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CARDIOLOGY

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INSIDE

Review of

ESC 2014

Barcelona, Spain

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CARDIOLOGY

EVERY AF PATIENT IS DIFFERENT.
ORAL ANTICOAGULANTS NEED TO ADDRESS THIS.

Treatment of AF should be tailored to the particular patient's needs.[1] Every patient presents with their own individual factors that need to be considered when initiating them on oral anticoagulation

References:
1. Basu Ray I. Atrial Fibrillation: present treatment protocols by drugs and interventions. *JIACM* 2003;4(3):213–227.
2. Ogilvie IM *et al*. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med* 2010;123(7):638–645.

AF= Atrial fibrillation

Date of preparation: July 2014. DSC/14/0015

Daiichi-Sankyo

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Cardiology


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Workflow meets wow
Choosing a new ultrasound system is all about balance. You want the latest technology that needs to be out of the box usable. You need accurate diagnostic information quickly, a simplified yet intuitive user interface, and easy access to the critical features to produce the results you need. All in an ergonomic design, to let you work with less reach and fewer steps.
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Welcome

The field of cardiology is a rapidly growing and developing one. Thanks to the progress which has been made within this area, the burden of cardiovascular disease (CVD) – accountable for over 10,000 deaths a year - as well as other heart diseases has been reduced. Thus, it is my hope that this issue of the *European Medical Journal Cardiology*, filled with the most up-to-date research as well as the most groundbreaking and game-changing updates, will be able to provide you with new and insightful ways of how to further reduce this burden.

The European Society of Cardiology (ESC), a premier cardiologic event, which took place this year in Barcelona, Spain, witnessed the beginning of a new era. The highlighted topic this year was innovation and the heart; Prof Keith Fox, Chair of the Congress Programme, said: "It is a theme which cuts right across the board – from blue sky science to innovations in clinical trials and guidelines."

During this event the ESC released their eagerly awaited guidelines, which are detailed for you in our 'Congress Review' section. Results from the eagerly awaited ODYSSEY, FOCUS, and EUROECO financial studies are also covered in this section.

Innovations, as well as new developments and discoveries, are the future in this field, and will be the driving force behind it. In the paper '*Imaging during transcatheter interventions for valvular heart disease*', Drs González-Gómez and Zamorano have shown how the developments in imaging techniques can benefit patients with valvular heart disease. The use of three-dimensional echocardiography, integrating live echocardiography and live fluoroscopy imaging, can potentially facilitate procedure guidance by allowing more detailed images to be produced, and can increase anatomical awareness as well as providing confidence during procedure guidance.

A newly developed neck cuff which is able to lower a patient's blood pressure (BP) without side-effects is detailed in our 'What's New' section. This cutting edge piece of technology was able to reduce the mean BP by 30% in rodent models; these results are very promising for patients suffering from this condition and who have been unsuccessful on prescribed therapy.

It is only through the sharing of knowledge, experience, and ideas that progression is made possible. Here at EMJ we are a big believer in that concept, which is why this journal is beneficial to any healthcare provider within this field. Prof Fox explained: "The reality is that although clinical settings differ we face similar challenges and can learn from each other." It is our hope that this journal is a platform which makes this possible, we hope that you find this issue inspiring and beneficial in your daily practice, and we wish you a pleasant read.

Spencer Gore

Director, European Medical Journal

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EMJ GORELY NEW MEDIA

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Foreword

Prof Dr Jawahar Mehta

Professor of Medicine, Physiology and Biophysics,
University of Arkansas for Medical Sciences, Arkansas, USA.

I would like to welcome you to this new issue of the *European Medical Journal Cardiology* 2014. Significant strides have been made this year with regards to research into prominent heart diseases such as cardiomyopathy and various valve diseases.

This year's European Society of Cardiology (ESC) congress in Barcelona, Spain, provided an excellent platform for cardiologists around the world to exhibit contemporary research that has the potential to alter our views on issues such as cardiovascular disease, the leading killer in the developed world. These forward-thinking contributions to Cardiology came from a variety of esteemed presenters who enlightened us on the latest research into a plethora of cardiovascular diseases, as well as potential treatments in the form of new drugs and implants.

EMJ has collected and collated the most prominent, interesting, and cutting-edge research from ESC 2014 and produced an extensive review in this journal, *EMJ Cardiology*, to allow researchers, clinicians, and healthcare professionals to stay up-to-date on the constantly evolving field of Cardiology. So if you were unable to attend, or simply want a refresher, the Congress Review is a must-read.

> "It is because of the abundance of innovative thinkers at ESC 2014 that I have great confidence in the improved treatments for those suffering from these cardiovascular illnesses."

