines, the infectious disease consultants recommended adjunctive therapy with gentamicin and levofloxacin while awaiting clinical improvement.

In addition to the nonspecific symptomatology on presentation, this case was made additionally challenging given the absence of risk factors in the patient. Interestingly, there have been several similar case reports over recent years (Table 1). Faure et al.[7] describe a young healthy female who presented with fevers, headache, and meningismus.[7] She was also eventually diagnosed with *H. parainfluenzae* endocarditis and underwent mitral valve repair. This report was helpful because the patient's initial course was very unclear and was made urgent by the severity of her illness. As in this case, careful physical examination and serial echocardiograms were required to demonstrate the presence of IE secondary to *H. parainfluenzae* and the progression of the mitral valvulopathy.

Table 1: Comparison of three patients with *Haemophilus parainfluenzae* endocarditis.

Age/sex	Location	Relevant laboratory tests	Echocardiography	Head imaging	Treatment
25-year-old female[¶]	Chapel Hill, North Carolina, USA	Thrombocytopenia Normal white blood cells Elevated CRP	Mitral valve vegetation with perforation	Unrevealing	Mitral valve replacement 4-week course of IV ceftriaxone
33-year-old female[7]	Lille, France	Thrombocytopenia Leukopenia Elevated CRP	Mitral valve vegetation	Unrevealing	Mitral valve repair 6-week course of IV ceftriaxone, rifampicin, and ciprofloxacin
27-year-old male[9]	Brooklyn, New York, USA	Thrombocytopenia Leukocytosis Elevated CRP	Mitral valve vegetation with perforation	Cerebral emboli Maxillary sinusitis	Mitral valve repair 6-week course of IV ceftriaxone

All three patients presented with acute onset of fever, chills, and myalgias.

[¶]The authors' case.

CRP: C-reactive protein; IV: intravenous.

H. parainfluenzae, a gram-negative coccobacillus, is part of the normal flora of the oropharynx. Though rare, it is a member of the HACEK group of bacteria, which are known to cause endocarditis in approximately 3% of cases.[8] Because of their oropharyngeal affiliation, HACEK endocarditis has been associated with risk factors such as dental work and nasopharyngeal infections.[9] The literature describing *H. parainfluenzae* endocarditis is sparse, but there are two reviews of *H. parainfluenzae* endocarditis that describe it as having a subacute onset (<2 months) and a predominance in young people, with a median age of onset of 27 years. Over half of the affected patients had no underlying valvular disease, the mitral valve was most commonly affected, and no portal of entry was identified in 80% of cases.[3,4,7-10]

H. parainfluenzae endocarditis has been associated with severe complications, including cerebral emboli and mitral valve perforation.[6] Given this pathogen's propensity to embolise, close attention should be paid to any new neurologic symptoms with a low threshold for neuroimaging to evaluate for a microbial aneurysm or embolism. Although no embolic phenomena were evident on imaging, this case supports its potential for leading to severe destruction of the valvular apparatus. Clinicians should pay particular attention to any new symptoms or dynamic changes to a patient's cardiac exams as this may indicate clinical deterioration and should prompt urgent echocardiography, as well as the early involvement of cardiothoracic surgery. Intraoperatively, the patient was found to have significant deterioration of the mitral valve which necessitated resection of most of the leaflets. There was also erosion into the annulus and ventricle requiring debridement.

CONCLUSION

This case describes a young female with no previous valvular heart disease who presented with aseptic meningitis and a dynamic murmur on cardiac exam who was ultimately found to have native mitral valve endocarditis as a result of *H. parainfluenzae*. Her course was complicated by acute severe MR requiring mechanical valve replacement. The extensive destruction of the patient's valve highlights the pathogen's virulence. *H. parainfluenzae* endocarditis remains an elusive disease entitity, and though rare, in the setting of culture-negative meningitis with new valvular dysfunction, the diagnosis should be considered by obtaining blood cultures and urgent echocardiography.

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The Evolution and Future Direction of The Cardiac Biomarker

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Abstract

A biomarker is any measurement taken that aims to improve a diagnosis, or predict the response, to treatment of disease. Although not limited to laboratory molecular markers, this variety have attracted the most interest and seen the greatest development in recent years. The field of cardiology was an early adopter of biomarkers, with transaminases having been used for the diagnosis of acute myocardial infarction since the 1970s. The use of biomarkers has become increasingly prevalent since then and provided ever more sensitive means to diagnose myocardial cell injury or heart failure. However, diagnosis of disease at an increasingly earlier stage leads to blurring of the line between health and disease and we may be reaching the limits of early detection. Biomarkers may evolve to provide a greater understanding of the pathogenesis of cardiac disease, and by extension, the differentiation of disease subtypes. This article will review the evolution of cardiovascular biomarkers, the advantages and pitfalls associated with their use, as well as the future direction of cardiac biomarker research.

INTRODUCTION

The use of biomarkers has become routine in many areas of medicine. Knowing how and why these became incorporated into medical practice allows us to use them to their maximum potential and helps guide future developments. Biomarkers are especially widespread in the field of cardiology where disease may manifest with subtle or no clinical signs.

This narrative review covers the evolution and current application of biomarkers for acute coronary syndromes (ACS) and heart failure (HF). Pitfalls in their use and areas of cardiology poorly served by existing biomarkers will be discussed. This review will not cover biomarkers used for cardiovascular risk prediction, including lipoproteins or homocysteine, nor more novel work regarding single nucleotide polymorphisms that may confer risk of coronary artery disease, which are covered elsewhere.[1-3]

SEARCH METHODOLOGY

The authors conducted a comprehensive search in the English-language literature to identify relevant studies, regardless of publication status

or year of publication. PubMed and Google scholar databases were searched combining the terms 'cardiovascular' OR 'cardiac' OR 'myocardial' OR 'heart' OR 'heart failure' OR 'myocardial infarction' OR 'AMI' AND 'biomarker' OR 'circulating marker' OR 'cardiac protein'. Studies could include early or late phase human trials. Backward (using reference list of paper) and forward (using studies citing a paper) snowballing were applied to identify further studies. An extensive list was developed, and a shortlist was created based on the limitations of the length of the narrative review and importance of the marker. A separate search was also done for papers relating to the individual markers in PubMed. The last search was performed in January 2020.

WHAT IS A BIOMARKER?

Definition of a Biomarker

A biomarker may be defined as 'a characteristic that is objectively measured and evaluated to aid in understanding one or more of: the prediction of disease, its cause, the diagnosis, and the response to intervention.'[4] Under this definition, even commonplace parameters such as blood pressure and heart rate are biomarkers. However, the modern conception relates to clinical biochemistry.

History of Cardiac Biomarkers

The first recorded example of a cardiac biomarker came from an observation in 1954 detailing a rise in blood aspartate aminotransferase concentration 3–4 hours after an acute myocardial infarction (AMI).[5] The following year, a similar increase in serum lactate dehydrogenase activity was also seen post-AMI.[5] Thereafter, creatine kinase (CK) was found to be far more sensitive than aspartate aminotransferase or lactate dehydrogenase, with ≤98% sensitivity within 72 hours.[6] However, these enzymes exist in skeletal as well as cardiac muscle, leading to many false positives. This problem was partly overcome by use of an isoenzyme of CK called CK-myocardial band (MB), constituting a far greater proportion in the myocardium despite also being present in skeletal muscle. The separation of serum isoforms of CK isoenzymes using polyacrylamide gel electrophoresis, thereby identifying the MB of CK, was first described in 1972[7] and heralded the ubiquity of use through the 1980s.

Measurement of peptides and proteins in biological fluid was revolutionised through the development of the radio-immunoassay by Berson and Yallow in late 1960s. Radio-immunoassays allowed for the precise and accurate measurement of tiny quantities of proteins, evident from the successful measurement of myoglobin in 1978.[8] However, the concerns of experimental complexity and radiation use led to the replacement of the radiolabel with enzyme labels in the immunoassay: the ELISA was born.[9] CK-MB mass was first measured by ELISA in 1985, replacing the more laborious electrophoretic method.[10]

In 1985, the Thrombolysis in Myocardial Infarction (TIMI) study group reported that patients with AMI received maximum benefits when receiving thrombolysis within 4–6 hours of chest pain.[11] Therefore, an early biochemical marker of AMI became crucial for the diagnosis of myocardial injury. This helped to promote the development of the troponin (Tn) assay.

TROPONIN

Tn are part of the thin filament in the sarcomere and are involved in the calcium-dependent interaction of actin and myosin. Tn are found in striated muscle; however, subunits T and I are cardio-specific (cTn). Tn release from the myocardium may occur as a result of normal cellular turnover (Figure 1):[12] apoptosis; cellular release of cTn degradation products; increased (reversible) cellular wall permeability; swelling of cardiomyocytes, leading to formation and release of membranous 'blebs'; and myocyte necrosis.[13]

In the late 1990s it was shown in patients who were Tn-positive (but CK-MB-negative) that early medical intervention significantly improved outcomes. This led to the redefinition of AMI in the year 2000 to use cTn instead of cardiac enzymes or CK-MB mass.[14]

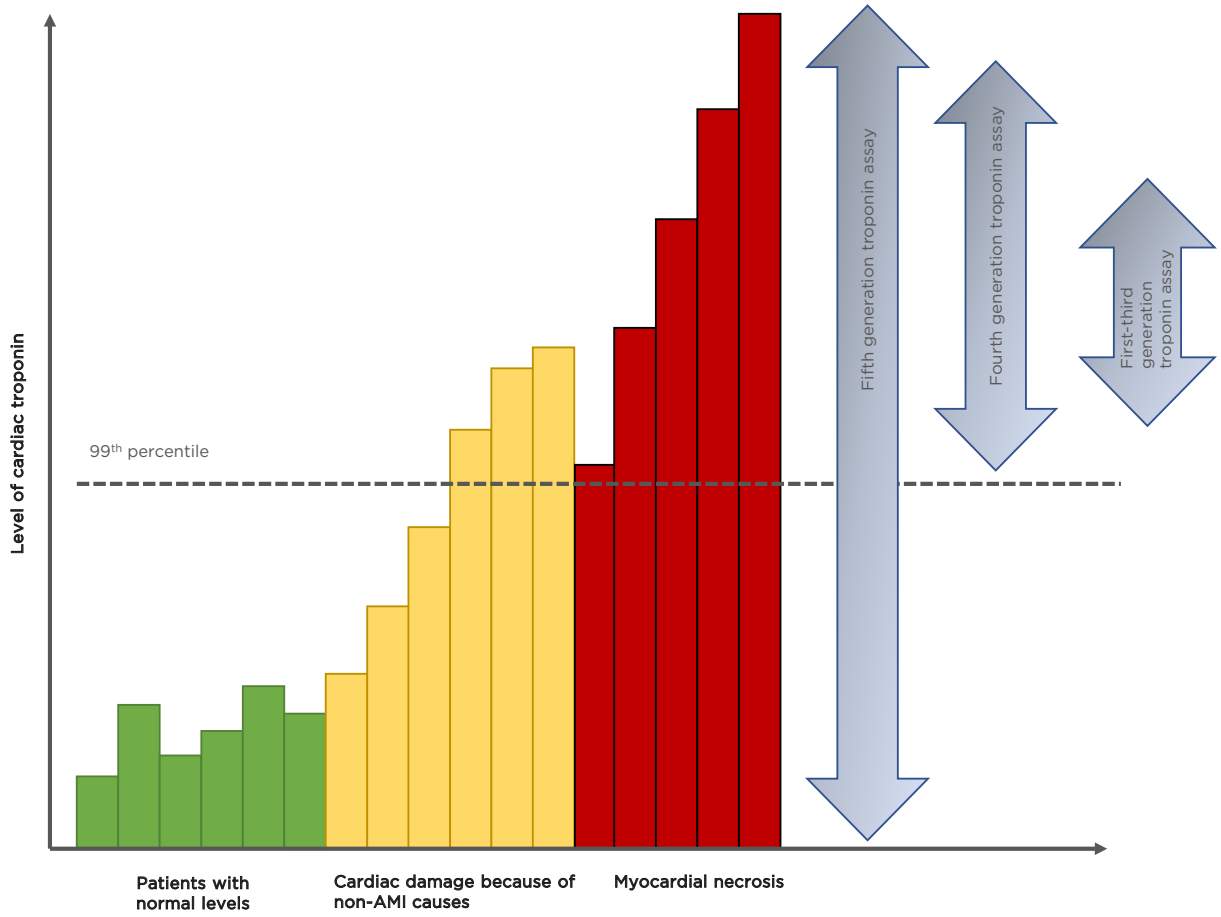

Figure 1: Improving sensitivities of troponin assays.

There is a background, normal, turnover of cardiac troponin (green bars). With the onset of AMI there is a rise in cardiac troponin that represents either ischemia-induced release of cytosolic troponin or micro-necrosis (orange bars). Between 2 and 6 hours there is a steep increase in cardiac troponin representing myocardial necrosis (red bars).

Modified from Garg et al.[12]

AMI: acute myocardial infarction.

High-Sensitivity Cardiac-Specific Troponin

High-sensitivity (hs)cTn assays are designated by their ability to detect cTn even in healthy individuals.[15] By definition these assays must be able to measure cTn concentrations in >50% of a healthy reference population (hence 50% of the population are above the lower limit of detection).[13] Therefore, 'high-sensitivity' refers to analytical and not clinical sensitivity. The latest generation of hscTn assays can detect troponin in >95% of a reference population.[16] Such high sensitivity is at the cost of low specificity, i.e., the ability to detect individuals without disease. The upper limit of the reference interval is considered to be the 99th percentile of the derivation population and assays must have a coefficient of variation (CV) <10% at that point.[17] Until recently this had been unachievable, but with advances in the immunoassay techniques the low CV has been met. The fifth generation hscTn assay is capable of measuring levels as low as 5 ng/L,[18] blurring the line between health and disease (Figure 1).[12] Almost 1 in 100 of the host population would have a raised hscTn: therefore how do we differentiate 'normal' from 'diseased'?[19]

Table 1: The fourth universal definition of myocardial infarction.

Type of MI	Description
Type 1	Spontaneous MI caused by atherothrombotic coronary artery disease, usually precipitated by plaque rupture or erosion.
Type 2	MI secondary to ischaemia caused by either increased oxygen demand or decreased supply, such as sepsis or tachyarrhythmias.
Type 3	Sudden, unexpected cardiac death with symptoms suggestive of MI, accompanied by presumed new ECG changes or ventricular fibrillation or MI detected by autopsy.
Type 4	MI associated with percutaneous coronary intervention (4a) or stent thrombosis (4b).
Type 5	MI associated with cardiac surgery

ECG: echocardiogram; MI: myocardial infarction.
Adapted from Thygesen et al.[13]

Perhaps surprisingly it is acceptable to calculate the 99th percentile (per sex) using as few as 300 males and 300 females.[20] Several factors are known to positively skew a troponin result, including age, male sex, low glomerular filtration rate (GFR), reduced left ventricular function, and systemic inflammation.[21]

The cut-off value by the 99th percentile rule will only be clinically useful when applied to patients with a high pre-test probability of ACS. This introduces the concept of Bayesian reasoning,[22] i.e., the diagnosis of AMI should always be made only after consideration of the patient history and 12-lead echocardiography, with hscTn concentrations interpreted within a well-defined and validated algorithm or pathway.[23,24]

The origin of the Tn assay was to determine whether a patient was having a Type 1 myocardial infarction, caused by coronary plaque rupture or erosion (Table 1). As assay sensitivity has improved, elevations caused by other pathologies are observed (such as Type 2 myocardial infarction; Figure 1).[12] This decreases the positive predictive value of a solitary Tn elevation for acute atherothrombotic coronary artery disease.[25] Changes in cTn values can be used to distinguish acute from chronic disease. Absolute changes are assay-dependent but appear superior to relative (percentage) changes using hscTn assays. High levels are associated with detrimental outcomes. The precision and reproducibility of hscTn assays allows for accurate, serial measurements in a short time. The value of the hscTn assay is not to identify more AMI, but to more quickly identify patients without disease.[26] Because of the low CV of the latest hscTn, the wait for a repeat test has fallen from 6–12 hours to 1 hour after symptom onset.[27] The European Society of Cardiology (ESC) recommends the '0/1h-approach' only if using hscTn with a validated algorithm in patients presenting >3 hours after chest pain onset; otherwise, the 0/3hr testing algorithm is recommended.[24] New point-of-care hscTn tests are becoming available, with high diagnostic accuracy.[16] These will facilitate the implementation of algorithms demanding fast decision making.

