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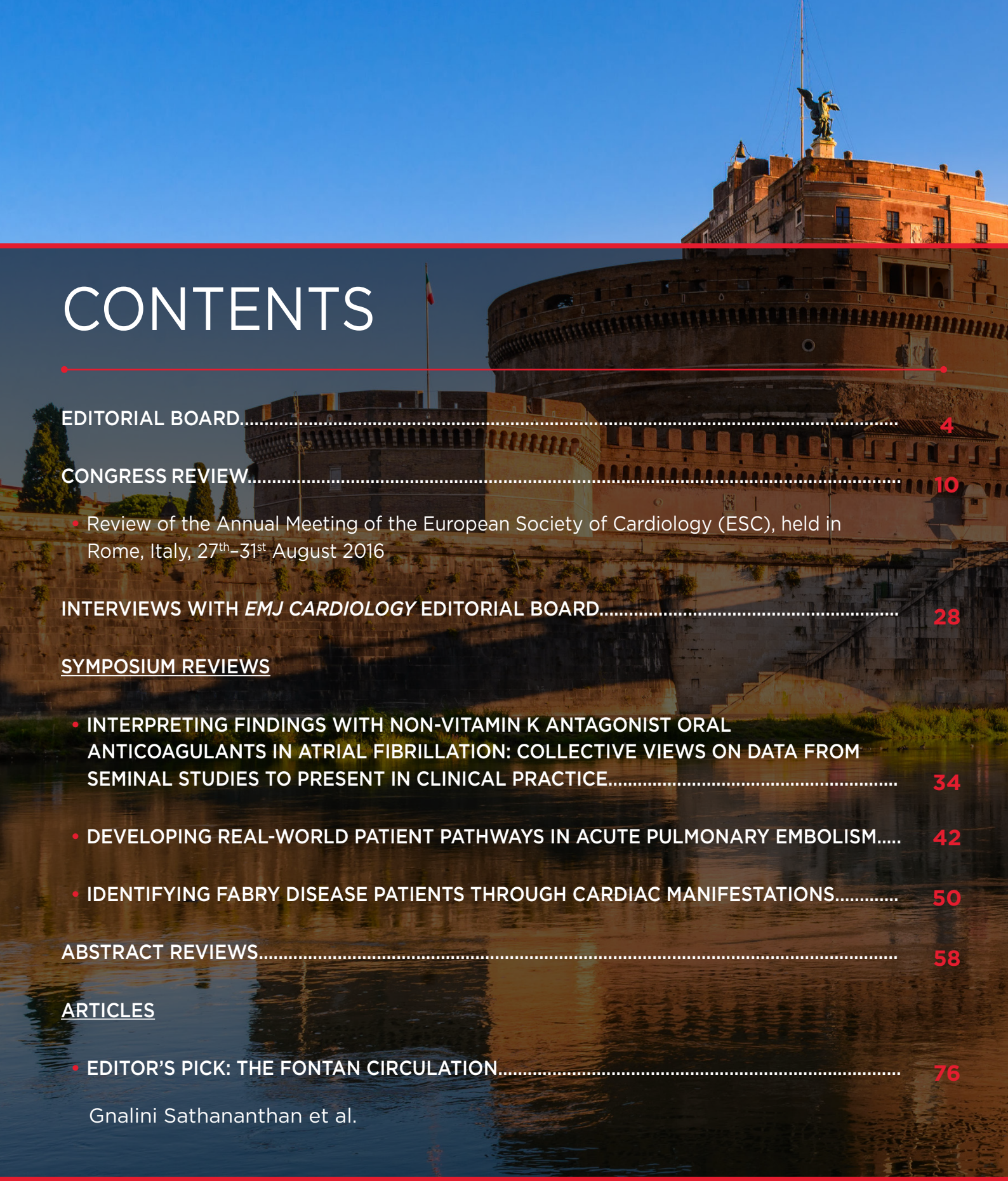
INSIDE
Review of
ESC 2016
Rome, Italy



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Welcome

Welcome to this year's edition of *EMJ Cardiology*. It is our pleasure to report on the latest innovations within this fast-moving and fascinating therapeutic area of medicine, as well as to bring you the latest news and updates from the biggest event in the cardiology calendar this year: ESC 2016.

This year's ESC congress was held in Rome, Italy, with a record number of attendees from around the world. The focus of the congress was on the role of the 'Heart Team'. The congress committee were also proud to present the brand new, innovative online learning platform that was launched this year, allowing attendees to revisit any of the sessions, discussions, or research presentations throughout the year, and allow interaction beyond the congress.

In this issue, you will find a comprehensive review of the ESC congress including summaries of the cutting edge research presented, written by the researchers themselves. We have also brought you the latest news stories in our congress review section, bringing you up-to-date on the huge volume of innovative studies that are being carried out across Europe and the world.

Alongside our congress review highlights, members of our esteemed Editorial Board have offered their thoughts, opinions, and career highlights in our Editorial Board interviews section. Here, you can read about the careers of several pioneering members of the cardiology sphere, gain insight into their research and professional goals for the year, and discover more about what a career in cardiology entails.

As always, we have a selection of peer-reviewed and high quality articles to accompany the congress review. Einvik et al. display how emergency treatment of cardiac arrest in pregnancy could change following a fascinating case study of a 27-year-old woman who arrested at a gestational age of 26 weeks. Corcoran et al. discuss the current status of diagnosis and management of ischaemic heart disease by considering a number of clinical trials in a thorough review article, and Hack-Lyoung Kim presents his findings on arterial stiffness and coronary artery disease.

We hope you will enjoy this edition of *EMJ Cardiology* and that the articles, abstracts, and congress review highlights will prove timely and useful to your own daily practice. We look forward to bringing you even more exciting research updates and congress highlights in the next edition from the ESC 2017 meeting in Barcelona, Spain!

Spencer Gore

Director, European Medical Journal

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Front cover and contents photograph: Rome, Italy, home of ESC 2016.

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Foreword

Dr Fernando Alfonso

Head, Cardiology Department, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa; Associate Professor of Medicine, Universidad Autónoma de Madrid, Madrid, Spain.

Dear Colleagues,

I have the pleasure of welcoming you to this new issue of *EMJ Cardiology*. The coming issue will focus on the recent European Society of Cardiology (ESC) Congress, held in Rome.

This ESC Congress represents the world's largest scientific meeting on cardiovascular diseases in 2016. The scientific programme of the ESC Annual Meeting was outstanding, addressing in a comprehensive and systematic fashion the most relevant developments in the diagnosis, management, and treatment of cardiovascular diseases. Notably, this year more than 11,000 abstracts were submitted. The programme payed special attention to 'practical sessions' based on key issues faced in actual clinical practice cases. The 'gladiator's arena' featured discussion on hot topics that were eventually evaluated by attendee vote. In addition, major new ESC Clinical Practice Guidelines were released, covering cancer treatments and cardiovascular toxicity (position paper), management of atrial fibrillation, management of dyslipidaemias, cardiovascular disease prevention in clinical practice, and acute and chronic heart failure. The spotlight of the ESC Congress 2016 was on the 'Heart Team', highlighting the importance of team work and the relevance of the interactions between the different professionals and specialties involved in the management of patients with cardiovascular diseases. Attending the meeting was a unique opportunity to hear, first-hand, the latest Hot Line and clinical trial results, and stay up-to-date with the latest ESC Clinical Practice Guidelines. Moreover, this meeting provided a unique opportunity for intense interaction with enthusiastic cardiologists from all over the world. You can read about some of the most exciting pieces of research presented here in the congress review section of the journal.

The articles this year cover a range of up-to-the-minute topics and challenges for cardiologists today. In this year's Editor's Pick, Gnalini Sathananthan et al. consider the use of the Fontan procedure among children born with congenital heart disease, reflecting on the negative long-term physiological impact on young patients. Other topics featured in the articles include forceful post-dilatation and optimal stent apposition, the risk score system in place to evaluate surgical morbidity and mortality, and resuscitation from cardiac arrest in pregnancy.

I hope you enjoy reading this edition of *EMJ Cardiology* and that you find the coverage of this year's ESC congress both helpful and insightful.

Kind regards,

Dr Fernando Alfonso

Head, Cardiology Department, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa; Associate Professor of Medicine, Universidad Autónoma de Madrid, Madrid, Spain.


Welcome
ESC CONGRESS
ROME 2016

ESC ANNUAL CONGRESS 2016

FIERA DI ROMA,
ROME, ITALY
27TH–31ST AUGUST 2016

Welcome to the *European Medical Journal* review of the Annual Meeting of the European Society of Cardiology

Rome is home to a plethora of art and culture and this year it was also home to the annual ESC Congress. Taking place over 5 days, this event included more than 500 sessions for its 33,000 attendees, who represented 140 different countries. The developments presented this year were of the highest quality, with nearly 11,000 initial submissions whittled down to just over 4,500 of the best abstracts. There were also 26 clinical trial updates and a number of 'gladiator style' debates on some of the most controversial issues.

Speaking at the Opening Ceremony in Rome, Chair of the Congress Programme Committee Prof Geneviève Derumeaux commended the attendees for their "enthusiasm and active contribution," and elaborated on her "personal wish to you that you will make it your own ESC congress. First you can take away from these 5 days of congress all the experience, knowledge, and learning you can get, that will make a difference for you, your heart team, and your patients."

His Holiness Pope Francis also gave an impassioned speech to the ESC delegates, in which he thanked the delegates for their work and dedication to their patients, as well as emphasising the "importance of scientific research for human life and health."

Two ESC gold medals were presented at the event; this is the highest honour that the society bestows upon individuals who have made a substantial contribution to cardiovascular medicine. Alain Cribier, France, who developed and performed the world's first transcatheter aortic valve implantation was the first recipient. The second was given to Bernard Gersh, USA, who has published pivotal research in atrial fibrillation, percutaneous coronary intervention, and many other topics. On receiving the medal, Gersh commented: "I am really thrilled by this totally unexpected honour. It is a highlight of my career. Awarding the ESC gold medal to non-Europeans emphasises the worldwide fraternity of academic cardiology."

The society also gave two Outstanding Achievement Awards; this award is given to basic researchers who have made significant developments early in their careers. The first of these was given to Charalambos Antoniades, UK, whose research

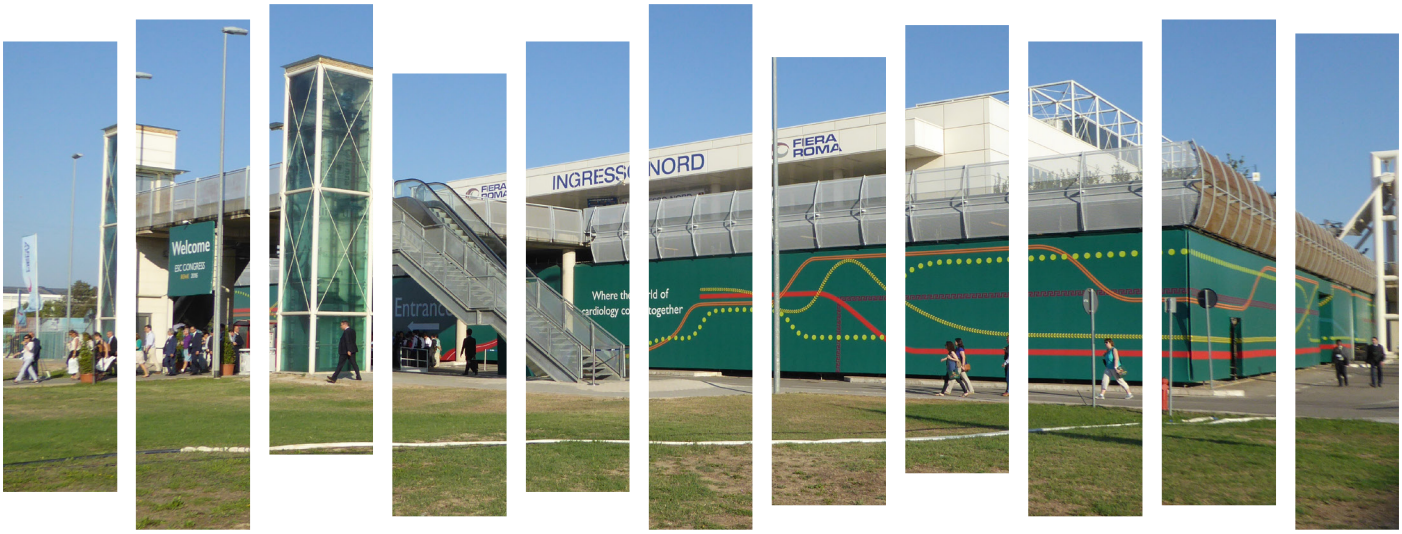
focusses on the interplay between adipose tissue and vascular/myocardial redox signalling. The second was awarded to Sabine Steffens, Germany, who conducts research in the field of atherosclerosis and vascular biology, with a particular focus on the endocannabinoid system.

This year also featured the development of four new guidelines in atrial fibrillation, heart failure, cardiovascular prevention and dyslipidaemia, and cardio-oncology. These reflect the ever-growing multidisciplinary team in cardiovascular medicine. Within these guidelines, you will find new information from the latest trials and systematic reviews to provide you with the most up-to-date clinical strategies to adopt into your own practice.

> “First you can take away from these 5 days of congress all the experience, knowledge, and learning you can get, that will make a difference for you, your heart team, and your patients.”

Moving forward, ESC President Prof Fausto Pinto announced a 5-year plan from 2016–2020, which involves plugging the gap between cardiovascular knowledge and routine clinical care, incorporating advocacy, research, education, congress, and membership. Key points include membership packages to engage cardiologists with activities and research, developing a think-tank to direct policy, and to create a virtual congress concept for improved information accessibility.

Further updates can be found in our congress review where we present some of the highlights of ESC 2016, including a look at the benefits of invasive imaging in percutaneous coronary intervention and a number of negative results that challenge conventional thinking. We also present a number of abstract reviews, where you will find summaries of some impactful presentations from the congress directly from the researchers themselves.



Invasive Imaging Improves Outcomes in Percutaneous Coronary Intervention

IMPROVED outcomes in percutaneous coronary intervention (PCI) have been achieved using an invasive imaging technique called optical coherence tomography (OCT) to visualise coronary arteries when treating acute coronary syndrome (ACS), according to a ESC press release dated 29th August 2016.

For the DOCTORS trial, 240 non-ST-segment elevation ACS patients were randomised 1:1 to standard fluoroscopy-guided PCI alone (the angiography group) or with the addition of OCT, in order to explore the procedural and functional implications of the latter.

Compared to standard angiography-guided PCI, OCT was found to be significantly more likely to reveal clinically relevant factors; for example, stent underexpansion in 42.0% versus 10.8% of patients, edge dissection in 37.5% versus 4.0%, and incomplete lesion coverage in 20.0% versus 17.0%, respectively.

OCT allowed clinicians to see more thrombi (69.0% versus 47.0%, p=0.0004) and calcifications (45.8% versus 9.0%, p<0.0001) prior to stent implantation. Thus, more frequent antiplatelet use occurred in the OCT group compared to angiography (53.3% versus 35.8%). Stent malapposition was identified in 32% of OCT patients, facilitating more frequent use of post-stent overinflation in the OCT group (43.0% versus 12.5%, p<0.0001) and a lower residual stenosis (7.0% versus 8.7%, p=0.01).

Along with procedural improvements, the trial highlighted positive functional outcomes. Fractional flow reserve (FFR) results were significantly better in the OCT group than the angiography group (0.94 versus 0.92, p=0.005). Measures of post-procedural FFR >0.90 were significantly higher in patients in the OCT group (82.5% versus 64.2%, p=0.0001). "The improvement in functional outcomes could translate into a clinical benefit in the longer term," concluded lead investigator of the trial Prof Nicolas Meneveau, Department of Cardiology, University Hospital Jean Minjoz, Besançon, France.

> The improvement in functional outcomes could translate into a clinical benefit in the longer term.

Although procedure time was increased by using OCT, as well as patient exposure to fluoroscopy and contrast medium, there was no increase in complications. Further prospective studies with clinical endpoints are required before considering the incorporation of OCT guidance as standard practice.

Non-Invasive Computed Tomography Guides Selective Invasive Coronary Angiography

COMPELLING evidence has displayed the significant benefits of using non-invasive coronary computed tomographic angiography (CCTA) to guide the selective use of invasive coronary angiography (ICA) in stable symptomatic patients with suspected coronary artery disease (CAD).

Investigators from the CONSERVE trial observed that this strategy was safe and less expensive than direct ICA, according to a ESC press release dated 29th August 2016.

"The message from the trial is that if we use CCTA as a gatekeeper to the catheterisation lab in stable symptomatic patients with suspected CAD, we will reduce costs with sufficient safety," commented Prof Hyuk-Jae Chang, Division of Cardiology, Yonsei University College of Medicine, Seoul, Republic of Korea.

In the randomised, controlled, multicentre trial, the patients (N=1,530) were randomised to direct versus selective invasive ICA, the latter of which was decided by physician referrals based on initial results of the CCTA. All the patients had indications for invasive angiography, based on current guidelines.

The computed tomography (CT)-guided strategy was associated with no variation in major adverse cardiovascular events (MACE), resulting in an 86% reduction in invasive procedures, which reduced costs whilst not affecting patient safety. The primary endpoint of 12-month MACE rates were 5% in both groups. The secondary endpoint of mean cardiovascular cost per patient was lower in the selective versus direct ICA arm ($2,883 versus $6,031).

> The message from the trial is that if we use CCTA as a gatekeeper to the catheterisation lab in stable symptomatic patients with suspected CAD, we will reduce costs with sufficient safety.

Prof Chang also argued that the significant reduction in invasive procedures is clinically important: "CT-guided strategy may uncouple the diagnosis-treatment cascade of ICA which promote[s] excess revascularisation and subsequently exposes patients to non-negligible risk related to invasive procedures."

These findings could therefore ensure that significant savings are made for healthcare systems in the future. Using Medicare costs, there was a $3,000 saving per person in the trial over 12 months. Based on these calculations, a potential $10 billion could be saved each year considering the 4.6 million catheterisations that take place.

DANISH Study Reveals Gap in Current Heart Failure Guidelines

ILLUMINATING new evidence has suggested that an implantable cardioverter-defibrillator (ICD) should not be used in all instances of systolic heart failure, revealing that current European and American guidelines may need updating. This is according to a ESC press release dated 28th August 2016.

Currently: "Prophylactic ICD implantation is a Class I recommendation in patients with heart failure and reduced left ventricular systolic function in both European and American Guidelines," explained Prof Lars Køber, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. However, this evidence is considerably weaker for non-ischaemic aetiology. The DANISH study indicated that in instances where a patient is suffering from non-ischaemic systolic heart failure, ICDs will not improve overall survival in comparison to the usual clinical care.

The study involved a total of 1,116 patients, 560 of whom were in the control group who received usual clinical care, consisting of guideline-recommended medication including beta blockers, renin-angiotensin inhibitors, and mineralocorticoid-receptor antagonists. The remaining 556 patients received an ICD. Across both groups, 58% of patients also needed cardiac-resynchronisation therapy.

The results of the study at a median follow-up time of 67.6 months showed no statistically significant difference when comparing the primary outcome of death from all causes, which occurred in 21.6% of ICD patients and 23.4% of the control group (hazard ratio [HR]: 0.87; 95% confidence interval [CI]: 0.68–1.12, p=0.28). Sudden death on the other hand occurred in 4.3% of the ICD patients and was almost double at 8.2% in the control group (HR: 0.50; 95% CI: 0.31–0.82, p=0.01). Device-related infection occurred in both groups.

Investigators of the study also pointed out the significance of age during the trial, determining that: "Patients younger than 68 years of age had a significant reduction in all-cause mortality if they received an ICD (HR: 0.64; 95% CI: 0.45–0.90, p=0.01), suggesting that younger patients may have a survival benefit with ICD implantation."

Wireless Cardiac Devices Reduce Financial Burden of Heart Failure

DIGITAL devices are innovating clinical procedures across the medical landscape. Remote monitoring (RM) of defibrillator therapy in heart failure (HF) patients was recently applied in order to explore its clinical and economic value according to a ESC press release dated 28th August 2016.

RM has previously been demonstrated to reduce the delay from cardiac event to clinical decision in HF patients, suggesting the potential for a further phase of study evaluating the outcomes of these devices. HF is common and imposes a financial weight at the level of both the individual patient and the healthcare system. In this respect, although the multicentre trial was underpowered to draw conclusions regarding its primary endpoint, the RM results illuminated some particularly relevant findings related to the use of healthcare resources.

Cardiology experts from over 140 countries

HF patients (N=917) were fitted with a biventricular defibrillator able to wirelessly transmit data. After 8 weeks patients were randomised, 455 patients were assigned standard in-office follow-up and 462 were scheduled for alternating remote and in-office checks. Despite an insignificant difference in primary endpoint at the median 24-month follow-up, the secondary outcomes proved insightful. HF imposes a financial weight on both the individual patient and the healthcare system, but through the alternation of follow-up procedure in the remote arm, the frequency of scheduled visits was reduced, resulting in 2-year savings of €2,899 per 100 patients (incidence rate ratio: 0.59, 95% confidence interval: 0.56–0.62, p<0.001).

"Healthcare resource utilisation for cardiovascular reasons was 38% lower in the remote versus the standard arm, and there was an estimated cost-saving that went along with that, both from the perspective of the healthcare system, but also in terms of personal patient travel costs," elucidated Prof Giuseppe Boriani, Cardiology Department, University of Modena and Reggio Emilia, Modena, Italy. Indeed, the individual 2-year travel cost savings were noted at an average of €145 per patient. Finally, although it was pointed out that real-world comorbidities may influence the relative impact of RM on these outcomes, there were no safety issues reported in this study.

Potential for Future Research Directions Following the HIJ-PROPER Trial

RESULTS from the HIJ-PROPER trial give potential research directions in the treatment of acute coronary syndrome (ACS) and dyslipidaemia with low-density lipoprotein (LDL) cholesterol-lowering medications. The study, which showed that treatment with a second-line cholesterol-lowering medication in addition to a standard statin did not significantly improve survival and other cardiovascular outcomes compared to statin treatment alone for these conditions, was presented in a ESC press release dated 29th August 2016.

The study randomised 1,734 patients with ACS and dyslipidaemia to either a combination of a statin (pitavastatin) plus a second-line, cholesterol-lowering drug (ezetimibe) aiming for an LDL level of ≤70 mg/dL, or to pitavastatin alone aiming for an LDL level of 90–100 mg/dL. The primary endpoint for the trial was a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, or revascularisation with percutaneous coronary intervention or coronary artery bypass grafting.

More intensive treatment was not associated with significantly better rates of any aspect of the primary endpoint (hazard ratio [HR]: 0.89, 95% confidence interval [CI]: 0.76–1.04, p=0.152) following 3-year follow-up. However, Dr Nobuhisa Hagiwara, Tokyo Women's Medical University, Tokyo, Japan, explained: "Although the results from our study were negative, they also suggest a potentially interesting direction for future research."

> “Although the results from our study were negative, they also suggest a potentially interesting direction for future research.”

A subgroup of patients with higher baseline levels (>2.2 µg/mL) of sitosterol, a cholesterol absorption marker, did gain significant benefit from receiving the intensive treatment course. This group had a significantly lower occurrence of the primary endpoint outcomes (HR: 0.71, 95% CI: 0.56–0.91, p=0.010). Currently, <30% of these higher-risk patients reach their target LDL cholesterol level when treated with a statin alone. This may be important as statins do not inhibit cholesterol absorption.

“We now think that inhibiting cholesterol absorption may be instrumental in reducing cardiovascular events in ACS patients with high cholesterol absorption. This subanalysis from the HIJ-PROPER trial suggests that combined inhibition of both cholesterol synthesis and cholesterol absorption may help us reduce cardiovascular events in these patients,” added Dr Haigwara.

Lower Cholesterol and Blood Pressure Reduces Cardiovascular Disease Risk

DRAMATIC reductions in the risk of developing cardiovascular disease could be achieved through the combination of slightly lower low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP) over a long period, as reported in a ESC press release dated 29th August 2016. Previous studies had shown that both LDL-C and SBP have causal and cumulative effects on the risk of cardiovascular disease, leading to the hypothesis that long-term exposure to lower LDL-C and SBP could be an effective prevention strategy.

Genetic scores were calculated for 102,773 individuals from 14 prospective cohort or case-control studies. These scores were based on inherited polymorphisms known to be linked with LDL-C or SBP and the number of alleles associated with raised LDL-C or SBP levels. Participants were separated into four groups: i) reference group; ii) LDL-C genetic score below the median; iii) SBP genetic score below the median; and iv) LDL-C and SBP genetic scores below the median. This enabled the researchers to analyse the cardiovascular risk associated with different genetic scores.

A composite of either coronary death, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularisation was the primary outcome, with 14,368 primary events recorded overall. The results showed that there was a 54.2% lower risk of the primary outcome in the lower LDL-C group, a 44.7% lower risk in the lower SBP group, and an 86.1% lower risk in the combined LDL-C and SBP group, compared with the reference group.

Lead investigator Prof Brian Ference, Wayne State University School of Medicine, Detroit, Michigan, USA, commented: “The results of our study confirm that cardiovascular disease is largely preventable and suggest that this prevention can be substantially simplified by focussing on programmes that promote long-

term exposure to the combination of both lower LDL and lower SBP." Future studies should focus on identifying for whom this early intervention would be most beneficial.

Short-Term Dual Antiplatelet Therapy: Is it Non-Inferior?

TREATMENT duration with dual antiplatelet therapy (DAPT), following the placement of a drug-eluting stent (DES), was under evaluation in a recent trial that set out to compare a shorter 6-month treatment course with a longer 18-month one.

For the study, 3,775 patients were enrolled with coronary artery disease or acute myocardial infarction who had undergone percutaneous coronary intervention and placement of a Nobori® bioabsorbable abluminal-coated stent. The cohort was randomised to receive DAPT consisting of aspirin (81–162 mg/day) combined with clopidogrel (75 mg/day) or ticlopidine (200 mg/day) for 6 or 18 months. Following an interim analysis, the study was terminated early, leaving 2,772 patients with a minimum follow-up of 18 months for scrutiny.

According to a ESC press release dated 28th August 2016, the primary outcome measured was the rate of net adverse clinical and cerebrovascular events (NACCE), including all-cause death and Q-wave or non-Q-wave myocardial infarction. The results showed that there was only a 0.46% difference in occurrence of NACCE between short-term and long-term DAPT treatment arms (1.92% versus 1.45%, respectively): the rate of bleeding events was similar (0.96% versus 0.73%, respectively) and the rate of stent thrombosis was identical. This led to the conclusion that the shorter period of DAPT was non-inferior to a longer duration of DAPT following DES placement.

However, trial investigator Prof Masato Nakamura, Toho University Ohashi Medical Centre, Tokyo, Japan, commented: "The results of the present study should be interpreted with caution before trying to draw firm conclusions." This is due to study limitations, including: the lack of adherence due to the non-double blinding of the trial, the lack of events resulting in an inadequate statistical power and wide non-inferiority margin, and the patient cohort potentially being unrepresentative of high-risk patients.

> "Based on these findings, a combination of short DAPT and a newer DES with bioabsorbable abluminal coating should be able to minimise the incidence of thrombotic events and bleeding complications simultaneously."

Despite these drawbacks, Prof Nakamura was confident in the results: "Based on these findings, a combination of short DAPT and a newer DES with bioabsorbable abluminal coating should be able to minimise the incidence of thrombotic events and bleeding complications simultaneously."

No Difference Between Prasugrel and Ticagrelor at 1 Month

FINDINGS from the PRAGUE-18 trial has shown similarities between the antiplatelet drugs prasugrel and ticagrelor in terms of safety and efficacy in patients with acute myocardial infarction and ST-segment elevation myocardial infarction (STEMI), according to a ESC press release dated 30th August 2016.

PRAGUE refers to a succession of academic randomised trials by the Cardiocenter of Charles University, Prague, Czech Republic, beginning in 2000.

The Hot Line study randomised 1,230 patients to treatment with either prasugrel (60 mg followed by 10 mg/day [reduced to 5 mg/day if >75 years or <60 kg]) or ticagrelor (180 mg followed by 90 mg twice a day) before primary percutaneous coronary intervention. Both treatments were to be taken for 1 year. The primary endpoint was defined as death, stroke, re-infarction, urgent target-vessel revascularisation, serious bleeding that required transfusion, and ongoing hospitalisation at 7 days. However, when an interim analysis indicated no difference in the rate of the endpoint between the two groups of patients (4.0% in the prasugrel group and 4.1% in the ticagrelor group, p=0.939), the study was terminated earlier than initially intended.

The secondary endpoint was defined as cardiovascular death, non-fatal myocardial infarction, or stroke within 30 days. Again, there was no difference in the rate of the secondary endpoint between the two groups (2.7% prasugrel group versus 2.5% ticagrelor group, p=0.864).

Prof Petr Widimsky, Cardiocenter of Charles University, Prague, Czech Republic, commented: "Our findings confirm previous indirect, non-randomised, comparisons of these two drugs, based on analyses of various registries." He added: "Thus, both drugs are very effective and safe and significantly contribute to the excellent outcomes of patients with acute myocardial infarction in modern cardiology."

For all patients, the final follow-up will be at 1 year, and the study will be completed in 2017.

"These study results offer more freedom to clinicians to select the antiplatelet agent added on top of aspirin for patients with STEMI who receive dual antiplatelet therapy," added Prof Widimsky.

No Benefit to Platelet Monitoring in Elderly Patients

INTERNATIONAL guidelines regarding testing platelet function in elderly patients following a heart attack have been challenged by the results of a recent study showing that the tests do not improve outcomes. The trial, according to a ESC press release dated 28th August 2016, is the first to examine platelet function testing in patients aged ≥75 years with a high risk of ischaemic and bleeding complications.

> "Platelet function monitoring led to a change of treatment in 44.8% of patients who were identified as being over or undertreated, yet this strategy did not improve ischaemic or safety outcomes."

For the ANTARCTIC study, 877 patients with acute coronary syndrome who had undergone coronary stenting were given the antiplatelet agent prasugrel (5 mg), of whom 435 were randomised to additional monitoring and dose adjustment where required. In this group, patients received the prasugrel dose for 14 days before undergoing a platelet function test on Day 14. Their medication was adjusted depending on the results of the test with further tests carried out on Day 28 if required. Alongside these patients, 442 were randomised to receive a standard therapy with no adjustment.

Composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, urgent revascularisation, and bleeding complication at 1-year follow-up were listed as the primary endpoints of the study, the rate of which was similar in both arms of the study. In the more closely monitored group, the rate was recorded at 27.6%, whereas in the control group 27.8% was recorded (hazard ratio: 1.003, 95% confidence interval: 0.78–1.29, p=0.98). The team similarly noted no significant difference between the two groups for the secondary endpoint, which comprised cardiovascular death, myocardial infarction, stent thrombosis, or urgent revascularisation. This was demonstrated in 9.9% of the monitored group and 9.3% of the control group.

"Platelet function monitoring led to a change of treatment in 44.8% of patients who were identified as being over or undertreated, yet this strategy did not improve ischaemic or safety outcomes," explained Prof Gilles Montalescot, Pitié-Salpêtrière Hospital, Paris, France. "I expect there will be adjustments of guidelines and practice in light of this."

Potential New Treatment Option for Refractory Angina

A POTENTIAL novel treatment for refractory angina has been exhibited in a study presented at ESC 2016. Lipoprotein apheresis was shown to significantly improve the primary endpoint of myocardial perfusion reserve, as measured by magnetic resonance imaging. The secondary endpoints included quality of life in patients with refractory angina with elevated levels of lipoprotein(a) (Lp[a]), in comparison to sham therapy.

"Angina, which is refractory to both medical therapy and revascularisation, is a debilitating condition that is increasing in frequency and there is a pressing need for novel treatments for these patients," explained lead investigator Dr Tina Khan, Royal Brompton and Harefield NHS Trust, London, UK, in a ESC press release dated 29th August 2016. There is also currently no effective pharmacologic treatment approved to treat raised Lp(a), which can be present in patients with refractory angina; however, lipoprotein therapy can effectively lower Lp(a) levels.

In the prospective, randomised, sham-controlled, blinded, cross-over study, 20 patients with refractory angina and elevated Lp(a) levels >500 mg/L were randomised to either weekly lipoprotein apheresis or sham treatments for 3 months before being crossed over for a further 3 months with a washout period of 1 month in between.

The primary outcome of myocardial perfusion reserve, measured with cardiac magnetic resonance imaging, increased from 1.45 to 1.93 with lipoprotein apheresis, with no significant changes following sham therapy. In addition, improvements were seen in the secondary endpoints after apheresis in comparison to sham. These were in carotid wall volume, distensibility, exercise capacity, and quality of life scores. There were also significant improvements in symptoms, as measured by the Seattle Angina Questionnaire (SAQ), such as physical limitation score (median change of +27.8 versus -4.2), and quality of life score (mean change of +25.8 versus +4.6).

"These findings suggest that lipoprotein apheresis provides significant clinical benefit to patients with refractory angina in the context of raised Lp(a), representing a much needed novel treatment option for this therapeutically challenging patient cohort," stated Dr Khan.

Non-Invasive Approaches Go Head-to-Head

THE PACIFIC trial, presented at this year's ESC Congress, is the first in its field to compare non-invasive coronary artery imaging techniques in order to determine which is best for coronary artery disease patients, according to a ESC press release dated 29th August. Evidence regarding the best course of action has previously been scarce and no real consensus currently exists among clinicians in both the USA and Europe.

The trial compared the most frequently used techniques to measure myocardial perfusion or coronary artery stenosis. Positron emission tomography (PET), single photon emission computed tomography (SPECT), and coronary computed tomography angiography (CCTA) went head-to-head.

> The results will definitely spark further research. There is always a lot of discussion whether we need to choose SPECT or PET as the initial functional test for our patients.

Initially, participants of the study (N=208) with suspected coronary artery disease underwent the gold-standard, invasive coronary artery angiography test. Participants then went on to receive PET, SPECT, and CCTA, as well as hybrid combinations of PET and CCTA, or SPECT and CCTA to enable a variety of assessments to be made.

The results of the study demonstrated that, at 85%, PET is significantly more accurate for diagnosing coronary ischaemia compared to SPECT (77%, $p<0.01$) and CCTA (74%, $p<0.01$). Regarding the sensitivity of these approaches, PET, SPECT, and CCTA were 87%, 57%, and 90%, respectively. Finally, the specificity between the approaches stood at 60% for PET, 84% for SPECT, and 94% for CCTA. Diagnosis was not enhanced by the hybrid techniques.

Dr Ibrahim Danad, Research Fellow, University Medical Center, Vrije University, Amsterdam, Netherlands, who presented the findings at this year's congress, signals the importance of such research stating that: "The results will definitely spark further research. There is always a lot of discussion whether we need to choose SPECT or PET as the initial functional test for our patients. I think we need to invest more in clinical PET imaging, which will be [the] future. It is more convenient for patients in terms of time, accuracy, and radiation dose."

YEARS Algorithm Reduces Need for Imaging of Pulmonary Embolism

SUSPECTED pulmonary embolism (PE) often requires computed tomography pulmonary angiography (CTPA) to verify whether a diagnosis can be made. However, CTPA exposes patients to radiation that can be harmful, and puts them at risk of contrast-induced nephropathy. A simple diagnostic algorithm, named YEARS, can now be used instead of CTPA in a large number of patients, according to a ESC press release dated 30th August 2016.

Dr Tom Van der Hulle, Leiden University Medical Center, Leiden, Netherlands, commented: "The advantage of the YEARS algorithm over existing algorithms is a 14% reduction in the need for CTPA imaging and with that, reduced potential for radiation-induced harm and overdiagnosis." The YEARS clinical decision rule includes a blood test which measures D-dimer (a protein produced by blood clots), and patients are evaluated according to clinical signs of deep vein thrombosis, haemoptysis, and whether the clinician considers PE to be the most probable diagnosis.

The YEARS study included 3,465 patients with a mean age of 53 years, 88% of whom were outpatients. The researchers used the algorithm to evaluate the patients, after which PE was excluded as a diagnosis and CTPA was unnecessary in 1,651 patients who showed no YEARS items and a D-dimer level <1000 ng/mL, or ≥1 YEARS item and a D-dimer level <500 ng/mL. CTPA was necessary for the remaining patients.

For those in whom PE was excluded, no treatment was given and they were followed-up over 3 months. Symptomatic venous thromboembolism presented in 0.43% of patients for whom PE was excluded using only the algorithm, and in 0.84% of patients for whom PE was excluded using CTPA.

> The advantage of the YEARS algorithm over existing algorithms is a 14% reduction in the need for CTPA imaging and with that, reduced potential for radiation-induced harm and overdiagnosis.

Dr Van der Hulle stated: "Using the YEARS algorithm, CTPA was not indicated in 48% of our patients at baseline, but this would have been only 34% of patients using the traditional algorithm." He added: "We expect that the YEARS algorithm can be easily implemented outside the participating study sites."

CHART-1 Investigators Hopeful for Future Trial Outcomes

RESULTS from a clinical trial testing a cardiopoietic regenerative therapy did not significantly improve outcomes in congestive heart failure patients, but may present critical insights leading into its second phase.

According to a ESC press release dated 28th August 2016, the CHART-1 trial (Congestive Heart Failure Cardiopoietic Regenerative Therapy) attempted to significantly improve outcomes by using bone marrow stem cells to repair the heart. However, the results indicated that there were no real differences between the benefits of using cardiopoietic cell therapy (involving the isolation of mesenchymal stem cells from the patient's own bone marrow) in comparison to a sham procedure.

A total of 271 patients were involved in the trial; 151 underwent the sham procedure and the remaining 120 were treated with the cardiopoietic cell approach. There were no significant differences at Week 39 when investigators compared factors such as all-cause mortality, worsening heart failure events, 6-minute walk distance, left ventricular end-systolic volume, ejection fraction, and Minnesota Living with Heart Failure Questionnaire total score.

Principal co-investigator Prof Jozef Bartunek, Cardiology Division, OLV Hospital, Aalst, Belgium, was nonetheless hopeful, stating that despite the neutrality of the results in the overall population, a subgroup analysis of patients with severe heart enlargement at baseline (diastolic volumes between 200 mL and 370 mL) had demonstrated some pleasing results: "Within a well-defined population, based on baseline heart failure severity, this therapy showed benefit. Lessons learned from CHART-1 will now provide the foundation for the design of the ensuing CHART-2 trial, which will target these patients." Additionally, investigators observed a modifying effect of treatment intensity, suggesting that greater benefit will be achieved at a lower number of injections. There were also no real differences in adverse clinical outcomes between the groups.

The CHART-1 trial may not have yielded the results expected, yet investigators are hopeful that ongoing analysis at 12 months will show more encouraging results, with the expectation that further trials will consider heart failure severity and therapeutic intensity in the future.

Intravenous Cardiac Stem Cell Therapy Offers Clinical Benefits

CULTURED stem cells have, for the first time, been used to treat non-ischaemic cardiomyopathy patients non-invasively, resulting in significantly improved measures of health status.

The Phase IIa multicentre trial, reported in a ESC press release dated 28th August 2016, investigated the safety and efficacy of intravenously administered ischaemia-tolerant mesenchymal stem cells (itMSCs) derived from healthy bone marrow. Cultured in a hypoxic environment, it was theorised that immune modulatory and anti-inflammatory properties of these cells would be amplified and that increased paracrine properties would facilitate improved cardiac function through a single infused dose of itMSC, reducing the need for direct myocardial injections.

The study was designed to randomise non-ischaemic cardiomyopathy patients to either intravenous itMSC therapy (n=10) or placebo (n=12), with a 90-day cross-over and 180-day follow-up. Three patients withdrew from the study, two prior to cross-over and one after. Although no significant difference was found in primary endpoints of all-cause mortality, all-cause hospitalisation, and adverse events, statistical improvements were found in a number of secondary endpoints.

Patients treated with infused itMSCs were able to walk 36.47 metres more than those in the placebo group, as measured by the 6-minute walk test (95% confidence interval [CI]: 5.98–66.97). Kansas City Cardiomyopathy Questionnaire scores also demonstrated functional and clinical improvements in the itMSC group, with scores of +5.65 (95% CI: -0.11–11.41, p=0.06) and +5.22 (95% CI: 0.70–9.74, p=0.02), respectively. Prof Javed Butler, Director of Division of Cardiac Medicine, School of Medicine, Stony Brook University, Stony Brook, New York City, New York, USA, concluded that the presentation of these results "demonstrated that a more convenient and less invasive infusion strategy is safe, well-tolerated, and shows improvements in multiple measurements of patient health status."

The next challenge will be to recruit larger cohorts to further explore the safety and efficacy of this treatment in both ischaemic and non-ischaemic patients, and particularly the potential of serial dosing as a means to conserve the enhanced stem cell properties and promote cardiac remodelling.

For the full interview with Prof Javed Butler at ESC click here.

Remote Monitoring Does Not Improve Outcomes for Heart Failure Patients

PATIENTS treated with a cardiac implantable electronic device (CIED) following heart failure do not benefit from remote monitoring of their condition, according to a ESC press release dated 28th August 2016. The results of a recent study were presented at this year's congress, showing that mortality rates and cardiovascular hospitalisations were no less frequent than with usual care.

The device, which stores data about a patient's condition for analysis by their physician, was put to the test in the recent REM-HF trial, in which 1,650 heart failure patients across nine British hospitals were randomised to receive either usual care (UC) or remote monitoring (RM). The mean age of the patients was 70 years, and each patient had one of three types of CIEDs suitable for use in remote monitoring.

Data from the patients selected for RM was accessed weekly and analysed by their healthcare professional, allowing them to offer advice regarding the patient's treatment and lifestyle, as well as recommending additional visits to the clinic, general practitioner, or accident and emergency when necessary. This was all in addition to their usual treatment routine.