Let it not be said that the field of Cardiology is in any way stagnating. The exciting work produced by Prof José Zamorano in the paper: '*Imaging during transcatheter interventions for valvular heart disease*,' which is featured in *EMJ Cardiology*, provides a fascinating insight into the constraints of the modern catheter laboratory, as well as suggesting the integration of a novel imaging modality to assist 3D echocardiography and fluoroscopy to facilitate procedure guidance and increase procedure efficiency for various valvular heart diseases.

It is because of the abundance of innovative thinkers at ESC 2014 that I have great confidence in the improved treatments for those suffering from these cardiovascular illnesses. It is, therefore, with unbridled excitement that I present to you the very latest edition of *EMJ Cardiology*, and I wholeheartedly implore you to visit ESC 2015 in London, UK, to stay up-to-date on the latest advancements in this fast-paced area of modern medicine.

Yours Sincerely,

Jawahar Mehta

Professor of Medicine and Physiology and Biophysics, Director, Molecular Cardiology, and Stebbins Chair in Cardiology, University of Arkansas for Medical Sciences; Staff Cardiologist, Central Arkansas Veterans Healthcare System, Little Rock, Arkansas, USA.

ESC ANNUAL CONGRESS 2014

FIRA GRAN VIA, BARCELONA, SPAIN

30TH AUGUST – 3RD SEPTEMBER 2014

Welcome to the *European Medical Journal* review of the European Society of Cardiology Congress 2014

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ESC ANNUAL CONGRESS 2014

FIRA GRAN VIA,
BARCELONA, SPAIN
30TH AUGUST – 3RD SEPTEMBER 2014

Welcome to the *European Medical Journal* review of the European Society of Cardiology Congress 2014

The prime event in any cardiologist's calendar is the meeting of the European Society of Cardiology (ESC). As the Chair of the Congress Programme, Prof Keith Fox said: "It is the place where the most innovative clinical and basic science studies get presented." It is the Congress 'where everything in cardiology comes together.'

This year the Congress was held in the beautiful and picturesque city of Barcelona, Spain, from the 30th August – 3rd September, where both culture and science were perfectly mixed together. In order to encourage development and progress within the field of cardiology the theme of the Congress was: 'Innovation and the heart', and it did not disappoint any of its 30,300 international delegates. The Congress showcased the latest advancements in education, technology, clinical practice, and scientific discovery, as well as their applications in clinical care, through 4,579 abstract presentations, 70 sponsored sessions, 27 clinical Hot Line presentations, 15 clinical trial updates, and 19 registry studies.

"This has been the strongest scientific programme yet, and the congress has broken records in attendance and scientific submissions. The quality of the work we received is outstanding and attracted doctors from all over the world. In the digital age, cardiologists want to attend our congress because we have used modern technology to enhance interaction and discussion and to allow participants to get behind the headlines. Delegates will go home not just knowing the headlines, but what is

"We have learnt a lot during this past week. The results from all these studies need to be carefully considered. New research has shown us many ways to improve our practice and procedures."

Prof Panos Vardas,
Past-President of the ESC

important, what will change practice, and what to look out for on the horizon," said Prof Fox.

All of the presentations which were featured during the Congress hope to equip cardiologists with the knowledge of how to reduce the burden of cardiovascular disease in Europe – this is the aim of the ESC. Cardiologists and engineers from Switzerland have designed a batteryless cardiac pacemaker based on an automatic wristwatch, which is powered by heart motion and does not require battery replacement. This device has managed to address the disadvantages seen in some pacemakers which are currently on the market. Innovations such as this, in this speciality, have extended the life expectancy of cardiovascular patients by 8-10 years.

Prof Panos Vardas, Past-President of the ESC, emphasised: "Cardiology has made huge advances with a steady decline of CVD mortality in most of Europe," but cardiologists still have a lot of work to do; however, other outlets can help to encourage the public to take up healthy lifestyles. One study, which included 22,000 young participants, found that obesity, along with hypertension, is on the rise in the young, with obese teenagers having a nearly 6-fold risk of hypertension. Results of other long-awaited studies included the PARADIGM-HF investigation, the ODYSSEY study, the EUROECO financial study, and the FOCUS study. "We have learnt a lot during this past week. The results from all these studies need to be carefully considered. New research has shown us many ways to improve our practice and procedures," said Prof Vardas.

Changing ESC guidelines generate great new interest

PRACTICE guidelines referring to non-cardiac surgery, hypertrophic cardiomyopathies, pulmonary embolism, aortic diseases, and myocardial revascularisation have been introduced by the ESC this year, which have been expertly developed by a number of Task Forces under the society's Committee for Practice Guidelines.

Since the changes, guidelines on non-cardiac surgery now consider surgical risk assessment, preoperative evaluation, and optimal perioperative management. They address certain cardiological and anaesthesiological issues in patients with specific cardiac diseases and frequent comorbidities.