The high sensitivity of hscTn means that the positive predictive value for AMI ranges from as low as 15% to up to 75%.[28] Many individuals will undergo further assessment, potentially delaying treatment of noncardiac causes of an elevated hscTn.[29] Is the increase in downstream testing worth it? Evidence suggests that hscTn improves the early diagnosis of AMI and risk stratification, and outcomes have improved following hospitalisation for AMI.[30] However, high sensitivity also leads to the epidemiological paradox called the 'Will Rogers phenomenon', in which individuals formerly considered 'healthy' are now considered 'ill'. Regardless, these individuals are not as ill as patients diagnosed

using older assays. Reclassification may therefore result in AMI having a 'better' outcome.

Future Tn research may be directed at development and validation of algorithms for estimation of the pre-test probability of ACS, as well as determination of optimal post-test probability thresholds for initiating therapy.[22]

NOVEL BIOMARKERS UNDER EVALUATION FOR ACUTE CORONARY SYNDROME

The rationales for newer biomarkers in ACS are to improve the prognostic performance of Tn; reveal the pathophysiology of myocardial ischaemia (improved specificity); or to instantly rule out AMI, without the need for additional blood draw (improved sensitivity). Many candidates have been proposed, but for brevity the most salient are discussed. These include early biomarkers of cardiomyocyte injury such as H-FABP and cMyBP-C; markers of neurohormonal activation, including copeptin and MR-proADM; and markers of vascular inflammation such as C-reactive protein (CRP) and MPO.

Copeptin is the C-terminal end of the vasopressin prohormone, co-released with arginine vasopressin within 0–4 hours of AMI symptom onset.[31] Arginine vasopressin is a stress hormone and has a short half-life, meaning copeptin acts as a surrogate marker. Because endogenous stress is invariably present at early presentation of AMI, copeptin may help to improve the sensitivity of cTn.[23] A similar conception underlies the use of MR-proADM. This is a more stable form of the adrenal stress hormone adrenomedullin. Elevated levels have been shown in AMI but has yet to clearly add prognostic value above established methods.[32]

The sarcomeric protein cMyBP-C is twice as abundant in the heart as cTn or cardiac-specific troponin 1 (cTnI) and is a specific marker of myocyte injury.[28] It is released more rapidly than cTn and may be superior for those experiencing chest pain for <3 hours.[29,33] Similarly, H-FABP is another intra-cardiomyocyte protein also proposed as a sensitive, early marker of myocellular injury; however, its incremental value to cTn has not been established.[34,35]

Acute cardiac injury induces myocardial infiltration of leukocytes and proliferation of fibroblasts.[2] Pro-inflammatory cytokines like IL-6 and acute-phase proteins such as CRP are upregulated in patients with AMI and the degree of inflammatory response has been linked to risk stratification.[2] MPO is an enzyme released by neutrophil degranulation and contributes to inflammation, thereby worsening cardiac remodelling and having long-term adverse cardiac sequelae.[2,36]

A multi-marker strategy combining biomarkers representing the components outlined above (myocardial stress, myocyte necrosis, and inflammation) may provide additive prognostic information.[36]

NATRIURETIC PEPTIDES

The clinical diagnosis of HF can be challenging.[37] Several clinical criteria exist (Framingham, National Health and Nutrition Examination Survey [NHANES], modified Boston, Gothenburg, and International Classification of Disease 9th Revision). The Framingham clinical criteria are the most sensitive (90–92%), but with 40–79% specificity.[38,39] A biomarker to aid in the diagnosis of HF was therefore welcomed following the discovery of an 'atrial natriuretic factor' in the early 1980s.[40]

Natriuretic peptides (NP) comprise atrial natriuretic peptide (ANP; formerly known as atrial natriuretic factor), brain natriuretic peptide (BNP), C-type natriuretic peptide, and urodilatin. The first discovery of this family of peptides was made by de Bold in 1981,[38] who showed that extracts of rat atrium contained a substance that increased salt and urine output in the kidney. BNP is a 32-amino acid peptide, structurally similar to ANP, with a common 17-amino acid sequence. It was isolated in 1988 from porcine brain extracts by Sudoh et al.[41] BNP is a misnomer as it is synthesised and released primarily from ventricular myocardium.[42] Cleavage of the prohormone proBNP produces the biologically active 32-amino acid BNP, as well as biologically inactive N-terminal proBNP (NT-proBNP; 76 amino acids). Both are released from ventricular cardiomyocytes in response to mechanical stretch[42] and proportionate to the severity of HF.[42-44] In the 'Breathing Not Properly'

study a threshold BNP of 100 pg/mL was more accurate for HF (83%) than either the NHANES criteria (67%) or the Framingham criteria (73%).[45] The optimal diagnosis of HF was made when BNP was used in conjunction with other clinical information.

Ventricular stretch may occur as a result of renal failure, just as much as HF. In pre-dialysis patients, the estimated GFR and left ventricular mass index correlated independently to plasma BNP and NT-proBNP concentrations.[46] Unlike NT-proBNP, which relies solely on renal clearance, plasma BNP is also cleared by endopeptidases and receptor capture, and so values are less dependent on GFR. BNP may therefore be more appropriate for use in chronic kidney disease.[46]

The newly licenced Sacubitril/Valsartan is the first agent in a new class of angiotensin receptor neprilysin inhibitors. Inhibition of neprilysin prolongs the half-life of ANP and BNP, allowing for greater vasodilatory and natriuresis effects.[47] Use of this medication will mean persistence of elevated BNP, whereas NT-proBNP level will continue to be reflective of volume status. Related to this is the question of whether HF medications may be titrated against NP; this was addressed by the GUIDE-IT trial, which suggested titration against NP was no more effective than a usual clinical strategy.[48] Conversely, a more recent meta-analysis has suggested a benefit.[49] The dissimilarity may reflect the approach to management in the control groups, more than the intervention.

The short half-life of ANP (2–5 minutes) has made it unsuitable as a biomarker. However, newer assays can measure mid-regional proANP (MR-proANP) which is the precursor hormone of ANP and more stable. MR-proANP may improve diagnostic certainty in acute HF when there is associated obesity or chronic kidney disease, and also more accurately predicts 90-day mortality than NT-proBNP.[50] There is insufficient evidence for MR-proANP to replace the clinical utility or BNP, although it is now included in the ESC guidelines.[51] These guidelines also recommend using cut-off values for diagnosing HF (BNP >35 pg/mL; NTpro-BNP >125 ng/mL) in stable patients. However, higher value BNP >100 pg/mL, or NT-proBNP >300 pg/mL, should be used in the acute setting.[51]

PROBLEMS WITH EXISTING BIOMARKERS IN HEART FAILURE

Stimuli for natriuretic release include myocardial ischaemia (even in the absence of necrosis),[52] and hypoxia via HIF.[53] The physiological considerations discussed above explain why factors including blood pressure,[43] kidney function,[54] anaemia,[55] and ageing[56] will affect circulating BNP directly. Extra-cardiac factors, e.g., sex or obesity, are also associated with elevated BNP.[56,57] Conversely, almost a quarter of patients with chronic symptomatic HF may have NP levels in the lower ranges.[58] HF is a complex clinical syndrome caused by progressive structural and mechanical dysfunction, which gives rise to a multifactorial, interlinked pathophysiology (Figure 2). This makes aetiological certainty difficult and currently we do not have biomarkers that allow for an individualised diagnosis or response to therapy. This may be particularly problematic in those with heart failure with preserved ejection fraction, who are already disadvantaged by a lack of treatment modalities with proven mortality benefit.

FUTURE CARDIAC BIOMARKERS IN HEART FAILURE

As illustrated (Figure 2), there is a multitude of new biomarkers under evaluation representing pathophysiological pathways including inflammation, oxidative stress, and fibrosis. Candidate markers include cytokines, peptides, proteins, metabolites, and circulating nucleic acids. The success or failure of these markers for case selection will be dictated not just by their accuracy and reliability, but by whether specific anti-inflammatory, anti-oxidant, and anti-fibrotic therapies become established.

Cardiomyocyte Remodelling

Fibrous tissue deposition in the cardiac interstitium can result from many types of cardiac injury and is associated with increased disease severity and adverse outcomes.[59,60]

ST2, also known as IL1-RL1, is a member of the Toll-like/IL-1 receptor superfamily. It is upregulated by mechanical stress of cardiomyocytes and cardiac fibroblasts.

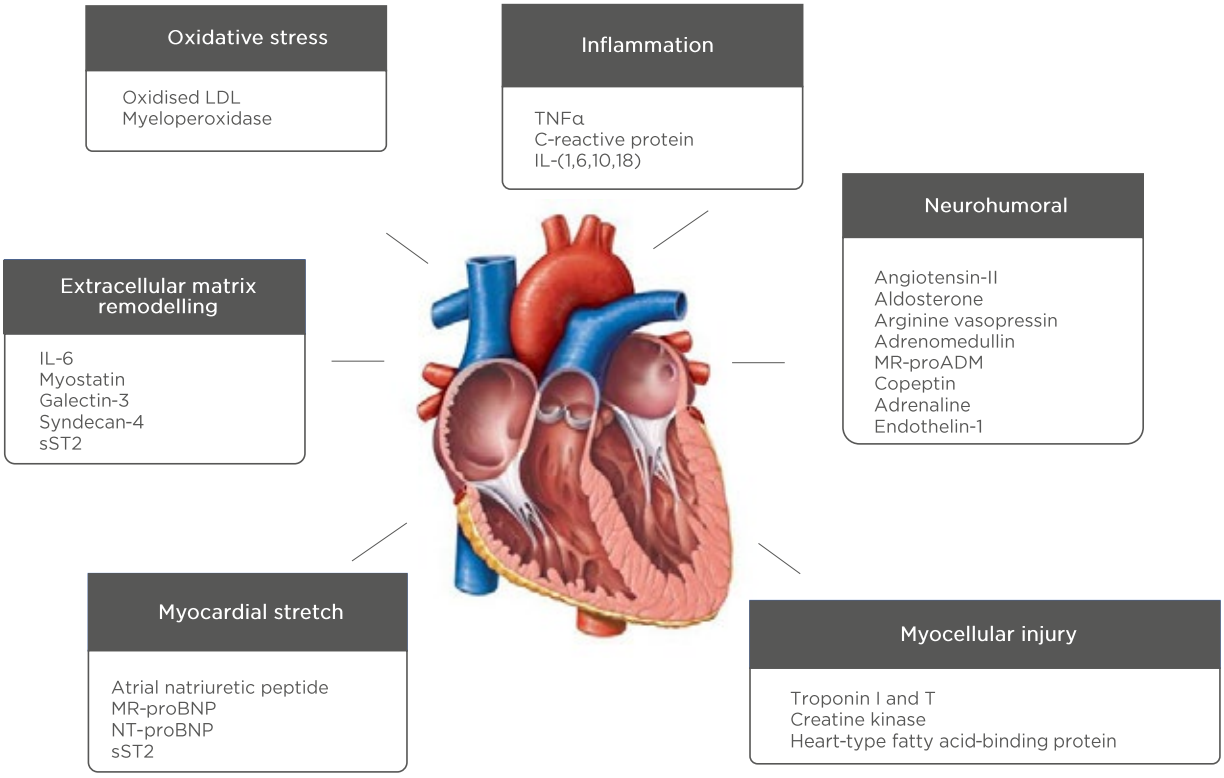

Figure 2: The pathophysiology of heart failure and potential biomarkers.

LDL: low density lipoprotein; MR-proADM: mid-regional pro-adrenomedullin; MR-proBNP: mid-regional-pro B-type natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; sST2: soluble suppression of tumorigenesis-2.

The ligand for ST2 is IL-33, and binding leads to a cardioprotective effect by inhibition of the Th2-dependent inflammatory response. However, soluble ST2 (sST2) circulating in plasma sequesters IL-33, meaning that the heart is more exposed to fibrotic change. sST2 levels are an independent predictor of mortality and HF hospitalisation in patients with acute or chronic HF, with an additive prognostic value to NP.[61] Better control of HF lowers sST2. Importantly, sST2 is relatively unaffected by age, sex, obesity, aetiology of HF, atrial fibrillation, and anaemia.[62]

Galectin-3 is a member of the lectin family secreted by activated macrophages. It may complement other biomarkers by providing an upstream signal in the fibrotic process. Given that cardiac fibrosis is irreversible, this provides a timely measure of risk to the myocardium. Galectin-3 is not acutely changed by cardiac decompensation, nor is it acutely responsive to standard therapies for HF. It is therefore less effective than NT-proBNP for diagnosing acute HF,[63] but nonetheless aids prognostication; subsequent to the DEAL-HF study, it was found that participants with elevated galectin-3 and NT-proBNP had worse survival than those with either marker elevated alone. However, the value of Galectin-3 for HF prognosis may diminish after adjusting for renal function.[64]

Inflammation

The association of high-sensitivity CRP with cardiovascular risk has been known for over two decades.[65] However, recent work suggests it may directly influence the inflammatory processes contributing to myocardial damage. In animal models, CRP removal after ST segment-elevated myocardial infarction reduced infarct size.[66] CAM1 is an ongoing trial looking at the benefit of eliminating CRP from serum in ST segment-elevated myocardial infarction. Preliminary results show a reduction of infarct size and improved ventricular wall motion.[67]

Multi-Marker Panels

Drawing biomarkers together in multi-marker prediction models has the potential to improve risk stratification. For example, the plaque disruption index consists of MPO, hsIL-6, MRP8/14, and PAPP-A, and is being tested to identify Type 1 AMI caused by plaque rupture (Table 1). In a pilot study, the plaque disruption index had better diagnostic accuracy than coronary angiography.[68] For HF, a panel including MR-proADM, hscTn, cFLC, hsCRP, and ST2 added prognostic value to standard measures of HF, whereas, individually, each added little.[69]

Multi-Omics

Genetic information is transcribed from DNA into RNA and translated into proteins, which can then produce metabolites. These components may be evaluated by genomics, transcriptomics, proteomics, and metabolomics, respectively. Measurement was once a laborious process but may now be done at scale and at speed. This leads to a vast amount of personalised data that needs to be integrated to facilitate diagnosis and provide a unique risk assessment and personalised treatment. In an early example of such an approach using mass spectrometry profiling, Cheng et al.[70] demonstrated that a metabolomic panel of histidine, phenylalanine, spermidine, arginine, and phosphatidylcholine C34:4 had higher prognostic value for the combined endpoints of death and HF-related hospitalisation than BNP.[70]

Micro RNA (miRNA) are small non-coding RNA molecules that act as post-transcriptional regulators of gene expression.[2] They can be released into the circulation, where they may be found attached to proteins or in extracellular vesicles. Increases or decreases of >30 miRNA may orchestrate changes to the transcriptome, and ultimately the proteome, during HF. This may, for example, lead to differentially expressed proteins involved in glycolysis, β-oxidation, and ketone metabolism in the failing heart,[72] as well as promote the development of cardiac fibrosis, e.g., as caused by miRNA-21.