The UC-selected patients underwent the routine remote management every 3–6 months in addition to the regular treatment cycle from their heart failure service. The researchers reported no significant difference between the two groups at the median follow-up point of 2.8 years. The primary endpoint of the study, the first event of death from any cause of unplanned hospitalisation for cardiovascular reasons, was seen in 42.4% of the RM group and 40.8% of the UC group (hazard ratio: 1.01; 95% confidence interval: 0.87–1.18; p=0.87).

The secondary endpoints of the study were listed as death from any cause, death from cardiovascular reasons, and unplanned hospitalisation. These were seen in a similar capacity to the primary endpoints in both groups. The researchers concluded that the results demonstrated no additional benefit to patients of RM over UC.

Effective Antidote for Anticoagulant Bleeding Discovered

AN EFFECTIVE ANTIDOTE has been discovered claiming to reverse life-threatening, anticoagulant-related bleeding. The ongoing ANNEXA-4 study has found that patients tolerate the antidote well and it has worked quickly according to a ESC press release dated 30th August 2016.

The results have shown that the drug andexanet alfa reduced anticoagulant activity by 89% within 30 minutes of being administered to patients with acute major bleeding who had been receiving a factor Xa (fXa) inhibitor. Effective haemostasis was also observed in the majority of patients after receiving the drug.

Included at this stage of the trial were 67 patients with a mean age of 77 years. Each required urgent reversal of acute major bleeding (gastrointestinal or intracranial) within 18 hours of receiving a fXa inhibitor. All patients initially received an andexanet bolus dosage over 15–30 minutes, followed by a 2-hour infusion. Patients went on to be assessed at baseline, end-of-bolus, at the end of 2-hour infusion, 4, 8, 12 hours after, and 3 and 30 days after infusion. The study was not randomised due to ethical reasons.

The assessment found an 89% decrease in anti-fXa activity among 47 patients from baseline to end-of-bolus for those exposed to rivaroxaban (n=26). A 93% reduction was also measured in those exposed to apixaban (n=20). After 12 hours from the initial administration of the antidote, clinical haemostatic efficacy was rated as 'good-to-excellent' in 79% of patients. Throughout the 30-day follow-up, 18% of participants suffered from thrombotic events.

Co-principal investigator Prof Mark Crowther, Chair of the Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Canada, explained the significance of the results stating: "Andexanet is the first specific agent designed for reversal of fX inhibitors. Although it has been shown to reduce anti-fXa activity in volunteers, until now we did not have experience in acutely bleeding patients. In these patients, andexanet reduced the anticoagulant effect of the factor Xa inhibitors and was associated with effective haemostasis in most patients."

New Clinical Decision Rule Validated for Women After Venous Thromboembolism

OVER half of women who report a first, unprovoked venous thromboembolism (VTE) could be spared the burdens, costs, and risks of lifelong anticoagulant therapy using a new clinical decision rule (CDR) tested in the REVERSE II trial.

The HERDOO2 rule is now the only validated CDR to assist in deciding which patients can discontinue anticoagulants after unprovoked VTE.

The HERDOO2 rule, presented in a ESC press release dated 30th August 2016, is named according to the four risk factors that must be considered in order to determine a patient's risk of VTE recurrence:

1. Hyperpigmentation, Edema, or Redness in either leg
2. D-dimer <250 μg/ml on anticoagulants
3. Obesity with BMI >30 kg/m^2
4. Older than age 65

The study enrolled 2,779 patients, men and women, with a mean age of 54.4 years and with a first, unprovoked VTE, following completion of anticoagulant therapy for between 5 and 12 months. The results at 1-year follow-up showed low-risk women, who had stopped anticoagulant therapy (n=591), had a 3% recurrence rate of VTE, compared to an 8.1% rate in high-risk patients who also stopped (n=323).

The HERDOO2 rule was prospectively validated as being able to identify whether

women were at a low risk of recurrence after an unprovoked VTE. Women who have one, or none, of the risk factors are considered low risk. Men, however, remain at high risk even if they too meet only one, or none, of these criteria.

Study investigator, Prof Marc Rodger, Chief and Chair of the Division of Hematology, Ottawa Hospital, Ottawa, Canada, reiterated the positive outcomes: "Since current consensus guidelines suggest anticoagulants should be continued indefinitely in all patients with unprovoked VTE and non-high bleeding risk, our results are potentially practice-changing."

Future studies will seek to answer the questions of whether indefinite anticoagulation is necessary in men, high-risk women, and post-menopausal women aged ≥50.

Alternative Anticoagulant Before Cardioversion Identified in Large Trial

THE LARGEST randomised clinical trial of anticoagulation for cardioversion in patients with atrial fibrillation (AF) has shown edoxaban to be a relatively safe alternative to conventional therapy for patients prior to electrical correction of their abnormal heartbeat.

The results of the ENSURE-AF trial indicate that edoxaban, a non-vitamin K antagonist (VKA) oral anticoagulant, has shown it is "an effective and safe alternative" to standard VKA therapy, according to a ESC press release dated 30th August 2016.

In the Phase IIIb study, 2,199 patients with non-valvular AF scheduled for electrical cardioversion after anticoagulation therapy were included from 239 different study sites across Europe and the USA. Edoxaban was administered once daily to 1,095 patients and the remaining 1,104 patients received the best conventional therapy (enoxaparin/warfarin) with dosage depending on patient characteristics. Cardioversion was performed on 988 (90.2%) of the patients receiving edoxaban and 966 (87.5%) of those receiving enoxaparin/warfarin.

The results showed a comparable rate of endpoint occurrence in both groups. The primary purpose of the study was to compare the incidences of the composite endpoint of stroke, systemic embolic event, myocardial infarction, and cardiovascular death at Day 28. The rate was measured at 0.5% among patients receiving edoxaban versus a rate of 1.0% among patients receiving enoxaparin/warfarin (odds ratio [OR]: 0.46; 95% confidence interval [CI]: 0.12–1.43).

The study also found a comparable rate in the primary safety endpoint of major and clinically relevant non-major bleeding events at Day 30, with a 1.5% rate in the edoxaban group and 1.0% in the standard therapy group (OR: 1.48; 95% CI: 0.64–3.55). Study investigator Prof Andreas Goette, Specialist in Internal Medicine and Cardiology, St. Vincenz-Krankenhaus hospital, Paderborn, Germany, explained that: "Edoxaban had similar rates of major bleeding and thromboembolism compared to well-managed, optimised enoxaparin/warfarin therapy. The results were similar whether transoesophageal echocardiography guidance was used or not, whether patients had received prior anticoagulation or not, and in patients with a broad range of associated comorbidities."

No Benefit in Intensive Medical Therapy for Heart Disease Patients

A PROACTIVE strategy in treating high-risk coronary artery disease (CAD) has been described as having no clinical benefit over conventional management by investigators from the ACTION study group according to a ESC press release dated 29th August 2016.

In high-risk CAD patients, an active strategy of detecting and treating asymptomatic multisite artery disease (MSAD) alongside a programme of intensive medical therapy had no significant differences in outcomes at 2-year follow-up compared to the approach of managing only symptomatic coronary and extra-coronary lesions.

No significant difference was found in the rates of all-cause mortality, rehospitalisation for an ischaemic event, or organ failure at 2-year follow-up by the AMERICA study.

The 521 CAD patients enrolled on the study were considered high-risk based on a diagnosed three-vessel disease within the past

6 months, or acute coronary syndrome in the past month (in patients ≥75 years old).

These patients were then randomised into groups: i) proactive prevention group (PAG), with a programme including revascularisation of asymptomatic MSAD when deemed necessary, alterations in lifestyle, and an aggressive pharmacological approach (n=263); or ii) a group receiving a conventional strategy (CSG) based on treatment of CAD and only symptomatic extra-coronary lesions (n=258).

Rates of the primary endpoint were not significantly different, with 44.9% in the PAG compared to 43.0% in the CSG. The outcome of the secondary endpoint, a composite of all-cause death, myocardial infarction, stroke, and any revascularisation, had similarly non-significant rates of 12.9% in the PAG and 13.6% in the CSG, while major bleeding events occurred at rates of 4.6% and 5.0% in the PAG and CSG, respectively.

"Possible explanations for the failure of the proactive strategy were that revascularisation of MSAD lesions was rare and that pharmacological treatment was close to optimal in both groups," explained lead investigator Prof Jean-Philippe Collet, Institut de Cardiologie, Hôpital de la Pitié Salpêtrière, Paris, France.

Stenting Deemed Unnecessary for One-Quarter of Myocardial Infarction Patients

AN ALTERNATIVE treatment process for heart attack patients has been identified, rendering the need for stenting to re-open patients' blocked arteries unnecessary in over one-quarter of patients. Instead, these patients can receive only antithrombotic medications, according to a ESC press release dated 30th August 2016.

Lead investigator Dr Ik-Kyung Jang, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, USA, commented: "If we can identify ACS patients with erosion without an invasive procedure, those patients may be triaged to a conservative therapy pathway instead of invasive catheterisation and stent implantation," following results from the EROSION study.

For 60% of patients, ACS is caused by plaque rupture, whilst for 25–44% of patients it is caused by plaque erosion, according to Dr Jang. The study used optical coherence tomography to identify plaque erosion and plaque rupture in 405 patients during coronary angiography. In 103 (25.4%) of the patients, plaque erosion was found to be the cause of ACS; 60 of these patients had a residual diameter stenosis of <70% on angiogram, thrombolysis in myocardial infarction (TIMI) flow grade of 3, and were stable, showing no symptoms.

These patients were given only antithrombotic medications, and stenting was considered unnecessary. They were treated with dual antiplatelet therapy, receiving aspirin and ticagrelor, as well as glycoprotein IIb/IIIa in 63.6% of patients.

The primary endpoint of the study was defined as a >50% reduction in the size of the clot. According to Dr Jang, the patients had a follow-up at 1 month, at which 47 of the 60 patients had met the primary endpoint and 22 of the patients had no clot at all. One patient died of gastrointestinal bleeding, and another showed no improvement in the stenotic artery at the 1-month follow-up. Generally however, clot volume decreased from 3.7 to 0.2 mm^3 and minimal flow area increased from 1.7 to 2.1 mm^2. Randomised controlled trials will be required to assess the long-term outcomes in these patients.

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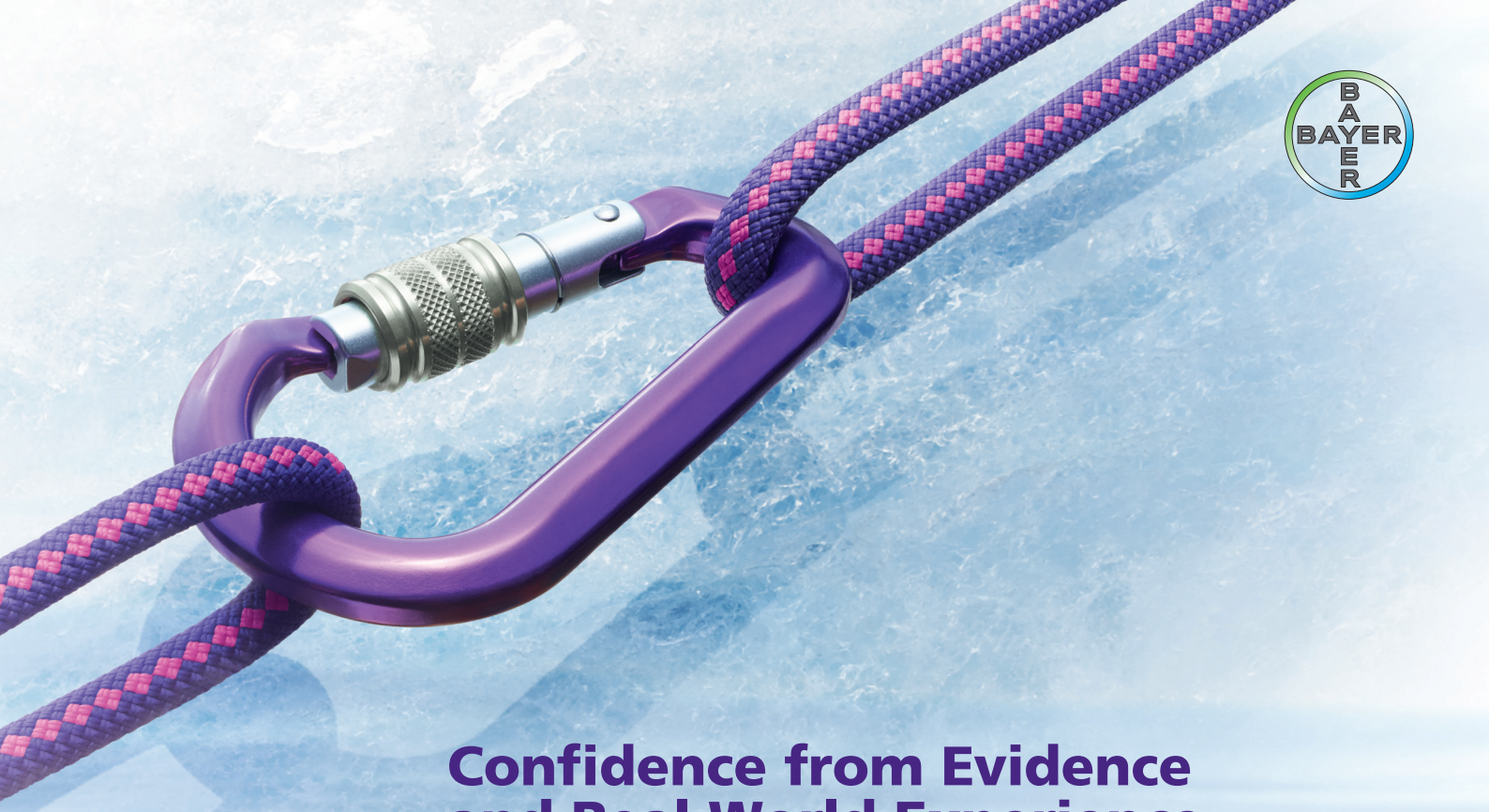

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NVAF, non-valvular atrial fibrillation; PE, pulmonary embolism; DVT, deep vein thrombosis; NOAC, non-vitamin K antagonist oral anticoagulant. Calculation based on IMS Health MIDAS Database: Monthly Sales June 2016. [a]Indications may vary by country.

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Classification for supply: Medicinal product subject to medical prescription. **Marketing Authorisation Holder:** Bayer Pharma AG, D-13342 Berlin, Germany **Further information available from:** xarelto.medinfo@bayer.com **Version:** EU/4

Xarelto 10 mg / 15 mg / 20 mg film-coated tablets (Refer to full SmPC before prescribing.) **▼ This medicinal product is subject to additional monitoring.**

Composition: *Active ingredient:* 10 mg / 15 mg / 20 mg rivaroxaban. *Excipients:* Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate, macrogol 3350, titanium dioxide (E171), iron oxide red (E172). **Indications:** *10 mg:* Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. *15 mg / 20 mg:* Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Special populations: Patients undergoing cardioversion: Xarelto can be initiated or continued in patients who may require cardioversion. **Contraindications:** Hypersensitivity to the active substance or any of the excipients; active clinically significant bleeding; lesion or condition if considered a significant risk for major bleeding; concomitant treatment with any other anticoagulants except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C; pregnancy and breast feeding. **Warnings and Precautions:** Clinical surveillance in line with anticoagulation practice is recommended throughout treatment. Xarelto should be discontinued if severe haemorrhage occurs. Increasing age may increase haemorrhagic risk. *Not recommended:* in patients with severe renal impairment (creatinine clearance <15 ml / min); in patients receiving concomitant systemic treatment with strong concurrent CYP3A4- and P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; in patients with increased bleeding risk; in patients receiving concomitant treatment with strong CYP3A4 inducers unless the patient is closely observed for signs and symptoms of thrombosis; *not recommended due to lack of data:* in patients below 18 years of age, in patients concomitantly treated with dronedarone. For 15 mg / 20 mg only: in patients with prosthetic heart valves, in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. *Use with caution:* in conditions with increased risk of haemorrhage; in patients with severe renal impairment (creatinine clearance 15 – 29 ml / min) or with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly with medicinal products affecting haemostasis; when neuraxial anaesthesia or spinal / epidural puncture is employed. For 15 mg / 20 mg only: specific dose recommendations apply for patients with moderate to severe renal impairment and in case of DVT / PE-patients only if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT / PE. In patients at risk of ulcerative gastrointestinal disease prophylactic treatment may be considered. Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations. Xarelto contains lactose. **Undesirable Effects:** *Common:* anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, gastrointestinal tract haemorrhage, gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous and subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage (menorrhagia *very common* in women < 55 years treated for DVT, PE or prevention of recurrence), renal impairment, fever, peripheral oedema, decreased general strength and energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Uncommon:* thrombocythemia, allergic reaction, dermatitis allergic, cerebral and intracranial haemorrhage, syncope, tachycardia, dry mouth, hepatic function abnormal, urticaria, haemarthrosis, feeling unwell, increases in: bilirubin, blood alkaline phosphatase, LDH, lipase, amylase, GGT. *Rare:* jaundice, muscle haemorrhage, localised oedema, bilirubin conjugated increased, vascular pseudoaneurysm. *Frequency not known:* compartment syndrome or (acute) renal failure secondary to a bleeding. *Post-marketing observations (frequency not assessable):* angioedema and allergic oedema, cholestasis and hepatitis (incl. hepatocellular injury), thrombocytopenia.

Classification for supply: Medicinal product subject to medical prescription. **Marketing Authorisation Holder:** Bayer Pharma AG, D-13342 Berlin, Germany **Further information available from:** xarelto.medinfo@bayer.com **Version:** EU/5

References: 1. Patel M.R., Mahaffey K.W., Garg J. *et al.* Rivaroxaban versus warfarin in non-valvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883–91. **2.** Camm J., Amarenco P., Haas S. *et al.* XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J.* 2016;37(14):1145–53. **3.** Tamayo S., Peacock F., Patel M. *et al.* Characterizing major bleeding in patients with non-valvular atrial fibrillation: a pharmacovigilance study of 27,467 patients taking Rivaroxaban. *Clin Cardiol*. 2015;38(2):63–8. **4.** Prins M.H. Lensing A.W.A., Bauersachs R. *et al*. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thrombosis J.* 2013;11(1):21. **5.** Ageno W., Mantovani L.G., Haas S., *et al.* Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. *Lancet Haemat.* 2016;3(1):e12–21. **6.** IMS Health MIDAS Database: Monthly Sales June 2016. **7.** Xarelto® (rivaroxaban). Summary of Product Characteristics as approved by the European Commission.

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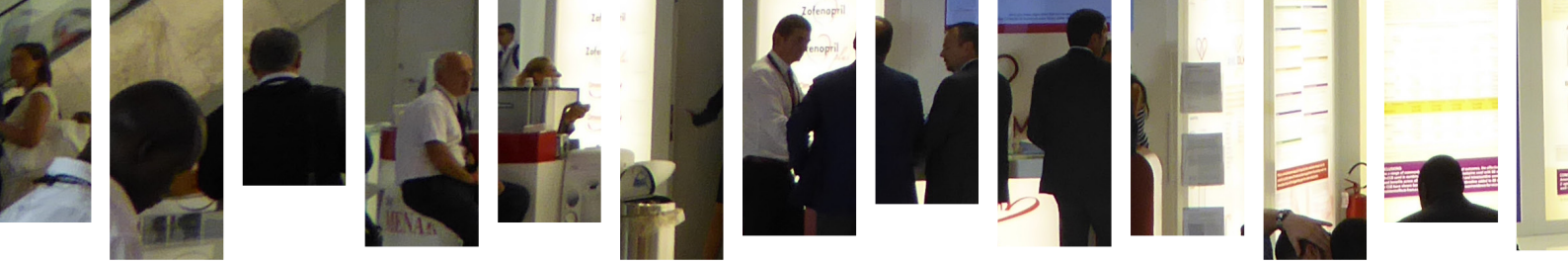


Giuseppe Biondi Zoccai

Assistant Professor, Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy.

Q: What specific areas of cardiology are you currently researching and what insights do you hope to achieve from doing so?

A: My main focus currently is on the role of advanced biostatistical methods to better understand large patient datasets, the modulation of inflammation to improve post-infarction cardiac remodelling, and cardiac regenerative therapy. The latter two indeed hold the promise of modifying pathophysiologic responses to reduce detrimental cardiovascular processes and support innate regenerative processes.

Q: In previous research, you have highlighted the common issue of underuse, non-compliance, and cessation of aspirin despite its benefits in the prevention of cardiovascular disease. Do you feel that improvements have since been made in tackling this issue, such as an increased awareness among both patients and clinicians?

A: There have been improvements in defining and tackling this apparently minor but clinically crucial issue. However, patients and physicians still have a long way to go to understand how even minor issues of non-compliance may translate into substantial morbidity and mortality burdens.

Q: Are there any other treatments for cardiovascular disease that are currently experiencing these same issues of mismanagement? How can these issues be overcome?

A: The issue with cardiovascular medicine is, to date, mainly with inappropriate care (i.e. misuse), underuse, and non-compliance. We need to maintain individualised decision-making for patients and physicians but also provide a formal framework to support best practices in prescribing and not prescribing and adhering to specific interventions and drugs.

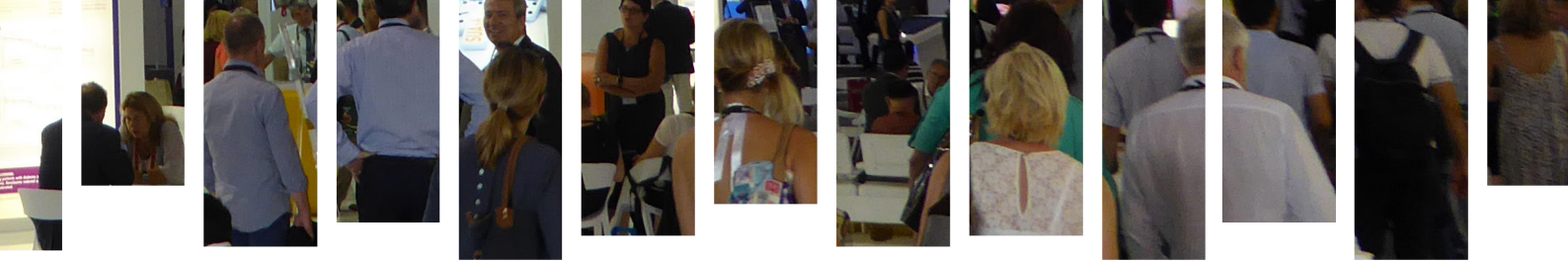
Q: How might the use of network meta-analysis have a positive impact on clinical decision-making? What other new methods are you employing in evidence synthesis?

A: Network meta-analysis currently represents the zenith of evidence synthesis; being able to summarise data from different randomised trials focussing on the same disease and a similar class of competing interventions (see for instance https://books.google.it/books?id=S3J8oAEACAAJ). Accordingly, it can provide an innovative yet precise framework to identify the most effective, safe, and cheap intervention for a given condition. The future, in my opinion, lies in umbrella reviews (i.e. overviews of reviews). They combine different competing treatments as well as complementary ones for a given condition and can also be used to provide statistical models identifying the best treatment combination or algorithm (see for instance https://books.google.it/books?id=wDeFCwAAQBAJ).

Q: In your opinion, are health institutions able to adequately apply these statistical methods in decision-making for the treatment of cardiovascular disease, or do potential obstacles, such as the ability to collect and analyse extensive amounts of valid data, still need to be overcome?

A: The main barrier to optimal use of modern approaches to big data lies in the technological frameworks and the work routine. Self-learning systems can easily be developed and applied but this needs awareness and willingness to adopt and follow them. We still have a long way to go in this field.

Q: Do you anticipate in the near-future any biotechnology improvements or innovations, in regards to data-collection, that will make these approaches more prevalent?



A: The combination of biometric data, big data from smartphones or smartwatches, implanted devices, and biologic parameters will enable more precise characterisation of patient conditions, and thus more accurate personalisation of diagnosis, risk-stratification, and treatment.

Q: Please tell us about your role in, and motivation for your involvement in the founding of the www.metcardio.org website. What impact do you feel this website has had on the use of meta-analysis and evidence-based medicine training in cardiology?

A: At first I felt there was a need for a relatively informal website devoted to cardiovascular meta-analysis, so this is the goal I had when I devised the website. Now, I actually only rely on it as a repository for educational materials and statistical tools for researchers interested in cardiovascular medicine.

Q: What advice do you have for practitioners and trainees working within the field of cardiology?

A: Try to keep abreast of all novelties and developments, remember that everything you learn during training will be obsolete in 10 years or less, maintain humility, and always work as a team in both research and clinical practice.

Rainer Wessely

Center for Cardiovascular Medicine (CIKA), Cologne; Professor of Medicine,
University of Technology Munich and Fresenius University of Applied Sciences, Cologne, Germany.

Q: What was your main motivation for specialising in cardiovascular medicine?

A: Cardiovascular medicine has been very successful within the last few decades. We have managed to decrease mortality and morbidity significantly. I like the combination of medical therapy with a growing field of cardiac and peripheral interventions to significantly decrease morbidity as well as mortality, and it is not over yet. We keep on refining existing treatments and developing novel efficient therapies on a continuous basis.

Q: What specific areas of cardiovascular disease are you currently exploring in your research and what insights do you hope to gain from doing so?

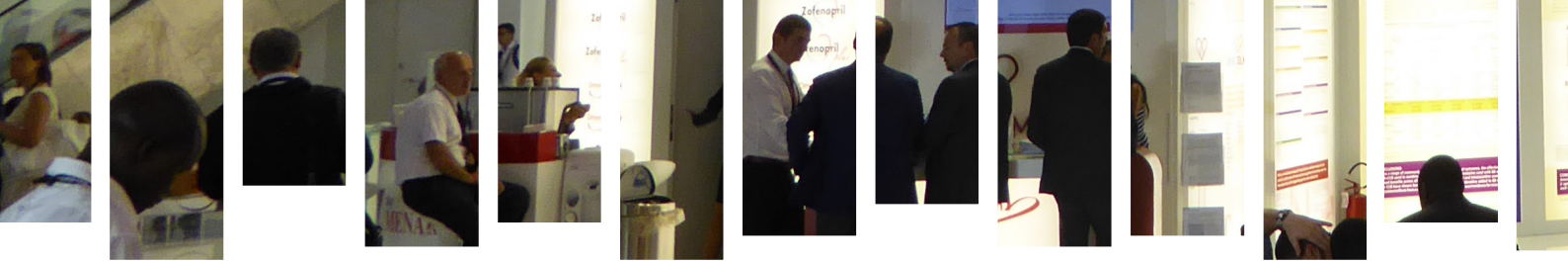
A: My main interest encompasses interventional cardiology and viral cardiomyopathy as well as contrast-induced acute kidney injury. We hope to improve the long-term outcome with ongoing research in these pivotal areas of cardiovascular medicine.

Q: Are there any emerging risk factors of cardiovascular disease that you feel are likely to continue to grow in significance? What steps can be taken to lessen patients' exposure to these risks?

A: We should continue to raise more awareness of fairly novel risk factors such as air pollution, sleep apnoea disorders, and vitamin D deficiency, amongst others. For myself, I am very much involved in raising the awareness that patients with cancer and chronic kidney disease face a considerable cardiac risk. A tight interaction between specialists from other fields that are primarily treating these patients is critical.

Q: Do you anticipate any innovations in therapeutic drugs within the next few years that will have a significant impact on the treatment of cardiovascular disease?

A: I hope that we will see, in particular, pharmacologic agents that will help us to improve the outcome of heart failure, as well as anti-arrhythmic drugs that can be safely administered



without significant side effects, particularly in patients suffering from atrial fibrillation and ventricular tachyarrhythmias. I am sure we will also witness an improvement of drugs primarily targeting other cardiovascular diseases as well as improved pharmacological treatments of primarily non-cardiac diseases that increase the risk of cardiac events, such as diabetes.

Q: What advances in cardiovascular medicine, such as technological developments or improvements in care-giving, do you believe would provide a significant benefit for the treatment of patients?

A: I guess we should probably rethink our long-lasting tendency toward further specialisation as it is of key interest for the patient that they are holistically treated by an experienced cardiologist, since cardiovascular disease is often complex and not the mere addition of pleiotropic diseases of the heart. We have to move on with our efforts to permanently improve interventional treatment options in order to decrease the need for procedures that are associated with an elevated risk of side effects.

Q: With the increasing clinical relevance of stem cell therapy across many areas of medicine, do you expect its use to become increasingly adopted in clinical practice?

A: In theory, stem cell therapy makes sense and has a strong potential. However, as with many novel treatment options such as gene therapy and others, we need first of all to understand the basic science, which could then help to evolve translational treatment strategies. To hop into a clinical trial without even knowing what is done on a molecular and cellular basis is counter-productive and could even harm the patient. In addition, clinicians considerably lose interest in new methodologies that have potential.

Q: What has been the proudest achievement of your career to date? What specific goals do you hope to achieve in your future work?

A: This is an easy and difficult question at the same time. I am proud that I have the opportunity to be part of a cardiovascular society helping me to bring patients the best current treatment strategies. Our enduring research regarding drug-eluting stents has been supported by the fact that mTOR inhibitors, such as everolimus and sirolimus, are the drugs of choice and that polymer-free coating is a valid option for patients suffering from coronary artery disease. We hope to continue this research in order to further improve outcomes.

Carl J. Lavie

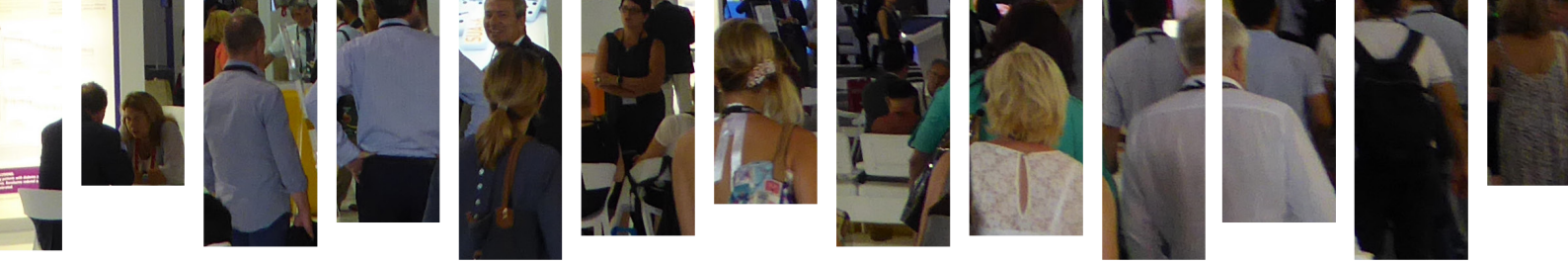
Medical Director, Cardiac Rehabilitation and Prevention, and Director, Stress Testing Laboratory, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, Louisiana, USA.

Q: What first brought you to the field of cardiovascular diseases? Was there an underlying motivation that still remains today?

A: Cardiovascular disease (CVD) is the leading cause of death in the USA and throughout the world.

Q: You have previously written on the 'obesity paradox' in cardiovascular disease in your ground-breaking book *The Obesity Paradox*. What is the essence of this concept, and what progress do you feel has since been made in our understanding and approach to this topic?

A: Obesity worsens most of the CVD risk factors and increases the risk of most CVD. However, of cohorts with established CVD, those who are overweight and obese tend to have a better



prognosis. As in most people, especially CVD, fitness predicts prognosis much more so than weight.

Q: What research are you currently working on? What do you hope it will lead to?

A: I publish approximately 1.7 papers per week, so the list is long, including cardiac rehabilitation, exercise, physical activity, fitness, psychological risk factors, left ventricular geometry, anti-thrombotic therapies, and many more topics. A recent list may be found on PubMed by searching 'Lavie C'.

Q: Regarding the role of fitness and exercise in cardiovascular health, do you think governments, doctors, and public health authorities are advising the public to undertake enough exercise to be able to maintain good cardiovascular health?

A: Yes, but most people are not following the advice. Schools also need to ensure an increase in the physical activity of children.

Q: What do you think will be the biggest development in cardiology within the next 5 years?

A: Transcatheter aortic valve replacement and other percutaneous valve procedures, as well as PCSK9 inhibitors.

Q: What are some of the biggest challenges currently being faced in cardiology research?

A: Funding, as in the USA many universities are reluctant to take much money from industries and the National Institutes of Health (NIH), American Heart Association (AHA), and so on do not have enough available funds, especially for young researchers.

Q: What has been the proudest achievement in your career so far?

A: Being able to combine full clinical loads with a high level of academic work, giving 2–3 lectures per week, publishing 1.5–2 papers per week, writing 3 books, being the editor of a journal, associate editor of several others, and serving on nearly 25 editorial boards, either personally reviewing or handling nearly 25 new manuscripts per week for all of my journals.

Pierfrancesco Agostoni

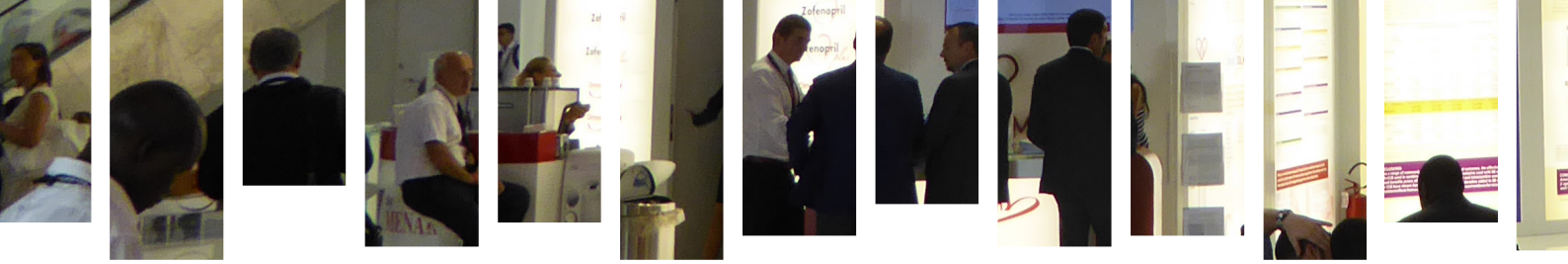
Interventional Cardiologist, Department of Cardiology, St. Antonius Hospital, Nieuwegein, Netherlands.

Q: What led you to a career as an interventional cardiologist?

A: During my medical studies I was attracted by surgical specialties, but I found that surgeons were too focussed on the pure technical aspect of their activities with poor focus on the global care of the patient. Medical disciplines were, on the other hand, very much focussed on the global care of the patient (medications, lifestyle, follow-up) but doctors could not fix major problems as they could not operate. I found in interventional cardiology the possibility to join the best of two worlds, in medicine and surgery. Interventional cardiologists are surgeons with a medical mind (or doctors with a surgical mind…).

Q: You have worked in several institutions across Europe. How do you feel cardiology practice varies across these countries and what more do you think can be done to standardise care?

A: I think that the overall quality of care in the countries where I worked (Italy, Belgium, Netherlands) is high as all the institutions offer a high level of care. Moreover, all countries where I worked, due to their social system, offer medical care to everyone and this is very valuable from an 'ethical' perspective. I think the next step to improve care and standardise practice would be to collect outcomes of our care and make it public. Value-based healthcare is the way to go. We are currently implementing this in the Netherlands by sharing outcomes among all heart centres. The project



is called 'Meetbaar Beter', (roughly translated as: 'Better measurable').

Q: What do societies such as the European Society of Cardiology (ESC) and European Association of Percutaneous Cardiovascular Interventions (EACPI) offer you, and how do they aid your clinical practice?

A: These societies are crucial to disseminate proper medical culture. They lead the way cardiologists and interventionalists work in their routine practice. Focus should be on research, education, and networking and I am convinced the leading authorities of these associations are doing great work. If I were to make a suggestion to the ESC and EAPCI, I believe it would be worthwhile to bring an initiative such as 'Meetbaar Beter' to a European level.

Q: What developments do you hope to see in the field of cardiology in the next few years?

A: As I mentioned before, I think a major focus will be to optimise the quality of our care. The possibilities we have in cardiology are huge, however we are not always good enough to implement the right decision and the right intervention for the right patient. I believe that if we were able to properly collect data on our results and share them with other colleagues in our institution and in our environment (at a regional, national, and European level), this would definitely lead to improved care. We do not only have to show that we are able to perform some kind of treatment, we need to prove it with numbers and figures. The challenge will be to find the right outcomes to collect in order to prove the value of our actions.

Q: What are the biggest challenges facing cardiologists at the moment?

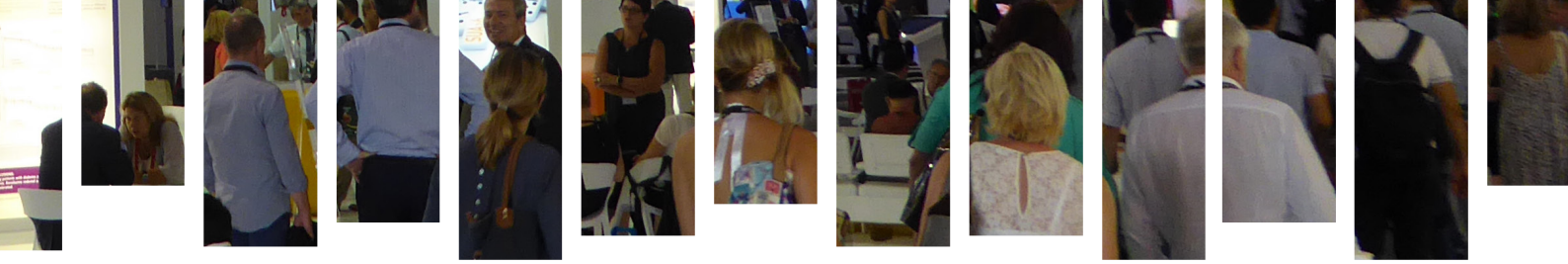
A: The are several major challenges. Unfortunately, economical restraints are definitely leading these challenges. This is particularly true for innovation. New therapies are difficult to implement in clinical practice because of their high costs. This can lead to disappointment for the motivated physicians.

Q: What are you most proud of in your career so far and why?

A: On a personal level I am proud of the fact that I never needed to apply for a job, I was always (up to now) asked to join a new group. I believe the huge amount of time (in the evenings and weekends, besides the routine working hours) spent during my training in improving my skills in the catheterisation laboratory, in research, in education, in expertise, and so on, paid back in this way. Furthermore, I was lucky I could always work with a group of friends from the beginning as a medical student and with these friends we could build up a nice and productive network. I am very proud of them and of being part of this network. Finally, I am proud of my first achievements, mainly in the field of interventional cardiology, of being able to test and use several devices as one of the first operators in Europe. I love innovation and I love changes, so I am very keen to try new devices and solutions.

Q: What research are you currently working on? Where do you hope it will lead?

A: My major focus is currently refractory angina pectoris. First, I believe a large part of patients with refractory angina have untreated chronic total occlusions (CTO). I am currently trying to spread in Europe the 'hybrid approach' to CTO. This is a systematic approach to CTO where you have four different strategies (antegrade lumen to lumen, antegrade dissection re-entry, retrograde lumen to lumen, and retrograde dissection re-entry), you choose the strategy with the highest chance to success according to the type of CTO you are facing, but you switch to another strategy if the previous failed. I am trying to combine this approach with the radial approach for intervention, developing a 'minimalistic hybrid approach' concept (the idea would be to maintain a large success rate in CTO limiting as much as possible the discomfort and the risks for the patient. The radial approach is well known to reduce discomfort and reduce risks as compared to the femoral approach, however according to others the technical feasibility of CTO procedures is reduced



by the radial approach. Second, in cases of patients who are symptomatic for refractory angina but do not have a CTO or the attempted CTO failed, new techniques such as the coronary sinus reducer have been developed to alleviate symptoms in this category of patients. A second part of the focus of my research is exactly this one: use the device, understand which kind of patient benefits the most from it, and understand its mechanism of action.

Q: What advice would you give to medical students who are considering a career in interventional cardiology?

A: This is my advice:

- Do not focus only on the clinical activities in the catheterisation laboratory but also try to develop research skills
- Work together with as many operators as possible and pick up the best out of each of them
- Try to spend some time in a core lab to increase analysis skills (such as quantitative coronary angiography, intravascular ultrasound, or optical coherence tomography analysis)
- Be 'severe' with yourself in case of complications (start from the thought that: "a complication is your fault unless..."), try to understand what happened and what you could improve in order to avoid a complication, share complications (and not successes) with colleagues, follow even more closely patients in whom a complication occurred and be ready to assume your responsibilities in case of mistakes
- Mainly, be ready to work very, very hard. It will pay back at a certain point

INTERPRETING FINDINGS WITH NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN ATRIAL FIBRILLATION: COLLECTIVE VIEWS ON DATA FROM SEMINAL STUDIES TO PRESENT IN CLINICAL PRACTICE

This symposium took place on 28th August 2016 as a part of the European Society of Cardiology (ESC) Congress, in Rome, Italy

Chairpersons

Jafna L. Cox,[1] Christoph Bode[2]

Speakers

Manesh R. Patel,[3] Eric D. Peterson,[4] Peter Verhamme,[5] Jafna L. Cox[1]

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3. Associate Professor of Medicine, Director of Interventional Cardiology, Duke University Health System, Durham, North Carolina, USA
4. Professor of Medicine, Director, Duke Clinical Research Institute, Durham, North Carolina, USA
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Disclosure: Prof Cox is an advisor/consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. He is also a speaker/speaker's bureau member for, and has received clinical research grants from, Bayer. Prof Bode is an advisor/consultant and speaker/speaker's bureau member for Bayer, Daiichi Sankyo, and MSD. He has also received clinical research grants from Bayer, Medtronic, MSD, and Sanofi. Prof Patel has received research funding from Janssen, AstraZeneca, Maquet, HeartFlow, CSI, and NHLBI, and has received consultancy/advisory board fees from AstraZeneca, Bayer, Janssen, and Genzyme. Prof Peterson has received research funding from Janssen and has received consultancy fees from Janssen, Bayer, Boehringer Ingelheim, Sanofi, AstraZeneca, Merck, Valeant, and Signal Path. Prof Verhamme provides honoraria and research support for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Ionis Pharmaceuticals, Leo-Pharma, Pfizer, and Sanofi.
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MEETING SUMMARY

Clinical trials show that non-vitamin K antagonist oral anticoagulants (NOACs) have good efficacy-safety profiles relative to warfarin across a broad spectrum of patients with non-valvular atrial fibrillation (NVAF). These findings are currently being confirmed for rivaroxaban through real-world evidence, with results from these studies consistent with results from Phase III randomised controlled trials (RCTs). Of all the NOACs, rivaroxaban currently has the most extensive real-world experience across different data sources (prospective and retrospective registries, database analyses, and prospective studies). Anticoagulant-related bleeding is still a concern amongst clinicians, however awareness of patient characteristics and other factors that can increase bleeding risk can assist in the proactive and effective management of bleeding episodes. Particularly, in atrial fibrillation (AF) patients with renal impairment who have an incrementally higher risk of bleeding and stroke, administration of NOACs versus vitamin K antagonists (VKAs) is beneficial. When dosed appropriately, NOACs such as rivaroxaban are effective in patients with renal impairment and offer an alternative to warfarin, with increased efficacy and decreased risk of critical bleeding events.