Those guidelines concerning hypertrophic cardiomyopathies (HCM) have also gained significant interest; they are now being based upon actual risk estimates, as opposed to the relative risks contained in the previous guidelines. Defined and characterised by the presence of an increased left ventricular wall thickness (not fully explained by abnormal loading conditions), HCM occurs in up to 0.23% of adults and 0.07% of children, and relies on genetic testing in order to confirm its diagnosis. A new risk score which may be used to predict sudden cardiac death as a continuous value has since been advocated.

The revision of the guidelines has also seen the first written recommendations on new oral anticoagulants in pulmonary embolism (PE), providing more comprehensive recommendations than ever before for the diagnosis and treatment of PE; healthcare practitioners may now stratify the risks in patients with potential PE, and provide the appropriate care and treatment with confidence.

Guidelines concerning aortic diseases have previously been constrained to diagnosing and managing aortic dissection. However, the revised document of 2014 also details aneurysms, calcifications, congenital diseases which lead to aneurysms, and aortic inflammations and tumours; a progressive flow chart has also been developed in order to provide patients with earlier diagnoses and faster treatments, thus improving patient outcomes.

Finally, the guidelines on myocardial revascularisation are based on a systematic review of 100 trials in >90,000 patients which found that, amongst those with stable coronary artery (CA) disease, CA bypass grafting successfully reduced risks of myocardial infarction, repeat revascularisation, and death, when compared with medical treatment, like no other revascularisation technology.

These guidelines will, no doubt, serve as an invaluable resource to clinicians throughout Europe and across the world, improving overall standards of patient diagnosis, treatment, and aftercare.

Heart-powered pacemaker ticks closer to cardiac coup

CARDIAC pacemaker technology seems set to move beyond its current reliance on pacemaker leads, as a batteryless pacemaker uses the engine of an automatic watch to derive electrical energy from heart motion.

"Pacemakers have two weak spots," explained Mr Adrian Zurbuchen, PhD candidate, Cardiovascular Engineering Group, ARTORG Center for Biomedical Engineering Research, University of Bern, Bern, Switzerland. "Leads are prone to fracture and the lifetime of batteries is limited. Replacing batteries with alternative power sources would spare patients from repeated interventions and make leads obsolete."

Success in the hearts of domestic pigs, which have represented the primary animal demonstration, has seemingly ushered in a new era of pacemaker technology, and Swiss scientists have managed to create a prototype using the harvesting device of an automatic wristwatch. Transforming mechanical energy to electrical energy is key to the function of automatic watches, with the internal device successfully harnessing energy from wrist movements.

A permanent solution to an ongoing cardiac conundrum may be close. The heart is a biological phenomenon, and if its relentless energy output can be utilised, the organ could be the future of pacemaker technology. The pacemaker is based on the construction of a commercially-available automatic watch; all external parts are removed to reduce weight and size, leaving behind the harvesting device at the device's core. This is surrounded by a custom-made plastic housing with eyelets which allows direct suture to the myocardium.

Similar to the watch mechanism, the eccentric mass of the clockwork rotates upon the prototype's exposure to external acceleration. This causes progressive rotation of a mechanical spring that, when fully charged, unwinds and spins an electrical micro-generator. Prior to live testing, scientists had success with an electronic circuit, which created and stored buffered energy from an energy harvesting device that eventually powered a custom-made cardiac pacemaker.

A 60 kg pig was fitted with the pacemaker during a study. The device produced a mean output power of 52 μW, far surpassing the 10 μW expenditure of a modern pacemaker. The end result marked a major cardiological breakthrough, as it was the first time that 132 beats per minute through batteryless overdrive-pacing has been recorded.

"The next step in our prototype is to integrate both the electronic circuit for energy storage and the custom-made pacemaker directly into the harvesting device," said Mr Zurbuchen.

Permanent atrial fibrillation doubling the risk of stroke

> "It is very important to acknowledge that regardless of its form and presentation, AF increased the risk of stroke."
>
> *Dr Thomas Vanassche, Population Health Research Institute, McMaster University, Hamilton, Canada*

RISK of stroke has doubled by permanent fibrillation (AF), when compared to paroxysmal AF, research in more than 6,000 patients demonstrates. These findings suggest that a simple clinical assessment of AF type could help doctors to better estimate risks.

AF is a major risk factor of stroke, the second cause of death in the EU. Its presentation can vary from short and self-limiting episodes of arrhythmia in people with otherwise normal heart rates (paroxysmal AF), to continuously abnormal rhythms (permanent AF). Yet a study has shown that an individual's risk of stroke is higher in patients for whom an arrhythmia is permanently present, when compared to those who only experience short episodes, even when correcting for other stroke risk factors; this subject has been one of controversy in the field for a significant time.

Researchers gathered data from two previously conducted clinical trials in order to extract their sample, none of whom were treated with anticoagulant medication which reduces one's risk of stroke. In comparison to population studies, where detection and verification of all strokes is difficult, all events in this trial were both detected and determined. It was found that patients with permanent AF had nearly doubled the risk of stroke, compared to those with permanent AF (yearly rates: 4.2% versus 2.1%).