Hower, the integrative analysis of 'omics' data are not straightforward and represents many logistical and computational challenges. Machine learning may be required to create clinically useful diagnostic panels.[72]

CONCLUSIONS

The last 70 years have witnessed huge progression in the development and sophistication of laboratory biomarkers: from laboriously measured single protein analyses, to multi-array platforms and miRNA. The future generation of biomarkers promise greater diagnostic and prognostic accuracy, as well as allowing for targeted therapy and measures of treatment response. However, the central tenet is likely to remain: that biomarkers are most useful when applied to a specific clinical question, and not before.

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High-Density Lipoproteins and Cardiovascular Disease

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Abstract

In the search to develop new cardioprotective therapies, considerable interest has focussed on approaches for targeting the biological functions of high-density lipoproteins (HDL). This is based on data from population and animal studies demonstrating a potentially protective impact of HDL on cardiovascular risk. The findings of recent clinical trials of a range of therapeutic interventions aimed at promoting HDL have been disappointing and raise considerable uncertainty regarding the potential utility of this target. More recent evidence has highlighted the importance of HDL functionality, which may ultimately be important in terms of its association with cardiovascular risk. This has led to ongoing efforts to develop new risk markers and therapeutics focussing on HDL quality as opposed to quantity. The evidence supporting a protective role for HDL and findings of clinical trials of HDL-targeted therapies are reviewed here.

INTRODUCTION

For >20 years, clinical trials have consistently demonstrated that the reduction of levels of low-density lipoprotein (LDL) cholesterol results in lower cardiovascular event rates, in both the primary and secondary prevention setting.[1] While guidelines for cardiovascular prevention have promoted widespread use of LDL cholesterol-lowering agents for patients at high vascular risk, many continue to experience clinical events.[2] This residual risk highlights the need to develop additional strategies to achieve a more effective reduction of cardiovascular risk in patients with atherosclerotic cardiovascular disease.

EVIDENCE SUPPORTING A PROTECTIVE ROLE OF HIGH-DENSITY LIPOPROTEINS

Following the early evidence that patients admitted to the coronary care unit with myocardial infarction had lower levels of high-

density lipoprotein (HDL) cholesterol, large population studies demonstrated an inverse association between HDL cholesterol levels and prospective cardiovascular risk.[3-6] Similar findings were observed in patients achieving very low LDL cholesterol levels, in which low HDL cholesterol continued to be associated with higher rates of cardiovascular events.[4] Animal studies demonstrated that promoting HDL functionality, via direct infusion or transgenic expression of its major proteins, had a favourable impact on both the burden and composition of atherosclerotic plaque.[7-12] Functional studies revealing that HDL exert favourable effects on inflammatory, oxidative, thrombotic, and apoptotic pathways, in addition to its well-characterised role in reverse cholesterol transport, are likely to underscore its impact on plaque.[9,13-16]

ESTABLISHED LIPID-MODIFYING STRATEGIES AND HIGH-DENSITY LIPOPROTEINS

Changes in lifestyle factors, including weight loss, accompanied by a reduction in abdominal adiposity and moderate alcohol consumption, have been reported to result in modest increases in HDL cholesterol.[17] While statin therapy can raise HDL cholesterol by 3–15%, in clinical trials this has been reported to be independently associated with favourable effects of statins on both plaque progression and cardiovascular events.[18,19] Fibrates raise HDL cholesterol by 5–20%, showing variable effects on cardiovascular events in multiple clinical trials.[20-22] Where a clinical benefit was observed, this was associated with an increase in small HDL particle concentration but not HDL cholesterol concentration overall.[23] Niacin is the most effective HDL cholesterol-raising agent currently used in clinical practice. While early studies using immediate-release formulations of niacin reported favourable effects on both angiographic disease and cardiovascular events,[24] more recent clinical trials of sustained formulations failed to demonstrate reductions in risk in statin-treated patients.[25,26] Niacin can prove challenging for patients because many experience the side effect of flushing. Efforts to administer niacin in combination with a prostanoid receptor antagonist reduced the rate of flushing, but did not produce clinical benefit.[25,26] Clinical development programmes, accordingly, have sought to develop more effective approaches for targeting HDL (Table 1).

HIGH-DENSITY LIPOPROTEIN INFUSIONS

On the basis of favourable effects on atherosclerosis and in-stent restenosis with infusions of reconstituted HDL,[7-9,12] interest has focussed on the potential benefits of this approach in humans. Early mechanistic studies in humans demonstrated that HDL infusions increased faecal sterol excretion, a surrogate measure of reverse cholesterol transport, and improved endothelial function.[27,28] A number of small clinical trials employed serial vascular imaging to evaluate the impact of various formulations of delipidated HDL on atherosclerotic plaque. The first study demonstrated that administration of five weekly intravenous infusions of a HDL mimetic containing recombinant ApoA-I Milano (previously known as ETC-216, now known as MDCO-216) promoted rapid regression of coronary atherosclerosis in patients following an acute coronary syndrome.[29] This provided a biological rationale to support observations that humans carrying ApoA-I Milano demonstrated a greater likelihood of longevity and protection from cardiovascular disease.[30] It also reaffirmed findings from preclinical studies, demonstrating atheroprotective properties of ApoA-I Milano.[31-33] The finding of regression at both 15 and 45 mg/kg doses in the human imaging study suggested a potential saturation effect of this mimetic on lipid transport out of the vessel wall.[29]

A second clinical development programme of a HDL mimetic, a combination of wild-type ApoA-I and a phospholipid (CSL-111), demonstrated a reduction in plaque lipid and macrophage content when administered 5–7 days prior to femoral endarterectomy.[34] A subsequent coronary imaging study in patients following an acute coronary syndrome reported a non-significant trend towards plaque regression and an improvement in plaque echogenicity, suggesting potentially favourable effects on plaque stability.[35] The potential for both mimetics, with different forms of ApoA-I, to exert beneficial effects supported the potential of delipidated HDL, as opposed to specific properties related to ApoA-I Milano.

Table 1: High-density lipoprotein-targeted therapies and cardiovascular effects in trials.

Therapeutic agent	HDL effect	Cardiovascular effect
Statins	5–20% increase	Associated with benefit on plaque progression and clinical events
Fibrates	Approx. 20% increase	Reduction in clinical events with gemfibrozil associated with increase in small HDL
Thiazolidinediones	5–20% increase	Lowering triglyceride/HDL ratio associated with slowing plaque progression
Novel PPAR	Approx. 20% increase	No benefit on clinical events
Niacin	Approx. 30% increase	Clinical benefit with immediate formulation prior to the introduction of statins No benefit with novel formulations in combination with statins
CETP inhibitors		
Torcetrapib	Approx. 60% increase	No clinical benefit
Dalcetrapib	Approx. 25% increase	No clinical benefit. Pharmacogenomics suggest potential benefit with *ADCY9* polymorphism
Evacetrapib	Approx. 120% increase	No clinical benefit
Anacetrapib	Approx. 130% increase	Modest clinical benefit associated with lowering atherogenic lipoproteins
Obicetrapib	Approx. 179% increase	Unknown
HDL infusions		
ETC-216/MDCO-216	Mild increase efflux	Early benefit on plaque not replicated in recent studies
CER-001	Mild increase efflux	No clear benefit on plaque
Autologous infusions	Mild increase efflux	Potential benefit on plaque
CSL-111/CSL-112	Greater increase efflux	Benefit on plaque histology No clear benefit on imaging. Event trial ongoing
Apabetalone	Approx. 8% increase	No clear benefit on plaque Modest outcome trial failed to demonstrate clear benefit

Approx.: approximately; CETP: cholesteryl ester transfer protein; HDL: high-density lipoprotein.

This was reaffirmed by the report that selective delipidation of a patient's HDL, followed by autologous infusion, as similarly associated with plaque regression.[36]

Synthesis of HDL mimetics, in quantities sufficient for human use, has proven to be a challenge and has required refinement of the manufacturing process to produce purified mimetics with a low potential for toxicity. This has led to a second generation of clinical studies which evaluate the impact of HDL mimetics on a background of more intensive lipid-lowering therapy. The findings to date have been variable. A repeat coronary imaging study of the mimetic containing ApoA-I Milano failed to demonstrate plaque regression.[37-39] Another mimetic, which contains recombinant ApoA-I and sphingomyelin (CER-001), has been evaluated in numerous imaging-based trials. While the first study failed to demonstrate a favourable benefit for plaque burden,[40] a post hoc analysis revealed regression in those treated with the lowest dose (3 mg/kg) and in patients with the greatest burden of plaque at baseline.[41] This observation was further tested; however, 10 weekly infusions failed to be beneficial.[42] Similarly, early observations of the potential benefit of CER-001 on carotid plaque volume and inflammatory activity failed to be replicated in prospective, randomised clinical trials.[43]

Despite the disappointing results of these trials, leading to cessation of the MDCO-216 and CER-001 development programmes, hope remains that other HDL mimetics may produce cardiovascular benefit. Refined manufacturing to produce CSL-112 has progressed to clinical evaluation. A large safety study of this formulation revealed no adverse clinical effects of any concern and a substantial increase in *ex vivo* cholesterol efflux capacity.[44] The potential improvement in lipid-transporting activity is much greater than that observed with other mimetics. Given the reported association between cholesterol efflux activity and protection from adverse cardiovascular outcomes, there remains considerable interest in the development of this mimetic. Accordingly, a large cardiovascular outcomes trial is currently in progress to determine whether administration of four intravenous infusions of CSL-112 will reduce cardiovascular event rates in patients following an acute coronary syndrome. This represents the first definitive attempt to determine whether the infusion of some form of HDL will favourably reduce clinical events.

CHOLESTERYL ESTER TRANSFER PROTEIN INHIBITORS

Cholesteryl ester transfer protein (CETP) facilitates the movement of esterified cholesterol from HDL to very-low-density lipoproteins and LDL in exchange for triglycerides.[45] CETP inhibition has received considerable attention, given its potential to substantially raise HDL cholesterol levels. Observational studies have reported an association between CETP activity and cardiovascular risk, supported by findings of genomic investigations.[45-48] In animal models, therapeutic lowering of CETP activity, using antisense oligonucleotides, vaccines, and small-molecule inhibitors, has been reported to have a favourable impact on plaque burden.[49-52] As a result, multiple development programmes have aimed to develop CETP inhibitors, with the potential to target the residual cardiovascular risk observed in many statin-treated patients.

However, experience to date with this class of agents has proved a challenge. The first CETP inhibitor to reach an advanced stage of development, torcetrapib, increased the risk of cardiovascular events and all-cause mortality in a large clinical outcomes trial.[53] In parallel, the ability of torcetrapib to raise HDL cholesterol by >60% and lower LDL cholesterol by 20%, in addition to statin therapy, failed to favourably impact the progression of carotid intima-media thickness and coronary atherosclerosis.[54-56] Subsequent studies revealed that torcetrapib possessed off-target effects, including adrenal excretion of aldosterone and cortisol, aortic wall expression of endothelin, and small elevations in blood pressure.[53,57,58] Because these changes were observed in murine models, which do not express CETP, they are likely to reflect a torcetrapib-specific effect that is not as a result of CETP inhibition. Accordingly, there remains interest in the development of other CETP inhibitors that lack such toxic effects.

A number of CETP inhibitors continued to progress in development on the basis that they lack torcetrapib-like toxicity. Dalcetrapib is a modest CETP inhibitor and raises HDL cholesterol

by approximately 25% with no effect on LDL cholesterol levels.[59,60] A large clinical outcomes trial was terminated prematurely because dalcetrapib did not reduce cardiovascular event rates.[61] Evacetrapib is a potent CETP inhibitor and raises HDL cholesterol by >120% and lowers LDL cholesterol by 25–30% when administered as either monotherapy or in combination with a statin.[62] However, these more potent lipid effects did not translate to clinical benefit, with another outcome trial stopped due to futility.[63] Anacetrapib is also a potent CETP inhibitor and raises HDL cholesterol by >130% and lowers LDL cholesterol by 30%.[64] A clinical trial with more extended treatment demonstrated a significant, albeit modest, reduction in cardiovascular events when anacetrapib was administered in combination with a statin.[65] This clinical benefit correlated with the degree of lowering of atherogenic lipoproteins, as opposed to the raising of HDL cholesterol. While this result provided some clinical validation that CETP inhibition may be cardioprotective, anacetrapib accumulates within adipose tissue[66] and has not progressed to clinical use.

A number of observations from these CETP inhibitor studies provide insights on potential clinical utility. All of the trials have demonstrated that CETP inhibitor use was associated with a lower rate of diagnosis of Type 2 diabetes mellitus.[67,68] In those patients with diabetes, CETP inhibitor use was associated with an improvement in glycaemic control.[67,68] Whether this reflects favourable effects of HDL on pancreatic β-cell function,[69,70] or an additional effect of CETP inhibition, remains uncertain. It may also have implications for broader use in patients at higher risk, who have evidence of prediabetes or insulin resistance.

Pharmacogenomic analysis of the dalcetrapib trial demonstrated a potential clinical benefit in patients harbouring a polymorphism of the *ADCY9* gene on chromosome 16. Patients with the AA genotype demonstrated a 39% reduction in cardiovascular events with dalcetrapib compared with placebo, while patients with the GG phenotype demonstrated an increase in events.[71] This finding was supported by the demonstration of a greater increase in cholesterol efflux activity and lesser rise in C-reactive protein levels with dalcetrapib treatment of patients with the AA polymorphism.[71] This has led to a new clinical trial of dalcetrapib, performed exclusively in patients identified to have the AA polymorphism.[72] A similar relationship was not observed with either evacetrapib or anacetrapib.[73,74] If demonstrated to be effective in a prospective trial, it would appear to reflect a dalcetrapib-specific phenomenon.

Additional genomic analyses and Mendelian randomisation have demonstrated the cardioprotective effect of having low CETP activity and levels.[46,47,75] This benefit was associated with reductions in levels of atherogenic lipoproteins, rather than raising HDL cholesterol. This benefit also appears greater in the presence, rather than absence, of HMGCR, the target of statins. If correct, this would suggest CETP inhibitors are more likely to be protective in the absence of concomitant statin therapy.[75] Accordingly, any further development of CETP inhibitors might focus more on LDL-lowering capability, as opposed to raising of HDL cholesterol. Obicetrapib is the most potent CETP inhibitor developed to date, with more profound effects on LDL and HDL cholesterol, using much lower doses than other agents. How development of this agent will proceed remains to be determined.