From Large-Scale Study to Larger-Scale Practice: How do Real-World Findings for Non-Vitamin K Antagonist Oral Anticoagulants Stack Up?

Professor Manesh R. Patel and Professor Eric D. Peterson

Results from RCTs are not always mirrored by evidence from real-world studies, which are inclusive of a more varied clinical setting and have a diverse patient population(s) more reflective of routine clinical practice.[1] Often, results reported in RCTs can depend upon the selection of the patient population studied; for example, in four trials investigating the use of NOACs, ARISTOTLE,[2] RE-LY,[3] ENGAGE AF,[4] and ROCKET AF,[5] estimation of stroke risk in AF using the $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, or transient ischaemic attack) score system, found that the patient populations in these studies had varying $CHADS_2$ scores. In ARISTOTLE,[2] RE-LY,[3] and ENGAGE AF,[4] 30%, 32%, and 53% of AF patients had a $CHADS_2$ score of 3–6, respectively; in contrast the ROCKET AF trial,[5] in which 87% of patients had a $CHADS_2$ score of 3–6, indicated that AF patients had a higher risk of stroke than patients in the other RCTs. The differences in patient characteristics across these trials, particularly in risk factor profiles, can make comparing trial outcomes for NOACs challenging. Data from two large registries, GARFIELD-AF[6] and ORBIT-AF,[7,8] which enrolled patients across the globe, demonstrated important differences between demographics of the AF population treated, particularly with regard to $CHADS_2$ scores.

A meta-analysis of Phase III trials from all four licenced NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) has shown that NOACs as a group deliver a greater benefit than risk, and are associated with significant reductions in haemorrhagic stroke (with a strong trend towards lower rates of ischaemic stroke), all-cause mortality (with a trend towards lower rates of myocardial infarction), and intracranial haemorrhage (ICH) when compared with warfarin therapy, although they also demonstrate an increased risk of gastrointestinal (GI) bleeding (Figure 1).[9] The meta-analyses reported the relative efficacy and safety of these NOACs as consistent across a wide range of AF patients,[9] but it is important to note that the usual limitations of meta-analyses mean that the efficacy and safety of the individual NOACs cannot be reliably compared.

In the real-world, prospective, observational XANTUS study, patients treated with rivaroxaban for stroke prevention in AF had low rates of both stroke (events per 100 patient-years: 0.7; 95% confidence interval [CI]: 0.5–0.9) and major bleeding (events per 100 patient-years: 2.1; 95% CI: 1.8–2.5),[10] reassuringly reflecting the safety profile observed in clinical trials as well as demonstrating effectiveness. The rate of stroke and major bleeding with rivaroxaban was also low across the Dresden NOAC and US Department of Defence real-world studies, consistent with results from ROCKET AF, although it must be noted that the mean $CHADS_2$ score was also lower in these real-world studies which may have contributed to the lower event rates.[5,10-12] Another recently published retrospective database analysis, the REVISIT-US study, compared the effectiveness and safety of rivaroxaban and apixaban relative to with warfarin in NVAF.[13] While both rivaroxaban and apixaban significantly reduced ICH versus VKAs ($p<0.05$), only rivaroxaban was associated with a non-significant decrease in ischaemic stroke versus warfarin, whereas for apixaban versus warfarin there was a non-significant increase in ischaemic stroke observed.[13]

Large-scale registry data show that oral anticoagulants in general are underused in those patients who stand to benefit the most from them. The underuse of anticoagulant therapy has been reported in the aforementioned GARFIELD-AF registry, where higher-risk patients ($CHADS_2$ score ≥2) were generally under-treated with 38% not receiving anticoagulant therapy, placing them at a higher risk of stroke.[6] Conversely, the same study found that 42.5% of low-risk patients ($CHADS_2$ score 0) were generally over-treated.[6] Although observational study of patients in community clinical practice can provide important data, limitations of such a study include enrolment or sampling biases and reporting bias, which may not give a true account of over versus under-dosing. An analysis from the ORBIT AF registry describes the proportion of patients on warfarin who had stable international normalised ratio (INR) values over an 18-month period.[14] The study found that only 26% of patients had stable INR values (2.0–3.0) over a 6-month baseline period and of these only 34% had stable INRs the following year; an indication that predicting INR stability on warfarin therapy is a difficult task for clinicians.

	Pooled NOAC (events)	Pooled warfarin (events)	Relative risk (95% CI)	p-value
Efficacy				
Ischaemic stroke	665/29,292	724/29,221	0.92 (0.83–1.02)	0.10
Haemorrhagic stroke	130/29,292	263/29,221	0.49 (0.38–0.64)	<0.0001
Myocardial infarction	413/29,292	432/29,221	0.97 (0.78–1.20)	0.77
All-cause mortality	2,022/29,292	2,245/29,221	0.90 (0.85–0.95)	0.0003
Safety				
Intracranial haemorrhage	204/29,287	425/29,211	0.48 (0.39–0.59)	<0.0001
Gastrointestinal bleeding	751/29,287	591/29,211	1.25 (1.01–1.55)	0.043

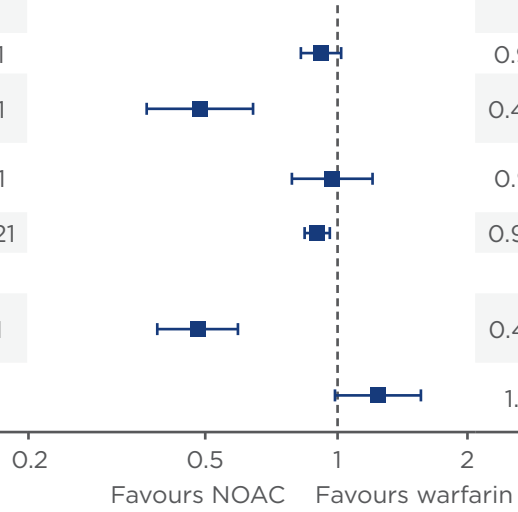

Figure 1: Anticoagulants deliver greater benefit than risk, NOACs more than VKAs.[9]
NOACs: non-vitamin K antagonist oral anticoagulants; CI: confidence interval; VKAs: vitamin K antagonists.

The appropriate dosing of the approved NOACs is an important topic and the criteria for dose adjustment of NOACs varies across RCTs. For example, in ROCKET AF, dose adjustment from 20 mg once daily to 15 mg once daily was made in 20.7% of patients, on the basis of renal insufficiency as measured by creatinine clearance (CrCl).[15] In ENGAGE-AF[9,16] and ARISTOTLE,[2] dose adjustments were made throughout the trial (ENGAGE-AF) or at random (ARISTOTLE) on one of a number of criteria (ENGAGE: dose adjustments at random or throughout for ≥1 of the following: CrCl 30–49 mL/min, weight ≤60 kg, strong P-glycoprotein [P-gp] inhibitors; ARISTOTLE: dose adjustments at random if ≥2 of the following: age ≥80 years, weight ≤60 kg, creatinine ≥133 µmol/L) in 25.4% and 4.7% of patients, respectively, whilst in RE-LY[3] there was no dose adjustment and patients were randomised to be treated with one of two doses, in contrast to the other RCTs mentioned (49.7% of patients were receiving the dabigatran 110 mg twice daily dose whilst 50.3 received the 150 mg twice daily dose).

Prescribing patterns across the globe show that, in practice, prescriptions for apixaban at the lower 2.5 mg dose are disproportionately high. Similar but less-marked patterns are also seen with dabigatran and rivaroxaban, although dose reduction with rivaroxaban and dabigatran offers the flexibility of a 25% or 27% dose reduction, respectively, whereas apixaban only offers the option of a 50% dose reduction.[2,3,15,17] Generally, preferences of physicians regarding doses of oral anticoagulant therapy are often based on the safety of the therapy, and physicians are generally more concerned about bleeding risk than stroke prevention. Dosing regimens should also be considered by clinicians, particularly with regards to adherence (the extent to which a patient acts in accordance with the prescribed length of treatment, frequency, and dose of a dosing regimen). In a Canadian analysis, 6% and 14% of patients who received rivaroxaban and warfarin, respectively, reported taking their oral anticoagulant twice daily instead of once daily, but importantly, 27% and 30% of patients who received dabigatran and apixaban, respectively, took their oral anticoagulant once daily instead of their recommended twice daily dosing regimens. There were significantly more missed doses with the twice daily dosing regimen compared with once daily medications.[18] Comparisons of discontinuation rates of rivaroxaban versus warfarin in real-world studies have shown a 34–37% lower risk of discontinuation with rivaroxaban versus warfarin.[19,20]

Overall, results from RCTs and real-world studies of rivaroxaban provide complimentary and consistent evidence that when dosed appropriately, NOACs such as rivaroxaban are effective and safe in patients in comparison to warfarin.

Day-to-Day Management of Patients with Atrial Fibrillation on Non-Vitamin K Antagonist Oral Anticoagulant Therapy: Practical Perspectives

Professor Peter Verhamme

The development of NOACs has changed the therapeutic landscape of anticoagulant therapy and provided patients with a therapeutic option that has a reduced risk of critical bleeding events versus VKAs. The ROCKET AF trial has shown that rivaroxaban reduces incidence of critical bleeding events versus VKAs in patients with AF; critical organ bleeding is reduced by 31% (p=0.007), ICH by 33% (p=0.02), and fatal bleeding by 50% (p=0.003).[5,21] In addition to a lower risk of critical bleeding events, NOACs also have a different bleeding pattern in comparison to VKAs and demonstrate a lower relative risk of ICH and other major bleeding events. This is likely due to the difference in mechanism of action of NOACs, which act to directly inhibit factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran), whereas warfarin reduces the functional levels of the coagulation factors II, VII, IX, and X.[22] Given the reduction in all non-GI bleeding, it is surprising that the risk of GI bleeding is increased with NOACs as a group versus warfarin.[9] One explanation may be the accumulation of active drug in the GI tract where NOACs have the potential to cause bleeding through both their systemic and local effects on the GI mucosa, in contrast to VKAs which can only cause GI bleeding through a systemic anticoagulant effect.[22]

When interpreting bleeding outcome findings for NOACs versus warfarin, it is also important to consider differences in patient characteristics across NOAC trials. High-risk patients ($CHADS_2$ score ≥3) had a higher risk of major bleeding in the ROCKET AF trial (2.0% major GI bleeding event rate/year; mean $CHADS_2$ score 3.5).[5] In the real-world study XANTUS, the major GI bleeding event rate/year was lower (0.9%; mean $CHADS_2$ score 2) than that seen in ROCKET AF, but is likely due to the difference in patient populations investigated in both studies.[10,23] A meta-analysis of observational cohort studies (N=8) examined the link between NOACs and real-world GI bleeding events.[24] The analysis included 10,713 patients treated with rivaroxaban and reported no significant increase in GI bleeding risk for rivaroxaban versus warfarin,[24] probably attributed to the fact that patients in the real-world setting generally have a lower risk profile than the patients recruited to ROCKET AF; this is reflected in lower major bleeding rates. Proactive measures can be taken to lower bleeding risk in patients on oral anticoagulants. Risk factors for bleeding include older age, male sex, high diastolic blood pressure, the use of platelet inhibitors, a history of GI bleeding, and anaemia.[25] Clinical guidelines call for clinicians to consider these risk factors when administering anticoagulant therapy with a more integrated clinical approach.[26] Another concern among clinicians and patients is traumatic ICH, particularly among older patients with AF who may be more prone to falls.[27] In a retrospective cohort study of 31,951 USA veterans (≥75 years) with AF, newly referred to anticoagulation clinics for VKA therapy (2002–2012), the incidence rate of hospitalisation for traumatic ICH was 0.48% per year, and of any ICH, 1.46% per year.[27] These results indicate that rates of traumatic ICH with VKAs may be higher than previously thought.

Initial management of serious bleeding events include identifying and controlling the source of the bleed and providing supportive care to stabilise the patient, using volume replacement and transfusion. Assessing the type and amount of drug as well as the time of administration, measurement of haemoglobin, and haemostasis (partial thrombin or activated partial thromboplastin time)[28,29] are also important considerations in bleeding management. In particular, supporting haemostasis using either procoagulants (prothrombin complex concentrates [PCCs]) or antifibrinolytics, or using reversal agents such as idarucizumab (not available in some countries) and andexanet (which has not yet received regulatory approval) may help with serious bleeding events in exceptional cases. In a randomised, double-blind, placebo-controlled study in which 12 healthy male volunteers received rivaroxaban 20 mg twice daily, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline, prolongation of partial thrombin and endogenous thrombin potential were completely reversed by PCC.[30] The European Heart Rhythm Association (EHRA) dosing recommendation for factor concentrates recommend PCC (50 U/kg), activated PCC (50 U/kg/day; maximum 200 U/kg/day), or recombinant factor VIIa (90 µg/kg) in patients with NVAF.[28] In fact, standard clinical measures are often sufficient to manage major bleeding in the majority of cases; in the Dresden NOAC registry, <10% of patients with major bleeds received PCCs

and no patients received recombinant factor VII.[31] More recently, interim results with reversal agents idarucizumab, which completely reverses the anticoagulant effect of dabigatran,[32] and andexanet, which reverses the anticoagulant effect of apixaban and rivaroxaban,[33] potentially offer additional alternatives in specific individual situations.

Less critical bleeding with NOACs and a more comprehensive understanding of what drives bleeding risk, plus a more informed and proactive approach to management of bleeding means that in the future bleeding risk is likely to be lower with anticoagulant therapy, offering better therapeutic options for clinicians and patients alike.

The Management of Patients with Atrial Fibrillation and Renal Impairment: Practical Perspectives

Professor Jafna L. Cox

A frequently asked question is how to treat renally-impaired patients with anticoagulant therapy, particularly those that are elderly. Data have shown that chronic kidney disease (CKD) is associated with an increased risk of stroke, systemic thromboembolism, and bleeding. Renally-impaired populations differed between NOAC Phase III trials,[15,34,35] as did the $CHADS_2$ score distribution across studies for patients with moderate renal impairment (CrCl 30–49 mL/min) (Figure 2). Of the patients with renal impairment, 45% had a $CHADS_2$ score of 3–6 in ARISTOTLE[34] and RE-LY,[35] whereas this number was much greater in ROCKET AF (91%), indicating a population at substantially higher risk of stroke and bleeding.[15]

A subgroup analysis of the meta-analysis of Phase III trials on NOACs and stroke prevention in NVAF by Ruff et al.[9] found that 19% of patients with renal impairment had a CrCl of <50 mL/min. The assessment found that treatment with NOACs of NVAF patients with renal impairment reduced the relative risk of stroke, systemic embolism, and major bleeding versus warfarin.[9]

Rivaroxaban is currently the only NOAC that has a prospectively tested, specific renal dose for patients with renal impairment that has been clearly assessed in a Phase III study.[36] ROCKET AF has demonstrated that rivaroxaban has a consistent efficacy and safety profile in NVAF patients with moderate renal impairment (CrCl 30–49 mL/min), and is associated with a significant 61% reduction in fatal bleeding events in this patient group. ICH and critical organ bleeding were also numerically lower versus warfarin therapy.[15] Additionally, a ROCKET AF sub-study aimed to determine whether the primary efficacy (stroke or systemic embolism) and safety (major bleeding and non-major clinically relevant bleeding) endpoints in the parent trial differed among participants with worsening renal function (defined as an absolute increase in serum creatinine) taking rivaroxaban versus warfarin. It found that among such patients with worsening renal function, rivaroxaban was associated with lower rates of stroke and systemic embolism compared with warfarin; importantly, this benefit was seen without any corresponding increase in the composite bleeding endpoint.[37]

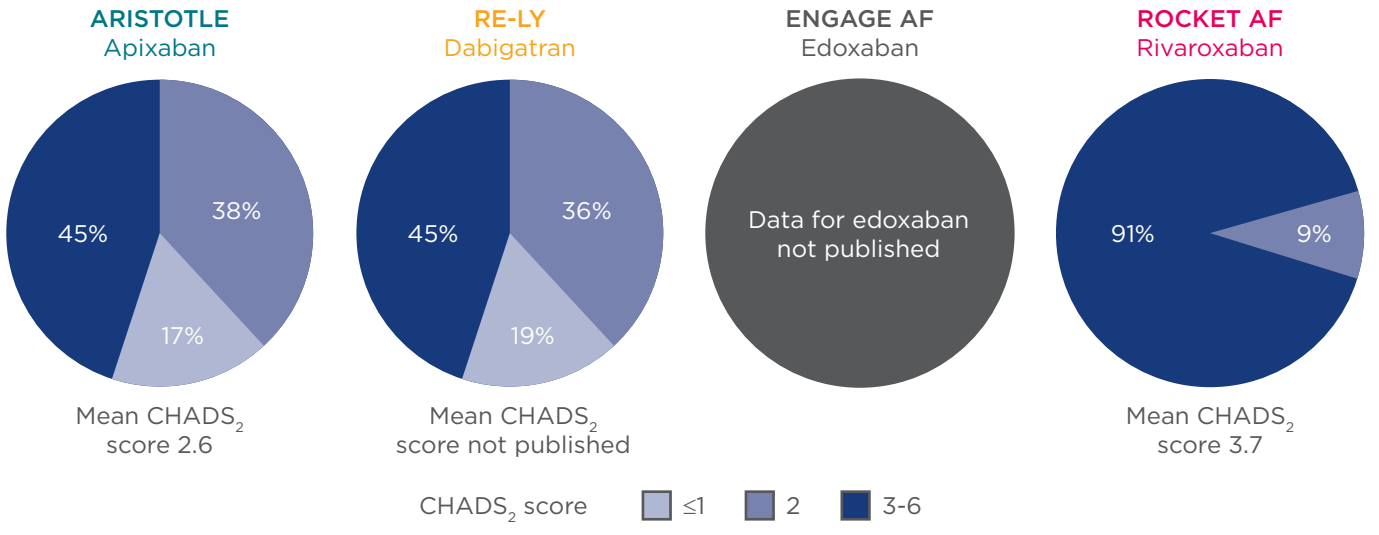

Figure 2: Renally-impaired populations differ between Phase III studies.[15,34,35]

Studying the real-world use of NOACs provides important insights into the effects of oral anticoagulant therapy in AF and CKD. A study of the Danish National Registry (1997–2008, including 132,372 patients with 3,587 patients with non-end-stage CKD [2.7%]) found that both AF and CKD significantly increased the risk of stroke ($p<0.001$) and bleeding ($p<0.001$) among patients with CKD, versus those patients without CKD.[38] A Swedish AF Cohort study has found similar results. This study comprised 307,351 patients with AF, of whom 13,435 had a previous diagnosis of renal failure (28% of whom were on warfarin therapy at baseline). Other baseline characteristics across patients with renal failure and with no renal failure were similar, however when the groups were stratified both by bleeding and stroke risk, the risk in each case was higher in the renal failure group. Interestingly and as previously discussed, the patients most at risk of stroke were under-dosed (warfarin at baseline) by 28%,[39] presumably out of fear of bleeding risk. However, in this study patients with both AF and renal failure were those found to benefit most from having the same anticoagulation treatment as is recommended for other patients with AF. As such, rather than be undertreated, they should be at least as aggressively treated as AF patients with normal renal function, if not more so. Adding additional points for renal failure to the $CHADS_2$ and CHA_2DS_2-VASc (with the additional 'stroke risk' modifiers of vascular disease, age 65–74 years, and a particular sex category) scores did not improve their predictive value.[39]

XARENO, an ongoing real-world study of rivaroxaban in patients with renal impairment, aims to assess CKD progression and the safety of rivaroxaban versus VKAs in NVAF patients with estimated glomerular filtration rates of 15–49 mL/min/1.73 m^2 in routine clinical practice. Patient selection and choice of type, dose, and duration of drug used will be at the discretion of the attending physician, and patients will either receive rivaroxaban, warfarin, or no oral anticoagulant for ≥3 months. Investigators will collect data at the initial visit, at 3 months, and then quarterly. The registry will collect clinical data relating to approximately 2,500 patients with CKD over an estimated mean follow-up of 18 months for the whole study cohort, and thereby offer important insights into the use of factor Xa inhibitors in renally-impaired patients with NVAF.[40]

Hub Session: Impact of Real-World Evidence on Patient Management: Addressing Open Questions

The aim of the Hub session was to provide an in-depth debate around the implications of clinical trial and real-world evidence.

Professor Manesh R. Patel

The GARFIELD-AF observational study has shown that patients with AF are not treated according to current guidelines, with under-treatment with anticoagulants in 38% of patients with $CHADS_2$ scores ≥2 (as previously mentioned).[6] There is often discrepancy between RCTs and real-world evidence in the treatment of clinically-challenged patients, such as those with renal impairment. Would the audience agree or disagree that real-world evidence is more important than Phase III clinical trial data for ascertaining expected drug effectiveness/safety?

Audience

There was a 50/50 split between agree and disagree.

Professor Jafna L. Cox

Real-world evidence, which is based on data from routine clinical practice, can provide valuable insights and knowledge for physicians to support patient care. Although RCTs are the gold standard of evidence-based medicine and feature highly controlled settings with predefined patient types and limited follow-up times, data from routine clinical practice generally involve varied medical settings with diverse patient populations.[1] Both types of data are important and can be viewed as complementary, as they address different questions.

Professor Christoph Bode

When looking at the XANTUS registry data, results from this study confirm those from clinical trials: rivaroxaban is highly effective and has a good safety profile.

Professor Peter Verhamme

In the case of bleeding control, management using standard clinical measures has been reported to be sufficient in the Dresden NOAC registry.[31]

Professor Manesh R. Patel

Using NOACs 'as they were tested' in patients with AF is critical to providing adequate stroke prophylaxis.

Professor Jafna L. Cox

Most clinical trials test specific dosages of drug, often without pre-specified dose titration, giving us limited insight into the effectiveness and safety of untested prescription amounts. However, many clinicians tend to take a conservative approach, often opting for lower doses of anticoagulant because of fear of bleeding.

Professor Manesh R. Patel

When prescribing NOACs for patients with AF, the simplicity of the dosing regime is an important consideration.

Professor Jafna L. Cox

It is important to have discussions with your patients about the dosing regimen they would prefer. Often complicated regimens with 2 or 3-times daily dosing is not the patient's preferred choice and can lead to reduced adherence.

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DEVELOPING REAL-WORLD PATIENT PATHWAYS IN ACUTE PULMONARY EMBOLISM

This symposium took place on 29th August 2016 as a part of the European Society of Cardiology (ESC) Congress in Rome, Italy

Chairperson

Stavros V. Konstantinides[1]

Speakers

Rodney Hughes,[2] David Jiminéz,[3] John Eikelboom[4]

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MEETING SUMMARY

This case-based satellite symposium chaired by Prof Konstantinides addressed important and topical aspects of the management of acute pulmonary embolism (PE) with a focus on effective management in a real-world setting. The objectives of the symposium were to provide information and expert guidance on the effective management of a patient with PE from diagnosis and assessment of severity, through to the practical use of non-vitamin K antagonist non-oral anticoagulants (NOACs) and the management of challenging cases found in routine clinical practice. Following Prof Konstantinides' introduction, Dr Hughes presented a low-risk PE case and discussed assessment of the severity of PE, the optimisation of hospital care, and the importance of patient discharge protocols and clear integrated management pathways. Dr Jiménez went on to illustrate the use of risk assessment and non-vitamin K antagonist (VKA) therapies through consideration of an intermediate high risk PE case with comorbidities. Finally, Dr Eikelboom presented an unprovoked PE case and discussed the key question of 'how long is long enough', emphasising the importance of adequate anticoagulation, both acutely and in prevention of recurrence, and the potential benefits of NOACs. In a final Question and Answer Hub session, the audience were able to participate in a lively case-based discussion.

Opening and Introduction

Professor Stavros V. Konstantinides

PE is the third most frequent acute cardiovascular syndrome and is associated with significant mortality, so all patients should receive anticoagulant treatment irrespective of severity.[1] Initially the NOACs were regarded as alternatives to standard of care,[1] but more recently the American College of Chest Physicians (CHEST)[2] has recommended them over the classical regimen of low molecular weight heparin (LMWH) combined with VKAs because of their equivalent efficacy and better safety profile, at least in terms of major bleeding. NOACs also allow for the possibility of earlier discharge and subsequent home treatment of selected patients with low-risk PE. This is currently being investigated in studies like the HoT-PE trial,[3] the primary objective of which is to determine whether early discharge and subsequent out-of-hospital management of patients with rivaroxaban is feasible, effective, and clinically appropriate in those fulfilling specific clinical, imaging, and social criteria of low-risk. Key clinical questions remain on: i) the best selection criteria for patients who can be treated in the outpatient setting, ii) how to decide the duration of treatment, and iii) how we should manage challenging patients such as those with concomitant deep vein thrombosis (DVT) and PE, or those at higher risk because of comorbidities.

Case 1: Assessing Pulmonary Embolism Severity and Optimising Hospital Care

Doctor Rodney Hughes

Patients with acute PE vary tremendously from the very low risk, who tend to be younger and fitter, through to a high-risk population for whom immediate reperfusion may be required. There is also an at-risk group of patients with the potential to deteriorate and have a further event within a short period, particularly if the anticoagulation is incomplete initially. Rapid risk stratification is therefore critically important to inform and optimise patient care.

The Pulmonary Embolism Severity Index (PESI) is a simple and well-validated[4] risk stratification tool enshrined in the European Society of Cardiology (ESC) guidelines,[1] which can help determine the potential mortality and outcome of patients with newly diagnosed PE. Used either as the simplified version (sPESI) or the full version and combined with an assessment of how the patient is coping, it builds a risk score classifying patients as high risk, intermediate high risk, intermediate low risk, or low risk. Its utility is exemplified by the case of a 49-year-old woman with no significant background risk factors for venous thromboembolism (VTE) who presented with low-grade tachycardia and slightly delayed onset of breathlessness. Blood pressure and oxygen saturations were normal but there was a saddle PE upon radiology. However, this patient's troponin was negative so, far from needing thrombolysis, her low PESI score indicated she was at a low risk of a significant adverse outcome.

The choice of anticoagulant is important and there is a plethora of data available on the new agents. Rivaroxaban has the only PE-specific study to date, EINSTEIN PE.[5] In this event-driven trial comparing rivaroxaban to the standard of care of enoxaparin/VKA, rivaroxaban met the criteria for non-inferiority in terms of the primary outcome of symptomatic recurrent VTE, but with a significantly better safety profile based on major bleeds. Pre-randomisation use of heparin did not significantly affect outcome.[6] Furthermore, a retrospective *post-hoc* analysis[7] indicated that the study included significant numbers of higher-risk patients and whilst no statistical comparison could be made, the data suggest that rivaroxaban may be equally effective for both low and high-risk patients according to sPESI.

But do results in clinical practice mirror those seen in clinical trials? XALIA,[8-9] is a large, real-world, Phase IV study comparing the safety of rivaroxaban with standard of care for the treatment of acute DVT in routine clinical practice. Although the age range of patients in XALIA was lower than average (55–60 years), the patients were otherwise representative of those seen in clinical practice. Results were consistent with those seen in the rivaroxaban Phase III programme, with an almost identical reduction in hospital length of stay for DVT and PE patients.[8-12] Figure 1 presents a comparison of the EINSTEIN PE and XALIA trials.

Based on the weight of evidence for NOACs, the CHEST guidelines[2] suggest that NOACs are preferred long-term anticoagulants over VKA for non-cancer associated VTE. Furthermore, use of these agents facilitates early discharge, either direct from the emergency department or after a couple of days' inpatient care. Indeed, the ESC

guidelines[1] advise that patients with a low risk of an early adverse outcome should be considered for early discharge and continuation of treatment at home if proper outpatient care and anticoagulant treatment can be provided.

Rapid patient assessment and minimisation of in-hospital care starts in the emergency department with timely diagnostic procedures and PESI-scoring, followed by a decision about whether the patient can be discharged rapidly. Successful implementation of that early discharge requires establishment of integrated VTE management pathways with robust associated patient education, discharge, and follow-up processes and communications. These, combined with a holistic approach to the management of the patient, can ensure seamless and effective management of the patient from acute care right through to long-term management in primary care.

Case 2: Managing Challenging Patients with Venous Thromboembolism

Doctor David Jiménez

Acute mortality for normotensive patients with acute symptomatic PE varies widely, so risk stratification is critical to identifying both the very low-risk patient who might benefit from early discharge or home therapy, and the very high-risk patient who might deteriorate soon after diagnosis, and so requires close monitoring or urgent recanalisation procedures. The risk stratification algorithm from the ESC[1] is very useful and may be refined in the near future to address questions regarding:

- Choice of scoring system for normotensive patients with PE, e.g. PESI, sPESI, or Hestia criteria
- In which patient subgroups should we combine clinical prognostic scores such as sPESI cardiac biomarkers and imaging?
- Definition of early discharge and home treatment for patients with acute symptomatic PE
- Better ways of differentiating between patients with intermediate high and intermediate low risk PE

Consider the case of a 76-year-old male admitted to the emergency department 2 days after a long haul flight with pleuritic chest pain and shortness of breath. Upon admission, his heart rate was 116 beats per minute, systolic blood pressure 99 mmHg, and oxygen saturation 93%. He had moderate renal impairment (creatinine clearance of 38 mL/min) and a high D-dimer of 3,122 ng/mL. Computed tomography (CT) scanning revealed a saddle pulmonary embolus. The patient was high-risk based on his sPESI and he had a positive troponin I (0.3 ng/mL) and right ventricular dysfunction on transthoracic echocardiography. Clinically, the question then was whether to thrombolyse.

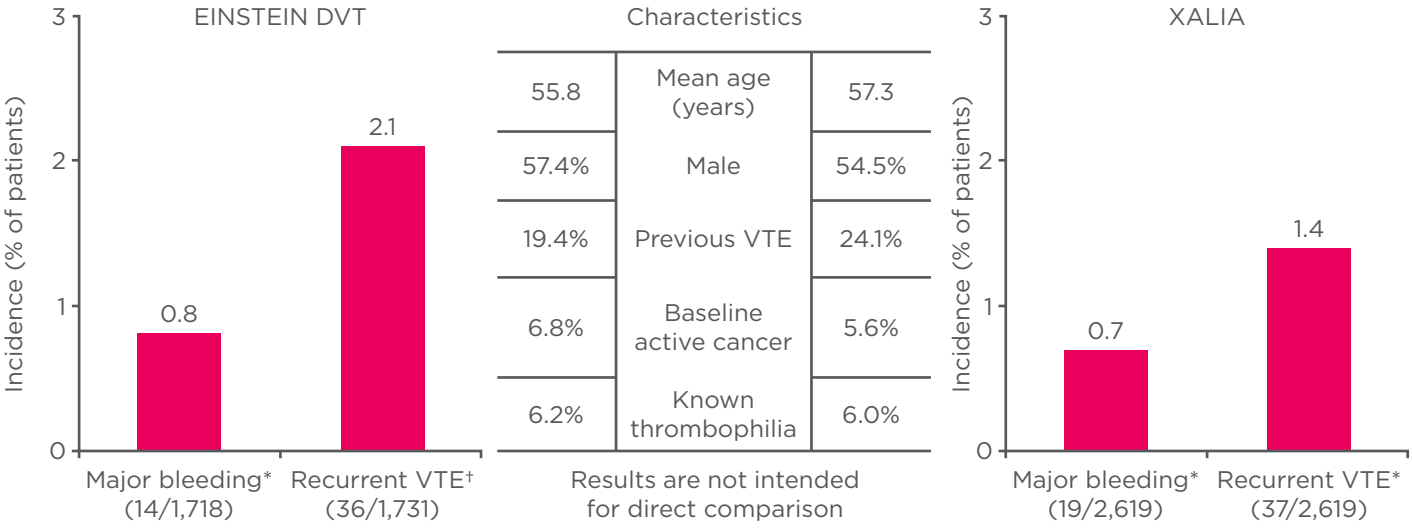

Figure 1: Comparison of the XALIA trial[8-9] versus EINSTEIN DVT.[10]
*Safety population (patients taking ≥1 dose of study drug) †intention-to-treat analysis.
VTE: venous thromboembolism.
Adapted from The EINSTEIN Investigators 2010,[10] Turpie et al.,[8] and Ageno et al. 2016.[9]

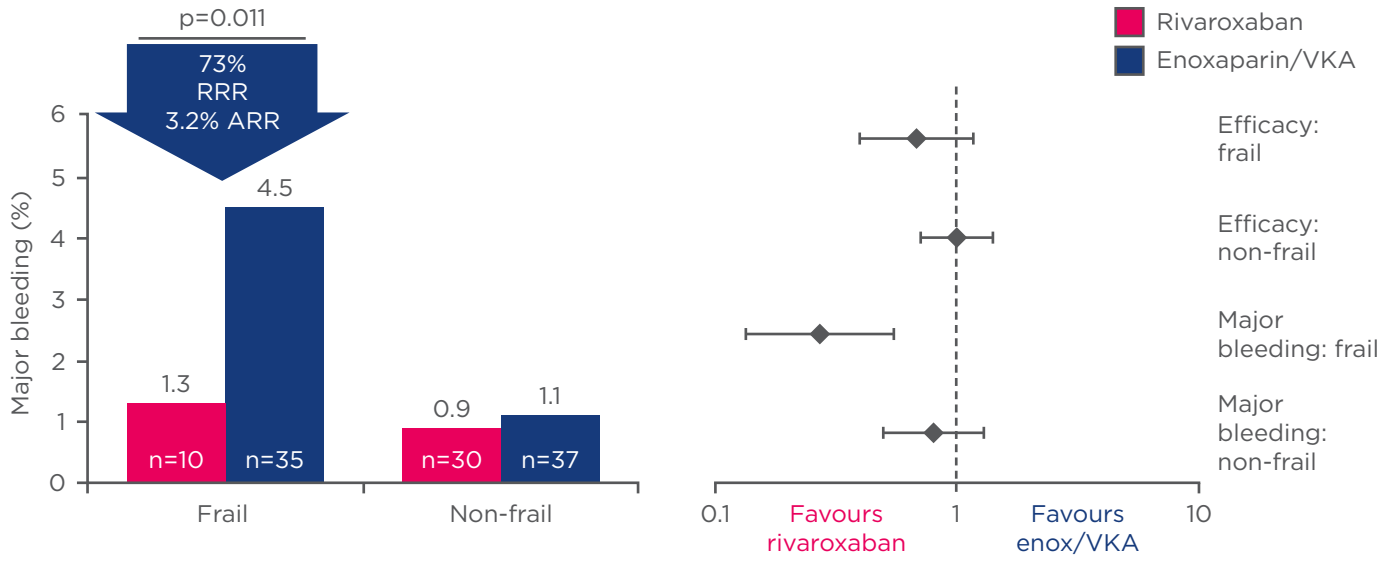

Figure 2: Sub-analysis of the EINSTEIN trials showing major bleeding events for rivaroxaban or enoxaparin/vitamin K antagonist-treated frail patients.[17]

ARR: absolute risk reduction; RRR: relative risk reduction; VKA: vitamin K antagonist; enox: enoxaparin.

The 2014 PEITHO trial[13] is informative in this regard. Patients with intermediate-risk PE, defined as the presence of right ventricular dysfunction and myocardial injury, were randomised to either tenecteplase or placebo as well as anticoagulant therapy. Whilst the primary outcome of thrombolysis was positive with a significant reduction in all-cause mortality or haemodynamic collapse during the first 7 days after randomisation, there was also a significant increase in bleeding-related death.[12] The ESC[1] and recent CHEST[2] guidelines therefore suggest not to thrombolyse normotensive patients with an acute symptomatic PE unless they deteriorate soon after diagnosis.

Based on the PEITHO[13] trial experience, the therapeutic options for this patient were traditional parenteral agents with bridging and followed with VKA, rivaroxaban, apixaban, or 1 week's LMWH followed by dabigatran or edoxaban.[14] Whilst some clinicians are reluctant to use direct oral anticoagulation for acute symptomatic PE, there are good data supporting their efficacy, as exemplified by the Van Es et al.[15] meta-analysis showing non-inferiority as compared to standard therapy with VKAs.

Not only has non-inferiority to VKA been reproducibly demonstrated for NOACs, there is also good evidence of actual clot regression.[16] In the EINSTEIN PE trial, after 21 days of treatment with rivaroxaban 88% of patients achieved complete or partial clot resolution, and there was no worsening of pulmonary vascular obstruction in the remaining 12% of patients.[16]

The elderly are a particular safety concern in the use of anticoagulation in clinical practice, but a sub-analysis of the EINSTEIN trials is reassuring, with major bleeding rates on rivaroxaban reduced by 73% compared with warfarin in patients aged >75 years with low body weight or creatinine clearance <50 mL/min (Figure 2).[17] Although patients with symptomatic VTE and renal impairment are at increased risk of recurrent VTE,[18] pooled analysis of the EINSTEIN DVT[9] and PE[5] trials indicates that the risk of major bleeding is not increased in rivaroxaban-treated patients.[18]

Based on the evidence, the final decision for our patient was not to thrombolyse but to follow the CHEST guidelines[2] and use weight-adjusted LMWH with monitoring. If there was no deterioration in 48–72 hours we would switch to NOACs and if there was deterioration, we would proceed to thrombolysis and to switch after 48 or 72 hours following stabilisation. Based on current guidelines,[2] the vast majority of patients with acute symptomatic PE should be treated with NOACs and low-risk patients might benefit from early discharge or even from outpatient therapy. For those patients with high-risk PE or deteriorating patients with intermediate-risk PE, parenteral anticoagulant agents such as LMWH or unfractionated heparin may be more suitable in the acute setting, with initiation of NOACs after stabilisation.[2]

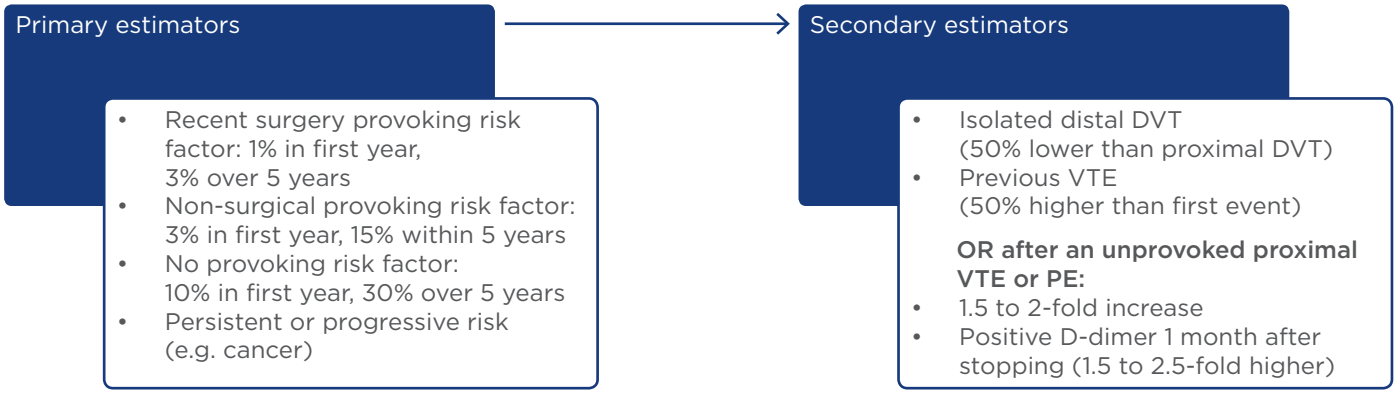

Figure 3: Assessing recurrence risk if anticoagulants are stopped.
DVT: deep vein thrombosis; VTE: venous thromboembolism; PE: pulmonary embolism.
Adapted from Kearon and Akl.[20]

Case 3: How Long is Long Enough?

Doctor John Eikelboom

In the last 20 years there have been significant strides in the acute and long-term treatment of VTE, but one of the most contended issues for clinicians remains that of the optimal duration of anticoagulation. Over the years this has been driven by the inconvenience and high risk of bleeding associated with warfarin. Today, the advent of the NOACs has substantially overcome this and treatment has evolved towards a single-drug approach using rivaroxaban or apixaban commenced at outset and continued long-term.[19]

The 2016 CHEST[2] guidelines are clear that treatment should be stopped at 3–6 months if the bleeding risk is high in a patient with an unprovoked event, but extended indefinitely if the bleeding risk is low or moderate. Where there is a transient risk factor, patients generally only require treatment for 3 months, but those with progressive or persistent risk factors should receive extended treatment.[2] The CHEST guidelines[2] now recommend NOACs over VKAs for the initial treatment of DVT or PE, and initial therapy choice can be extended where required, the only exception to this being cancer-associated thrombosis where LMWH remains the treatment of choice for extended/long-term treatment. A typical case of a 63-year-old male with unprovoked and fairly severe bilateral PE, elevated troponin, and evidence of right heart strain on imaging is illustrative of patients in whom the acute event has been treated after 3–6 months, but for whom there is a high risk of recurrence warranting extended treatment.