Dr Thomas Vanassche, research fellow and presenter of the findings, McMaster University, Hamilton, Ontario, Canada, commented on the results: "It is very important to acknowledge that regardless of its form and presentation, AF increased the risk of stroke. Therefore, all patients with AF should be assessed for risk, and if the risk is sufficiently high, they should be treated with anticoagulants. Thus, our results strengthen the existing recommendations."

The findings provide support for the notion that 'a lot of AF' carries more risk than 'a little', and where there is doubt about a patient benefiting from anticoagulant therapy, AF presentation could now be an additional factor to consider.

Hypertension: a growing problem for obese youths

OBESE children have almost a 6-fold risk of hypertension according to a German study conducted in >22,000 youngsters from the Prevention Education Program (PEP) Family Heart Study.

Prof Peter Schwandt, lead investigator, Arteriosklerose Praeventions Institut Munich-Nuremberg, Ludwig-Maximilians-University of Munich, Munich, Germany, said: "The prevalence of hypertension and obesity in children and adolescents is continuing to rise in most high and middle-income countries. Because adiposity is considered a driving force for cardiovascular disease, we examined whether elevated blood pressure [BP] was associated with body fat [BF] distribution in young people."

The study used a sample of both children and adolescents, and in each subject researchers measured BP, body mass index, waist circumference, wait-to-height ratio, skinfold thickness (SFT), and percentage of BF. These measures are both inexpensive and risk-free, and can be used in a variety of settings; however, Prof Schwandt emphasises that such dimensions must be performed correctly, and that age and gender-specific cut-off values need to be used.

Hypertension was defined as a BP reading over the 95th percentile of the BP curve for children and adolescents, with prehypertension describing a reading between the 90th and 95th percentile. Several different measurements of this influenced diagnoses. The findings showed that when compared with children of normal weight, overweight youngsters' risks of hypertension were significantly higher (1.6-fold higher in overweight and 2.4-fold higher in obese boys, and 1.8-fold higher in overweight and 3.3-fold higher in obese girls).

Furthermore, associations with adverse fat patterning were even greater for risking hypertension; obese boys had almost a 6-fold increased risk, compared to boys of normal weight, and the girls' risk was more than 4-times greater. Elevated BP levels appeared to increase with body weight, and researchers also found an increased risk of hypertension with higher SFT, BF, and abdominal adiposity.

Prof Schwandt commented: "Our study clearly shows that the fatter young people are, the greater their risk of prehypertension and hypertension. Any weight loss they can achieve will help reduce their risk."

He further concluded: "General and abdominal adiposity, estimated using simple and inexpensive methods, are already significantly associated with prehypertension and hypertension in children and adolescents. This is of great importance because of the ongoing rise in the prevalence of hypertension and overweight/obesity in young people and the tracking of childhood overweight into adulthood."

Wine and exercise – the healthy diet

PROTECTION from cardiovascular disease (CVD) may be found in a glass of wine, but only for those individuals who regularly exercise.

Since the early 1990s, evidence has been building suggesting that mild-to-moderate consumption of wine protects against CVD; retrospective studies have found that the drink increases levels of high-density lipoprotein (HDL), known as the 'good' cholesterol.

Presently, no long-term, prospective, randomised study comparing the effects of red and white wine on HDL cholesterol, and other markers of atherosclerosis, has been demonstrated. Yet progress has been made with the 2014 In Vino Veritas study, which highlights the potentially beneficial effects of wine consumption upon cholesterol, when accompanied by regular exercise.

146 participants with mild-to-moderate risk of CVD were included in the study, according to the interactive Heartscore tool, which predicts and manages an individual's risk of heart attack and stroke. Subjects were randomised to a year of moderate consumption of either red or white wine; moderate consumption was defined by the WHO guidelines: 0.2 L for women and 0.3 L for men (maximum of five times a week).

Participants resumed their usual diet, whilst keeping a journal of their consumption, medication use, and amounts and types of exercise. Results showed that there was no difference between HDL cholesterol levels at the beginning of the study, when compared to 1 year, in either red or white wine groups. Low-density lipoprotein (LDL) or 'bad cholesterol' was lower in both groups after 1 year; total cholesterol was lower only in the red wine group.

Prof Milos Taborsky, Head, Department of Internal Medicine, Cardiology, Faculty of Medicine and Dentistry, Palacký University, Olomouc, Czech Republic, said: "The only positive and continuous result was in the subgroup of patients who took more exercise, which means regular exercise at least twice a week, plus the wine consumption. In this group HDL cholesterol increased and LDL and total cholesterol decreased in the red and white wine groups. There may be some synergy between the low dose of ethyl alcohol in wine and exercise which is protective against CVD."

Future studies will continue to compare the effects of wine in patients at high risk for CVD who take statins and do regular exercise.