ADDITIONAL HIGH-DENSITY LIPOPROTEIN-TARGETED STRATEGIES

A number of other approaches have been investigated, with regard to their potential impact on HDL and cardiovascular risk. Pharmacological agonists of the PPAR family have modest effects on HDL, with variable impact on clinical outcomes. Fibrates are modest PPAR-α agonists, with modest HDL cholesterol raising capabilities and evidence of cardiovascular benefit in some,[76,77] but not all,[22,78] clinical trials. Meta-analyses of these trials demonstrated a borderline clinical benefit of widespread fibrate use, but more definitive benefit when used in patients with evidence of hypertriglyceridaemia at baseline.[20] Subsequent analysis of the gemfibrozil studies suggested that its cardiovascular benefit may be associated with the observed 21% increase in small HDL particles.[23] In a similar fashion, thiazolidinediones are PPAR-γ agonists which mildly raise HDL cholesterol in addition to their primary role in improving insulin sensitivity. The effect of these agents on HDL is likely to contribute to their potential clinical benefit, with

evidence that reducing the triglyceride/HDL cholesterol ratio is most strongly associated with the ability of these agents to slow progression of coronary atherosclerosis on serial imaging.[79] Attempts to develop more potent PPAR agonists,[80] or agents targeting multiple PPAR,[81] have had difficulty with either toxicity or a lack of clinical benefit. The recent development of selective PPAR modulators has the potential to derive specific metabolic benefits without the toxicity observed with standard PPAR agents,[82] although the clinical benefit of this approach has yet to be established.

Apabetalone is a selective inhibitor of bromodomain and extraterminal proteins: epigenetic regulators of lipoprotein metabolism, inflammation, and vascular calcification.[83,84] Early studies of apabetalone focussed primarily on its potential impact on HDL functionality, on the basis of reports of stimulated ApoA-I synthesis and increase in cholesterol efflux capacity in non-human primates.[85] Early clinical trials of apabetalone in statin-treated patients demonstrated modest effects on HDL cholesterol levels[86] and progression of coronary atherosclerosis[87] with short-term treatment. Pooled analyses of these trials demonstrated fewer cardiovascular events in apabetalone-treated patients compared with those who received placebo.[87] This led to a moderate-sized clinical outcomes trial, which failed to demonstrate a significant reduction in clinical events with apabetalone when administered in patients with diabetes and low HDL cholesterol levels, following an acute coronary syndrome.[88]

Additional approaches to targeting HDL have focussed on specific factors implicated in reverse cholesterol transport. Upregulation of ABCA1, a pivotal factor facilitating cholesterol efflux to receptors such as HDL particles, may mobilise lipids without necessarily modulating systemic HDL concentrations.[89] LCAT promotes esterification of cholesterol on the surface of HDL particles, which is subsequently stored within the particle core, maintaining a low concentration of free cholesterol and an environment favouring ongoing transfer of lipids to HDL. Pharmacological LCAT agonists are currently undergoing early evaluation in human studies.[90,91] Advocates of genetic replacement therapy have proposed that the ability to upregulate hepatic ApoA-I expression may have the potential to increase generation of nascent HDL particles.[92] While early proponents of such an approach suggested a potential role in patients with genetically low ApoA-I levels, evolving approaches in gene editing may provide a more widespread therapeutic option in the future.

DYSFUNCTIONAL HIGH-DENSITY LIPOPROTEINS

While the early work in HDL therapeutics focussed on raising HDL cholesterol levels, the poor results of clinical trials and lack of association between genetic polymorphisms regulating HDL cholesterol levels and cardiovascular risk[93] have suggested this may not prove useful. In parallel, the potential benefit of HDL infusions, in the absence of raising HDL cholesterol levels and in addition to reports of the association of cholesterol efflux activity with cardiovascular risk,[94] highlights the likelihood that HDL functionality may be more important. This is supported by reports of cardiovascular events in patients with very high HDL cholesterol levels[95] and by reports that the functional properties of HDL may be impaired in the setting of hyperglycaemia, inflammation, and carbamylation.[96-101] HDL circulates as a heterogenous population of particles, varying in size and composition of both protein and lipid. It may be that different sub-particles may possess varying functional activity. The small, lipid-deplete particles, as evidenced in infusion mimetics, are potent promoters of cholesterol efflux activity. Therapeutic increases in small HDL particles were reported to be associated with the clinical benefit of gemfibrozil.[23] In contrast, generation of large, cholesterol-rich HDL particles with CETP inhibition, though proposed to potentially impair efflux activity, was never demonstrated. Nevertheless, future approaches to HDL therapeutics might consider targeting specific HDL subgroups. Measures of dysfunctional HDL may also play a role in risk prediction.[102] Furthermore, it is possible that modulating factors that render HDL dysfunctional may provide a novel approach to therapeutic targeting of HDL in patients at a high risk. This remains an active area of research interest for investigators still working to develop HDL-focussed approaches to reducing cardiovascular risk.

CONCLUSION

Considerable work has tried to enhance potentially protective properties of HDL to reduce the residual cardiovascular risk in statin-treated patients. While raising HDL cholesterol has proven to be a disappointing strategy, ongoing efforts have focussed on targeting the functional activities of HDL. Whether any such strategies are ultimately likely to be of clinical benefit will require more clinical trials. To facilitate this, the field will need to embrace the need to pivot the HDL story as a narrative worth pursuing. Only time will tell whether this will alter the course of cardiovascular risk.

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Raiders of the Lost Wire

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Abstract

Introduction: An angiographic guidewire is a basic, yet essential piece of equipment in the interventional cardiologist's armamentarium. Complications associated with angiographic guidewires can be catastrophic to the safe completion of a coronary procedure. In this article, the authors report a case of angiography guidewire fracture and explore the options for management of this rare but serious complication.

Case presentation: A 77-year-old man with multiple cardiovascular risk factors was admitted with an anterior ST segment elevation myocardial infarction. Diagnostic angiography was performed via right radial access and revealed a subocclusive stenosis of the mid and distal left anterior descending artery (LAD) with thrombolysis in myocardial infarction 1 flow and a 70% stenosis of the proximal diagonal branch. Primary percutaneous coronary intervention was attempted and a HI-TORQUE Balance Middle Weight Universal II guidewire (Abbott Vascular Inc., Santa Clara, California, USA) was chosen. Guidewire manipulation was difficult because of significant calcification and tortuosity of the LAD. Consequently, the guidewire fractured and became trapped in the mid-LAD. The complication was ultimately resolved by stenting across the fractured guidewire and the patient was not afflicted by any adverse sequelae.

Discussion: This case highlights a rare but potentially serious complication of coronary intervention. Proposed management varies from leaving the fractured wire *in situ* and stenting across it, to varying techniques for removing the fractured wire. However, no consensus exists as to the best strategy. The authors have therefore performed a review of the current literature and propose an algorithm for the management of this rare complication.

INTRODUCTION

An angiographic guidewire is a basic, yet key piece of equipment in the interventional cardiologist's armamentarium. The complications associated with angiographic guidewires can be catastrophic to the safe completion of a coronary procedure. In this article, the authors report a case of angiography guidewire fracture and explore the options for management of this rare but serious complication.

CLINICAL CASE

A 77-year-old man with a history of diabetes, hypertension, and hyperlipidaemia was admitted to the emergency room with an anterior ST segment elevation myocardial infarction (STEMI). Diagnostic angiography was performed via 6F right radial access and revealed a subocclusive stenosis of the mid and distal left anterior descending artery (LAD) with thrombolysis in myocardial infarction (TIMI) I flow, 70% stenosis of the proximal diagonal branch, and 60% stenosis of the proximal posterior descending artery. The authors therefore proceeded to primary percutaneous coronary intervention (PCI) of the culprit artery using a 6-French XB 3.0 guide catheter and a 0.014″ HI-TORQUE Balance Middle Weight (BMW) Universal II guidewire (Abbott Vascular Inc., Santa Clara, California, USA). A 2.0 x 12 mm noncompliant balloon was used for initial predilation; however, passage of the balloon was impeded by both the tortuosity and significant calcification of the LAD. A second 0.014" BMW Universal II guidewire to increase support (a 'buddy wire') was advanced into the distal vessel and a guiding catheter extension was also added. Despite this, a second noncompliant balloon failed to transverse the lesion. At this point, it was decided that a wire with greater support was required and therefore a microcatheter was advanced with the intention of exchanging one of the BMW Universal II wires for an ASAHI Grand Slam wire (ASAHI, Tokyo, Japan). However, while retracting the BMW wire it became trapped in the proximal portion of the lesion. Gentle counter traction failed to free the wire, so an attempt was made to remove both the wire and the microcatheter altogether. This manoeuvre, however, resulted in complete fracture of the wire tip, leaving the floppy portion of the wire free-floating in the proximal LAD (Figure 1).

The first strategy employed to resolve this situation was an attempt to retrieve the wire fragment. Multiple wires were advanced into the vessel, with a plan to entrap the fractured segment, but to no avail. Multiple balloon predilations of the lesion were then performed in an attempt to fracture the plaque and free the wire; however, this technique was also unsuccessful. A decision was then made to deploy a stent across the fractured wire tip, thereby trapping it; however, despite multiple attempts to deploy various stents, the operators were unsuccessful. Poor guide-catheter support from the XB 3.0 via the radial artery significantly hampered the attempts at percutaneous stenting. Despite these unsuccessful attempts,

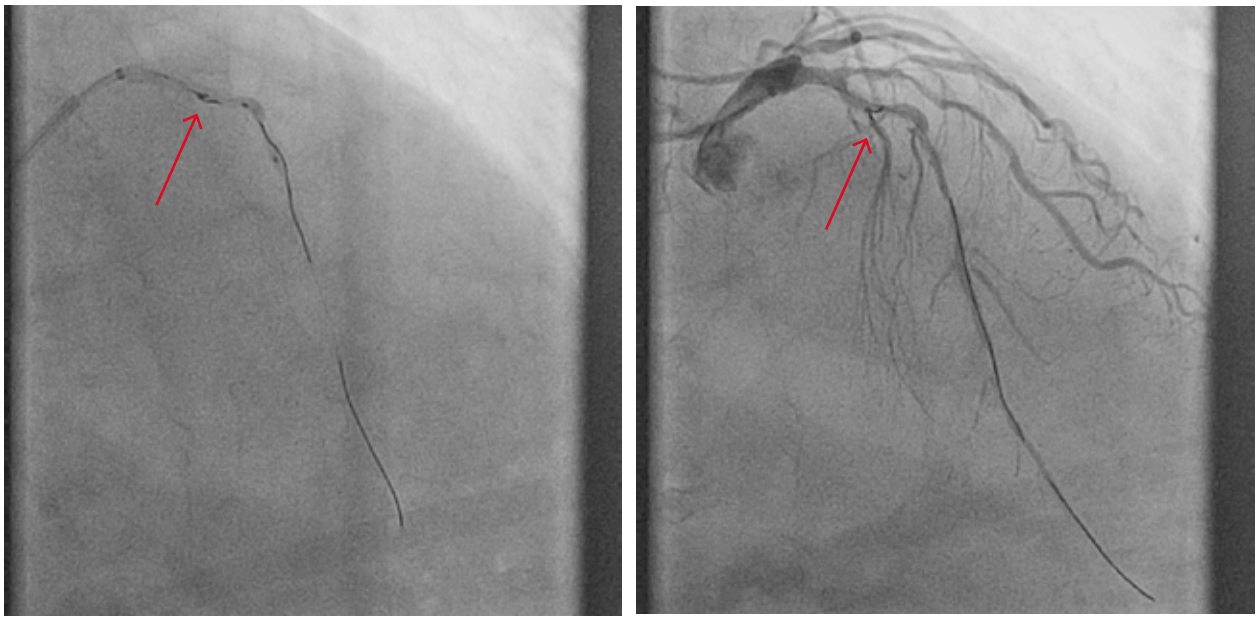

Figure 1: Fractured fragment of guidewire (arrow) in the proximal left anterior descending artery abandoned despite multiple retrieval attempts.

the culprit vessel now had TIMI 3 flow with resolution of the patient's chest pain and, consequently the procedure was abandoned.

The case was discussed at the authors' multidisciplinary Cardiology–Cardiothoracic Surgery meeting. The consensus agreement was that a second procedure should be undertaken using a different access point with larger sheaths and a larger guide catheter for increased support. The second procedure was performed via femoral access using an 8Fr sheath. The left main stem was engaged with a JL5, 7Fr guide catheter. An ASAHI SION guidewire (ASAHI) was advanced into the distal vessel and exchanged via a microcatheter for an ASAHI Grand Slam wire (ASAHI), which provided the required support. With this extra support, a balloon was passed through the lesion and it was successfully predilated followed by the deployment of three drug-eluting stents covering both the culprit lesion and jailing the free-floating BMW Universal II guidewire tip (Figure 2). The patient recovered without any significant sequelae and remains well at the time of last review.

DISCUSSION

The fracture or retention of the guidewire is a thankfully rare, but potentially life-threatening, complication that occurs more frequently in complex interventional procedures, such as chronic total occlusion, tortuous vessels, severe calcification, bifurcations, and in-stent restenosis.[1-3] The estimated incidence is 0.1–0.2%.[1,2] Complications can include thrombosis with subsequent vessel occlusion, local or systemic embolisation, vessel perforation with consequent pericardial effusion and tamponade, and wire induced arrhythmias.[1-4] Prevention of guidewire fracturing is multifaceted and starts with careful selection of the guidewire to be used prior to attempted intervention. Lesion characteristics, such as calcification, tortuosity, and chronicity, influence the choice of guidewire with the correct properties to safely treat the lesion. Excessive rotation while trying to navigate a torturous and/or calcified vessel segment is the main cause of guidewire fracture. Lateral stress generated by excessive torque or bending of the wire tip have been highlighted as potential causes of wire tip fracture and, as such, rotational manipulation of the wire should not exceed 180 degrees.[1,2]

Once the wire tip has fractured and is free-floating in the coronary artery, a dilemma ensues as to the best course of action which, in the absence of consensus opinion, has been informed mainly by case reports and small case series. Three options are available: percutaneous techniques, surgical removal, or conservative management.[1,2,5,6]

Percutaneous Management

Percutaneous removal is the most attractive and by far the most widely reported technique and in the authors' opinion should be the first method employed. A number of percutaneous options are available, including the 'double' or 'triple' wire technique, whereby a number of angioplasty wires are advanced alongside the retained wire segment and rotated to entangle and remove the free-floating segment; deep wedging of the guide catheter or advancement of a microcatheter such that the free-floating wire tip is in the catheter and a balloon can be advanced and inflated at the mouth of the catheter to trap the wire, with the whole system then being removed en mass; retrieval by snare loop; extraction with bioptome; and laser extraction.[1,2] All of these techniques have been used in case reports with varying success.[1,2] Different techniques may be required for different situations. Snare loop and bioptome retrieval are only suitable in vessels of relatively large calibre, with bioptome being more useful when the entrapped wire is near the vessel ostium. Upsizing the guide catheter may be required to accommodate the equipment used for the attempted retrieval and alternative vascular access, such as femoral approach, may also be required. The multiple wire technique represents the simplest wire removal technique and may not require a change of guide catheter.[1] Another percutaneous option, and the authors' chosen option in this case, is permanent jailing or trapping of the wire behind a stent (i.e., wire exclusion). Of the aforementioned options, exclusion of the wire fragment with a stent is by far the most feasible and involves the least amount of manipulation of the coronary artery, albeit with the trade-off of having wire retained in the vessel. Complete coverage eliminates the risk of migration, and subsequent epithelialisation reduces the risk of thrombosis.[1,2] The necessary duration of dual antiplatelet therapy after wire exclusion by a stent is currently unclear, with

no available data. Interval intravascular imaging may be useful in providing the treating physician with some guidance on antiplatelet therapy duration. Percutaneous removal techniques are not without accompanying risks of coronary dissection, rupture, or thrombosis, particularly if excessive manipulation within the coronary vessel is required.