Decision-making based on estimated risk of recurrent VTE has been both enhanced and complicated by consideration of factors such as male sex and presence of positive D-dimer, but Kearon and Akl's 2014 paper[20] elegantly integrates that information with clinical information on risk of recurrence. Clinical risk factor status is the primary determinant of decision-making on treatment duration and our 63-year-old male has no provoking risk factor, therefore having a high recurrence risk in the first year of stopping of 10%, rising to 30% over 5 years and approximately 40% at 10 years.[21]

Historically, warfarin has been stopped after 3–6 months, but in the PADIS-PE trial,[22] where extended treatment with warfarin to 18 months was compared with a placebo, event rates in the treated group increased gradually in the 24 months after stopping, reaching those of the placebo group by the end of the trial. This underlines the importance of ongoing long-term treatment in patients at risk of recurrence; however, bleeding risk, the need for injections, and the routine anticoagulation monitoring remain significant barriers to long-term anticoagulation with the older agents. Head-to-head trials confirm that NOACs such as rivaroxaban, apixaban, dabigatran, and edoxaban have similar efficacy to warfarin but a better safety profile, making them attractive for long-term treatment. Long-term treatment continues to be an important area of research and we particularly await the results of the EINSTEIN-CHOICE study,[23] which compares the standard 20 mg dose of rivaroxaban with 10 mg of rivaroxaban and with 100 mg of aspirin over a 12-month period in 2,850 patients with symptomatic VTE and/or PE.

The primary endpoints are symptomatic recurrent VTE and major bleeding. The trial is expected to be completed towards the end of 2016.[23]

Question and Answer Session

Q: If Dr Hughes' patient (Case 1) had been thrombolysed, when would he have started the oral drug?

Dr Hughes' practice is to anticoagulate with LMWH for 48–72 hours and then consider transitioning to a NOAC if the patient is stable.

Q: Would Dr Jiménez consider low-dose thrombolysis in his patient (Case 2)?

The panel agreed that although theoretically attractive, there are no good quality data to support this. They indicated that they would thrombolyse with full systemic doses.

Q: If an intermediate-risk patient on a NOAC starts to deteriorate in the first 48 hours, suggesting the need for thrombolysis, do you try to reverse the NOAC pre-thrombolysis?

Drawing an analogy to the myocardial situation, the panel agreed that in the case of a PE they would treat this as an emergency and simply treat with lysis, without attempting to reverse the NOAC.

Hub Question and Answer Session

After the symposium, delegates had the opportunity to explore additional case studies in a Question and Answer Hub session.

Case A

Dr Jiménez' case concerned a 48-year-old woman who presented with ischaemic stroke after saphenectomy. Lower limb ultrasound proved negative for DVT but a multi-detector CT scan confirmed acute symptomatic PE, which was managed acutely with LMWH followed by VKA. However, saphenectomy is a transient risk factor so for how long should the patient be treated? Subsequent echocardiography revealed a foramen ovale, putting the patient at high risk of ischaemic stroke, so indefinite anticoagulation was the best course of action. Despite the potential risks, this patient underwent closure of the foramen ovale after 3 months and anticoagulant therapy could then be stopped. Dr Jiménez emphasised the importance both of reviewing bleeding occurrence in patients with unprovoked PE who continue treatment and event recurrences in those whose anticoagulation therapy is stopped.

Q: When would you consider anticoagulation in a patient with ischaemic stroke if you have a confirmed coexistent VTE?

Dr Jiménez responded that in the absence of good control data, his clinical practice is to start with full dose LMWH for 8 hours after the diagnosis of an ischaemic stroke and then switch to a direct oral anticoagulant 1 week after diagnosis of ischaemic stroke.

Q: Do you use scanning and imaging to follow-up these patients?

Dr Jiménez responded that most patients recover in terms of clinical signs and clot regression is assumed. He rarely rescans these patients unless they deteriorate and have a suspected recurrent VTE.

Case B

Dr Hughes presented the case of a 38-year-old woman who was usually fit and healthy with no history of VTE, but who was taking a second-generation combined oral contraceptive pill (COCP). She developed acute onset of pleuritic chest pain and borderline tachycardia, but was stable with regard to blood pressure and oxygen saturations. A CT scan showed lobar PE and her right ventricle/left ventricle ratio was normal.

Q: Is this a provoked or an unprovoked event and how long would you continue anticoagulation?

On balance, the audience agreed this to be a provoked event, presumably because of the use of the COCP. However, this is a controversial area and many would consider this to be a 'minimally provoked' VTE, i.e. the patient is relatively low-risk, implying that some other underlying condition is increasing her overall risk. The recurrence rate for PE is high at about 30% within 5 years for most individuals with an unprovoked event, so this issue is important for clinical decision-making. The PADIS-PE22 study suggests that if anticoagulation is withdrawn, even after 18 months, recurrence rates catch up very quickly. If the unprovoked patient is not on indefinite anticoagulation, there remains an increased likelihood of recurrence.

The Importance of Patient Preference

One audience member advocated the importance of patient preference in decision-making about ongoing anticoagulation, particularly where the clinical evidence is unclear. Patients may have strong views, or their fears about quality of life, recurrence, and bleeds may influence their preference. Dr Hughes and Dr Jiménez agreed that this was an important part of the informed consent process, but noted that it should not override good, evidence-based practice.

Risk Assessment in Women, Especially Those on Oral Contraception

Prediction scores are many and varied, but are consistent in suggesting that most, if not all, men need to go on long-term anticoagulation if they present with symptoms. However, there is controversy around risk assessment and duration of therapy in women, particularly in relation to oral contraceptive use, and this dichotomy is reflected in the different prediction models in use.[24] Rodger et al.[25] concluded that low-risk women rated by HERDOO2, which rates hormone-related index events as unprovoked, could safely discontinue anticoagulation. Based on recent evidence that oestrogen-treated women who have had a PE or DVT are at very low risk, Dr Hughes treats the pill as a transient risk factor.

Q: Can D-dimer be used to aid decision-making about extending anticoagulation and when should this be tested?

Audience consensus was to test D-dimer 2 weeks after cessation of anticoagulation. Dr Hughes rarely tests for D-dimer in clinical practice but would consider it in younger women who are on oral contraceptives; based on warfarin data, he would test 3 weeks after cessation of anticoagulation.

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IDENTIFYING FABRY DISEASE PATIENTS THROUGH CARDIAC MANIFESTATIONS

This satellite symposium took place on 27th August 2016 as a part of the European Society of Cardiology (ESC) Congress, in Rome, Italy

Chairperson
Aleš Linhart[1]

Speakers
Perry Elliott,[2] Jean-Claude Lubanda,[1] Christoph Kampmann (unable to attend)[3]

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MEETING SUMMARY

The meeting's objectives were to review the principles in diagnosing Fabry disease according to the European Society of Cardiology (ESC) guidelines on hypertrophic cardiomyopathy (HCM); to discuss the practical challenges in diagnosing Fabry disease in clinical practice; to investigate the long-term benefit of enzyme replacement therapy (ERT) for patients with Fabry disease; and to identify key patient populations with Fabry disease at risk of misdiagnosis.

Prof Aleš Linhart opened the symposium by highlighting that a significant number of cardiologists are not aware of Fabry disease and that the average time to diagnosis is >10 years.[1] The need for treatment of rare cardiomyopathies was also discussed. Prof Perry Elliott reviewed the ESC guidelines on diagnosis and management of HCM, and how they apply to Fabry disease. Prof Linhart then outlined how these guidelines can practically be applied, using case studies to illustrate the challenges in accurately identifying patients with a potential diagnosis of Fabry disease. Prof Linhart then demonstrated the long-term benefits of ERT for patients diagnosed with Fabry disease observed in Mainz, Germany, on behalf of Prof Christoph Kampmann, while Assoc Prof Jean-Claude Lubanda highlighted key patient populations with an increased prevalence of Fabry disease who should be targeted for screening to improve therapy and clinical outcomes.

Introduction

Professor Aleš Linhart

Diagnosing the underlying disorder in a patient presenting with a cardiomyopathy, defined as a structurally and functionally abnormal heart muscle not caused by abnormal loading conditions or coronary disease, can be difficult.[2] Cardiomyopathies can be isolated or associated with a variety of extracardiac symptoms and the pathology may have a genetic or non-genetic origin.[2] Therefore, the ESC has issued guidelines to assist healthcare professionals in accurately diagnosing the underlying aetiology of hypertrophic cardiomyopathies.

Using ESC Guidelines in Clinical Practice to Identify Patients with Fabry Disease

Professor Perry Elliott

HCM is defined by an increased left ventricular (LV) wall thickness that cannot be explained by abnormal loading conditions.[2] In adults, HCM is defined by a LV wall thickness of ≥15 mm in one or more myocardial segments, whereas in children, HCM is defined by a LV wall thickness of more than two standard deviations above the age and size-predicted means. It is recognised that a variety of genetic and non-genetic diseases may underpin this clinical presentation, which influences both the treatment modality used and the prognosis, and in 40–60% of cases HCM is related to a sarcomeric protein gene mutation (Figure 1).

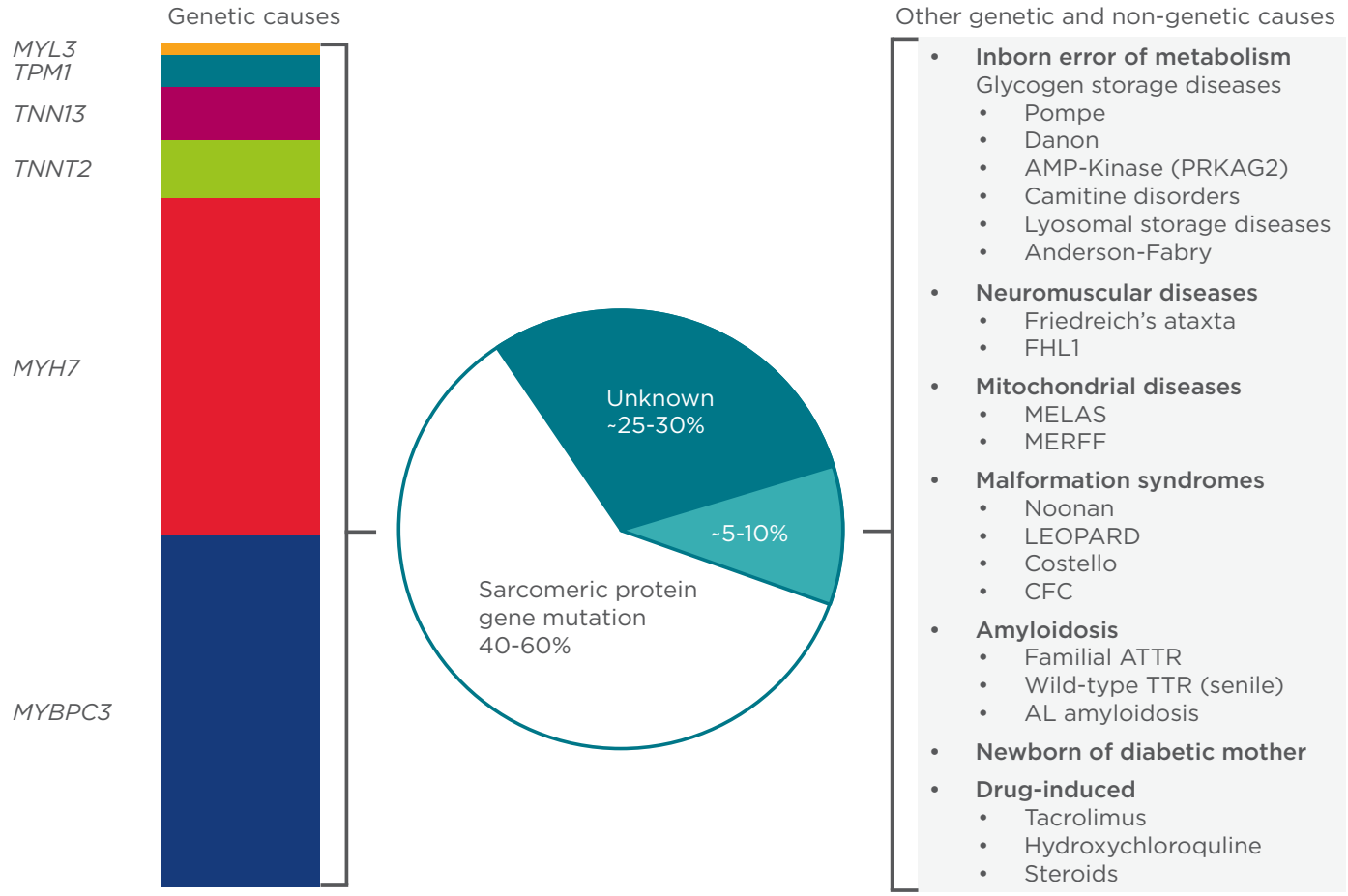

Figure 1: Aetiology of hypertrophic cardiomyopathy.
MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke; MERFF: myoclonic epilepsy and ragged red fibre disease; LEOPARD: lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitals, retarded growth, deafness; CFC: cardiofaciocutaneous syndrome; ATTR: transthyretin-related amyloidosis; TTR: transthyretin; AL: amyloid light-chain.
Adapted from the 2014 Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the ESC Guidelines.[2]

Consequently, the underlying cause of increased LV wall thickness in the absence of loading abnormalities should be clinically investigated. This is of particular importance as numerous genetic disorders are associated with an increased LV wall thickness, including Fabry disease and amyloidosis, which may present as HCM phenocopies (diseases with similar clinical phenotypes).[2] Although HCM phenocopies are rare, their exclusion or identification is critical for disease management, as delays in diagnosis can worsen prognosis.[3]

Several cardiac investigative techniques, such as electrocardiogram (ECG), echocardiogram, and cardiac magnetic resonance imaging (MRI), are able to identify diagnostic 'red flags', which can assist in making a diagnosis of Fabry disease when assessed in conjunction with age, clinical history, and family history. Some ECG features can be indicative of specific diseases and useful for selecting further tests to help obtain a definitive diagnosis. For example, a short PR interval with pre-excitation in a young patient can be a normal variant, whereas in an older patient (>30 years) with a short PR interval, no pre-excitation, and with concentric left ventricular hypertrophy (LVH), could indicate Fabry disease.[2,4] Images obtained from an echocardiogram can also provide further evidence towards a diagnosis; for example, if an older patient (>70 years) presents with concentric hypertrophy, where every segment is the same thickness, it provides evidence of mitochondrial disease or amyloidosis. Cardiac MRI of the interventricular septum is also advantageous in facilitating a differential diagnosis, where a reduction in T1 signal in a patient with concentric LVH is a feature almost exclusive to Fabry disease.[5]

Recent years have also seen the adaptation of old diagnostic tests for new applications. Use of the bone tracer technique 99m-technetium-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy has been demonstrated to be a highly sensitive and specific test for accurately diagnosing patients with transthyretin-related amyloidosis.[6] When used in a prospective cross-sectional study in Spain, it was found that 13% of patients with heart failure with a preserved ejection fraction have amyloidosis, suggesting that the prevalence of amyloidosis may be underestimated.[7]

The ESC guidelines also recommend the use of simple blood tests in identifying some causes of HCM. Examples include the measurement of alpha-galactosidase A in men, to confirm a diagnosis of Fabry disease, and serum creatine phosphokinase levels, which are raised in a variety of metabolic and neuromuscular disorders.[2,8] Genetic screening may be warranted for the relatives of patients fulfilling the diagnostic criteria for HCM,[2] however a possible barrier to the adoption of genetic testing is the limited knowledge amongst cardiologists regarding when to initiate a genetic test and how to interpret the results.

In conclusion, a multidisciplinary approach should be used when diagnosing the underlying cause of HCM, as many conventional cardiac tests, when used independently, are insufficient for generating a definitive diagnosis. In the case of Fabry disease, clinicians need to be aware of diagnostic red flags, such as a short PR interval on an ECG and a reduction in the T1 signal on a cardiac MRI, and consider these in conjunction with laboratory tests, symptoms, and family history, prior to making a diagnosis.

Guess Who: Can You Spot the Patient with Fabry Disease? Putting Guidelines into Practice

Professor Aleš Linhart

Patients generally present to their doctor with symptoms and a personal history, not details of an underlying genetic disorder. Patients with Fabry disease may not present with cardiovascular symptoms, but anyone referred to a cardiologist is likely to undergo basic tests, such as an ECG, echocardiography, and cardiac MRI.[9] A high proportion of patients with Fabry disease present with HCM, particularly concentric diffuse hypertrophy.[10-12] In particular, posterior or posterolateral scars that do not appear to be a result of ischaemia when associated with HCM may be a marker of Fabry disease.[13] Alternatively, patients with Fabry disease may present with a mitral valve prolapse.[10]

However, HCM is a phenotype that is shared by many genotypes. For example, in the instances where Fabry disease patients present with asymmetric septal hypertrophy, it may be difficult to distinguish the structural differences in the myocardium from those observed in patients with sarcomeric HCM.[10] Therefore, it is important for cardiologists to investigate issues involving any other organs as this can provide insight into the underlying disorder.

As a syndrome, classical multi-organ disease may first be observed in patients with Fabry disease, including kidney ailments and strokes starting at 20 years of age.[12] In particular, patients presenting with a late-onset variant of Fabry disease will present largely with cardiomyopathy, possibly alongside cornea verticillata and microalbuminuria or proteinuria.[12] However, in a phenotype that suggests kidney damage could be symptomatic of many different cardiomyopathies, endomyocardial biopsies and genetic analysis may be necessary to confirm a diagnosis of Fabry disease. A renal biopsy showing typical lesions within the glomerulus and zebra bodies on electron microscopy, resulting from globotriaosylceramide being stored within the lysosomes, may also be indicative of Fabry disease.[14]

As Fabry disease is an X chromosome-linked disease that presents as a syndrome that can affect almost any system in the body, investigating family history may also be useful in obtaining a diagnosis, as a clear-cut pattern of inheritance could provide an indication of the underlying disease.[15] However, the X-linked inheritance pattern of Fabry disease can also make a diagnosis guided by family history difficult, because heterozygous females can be oligosymptomatic, if not asymptomatic, meaning that familial inheritance may not be immediately apparent.[16]

Therefore, identifying and correctly diagnosing patients with Fabry disease can be difficult and somewhat of a puzzle. While typical patients are described in the literature as having diffuse HCM with extracardiac manifestation, proteinuria, renal insufficiency, nephropathy, and/or skin lesions, not all patients will present with this phenotype.[12] Therefore, Fabry disease should be considered for all patients with unexplained LVH. While it is important to diagnose Fabry disease early when ERT treatment is most effective, an accurate diagnosis in patients with later-stage disease is also important because it may allow renal function to be stabilised, preventing further nephropathy progression.[3,12]

Ten Years of Enzyme Replacement Therapy: Long-Term Treatment Outcomes in Fabry Disease

Professor Aleš Linhart on behalf of Professor Christoph Kampmann

ERT for patients with Fabry disease became widely available approximately 15 years ago.[17] Since then, there has been increasing interest in long-term outcomes for patients diagnosed with Fabry disease. Cardiac alterations that manifest as dyspnoea, angina, fatigue, and palpitations are one of the predominant features of Fabry disease.[18] These symptoms are often a result of progressive HCM,[18] so the long-term effect of ERT on progressive HCM is of interest.

A single-centre, retrospective study aimed at evaluating the long-term effectiveness of agalsidase alfa on the progression of cardiomyopathy in patients with Fabry disease, reviewed the records of 45 patients (21 male, 24 female) with confirmed Fabry disease who had been treated with agalsidase alfa 0.2 mg/kg intravenously every other week over a median of 10.8 years.[19] Results from the study demonstrated that long-term treatment with agalsidase alfa improved or stabilised symptoms of heart failure, with 13 out of 14 patients with New York Heart Association (NYHA) Class II or III heart failure improving by at least one functional class.[19] Only one patient in the study (baseline: NYHA Class I) exhibited deterioration of heart failure symptoms.[19] Angina symptoms, measured using the Canadian Cardiovascular Society (CCS) scoring system, also improved (15/42; 36%) or stabilised (26/42; 62%) in most patients.[19] Furthermore, CCS angina scores for all patients with a baseline score of II or above (n=11) were reduced to score I or lower following ERT.[19]

When discussing the impact of ERT on LVH, it is important to place any results in the context of the progressive nature of cardiac alterations over the course of the disease.[18] After 10 years of ERT, symptoms of cardiomyopathy were stable or improved, and progression was generally attenuated in both males and females.[19] In patients administered agalsidase alfa therapy, LVH progression also stabilised with no significant change in left ventricular mass index (LVMI) in male patients with a baseline LVMI <50 g/m$^{2.7}$ and in all females (Figure 2).[19] In males with a baseline LVMI ≥50 g/m$^{2.7}$ (n=15), LVMI was significantly reduced after 10 years of agalsidase alfa therapy

(p=0.0061) (Figure 2).[19] Cardiac and renal function, measured by LV ejection fraction and estimated glomerular filtration rate (eGFR), respectively, also remained stable after 10 years of treatment.[19]

Notably, whilst similar studies have been performed,[20,21] few have managed to account for multiple cardiac and renal parameters, such as heart failure and angina status, LVH, eGFR, and proteinuria, over such a long duration of treatment. However, these outcomes are largely supported by a recent retrospective analysis of the Fabry Outcome Survey (FOS), which assessed cardiac and renal outcomes in patients receiving ERT over 10 years.[22]

FOS is an international registry which includes patients with Fabry disease who are receiving, or are candidates for, ERT with agalsidase alfa.[23] The recent analysis incorporated data from three cohorts:[22]

- Patients (n=382) who received agalsidase alfa therapy for a minimum of 10 years
- A renal cohort (n=105) taken from the treated cohort, with at least three available eGFR measurements
- A cardiac cohort (n=50) who had at least three available LVMI measurements

Analysis of the cardiac cohort demonstrated that over 10 years of agalsidase alfa therapy, LVMI stabilised among patients with no LVH at baseline.[22] In patients with LVH at baseline, small increases in LVMI were evident over time.[22] In addition, renal function remained relatively stable in females and demonstrated non-significant decreases in males.[22]

Long-term evidence from a single-centre study and the FOS analysis demonstrated that treatment with agalsidase alfa over 10 years stabilised or improved cardiac symptoms and cardiac structure.[19,22] In addition, renal function is generally preserved and cardiac function stabilised over time.[19,22] Although limited by small numbers because of the rarity of Fabry disease, these findings are supported by similar studies of shorter duration, and suggest that agalsidase alfa offers long-term benefits for patients with Fabry disease-associated cardiomyopathy.[19]

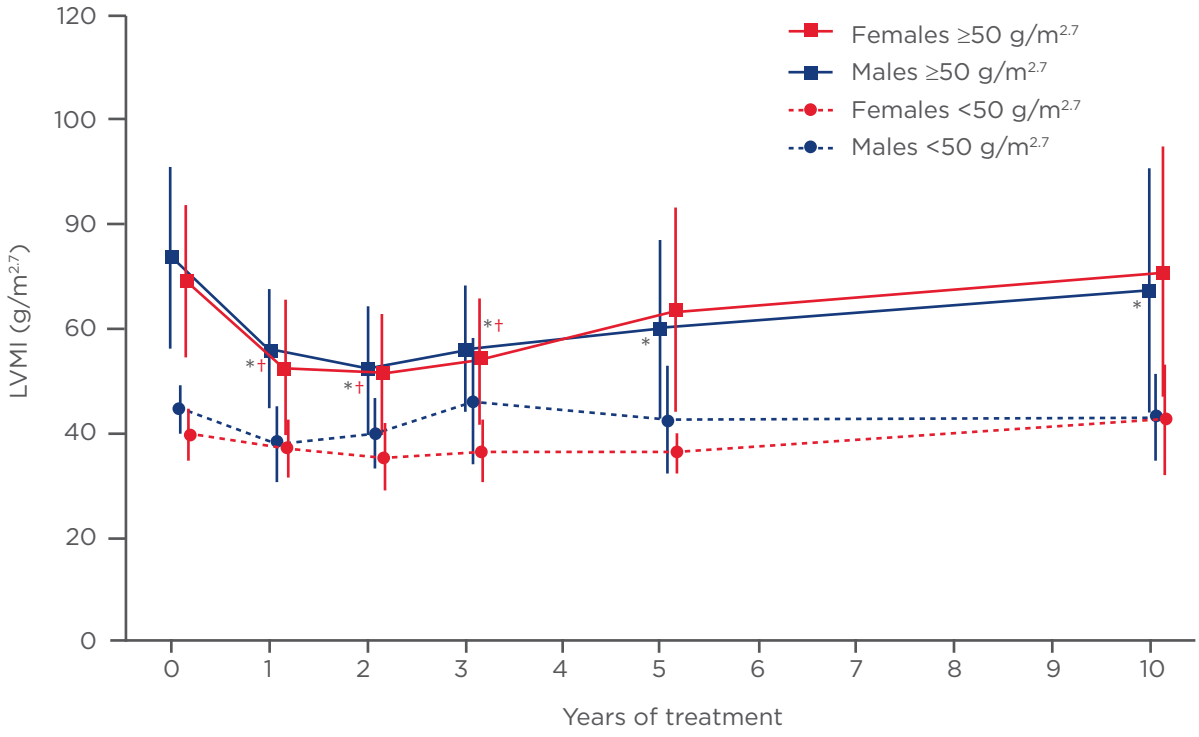

Figure 2: Mean left ventricular mass index (±SD) during 10 years of agalsidase alfa therapy stratified by gender and baseline left ventricular mass index.

*p<0.05 versus baseline for males with LVMI ≥50 g/m$^{2.7}$; †p<0.05 versus baseline for females with LVMI ≥50 g/m$^{2.7}$.

LVMI: left ventricular mass index; SD: standard deviation.

Adapted from Kampmann 2015.[19]

What is the Value in Screening Programmes for Rare Diseases?

Associate Professor Jean-Claude Lubanda

Diagnosing Fabry disease can be challenging for clinicians because patients can present with symptoms that are synonymous with several conditions, including pain, paraesthesia, hypohidrosis and hyperhidrosis, or angiokeratomas.[12] Additionally, physical examinations and imaging tests are extremely relevant for correctly identifying cases of Fabry disease, particularly in patients who present with atypical symptoms.[24]

Fabry disease is caused by a deficiency in the α-galactosidase A (α-GAL A) enzyme encoded by the *GLA* gene.[25,26] Assays of α-GAL A activity are not considered to be reliable enough to form a diagnosis, especially as there are differences in activity between males and females. Therefore, genetic analysis of the *GLA* gene is considered to be a more appropriate diagnostic method and is the only reliable test for Fabry disease females.[27] Nevertheless, measuring plasma globotriaosylsphingosine (lyso-Gb3) levels as part of a dried blood spot test may be useful because it is an important biomarker for the pathogenesis of Fabry disease.[28,29] However, genetic confirmation in females is still required for a final diagnosis.[28]

Given the numerous tests that can be used to screen for Fabry disease, the question of which specific population should be subjected to extensive testing still remains. Historically, family screening has been the most commonly used method for diagnosing Fabry disease. While screening newborns may have benefits, the low prevalence of 0.03% makes this challenging.[25] Therefore, screening methods tend to focus on evaluating the prevalence of Fabry disease in high-risk populations.

Cardiologists are specifically interested in patients with LVH, a distinguishing feature of Fabry disease. For example, screening of patients with LVH and low plasma α-GAL A activity, but no other symptoms of Fabry disease, indicated that approximately 3% of patients had Fabry disease-related mutations.[30] A similar prevalence of 4% was reported following systematic screening for undiagnosed Fabry disease in patients with LVH by another group.[31] Patients with end-stage kidney disease are another target population for plasma α-GAL A screening given severe kidney disease is also a common symptom of Fabry disease. Within this population, Fabry disease confirmed by gene mutation has a reported prevalence of 0.7%,[32] and 0.2% amongst patients undergoing haemodialysis assessed using dried blood spot screening.[33] This highlights how patients with Fabry disease, whose symptoms are classified into broad categories (e.g. HCM), or who suffer comorbid diseases, can be misdiagnosed and given ineffective treatment, which can negatively affect their prognosis. Additionally, in the case of Fabry disease, a positive diagnosis and subsequent screening of other members of the family can facilitate early treatment, improving an at-risk patient's prognosis.[15] Other populations that could potentially benefit from screening for Fabry disease include patients with other unexplained symptoms, such as cryptogenic stroke. Surprisingly, 4.9% of males and 2.4% of females who have suffered a cryptogenic stroke were found to have *GLA* mutations after being screened for α-GAL A activity.[34]

Overall, it has been demonstrated that screening for Fabry disease, despite its rarity, is important. There is now evidence to suggest that the prevalence of Fabry disease has been historically underreported because of the variability in symptom presentation. Patients with LVH, end-stage kidney disease, or cryptogenic stroke have a relatively high prevalence of Fabry disease that may justify routine screening, ultimately leading to more effective treatment for these patients. This is especially important in atypical cases where patients may not present with any other symptoms of the disease. Additionally, a positive diagnosis for Fabry disease following screening may allow a patient's family members to also be screened and to receive early treatment, if necessary, improving their prognosis.

Question and Answer Session

Q: Does every patient with HCM need to be tested for Fabry disease?

Prof Linhart suggested that a test for Fabry disease should be included in the panel of tests used for all patients with HCM, especially because there can be overlap between the clinical features of Fabry disease and sarcomeric gene mutations. Also, if sarcomeric gene mutations have been excluded, this increases the probability that a patient with HCM has Fabry disease.

Q: Should an 18-year-old patient with LVH be tested for Fabry disease?

Prof Linhart replied that registry data indicate that significant LVH, that meets the criteria for HCM, is unlikely to be present in Fabry disease affected males aged <25, or females aged <30. However, Fabry disease should not be discounted in patients who have reached these ages and have mild LVH.

Q: Should different screening tests for Fabry disease be used for men and women?

Assoc Prof Lubanda outlined that enzyme testing in women is problematic, because enzyme levels may appear normal in female patients with Fabry disease. Therefore genetic testing is always recommended, especially in women, but enzyme activity testing offers a useful screening method for men because low activity is a reliable sign of the disease. Genetic confirmation of a pathogenic mutation in the *GLA* gene is mandatory for a final diagnosis.

Q: When should endomyocardial biopsy be used for diagnosing Fabry disease?

Prof Linhart indicated that different mutations that can lead to Fabry disease can have differential effects on the patient. Therefore, looking for lysosomal lyso-Gb3 storage in endomyocardial biopsies following an enzymatic or genetic diagnosis of Fabry disease is useful when confirming the heart is impacted by the disease.

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IMPACT OF CARDIAC RESYNCHRONISATION THERAPY WITH DEFIBRILLATION BACK-UP IMPLANTATION ON CLINICAL OUTCOMES AND HEALTHCARE RESOURCE UTILISATION: AN ITALIAN COHORT STUDY

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INTRODUCTION

Cardiac resynchronisation therapy with defibrillation back-up (CRT-D) is an important therapy for the treatment of heart failure. While there are high upfront costs of CRT-D devices, the benefits of the therapy accrue over the lifetime of the device. Thus, when evaluating costs and benefits of the device, it is important to collect data over a long follow-up period to account for changes in mortality and healthcare resource utilisation. We assessed clinical outcomes and the related healthcare resource utilisation in patients implanted with CRT-D devices in one Italian region.

METHODS

Individual patient data from the Lombardy Healthcare Administrative Databases (LHAD) were merged with clinical data recorded in the Italian Pacemaker and Defibrillator Registry (IRCAB Foundation) and patients who received an implant from 2000–2010 were identified. Using this approach, 85.8% of LHAD patients have been linked with IRCAB files using an individual patient identifier. Patients hospitalised for the first CRT-D implantation from 2003–2010 were selected in order to compare healthcare resource utilisation (hospitalisation identified by Clinical Modification codes from the International Classification of Diseases, Ninth Revision [ICD-9], outpatient visits, and drug consumption) after a 3-year pre and post-device implantation period.

RESULTS

From 2003–2010, 4,404 patients (78.3% males, mean age: 67.6±9.2 years) underwent a *de novo* CRT-D implantation; 4,080 patients (92.6%) had dilated cardiomyopathy (39.9% ischaemic, 52.7% idiopathic) and 65.1% had a left ventricular ejection fraction <30%; 3,018 patients (69%) were implanted in primary prevention and 1,386 patients (31%) in secondary prevention. The number of first CRT-D implantations increased over time from 5 implants in 2000 to more than 600 implants per year in 2006, and thereafter. Primary prevention indication increased from 27% before 2004 to over 70% in 2007. The mean annual cardiovascular hospitalisation rate fell from 107% (95% confidence interval [CI]: 103.9–110.2) in the year before implantation to 52% (95% CI: 49.6–54.9, $p<0.05$) in the 2nd year after CRT-D implantation. The total annual cardiovascular care cost per patient (cardiovascular outpatient visits, drugs, and cardiovascular hospitalisations minus the hospital admissions for device replacement due to battery depletion) decreased significantly from €5,573.6

(95% CI: €5,337.0–€5,828.4) in the year before the implantation to €2,565.1 (95% CI: €2,383.9–€2,781.4) in the 2nd year after the implantation ($p<0.05$). The observed reduction in cardiovascular costs was due to a significant decrease in the total annual costs per patient for cardiovascular hospitalisations, from €4,755.4 (95% CI: €4,516.9–€4,980.2) in the year before the implant to €1,711.1 (95% CI: €1,529.1–€1,870.8) in the 2nd year after the implant ($p<0.05$), while outpatient visits and drug costs did not change significantly. On the other hand, the mean annual patient cost for CRT-D replacement due to battery depletion increased significantly from the 3rd year after the implant, reaching its peak during the 5th year with a cost of €4,574.6 (95% CI: €4,142.0–€5,040.9).

CONCLUSIONS

CRT-D implantation appears to be effective not only in improving outcomes, but also in decreasing cardiovascular costs, mainly due to a reduction in cardiovascular hospitalisation rates. On the other hand, due to battery depletion, a significant increase in hospitalisation rates for device replacement was observed during the 4th and 5th years after implantation, increasing the related costs. Thanks to improved battery technology and the availability of specific algorithms for automatic pacing output adjustment, recent-generation CRT-Ds display better longevity and, consequently, costs related to replacements will be reduced.

ASSESSING THE INFLUENCE OF THE GENETIC BACKGROUND ON ANTHRACYCLINE-INDUCED CARDIOTOXICITY WITH HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES

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This poster focussed on the genetic susceptibility to anthracycline-induced cardiomyopathies and was presented on the first day of the ESC 2016 congress during the 'Heart Failure Left Ventricular Dysfunction' session. Doxorubicin (DOX) belongs to anthracyclines, a class of cancer drugs that are used effectively during chemotherapy. However, its use is limited by its cardiotoxicity. Patients may develop severe cardiomyopathies after chemotherapy that are characterised by a decrease in the left ventricular ejection fraction and can ultimately lead to heart failure. The pathomechanisms of anthracycline-induced cardiotoxicity (ACT) are still unclear and several seemingly independent pathways have been postulated. DOX damages the DNA by intercalation and binding to to poisomerase-2, causing changes in gene expression and apoptosis.[1] Organelle damage and apoptosis are described as a result of DOX-induced reactive oxygen species production.[2] Since the development of ACT varies strongly between patients and DOX dose, a genetic susceptibility has been proposed and several single nucleotide polymorphisms (SNPs) have been found to be associated with ACT.[3,4]

We based our work on the study of Wojnowski et al.[3] which showed a statistical connection between SNPs in subunits of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the risk of developing ACT. Dermal fibroblasts from donors who received DOX during chemotherapy were reprogrammed into induced pluripotent stem cells (iPSCs). Donors with predisposing SNPs who also developed ACT were classified as the ACT patient group, while donors without SNPs and without cardiac symptoms were defined as the control group. The iPSCs were differentiated

in vitro into a 90–95% pure culture of iPSC-derived cardiomyocytes (iPSC-CMs) that expressed typical cardiac markers. Interestingly, DOX treatment resulted in a significant decrease of troponin T and α-myosin heavy chain expression in the ACT iPSC-CMs, and a decreased sarcomere organisation in both groups.

We then analysed the reactive oxygen species production in iPSC-CMs and found a significant increase of H_2O_2 production in both groups after treatment, with physiological DOX concentrations of 0.1–0.5 μM. Importantly, H_2O_2 generation was higher in ACT patients compared with the control donors in all tested DOX concentrations (0.5 μM DOX: $p<0.05$). In order to examine if the analysed SNPs have an influence on gene expression of NADPH oxidase subunits and may account for the increased H_2O_2 production, we investigated NOX2, NOX4, CYBA, RAC1, and RAC2 by real-time polymerase chain reaction. We found a higher expression of RAC2 and CYBA in iPSC-CMs of ACT patients compared with the controls. DOX treatment resulted in decreased expression of all investigated genes in both groups.

To analyse the functional phenotype, engineered heart muscles were generated. We observed a significantly greater decrease of contraction force in ACT patients compared with the control donors upon DOX treatment. The DOX-induced increase of beating frequency was significantly higher in the ACT patient group. However, DOX caused an equal increase in irregular beating in both groups.

In conclusion, iPSC-CMs generated from ACT patients were more susceptible to DOX than control cells; this was indicated by a reduced contraction force, increased H_2O_2 production, and decreased expression of sarcomeric genes. These data suggest a genetic predisposition for ACT. Several interesting questions were discussed during the session which were about ongoing analyses such as calcium imaging and apoptosis, highlighting the complexity of ACT pathomechanisms. Comments about the difficulty to interpret results of studies in the literature using different models and DOX applications demonstrated the need to model ACT reliably in a human system.

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THE IMPACT OF CD4$^+$CD28^{NULL} T LYMPHOCYTES ON ATRIAL FIBRILLATION AND MORTALITY IN PATIENTS WITH CHRONIC HEART FAILURE

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The development of cardiac arrhythmias, such as atrial fibrillation (AF), represents a common and severe complication in patients with chronic heart failure (CHF), resulting in haemodynamic deterioration. Recent evidence suggested that chronic inflammatory processes have a pivotal

impact on the development of both AF and CHF. However, less attention has been paid to cellular immunity.

Cytotoxic T cells characterised by the loss of the surface-protein CD28 ($CD4^+CD28^{null}$) are crucially involved in chronic inflammatory conditions. Due to the lack of the CD28 antigen, this T cell subset loses its sensitivity for apoptosis induction triggered by regulatory T cells and is less susceptible, leading to an unimpaired inflammatory response, or even showing autoreactivity.

We therefore analysed and compared T cell subsets of CHF-patients presenting with AF, with CHF-patients free of AF. We found a significantly higher fraction of $CD4^+CD28^{null}$ cells in individuals presenting with AF. Moreover, after a median follow-up of 4.5 years, 32 (28.6%) patients died due to cardiovascular causes. Interestingly, $CD4^+CD28^{null}$ cells were significantly associated with cardiovascular mortality in patients presenting with AF but not in patients free of AF.

Tissue damage promoted by autoimmune $CD4^+CD28^{null}$ cells among the cardiac atria may represent a potential explanation for the strong association between this T cell subset and AF. Furthermore, multiple micro-scar formations in atrial tissue due to cell necrosis may impact on electrical atrial conduction, resulting in the development of AF and faster progression of CHF leading to fatal cardiovascular events.

This data gives novel insights into potential pathophysiological mechanisms on the development of AF. Moreover, the results may improve suitable risk assessment and secondary prevention in patients with CHF presenting with AF.

PHYSICAL ACTIVITY, BODY MASS INDEX, AND MORTALITY AMONG SUBJECTS WITH CORONARY HEART DISEASE: DATA FROM THE NORD-TRØNDELAG HEALTH STUDY

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At the European Society of Cardiology (ESC) 2016 congress in Rome, Italy, we presented our abstract on how physical activity seems to alter the relationship between obesity status and subsequent prognosis in patients with coronary heart disease (CHD). Our objective was to assess the isolated and combined associations between physical activity, BMI, and mortality in subjects with CHD. In this population, previous observational studies have suggested an obesity paradox; improved survival in subjects who are overweight or mildly obese.[1]

In our study, including more than 5,000 participants with angina pectoris and/or myocardial infarction from the Nord-Trøndelag Health Study (HUNT) in Norway, we found 15–20% lower mortality in those with BMI between 25.0 kg/m^2 and 34.9 kg/m^2, compared with the reference group of BMI 18.5–22.4 kg/m^2. However, when we stratified for physical activity level, we observed an obesity paradox only in those who reported to be inactive, with reduced mortality risk in all BMI categories above 25.0 kg/m^2. In those with a low physical activity level (i.e. doing some activity but not meeting current recommendations of >150 minutes of moderate or >60 minutes of vigorous intensity exercise per week),[2] we observed a significantly reduced

mortality risk only in those with BMI 22.5–24.9 kg/m^2 and 25.0–27.4 kg/m^2. In subjects who were adhering to or exceeding the physical activity recommendations, we observed no relationship between BMI and mortality risk. Physical activity was associated with an 18–31% reduced mortality risk, with higher reductions in those who adhered to or exceeded the current recommendations.

We think the main clinical implication of our research is that CHD patients should be physically active. In our study, and in line with previous data, even physical activity below the recommended level is associated with reduced mortality risk in this population. We still do not know exactly how to explain why being overweight or obese can be protective in CHD. During the conference, there were some discussions about whether the use of BMI as an indicator of adiposity can limit the validity of studies like ours. However, BMI is the most widely used measure for body size and some studies even indicate that having a high fat percentage is associated with improved survival in this population.[3,4]

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SHOCK INDEX AS A PREDICTOR OF HOSPITAL MORTALITY: BETTER THAN SYSTOLIC BLOOD PRESSURE?

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Cardiogenic shock (CS) in the context of acute coronary syndrome (ACS) remains associated with a mortality rate of 40–50%. The aim of this study was to identify predictors of evolution to CS and to assess the accuracy of the shock index (SI) (ratio of systolic blood pressure [SBP] and heart rate [HR] at admission) compared with a SBP of <90 mmHg at admission in predicting hospital mortality.

The authors performed a retrospective analysis of ACS patients admitted between 2010 and 2014 enrolled in the Portuguese Registry of ACS. The study included patients without CS at admission (Killip Class <IV). Patients were divided according to hospital evolution: CS (Group 1 [G1]) and without CS (Group 2 [G2]). Clinical, electrocardiographic, and echocardiographic characteristics at baseline were collected and predictors for CS were determined. The authors calculated the cut-off SI that predicts CS and hospital mortality.