Heart health hampered by high-energy drinks

ENERGY drinks can cause a number of heart problems as well as other severe conditions, a thought-provoking study from France has revealed.

"So-called 'energy drinks' are popular in dance clubs and during physical exercise, with people sometimes consuming a number of drinks one after the other. This situation can lead to a number of adverse conditions including angina, cardiac arrhythmia (irregular heartbeat), and even sudden death," said Prof Milou-Daniel Drici, Professor of Clinical Pharmacology, Department of Pharmacology, University of Nice Sophia Antipolis, Nice, France.

Spanning nearly 4 years (1st January 2009 - 30th November 2012), a research investigation involving a wide range of specialists - including cardiologists, psychiatrists, neurologists, and physiologists – analysed the adverse effects of these highly consumed drinks.

A significant increase of 30% consumption of 103 energy drinks in France was recorded between 2009 and 2011, equating to more than a staggering 30 million litres. The leading brand accounted for 40% of the drinks consumed, and furthermore two-thirds of the drinks were most likely to be consumed outside of the home environment.

During this same timeframe, 257 cases were reported to the French Agency for Food, Environmental, and Occupational Health & Safety, where information collected from 212 cases prompted the need for a safety evaluation. In the reported adverse events, it was revealed that 95 cases had cardiovascular symptoms, 74 psychiatric cases, and 57 cases with neurological warning signs. These events further overlapped each other. In at least 8 cases there were cardiac arrests and sudden or unexplained deaths, while heart rhythm disorders had affected 46 people, 13 had angina, and 3 had hypertension.

Prof Drici concluded: "Patients rarely mention consumption of energy drinks to their doctors unless they are asked. Doctors should warn patients with cardiac conditions about the potential dangers of these drinks and ask young people in particular whether they consume such drinks on a regular basis or through binge drinking."

"Doctors should warn patients with cardiac conditions about the potential dangers of these drinks and ask young people in particular whether they consume such drinks on a regular basis or through binge drinking."

Prof Milou-Daniel Drici, Professor of Clinical Pharmacology, University of Nice Sophia Antipolis, Nice, France

LCZ696: game changer for heart failure patients

> "The major benefit is that the natural course of the disease is changed. I do not think it changes the natural history of HF – I know it does."
>
> *Dr Milton Packer, Professor and Chair, Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, USA*

CHRONIC heart failure (HF) patients may reap the benefits of a new major drug breakthrough, LCZ696, which has produced significantly impressive results in clinical trials.

LCZ696, an angiotensin receptor-neprilysin inhibitor, has been granted FDA Fast Track status – a title designated for certain selected drugs for quicker drug development - to treat serious conditions so that this new drug may be given to patients earlier.

"The purpose of using a drug like this is not to make people feel better," said Dr Milton Packer, co-principal investigator, Professor and Chair, Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, Texas, USA. "The major benefit is that the natural course of the disease is changed. I do not think it changes the natural history of HF – I know it does."

8,399 participants with Class 2-4 HF and an ejection fraction of 40% or less took part in the PARADIGM-HF trial and were randomised to either 200 mg LCZ696 or 10 mg enalapril groups, with treatments taken twice daily, as well as recommended therapy. Death from cardiovascular causes or hospitalisation for HF occurred in 21.8% of the LCZ696 group, in comparison to 26.5% for the enalapril group, after a median follow-up of 27 months.

Dr Packer noted that when LCZ696 was compared to enalapril, the former drug had a 20% reduction in the risk of death from cardiovascular causes and a 21% reduction in the risk of hospitalisation for HF.

"Given the survival advantage of LCZ696 over currently available drugs, once this drug becomes available, it would be difficult to understand why physicians would continue to use traditional angiotensin converting-enzyme inhibitors or angiotensin receptor blockers for the treatment of HF," commented Dr Packer.

Iron supplementation: the elixir of life for heart failure patients

SIGNIFICANT improvements in functional capacity, quality of life (QoL), and a reduced risk of hospital admission can be potentially achieved by heart failure (HF) patients with iron deficiency, with at least two intravenous doses of an iron supplement.

"Iron deficiency has recently been reported as a frequent comorbidity in HF and has been associated with impaired functional capacity, poor QoL, and increased mortality, irrespective of the presence of anaemia. Therefore, correction of iron deficiency itself should be considered an attractive therapeutic target in this population," said Prof Piotr Ponikowski, lead investigator, Head of the Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland.

This claim was investigated in a double-blind, placebo-controlled trial, CONFIRM-HF, which included 304 HF patients from 41 sites across 9 European countries. Participants were randomised to either receive ferric carboxymaltose solution (FCM) or normal saline solution for 52 weeks. The baseline of the investigation was the completion of a 6-minute walk test (6MWT) and improvement at week 24 marked the study's endpoint.

Prof Ponikowski commented: "Iron depletion impedes oxygen transportation and utilisation and so we expected that targeting this depletion would improve patients' exercise tolerance."