Surgical Management

Surgical wire removal allows for the option of removing the wire while simultaneously proceeding with coronary artery bypass grafting (CABG), particularly in the case of noncompletion of the original percutaneous stenting procedure. This may be an attractive option if the patient has multivessel disease warranting treatment or has other comorbidities that may make CABG more attractive, such as valvular heart disease or diabetes. However, surgical wire removal carries a mortality risk, as well as significant morbidity, and should therefore be a secondary option if percutaneous techniques unsuccessful. A summary of factors to consider when deciding between percutaneous stenting and CABG is given in Table 1.

Table 1: Factors favouring percutaneous coronary intervention versus coronary artery bypass grafting.

Favouring percutaneous coronary intervention	Favouring coronary artery bypass grafting
• Single vessel disease • Low syntax score • High surgical risk • Wire unlikely to be retrieved surgically	• Multivessel disease • Left main stem disease • High syntax score • Concomitant valvular heart disease • Diabetes • Low surgical risk • Wire likely to be retrieved surgically

Table 2: Preventative strategies.

	Factors to consider
Access: Radial versus femoral	• Support required • Calibre sheath required • Planned guide catheter • Equipment required to complete procedure
Guide catheter	• Access route to be used • Support required • Equipment to be used
Coronary lesion	• Severity • Tortuosity • Calcification • Chronicity • Scoring systems - AHA classification - JCTO score
Guidewire	• Support • Torque control • Trackability • Coatings
Procedural aspects	• Avoidance of wire excessive rotation

AHA: American Heart Association; JCTO: Japanese chronic total occlusion.

Conservative Management

Occasionally, conservative management may be appropriate. Wires that have become fractured and entrapped in distal vessel segments or very small coronary branches are unlikely to cause significant clinical consequences should they thrombose. In these cases, a careful weighing of the risk–benefit ratio of wire retrieval must be carried out and, preferably, in the authors' opinion, in the context of a heart team. A summary of these recommendations is given in Table 2.

Prevention of wire entrapment and fracture is the first step in avoiding this complication. A number of aspects must be taken into account to avoid wire fracture. Firstly, procedural planning is crucial. In the context of an acute STEMI, as in the presented case, there may be little time for procedural planning; however, in the case of planned PCI, procedural aspects should be well thought out. The route of access must be considered in terms of its ability to accommodate all of the equipment that one plans to use and to provide adequate support in terms of the guide catheter choice. Secondly, the guide catheter must be considered, and a catheter chosen that will both provide adequate support and is of appropriate calibre to accommodate all of the required equipment. Thirdly, the lesion itself must be considered and a thorough assessment of the lesion including severity, tortuosity, calcification, and chronicity must all be taken into account. Finally, the choice of guidewire must be carefully considered. Characteristics of the lesion will dictate the ideal guidewire to use in each circumstance and guidewire properties, such as the support provided, torque control, trackability, and coating properties (hydrophilic versus hydrophobic), need to be carefully considered prior to undertaking the PCI. While all interventional cardiologists employ the use of a 'workhorse' wire in the majority of cases, familiarity with other wires and their properties will allow safer completion of the PCI and management of complications. In the presented case, the use of a SION wire in the second procedure provided better trackability through the tortuous lesion, and exchanging for a Grand Slam wire provided the support required to railroad the balloons and stents across the lesion. Finally, avoidance of excessive rotation of the wire and maintaining wire rotation to <180 degrees greatly decreases the risk of wire fracture as it navigates lesions.

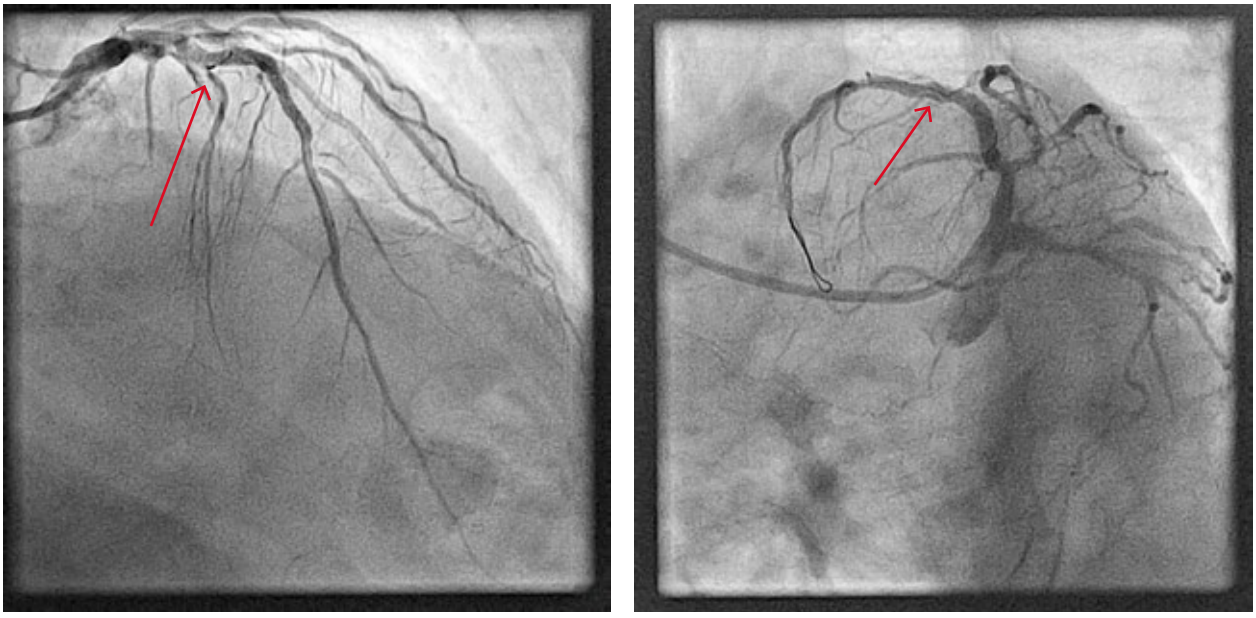

Figure 2: Final result sealing the fragment guidewire (arrow) with a drug-eluting stent with thrombolysis in myocardial infarction III flow.

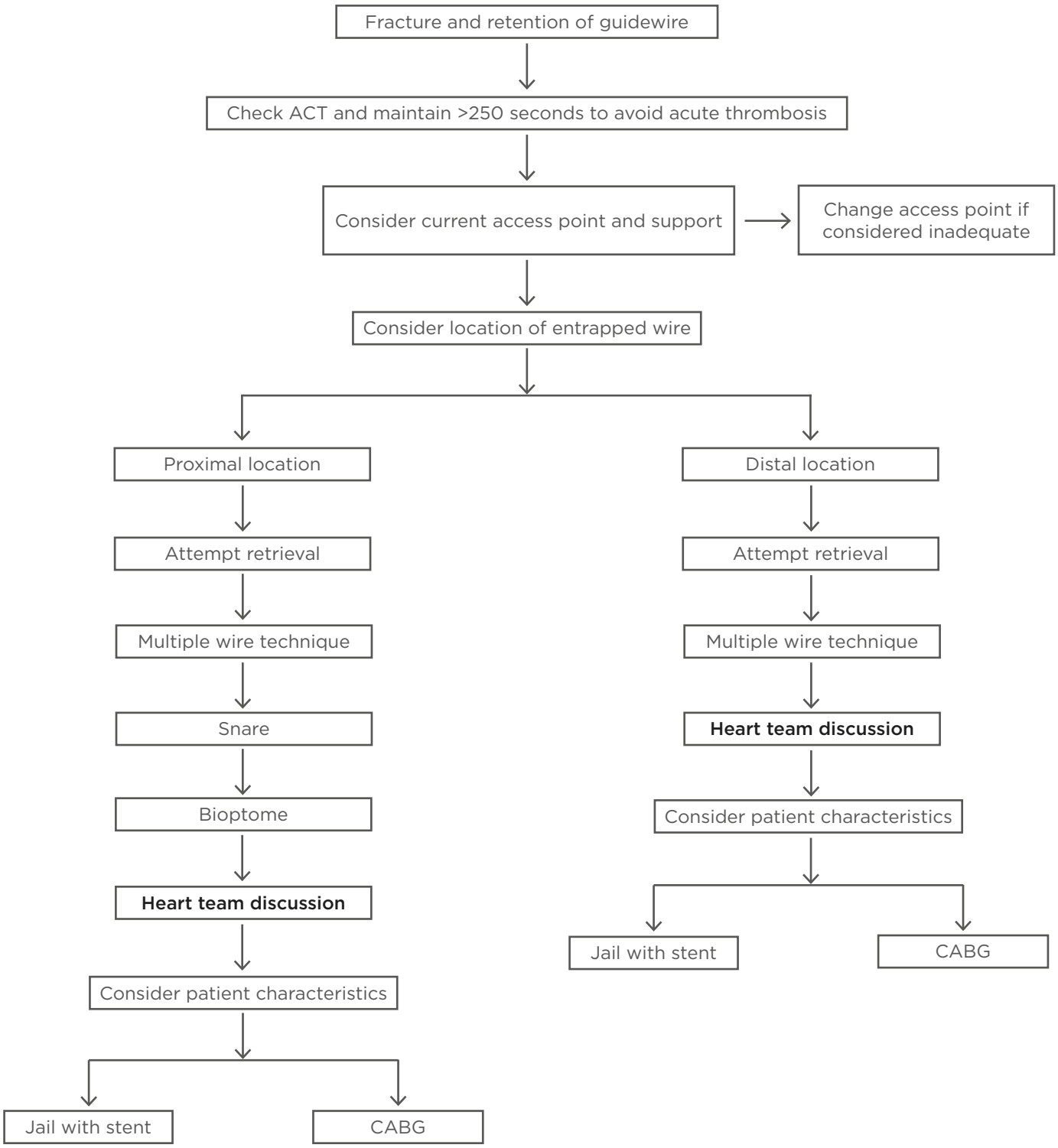

Figure 3: The authors' proposed algorithm for the management of angiography guidewire fracture.

ACT: activated clotting time; CABG: coronary artery bypass grafting.

CONCLUSION

Based on the above considerations, the authors propose an algorithm for the management of this rare complication, incorporating prevention strategies, as well as a sensible approach to wire retrieval (Figure 3). The authors suggest the proposed management of this complication

based mainly on the location of the fractured segment, which is the most important factor regarding how to manage this complication. Firstly, because thrombosis can easily occur on the fractured guidewire, the authors recommend that the adequacy of anticoagulation be checked in the first instance by checking activated clotting time and maintaining this for >250 seconds with additional doses of unfractionated heparin as required. Secondly, the authors suggest considering the current access point and its ability to provide the required support for what may be a complex procedure. Changing the access point from radial to femoral early in the procedure may save excessive contrast and radiation use, as well as aid in completion of the procedure as efficiently as possible.

Finally, the location of the ruptured wire segment must be considered. If located proximally within the vessel, it is more likely to be amenable to retrieval, whereas distally located ruptured wires may be better managed by jailing behind a stent. Difficult to manage cases should be discussed within the context of the heart team, including interventional cardiologists and cardiothoracic surgeons, and a consensus approach should be taken.

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A Clinical Review of Ventricular Arrhythmias in Patients with Congestive Heart Failure

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Abstract

Heart failure is an increasingly prevalent condition, which is associated with ventricular arrhythmias. The reduction in cardiac pumping efficiency leads to the activation of several compensatory mechanisms. These mechanisms eventually lead to cardiac remodelling and a decline in haemodynamic status, contributing to the formation of a substrate conducive to arrhythmias, including increased automaticity, triggered activity, and, most commonly, re-entry circuits. In turn, ventricular arrhythmias can lead to the worsening of heart failure. A diagnosis of heart failure and ventricular arrhythmias is obtained using the patient's history, examination findings, and investigation results. A key tool in this is echocardiogram imaging, which visualises the cardiac chambers, determines ventricular ejection fraction, and identifies structural abnormalities. A reduction in ejection fraction is a significant risk factor for the development of ventricular arrhythmias. Arrhythmias are diagnosed by ECG, Holter monitoring, and telemetry or event monitoring, and should initially be treated by optimising the medical management of heart failure. Anti-arrhythmic drugs, including beta-blockers, are usually the first-line therapy. Sudden cardiac death is a significant cause of mortality in heart failure patients, and implantable cardioverter defibrillator devices are used in both primary and secondary prevention. Anti-arrhythmic drugs and catheter ablation are important adjunctives for minimising shock therapy. In addition, autonomic modulation may offer a novel method of controlling ventricular arrhythmias. The objective of this review is to provide a practical overview of this rapidly developing field in relation to current evidence regarding the underlying pathophysiology, burden of disease, and management strategies available.

INTRODUCTION

Pump failure and sudden cardiac death are the leading causes of death in heart failure patients; sudden cardiac death accounts for 30–50% of deaths.[1,2] Heart failure increases the risk of sudden death by 6–9 times and most cases are the result of ventricular arrhythmias,[3] which include ventricular tachycardia (VT) and ventricular fibrillation (VF).

Ventricular arrhythmias also cause significant morbidity and mortality, and heart failure patients have an increased burden of ventricular arrhythmias, particularly in advanced disease.[2]

Indeed, non-sustained VT is found in 20–80% of patients with heart failure.[2] Ventricular arrhythmias manifest as palpitations, dyspnoea, dizziness, syncope, and sudden cardiac death. In addition, ventricular arrhythmias may lead to the progression of heart failure.

Implantable cardioverter defibrillator (ICD) devices are the principal intervention for primary and secondary prevention of sudden cardiac death in heart failure patients;[4,5] however, there is increasing evidence supporting the use of pharmacological agents and catheter ablation to minimise ICD shocks.

EPIDEMIOLOGY

An estimated 26 million people worldwide have been diagnosed with heart failure and it accounts for >1 million hospitalisations annually in Europe and North America.[6] The overall prevalence of heart failure is 1–2% in the Western world, with most patients >50 years old. The prevalence increases sharply with age, affecting >10% of those aged ≥85 years.[7] Annual mortality varies according to the severity of heart failure, although the relative proportion of sudden deaths is substantial across all classes. The yearly mortality rate from sudden death is 12–15% within the New York Heart Association (NYHA) functional class I and II, while class IV has a sudden death rate of 50–60%. Sudden death accounts for 50–60% of all deaths in NYHA functional class I and II, while class IV has a rate of 20–30%.[8]

Ventricular arrhythmias have been presumed to be the cause of a significant proportion of sudden deaths; other causes include bradyarrhythmias and pulseless electrical activity.[9,10] Given their spontaneous nature, the prevalence of ventricular arrhythmias in heart failure patients is difficult to assess; however, ventricular arrhythmias have been noted to be particularly prevalent in patients with reduced ventricular ejection fraction and underlying cardiac ischaemia.[11] The risk of ventricular arrhythmias is further increased by coexisting comorbidities, including obstructive sleep apnoea, hypoxaemia, electrolyte disturbances, catecholamine excess, pro-arrhythmic drug effects, hepatic dysfunction, and renal dysfunction.[12] While ventricular arrhythmia encompasses several rhythm disturbances, it is important to note that VF and sustained VT have a higher disease burden and risk of sudden death compared to non-sustained VT and premature ventricular contraction.

PATHOPHYSIOLOGY

Heart failure occurs due to a reduction in the pumping efficiency of the organ as a result of myocardial injury. The most common cause of myocardial injury is ischaemic heart disease, although structural damage may also occur as a result of hypertension, diabetes, valvular disease, cardiomyopathies, infections, and toxin exposure (e.g., alcohol and chemotherapeutic agents).