Of 12,545 ACS patients admitted without CS, 334 (2.6%) were included in G1 and the remaining in G2. G1 patients were older (74±11 versus 66±13 years; p<0.001), there were fewer smokers (18.0% versus 28.1%; p<0.001), more cases of heart valve disease (6.8% versus 3.1%; p<0.001), previous stroke (12.1% versus 7.9%; p=0.005), and chronic kidney disease (11.7% versus 6.0%; p<0.001). The majority of G1 patients had an ST elevation myocardial infarction (STEMI) compared to the G2 patients (64.7% versus 39.9%; p<0.001) and ACS in an anterior location (59.3% versus 48.1%; p=0.001). The time to reperfusion in STEMI patients was <120 minutes in 4.2% of patients in G1 versus 8.9% of patients in G2 (p=0.520). At admission, HR was higher

in G1 patients (86±25 versus 77±19 bpm; p<0.001) and SBP lower (121±29 versus 140±28 mmHg; p<0.001). SI was significantly different between the two groups (0.75±0.28 versus 0.57±0.19; p<0.001). Predictors of CS were female (odds ratio [OR]: 1.34; p=0.038), age (OR: 1.04; p<0.001), creatinine level at admission (OR: 1.20; p<0.001), STEMI (OR: 2.77; p<0.001), HR (OR: 1.01; p=0.003), SBP (OR: 0.98; p<0.001), and a left ventricle ejection fraction of <50.0%, particularly one lower than <30.0% (OR: 17.89; p<0.001). The cut-off SI value that predicts CS was 0.64 (sensitivity of 75.3%, specificity of 82.3%, area under the receiver operating characteristic [ROC] curve of 0.864) and the cut-off for predicting hospital mortality was 0.59 (sensitivity of 66.3%, specificity of 63.9%, area under the ROC curve of 0.690); by comparison a SBP of <90 mmHg has a sensitivity of 8.9% and a specificity of 98.0% in predicting hospital mortality.

In conclusion, a SI of 0.64 predicts CS with a sensibility of 75.3% and a specificity of 82.3%. A SI of 0.59 predicts hospital mortality with more sensibility but lower specificity compared with a SBP of <90 mmHg at admission.

TRANSLATION OF HOME-BASED MOBILE HEALTH CARDIAC REHABILITATION IN REAL PRACTICE

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BACKGROUND

Cardiac rehabilitation (CR) is pivotal to the recovery of individuals surviving a cardiac event. Despite large benefits such as reduced cardiovascular mortality and hospitalisations,[1] uptake and completion of these programmes remain low for traditional centre-based CR.[2] In an effort to overcome some of the barriers to CR participation, the Australian e-Health Research Centre in collaboration with Queensland Health designed and developed an innovative home-based care model utilising smartphones and the internet to deliver CR to eligible patients' homes. This model was tested in a randomised controlled trial, becoming the first clinically validated mobile health delivery of CR.[3] Based on the positive outcomes and learnings, we re-engineered the platform, which is now called MoTER (Mobile Technology Enabled Rehabilitation). The MoTER platform is illustrated in Figure 1. The MoTER smartphone app is tailored to each patient's individual requirements through a clinician web portal. Selected relevant health measures are entered on the app as often as recommended by CR clinicians. Steps are recorded by the phone's built-in accelerometer but additional exercise such as swimming, gym, etc. can also be entered. Weekly telephone consultations are scheduled to motivate and guide patients to reach their goals and discuss symptoms. Other features of the app include regular messages, educational media (videos), links to websites such as The Heart Foundation, and also the option of relaxation audio. Data automatically updates to a central database which allows clinicians to review patient progress through text and/or graphical presentations via the clinician web portal prior to phone interventions. Clinicians are guided through weekly themes and topics for discussion and they have the ability to enter free text during the conversations. These can be printed as progress notes at the end of the CR programme as a medical record.

IMPLEMENTATION

MoTER was implemented in May 2015 within Ipswich CR Services (Queensland, Australia) with a catchment area of relatively small regional and rural towns. A total of 29 patients enrolled in MoTER CR over 12 months, which included patients who

needed to return to work sooner and those who experienced transport issues such as large distances or a lack of public transport. Of these, 27 commenced with the programme (17 male and 10 female; average age: 53 years old [range: 34–67 years]) and 24 completed it (adherence: 89%). Similar to findings of the randomised controlled trial,[3] clinical results at 6 weeks showed significant improvement in functional capacity and weight (Figure 2). There was a reduction in hip circumference (albeit not significant) and blood pressure (both systolic and diastolic) did not show significant change but were generally within normal range.

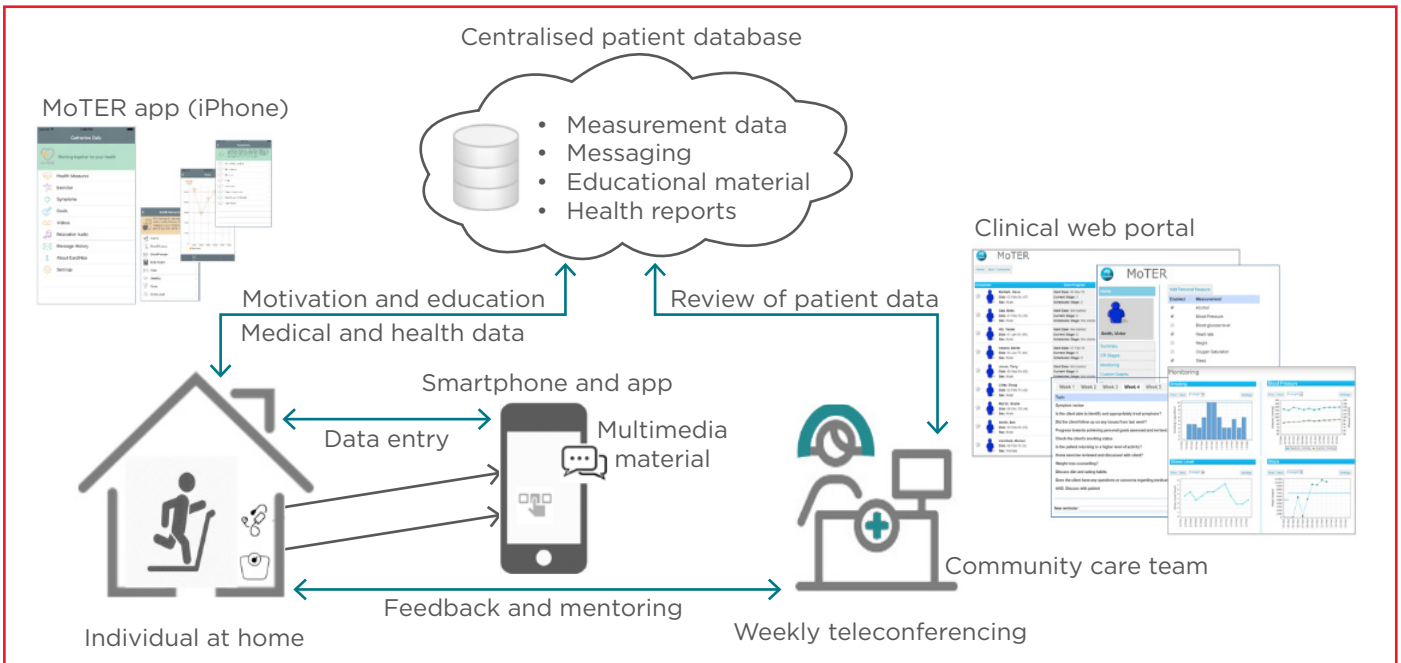

Figure 1: Schematic presentation of the MoTER cardiac rehabilitation platform.
MoTER: Mobile Technology Enabled Rehabilitation.

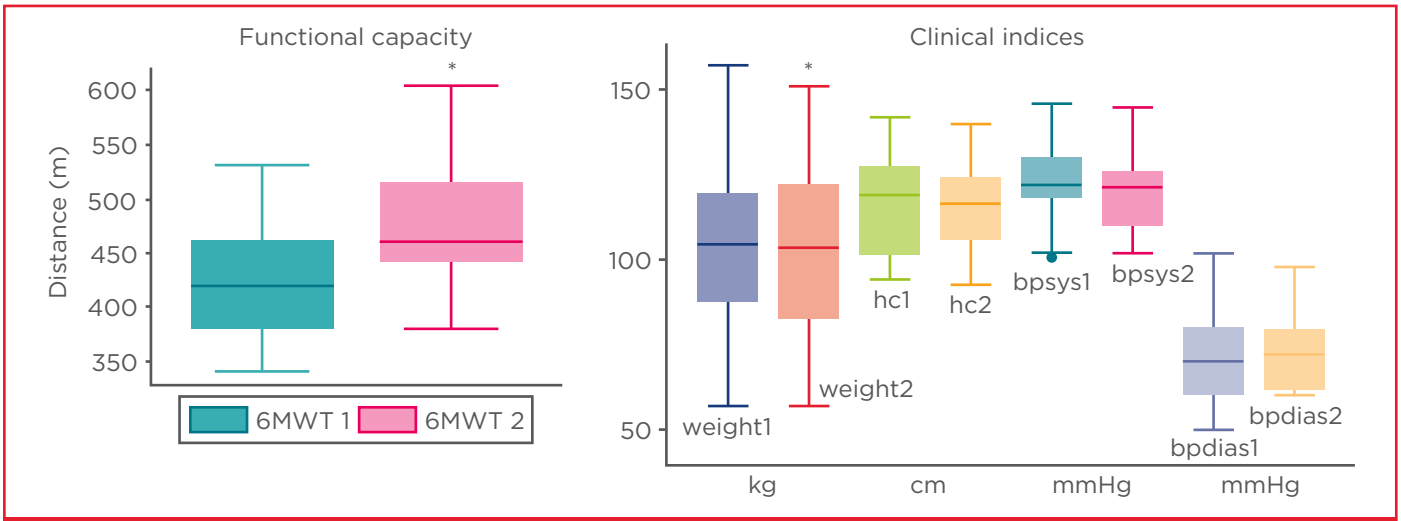

Figure 2: Functional capacity and clinical index changes at 6 weeks.
6MWT: 6-minute walk test; hc: hip circumference; bpsys: blood pressure systolic; bpdias: blood pressure diastolic; 1: baseline; 2: at 6 weeks.
*p<0.05

Self-assessment of health and wellbeing were gathered from responses to an evaluation questionnaire. These were very encouraging with exceptionally high percentages of patients at least partly showing improvements (when applicable) in many of the cardiovascular disease-related risk factors. These included smoking cessation, becoming fitter, losing weight, and decreasing and better management of stress. User perceptions were very positive and all patients found the MoTER app useful with most agreeing that it was easy to use and that it motivated them to reach their goals.

Challenges experienced during the implementation such as a slow start due to structural changes within the health service, infrastructure challenges, and staff deployment will serve well as lessons learned for future implementation in a number of other Queensland hospitals. We conclude with a statement by the 2016 European Guidelines on cardiovascular disease prevention in clinical practice: "Thus telerehabilitation could further widen participation to more patients and provide monitoring and greater individualized behavioural support, but large-scale randomized trials are needed,"[4] a statement which is supported by the outcomes of this study.

Acknowledgments

Ipswich Cardiac Rehabilitation Centre staff, West Moreton Hospital and Health Services, Queensland, Australia; AEHRC MoTER Engineering team, CSIRO, Australia.

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MAGNETIC RESONANCE IMAGING AS AN ASSESSMENT TOOL IN HYPERTENSION

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BACKGROUND

European guidelines recommend that patients with hypertension are assessed for target organ damage.[1] Patients with early onset (<40 years) or drug-resistant (office blood pressure ≥140/90 mmHg despite ≥3 antihypertensives) hypertension should also be investigated for secondary causes.[2] We proposed that a single magnetic resonance imaging (MRI) scan could provide all the imaging required for an evaluation of patients with hypertension in the context of a tertiary hypertension clinic.

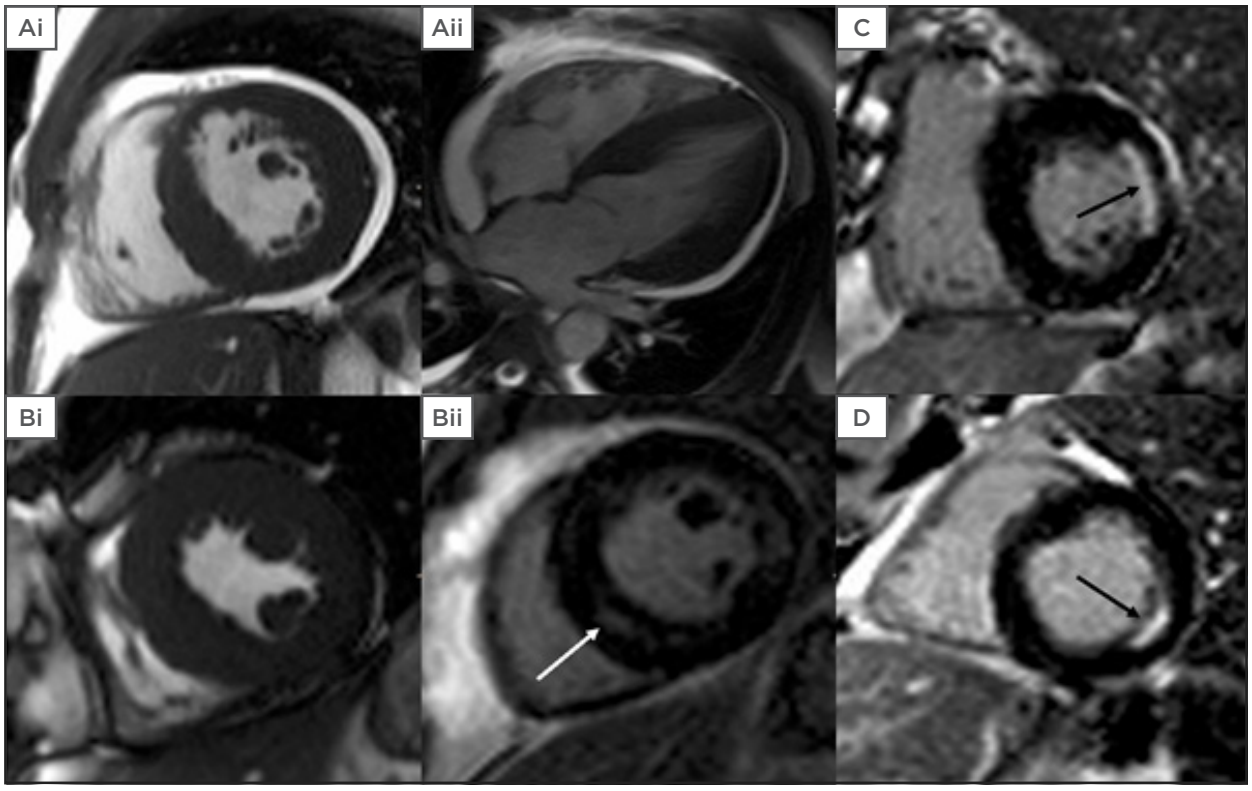

Figure 1: Magnetic resonance imaging of target organ damage in hypertension.
Ai and Aii) Left ventricular hypertrophy; Bi and Bii) left ventricular hypertrophy with patchy mid-wall replacement myocardial fibrosis consistent with hypertrophic cardiomyopathy; C and D) myocardial infarction (subendocardial fibrosis).

METHODS

Data from 200 consecutive patients investigated through our specialist hypertension clinic between 2011 and 2015 were presented. Imaging at 1.5 Tesla included assessment of cardiac volumetrics and fibrosis (late gadolinium enhancement), as well as imaging of the kidneys, renal arteries, adrenals, aorta, and cerebral vessels. Comparisons were made with other imaging modalities where available; 84 patients had previous echocardiograms, 81 patients had a renal ultrasound, and 11 patients had a renal computed tomography angiography.

RESULTS AND DISCUSSION

The 200 patients, of whom 56% were male aged 51±15 years, were taking 3.1±2.0 antihypertensive medications and had an average office blood pressure of 168±30/96±16 mmHg. Of the patients, 38% were drug-resistant, 32% had young onset hypertension, 18% were uncontrolled on <3 medications, and 12% had alternative difficult-to-treat hypertension (e.g. highly labile blood pressure or accelerated hypertension).

Overall, 79% of patients had evidence of target organ damage and 61% had left ventricular hypertrophy (LVH). The prevalence of LVH was considerably higher than the 36–41% rate seen in the general hypertensive population.[3] Of the patients, 14% had a reduced ejection fraction, 14% had impaired diastolic function, and 42% had impaired long-axis function, indicating that not all patients with a normal ejection fraction had normal ventricular function. Of those imaged, 27% had ≥1 accessory renal artery and whilst this did not represent a secondary cause of hypertension, it provided useful screening information about patients being considered for renal denervation.

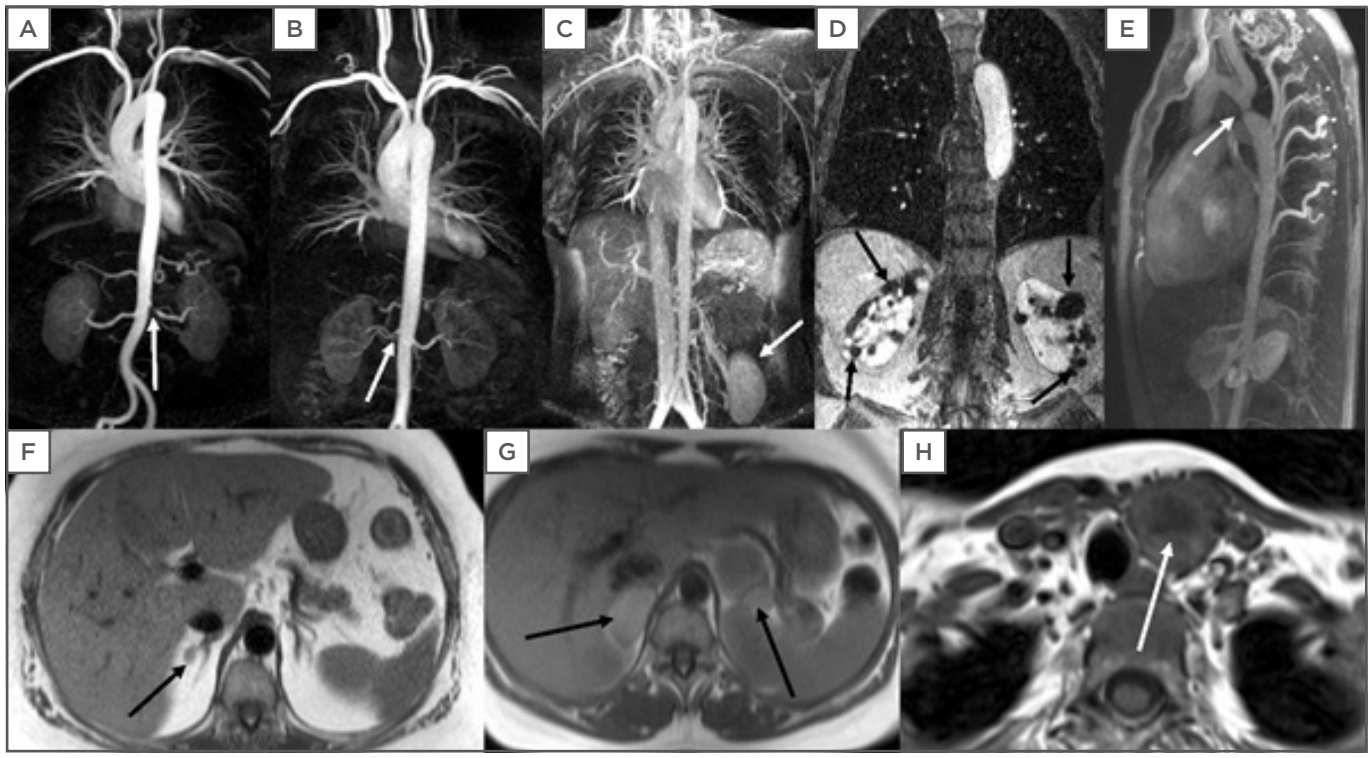

Figure 2: Potential secondary causes of hypertension demonstrated on magnetic resonance imaging. A) Left ostial renal artery stenosis; B) right accessory renal artery; C) single left mal-rotated and inferiorly-positioned kidney (renal coloboma syndrome); D) polycystic kidney disease; E) aortic coarctation with numerous collateral vessels (*); F) right benign adrenal nodule; G) bilateral adrenal phaeochromocytomas (multiple endocrine neoplasia type IIa); H) large left thyroid nodule.

We identified 15 individuals with subendocardial fibrosis consistent with previous myocardial infarction. In five of these patients this was a new diagnosis and resulted in the instigation of secondary prevention, six patients showed evidence of cerebral or peripheral vascular disease, and four patients were reclassified with probable hypertrophic cardiomyopathy. Examples of target organ damage are shown in Figure 1.

Twenty-nine patients had potential secondary causes of hypertension on imaging; 12 (6%) adrenal masses (including 2 phaeochromocytoma), 10 (5%) renal artery stenoses, 7 thyroid abnormalities, 1 aortic coarctation, 1 enlarged pituitary gland, 1 polycystic kidney disease, and 1 renal coloboma syndrome (Figure 2).

If we regard cardiac MRI as the gold standard, then echocardiography overdiagnosed LVH in 15% of patients and missed it in 14%. Renal ultrasound reports were normal in four cases of renal artery stenoses. MRI was unable to detect one adrenal adenoma seen on subsequent computed tomography imaging in a patient with biochemistry indicating hyperaldosteronism.

CONCLUSION

MRI is a safe and effective method of screening for target organ damage and secondary causes of hypertension that can be used alongside standard endocrine testing. It could replace the combination of echocardiography, renal ultrasound, and computed tomography imaging used to investigate those with young onset and resistant hypertension. However, limitations raised for discussion included the cost-effectiveness of the technique, the management of incidental findings, and whether further specialist imaging was still required in the case of positive MRI findings. In our experience,

MRI was both effective and efficient in the population studied as those requiring specialist hypertension assessment are more likely to have target organ damage or a higher clinical suspicion of secondary hypertension than the general population. MRI also provides additional information for patients being considered for renal denervation, and gives insight into the pathological changes seen in the myocardium in hypertensive heart disease.

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THE FINDING OF A FOUNDER MUTATION C.3344C>t(p.Pro1115Leu) IN THE *EIF2KA4* GENE IN IBERIAN ROMANI PATIENTS WITH PULMONARY VENO-OCCLUSIVE DISEASE: A FAMILY MATTER

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INTRODUCTION

Pulmonary veno-occlusive disease (PVOD) is an infrequent form of pulmonary hypertension characterised by low carbon monoxide diffusing capacity, typical radiological findings, occult alveolar haemorrhage, and is associated with a worse prognosis. PVOD may come in many forms, including a heritable form. With a difficult-to-diagnose disease such as this, genetic study arises as an essential tool in the diagnosis.

Biallelic mutations in *EIF2KA4* in a cohort of French patients have been described in 25% and 100% of sporadic and heritable PVOD cases, respectively, by Montani et al.[1]

Our group previously described the founder mutation c.3344C>t(p.Pro1115Leu) in a Romanie population in Spain in the *EIF2KA4* gene.[2] This mutation appeared with a severe phenotype as described by other authors.

The aim of our study was to analyse the prevalence of *EIF2KA4* mutations in a Spanish cohort of heritable PVOD Romani patients to describe their clinical profile and outcomes and to perform the family study.

Table 1: Baseline characteristics.

Parameter	Value
Age (years)	27.21±8.45
Male sex (%)	50
New York Heart Association Class III–IV	9 (64, 3%)
6-minute walk test (metres)	391.85±119.80
Mean pulmonary artery pressure (mmHg)	46.42±14.92
Cardiac index (litres/min/m^2)	2.73±0.85
Diffusing capacity of the lungs for carbon monoxide (%)	30.14±8.97
Lung transplant or death within the first 12 months	9 (64%)

For this analysis heritable PVOD patients were included. PVOD diagnosis was based on clinical, functional, radiological, and haemodynamic findings. Patients were screened for *EIF2KA4* mutations, as well as their first and second-degree relatives.

The relevant findings of our study show that in the 14 patients belonging to 7 unrelated families who attended 3 participating centres from November 2011 to June 2015, the genetic analysis revealed a biallelic mutation c.3344C>t(p.Pro1115Leu) in all the patients. Baseline characteristics are shown in Table 1. Most of the patients presented an aggressive form of PVOD, as 64% deceased or underwent lung transplantation in Year 1. A total of 76 relatives underwent genetic testing. In this group, an elevated number of unaffected heterozygous members were detected (35%). This finding is of great importance due to the high rate of consanguinity as well as the possibility of fathering children with homozygous mutation. We detected two unaffected homozygous carriers (10.5%) who are in close clinical monitoring at present.

RESULTS FROM THE DISCUSSION

Important advances have been made in the field of pulmonary veno-occlusive diseases, a form of pulmonary hypertension that is not widely understood, underdiagnosed, and has an especially poor short-term prognosis. However, a recent clinical practice guidelines consensus between the European Society of Cardiology and European Respiratory Society synthesises knowledge about risk factors and genetic bases.

In Spain alone there are approximately 750,000 Romanie. Since this ethnic group has had different migration patterns, the expression and burden of this mutation spreads across Europe but remains unknown.

Our study is a plea to the medical community to be aware of the seriousness of this disease and the implications of genetics in this group of Romani who are young and have very low diffusion capacity. One must also be aware of heterozygous healthy carriers to implement an adequate programme of genetic counselling due to the high rate of consanguinity.

In light of our results, a high degree of suspicion is warranted when facing a Romani patient with dyspnoea and diminished carbon monoxide diffusing capacity, and genetic testing of *EIF2KA4* should be offered in order to achieve an early diagnosis and referral to a centre able to provide lung transplantation.

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MIDREGIONAL PROADRENOMEDULLIN AND GROWTH DIFFERENTIATION FACTOR-15 ARE NOT INFLUENCED BY OBESITY IN HEART FAILURE PATIENTS

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AIMS

Obesity is a risk factor for heart failure (HF), but the identification of symptomatic, obese HF patients is challenging because obesity can mimic HF symptoms. We aimed to evaluate novel biomarkers for HF in obese subjects of the general population.

METHODS AND RESULTS

Midregional pro-adrenomedullin (MR-proADM), growth differentiation factor-15 (GDF-15), midregional pro-atrial natriuretic peptide (MR-proANP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured in 5,000 individuals of the population-based Gutenberg Health Study, including 1,204 obese individuals (BMI ≥30 kg/m^2) and 107 individuals with HF. NT-proBNP and MR-proANP were lower in obese versus non-obese HF individuals (p=0.013 and p=0.01, respectively), whereas GDF-15 was similar and MR-proADM was higher in obese versus non-obese HF individuals. All biomarkers increased the odds ratio of prevalent HF. For NT-proBNP and MR-proANP, this increase was lower in obese versus non-obese individuals, whereas it was comparable in MR-proADM and GDF-15. All biomarkers were associated with increased all-cause mortality (median follow-up 7.3 years, 211 events). Results were validated in 8,373 individuals (n=1,734 with BMI ≥30 kg/m^2) of the Finland Cardiovascular Risk study, with a median follow-up of 13.8 years (1,030 events). Using a dichotomised biomarker cut-off for HF, the best predictor for all-cause mortality in obese subjects was GDF-15 (p<0.001).

CONCLUSION

All biomarkers were associated with HF and higher risk for all-cause mortality in the general population. In contrast to the natriuretic peptides NT-proBNP and MR-proANP, the novel biomarkers MR-proADM and GDF-15 were not lower in obese HF individuals, indicating their potential tofacilitate HF diagnosis and prognosis in an increasingly obese HF population.

NOVEL NANOSYSTEMS TO COMBAT ATHEROSCLEROSIS: FUNCTIONAL EFFECTS ON ENDOTHELIAL AND MONOCYTIC CELLS

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The potential clinical impact of nanotechnology in terms of detection and management of cardiovascular diseases is enormous. By coating nanoparticles with plaque-specific ligands, significantly increased accumulation of these agents at the atherothrombotic sites could be achieved, leading to improved detection and characterisation of the plaques. Furthermore, treatment outcomes can be dramatically improved

if the drug-carrying nanoparticles are directly targeted at the diseased artery region, thus reducing systemic side effects. However, in spite of promising results obtained in the vast number of bench investigations, no specific nanoparticle-based system has been approved for diagnosis or therapy of atherosclerosis in humans. Hence, our goal is the development of effective, safe, and innovative nanoparticle-based systems for the diagnosis and therapy of clinically relevant atherosclerosis.

To ensure future clinical safety, the nanosystems intended for intravascular applications must first be tested and proven safe *in vitro*. Thus, the objective of our work was to investigate the effects of different types of nanoparticles on endothelial cell (EC) and monocytic cell (MC) functions. We synthesised and investigated diverse nanosystems, comprising liposomes, lipid nanoparticles, and polymeric and iron oxide nanoparticles. Some of the tested nanosystems contained a P-selectin-targeting agent (fucoidan), or contrast agent (e.g. gadolinium chelate, iron oxide).

In static conditions, long-term effects of nanoparticles on EC viability were assessed by real-time cell analysis and live cell imaging. To determine the effect of nanoparticles on tumour necrosis factor alpha (TNF-α)-induced MC recruitment, ECs grown in bifurcating slides were exposed to chronic non-uniform shear stress in the presence or absence of different nanoparticle types, followed by stimulation with TNF-α and dynamic monocyte adhesion assay. Spontaneous EC migration and chemotaxis of MCs towards monocyte chemoattractant protein-1 were determined using a barrier assay and a modified Boyden chamber assay, respectively. Furthermore, a pilot study in pigs was done to assess the complement activation-related pseudoallergy upon the intravenous administration of several nanoparticle types.

Based on the experimental results, the majority of tested nanoparticles were well tolerated by ECs up to the concentration of 100 µg/mL in static and up to 400 µg/mL in dynamic conditions. Fucoidan-coated polymeric nanoparticles at 50 µg/mL inhibited EC migration, but had a beneficial suppressive effect on MC recruitment under non-uniform shear stress. Lipid nanoparticles also dose-dependently reduced MC adhesion to ECs under non-uniform shear stress. No significant effects of iron oxide nanoparticles on EC migration or MC recruitment were observed but one of the formulations (lauric acid and albumin-coated) inhibited MC chemotaxis. Liposomal nanoparticles had no effect on cell migration, but slightly induced MC recruitment under non-uniform shear stress. The results of a pilot study in a pig model showed that intravenous administration of empty liposomal nanoparticles (1 mg/kg), gadolinium-loaded liposomes (1 mg/kg), or novel dextran-coated iron oxide nanoparticles (SEON^{DEX}, 5 mg/kg) did not evoke the hypersensitivity reaction, indicating a low immunogenicity of these nanoparticles.

Taken together, the majority of the tested nanosystems had favourable safety profiles for potential cardiovascular imaging and drug-targeting applications. Depending on the envisioned application, the specific effects of nanosystems on ECs and MCs should be taken into consideration. Our studies represent an attempt to advance the nanosafety by utilising a systematic approach to the comparative analysis of nanoparticle effects on human ECs and MCs. In the future, a substantial amount of *in vivo* studies will be necessary before the nanosystems with proven *in vitro* safety and efficacy can be translated into clinical trials. Despite multiple regulatory constraints, the future progress in diagnosis and treatment of cardiovascular disorders is expected to benefit strongly from the development of novel nanotechnology-based strategies.

ATRIAL FIBRILLATION IN THE SETTING OF ACUTE CORONARY SYNDROMES: INSIGHTS FROM THE ACUTE MYOCARDIAL INFARCTION IN SWITZERLAND PLUS REGISTRY EXPERIENCE

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The complex interaction between acute coronary syndromes (ACS) and atrial fibrillation (AF) has been extensively studied since the 1970s. Many scientific works confirmed that this association is very common, with an incidence varying between 5% and 20% depending on the registry. Furthermore, patients affected by ACS and AF are characterised by larger comorbidity burden; the association is more common in the elderly, in patients with more cardiovascular risk factors, peripheral and coronary artery disease, heart failure, and chronic kidney insufficiency. The advanced age and the burden of comorbidities, including AF, correlates with higher mortality and morbidity in ischaemic patients, either in-hospital or at long-term follow-up.

Despite large amounts of literature available on the topic, coming from historical data from American registries such as the Global Registry of Acute Coronary Events and from retrospective analysis of Medicare reports, there is still debate on the prognostic significance of the different forms of AF, on the prognostic impact of new onset AF in acute myocardial infarction (AMI), and on the therapeutic strategies to optimise outcome and minimise the haemorrhagic risk associated with the combination of antithrombotic medications and anticoagulants.

Therefore, we analysed data from the Acute Myocardial Infarction in Switzerland (AMIS) Plus registry, a nationwide database with voluntary participation, collecting data on patients with ACS since 1997 from 82 Swiss hospitals with the aim to shed light on actual incidence trends, therapeutic approaches, morbidity, and mortality in patients with AMI and AF.

We compared the clinical characteristics of patients with pre-existing and new onset AF with the hypothesis that the two forms of AF could represent separate entities with peculiar therapeutic and prognostic impact. Preliminary results of our analysis were presented during the last congress of the European Society of Cardiology (ESC) held in Rome, Italy.

Among the 36,000 patients enrolled in the registry between 2004 and 2014, the incidence of pre-existing and new onset AF in the context of ACS has remained stable, at 4.5% and 1%, respectively. In line with the data from the medical literature, patients with pre-existing AF were older and had a worse cardiovascular risk profile and comorbidity burden compared with the control population. On the contrary, patients with new onset AF show a cardiovascular risk profile and a comorbidity burden similar to the general population of patients with ACS. We also noticed how the clinical presentation

of patients with ACS and AF differ from those without the arrhythmia. Signs of pulmonary congestion (shortness of breath and Killip Class >3) were more common in patients with AF. Furthermore, ST-segment elevation myocardial infarction presentation, as well as the need for circulatory support, either pharmacologic or with intra-aortic balloon pump, were frequently associated with new onset AF. As known from previous studies, in patients with pre-existing AF, there is a reduced access to evidence-based therapies for ACS such as dual antiplatelet therapy and percutaneous coronary revascularisation; the latter is only used in half the patients with AF compared with 80% of control patients.

Despite the different risk profile, in-hospital mortality in patients with pre-existing and new onset AF was comparable, at 10% and 13%, respectively, figures significantly higher than observed in patients without AF. One-year mortality was also comparable at 13% in patients with pre-existing AF and 11% in patients with new onset AF versus 3% in control patients.

Our data, therefore, provide a contemporary European picture of the prognostic impact of AF, either pre-existing or as a complication of ACS. Our data can only partially confirm the classic axiom that, in the context of ACS, chronic and new onset AF share the same pathophysiologic mechanisms and confer different outcomes. In fact, although new onset AF is a marker of worsening haemodynamic impact of ACS (with consequent acute reduction of cardiac output, increased atrial filling pressure, increased autonomic tone, and higher propensity to desynchronisation), our data clearly shows that both classes of patients share a similar prognosis, with a comparable in-hospital and 1-year increase in mortality, 3-times higher than the general population affected by ACS. This evidence constitutes a stimulus to identify new therapeutic strategies to minimise mortality in this class of high-risk patients.

THIOREDOXIN OVEREXPRESSION PROTECTS CARDIOMYOCYTES BUT ENHANCES CANCER CELL APOPTOSIS IN RESPONSE TO DAUNOMYCIN

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Anthracyclines are potent anti-cancer drugs that are widely used for the treatment of a variety of cancers including leukaemia. Currently, 270,000 children in the USA and more than 20,000 in the UK are cancer survivors after anthracycline chemotherapy. Some of these children will develop clinical heart failure (CHF) or other cardiac complications in later life due to the cardiotoxicity of anthracyclines. A particular limitation of anthracycline chemotherapy is the dose-dependent cardiotoxicity that can lead to CHF. Among the serious cardiac complications that have been reported are arrhythmias, myocardial necrosis causing dilated cardiomyopathy, and vaso-occlusion or vasospasm resulting in angina or myocardial infarction. The precise mechanism underlying CHF is not fully understood, but is believed to be due, in part, to lipid peroxidation and the generation of free radicals by anthracycline-iron complexes. The therapeutic activity of anthracyclines is mediated by their insertion into the DNA of replicating cells, causing DNA fragmentation; inhibition of polymerases; and decreased DNA, RNA, and protein synthesis. The mechanism of myocardial damage is unlikely to involve the same mechanism, since myocytes are not actively replicating.

The objective of this study was to determine whether cardiomyocytes would be protected against anthracycline toxicity due to increased expression of thioredoxin (Trx), a potent

antioxidant and protein-disulfide reductase, while enhancing the toxicity in cancer cells. We utilised rat embryonic cardiomyocytes (H9C2) as our model system to determine differential toxicity of cancer cells and cardiomyocytes in response to daunomycin, a potent anthracycline. H9C2 or cancer cells (HCT116, A431, U937, MCF7, and MDA-MB231) were exposed to daunomycin, and apoptosis was determined by cleavage of poly(ADP-ribose) polymerase (PARP), cytochrome C release, p53 expression, and cell viability studies. We also utilised normal cells, such as human mammary epithelial cells and human microvascular endothelial cells, to determine the effect of Trx on anthracycline-mediated toxicity of normal cells.

Our results indicate that cancer cells from various tissue origins undergo enhanced apoptosis due to daunomycin treatment in the presence of high levels of human (h)Trx. However, in the presence of high levels of Trx, cardiomyocytes or normal cells did not undergo enhanced apoptosis in response to daunomycin, as determined by PARP cleavage. This apoptosis potentiation by Trx is limited to only anthracyclines as etoposide, another topoisomerase II inhibitor, did not increase apoptosis in the presence of increased hTrx. In contrast, hTrx protected against etoposide-induced apoptosis of cancer cells. These findings indicate a specific effect of Trx in potentiating anthracycline toxicity in cancer cells, but not in cardiomyocytes. Collectively, our data suggest that Trx potentiates the apoptotic death of cancer cells in response to anthracycline treatment, but protects cardiomyocytes and non-transformed cells against daunomycin toxicity. This pro-oxidant and pro-apoptotic role of Trx in the presence of anthracyclines is not only novel, but also quite intriguing, because Trx is widely accepted as an antioxidant, and protects cells and tissues against oxidant-mediated apoptosis.

We conclude that Trx enhances the anthracycline redox cycling in cancer cells, but not in cardiomyocytes, as they are non-cycling cells. Additionally, Trx could protect against daunomycin mediated reactive oxygen species generation due to scavenging of superoxide anions and H_2O_2-Fe_{2+} mediated hydroxyl radicals, via increased peroxiredoxin expression.

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EDITOR'S PICK

In our editor's pick for this edition, Sathananthan et al. delve into the history and provide an overview of the Fontan operation, an innovative procedure first introduced in the 1970s to treat complex heart disease in children. Although a small minority face long-term negative physiological consequences from the procedure, Sathananthan and colleagues remark that, nonetheless, the procedure has had an overwhelmingly positive impact on the majority of patients, who have gone on to have a good quality of life. The authors stress the importance of early detection and management in instances of congenital heart disease as being key to long-term survival.

THE FONTAN CIRCULATION

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ABSTRACT

The original Fontan procedure was first introduced in the 1970s. The concept behind this surgical technique was revolutionary. It has subsequently transformed the lives of children born with complex congenital heart disease which was once thought to be inoperable and resulted in early death. The procedure itself has had several modifications over the decades, with subsequent improvements in long-term outcomes for these patients. Fontan patients are now surviving well into adulthood and the majority are able to live wholesome fulfilling lives. There are, however, a small proportion who are faced with the negative long-term physiological effects of this unconventional circulation. Early detection and management of these patients is the key to their long-term survival.

Keywords: Fontan, congenital, survival, quality of life.

INTRODUCTION

As recently as the 1970s, congenital heart disease was predominantly a disease of childhood. With advances in surgical techniques, cardiopulmonary bypass, anaesthetics, and critical care medicine, nearly 85% of children with cardiovascular anomalies are expected to reach adulthood.[1] By the year 2000, there were approximately equal numbers of adults and children with severe congenital heart disease.[2,3] As these individuals with complex congenital heart disease reach adulthood, we are developing an increased understanding of the long-term sequelae of these early repairs.

THE FONTAN OPERATION

The Fontan operation is the definitive surgical palliation for patients with congenital heart disease in which septation into a biventricular system is not possible. This includes tricuspid atresia, double inlet left ventricle, hypoplastic left heart syndrome, and pulmonary atresia with intact septum. These diagnoses represent the most severe end of the spectrum of congenital heart disease and until the 1970s these patients usually died at a young age.

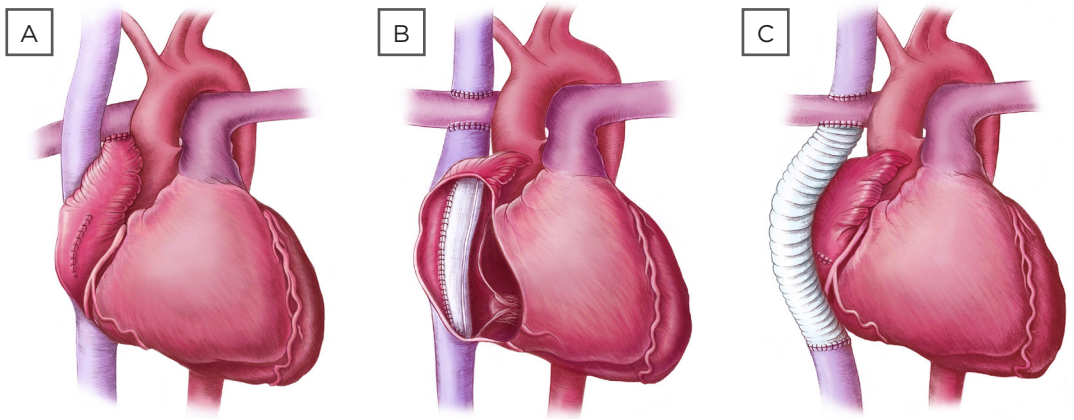

Figure 1: Different types of Fontan procedure.
A) atriopulmonary Fontan; B) lateral tunnel Fontan; C) extracardiac Fontan.