"Iron depletion impedes oxygen transportation and utilisation and so we expected that targeting this depletion would improve patients' exercise tolerance."

Prof Piotr Ponikowski, Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland

The FCM group had higher increase in distance completed in the 6MWT than those in the placebo group. At the study's endpoint, the FCM group had completed 33 extra metres in the 6MWT at week 24, furthermore, this group covered 42 extra metres at week 36, and 36 extra metres at week 52.

Fatigue scores were significantly increased and there was a reduction in hospitalisations experienced by those in the FCM group. The death rate was similar in both groups, but a longer timeframe would be needed to detect differences in mortality. To build the case for iron depletion among HF patients, an enhanced study with sufficient follow-up would also be required.

Cardiac resynchronisation therapy patients to benefit from alternative lead location

HEART failure (HF) patients receiving cardiac resynchronisation therapy (CRT) are likely to experience similar outcomes when right ventricular (RV) lead placement is performed in the mid-septum, as to when the procedure is carried out in the conventional apical position. This discovery brings with it particularly important implications for HF patients, as CRT is only successful in two out of three subjects, and the positioning of RV leads is still heavily debated.

263 CRT patients with a mean age of 63.4 years were enrolled in the SEPTAL-CRT study; subjects were randomised to either conventional RV lead positioning in the apex, or positioning in the mid-septum. The left ventricle lead was inserted into the coronary sinus, as conventionally practised. Researchers wanted to highlight the RV septal position as non-inferior to apical positioning in terms of changes in the left ventricular end systolic volume (LVESV).

"Conventional lead placement in the apex of the right ventricle can induce cardiac dyssynchrony and thus increase morbidity and mortality. Therefore, knowing that we have an alternative position for RV lead placement means there is potentially a way to improve CRT success rate," said Prof Christophe Leclercq, study investigator, Professor of Cardiology, Department of Cardiology, Rennes University Hospital, Rennes, France.

At 6 months follow-up, both septal and apical groups showed similar decreases in LVESV from baseline. Additionally, there was no difference in clinical outcome between the two groups; both showed matching benefits in the 6-mile walk test and the Milton Packer score. The placing of the RV lead in the mid-septal position was further associated with the same success/complication rates as conventional positioning.

"The SEPTAL-CRT trial is the first prospective, multicentre, randomised trial demonstrating the non-inferiority of the mid-septal location as compared to the conventional apical location of the RV lead in CRT patients on left ventricular reverse remodelling," said Prof Leclercq.

He concluded: "The implantation success rate was similar in both groups, and the clinical outcome was also similar at 1 year. Therefore, bothimplantation sites are appropriate and could be used for CRT."

Home comforts for implantable cardiac defibrillator users

COSTS of implantable cardiac defibrillator (ICD) home monitored (HM) follow-ups are equal for physicians, hospitals, and insurance providers when compared to traditional in-office monitoring, according to research.

Approximately a decade after telemonitoring capabilities were introduced in ICDs, the European Health Economic Trial on Home Monitoring in ICD Therapy (EuroEco), which evaluated the costs to physicians and hospitals where depending on HM-based follow-up compared to in-office follow-up, spotted broad European variations in the financial load faced by a switch to the home monitoring approach. Furthermore, HM reimbursement could be a strong indicator as to which countries decide to pursue this practice.

"Since our study shows that total insurance costs do not increase, and HM actually reduces hospitalisations and length of stay as seen in prior trials, we hope our results will allow informed discussions between payers, providers, and manufacturers to come to balanced reimbursement scenarios in order to stimulate reorganisation towards remote monitoring-based care," said Dr Hein Heidbuchel, principal investigator, Heart Center Hasselt, Hasselt, Belgium.

303 subjects who were booked to receive a single or dual-chamber ICD, equipped with home monitoring (HM) technology, and of an average age of 62.4 years, with a male proportion of 81%, took part in the study. Following ICD placement, patients were randomised to HM ON or HM OFF and tracked for 2 years.

In spite of a much greater number of office visits unplanned in the HM ON group next to the HM OFF group, there was a drastic drop in the total number of visits for HM ON compared to HM OFF with 3.79 to 5.53 recorded visits, respectively. However, subject self-recorded quality of life was the same in both groups. Most significantly, total follow-up cost remained equal for providers for HM ON and HM OFF, charged €204 and €213, respectively.

"Reimbursement protects income for physicians and hospital, creating an incentive to adopt remote monitoring. EuroEco shows that this is possible without increased overall costs to insurers, which is a strong argument for reimbursing remote monitoring," explained Prof Heidbuchel.

"The EuroEco data serve to further specify these recommendations. Our study's findings of similar to decreased payer costs associated with home monitoring show that there is certainly room for proper compensation of providers and adequate financing of the technology itself to stimulate remote-based care. In my opinion, that is the direction for future medicine," he added.