Several compensatory mechanisms are activated in response to cardiac injury, including the Frank–Starling mechanism, neurohormonal activation, and ventricular remodelling. Although initially beneficial, these compensatory mechanisms eventually lead to an exacerbation of haemodynamic instability and thereby encourages further compensatory mechanisms, which produces a cycle of worsening heart failure.[13] Changes in the electrical and mechanical function of the heart, including fibrosis and regional hypertrophy, can predispose a patient towards the development of ventricular arrhythmias.[14] The primary mechanisms for initiating and perpetuating ventricular arrhythmias include abnormal automaticity, increased triggered activity, and development of re-entry circuits, which is the most common mechanism.[15] The electrical instability in ventricular arrhythmias can lead to haemodynamic collapse and consequent sudden death. Ventricular arrhythmias can degenerate to asystole.

It is important to note that there is a complex interplay between heart failure and ventricular arrhythmias (Figure 1).[16] While heart failure can lead to the development of a substrate conducive to arrhythmia formation, ventricular arrhythmias may in turn accelerate the pathological mechanisms of heart failure.[16] A 2006 study[17] found that appropriate shocks for ventricular arrhythmias in advanced heart failure were associated with a significant increase in pump failure death. It was unclear whether the shocks were the cause of the adverse outcomes or if they were a marker of disease progression; however, the 2013 ALTITUTIDE survival by rhythm study found that the mortality risk was associated with the underlying rhythm (either

ventricular tachycardia or atrial fibrillation) rather than the shock therapy itself.[18] There was no significant difference in survival between no shocks and inappropriate shocks for sinus tachycardia or noise/artefact/oversensing. In comparison, patients who received their first shock for monomorphic VT (hazard ratio: 1.65; p<0.0001) or VF/polymorphic VT (hazard ratio: 2.10; p<0.0001) had a significantly higher mortality compared to patients who did not receive shocks.[18] These results suggest that the underlying rhythm accounts for the difference in mortality. The method with which ventricular arrhythmias lead to the progression of heart failure requires further investigation. It has been recently proposed that it may be a result of delayed myocardial recovery, producing a bioenergetic crisis that leads to a cycle of increasing pump failure and arrhythmias.[16]

ARRHYTHMIA MECHANISMS

Automaticity

The normal depolarisation sequence of the heart is set by pacemaker cells, which spontaneously depolarise. Cellular damage and the associated increase in sympathetic activity can disturb the automaticity of pacemaker cells.[15] Abnormal automaticity has been found in subendocardial Purkinje fibres following ischaemia, which may be a result of underlying abnormalities in calcium handling.[19]

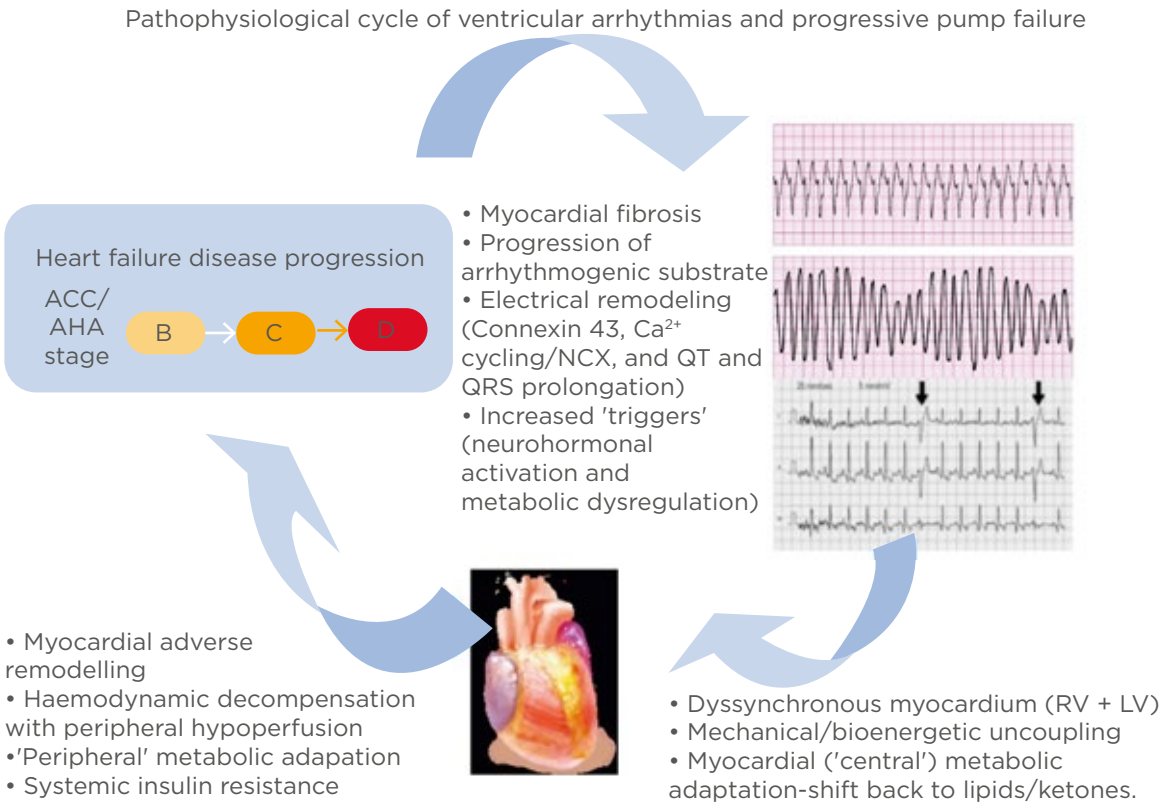

Figure 1: Schema illustrating the pathophysiological cycle of ventricular arrhythmias in advanced heart failure.

ACC/AHA Heart Failure Classification
Stage B: patients with structural heart disease without symptoms of heart failure.
Stage C: patients who have developed clinical heart failure.
Stage D: patients with refractory heart failure requiring specialised interventions.

ACC: American College of Cardiology; AHA: American Heart Association; A-HF: advanced heart failure; LV: left ventricle; RV: right ventricle; VA: ventricular arrhythmia.

Adapted from Santangeli P et al.[16]

Triggered Activity

Triggered activity refers to abnormal potentials triggered by a preceding action potential and includes early and late afterdepolarisations. Myocardial stretch in heart failure has been shown to contribute to increased triggered activity through the reduction in action potential duration.[20] Early afterdepolarisation manifests when there is a net inward current, which can occur in slow heart rates because of a reduction in the outward K^+ currents.[21] An increase in intracellular Ca^{2+} concentration accounts for late afterdepolarisations, which ultimately leads to an increased inward Na^+ current through the activation of the Ca^{2+}/Na^+ exchanger.[22]

Re-entry

Re-entry is the most common and significant mechanism of ventricular arrhythmias in heart failure. It occurs as a result of the disorganisation and slowing of action potential conduction, allowing electrical re-entry circuits to form around regions of scarring. Heart failure contributes to this pathology through neurohormonal pathway disruption, myocardial remodelling and fibrosis, and the disruption of metabolic homeostasis.[16]

In addition to reducing cardiac function and reserve, fibrosis provides an electrophysiological substrate to trigger and sustain arrhythmias. The volume and distribution of scarring has been shown to correlate with ventricular arrhythmias.[23] Cardiac resynchronisation therapy (CRT) decreases fibrosis and reduces remodelling.[24] The reversal of cardiac remodelling achieved by CRT has been associated with a reduction in the risk of life-threatening ventricular arrhythmias in cases of mild heart failure.[25] In contrast, the prevalence of ventricular arrhythmias following implantation of left ventricular assist devices remains high.[26] Therefore, disease regression in heart failure does not necessarily lead to a reduction in arrhythmias, but it depends on the mechanism through which regression is achieved. Neurohormonal blockade with mineralocorticoid receptor antagonists and angiotensin-converting enzyme inhibitors has also been shown to be effective at reducing the burden of ventricular arrhythmias.[27]

CLINICAL MANIFESTATIONS

Heart failure is a clinical syndrome characterised by impaired heart function and an inability to pump blood to adequately maintain circulation. Heart failure can be subclassified according to the ventricular ejection fraction: the percentage of ventricular blood ejected with each beat. An ejection fraction <50% is considered heart failure with reduced ejection fraction (HFrEF), whereas >50% is considered preserved (HFpEF). Approximately 50% of symptomatic heart failure patients have a preserved ejection fraction.[28] Patients with HFrEF have a higher prevalence of ventricular arrhythmias and increased risk of sudden death.

The symptoms of heart failure are predominantly due to congestion, which commonly presents as dyspnoea on exertion.[10] Patients also complain of orthopnoea (breathlessness when lying down) and paroxysmal nocturnal dyspnoea (sudden attacks of breathlessness during the night). Congestion may also occur in the liver, intestines, and peripheries. Signs of heart failure include gallop rhythm with a third heart sound (S3), elevated jugular venous pressure, hepatomegaly, ascites, and peripheral oedema.

Ventricular arrhythmias primarily produce cardiac symptoms, including palpitations, chest pain, dyspnoea, dizziness, syncope, and sudden cardiac death. Ventricular arrhythmia should be suspected in cases of syncope occurring at rest or when lying down.

EVALUATION AND RISK STRATIFICATION

A detailed history and examination are required when assessing patients with heart failure. Routine laboratory tests and imaging studies can support the diagnosis of heart failure and assist in risk stratification. Although there are a large number of risk factors identified for sudden cardiac death in heart failure, developing a comprehensive risk stratification strategy remains a clinical challenge that requires the analysis of multiple parameters.[22,29] Currently, there is no combination of tests that can definitively predict arrhythmic events. However, a depressed ejection fraction and symptoms of heart failure are the most consistent predictors

of sudden cardiac death.[29] Indeed, many international guidelines suggest that an ejection fraction <30% in NYHA class I, or <35% in class II and III, is an indication for ICD implantation in heart failure patients.[29] Other parameters that may be useful in risk stratification include T wave alternans, signal-averaged ECG, autonomic tone, and electrophysiology studies or ischaemic substrates.

Imaging studies

Transthoracic echocardiogram is usually the first study undertaken in all patients with suspected heart failure, by virtue of its simplicity and widespread availability. Echocardiogram is central in identifying structural abnormalities, characterising the function of the chambers and valves, and evaluating suitability for further interventions; additionally, the technique can characterise ventricular ejection fraction, wall thickness, wall motion, geometry, and volume.[30] Serial echocardiograms may be employed to monitor responses to treatment. Echocardiograms are key for differentiating between preserved and reduced ejection fraction heart failure. A reduction in ejection fraction, which is typically considered as an ejection fraction <50%, has a higher mortality rate and is the most consistent predictor of sudden cardiac death in heart failure.[22] According to the American College of Cardiology (ACC) and the American Heart Association (AHA), heart failure with preserved ejection fraction can be diagnosed based on clinical symptoms and signs if there is no evidence of valvular abnormality nor impairment of ejection fraction.[31]

Advances in cardiac MRI have permitted novel methods in identifying structural abnormalities and scarring.[22] Gadolinium-enhanced imaging allows for a detailed analysis of cardiac tissues and identification of areas of tissue scarring. Areas of fibrosis detected on MRI scans have been associated with a significant increase in risk of ventricular arrhythmias and sudden cardiac death.[32] MRI may also be used to differentiate between heart failure patients with ischaemic and nonischaemic aetiology.[33]

Chest radiography may be used in the work-up for heart failure to exclude alternative conditions and support the diagnosis. Findings of heart failure include cardiomegaly, pulmonary oedema, and pleural effusion.

Electrocardiogram

The 12 lead ECG in heart failure patients typically shows a variety of abnormalities, although none of them are specific to heart failure.[30] Patients may present with QRS complex and T wave abnormalities, including bundle branch blocks and atrioventricular block.[31] Underlying ischaemia or myocardial stress can produce changes in the Q waves, T waves, and ST segment of the ECG.[30] Remodelling, induced by compensatory mechanisms, can lead to supraventricular or ventricular arrhythmias.[34] While an ECG cannot predict the risk of sudden cardiac death, it is useful for uncovering conditions which may predispose to arrhythmias, such as Wolff–Parkinson–White syndrome, long QT syndrome, or Brugada syndrome.[35] Moreover, a recording of VT or premature ventricular complexes can help determine the targets for catheter-based ablation procedures.[15]

The signal-averaged ECG is a high-resolution technique, whereby electrical signals from the heart are averaged with high-gain amplification and filtering, allowing low amplitude deflections in the terminal part of the QRS complex to be detected.[36] These late potentials reflect the presence of substrate for re-entry and are thought to correlate with areas of delayed endocardial activation.[22,37] While the negative predictive value of signal-averaged ECG recordings is high for sudden cardiac death, it has a low positive predictive value, which limits its usefulness as a prognostic tool.[35,38] Ambulatory ECG monitoring can be employed with a Holter monitor, an event monitor, or an implantable loop recorder; however, there is conflicting evidence for their predictive value for ventricular arrhythmias in heart failure.[38]

Biomarkers

Brain natriuretic peptide (BNP) and N-terminal pro-BNP are blood markers of myocardial stretch that have seen increasing use in evaluating the presence and assessing severity of heart failure.[30] Cardiac markers of injury, such as troponin I, may be used to ascertain the presence of acute coronary syndrome, although it should be noted that they are commonly elevated in heart failure despite the absence of recent infarction.

Electrophysiology Studies

The underlying pathologic substrate and arrhythmic presentation determine the diagnostic and prognostic value of electrophysiological testing.[38] The inducibility of monomorphic VT with programmed electrical stimulation is a powerful marker for increased risk of ventricular arrhythmias in heart failure patients with reduced ejection fraction and prior myocardial infarction.[39] In contrast, patients with non-ischaemic aetiology have a much lower inducibility of arrhythmias and the predictive value of these electrophysiological studies remains limited in this population because clinical outcomes do not correlate with inducibility.[40]

MANAGEMENT STRATEGIES

The initial management of heart failure relies on lifestyle modification and pharmacological therapy. Ventricular arrhythmias should be managed with treatment of the underlying cardiomyopathy, addressing reversible factors, and optimising heart failure status.[41] ICD provide the best protection against sudden cardiac death from ventricular arrhythmias; however, recurrent ICD shocks are associated with long-term morbidity and mortality.[41]

Consequently, anti-arrhythmic drugs and catheter ablation are important adjuncts for minimising ICD shocks in recurrent ventricular arrhythmias (Figure 2).[42]