The Fontan operation was first undertaken in 1968 in a patient with tricuspid atresia and was later described by Fontan and Baudet in 1971.[4] It has transformed the outlook for patients with previously inoperable congenital heart disease.

The Fontan circulation allows for systemic venous blood to pass directly into the pulmonary circulation without the need for a subpulmonary ventricular pump (Figure 1). Flow through the lungs is therefore passive and is dependent on increased systemic venous pressure, active diastolic ventricular filling, and the effect of respiration to help move blood into and out of the pulmonary vasculature.

Not all patients, however, are suitable to undergo Fontan surgery and choosing the appropriate patient is a highly selective process. The recommendations for successful Fontan surgery have been refined since the procedure was first introduced but the general principles remain the same. An unobstructed connection between the systemic veins and the pulmonary artery, and patent pulmonary veins is a prerequisite. The ventricle itself should have a competent atrioventricular valve, outflow valve, and good systolic function, and the pulmonary arteries should be of good size with normal pulmonary vascular resistance.[5]

EVOLUTION OF THE FONTAN PROCEDURE

Over the last four decades, there have been modifications to the Fontan procedure in an attempt to further improve survival and minimise long-term complications. The original Fontan surgery was the atriopulmonary connection in which the right atrial appendage was anastomosed to the main pulmonary artery (Figure 1A). This technique was complicated by progressive right atrial dilatation, frequent atrial arrhythmias, and serious thromboembolic complications. The atriopulmonary Fontan has subsequently been superseded by the lateral tunnel Fontan (Figure 1B) and the extracardiac Fontan (Figure 1C). Both of these techniques achieve a total cavopulmonary anastomosis.[6] The Fontan procedure is usually performed as a staged repair. The first stage is known as the bidirectional Glenn procedure or a hemi-Fontan. This involves redirecting superior vena caval flow directly to the pulmonary circulation whilst the inferior vena cava remains connected to the heart. The use of this staged technique avoids rapid volume loading on the pulmonary circulation.[7]

The lateral tunnel Fontan uses a baffle within the right atrium to directly channel the inferior vena cava to the right pulmonary artery and was first introduced in 1988.[6] Like the atriopulmonary Fontan, this option also uses a right atriotomy approach and therefore can be subject to atrial arrhythmias. The extracardiac conduit on the other hand uses synthetic, usually Gore-Tex® tubing to connect the disconnected inferior vena cava to the right pulmonary artery. This technique was first introduced in 1990. The theoretical advantage of this technique is the avoidance of right atrial incisions and suture lines. It also avoids significant pressure loading and therefore dilation of the right atrium. The removal of these arrhythmic substrates is expected to reduce the propensity for intra-atrial re-entry tachycardia (IART).[8] The extracardiac Fontan has subsequently become the technique

of choice at many centres and has been the sole method of Fontan completion performed in Australasia since 2007.[9]

SURVIVAL

The perioperative mortality rate for initial Fontan surgery has decreased steadily over time. A large single-centre study from Boston, Massachusetts, USA, described a perioperative mortality rate of 36.7% for a first Fontan surgery performed before 1982 compared with 1.9% if performed in 1990 or later.[10] These figures are partly a reflection of the type of Fontan procedure used in that era, partly increased surgical and anaesthetic expertise, and partly dueto an improvement in the understanding of optimal early postoperative care following this procedure. The recently published Australasian multicentre results show a perioperative mortality rate of 8% for initial Fontan surgery carried out before 1990 compared with 1% for those operated on after 2001. This comparatively low perioperative mortality rate in the earlier era may be partially explained by the somewhat more recent cohort and also by the more conservative patient selection in Australasia at the time.[9]

The Mayo Clinic, Rochester, Minnesota, USA, recently reported their overall 10, 20, and 30-year survival after the Fontan operation as 74%, 61%, and 43%, respectively. The centre found that operations carried out prior to 1991, use of preoperative diuretics, asplenia, and lack of preoperative sinus rhythm were all factors associated with decreased survival. Individuals with an extracardiac Fontan had a significantly better 30-year survival of 62% compared with the 46% and 39% for those with atriopulmonary and lateral tunnel Fontans, respectively.[10]

The Australasian figures showed an overall survival estimate at 15, 20, and 25 years as 93%, 90%, and 83%, respectively. The 25-year survival for the atriopulmonary Fontan was 76% compared with a 90% survival for the lateral tunnel at 20 years and a 97% survival for the extracardiac Fontan at 13 years.[11] Although the survival estimates appear better when compared with cohorts elsewhere, this was a somewhat later cohort and follow-up times were shorter for the lateral tunnel and extracardiac Fontan.

Death in the Boston group's Fontan population was found to predominantly occur perioperatively (68.4%) followed by sudden death (9.2%), thromboembolism (7.9%), heart failure (6.7%), sepsis (2.6%), and other (5.2%). Sudden death was presumed to be largely arrhythmic in origin.[12] The Mayo Clinic reported similar aetiologies for late death.[13] Independent risk factors for heart failure death were protein losing eneteropathy, single morphological right ventricle, and higher right atrial pressure.[12]

QUALITY OF LIFE

Fontan patients have a significantly reduced exercise capacity compared with healthy subjects.[14-16] Patients with total cavopulmonary circulation had an exercise capacity reaching only about 60% of their reference values and only one-third of Fontan patients had a peak VO_2 within the normal range.[17,18]

Fontan patients, however, generally have a good perception of their own health status.[18,19] Eighty percent of adult Fontan patients rated their own health as excellent and a similar proportion thought their physical status was improved post-Fontan surgery.[11] In a Danish case control study, more than half of the Fontan patients were leading a normal life and were able to work or study full-time. A quarter of the patients had mild symptoms and were still able to work part-time.[20] Australian data on Fontan patients who were arrhythmia free reported that despite having restricted exercise capacity, patients had a normal quality of life in their reports of psychiatric symptoms and personal relationships.[21] The majority of Fontan patients have an overall good quality of life and are largely unaffected by their cardiac diagnosis.

PREGNANCY

The physiological changes of pregnancy, namely increased blood volume, chronotropic incompetence, and compression of the inferior vena cava in the gravid state can all compromise the finely balanced Fontan circulation. There is a tendency for arrhythmias and thrombosis in Fontan patients and the likelihood of this is further increased during pregnancy.[22]

Pregnancy in the Fontan population has previously been strongly discouraged but this opinion has gradually changed over time. The number of Fontan patients at any one centre who have undergone a pregnancy remains limited and therefore so too does the literature. In 2006, Drenthen et al.[23] reported that Fontan patients

were able to successfully complete a pregnancy without any long-term sequelae. This was however at the expense of other complications, namely deterioration in functional status, atrial fibrillation, gestational hypertension, premature rupture of membranes, premature delivery, fetal growth retardation, and neonatal death. Fifty percent of patients in this small cohort had miscarriages. This is supported by more recent data reporting that pregnancy in Fontan patients is associated with a high rate of miscarriage, preterm delivery, and low birth weight.[24] Another recent study of 59 pregnancies in 37 Fontan patients, one of the largest to date, found there was a cardiac complication rate of 10%, with atrial arrhythmias being the most common followed by thromboembolism and heart failure. There were no maternal deaths. Twenty-seven percent of these pregnancies however ended in miscarriage, predominantly occurring in the first trimester.[25]

Pregnancy outcomes in Fontan patients can potentially be favourable, however this may be compromised by the presence of cardiac and extracardiac complications of the Fontan circulation. Fontan patients therefore need individualised pre-pregnancy counselling and advice on both maternal and fetal outcomes. This should take into account their functional status, ventricular function, arrhythmia burden, comorbidities, and objective exercise data wherever possible.[26] These patients will need close monitoring throughout the pregnancy and ideally at a specialised tertiary level hospital.

LONG-TERM COMPLICATIONS

Arrhythmias

Sinus node dysfunction has been reported in up to 40% of patients with atriopulmonary connections and in 25% of those with lateral tunnel or extracardiac connections.[27,28] The haemodynamic consequence of non-sinus rhythm in the Fontan population can be marked, as the contribution of atrial systole to ventricular filling contributes significantly to optimising forward flow through the pulmonary vasculature. Loss of sinus rhythm may therefore increase pressure within the Fontan circuit and central veins thereby also reducing cardiac output.

Atrial arrhythmias are not infrequent in the Fontan population and are driven by elevated right atrial pressures and the effects of direct surgical intervention on the right atrium. The more recent modifications to the Fontan procedure have however resulted in a lower incidence of atrial arrhythmias. In the Australia and New Zealand Fontan Registry, predictors for supraventricular tachycardia were found to include atriopulmonary and lateral tunnel Fontan, compared with the extracardiac Fontan.[11] A study from the Royal Brompton Hospital showed that right atrial size was the strongest predictor of IART in those with the atriopulmonary Fontan.[29] The extracardiac Fontan meanwhile maintains low pressure in the right atrium thus avoiding atrial dilation. This is likely to explain the lower incidence of atrial arrhythmias in this group.[8]

Episodes of IART may lead to rapid haemodynamic decompensation in the setting of a Fontan circulation and may also represent a high risk of thrombus formation within the dilated right atrium. The termination of an acute episode of atrial tachycardia within 24 hours from onset is therefore recommended. Ventricular arrhythmias are rare in Fontan patients and if seen, are in the context of severe ventricular dysfunction.

Thromboembolism

Fontan patients are at an increased risk of thromboembolism compared with the general population due to a combination of factors including: diminished cardiac output, absence of pulsatile flow in the pulmonary arteries, abnormal patterns of venous flow, and the presence of prosthetic material. There have also been several reports of clotting factor abnormalities and increased platelet reactivity in Fontan patients.[30,31] Despite this, the Australia and New Zealand Registry found that 82% of Fontan patients were free from overt thromboembolic events at 25 years.[10] Currently, treatment strategies to prevent thromboembolism vary between institutions.

Khairy et al.[12] demonstrated thromboembolism as a cause of late death in Fontan patients in the absence of antiplatelet agents or anticoagulation. Meanwhile, Robbers-Visser et al.[32] found no difference in thromboembolism between those with a lateral tunnel Fontan circulation and those with an extracardiac conduit. This was also irrespective of the postoperative use of antiplatelet agents or anticoagulants.

A recent meta-analysis of 10 studies however found that there was a significantly lower incidence of thromboembolism in Fontan patients if either

aspirin or warfarin was used. There was also no significant difference in thromboembolic events in patients receiving aspirin compared with warfarin. The results were similar when the seven studies using the newer-generation Fontan patients were looked at exclusively.[33] Although this data suggests that there is no clear benefit of warfarin over aspirin, the event rate is likely to be low and occur over a long period of follow-up, making it difficult to draw definite conclusions.

The use of warfarin in clinical practice however is highly variable and hard to accurately represent in studies. Additionally, one study found aspirin resistance in up to 52% of adult Fontan patients.[34] Therefore although aspirin does appear to be a reasonable alternative to warfarin, the results of this meta-analysis may not necessarily change the way of practice in many centres just yet. The use of novel anticoagulants in the Fontan population is yet to be studied but is undoubtedly an area of great promise for this relatively young patient population, who may find compliance with international normalised ratio testing difficult.

Ventricular Dysfunction

Progressive ventricular systolic dysfunction and atrioventricular valve sufficiency are late complications in Fontan patients. Eicken et al.[35] used cardiac magnetic resonance imaging to show a progressive decline in ventricular systolic function at 10-year follow-up, with a median ejection fraction of 49.3% (range 20–63%). The Boston group found that the presence of a pacemaker before Fontan operation was associated with an increased probability of late failure whilst the morphology of the ventricle itself was not a predictor.[36]

Diastolic dysfunction was assessed in a small cohort of Fontan patients: 57% were noted to have diastolic dysfunction, 7% had impaired relaxation, 29% had pseudonormalisation, and 21% had restrictive physiology. Those with diastolic dysfunction were noted to have a lower peak VO_2 on exercise testing.[37] Diastolic dysfunction and reduced ventricular compliance, if present, was seen to persist even late after Fontan surgery.[38]

Complications Related to High Venous Pressure

The Fontan circuit allows for passive venous flow into the lungs via the vena cava without pulsatile ventricular contraction. As a result, the systemic venous pressure in a Fontan circulation remains obligatorily elevated. Venous congestion and decreased perfusion are the hallmarks of this circulation. The resultant long-term complications from such a circulation include protein-losing enteropathy and plastic bronchitis. Both of these complications have been regarded as representing a 'failing' Fontan circulation and are associated with a high risk of adverse outcomes, including death in the short-to-medium term.

Liver Disease

Liver disease is being reported with increasing frequency in adult Fontan patients and was previously only reported in small cohorts.[39-41] Fontan-associated liver disease is thought to be multifactorial and begins with the onset of multiple liver insults during childhood. This includes episodes of hypoxaemia and numerous perioperative episodes of liver injury. In adulthood, chronic venous congestion and diminished cardiac output lead to reduced portal flow and portal vein saturation. This impairs the liver's ability to autoregulate its own blood flow and liver disease ensues.[42]

The pattern of liver injury in adult Fontan patients is similar to other forms of cardiac cirrhosis in both its gross and histological features.[42,43] The severity of Fontan-associated liver disease has been found to correlate best with the duration of the Fontan circulation and hepatic venous pressure.[39] The routine screening of the liver in Fontan patients is now recommended, although the optimal imaging modality in this subset of patients is yet to be determined.

MANAGEMENT OF THE 'FAILING' FONTAN

The 'failing' Fontan refers to the physiological deterioration of the Fontan circulation and the consequential extracardiac manifestations that follow. Therapeutic options for the management of the failing Fontan are in general limited to Fontan conversion surgery or heart transplantation.

Fontan Conversion

As previously discussed, the outcomes following the lateral tunnel and extracardiac Fontan appear to be superior to those following the atriopulmonary Fontan. This has led various groups to perform surgery to convert patients from the atriopulmonary Fontan circulation to a total

cavopulmonary connection which today would be the extracardiac Fontan. Fontan conversion surgery was first championed by Mavroudis et al.[44] with good results. A transatlantic multicentre study later published by Marcelletti et al.[45] found that Fontan conversion surgery could be performed with relatively low morbidity and mortality, whilst improving functional class.

In most centres the predominant indication for Fontan conversion surgery has been recurrent atrial arrhythmias. Radiofrequency catheter ablation of IART in the adult Fontan population has been found to have a higher incidence of recurrence compared with other forms of congenital heart disease.[46] Therefore arrhythmia surgery in the form of a right atrial +/- left atrial Maze procedure is often combined with Fontan conversion surgery. Many groups also incorporate pacemaker implantation. The Chicago group found promising results with this approach. As well as an improvement in both New York Heart Association (NYHA) class and exercise tolerance, follow-up at 15 years showed 80% freedom from death or transplantation and 85% freedom from recurrent tachycardia.[47-49]

Cardiac Transplantation

The appropriate time to list adult Fontan patients for cardiac transplantation is highly controversial. Survival following transplantation after a previous Glenn or Fontan procedure in adults was reported as 71.5% at 1 year and 67.5% at 5 years. The early perioperative mortality rate in the Fontan patients was however 37.5% and was predominantly due to haemorrhage and infection. Of those with pre-existing protein-losing enteropathy, 40% died within 6 weeks post-transplant. In those who survived the first year however, the late mortality rates were not significantly different when compared with patients transplanted for other aetiologies.[50,51]

In adult Fontan patients, the development of haemodynamic abnormalities and extra-cardiac complications are often gradual and insidious. The detection of a failing Fontan is complicated by chronic functional limitation and the lack of new symptoms in many patients. Identifying at-risk Fontan patients before they develop irreversible multi-organ dysfunction is the key to improving long-term outcomes in these patients and early listing should be considered for patients with evidence of hepatic dysfunction. The 2008 Adult Congenital Heart Disease guidelines give a Class IIb indication for heart transplantation for severe ventricular dysfunction or protein-losing enteropathy in Fontan patients.[52] There are at present no well-established criteria to assist with the timing of transplant listing for adult patients with Fontan failure and the development of such guidelines will be the key to the successful ongoing management of these patients.[53-57]

CONCLUSION

The Fontan operation is one of the most innovative techniques in the congenital cardiac surgical repertoire and has transformed the outlook for children born with complex congenital heart disease. A large proportion of adult Fontan patients are able to enjoy a good quality of life and are largely unaffected by their cardiac diagnosis. There is however a small minority who are faced with the long-term negative physiological consequences of this circulation, manifesting as both cardiac and extra-cardiac sequelae. Meticulous monitoring of these patients will allow for optimisation of their cardiac status whenever possible as well as early referral for either Fontan conversion surgery or cardiac transplantation when indicated.

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ARTERIAL STIFFNESS AND CORONARY ARTERY DISEASE

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ABSTRACT

Although there have been marked improvements in both diagnostic and therapeutic interventions over several decades, coronary artery disease (CAD) remains the leading cause of death worldwide. Intensive modification of classic risk factors such as hypertension, diabetes mellitus, dyslipidaemia, and cigarette smoking has significantly reduced the development of CAD. The high prevalence of residual cardiovascular events does however require improvements in identification and risk stratification strategies. In this context, arterial stiffness, which reflects arterial ageing, damage, and arteriosclerosis has emerged as an important risk factor for cardiovascular disease. The measurements of arterial stiffness are easy to make using several non-invasive methods such as pulse wave velocity. The clinical utility of the measures has been validated in many prior studies. Recent evidence has suggested that the measures of arterial stiffness are correlated with the presence and extent of CAD. More importantly, increased arterial stiffness is an independent predictor of CAD-related morbidity and mortality beyond classic risk factors. Considering its non-invasiveness, simplicity, and reliability, arterial stiffness could serve as a useful marker of CAD and help identify high-risk patients who may benefit from more aggressive management.

Keywords: Arterial stiffness, coronary artery disease (CAD), pulse wave velocity (PWV), non-invasive.

INTRODUCTION

Coronary artery disease (CAD) remains one of the leading causes of death and disability worldwide.[1,2] The underlying pathophysiology of most CAD is atherosclerosis, a complex process governed by multiple factors. Classic risk factors such as hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, and obesity, have been well-documented as significant contributors to the development of atherosclerosis and CAD.[3,4] In fact, aggressive treatment of these factors has significantly reduced the risk of future cardiovascular events.[5] By the strength of evidence supporting their role in the pathogenesis of CAD, these classic risk factors have usually been a primary therapeutic target in patients with known or suspected CAD. Indeed, with many efforts focussed on these classic risk factors, there has been significant progress and improvement in prevention, diagnosis, and therapy however, the burden of CAD is still substantial. It is now generally accepted that classic risk factors cannot fully explain the increasing burden of CAD and that more than 50% of patients with CAD do not have any of these risk factors.[6,7] Although several risk prediction models using a combination of individual classic risk factors have been suggested, they have a low diagnostic yield in the prediction of future cardiovascular events, depending on population and ethnicity.[8,9] These findings suggest that other factors are clearly involved and raise the need for another tool to improve prevention and management of CAD beyond classic risk factors.

Arterial stiffness is accelerated by ageing, arterial damage, and arteriosclerosis.[10] Arterial stiffness is an important reflection of degeneration of the arterial wall as a consequence of repetitive cyclic stress.[10] From the pathologic point of view, arterial stiffening is characterised by the loss of elastic fibres and increases collagen deposition and cross-

linking within arterial walls.[10] Emerging evidence suggests that arterial stiffness is one of the earliest detectable signs of functional and structural changes in the arterial wall.[11,12] The measurement of arterial stiffness could be advantageous in early detection and prevention of vascular disease. More importantly, arterial stiffness can predict adverse cardiovascular events beyond classic risk factors, in patient groups with different diseases[13-16] and in the general population.[17,18] Recent studies have reported that arterial stiffness is associated with the presence and extent of CAD[19-23] and cardiovascular outcomes.[13,14,17,24] Special attention has been focussed on the measurement of arterial stiffness as a reliable and useful non-invasive tool to improve detection and risk stratification of patients with CAD. The present review summarises how to assess arterial stiffness and provides clinical evidence for the detection of CAD and the prediction of CAD-related outcomes based on arterial stiffness.

MEASUREMENTS OF ARTERIAL STIFFNESS

Pulse Wave Velocity

Arterial stiffness can be assessed using several non-invasive and invasive methods. Among them, pulse wave velocity (PWV) is the most widely and frequently used tool to quantify arterial stiffness, because its measurement is non-invasive, simple, and reproducible.[10,12] Of note, there has been much data indicating the clinical values of PWV in the prediction of cardiovascular events.[13-15,25,26] PWV is the measure of the speed of the arterial pressure waves travelling along the aorta and large arteries. Therefore, PWV can be determined by dividing distance with transit time of pressure waveforms at the two recording sites.[12] PWV is inversely correlated with arterial compliance; it is faster in a more stiffened artery. According to arteries measured, there are several types of PWV. Carotid-femoral PWV (cfPWV), which is made by recording pressure waveforms at the carotid artery followed by the femoral artery, is most validated, and has been considered a reference standard technique to assess arterial stiffness.[27] However, the wide use of cfPWV in clinical practice is hindered by the need for technical skills during the carotid and femoral pulse acquisition. In addition to this, cfPWV measurement causes some discomfort to subjects and is time-consuming. To overcome these drawbacks of cfPWV, the newly developed and simpler measurement, brachial-ankle PWV (baPWV), has been used in research and clinical fields. The baPWV measurement does not require technical expertise and it can be done by simply wrapping blood pressure cuffs around the four extremities.[28] Therefore, the measurement of baPWV is simple and timesaving. Furthermore, baPWV is well-correlated with cfPWV[29] and invasive parameters,[28] and the diagnostic and prognostic values of baPWV have been proven in many clinical studies,[20,22,24,28,30-32] and in a meta-analysis.[26] There has been some criticism that baPWV cannot reflect pure central arterial stiffness because it includes a much more peripheral component.[33] However, considering its simplicity and clinical values, baPWV is expected to be more widely used in clinical practice, especially for the purpose of mass screening.

Pulse Pressure and Augmentation Index

Pulse pressure (PP) is defined as the difference between systolic blood pressure and diastolic blood pressure. Augmentation index (AIx) is defined as augmented pressure divided by PP. Elevated PP and AIx are regarded as a manifestation of increased arterial stiffness, although AIx is a more complex measure of wave forms propagated during systole with the reflected waves from peripheral arteries. In a stiffened artery, a reflected wave from the periphery returns faster and arrives earlier at the central aorta during myocardial systole which increases PP and the pressure at the late systolic phase (equalling augmentation pressure). PP and AIx are closely related to target organ damage, and they are important predictors of cardiovascular events.[18,34] However, it should be considered that PP and AIx are potentially confounded by factors related to cardiac function such as heart rate and stroke volume.[35] In addition, AIx has been found to have limited value as a marker of arterial stiffness in older individuals, particularly after 60 years of age.[36]

Central Aortic Pressure

An invasively measured aortic pulsatile component is considered the gold standard for assessing central arterial stiffness. Anatomically, the central aorta is closer to the brain, heart, and kidneys, therefore the impact of aortic pulsatile stress is more pronounced to these vital organs than that of peripheral artery.[37] It has been reported that the stiffness of the central elastic artery is more strongly correlated with cardiovascular and all-cause mortality than that of the peripheral artery.[37] Indeed, intra-aortic haemodynamic parameters, as recorded

during invasive coronary angiography (ICA), have been shown to be a valuable measure of aortic stiffness.[37-40] Therefore, measurement of central aortic pressure has been emphasised.[37] However, difficulty in performing this invasive examination limits its use in clinical practice. Although current non-invasive techniques can estimate central pressure by analysing radial or carotid pulse waves using a mathematical relationship to peripheral pressure,[41,42] the possibility of calculation error is not negligible.[43]

Other Modalities

Magnetic resonance imaging and echocardiography can assess arterial stiffness of deep large arteries such as the aorta.[12,44] However, these methods are expensive, time-consuming, and technically difficult. Therefore, they are impractical for wide clinical use.

ASSOCIATION BETWEEN ARTERIAL STIFFNESS AND THE PRESENCE AND EXTENT OF CORONARY ARTERY DISEASE

Prior studies have documented a direct relationship between arterial stiffness and the presence or extent of CAD. Recently, our study group investigated 470 patients who underwent both baPWV measurement and coronary computed tomography angiography (CCTA), and showed good correlations between baPWV and the CCTA parameters of CAD extent.[20] Xiong et al.[22] also used baPWV as a measure of arterial stiffness in 321 patients and reported an independent association between baPWV and CAD severity as assessed by ICA and SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score. Alarhabi et al.[19] demonstrated in a study of 92 patients undergoing ICA, that arterial stiffness measured through cfPWV is independently associated with multivessel disease. In accordance with these findings, Lim et al.[21] performed a prospective study of 326 consecutive patients undergoing ICA and showed that cfPWV was significantly associated with the severity of CAD, expressed as one, two, or three-vessel disease. Invasive measurement of aortic pressure is feasible and parameters of central haemodynamics have provided useful information in patients undergoing ICA. A study by Nakayama et al.[39] has indicated the usefulness of invasively measured pulsatility index of the ascending aorta as a predictor of in-stent restenosis after percutaneous transluminal coronary angioplasty. Philippe et al.[23] invasively measured aortic PP in 99 patients undergoing ICA and showed that aortic PP is independently correlated with the CAD extent. Jankowski et al.[40] measured aortic pulsatile components in 423 consecutive patients undergoing ICA and also demonstrated that aortic PP, fractional PP, and pulsatility index are risk factors for three-vessel disease.

ARTERIAL STIFFNESS AND CORONARY ARTERY DISEASE-RELATED OUTCOMES

Recent longitudinal studies have suggested that arterial stiffness is an important predictor for CAD-related morbidity and mortality in patients with different diseases as well as in the general population. In those studies, the prognostic value of arterial stiffness persists even after controlling for potential confounding effects by classic risk factors such as age, hypertension, diabetes mellitus, and dyslipidaemia. Boutouyrie et al.[14] measured cfPWV in 1,045 hypertensive subjects and showed that cfPWV is significantly associated with the occurrence of coronary events during a mean follow-up of 5.7 years even after adjustment for the Framingham Risk Score or classic risk factors. Blacher et al.[13] investigated 241 patients with end-stage renal disease undergoing haemodialysis, and reported that increased aortic stiffness measured by aortic PWV is a strong independent predictor for all-cause and cardiovascular mortality. Another study of 2,231 patients with acute myocardial infarction accompanied by left ventricular (LV) dysfunction over a 42-month follow-up period, documented that there is a close link between PP and subsequent cardiovascular events.[16] Kim et al.[15] studied 1,765 patients with acute ischaemic stroke during a mean follow-up period of 3.3 years and showed an independent association between baPWV and all-cause and vascular death. In a recently published article, with 2 years of clinical follow-up in 1,126 subjects >80 years old, it has been found that increases in carotid and brachial PP amplification is associated with reduction of total mortality and cardiovascular events.[18] A more recent study performed by our study group, involving 350 subjects undergoing myocardial perfusion imaging, showed that baPWV provided additional prognostic value to classic risk factors and myocardial perfusion imaging in predicting cardiovascular events during the 441 days of

clinical follow-up.[32] The value of aortic PWV in predicting future cardiovascular events and all-cause mortality was also proven in a meta-analysis of 17 longitudinal studies of 15,877 subjects with a mean follow-up period of 7.7 years.[25] The authors indicated that the risk of cardiovascular events and cardiovascular mortality is more than 2-times higher in subjects with high aortic PWV than in those with low aortic PWV.[25]

POSSIBLE MECHANISMS UNDERLYING THE LINK BETWEEN ARTERIAL STIFFNESS AND CORONARY ARTERY DISEASE

Precise mechanisms underlying the link between arterial stiffness and CAD have not been clearly established. Multiple complicated factors may be involved and interact with each other to a greater or lesser extent. There are however several accepted explanations of the association between increased arterial stiffness and CAD. First, increased arterial stiffness is the main cause of premature return of reflected waves in the late systole which is associated with increased PP and the afterload of LV. Increased LV load subsequently increases in LV mass and oxygen demand.[45] In addition to increased load on the LV, increased arterial stiffness decreases diastolic pressure which is closely linked to impaired coronary perfusion and myocardial ischaemia.[46] These unfavourable pathophysiological changes may lead to the progression of coronary atherosclerosis. Considering the fact that PP increases significantly only after the fifth decade,[47] it is a natural hypothesis that the role of arterial stiffness in the evaluation of CAD is more valuable, especially in elderly people. Secondly, arterial stiffness itself reflects the burden of underlying systemic atherosclerosis and the presence of end-organ damage, both of which are associated with CAD and CAD related outcomes. Thirdly, arterial stiffness changes mainly with age.[48] The prevalence of traditional risk factors for CAD is also increased with age. Therefore, arterial stiffening and CAD are considered to share many risk factors, including ageing, hypertension, diabetes mellitus, dyslipidaemia, and smoking.[10,12] These risk factors for atherosclerosis may have a worse impact on both arterial stiffening and the development and progression of CAD. For these reasons, it can be postulated that the association between increased arterial stiffness and CAD is incidental. Accordingly, the clinical importance of arterial stiffness is frequently underestimated in patients with CAD because arterial stiffness changes with age. However, considering that the prognostic value of arterial stiffness does not change even after adjustment for age and other classic risk factors,[13-18] it is evident that arterial stiffness is an independent predictor for future atherosclerotic cardiovascular events beyond classic risk factors. Finally, recent evidence has shown that inflammation can affect arterial stiffness.[49] Given that chronic systemic inflammation is also closely related to cardiovascular risk,[50] the association between increased arterial stiffness and CAD may be at least partially mediated by inflammation.

MANAGEMENT STRATEGY REDUCING ARTERIAL STIFFNESS

Several prior studies have shown that some pharmacological and non-pharmacological interventions may improve arterial stiffness. Although the degree of arterial stiffness reduction is different according to drug classes, doses, and treatment duration angiotensin converting enzyme inhibitor has been shown to be the most effective drug in reducing both peripheral and central arterial stiffness in long-term treatment.[12,37,51] Recent studies have also reported that non-pharmacological interventions, including aerobic exercise training and continuous positive airway pressure in patients with sleep apnoea, improve arterial stiffness.[12] However, whether the reduction of arterial stiffness by these pharmacological and non-pharmacological interventions can lead to a favourable clinical outcome remains to be determined in further studies.

CLINICAL IMPLICATIONS

Although there has been a marked improvement in both diagnostic and therapeutic interventions over several decades, CAD remains the leading cause of death worldwide.[1,2] Intensive modification of classic risk factors has significantly reduced the development of CAD, however the high residual prevalence of cardiovascular events requires further improvements in identification and risk stratification strategies. Recent cardiovascular risk scoring strategies are not sufficient to identify patients at a high risk of CAD.[8,9] Accurate assessment of CAD and its complications remains problematic for clinicians. Arterial stiffening is one of the earliest manifestations of vascular damage and atherosclerosis. However, it is difficult to recognise

such subclinical changes in routine medical practice. Simple and non-invasive measurement of arterial stiffness, such as PWV, can detect functional and structural changes in arterial wall even in early stages. As mentioned above, many cross-sectional and longitudinal studies have confirmed that arterial stiffness is closely related to CAD and CAD-related outcomes. Therefore, arterial stiffness measurement could serve as an important tool to identify patients at a high risk of CAD. Improved ability to identify such patients would lead to better risk stratification and more effective preventive therapy. Additionally, arterial stiffness can be a target or monitoring tool for therapeutic intervention.[12,35] Appropriate medications reducing arterial stiffness may offer potential advantages in the management of patients at a high risk of CAD.

CONCLUSIONS

The measures of arterial stiffness are well-correlated with the presence and extent of CAD. More importantly, arterial stiffness is an independent predictor for CAD-related mortality and morbidity in various populations which are beyond prediction, based on classic risk factors. Considering its non-invasiveness, simplicity, and reliability, arterial stiffness could serve as a useful marker of CAD and help detect high-risk patients who may benefit from more aggressive management.

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RECURRENT CORONARY PERFORATIONS IN AN ANEURYSMAL CORONARY ARTERY TREATED WITH COVERED STENT

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ABSTRACT

An elderly hypertensive lady presented to us with acute coronary syndrome; an angiogram revealed total thrombotic occlusion of large left circumflex artery. After thrombosuction, there was proximal tight stenosis followed by an aneurysmal segment of the culprit vessel that was stented successfully. Subsequent post-dilatation at the site of aneurysm produced a large perforation, which was sealed off immediately with a covered stent. Unfortunately, the patient had sudden cardiac tamponade and arrest later in the intensive cardiac care unit due to repeat perforation, and could not be resuscitated from this complication. Aneurysmal and ectatic arteries have fragile walls and aggressive post-dilatation for achieving optimal stent apposition should be avoided.

Keywords: Coronary artery aneurysm (CAA), coronary perforations, covered stent.

INTRODUCTION

Coronary artery aneurysm (CAA) is defined as coronary dilatation that exceeds the diameter of normal adjacent segments or the diameter of the widest coronary artery by a factor of 1.5.[1] It differs from coronary artery ectasia where >50% of the length of the artery is dilated. The mean incidence of CAAs is 1.65%[1] and the most common cause for CAA is atherosclerotic coronary artery disease (CAD), especially in adults. The common causes in children are vascular inflammatory diseases such as Kawasaki disease, systemic vasculitis, and congenital aneurysms.[2] In the majority of cases, these aneurysms are identified incidentally during angiography procedures, but can also present with symptoms when they develop complications such as thrombosis followed by embolisation, vasospasm, and occasionally rupture. Management of CAA during acute coronary syndromes may represent a unique clinical challenge, as they have a high thrombus burden. Controversy surrounds whether conservative, surgical, or catheter-based management should be considered in these rare cases,[1,2] as high thrombus burden, tortuosity, and significant spasms make intervention quite challenging and complex. Perforation, as a complication during intervention, has not been discussed before. Shimony et al.[3] found, after meta-analysis of several studies, that the incidence of coronary artery perforations during percutaneous interventions was 0.43%.[3] There are many causes for iatrogenic coronary perforations, depending on the lesion complexity.[3] There are a few case reports of high-pressure,[4,5] post-dilatation related coronary perforations in the literature, but none while intervening in ectatic or aneurysmal arteries. Moreover, recurrence of perforation after treatment in the catheterisation laboratory by covered stents has not been reported until now. We learned an important lesson during the initial case, and for subsequent cases we adopted a less aggressive approach while stenting aneurysmal or ectatic coronary arteries by avoiding high-pressure post-stent dilatations.

CASE REPORT

The first case was a 62-year-old hypertensive female, with no other cardiac risk factors, who presented

to the emergency department following 2 days of intermittent angina at rest. An electrocardiogram showed inferolateral ST depressions with T wave inversions. An echocardiogram (ECHO) showed inferior wall hypokinesia with an ejection fraction of 54% and blood tests revealed elevated cardiac enzymes. The patient was diagnosed as having experienced a non-ST-segment elevation myocardial infarction, and initially given intravenous heparin, nitrates, and glycoprotein IIb/IIIa inhibitors. Later, due to persisting chest pain, an invasive strategy was planned. A coronary angiogram showed the mid-left anterior artery with 90% discrete short segment stenosis and large left circumflex artery (LCx) with proximal total thrombotic occlusion. Immediate percutaneous coronary intervention (PCI) of the culprit vessel was performed. The lesion was crossed with Runthrough® wire (Terumo, Tokyo, Japan) and thrombosuction was carried out with the Export® catheter (Medtronic, Fridley, Minnesota, USA). After the proximal vessel thrombosuction, some recanalisation was achieved and checkshot revealed a tight stenotic lesion, which required pre-dilatation with a Maverick™ 2.0x12 mm balloon (Boston Scientific, Marlborough, Massachusetts, USA). There was an aneurysmal segment in the LCx after the tight stenosis, and the entire lesion was covered with a 3.0x33 mm Promus Element™ stent (Boston Scientific, Marlborough, Massachusetts, USA), deployed at 12 atm. The stent at the aneurysmal region appeared malapposed, and hence post-dilated with 3.5x8.0 mm non-compliant balloon at 14–16 atm. To our dismay, the LCx artery developed a large Type III coronary perforation at the mid-portion of the stent, which was temporarily occluded with the stent balloon. Heparin was reversed with intravenous protamine and the surgeons were alerted of the complication. ECHO showed only mild pericardial effusion and, as the patient was haemodynamically stable, pericardiocentesis was not immediately performed. The perforation was sealed with 3.0x19 mm Graftmaster® covered stent (Abbott Vascular, Chicago, Illinois, USA) deployed within the previous stent at 12 atm by slow inflation (Figure 1).

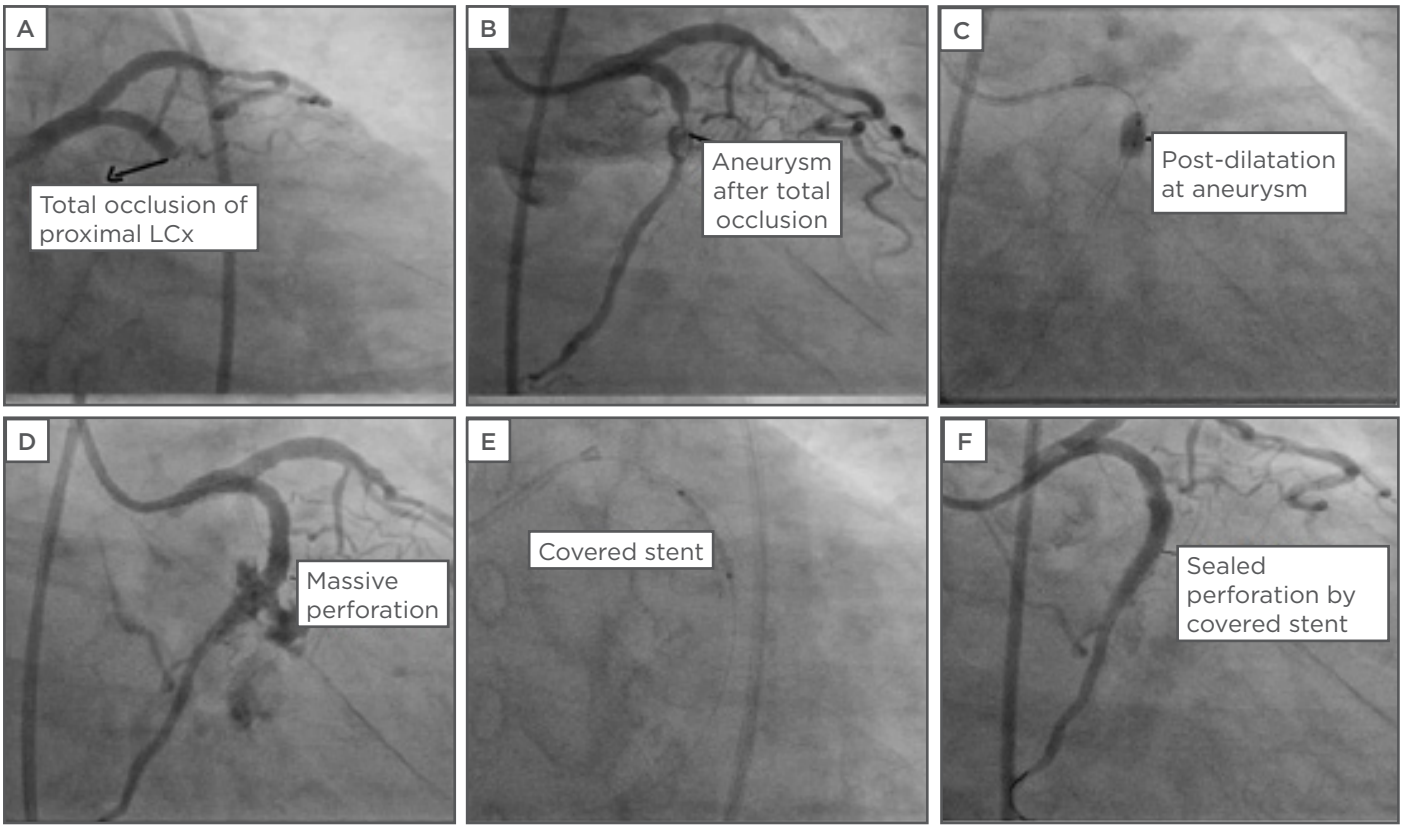

Figure 1: Coronary angiography during stenting procedure.
A) Total thrombotic occlusion of LCx; B) post-thrombosuction stenosis followed by aneurysm; C) post-dilatation of LCx; D) massive perforation at mid portion of stent; E) successful sealing of perforation by covered stent.
LCx: left circumflex artery.

The patient was later transferred to the intensive cardiac care unit (ICCU) and was monitored for increased pericardial effusion or signs of stent thrombosis, as there were four layers of metal and no anticoagulation or antiplatelet drugs were administered. The patient remained haemodynamically stable overnight and serial ECHOs showed only minimal pericardial effusion with no evidence of tamponade, a similar profile to that observed at the end of the complicated PCI. Eighteen hours post-procedure, the patient developed sudden cardiac arrest in the ICCU and bedside ECHO showed large pericardial effusions with hypokinetic inferoposterior and lateral walls. Without delay, bedside pericardiocentesis was performed, immediately draining a significant amount of haemorrhagic fluid. Despite the maximum efforts, the patient's vitals never recovered, and after unsuccessful cardiopulmonary resuscitation, the patient was declared dead in the ICCU.

The second case was a middle-aged female with an aneurysm in the LCx, and this time without pre or post-dilatation, we stented the aneurysmal lesion with 2.5x33 mm long bare-metal stent (BMS) (Figure 2). This patient had a higher bleeding-risk profile, the reason for which a BMS was chosen. The patient is doing well after 1 year of follow-up.