Time for a hearty cup of tea

> "I think that you could fairly honestly recommend tea drinking rather than coffee drinking and even rather than not drinking anything at all."
>
> *Prof Nicolas Danchin, Consultant Cardiologist, Hôpital Européen Georges Pompidou, Paris, France*

DRINKING tea facilitates the curbing of non-cardiovascular (CV) mortality by 24% - this is the latest revelation from a large population study in France.

A staggering 131,401 participants aged 18-95 years, who had a health check between January 2001 and December 2008, enrolled in the study. Self-administered questionnaires were used to assess coffee and tea consumption in one of three classes: none, 1-4 cups, or >4 cups per day. Overall, in the mean 3.5 years follow-up, there were 95 deaths from CV and 632 deaths from non-CV causes.

Results revealed that subjects in the coffee-drinking group had a higher CV-risk profile than their non-drinking counterparts, especially those that also smoked. Although the heavy coffee drinker group was older, on average, than the non-drinkers, when adjusted for age, the difference in blood pressure was small. Heavy coffee drinkers had a slightly lower systolic blood pressure (SBP) and higher diastolic blood pressure (DBP) than their non-drinking equivalents.

A reverse profile was observed among the tea drinkers, where a better CV risk profile was seen in those that consume tea compared to those who do not. Tea had a significant effect on the subjects' blood pressure, with a 4-5 mmHg decrease in SBP and a 3 mmHg decrease in DBP in heavy tea drinkers, when compared to their non-drinking counterparts.

Commenting on this difference, Prof Nicolas Danchin, Consultant Cardiologist, Head of the Department of Coronary Artery Disease and Intensive Cardiac Care, Hôpital Européen Georges Pompidou, Paris, France, concluded: "Tea has antioxidants which may provide survival benefits. Tea drinkers also have healthier lifestyles so does tea drinking reflect a particular person profile, or is it tea, *per se*, that improves outcomes - for me that remains an open question. Pending the answer to that question, I think that you could fairly honestly recommend tea drinking rather than coffee drinking and even rather than not drinking anything at all."

Synthetic hormone battles worsening heart failure

SYNTHETIC serelaxin, a version of the naturally occurring hormone, relaxin (present in both sexes), has been found to reduce occurrences of in-hospital worsening heart failure (HF) by nearly 50% in patients admitted for acute HF.

According to the co-principal investigator of the RELAX-AHF trial, Prof John R. Teerlink, Director of Heart Failure, San Francisco Veterans Affairs Medical Center, University of California, San Francisco, California, USA, serelaxin is produced in large quantities during pregnancy, and is thought to improve kidney, heart, and blood vessel function; such beneficial effects have provided the means for investigating the hormone in HF patients, whose functions in these areas are abnormal.

The study was a randomised, double-blind controlled trial that included 1,161 subjects admitted to hospital with acute HF, and in whom the effects of a 48-hour infusion of the intravenous drug were analysed. Current evaluation compared serelaxin and placebo groups for the occurrence of worsening HF within 5 days of hospital admission, and researchers found that within this period, 12.2% of patients treated with standard of care had an episode of worsening HF, whereas this occurred in only 6.7% of those treated with serelaxin.

Serelaxin further reduced repeated episodes of worsening HF; a total of 87 worsening HF or death events in the placebo group were compared to 43 in the hormone-treated patients, and this was evident in subjects regardless of the type and intensity of the rescue therapies given. Finally, the analysis found that patients with worsening HF spent an average of 5 and 8 days longer in intensive care, for a longer time on intravenous medication.

"These findings demonstrate immediate improvement in the patient's clinical course with serelaxin treatment and also support the earlier finding of an improvement in 180-day mortality with a 48-hour infusion of serelaxin."

Prof John R. Teerlink, University of California - San Francisco, San Francisco, USA

Prof Teerlink said: "These findings demonstrate immediate improvement in the patient's clinical course with serelaxin treatment and also support the earlier finding of an improvement in 180-day mortality with a 48-hour infusion of serelaxin. We are attempting to confirm the findings of improved survival with serelaxin in the ongoing RELAX-AHF-2 trial."

He promptly added that patients admitted for HF can experience a worsening of their condition despite present therapies, which can result in shortness of breath or the sensation of drowning in their own fluids; predicting just whose condition will decline is extremely difficult.

Yet, ultimately, the results of the RELAX-AHF trial have provided promising results for the future treatment of HF and the provision of aftercare for inpatients across Europe.

A change in the direction of heart attacks

"The early separation of the curves in CvLPRIT suggests a delayed staged out-patient complete strategy may not be as effective."

Prof Anthony Gershlick, University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, UK

ONE-SIZE-FITS-ALL strategy has been strongly encouraged in the wake of a high-profile study into treating heart attack (HA) patients, with a complete uprooting of all significantly blocked arteries seen as the way forward, rather than removing only the responsible artery.