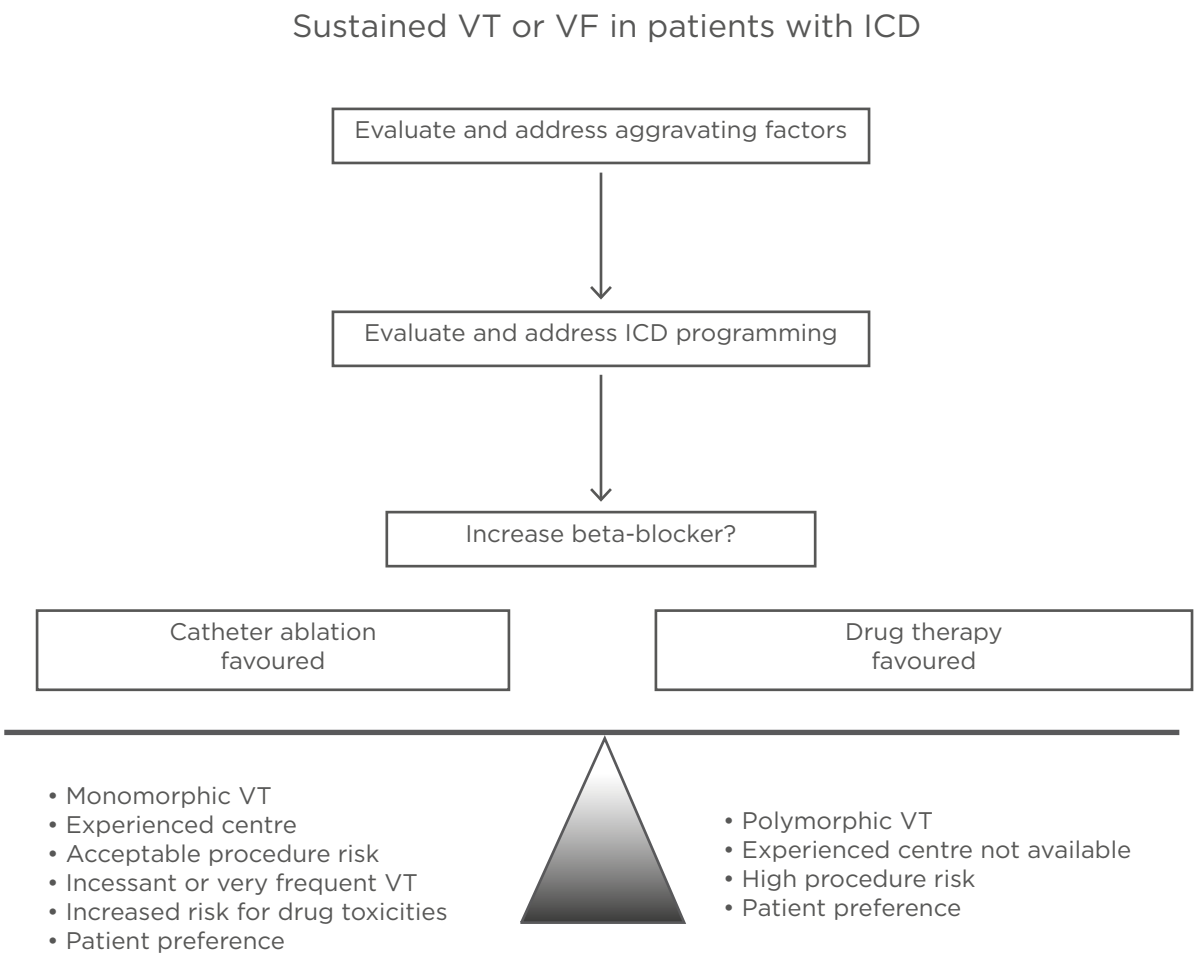

Figure 2: Illustration of an approach to the patient with an implantable cardioverter defibrillator who has a ventricular tachycardia recurrence.

ICD: implantable cardioverter defibrillator; VF: ventricular fibrillation; VT: ventricular tachycardia.

Adapted from Stevenson WG.[42]

Implantable Cardioverter Defibrillator Devices

ICD therapy effectively terminates ventricular arrhythmias with overdrive (anti-tachycardia) pacing or defibrillation shocks. It is recommended for most heart failure patients with a history of ventricular arrhythmias (secondary prevention) or those that are at an increased risk of sudden death (primary prevention).[42] Primary prevention is most commonly used in patients exhibiting HFrEF (≤35%), although it may be recommended in those with genetic diseases that predispose them to sudden death, including hypertrophic cardiomyopathy and Brugada syndrome.

Prophylactic treatment with ICD for VT has been shown to improve prognosis in two large-scale randomised trials that compared ICD therapy with standard medical therapy in patients with predefined risk (MADIT and MUSTT);[35] however, it is important to note that ICD shocks treat but do not prevent the recurrence of arrhythmias. Recurrent ICD shocks are associated with increased mortality and a reduction in quality of life.[41] Anti-arrhythmic drugs and catheter ablation should be considered in cases of recurrent arrhythmias. The MADIT-RIT and PREPARE studies evaluated ICD programming strategies to minimise shocks.[43,44] The strategies that were effective in reducing shocks and improving mortality included anti-tachycardia pacing, increased tachycardia detection rate, delayed-therapy programming, and supraventricular discrimination algorithms.

Pharmacological Agents

Beta-blockers have been shown to reduce morbidity and mortality in heart failure.[41] Therefore, given their benefits in improving haemodynamic status, beta-blockers should be offered to all patients without a major contraindication. Furthermore, in cases where patients present with ventricular arrhythmias and ICD shocks who are on optimal beta blocker therapy, the addition of other anti-arrhythmic drugs should be considered.

Anti-arrhythmic drugs are primarily used to minimise and prevent ICD shocks;[15] nevertheless, there is limited data supporting the efficacy and safety of these drugs in patients with heart failure.[45] While they may decrease arrhythmic burden, many anti-arrhythmic drugs have negative inotropic effects that can lead to the worsening of haemodynamic status. In particular, there is very little data on the efficacy and safety of short-term pharmacological management of recurrent VT. Intravenous lignocaine is used because of its short half-life and good safety profile,[46] but intravenous amiodarone may be considered. Long-term management with negatively inotropic agents, such as sotalol and procainamide, should be avoided.

Most class I anti-arrhythmic agents, which act by blocking the Na^+ channel, have been shown to increase mortality in structural heart disease patients because of the negative inotropic effect and potential proarrhythmic action.[47] Nevertheless, quinidine and mexiletine have some evidence of effective anti-arrhythmic action, although they have never been evaluated in randomised controlled trials.[48,49] It should be noted that mexiletine should be used with caution because it may worsen haemodynamic status in advanced heart failure through its negative inotropic and increased peripheral vascular resistance effects.[50]

Randomised control trials have shown that amiodarone is the only class III anti-arrhythmic drug with a significant treatment effect on ventricular arrhythmias in advanced heart failure.[45] A systematic review and meta-analysis[45] on the effectiveness of anti-arrhythmic drugs for the prevention of recurrent ventricular arrhythmias analysed eight trials, which showed that amiodarone significantly reduced appropriate ICD interventions (odds ratio=0.3; $p<0.001$), while sotalol did not have a significant impact (odds ratio=0.83; p=0.594); however, amiodarone is associated with end-organ toxicity, significant side-effects, and a possible increase in all-cause mortality.[51,52]

Class IV drugs non-dihydropyridine Ca^{2+} channel blockers should be avoided as they have poor efficacy in ventricular arrhythmias on a background of heart failure, and may increase overall mortality.[41] Analysis of 15 randomised trials has shown that using amiodarone has an unfavourable profile with a number needed to treat of 38 for prophylaxis of sudden cardiac death, compared to the number needed to harm of 14 from amiodarone-associated thyroid toxicity, hepatic toxicity, pulmonary toxicity, or bradycardia.[51]

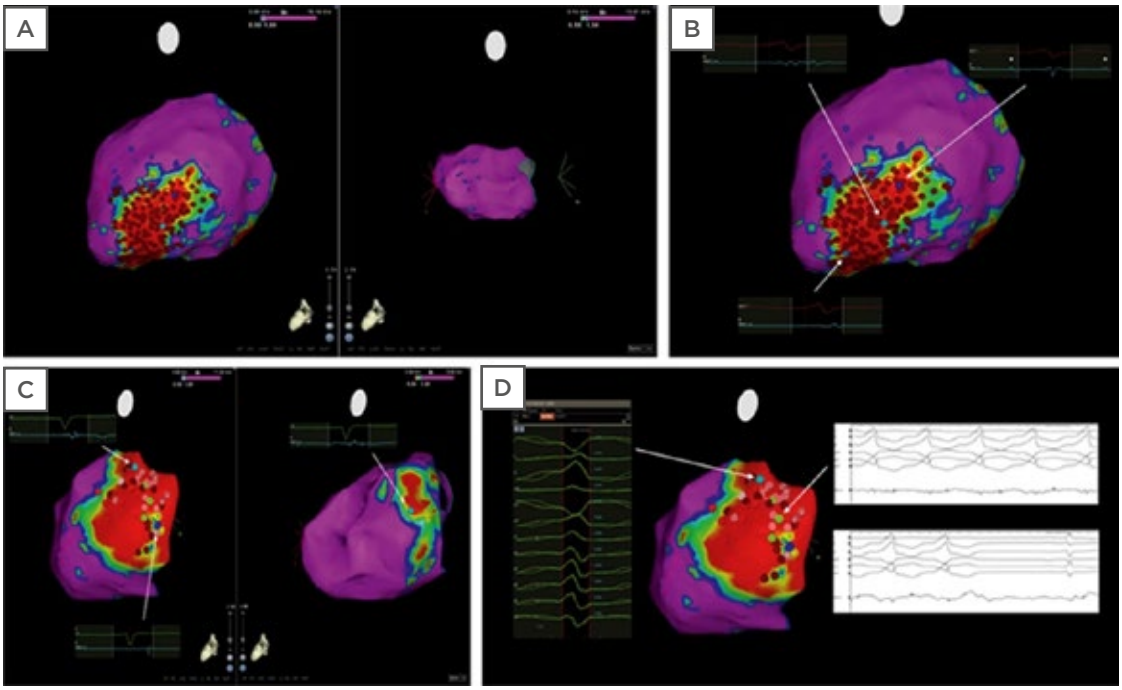

Figure 3: Electroanatomic maps of sample ablation lesions.

Electroanatomic maps (A, B) showing an example of extensive radiofrequency catheter ablation (red dots) in the scar zone (i.e., 'scar homogenisation') in a patient with ventricular tachycardia, nonischaemic cardiomyopathy, and epicardial scar. Normal voltage was present in the endocardium (A; right panel), while scar was present in the epicardium. In a different patient, maps show limited ablation performed in the epicardial scar zone (C), with mapping and termination of the ventricular arrhythmia during ablation (D).

Colours: Red regions represent scar tissue (bipolar voltage <0.5 mV); purple regions represent normal myocardium (bipolar voltage >1.5 mV); other coloured regions represent 'border zones' (bipolar voltage between 0.5 and 1.5 mV).

Dots: Light blue = fragmented potentials; dark blue = late potential; light and dark red = ablation sites; and green = sites of VT termination during radiofrequency ablation.

Adapted from Gökoğlan Y et al.[53]

Catheter-Based Interventions

Catheter ablation can be used as an adjunctive treatment in patients with frequent ventricular arrhythmias and ICD shocks despite pharmacological therapy. The benefits of this intervention depends on the location of the circuit, the underlying substrate, arrhythmia inducibility and NYHA heart failure status (Figure 3).[15,53] A recent large single-centre study reported that arrhythmia-free survival rates, at a median of 6 years post-VT ablation, were 54% ±4% in patients with ischaemic cardiomyopathy and 38%±4% in non-ischaemic cardiomyopathy.[54] Earlier adoption of ablation strategies in post infarct VT has been associated with better outcomes.[55]

Catheter ablation is the most effective monomorphic VT therapy, although it has been shown to be efficacious in some cases of polymorphic VT and VF.[42] The central isthmus, an essential component of the re-entry circuit, is usually targeted in monomorphic VT;[56] however, haemodynamic instability often hinders the ability to effectively map the circuit. In such cases, scars can be defined during sinus rhythm using voltage mapping as the central isthmus is usually found between areas of dense scarring.[57] While the acute success rate in abolishing VT using ablation is approximately 70%, at 12 month of follow-up, 26–50% of patients will experience recurrence of VT.[42] There is limited data on the use of catheter ablation for VT in severe heart failure because of the increased mortality risk and safety concerns.

A recent paper reported that radiofrequency ablation of VT in NYHA class IV patients can

be safely performed despite the higher rate of comorbidities and reduces mortality.[58] It reported that NYHA class IV patients without recurrent VT had similar survival rates to NYHA class II and III patients with recurrent VT.

Autonomic modulation

Sympathetic stimulation and parasympathetic downregulation contribute to the compensatory mechanisms that lead to cardiac remodelling and fibrosis. Therefore, 'neuraxial modulation', targeting the autonomic nervous system has provided a novel therapeutic strategy for managing refractory ventricular arrhythmias.[16,59] In a study of 14 patients with a mean follow-up of 6 months, left cardiac sympathetic denervation (stellate ganglionectomy) or thoracic epidural anaesthesia resulted in a significant reduction in ICD shocks, and 48% of patients had complete suppression of ventricular arrhythmias.[59] It has been shown that renal denervation can significantly reduce VT burden.[60] A recent multicentre study reported a significant reduction in the burden of ICD shocks in patients undergoing left or bilateral cardiac sympathetic denervation.[61] At a median follow-up of 1.1 years, ICD shocks reduced from a mean of 18±30 to 2.0±4.3. Factors associated with less successful outcomes included advanced heart failure, longer VT cycle lengths, and left-sided only denervation.

CONCLUSION

The increasing age of the worldwide population is contributing to a growing incidence of heart failure. The consequent increase in ventricular arrhythmias represents a significant cause of morbidity and mortality. The pathophysiology underlying the interaction between heart failure and arrhythmias is complex; each condition may predispose to or worsen the other. Technological advances in imaging and biomarkers aid early diagnosis, risk stratification, and treatment. ICD device implantation has been the focus of clinical management of ventricular arrhythmias in recent decades given the strong evidence of efficacy; however, there is also evidence for the role of pharmacological therapy and invasive catheter ablation procedures. The outcomes of different management strategies for ventricular arrhythmias in heart failure requires further elucidation with further prospective studies.

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Edge-to-Edge Repair After Prior Left-Sided Pneumonectomy

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Abstract

Cardiac surgery procedures for patients following previous pneumonectomy are challenging because of anaesthetic and cardio-surgical technical difficulties. Here, the case of a patient who had received a left-sided pneumectomy 13 years prior as a result of nonsmall cell lung cancer is presented. A mitral edge-to-edge clipping was applied with excellent success in treating severe mitral regurgitation attributable to flail of the posterior mitral valve leaflet (fibroelastic deficiency). Because the heart was severely left-displaced, the use of transoesophageal echo during the preinterventional screening was challenging but feasible, and imaging quality was good. The absence of left pulmonary veins demanded a guide catheter and clip delivery system to be introduced during the procedure through the use of a spiral, preshaped, stiff guidewire. The procedure was performed under general anaesthesia with the patient extubated on a table. No complications arose during the periprocedural period and hospital stay, and after 3 months' follow-up the patient showed significant functional improvement.

INTRODUCTION

Cardiac procedures and operations following pneumonectomy present with serious challenges, both surgical and anaesthetic. Only a small number of reports of cardiac operations after previous pneumonectomy have been reported.[1] General anaesthesia must be performed with special respect to the single lung respiratory status[1] whilst also bearing in mind the mediastinal displacement and previous thoracotomy. Common problems concern the respiratory system, where the hyperinflation and unique anatomical situation of the remaining lung presents challenges after pneumonectomy. Anatomically, some changes influence the feasibility of a heart operation and are somehow different after right-sided or left-sided pneumonectomy. After left-sided pneumonectomy, the heart moves laterally to the left and can reach the left thorax wall, as shown in Figures 1A and B. This can result in difficulties with surgical access and operability; therefore, as an alternative to conventional surgical repair in patients with severe mitral regurgitation and

indication for repair, edge-to-edge therapies have evolved as a reasonable and superior therapeutic means, especially in patients with functional mitral regurgitation.[2] The heart team decision as to whether a conventional or edge-to-edge repair should be attempted is strongly dependent on the perioperative risk and the chance of good operational repair result.[3]

The use of risk stratification scores is routinely used to help decide the better option for patients in need of valvular interventions. According to the latest European guidelines for the management of valvular heart disease, the EuroSCORE II and the Society of Thoracic Surgeons (STS) score[4] are the most routinely used, and for this purpose are recommended. Because these scores have some major limitations, decision making is usually an individual process; in this case the usual scores were not able to properly reflect the expected risk by not taking the status after pneumonectomy into consideration in their calculations.