DISCUSSION

Based on the analysis of several angiography studies, the incidence of CAAs was found to range widely: 0.3–5.3%,[1] and one of the reasons for the variability is the difficulty of distinguishing aneurysms from ectasia.[2] CAA incidence is much higher in Indian patients than the general population, and they often have diffuse involvement of multiple arteries (10–12%).[1,6] Aneurysms can be saccular (the transverse larger than the longitudinal axis) or fusiform (longitudinal at least twice the transverse axis),[2] and the diameters of aneurysms range from 4.0–22 mm. CAAs and ectasia are variants of atherosclerotic disease and not a separate entity.[2] The right coronary artery is the most commonly involved (40–87%) followed by the left anterior descending artery and LCx.[1] Other CAA aetiologies include congenital, (accounting for 20–30% of cases and tending to be massive), inflammatory vasculitis, and connective tissue disorders.[2] Iatrogenic aetiology following attempted PCI is rare but has been documented,[7] resulting from residual dissection and deep-arterial wall injury following the use of oversized balloons or stents, high-pressure inflations, and atherectomy.

In adults, atherosclerotic disease is the most common cause of aneurysms, which tend to occur after obstructive lesions, such as the cases outlined above. Associated CAD is more severe in patients with discrete aneurysms than in those with diffuse ectasia. The combination of a proximal tight stenosis and a region of slower coronary blood flow immediately adjacent within an aneurysmal artery acts as a powerful nidus for thrombus formation. Additionally, turbulent post-stenotic flow within the coronary aneurysm promotes endothelial activation, attracting platelets and thrombin.

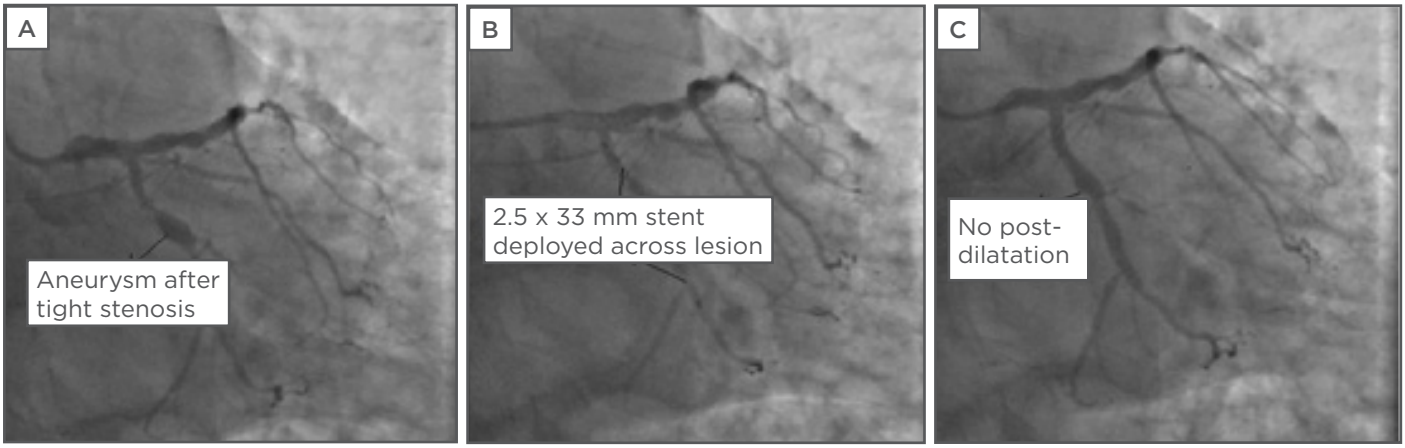

Figure 2: Coronary angiography images of bare-metal stenting of an aneurysmal lesion.
A) Stenotic lesion followed by aneurysm in LCx; B & C) lesion stented without post-dilatation.
LCx: left circumflex artery.

Histopathologic findings of autopsies have revealed extensive atherosclerotic changes with destruction or thinning of the tunica media of the vessel walls similar to that seen in atherosclerotic CAD.[1] Matrix metalloproteinases have been implicated in the pathogenesis of CAA formation through increased proteolysis of extracellular matrix proteins.[2] The heterogeneous depth of vascular injury caused by inflammation and atherosclerosis leads to varying degrees of remodelling within the coronary artery, whereby aneurysmal segments may lie adjacent to segments of stenosis. CAA occurs when the atheromatous process affects the intima, media, and adventitial parts of the vessel, leading to remodelling and dilatation. CAA then progresses according to Laplace's law (increasing diameter leads to increasing wall stress), which in turn causes progressive dilatation of the affected arterial segment.[2,8] In view of rare occurrence, clinical trials are not possible, only case reports or series are available, and treatment has to be individualised. It is generally opined that CAAs do not rupture unless extremely large.

If these lesions are detected incidentally during angiography, it is advisable to manage medically, rather than surgically, due to uncertain procedural outcomes. Some advocate chronic anticoagulation to prevent thrombosis of aneurysmal arteries, but sometimes despite anticoagulation, patients develop thrombotic occlusion, suggesting that other mechanisms, such as plaque rupture, are involved in the development of acute coronary, in this context.[1] If patients present with acute coronary syndromes, they are treated with antiplatelets, nitrates, thrombolysis, or glycoprotein IIb/IIIa inhibitors. Either BMS or drug-eluting stents (DES) may be considered with PCI of aneurysmal arteries, but stent malposition is potentially problematic and may lead to stent thrombosis, restenosis, or thrombus embolisation producing slow or no reflow. Some authors suggest using polytetrafluorethylene (PTFE)-covered stents as a better method to trap thrombi and exclude aneurysmal portions of coronary arteries, but this presents a risk of branch-vessel occlusion and high incidence of restenosis.[9] PTFE-covered stents should be used when the aneurysm diameter is <10 mm, but surgery is preferable for larger diameter aneurysms.[1] As there are no guidelines available, the optimal approach is decided on a case-by-case basis depending on the technical expertise available, patient factors, and lesion characteristics. For example, if the vessels were heavily calcified or tortuous, PTFE-covered stent delivery would be difficult, and if the lesion is very long (as in the above cases), the correct size of covered stent may not be available, especially in emergency situations.[2] However, if they are successfully delivered, they can theoretically seal the aneurysm, thereby preventing the risk of rupture or distal embolisation of debris. If PTFE-covered stents cannot be used due to their various disadvantages, DES or BMS must be considered. While initial reports suggested that implantation of first-generation DES led to higher incidence of associated late CAA compared with BMS (1.4% versus 0.2%), there are limited data on the current generation of DES.[10] Other indications for surgery in CAA treatment are involvement of the left main coronary artery, associated multi-vessel CAD, and bifurcation of significant side-branch vessels.[2] The most common treatment is surgery, especially in adults, according to a coronary artery surgery study (CASS) sub-study, which concluded that surgery in CAA patients had comparable results to routine coronary artery bypass grafting.[11] In both of the aforementioned cases, surgery was not primarily considered due to isolated circumflex artery involvement. Use of self-expanding stents is another treatment option with PCI of these arteries. Regardless, due to the high propensity of developing thrombosis and embolisation, dual antiplatelet therapy must be continued for a long duration after artery stenting. Aspirin and oral anticoagulants may be used to maintain the international normalised ratio in the 2.0–2.5 range if thrombosis recurs on dual antiplatelet therapy. The role of novel oral anticoagulants is not clear in these types of cases.

Important risk factors for coronary perforations can be divided into patient-related factors and angiographic characteristics of the lesions. Patient-related risk factors include: older age, female sex, hypertension, history of heart failure, renal failure, and prior use of antithrombotics. Angiographic factors include coronary calcification, chronic total occlusions, lesions >10 mm in length, tortuous lesions, Type C lesions, use of hardware such as hydrophilic or stiff wires, atherectomy devices, intracoronary ultrasounds, and post-dilatation of stents at very high pressures. Aneurysmal coronary arteries and ectatic arteries were not mentioned as risk factors for coronary perforation during interventions.[8,12] There are different methods of treating coronary perforations, ranging from a simple reversal of anticoagulation in the case of

guidewire-related perforations, to emergency surgery in the case of large perforations, but the use of PTFE-covered stents has emerged as the standard treatment.[13] The main concerns regarding the use of PTFE-covered stents in perforation setting are occurrence of stent thrombosis and in-stent restenosis. Initial studies have reported rates of 33% for stent thrombosis, and 50% for in-stent restenosis at 6 months, due to delayed stent endothelisation with the PTFE membrane.[14]

Sealing perforations with a covered stent may be unsuccessful, as the entire vessel wall may be diseased, leading to the eventual giving-way of adjacent areas, and reperforation. As a result of the previously mentioned case, we dealt cautiously with ectatic or aneurysmal artery PCI, avoiding high-pressure post-stent dilatations at aneurysm sites. Gaps between unopposed stents and aneurysmal walls are sealed in due course, and routine antiplatelets with a short course of anticoagulation suffice as treatment.

CONCLUSIONS

CAAs are risk factors for coronary perforation, and high-pressure post-stent dilatation to treat stent malapposition at aneurysmal sites should be avoided.

Ethical Considerations

Informed consent was obtained from all individual participants included in the study.

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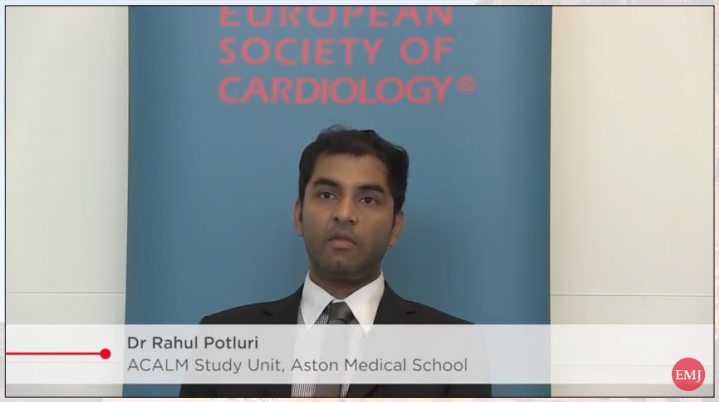

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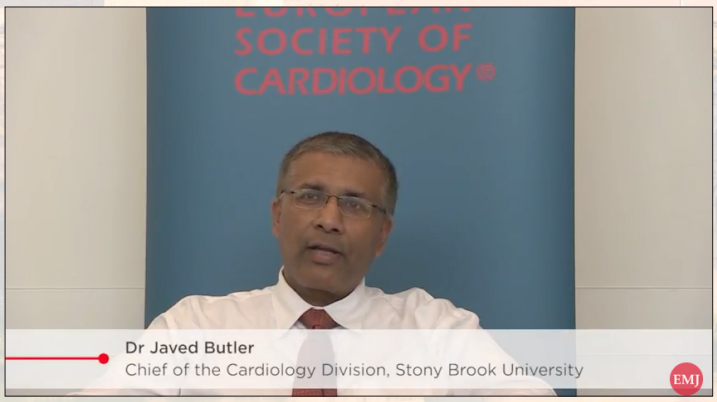

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CURRENT CONCEPTS IN CORONARY ARTERY SPASM

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ABSTRACT

Coronary artery spasm is an abnormality of coronary vascular smooth muscle contraction that is associated with significant morbidity and mortality. The underlying pathophysiological process has remained unclear since Myron Prinzmetal described it in 1959. This article reviews current literature of the pathogenesis and outlines clinical features, diagnosis, and treatment options.

Keywords: Coronary artery disease, coronary spasm, Prinzmetal's angina, provocative testing.

INTRODUCTION

Coronary artery spasm (CAS) is caused by abnormal coronary artery vascular smooth muscle (VSM) contraction.[1] The pathophysiological process underlying CAS remains uncertain, leading to numerous incongruous descriptions of this disease. In 1959, Prinzmetal et al.[2] first realised variant angina as being a separate entity from classical angina pectoris, described by Heberden.[3] Prinzmetal et al. described a syndrome independent of physical exertion, during which ST-segments are transiently and often remarkably elevated but almost always terminate spontaneously. It was thought that this transient myocardial ischaemia was brought on by temporary occlusion of a large diseased artery due to an increase in vascular wall tone.[3]

The advent of coronary angiography has allowed for direct visualisation of the coronary arteries during episodes of CAS. This demonstrated patients with angiographically unobstructed coronary arteries,[4,5] leading to the idea that variant angina represented focal spasm of coronary arteries in otherwise disease-free vessels.[6] More recently there has been discussion that CAS occurs at the site of atherosclerotic plaque lesions.[7]

EPIDEMIOLOGY

The prevalence of CAS is difficult to characterise due to variation within different populations, variable use of provocative testing, and differing diagnostic criteria. CAS is more prevalent in males, with most patients aged between 40–70 years, but this prevalence tends to decrease after the age of 70 years.[8,9] Japanese populations have a greater frequency of CAS[10] (thought to be secondary to hyperreactive coronary arteries) when compared with their Caucasian counterparts.[11] Western studies have demonstrated, in selected population groups, the prevalence of CAS amongst patients with angiographically unobstructed coronary arteries (no focal obstruction >50%) undergoing provocative testing at 49% and 33.4%, respectively.[12] In addition, the frequencies of multiple regions of spasm during provocation testing in Japanese (24.3%) and Taiwanese (19.3%) populations are higher than those of Caucasian populations (7.5%).[13]

Although not supported by robust epidemiological data, the incidence of CAS is thought to be declining.[14] The decreased incidence of smoking is thought to be a major contributing factor, along with the increased use of calcium channel blockers (CCBs)[15] for hypertension, and statins for primary and secondary prevention of ischaemic heart disease. There is also thought to be a reduced interest in performing time-consuming provocative

testing in the cardiac catheterisation laboratory[14] and a presumed diagnosis of CAS is normally managed with a trial of CCBs.

CLINICAL FEATURES

CAS can manifest clinically as a wide spectrum of coronary syndromes, which can make diagnosis challenging. It is suspected in the presence of severe chest pain at rest, with concurrent electrocardiogram (ECG) changes showing transient ST-segment elevation. Although chest pain remains the most common symptom of CAS, it is worth noting that many attacks of CAS can be asymptomatic or silent.[16] Syncope may occur during these silent ischaemic episodes.[17] A distinguishing feature of CAS is that angina is thought to occur predominantly at rest and not during exercise; this has preponderance for occurring late at night or early in the morning, with a peak frequency reported as 5 am.[18,19] Interestingly, light exercise, when performed early in the morning, has been shown to induce episodes of spasm, whereas strenuous exercise in the afternoon did not provoke the same episodes.[20] Therefore, CAS is thought to follow diurnal circadian variations possibly related to the contributions of the autonomic nervous system (ANS).

DIAGNOSIS

Electrocardiogram

Although Prinzmetal's angina is most commonly associated with ST-elevation, the ECG findings of CAS are extremely varied and may in fact be absent. Traditionally, a total or subtotal spasm of a major coronary artery will lead to ST-elevation in the corresponding distribution of that artery. CAS is also frequently associated with ST-segment depression rather than ST-elevation.[21] There are a number of associated arrhythmias including sinus bradycardia, sinus arrest, atrioventricular block, paroxysmal atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and asystole, lending further credence to the argument that CAS encompasses a spectrum of diseases and can present in a wide variety of ways. Sudden death may also result from CAS, with bradyarrhythmia rather than tachyarrhythmia being the most common terminal event.[22,23]

CORONARY ANGIOGRAPHY

Yasue et al.[16] suggested that CAS can be diagnosed clinically if the anginal attacks disappear quickly upon administration of nitroglycerin and any one of five specific criteria are met: attacks appearing at rest in the morning, diurnal variation in exercise tolerance, presence of transient ST-elevation, attacks induced by hyperventilation, or ability of CCBs to suppress the attacks.

Angiography may reveal normal, or near normal, coronary arteries.[24,25] The presence of angiographically normal coronary arteries in CAS has been widely documented in studies from Japan.[16] This may be due to environmental and genetic factors that have been suggested to give a higher prevalence of CAS in the Japanese population.[1,10] More recently it has been suggested that the presence of normal coronary arteries is actually overstated and that atherosclerotic disease, in the form of focal irregularities along the coronary vasculature, contributes to almost all focal CAS.[14] This is supported by evidence of focal irregularities detected by intravascular ultrasound in angiographically 'normal' coronary arteries.[26,27] Therefore, the higher proportion of normal coronary arteries seen in the Japanese population may be a result of a lower threshold for describing a coronary artery as 'normal' on angiography.

PROVOCATIVE TESTING

The diagnosis of CAS should ideally be made by witnessing a CAS angiographically during an attack, however this is often not possible. Provocative testing allows for the induction of CAS by certain physiological processes or pharmacological agents in order to demonstrate the vasculature's abnormal predisposition to contraction. Hyperventilation,[28] exercise testing,[29] and cold pressor tests have all been used to physiologically induce CAS, however these are limited by modest sensitivity. Ergonovine and acetylcholine are the most commonly used agents for this purpose and cause contraction of smooth muscle cells that are more sensitive to these agents due to the presence of endothelial dysfunction.[30-33] Although provocative testing with ergonovine or acetylcholine has good sensitivity for the detection of CAS,[34] associated complications have resulted in a decline in utilisation, especially in Europe and North America.[35] However, a recent study demonstrated that when performed in controlled environments,

the use of acetylcholine provocation testing can be safe and effective at demonstrating diffuse CAS in patients with unobstructed coronary arteries (<50% obstruction).[35,36]

PATHOPHYSIOLOGY

The causes of CAS are multifactorial and remain poorly defined. Much has been made of the potential role of the ANS in the development of spasm, yet the relationship remains complex and not fully explained. The parasympathetic system was initially thought to be central to CAS as it has preponderance for occurring at night when vagal tone is highest,[37,38] and acetylcholine is known to induce CAS.[16] However, alpha adrenergic vasoconstriction by the sympathetic nervous system has also been suggested as a possible trigger for CAS.[39,40] Propranolol has been shown to exacerbate spasm, presumably because of the resultant unopposed alpha adrenergic vasoconstriction.[41] Despite the above evidence, therapies aimed at manipulating the effects of the ANS have failed to translate into effective treatments.[42,43]

Endothelial dysfunction, although not always present in patients with CAS,[44] is thought to be central to the hyperreactive vasomotor response of coronary arteries. In 'normal', healthy individuals, acetylcholine causes arterial vasodilatation,[45] however in vessels prone to spasm it causes abnormal constriction and hence is used in provocation testing.[35] Ergonovine and acetylcholine both cause vasodilatation in normal vessels via the release of nitric oxide, therefore dysfunctional endothelial nitric oxide synthase has been suggested as a possible contributor to CAS.[46] Underlying atherosclerotic lesions are often the substrate on which these changes in the endothelium take place. Statins and vitamin E have both been shown to improve endothelial function and reduce symptoms of CAS.[47,48] Smoking is a known risk factor for CAS and may contribute to the development of endothelial dysfunction through chronic low-grade inflammation.[49] High levels of circulating inflammatory cytokines have been shown to be independently associated with a diagnosis of CAS,[50] and chronic inflammation of the vascular endothelium is thought to predispose arteries to abnormal spasm.[51]

The effectiveness of CCBs at reducing the frequency of symptoms of CAS may be directly linked to the hypercontractility of VSM in affected arteries. Animal models have suggested a role for increased Rho kinase activity which can directly increase the sensitivity of myosin light-chain to calcium, augmenting its phosphorylation and thus favouring contraction of the smooth muscle cell.[52]

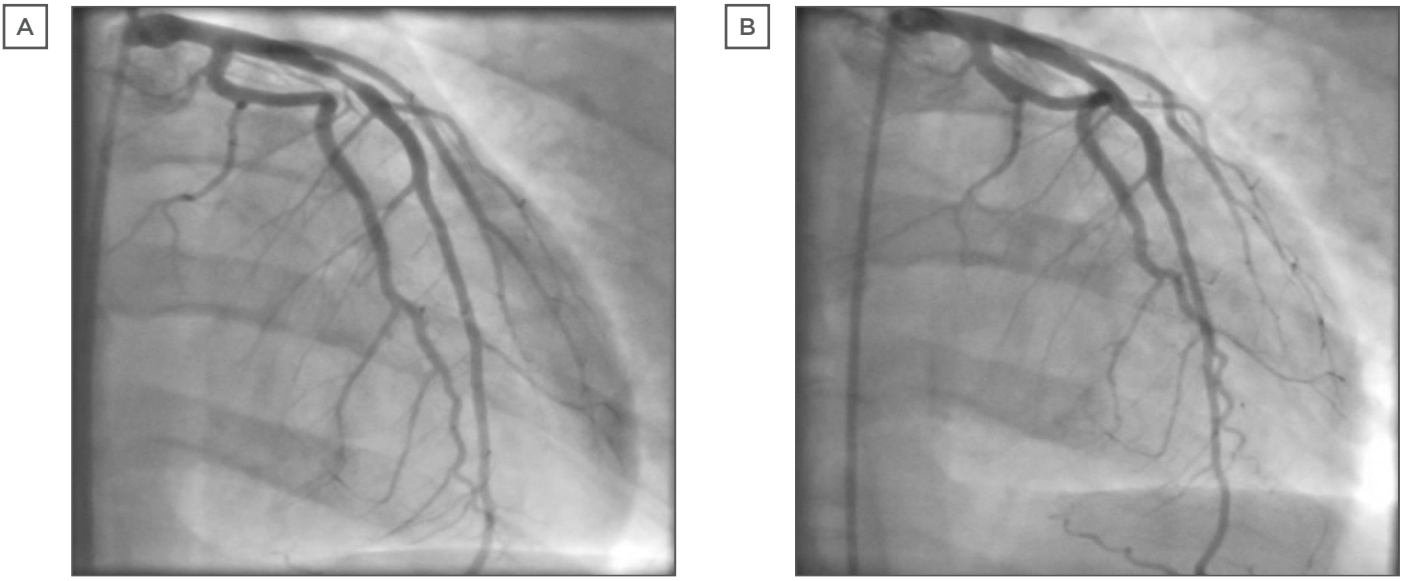

Figure 1: Coronary angiogram.
A) Left coronary system demonstrating significant obstructive proximal LAD artery stenosis secondary to coronary spasm; B) Left coronary system after intracoronary nitrate demonstrating resolution of proximal LAD artery stenosis.
LAD: left anterior descending.

Other animal models have suggested a number of pathways through which hypercontractility in smooth muscle cells may be induced, however their relevance remains to be clarified.[53,54]

TREATMENT

In the acute setting, early treatment of CAS is important to the prevention of significant complications such as myocardial infarction, arrhythmias, and sudden cardiac death. Sublingual, intravenous, or intracoronary nitroglycerin in the acute phase has been shown to be effective for relieving attacks (Figure 1).[55]

Cessation of smoking is the most effective non-medical intervention for the prevention of further attacks of CAS. As CAS is likely to occur in the context of existing atherosclerotic disease, controlling risk factors for ischaemic heart disease must also be undertaken to try and control recurrent episodes of spasm.[49] Other non-medical treatments include avoiding drugs which induce spasm, reducing alcohol intake,[56] avoiding emotional stress, and replacing any magnesium deficiency.[1,57,58]

CCBs have demonstrated efficacy at reducing the frequency of attacks of CAS by inhibiting the contraction of VSM.[59] The use of CCBs has been shown to be an independent predictor of survival and can successfully reverse provocative testing, allowing for the safe discontinuation of medical treatment if necessary.[60] Interestingly, complications of CAS such as atrioventricular block have been terminated with CCB therapy.[61] High-dose long-acting CCBs are used as the initial treatment and are uptitrated according to symptomatic response, with the occasional requirement of using two agents to control symptoms. Given the preponderance for attacks of CAS to take place at night and in the early hours of the morning, CCBs should be taken at night before bed to be most effective.[1]

Long-acting nitrates, despite not having any prognostic benefit, also act at the level of the VSM to promote relaxation and prevent episodes of spasm. They have not been shown to be as effective as CCBs and their use is limited by their side effect profile[62] and the development of tolerance.[63] Despite this, they can be used safely in combination with CCBs to try and suppress recurrent episodes of spasm. Nicorandil, a potassium channel activator, may also be used in the management of recurrent episodes of spasm refractory to CCBs or nitrates.[64] Other agents, including magnesium, antioxidants, Rho kinase inhibitors, statins, and pioglitazone[65] have all been suggested as possible treatments for CAS due to their effects on vascular endothelial function, however their integration into clinical practice remains to be seen.

Non-medical treatment of CAS has included attempts at using angioplasty and coronary artery bypass grafting to try and prevent further episodes of spasm. The reports of cases treated with coronary artery bypass grafts (CABG) have given variable results.[66] The success of this operation in the treatment of CAS is most likely dependent on the degree of atherosclerosis present and to what extent that disease is contributing to the spasm. If there is a focal site of spasm caused by atherosclerotic disease, then it could be effectively bypassed. However, if the spasm is multivessel and diffuse, CABG would be less efficacious. In order to address this problem, one approach considered was to perform a sympathectomy to prevent diffuse spasm. This seems to improve the outcome. Sympathectomy has recently been used in the treatment setting of acute CAS causing life-threatening complications.[67]

Primary percutaneous coronary intervention (PCI) has been presented as another possible treatment for refractory CAS.[68] PCI may provide a rapid and effective treatment for focal spasm that presents as a life-threatening complication. Unfortunately, the long-term outcomes following PCI remain variable.[69] Once again this most likely represents the wide spectrum of underlying pathology in CAS. Some cases demonstrate the diffuse spasm of multiple arteries, which are clearly not suitable for a targeted intervention such as PCI. Each case must be considered individually and the appropriate non-medical treatment applied depending on the nature of the spasm (diffuse or fixed), the possible underlying atherosclerotic disease, and the acuteness of the presentation. More research is required and a randomised controlled trial should be performed, investigating the possibility of PCI as a treatment for CAS. (Table 1)[59,60,69-76]

PROGNOSIS

Major adverse cardiovascular events (including death and myocardial infarction) for CAS are difficult to quantify due to the lack of consensus in diagnostic criteria. Initial studies reported 3-year

major adverse cardiovascular events rates between 5% and 37%. However, more recent studies have described rates of ≤1%. Of note, the period of highest major adverse cardiovascular event rates is within 3 months from onset of symptoms. This highlights the importance of early recognition and diagnosis, especially in patients presenting with acute coronary syndromes without culprit lesion, unexplained syncope, or aborted sudden cardiac death.[7] The Japanese Coronary Spasm Association (JCSA) risk score can be utilised for risk assessment and prognostic stratification of CAS patients.[77]

Table 1: Treatment for coronary spasm.

Author	Year	N	Type of report	Intervention	Outcome
Calcium channel blockers					
Waters[60]	1981	22	Non-randomised trial	Patients with known variant angina, diagnosed by provocative testing, treated with CCBs for an average of 9.4 months	All patients free from anginal attacks; 12 out of 22 patients who had no repeat provocative testing were negative, suggesting the possibility to withdraw CCBs
Kimura and Kishida[71]	1981	286	Examination of drug effectiveness	Data collected from 11 cardiology institutes to determine the effectiveness of CCBs	Survey of drug treatment demonstrated CCBs were effective in 92.5% of patients
Yasue et al.[70]	1988	245	Prospective cohort study	245 patients followed-up for an average of 80.5 months	The use of CCBs was established as an independent predictor of survival
Chahine et al.[59]	1993	52	Double-blinded randomised controlled trial	Randomised to receive either amlodipine 10 mg or placebo	Significant decrease in anginal episodes with amlodipine compared with placebo
Nitrates					
Lombardi et al.[73]	1993	21	Double-blinded randomised trial	Patients received placebo, ISMN, or nifedipine, then underwent echo-ergonovine test	Nifedipine and ISMN caused a significant reduction in spontaneous and induced anginal episodes
Takahashi et al.[74]	2015	1429	Multicentre registry study	Median follow-up 32 months, primary endpoint major adverse cardiac events	Cumulative incidence of major adverse cardiac events was similar between both patients taking, and not taking, nitrates, suggesting no prognostic benefit to nitrate therapy
Nicorandil					
Kishida and Murao[76]	1987	32	Single-blinded trial	32 patients with angina pectoris given pretreatment with placebo, 3 days of nicorandil (20 mg/day), and post-treatment placebo	Significant reduction in the number of anginal attacks in the nicorandil treatment time; significant increase in anginal attacks with ST-elevation following withdrawal of the drug
Lablanche et al.[75]	1992	13	Randomised, placebo-controlled, crossover study	Patients received either nicorandil, nifedipine, or placebo for 2 days then had ergometrine testing	Nicorandil gave negative ergometrine tests in nine patients; nifedipine and nicorandil shown to be equally effective at suppressing ergometrine testing
PCI					
Gasparadone et al.[69]	1999	9	Non-randomised trial	Patients with refractory variant angina had stent implanted at site of spasm	Six patients were asymptomatic at follow-up and three patients developed recurrent spasm
Tanabe et al.[72]	2002	45	Non-randomised trial	Underwent spasm provocative testing 7 months after PCI for vasopastic angina	Spasm frequently produced at different sites to the original spasm site requiring PCI, suggesting diffuse nature of spasm and ineffectiveness of PCI

CCBs: calcium channel blockers; ISMN: isosorbide-5 mononitrate; PCI: percutaneous coronary intervention.

CONCLUSION

CAS is caused by abnormal coronary artery VSM contraction and can manifest clinically as a wide spectrum of coronary syndromes, which can make diagnosis challenging. The prevalence of CAS is difficult to characterise due to variations within different populations. CAS is more prevalent in males, with most patients aged 40–70 years. The Japanese Coronary Spasm Association risk score can be utilised for risk assessment and prognostic stratification of CAS patients. CAS is suspected in the presence of severe chest pain at rest, with concurrent ECG changes showing transient ST-segment elevation. Chest pain remains the most common symptom of CAS, although silent attacks can occur, for example with syncope.

The causes of CAS are multifactorial and remain poorly defined. The ANS and endothelial dysfunction are thought to play an integral role in the pathophysiology of CAS. Treatment of CAS includes sublingual or intravenous nitroglycerin in the acute phase. In addition, long-acting nitrates, CCBs, and nicorandil all have a role in the treatment of CAS. There is limited evidence of invasive therapy with PCI or CABG, which should be considered in refractory cases.

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VALVULAR HEART DISEASE AND RISK SCORE SYSTEMS IN CLINICAL PRACTICE

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ABSTRACT

Heart valve disease is a very common medical condition; the most frequent aetiology is degenerative valve disease, mainly represented by calcific aortic stenosis in the elderly. In developing countries, valvular heart disease triggered by rheumatic fever is the most important aetiology and can lead to a heterogeneous heart valve disease, mainly represented by mitral stenosis in young female patients. The need for heart valve surgery is common in this context and preoperative risk stratification is essential in making surgical decisions. To evaluate the preoperative risk of these valve heart disease patients, risk scores have been created to assess the surgical morbidity and mortality.

In this article, we aim to discuss the current risk score systems, and the applicability and effectiveness of these systems in specific populations of heart valve disease taking into account the epidemiological characteristics of the studied populations.

Keywords: EuroSCORE (ES), valvular surgery, valvular heart disease.

INTRODUCTION

Valvular heart disease is a worldwide health problem with approximately 275,000 surgeries every year and a mortality rate between 1% and 15%.[1] The main aetiology in the USA and most developed nations is degenerative valve disease, represented by calcific aortic stenosis. Degenerative disease is increasing as a result of population ageing and is the third most common cardiovascular disease after hypertension and coronary artery disease in industrialised countries.[2] In Brazil, and most likely in many other countries in which valvular heart disease is widely prevalent, the major aetiology is rheumatic fever. Rheumatic heart disease (RHD) is by far the most important form of acquired heart disease in children and young adults living in developing countries.[3,4] Despite the fact that it is a preventable illness, approximately 19 million people are affected by it.[5,6] RHD accounts for about 15% of all patients with heart failure in endemic countries[3,4] and 30% of all cardiac surgeries.[3] In RHD, the mitral valve is involved in nearly all cases and the aortic valve is involved in about 30%. The tricuspid valve is commonly affected but is frequently subclinical and associated with mitral valve disease.[3,4]

Rheumatic aetiology presented epidemiological and comorbidity differences when compared with the worldwide population of valvular heart disease. The main differences are represented by a younger age, mostly female, high prevalence of pulmonary hypertension, and atrial fibrillation.[3] Treatment options include medication, percutaneous balloon valvuloplasty, transcatheter replacement, and valve surgery (repair or replacement).[2]

Preoperative risk stratification is essential in making sound surgical decisions. Risk scoring systems have been developed to predict mortality after cardiac surgery in adults. It is worth noticing that scores were developed in the USA and Europe, countries

with lower prevalence of RHD and different patient profiles. The main risk factors related to surgical outcomes are: older age, female sex, reduced ventricular ejection fraction, New York Heart Association (NYHA) classification, pulmonary arterial hypertension, reoperation, renal disease, obstructive pulmonary disease, urgent/emergency surgery, infectious endocarditis, and concomitant coronary artery disease.[1,2,7]

With the development of transcatheter aortic heart valve replacement in recent years, indications of valve replacement should be based heavily on the valvular heart team[7] and risk scores. The importance of score validation consequently increases, especially for finding patients with higher risk. Risk scores also support the comparison of outcomes between institutions and surgeons, and make the clinical research communication simple. Therefore, the objective of this article is to review risk stratification in valvular surgery, its limitation in clinical practice, and debate its use in as specific a population as the rheumatic patients.

REVIEWING THE RISK SCORES

Estimating cardiac surgery risk can be challenging, so several scores were created and modified throughout previous decades to help clinicians and surgeons accomplish this task. The scores, mostly used in the context of valve surgery, are: EuroSCORE (ES) II,[8] Society of Thoracic Surgeons (STS) score,[9] and Ambler score.[1] Each score has its own specifications. The ES emerged from the European database with approximately 19,000 patients. Of these, 29% underwent valve surgery. This model has been replaced by the 2011 ES II model which was based upon data from 22,381 patients in 43 countries who were operated on between May and July 2010.[8] Of these, 46% underwent valve surgery. Overall mortality was 3.9% which is lower than would have been predicted by old risk models (ES additive predicted 5.8% and ES logistic predicted 7.6%). The STS score was generated from the USA database which was separated into three large cohorts with >100,000 patients in each. In Groups 2 and 3, only valve surgeries (aortic valve replacement, mitral valve replacement, and mitral valve repair), and combined valve surgery and coronary artery bypass grafting (CABG) were respectively included. The Ambler score, based on 32,839 patients in Great Britain and Ireland, was specifically designed for heart valvular surgery (aortic and mitral) with or without CABG, bringing to discussion the differences among diseases and risks in various procedures.

Two Brazilian models were also proposed for the specific setting of valvular heart disease: the Guaragna score from 2010[10] and the VMCP (heart Valve lesion, Myocardial function, Coronary artery disease, Pulmonary artery pressure).[11] The Guaragna score analysed data from 768 patients, identifying nine predictors of mortality: age >60 years, ejection fraction <45%, female sex, pulmonary hypertension, NYHA III/IV, renal insufficiency, emergency surgery, and concomitant CABG. The score had good validation (area under curve receiver operating characteristic [AUC ROC]: 0.83, 95% confidence interval: 0.78–0.86). VMPC could not predict mortality on the statistical analyses, but a VMPC score >8 was associated with a more advanced illness and increased need for care after procedure. The authors supposed that this lack of prediction in death was due to the small number of patients; both scores were developed with single institution data. Such risk scoring systems are more applicable when the preoperative patient characteristics and treatment profiles are comparable with those from which the system was developed.

Table 1: Score systems and their relevance for valvular heart disease patients.

Score system	Strength of recommendation
EuroSCORE II*	++
STS	++
Ambler	+

*Most studied score system in Brazilian heart valve patients.
STS: Society of Thoracic Surgeons; VHD: valvular heart disease patients.
++strongly recommend; +weakly recommend.

To implement those models, statistical analyses are necessary. The performance is evaluated by the AUC ROC. The STS,[9] Ambler,[1] and ES[8] AUC were 0.80, 0.77, and 0.72, respectively. Usually produced by the Hosmer–Lemeshow test, these scores demonstrated good calibration, on which the mortalities predicted and observed were then compared.

LIMITATION OF THE RISK SCORES IN CARDIAC SURGERY AND ITS APPLICATION IN RHEUMATIC VALVULAR DISEASE

Although risk scores were well validated in many countries[12,13] with significant sample size, they can be inaccurate when evaluating application and individual care in different populations. The choice and total amount of a given risk factor composing a risk model depends on clinical intention,[14] and other factors that could change results are not included in many models such as nutritional status, intra-operatory complications, and frailty. Socioeconomic status, ethnicity, cardiac team experience, healthcare, and living standards, especially in developing countries with high prevalence of rheumatic disease due to the particular differences in this disease population, may also influence surgical results.[13] Local validation should always be conducted and a number of publications have advocated the strategy of local risk score development using particular institution databases.[14-16] An example of inaccuracy can be seen in the comparison of a patient aged 60 years with severe left ventricular dysfunction and an additive ES of 4, and a female 73-year-old patient with no comorbidities who also had an additive ES of 4. These patients definitely do not have the same operative risk, yet they have the same ES risk.[17]

A meta-analysis from Parolari et al.[18] including 26,621 patients showed low discriminatory power of the ES in valvular surgery, as it overestimated mortality rate. An earlier discussion by Ranucci et al.[19] stated that a simpler score with a limited number of risk factors (age, serum creatinine, and ejection fraction) could predict mortality with a good accuracy, although this study was limited to elective cardiac surgery.

ES II is based on recent data and has corrected some variables that could cause loss of discriminatory capacity, and studies are showing better performance. Recently, Billah et al.[15] compared ES and ES II in the estimation of 30-day mortality in valvular surgery, with calibration being markedly improved with ES II. A Pakistani validation study[20] compared ES II with ES and STS in patients undergoing valvular surgery with and without CABG, with better results among ES II.

An important question is the applicability of the scores for all aetiologies in valvular heart disease due to variation of population characteristics and pathophysiology. Few studies have evaluated the risk and validated scores in a population composed only of rheumatic valvular patients. An Australian review from 2014[21] and a Brazilian study[17] found that these patients were younger, needed more frequent reoperation, often had multi-valve repair, and had less need for CABG than other aetiologies. Both studies showed a higher rate of female patients, data of relevance due to the need to manage anticoagulation demands during pregnancy. Despite this consideration, a study published recently showed good application of ES and ES II in a population with high prevalence of rheumatic valve disease.[17]

Aortic stenosis is the most commonly acquired valvular disease. When it is severe and symptomatic, a surgical approach is the gold standard therapy. In this setting, risk scoring plays an important role, identifying high-risk patients who could benefit from a percutaneous approach. However, there are presently no specific scores for mortality prediction in transcatheter aortic valve implantation (TAVI). The current score models have modest accuracy, with C statistic values ranging from 0.59–0.71[22-24] to predict mortality after TAVI. An explanation of the current scores in this scenario is that they were developed within the parameters of a procedure that involves cardioplegia, sternotomy/thoracotomy, extracorporeal circulation, and other clinical characteristics that may not influence survival after TAVI.[25]

CONCLUSION

It is essential to remember that clinical judgement must always be taken into account as well as a valve specialist's and heart team's opinions. Cardiac surgery and percutaneous replacement are also improving, thus models developed based on the current techniques may become inadequate for effective risk verification in this particular class of patients. In summary, all the score systems may be used (Table 1) within the scope of valvular heart disease with varying accuracy and we recommend a local validation test before use.

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CARDIAC ARREST IN PREGNANCY: END-TIDAL CO_2 MONITORING COULD GUIDE MANAGEMENT IN THE PREHOSPITAL SETTING

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Steinar Einvik was the prehospital physician on-site. Ingrid Marie Ringen performed perimortem caesarean section in the Emergency Department. Thomas Lafrenz and Stein-Vegar Johansen were the leading physicians inside the hospital Emergency Department. Per P. Bredmose made important contributions to the discussion section. Steinar Einvik was the major contributor to the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

This case report describes a 27-year-old pregnant woman with a gestational age of 26 weeks and 3 days who developed cardiac arrest in her home. Resuscitation was started immediately and continued on arrival at the hospital. Guidelines for resuscitation of cardiac arrest during pregnancy in-hospital include that a perimortem caesarean section (PMCS) should be performed if there is no return of spontaneous circulation within 4 minutes. The guidelines for prehospital treatment in such circumstances are more controversial. The triage on-site was based on the end-tidal carbon dioxide ($ETCO_2$) monitoring showing that the quality of resuscitation being done was proficient and after a short on-scene time the patient was transported to the emergency department for PMCS on arrival. The resuscitation of the mother was not successful but the baby survived with no known sequelae after a total arrest time of 28 minutes before delivery. Monitoring of $ETCO_2$ in resuscitation of cardiac arrest in pregnancy might be helpful in making the decision on whether to perform PMCS on-site or at a somewhat more appropriate location in the hospital.

Keywords: Perimortem caesarean section (PMCS), return of spontaneous circulation, end-tidal carbon dioxide ($ETCO_2$), ventricular fibrillation, arrhythmogenic right ventricle dysplasia (ARVD).

INTRODUCTION

Cardiac arrest in pregnancy is rare, occurring in only 1 in 30,000 pregnancies, and survival from such an event is exceptional. A comprehensive scientific statement about cardiac arrest in pregnancy includes a recommendation that a perimortem caesarean section (PMCS) should be performed if there is no return of spontaneous circulation within 4 minutes.[1] End-tidal carbon dioxide ($ETCO_2$) predicts survival in out-of-hospital cardiac arrest and low values predict poor survival in the non-

pregnant population.[2] We present a case from St. Olavs Hospital, a hospital caring for 4,000 births annually.

CASE REPORT

A 27-year-old woman, *gravida* four, *para* one, was pregnant at gestational age of 26 weeks and 3 days. She had complained of several episodes of palpitations, which were self-limiting. On one occasion she sought medical attention and was referred to cardiologic outpatient clinic. Unfortunately, there is no electrocardiogram available from this consultation. She had not seen the cardiologist by the time of the arrest.

At home on the day, she had felt uncomfortable with palpitations for some seconds before she lost consciousness. Bystanders immediately called the emergency dispatch centre. After a minute, bystanders started chest compressions guided by the dispatch operators. The first heart rhythm upon arrival by ambulance personnel 7 minutes later showed low amplitude ventricular fibrillation. Two shocks of 200 joules were delivered with standard placement of pads without effect. Advanced cardiac life support was continued and a laryngeal mask was successfully inserted. Three minutes after the arrival of the air ambulance crew (flight anaesthesiologist and paramedic) the heart rhythm had degenerated to asystole and the patient was put on an automated chest compression device (LUCAS™, LUCAS 2, Jolife, Lund, Sweden). $ETCO_2$ showed 5.5 kPa (41 mmHg) with LUCAS ongoing, but no pulses were detected and rapidly diminishing $ETCO_2$ values were seen when LUCAS was paused. The air crew personnel decided to 'load and go' to the Emergency Department (ED) at St. Olavs Hospital, a 5-minute drive from the scene.

The relevant hospital resources were alerted by the dispatch centre when the ambulance started driving to the hospital. In the ambulance, the patient was tilted to the left side with continuous chest compressions using LUCAS. $ETCO_2$ remained between 5 and 6 kPa (37.5 and 45.0 mmHg).

Within 2 minutes after arrival in the ED, the baby was delivered by PMCS, some 28 minutes after the maternal arrest. Initially the baby was bradycardic (heart rate 70–80 bpm) which rapidly rose with ventilations. No chest compressions were needed. The Apgar score was 1-2-3. The baby was immediately intubated and put in an incubator for proper treatment.

The resuscitation of the mother continued following guidelines for adult advanced cardiac resuscitation.[3] The $ETCO_2$ was kept at approximately 5–6 kPa (37.5–45.0 mmHg) throughout the resuscitation, correlating to an arterial blood gas value of 10 kPa (75 mmHg). The first lactate value was 9.2 mM, corresponding to a pH of 6.95. The resuscitative efforts gave no improvement in physiologic status and the patient was put on extracorporeal membrane oxygenation (CARDIOHELP™ Extracorporeal Life Support System, Maquet Medical Systems, Getinge Group, New Jersey, USA) which was accomplished 45 minutes after arrival in the ED.

In the Cardiothoracic Intensive Care Unit, the patient was dependent on full extracorporeal life support. The resuscitative efforts were futile and approximately 10 hours after the arrest the circulatory support was withdrawn and the patient died.

The autopsy concluded with a diagnosis of arrhythmogenic right ventricle dysplasia (ARVD), confirmed by histological examination.

DISCUSSION

This case, in our view, illustrates some interesting learning points:

1. Prehospital Care

The algorithm of prehospital resuscitation of cardiac arrest in pregnancy points out the need for PMCS to be done on-site given there was no response to cardiopulmonary resuscitation for 4 minutes.[3,4] The main reason for this is to improve the circulation to the mother by relieving the aortocaval pressure caused by the enlarged uterus at 20–24 weeks of pregnancy.[5] Hence the mother is prioritised when pregnant and in cardiac arrest. In our case, the high $ETCO_2$ at all times illustrated effective resuscitation,[2] although the best cardiac output in resuscitation of the non-pregnant population is 30% of normal.[3] Another indicator of good resuscitation is the fact that a surviving child is delivered, who survives with no cerebral sequelae detected 12 months after the incident. The child's psychomotor development will be monitored by paediatric out-patient examinations twice annually.

It was a 5-minute drive to the ED, where all appropriate resources needed were available. If the on-site $ETCO_2$ values had been lower i.e. 1–2 kPa (7.5–15.0 mmHg), the suspicion for an

obstruction to the circulation like pulmonary or amniotic fluid embolism would have been stronger. Resuscitation in such conditions is often futile.[6] In this situation, with low $ETCO_2$, there would have been an urgent need for immediate PMCS to relieve aortocaval compression. The prehospital anaesthetist on scene decided to 'load and go' to the ED, the alternative was to stay on-site and perform PMCS.

The prehospital anaesthetist was not trained to do such a procedure and the risk was then extensive bleeding to the mother with no health personnel available to take care of the child. Instead, the patient was met by a team in the ED, where the obstetrician recently had been in the Medical Simulation Center at St. Olavs Hospital training for this procedure (PMCS). The main reason for the 'load and go' decision to the ED was the relatively high $ETCO_2$ when compressions were carried out with the LUCAS.

Prehospital PMCS has very limited survival rates, as reported by others, and is so seldom performed worldwide that it cannot be regarded as a standard of care.[7] If there is indication for prehospital PMCS to be done, we think there should be an experienced prehospital physician to do the procedure.

2. Why Did the Patient Arrest?

The main hypothesis is thought to be that the patient arrested due to a primary arrhythmia, most likely ARVD as mentioned. ARVD is an autosomal dominant inherited disease of the heart muscle characterised by fibrofatty degeneration of the cardiomyocytes which leads to electrical instability and contractility abnormalities.[8] During pregnancy, plasma volume, cardiac output, and heart rate increase by as much as 30% compared to a normal non-pregnant state.[1] This means the heart has an increased workload and in susceptible individuals this could lead to a fatal arrhythmia.[8] Prior to the day that the patient arrested, she had several syncopal episodes, most likely because of a self-limiting malignant arrhythmia. On the day she arrested the main hypothesis is that her heart rhythm rapidly degenerated to ventricular fibrillation as opposed to the more benign developing episodes as described above. We do not know whether cardiac arrest caused by ARVD is especially difficult to resuscitate. Theoretically, as outlined above, cardiac arrest caused by pulmonary or amniotic fluid embolism might have low $ETCO_2$ values when resuscitated.[6] In such cases PMCS on-site could be more beneficial than in our case to improve the circulation. In this case the $ETCO_2$ levels were indicating no obstruction to the circulation, and that good quality resuscitation was being done.

3. Why Did the Child Survive with No Cerebral Sequelae Detected 12 Months After the Incident While the Mother Died?

The main hypothesis supporting this fact is the good-quality resuscitation done by the bystanders immediately available on scene when the mother arrested. This resuscitation continued when the ambulance personnel arrived and during transportation to the ED with the automated chest compression and ventilation devices working and being delivered to the patient. The $ETCO_2$ values were satisfactory at all times throughout the resuscitation, illustrating that the circulation was as good as it could have been in this critical situation.

The caesarean section team in the ED finished the procedure within 2 minutes after arrival. There was a neonatal intensive care team taking care of the child when delivered; this slowly improved the child's clinical condition, despite the Apgar score being 3 after 10 minutes.

The baby was delivered some 28 minutes from the arrest mark, which is an unusually long time span considering the good outcome. This time frame has been described previously in the literature although it is rare.[9]

CONCLUSION

Cardiac arrest in pregnancy is a critical condition with high mortality. In this case we describe a surviving baby and a non-surviving mother after a high-quality resuscitation and a long time span from arrest to delivery. Monitoring of $ETCO_2$ in resuscitation of cardiac arrest in pregnancy might be helpful in deciding whether to perform PMCS on-site or at a somewhat more appropriate location in the hospital.

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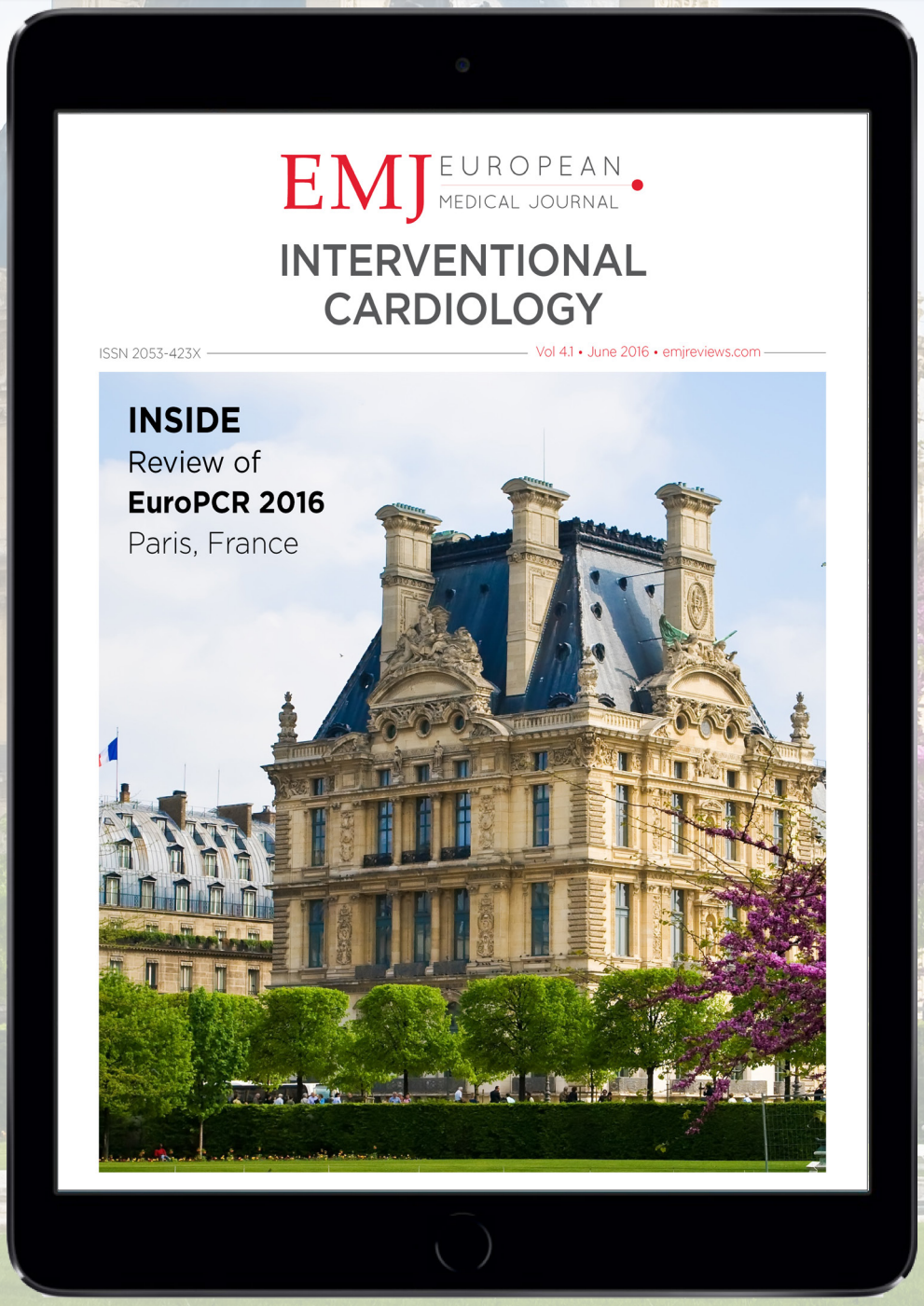

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CLINICAL TRIALS FOR THE DIAGNOSIS AND MANAGEMENT OF STABLE ISCHAEMIC HEART DISEASE: CONTEXT, STATUS, AND FUTURE IMPLICATIONS

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ABSTRACT

Chest pain and coronary artery disease (CAD) impose a substantial burden on public health and society. Diagnostic imaging tests are used by clinicians to identify the presence and extent of epicardial coronary disease and/or its consequences, including ischaemia, infarction, and left ventricular dysfunction.

In this article, we discuss current practice guideline recommendations for the diagnosis and management of patients with suspected or known CAD, and the need for more evidence from clinical trials. We then focus on the recently published and ongoing multicentre clinical trials of imaging-based strategies for the diagnosis and management of ischaemic heart disease, and the potential future impact of these trials on clinical practice. The results of these trials have the potential to bring radical changes to the practice of cardiology in the future.

Keywords: Angina, risk stratification, coronary artery disease (CAD), ischaemia, clinical trial, microvascular.

INTRODUCTION

Coronary artery disease (CAD) is an important global public health burden, with a mortality rate of 1.2–2.4% per annum.[1] The diagnosis of ischaemic heart disease (IHD) in patients with stable symptoms can be challenging because of variations in the pre-test probability of CAD, as well as the accuracy, cost, and availability of diagnostic tests and related management strategies.[2,3] New diagnostic imaging-guided strategies have emerged for the detection and management of stable CAD, and gaps in clinical evidence for these diagnostic approaches contribute to important differences in global clinical practice.[1,4] In this article, we briefly review contemporary practice and knowledge gaps around the diagnosis and management of patients with suspected or known CAD. We then focus on recently published and ongoing clinical trials in this area, and their potential impact on clinical practice in the future.

CLINICAL CONTEXT

Functional stress testing, mainly with electrocardiogram exercise treadmill testing (ETT) and stress myocardial perfusion scintigraphy (MPS), are established standard-of-care diagnostic tests for CAD. Technological developments now enable more advanced non-invasive imaging-guided strategies. These diagnostic approaches comprise functional assessments of ischaemia, including stress echocardiography, stress perfusion cardiac magnetic resonance (CMR), and stress positron emission tomography (PET) (Table 1).

Table 1: Sensitivity and specificity of non-invasive diagnostic tests for coronary artery disease and international practice guideline recommendations.

	Diagnosis of CAD		European guideline		American guideline	
	Sensitivity (%)	Specificity (%)	Class	Level of evidence	Class	Level of evidence
Exercise ECG	45–50	85–90	1 (15–65%)	B	1	A
Exercise stress echocardiography	80–85	80–88	1	B	2b	C
Exercise stress MPS	73–92	63–87	1	B	2a	B
Dobutamine stress echocardiography	79–83	82–86	1	B	3	C
Dobutamine stress CMR	79–88	81–91	1	B	3	C
Vasodilator stress echocardiography	72–79	92–95	1	B	3	C
Vasodilator stress MPS	90–91	75–84	1	B	3	C
Vasodilator stress CMR	67–94	61–85	1	B	3	C
CTCA	95–99	64–83	2a (15–50%)	B	2b	B
Vasodilator stress PET	81–97	74–91	1	B	N/A	N/A

The North American practice guideline recommendations account for the patient's ability to exercise, the presence of an interpretable ECG, and an intermediate-high pre-test probability of CAD.[4]
CAD: coronary artery disease; ECG: electrocardiogram; MPS: myocardial perfusion scintigraphy; CMR: cardiac magnetic resonance; PET: positron emitting tomography; CTCA: computed tomography coronary angiography.
Adapted with permission from Montalescot et al.[1]

Alternatively, anatomical imaging of CAD with computed tomography coronary angiography (CTCA) is an emerging diagnostic option. CTCA may be combined with functional imaging, i.e. CTCA-perfusion and computed tomography-fractional flow reserve (CT-FFR). Concordant with good clinical practice, clinical judgement and informed patient preferences are important.[4]

Diagnostic Uncertainties and the Justification for Randomised Clinical Trials

The coronary artery disease hypothesis and anatomical imaging

The 'CAD hypothesis' states that detection of epicardial CAD through coronary artery imaging enables risk stratification for therapy, including non-pharmacological, medical, and invasive intervention, leading to future health benefits.[1,4] The evidence for management strategies based on CAD imaging with invasive coronary angiography (ICA) is well established,[1,4] whereas evidence is lacking for non-invasive imaging-guided strategies. This evidence gap supports the rationale for the ongoing and recently published randomised trials. Importantly, diagnostic accuracy based on visual interpretation of invasive angiographic images alone may not be appropriate due to the poor correlation between visually assessed angiographic anatomical stenosis severity and the physiological significance of a stenosis.[5]

The ischaemia hypothesis and functional testing

Myocardial ischaemia occurs when demand for perfusion exceeds supply.[6] Ischaemia may result from obstructive epicardial CAD limiting coronary blood flow, coronary microvascular disease (CMD) reducing myocardial perfusion, or systemic problems (e.g. anaemia or tachyarrhythmia) resulting in a supply-demand mismatch.[7] Myocardial ischaemia may result in typical angina pectoris, atypical symptoms (e.g. exertional dyspnoea), or may be clinically silent.[8] Ischaemia revealed by functional imaging is associated with an adverse long-term prognosis.[9] The 'ischaemia hypothesis' supposes that ischaemia is an adverse prognostic attribute, and that reducing the ischaemic burden by medical therapy with or without coronary revascularisation will result in improved clinical outcomes, as observedin the COURAGE trial MPS sub-study.[10,11]

Anatomical versus functional tests in suspected or known stable coronary artery disease

Practice guidelines now recommend anatomical approaches in lower-risk patients with CTCA and ICA in higher-risk patients, recognising that randomised trial evidence is limited (levels B/C).[1,4]

The ideal non-invasive diagnostic test would have high spatial resolution (for coronary lesions, perfusion, or ischaemic defects), allow quantitative assessment of ischaemia severity, avoid or minimise ionising radiation exposure (concordant with the principle of 'As Low As Reasonably Achievable'), and provide additional diagnostic information such as assessment of myocardial function and scarring.

CONTEMPORARY PRACTICE GUIDELINES FOR STABLE CORONARY ARTERY DISEASE AND THE NEED FOR MORE CLINICAL EVIDENCE

European guidelines do not recommend non-invasive diagnostic tests in patients with a pre-test probability of CAD <15% or >85%.[1] The UK National Institute of Clinical Excellence (NICE) guidelines recommend that diagnostic testing is not indicated in chest pain patients with a pre-test probability of CAD <10%.[12] In very low-likelihood groups, medical management is recommended, whereas in the high-likelihood groups, ICA is suggested. ETT has been omitted and replaced with CT calcium scoring±CTCA for low-risk patients (given the high sensitivity and negative predictive value, but relatively lower specificity, of CTCA), and non-invasive stress imaging with echocardiography, MPS, or CMR in intermediate pre-test risk.

Estimates of obstructive CAD are based on historical data, which potentially overestimate risk, and European guidelines may increase the rate of unnecessary ICA.[13,14] Since CAD is endemic in many developed countries, routine CTCA in adults with chest pain will commonly disclose CAD and result in ICA. The presence of CAD does not equate to causality, and non-cardiac causes of chest pain may coexist. This supports the case for ischaemia testing invasively (i.e. FFR) or non-invasively (i.e. CT-FFR or stress imaging).

Attributes and Limitations of Imaging Strategy Trials

There is uncertainty surrounding the comparative effectiveness of imaging-based diagnostic strategies for the detection and management of CAD. This lack of evidence underpins the rationale for several large clinical trials that have recently reported or are ongoing. The trials may be summarised as:

- Trials designed to assess the most effective imaging strategy for the diagnosis and management of suspected angina (anatomical versus functional imaging-guided strategies, and non-invasive versus invasive strategies)
- Trials designed to assess the health outcomes of invasive management versus medical management

TRIALS OF THE STRATEGIES

Detection of Coronary Artery Disease and Diagnosis of Angina in Patients with Chest Pain of Suspected Cardiac Origin

SCOT-HEART trial

The SCOT-HEART trial is a multicentre randomised controlled trial of 4,138 patients referred from primary care to a cardiology clinic for chest pain assessment. SCOT-HEART evaluated the role of routine CTCA in addition to standard care (typically with ETT) versus standard care alone in the investigation and risk assessment of patients with suspected angina.[15] SCOT-HEART[16] assessed whether anatomical delineation of the presence or absence of obstructive or non-obstructive CAD alters the diagnosis, management, and outcomes of patients with chest pain attending a rapid access chest pain clinic. Patients aged 18–75 years were randomised (1:1) to standard care, or standard care plus coronary artery calcium scoring and CTCA. Eligibility criteria were not restricted by the pre-test likelihood of CAD or a prior history of CAD, so patients with any pre-test risk may have been enrolled. Also, angina class was not an eligibility criterion, thus patients with crescendo or unstable angina may have been included. The primary outcome was the certainty of the diagnosis of angina secondary to CAD at 6 weeks.

The primary outcome was increased in the group randomised to CTCA (relative risk: 1.79, 95% confidence interval: 1.62–1.96). At 6 weeks, CTCA reclassified the diagnosis of CAD in 27% of patients, and the diagnosis of angina due to CAD in 23%. At 1.7-year follow-up, there was a trend towards a reduction in fatal and non-fatal myocardial infarction (MI) with CTCA, but this did not reach significance (p=0.0527, absolute difference between the groups: 16 events). Longer-term follow-up is planned for 5 years. Figure 1 presents a patient case study from this trial.

By design, SCOT-HEART did not have concealment of the diagnostic intervention, and consequently the management and outcomes were susceptible to unmeasured confounding.

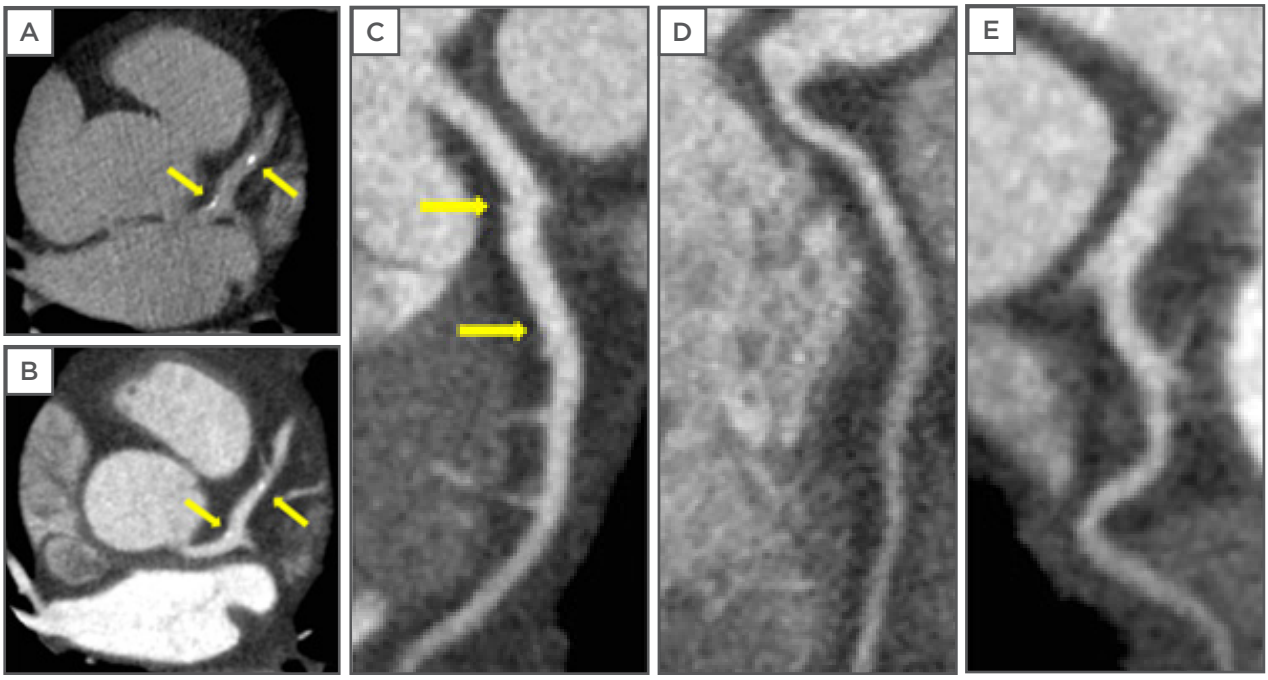

Figure 1: Computed tomography of a SCOT-HEART trial participant.
A 60-year-old male presented to the rapid access chest pain clinic with a history of typical angina. He had no risk factors for CAD. A treadmill exercise tolerance test was interpreted to be positive for myocardial ischaemia. As part of the SCOT-HEART trial, he underwent computed tomography imaging with a 320 multi-detector scanner using iterative reconstruction. A non-contrast scan was performed to assess coronary artery calcification. A) The Agatston coronary artery calcium score was 51 Agatston units. CTCA identified mild calcified and non-calcified atherosclerotic plaque in the left anterior descending artery (arrows). B) Shows axial images of the left anterior descending artery at the same position as the non-contrast images, and curved planar reformations are shown of: C) the left anterior descending artery, D) the right coronary artery, and E) the left circumflex artery. Despite these reassuring findings, the attending clinician still referred the patient for invasive coronary angiography because of ongoing symptoms. There was no angiographic evidence of CAD and the patient has had uncomplicated progress on medical therapy. This case provides an example in which the exercise ECG overestimated the likelihood of CAD and CTCA might have prevented the requirement for invasive investigations.
CTCA: computed tomography coronary angiography; ECG: electrocardiogram; CAD: coronary artery disease.
This case was kindly provided by Dr Michelle Williams, Clinical Research Fellow, and Prof David Newby, Principal Investigator for the SCOT-HEART trial.

The trial was not powered for health outcomes and the event rate was low (1.6% rate of death or MI at 1.7-year follow-up), indicating that the results are hypothesis-generating, and the 5-year outcomes are eagerly anticipated. Routine CTCA in this strategy is anticipated to be associated with increased costs, predominantly related to the cost of the scan. Information on quality of life and the health economic analysis are awaited.[17]

CEMARC 2 TRIAL

The CEMARC 2 trial is a prospective multicentre, three-arm parallel group, randomised controlled trial of routine functional imaging versus guideline-based management.[18,19] CEMARC 2 randomised 1,202 patients (2:2:1) to 3.0 Tesla stress perfusion CMR, MPS (according to American College of Cardiology [ACC]/American Heart Association [AHA] appropriate-use criteria), or to management based on the pre-test probability of CAD (CT calcium scoring±CTCA: 10–29%; MPS: 30–60%; ICA: 61–90%), concordant with UK NICE guidelines.[12] Patients aged >30 years with known or suspected angina and a pre-test likelihood of CAD 10–90% were enrolled. The primary outcome is the occurrence of unnecessary invasive angiography, with secondary outcomes including a major

cardiovascular event (MACE) at 1 and 3 years, and a cost-effectiveness analysis. Unnecessary ICA is defined as: i) negative FFR (>0.80) and a positive non-invasive test (i.e. false-positive test result); ii) negative FFR with a high pre-test probability (61–90%) proceeding directly to ICA in the NICE guidelines-based group (i.e. false-positive for the strategy); iii) negative FFR and a negative non-invasive test (i.e. true-negative strategy result where the imaging result was 'not believed' by the treating cardiologist [intention-to-treat principles]); iv) negative FFR and an inconclusive non-invasive test in which angiography was performed to make the diagnosis (i.e. failure of the strategy to produce a diagnosis).

The primary outcome occurred in 69 (28.8%) patients in the NICE guideline-managed group, and 36 (7.5%) and 34 (7.1%) in the CMR and MPS groups, respectively. There was a statistically significant lower adjusted odds ratio (OR) of unnecessary angiography in the CMR versus NICE guidelines group (OR: 0.21, p<0.001), with no difference between the CMR or MPS group (OR: 1.27, p=0.32). There was a trend towards a reduction in the secondary outcome of MACE at 12 months in the NICE guidelines group (1.7%), compared to the CMR (2.5%) and MPS (2.5%) groups, but this was not statistically significant. CEMARC 2 demonstrates a significant reduction in unnecessary angiography with a CMR-guided strategy. The NICE guideline-based strategy resulted in significantly more unnecessary invasive angiograms. Future guidelines may utilise improved risk stratification models.[20]

In contrast, a strategy of stress PET imaging has high diagnostic accuracy for CAD. The PACIFIC trial results were presented in August 2016 but are not yet published.[21] PACIFIC enrolled 208 patients from a single centre referred for ICA following a first-presentation with chest pain secondary to suspected CAD. Participants had an intermediate pre-test likelihood of CAD and were aged >40 years. All patients underwent ICA with FFR measurement to define flow-limiting epicardial CAD. Patients then underwent stress PET, MPS, or CTCA alone, with some patients undergoing hybrid anatomical/functional imaging with PET/CTCA or MPS/CTCA. The diagnostic accuracy of PET (85%) was significantly greater than MPS (77%, p<0.01) and CTCA (74%, p<0.01), with no improvement in diagnostic accuracy with the hybrid imaging approaches. PACIFIC confirmed the high diagnostic accuracy of stress PET imaging, however there is generally limited access to this modality worldwide.

Management Strategies Involving Imaging of Coronary Anatomy Versus Functional Testing in Patients with Low-Intermediate Likelihood of Coronary Disease

PROMISE trial

PROMISE was an open-label multicentre imaging study comparing CTCA versus non-invasive functional stress testing (ETT, MPS, or stress echocardiography) in 10,003 patients with chest pain due to known or suspected angina.[22,23] PROMISE tested the hypothesis that an initial anatomical testing strategy would inform subsequent patient management resulting in superior long-term health outcomes, as compared to an initial functional testing strategy. The functional test was selected at the clinician's discretion, and may have reflected local availability. The primary outcome was time to the first MACE.

Compared with non-invasive functional testing, CTCA did not improve clinical outcomes at a median follow-up of 2 years compared with functional testing (3.3% versus 3.0%). The interpretation of PROMISE may be limited by the low event rate and relatively short follow-up period. Contemporary non-invasive functional tests such as stress perfusion CMR and PET, which have a higher sensitivity for detecting ischaemia, were not included. There was a significant difference in the revascularisation rates at 90 days between the CTCA and functional testing group (6.2% versus 3.2% of patients, p<0.001), however if functional results for ischaemia (e.g. invasive FFR) were lacking, the appropriateness of these revascularisations is uncertain. PROMISE concluded that either a routine functional or routine anatomical strategy is reasonable.[17] In comparison, CT-FFR may allow a hybrid anatomical and functional imaging strategy and extend the role of CT-based strategies. CT-FFR is assessed using proprietary software which applies three-dimensional blood flow simulations using the principles of computational fluid dynamics.[24,25]

RESCUE trial

The RESCUE study[26] is a multicentre randomised controlled trial of 4,300 patients, comparing two different diagnostic imaging modalities: CTCA versus MPS. In addition, building on the results of the COURAGE trial,[11] all patients without evidence of left main stem disease will be treated with optimal medical therapy (OMT). The primary endpoint is a combination of MACE and

revascularisation. It is hypothesised that CTCA is cheaper and patients will be exposed to less radiation with no increase in the rate of MACE or revascularisation, with a 24-month follow-up. On 27 October 2014 the study was terminated because the funding timeline had completed. By September 2014, 1,050 participants had been randomised. No further information is available at this time.

CARE-CTCA trial

The CARE-CTCA trial is a multicentre randomised trial of 1,050 patients investigating the cost-effectiveness and health outcomes of a CTCA versus MPS-guided management strategy in patients with an intermediate risk of CAD.[27] Patients aged 30–80 years with an intermediate probability of CAD will be randomised (1:1) to either CTCA or MPS. The primary outcome is a cost-effectiveness analysis at 1 year.

Taken together, the results of these ongoing trials[26-28] will provide information on whether or not a CTCA-guided approach improves symptoms, prognosis, and cost-effectiveness compared to functional approaches, in which MPS will likely be used in the majority of the participants.

Non-Invasive Imaging Versus Invasive Coronary Angiography in Patients with Intermediate-High Likelihood of Coronary Artery Disease

MR-INFORM trial

MR-INFORM is a multicentre randomised controlled non-inferiority trial designed to compare 1.5 Tesla stress CMR to routine ICA with FFR measurement, in order to guide revascularisation in patients with stable angina.[29] MR-INFORM participants would be eligible for ICA based on clinical criteria concordant with clinical guidelines.[1,12] The trial includes 918 patients who will undergo perfusion CMR prior to angiography, and will then be randomised (1:1) to either CMR-guided management or FFR-guided management (perfusion CMR result not disclosed) of intermediate angiographic lesions (≥40% to <99% severity). Inclusion criteria are age >18 years, typical angina, plus ≥2 cardiac risk factors, or positive ETT. Figure 2 presents a patient case study from this trial.

MR-INFORM hypothesises that in patients with a high likelihood of CAD, management based on a functional test without knowledge of coronary anatomy could be an acceptable alternative approach to invasive management. MR-INFORM will provide further evidence on the safety and efficacy of perfusion CMR in the investigation of CAD. By design, CEMARC 2 involved a lower-risk patient population than MR-INFORM and so these trials should provide complementary information.

In contrast to these functional strategies, the DISCHARGE study tests the hypothesis that an anatomical CTCA-guided strategy is superior to ICA in patients with a low-to-intermediate pre-test likelihood of CAD.[30] DISCHARGE will randomise (1:1) 3,546 patients with stable chest symptoms, aged >30 years, and with a pre-test likelihood of CAD of 10–60%, to CTCA or ICA. The enrolment period will be 2 years and the maximum follow-up is 4 years. DISCHARGE is a superiority trial and the primary outcome measure is major adverse cardiac and cerebrovascular events. Secondary outcomes include symptoms, quality of life, and cost-effectiveness. Contemporary practice guidelines do not recommend routine invasive angiography as a first-line test in patients with a pre-test CAD likelihood of 10–60%, yet this is the likelihood range for inclusion in this trial.

Non-Invasive Versus Invasive Management of Symptomatic Patients with Non-Invasive Evidence of Moderate-Severe Ischaemia

ISCHEMIA trial

The ISCHEMIA trial is a multicentre randomised controlled trial of 8,000 patients.[31,32] It tests the hypothesis that an initial strategy of ICA followed by percutaneous coronary intervention (PCI) if feasible, in addition to OMT, will reduce the composite primary endpoint of cardiovascular death or non-fatal MI in patients with at least moderate ischaemia on stress imaging (echocardiography, MPS, or CMR), compared with an initial conservative strategy of OMT alone, with ICA reserved for failure of OMT.

International guidelines recommend that revascularisation is targeted towards relieving ischaemia rather than anatomical lesions in the epicardial coronary arteries.[33,34] Anatomical assessments of CAD alone are inadequate to accurately identify functionally significant disease.[35] The results of the FAME and FAME-2 trials indicate that patients with symptoms and ischaemia (FFR ≤0.8) derive prognostic benefits from PCI versus medical therapy alone,[36,37] whereas those with functionally insignificant lesions (FFR >0.8) do not. FAME-2 supports the validity of the ischaemia hypothesis, however this trial was not designed or powered to provide information on the 'hard' spontaneous outcomes of death or MI.

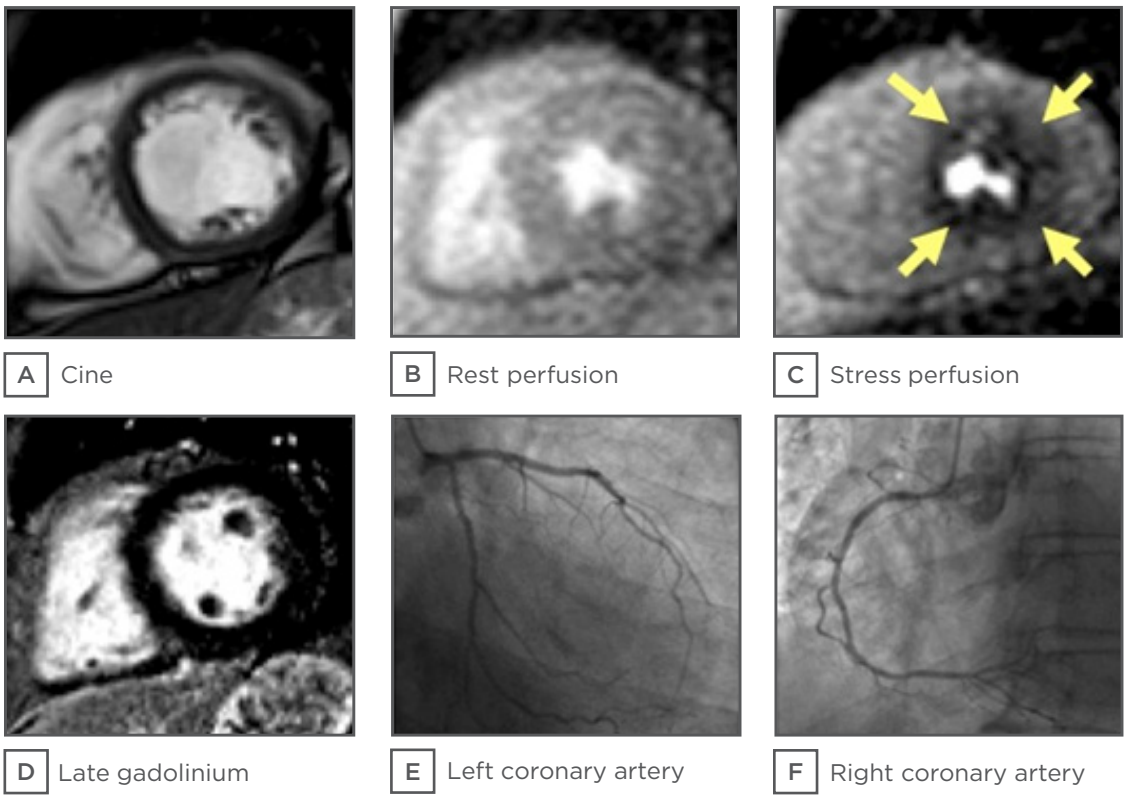

Figure 2: Magnetic resonance imaging of a MR-INFORM trial participant.
A 61-year-old female cigarette smoker with a history of symptoms consistent with angina was referred by her primary care physician for out-patient cardiology investigations. Based on this history, the pre-test probability of CAD was estimated to be 68% and a referral for invasive coronary angiography was made in line with contemporary guidelines. The woman fulfilled the eligibility criteria for MR-INFORM and, based on informed consent, she was randomised to the MR-guided group. CMR cine imaging revealed A) normal left ventricular systolic function, and compared with first-pass CMR imaging at rest; B) adenosine stress perfusion CMR; C) revealed a circumferential subendocardial inducible perfusion defect; D) the absence of late gadolinium enhancement imaging ruled out an infarct scar; E and F) invasive coronary angiography revealed minimal non-obstructive CAD. A diagnosis of microvascular angina was established and she was treated with 20 mg of isosorbide mononitrate twice daily, 75 mg of aspirin daily, and 40 mg of simvastatin daily.
CMR: cardiac magnet resonance; CAD: coronary artery disease.
Reproduced with permission from Dr David Carrick, Golden Jubilee National Hospital, Glasgow, and Prof Eike Nagel, principal investigator for the MR-INFORM trial.

The ISCHEMIA trial will further inform the hypothesis that invasive management with clinically-indicated revascularisation may improve health outcomes in patients with stable CAD and a moderate-to-large ischaemic burden, compared to OMT. The ISCHEMIA trial has pivotal importance for the future management of CAD.

The ISCHEMIA-CKD[32] sub-study investigates the same questions as the ISCHEMIA trial but in patients with advanced renal disease, a group of patients that is particularly challenging to diagnose and manage effectively and safely.

Anatomical Imaging and Coronary Microvascular Disease

PROMISE enrolled 10,003 patients, with 1,015 undergoing diagnostic ICA within 90 days of randomisation.[23] A predefined secondary endpoint of non-obstructive CAD on ICA occurred in 3.4% of the CTCA group and 4.3% in the functional testing group (p=0.02). Does this cohort with anginal symptoms and non-obstructive CAD (some with positive non-invasive stress testing) represent patients with a non-cardiac aetiology for their symptoms, false-positive non-invasive stress testing, or might CMD contribute? Angina may occur in

the absence of flow-limiting epicardial CAD. In this situation, patients may receive no further diagnostic testing and be reassured that they have a non-cardiac cause for their symptoms. However, a significant number may have coronary CMD and 'microvascular angina'.[38] In comparison to the literature concerned with epicardial CAD, there is a nascent evidence-base for the diagnosis and therapeutic interventions in coronary CMD.

There is no available technique which allows direct visualisation of the coronary microcirculation *in vivo*. Increasing use of invasive diagnostic tests to assess parameters of coronary physiology (coronary pressure, flow, and microvascular resistance) are providing new, clinically relevant diagnostic and prognostic information.[39] Additionally, coronary endothelial dysfunction may result in angina which may be evaluated with vaso-reactivity testing.[40] These observations have challenged the dogma that IHD equates to obstructive epicardial CAD.[41] Non-invasive functional tests have lower sensitivity and specificity for CMD, although the kinetics and distribution of perfusion abnormalities revealed by stress perfusion CMR can be diagnostic. A limitation of the CAD hypothesis is that anatomical diagnostic tests, such as CTCA, are of limited value for the diagnosis of microvascular angina. There are several comparatively small multi-modality imaging studies in patients with microvascular angina, including iPOWER,[42] however large randomised trials of therapeutic interventions are lacking. In summary, reflecting the heterogeneous causes of angina, we propose 'stable coronary artery syndrome' as a new unifying diagnostic term.

Summary of Imaging Studies

Clinical trials also have limitations; trials involve patient selection that commonly excludes real-world patients with multi-morbidity and advanced disease (e.g. patients with advanced renal disease in CMR trials). The timing of randomisation is also key; randomisation performed close to the time of consent and prior to diagnostic testing should lead to enrolment of a study population more representative of real-world patients compared to randomisation performed downstream. Other important design considerations include concealment of treatment allocation, as this may lead to a falsely enhanced magnitude of treatment effect[43] and blinded and independent assessment of primary and secondary outcomes.

TRENDS IN CURRENT PRACTICE AND FUTURE DIRECTIONS

An analysis of 397,954 patients with chest pain and no history of CAD who underwent ICA found that only 37.6% had angiographic evidence of epicardial CAD, whilst 39.2% had no epicardial CAD.[44] This calls into question the initial diagnostic basis for referral, and also the work-up for CMD if obstructive epicardial CAD is excluded. Adoption of non-invasive and invasive tests of flow-limiting coronary disease has increased since these results emerged. Key questions around the roles of anatomical and functional testing and non-invasive versus invasive management are being prospectively assessed in large clinical trial populations. The current clinical guideline recommendations that are not supported by randomised trial evidence (i.e. level C for CTCA recommendations)[1,4] are currently subject to prospective assessment. Finally, a doctor's clinical opinion should be individualised to the patient, who is entitled to have options wherever possible to enable an informed decision.

CONCLUSION

The current diagnostic trials in stable CAD involve >30,000 patients globally. The ongoing trials are expected to report within the next 5–7 years and, depending on their results, the trials have the potential to bring radical changes to the practice of cardiology. A recognition that stable IHD may not only be due to obstructive epicardial CAD, but also to coronary microvascular and vasomotor abnormalities, may prompt further research into non-invasive functional testing. Anatomical and functional non-invasive imaging in epicardial and microvascular CAD will ultimately need to be demonstrated to improve health outcomes to enter daily clinical practice.

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