Technical challenges of mitral clipping after left-sided pneumonectomy include the problem of introducing the trans-septal sheath into the left atrium because there is no left lung, and thus no pulmonary veins, to be used to 'park' the stiff guidewire. For the surgical phase, difficulties include access problems for minimally invasive right-sided minithoracotomy, in addition to the fact that this is considered a resternotomy. Added to these difficulties are the anaesthetic considerations concerning the single lung status.

REPORT

A 64-year-old male patient (180 cm; 80 kg) was referred to the authors' centre reporting progressive dyspnea during the previous 6 months, primarily attributable to severe mitral and tricuspid regurgitation (functional New York Heart Association [NYHA] status IV). In accordance to the clinical symptoms and the echocardiographic findings, the neurohormonal activation was present with a NT-proBNP value of 2,759 pg/mL (age adjusted normal range 0.0–57.2 pg/mL). The medical history revealed that the patient had a pneumonectomy followed by adjuvant chemotherapy 13 years ago, these were performed following a diagnosis of nonsmall cell lung cancer. The therapy was considered successful because there was no recurrence of the tumour for >10 years. The patient presented with severe degenerative mitral regurgitation. The monoplane vena contracta was 7 mm, the effective regurgitant orifice area was 0.3 cm^2 with a regurgitational volume of 45 mL/beat, and there was flow reflux into the pulmonary veins. Systolic function was slightly reduced (left ventricular ejection fraction: 50%), and there was a lack of leaflet coaptation in the A2/P2 and A1/P1 segments which was attributable to the degenerative process, with a flail leaflet prolapse of the posterior leaflet in the P1-P2 segments.

Coronary angiogram (Figure 1A) results showed no relevant coronary artery disease.

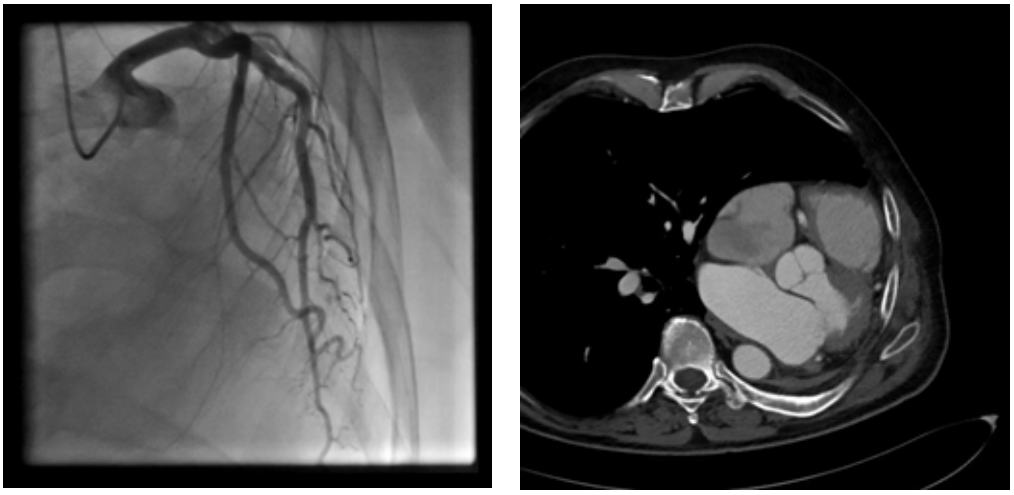

Figure 1: A) Coronary angiogram showing the left displacement of the heart.[6] B) CT showing the left-lateral displacement of the heart after pneumonectomy.

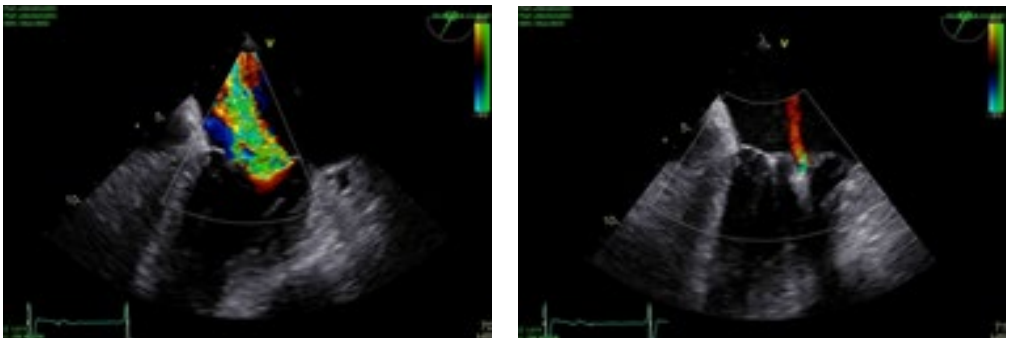

Figure 2: A) Transoesophageal echocardiograph in a high grade mitral regurgitation B) Transoesophageal echocardiograph in a trivial mitral regurgitation following implantation of two clips.

Because of their otherwise good general condition, and with the usual risk scores suggesting low operative risk, the patient was primarily referred to the authors' surgical department for mitral valve reconstruction. However, after chest x-ray there were concerns about the technical operability following a prior pneumonectomy. These included the impossibility of maintaining a minimally invasive approach via a right-sided minithoracotomy, the risk of injury of the compensatory expanded right lung when performing resternotomy, and the risk of postpneumectomy syndrome (Figure 1B).[5] Thus, although the patient had a low STS score of 2.9%, the heart team recommended an edge-to-edge repair using a MitraClip™ (Abbott, Illinois, USA) because of concerns about surgical accessibility. The decision was also triggered by other clinical comorbidities: the status after traumatic splenectomy under anticoagulation with rivaroxaban in the year prior to the intervention, the consecutive development of a postoperative pancreatic fistula, and reports of a slow-growing (10 years) haemangioma in the right lung. These comorbid factors, despite not influencing the STS and EuroScore II scores in many cases, led to the decision in favour of an interventional approach taking into account a nonoptimal reconstructive result.

The procedure was performed using both fluoroscopy and three-dimensional (3D) transoesophageal guidance. The standard right femoral venous approach was used to gain access for the guiding catheter, and a percutaneous closure system (ProGlide [Abbott, Santa Clara, California, USA]) was used afterwards to close the puncture site. No bleeding complications were reported during or after the peri-interventional period.

Specific challenges were encountered throughout the procedure. The first regarded the acquisition of good transoesophageal images attributable to the leftward displacement of the heart, as observed in the chest x-ray and CT. Fortunately, this was easily achieved by performing the transoesophageal echo in the supine position, which was the standard position for the procedure. The authors believe that this might be facilitated by a similar left displacement of the oesophagus to other thorax organs.

A second concern regarded introducing the MitraClip™ guide system safely into the left atrium after trans-septal puncture while avoiding perforation of the left atrium. The routine method to introduce a stiff wire into the left upper pulmonary vein and then place the guide system over this stiff wire was not possible because of the missing pulmonary veins. After several attempts to place the stiff wire (Boston Scientific, Massachusetts, USA) in the left atrium in a safe manner, concerns were raised that the flexible tip would not grant safe introduction of the sheath, and that the stiff-part of the wire would still perforate the wall of the left atrium. This challenge was solved by first introducing a spiral preshaped guidewire (Safari [Boston Scientific, Massachusetts, USA]) into the left atrium and then exchanging the trans-septal sheath for the MitraClip XTR (Abbott, California, USA) guide system and safely advancing it over the preshaped wire

into the left atrium. To achieve that used similar technique to that To achieve this, the authors used a similar technique to that used for introducing preshaped wires into the left ventricle during TAVR procedures. First, a pigtail catheter was introduced trans-septally into the left atrium, then the stiff wire was removed and the preshaped spiral guidewire was safely placed into the left atrium: this helped to safely introduce the trans-septal sheath into the area. The first clip was implanted centro-medially, which reduced mitral regurgitation from severe to moderate (Grade 3 to 2; mean pressure gradient after the first clip: 1.68 mm Hg; or mean flow velocity 0.56 m/s). A second clip was then implanted in the centro-lateral position, achieving an excellent result with only minimal (trace) regurgitation. The mitral regurgitation was successfully reduced from severe grade to trivial (3D effective regurgitant orifice area was not eligible because of the small regurgitation amid artefacts from the clips around it). The procedure was performed under general anaesthesia (procedure time was approximately 2 hours; anaesthesia duration was 3 hours and 12 minutes) with the patient extubated on table and no respiratory complications reported (Figures 2A,B, and 3).

Postoperatively the patient was transferred to the intensive care unit and stayed for 2 days. No serious complications were reported during the postoperative period. Rate control of the known paroxysmal atrial fibrillation was the cause of the prolonged monitoring; the patient was transferred after a few days to a cardiac rehabilitation unit. Echocardiographic results 3 weeks later showed no residual mitral regurgitation and, interestingly, a reduction in the tricuspid regurgitation from severe to moderate, with a pulmonary artery pressure of 31 mm Hg plus central venous pressure (preoperative value was 45 mm Hg plus central venous pressure). The patient completed the 3-week rehabilitation programme with very good improvement of their functional capacity. The patient was placed in NYHA functional status II 3 months after the intervention.

DISCUSSION

Only few reports exist on cardiac surgery procedures performed after pneumonectomy. In these publications, many concerns are focussed on anaesthesiological and surgical aspects. Kumar et al.[1] identified reports of roughly 30 such cardiac operations, most of which involved coronary artery bypass grafting and only few valve surgeries. In this present case, interventional edge-to-edge repair was demonstrated to be a feasible alternative to surgical treatment of severe mitral regurgitation in a patient after pneumectomy.

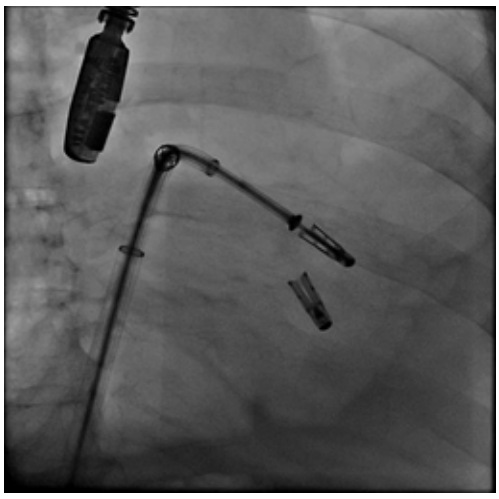

Figure 3: Fluoroscopic view while implanting the second clip.

The use of a spiral curved guide wire enabled a safe introduction of the guiding sheath into the left atrium. Concerns existed regarding echocardiographic imaging in the left displaced mediastinum, but in this case the transoesophageal echo imaging was possible and the images were good. This might be because the oesophagus is also concordantly displaced. The authors still advise this to be checked in the preinterventional screening. By extubating the patient on a table, respiratory complications were avoided, and the early ambulation of the patient prevented further morbidities from the procedure.

SUMMARY

Cardiac surgery procedures for patients after previous pneumectomy are challenging because of anaesthetic and technical difficulties. In this case of a left-sided pneumectomy patient, a mitral edge-to-edge clipping was applied with excellent results in treating severe mitral regurgitation attributable to flail of the posterior mitral valve leaflet (fibroelastic deficiency). Although the heart was severely left displaced, the use of transoesophageal echo was feasible and the imaging results were good. Because of the nonexistent left pulmonary veins, the guide catheter and the clip delivery system was introduced by using a spiral preshaped stiff guidewire. The procedure was performed under general anaesthesia with the patient extubated on table. No complications occurred during the periprocedural period and the hospital stay. After 3 months' follow-up, the patient showed significant functional improvement.

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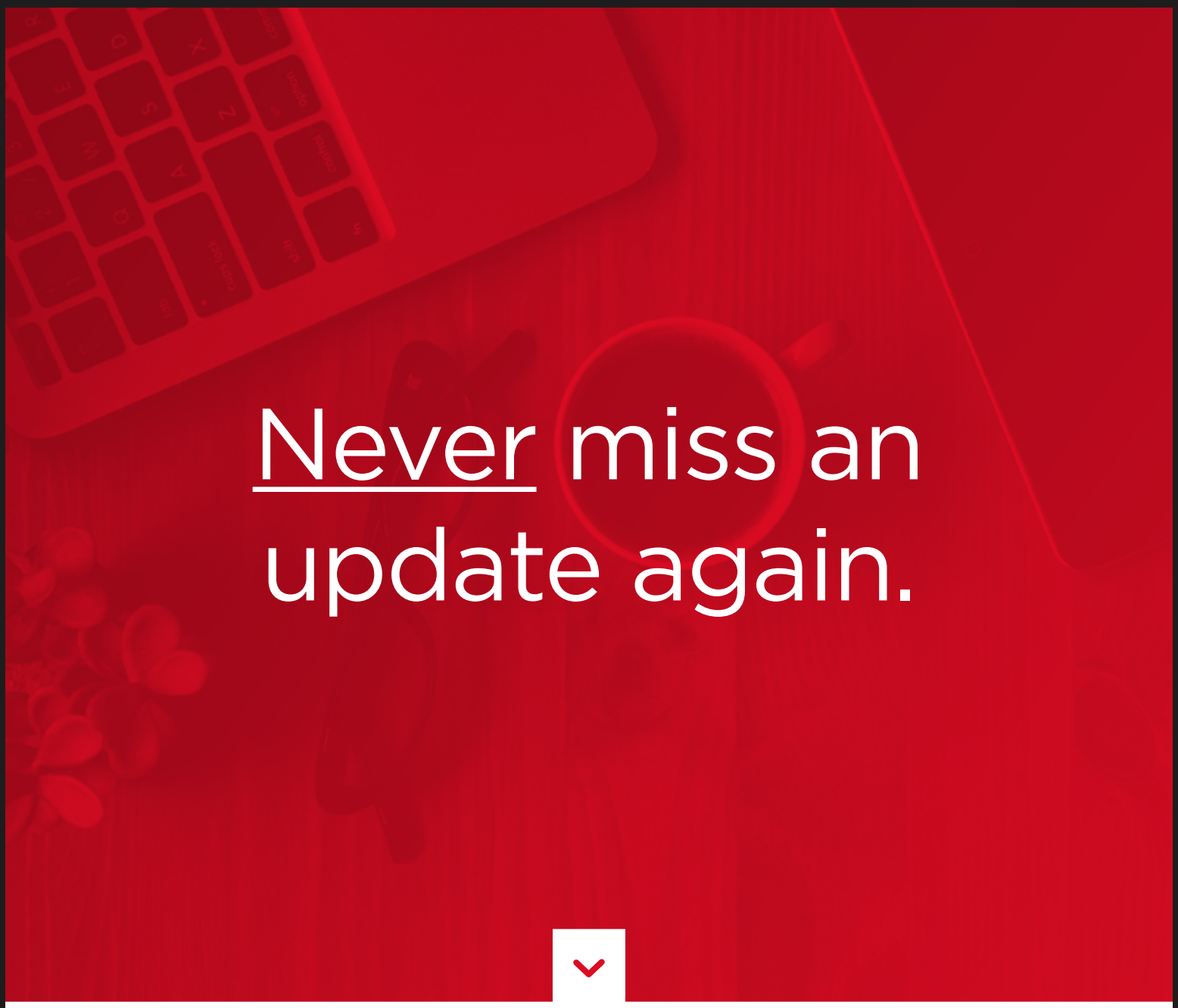

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