Prof Anthony Gershlick, study investigator, Consultant Cardiologist and Professor of Interventional Cardiology, University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, UK, said that the results of the CvLPRIT study could potentially be revolutionary: "Until now there have been conflicting data regarding the optimal management of patients who, whilst undergoing primary percutaneous coronary intervention [P-PCI] after myocardial infarction [MI] are also found to have lesions in their non-infarct related artery [N-IRA]."

296 HA subjects who presented at seven UK interventional cardiology centres were involved in the CvLPRIT study. Subjects were randomised to receive either IRA-only revascularisation (n=146) or complete revascularisation of all N-IRAs (n=150), shown as being highly blocked, as well as the 'culprit' IRA.

Complete revascularisation involved treating the IRA first, then the N-IRAs. Subjects in this group had significantly better outcomes at 12 months than those in the IRA-only revascularisation group, according to a composite endpoint of major adverse cardiac events (MACE) including all-cause mortality, recurrent MI, heart failure, and ischaemic-driven revascularisation.

The difference between the groups was observed early on, with 21.2% of the IRA-only arm and 10.0% of the complete revascularisation group suffering MACE, respectively. In spite of a higher procedure time and contrast volume load in the complete revascularisation group, the risk of stroke was no higher compared to the IRA-only group.

Prof Gershlick noted that the CvLPRIT results greatly matched those of the earlier PRAMI study. "The PRAMI trial reported clear clinical benefit in treating both IRA and N-IRAs at the index P-PCI, but there was some criticism of the trial design," he said. "As a result, PRAMI has not led to widespread changes in clinical practice, with IRA-only revascularisation at P-PCI remaining by far the more common practice."

However, Prof Gershlick also highlighted that the CvLPRIT study greatly bolstered the conclusions of PRAMI, indicating a potential change in direction for future HA treatment, commenting: "The early separation of the curves in CvLPRIT suggests a delayed staged out-patient complete strategy may not be as effective."

Vagus stimulation leads to improvement in cardiac function

SIGNIFICANT improvements in cardiac function and symptoms of chronic heart failure (HF) can be obtained through the low amplitude stimulation of the vagus nerve; the device providing the stimulation can either be implanted in either the left or right vagus nerve.

According to Dr Inder Anand, principal investigator, Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA, left-sided vagal nerve stimulation (VNS) is used in the treatment for epilepsy and has not been evaluated in HF patients until now.

"Left-sided VNS could be an advantage in some HF patients because it can be combined with cardiac devices such as implantable cardioverter-defibrillators and cardiac resynchronisation therapy devices, the vast majority of which are implanted on the left side of thorax," Dr Anand noted.

The ANTHEM-HF study was designed to demonstrate the safety and efficacy of VNS in HF patients. 60 patients, aged approximately 51 years, with reduced ejection fraction and receiving pharmacological therapy, took part in the study.

Subjects were randomised into two groups: those that would have the VNS device implanted in the left side (n=31) and those in which the device would be implanted in the right side (n=29). To determine the best-tolerated intensity, stimulation to the vagus nerve was titrated over a 10-week period. After titration, VNS was delivered for 6 months at amplitude of 2.0 (±0.6) mA and a constant frequency of 10 Hz.

> "This preliminary assessment shows promising results which need to be confirmed in a larger, controlled trial."
>
> *Dr Inder Anand, University of Minnesota Medical School, Minneapolis, USA*

Among all of the patients, there were significant improvements (mean 4.5%) from baseline in left ventricular ejection fraction with no statistically significant differences between left and right-sided VNS. There was no statistically significant improvement in left ventricular end systolic volume. A mean improvement of 56 m in the 6-minute walk test was also observed, but this improvement was significantly higher in the right side (mean 77 m) than in the left-sided VNS (mean 34 m).

Both groups experienced similar device-related adverse events, including transient mild dysphonia, cough, and oropharyngeal pain, which eventually resolved during the study. There was one fatality, which was attributed to the fact that the patient had a history of carotid atherosclerosis and had suffered an embolic stroke during the implantation of the device.

"This preliminary assessment shows promising results which need to be confirmed in a larger, controlled trial," concluded Dr Anand.

The SERVE-HF trial: changing the game for sleep apnoea patients

Interview with Prof Martin Cowie, Co-principal Study Investigator.

THE BACKGROUND

Prof Martin Cowie, Consultant Cardiologist, Royal Brompton Hospital, Professor of Cardiology, National Heart and Lung Institute, Imperial College London, London, UK, and co-principal investigator of this study, spoke to the *European Medical Journal* exclusively about ResMed's SERVE-HF trial. Commenting on the study, Prof Cowie remarked: "*It is a very exciting study: it is expensive, it has been going for years, and the cardiology community is now just waking up to the fact that we will have the results this time next year. If it is positive of course it means that cardiologists, and other physicians who look after patients with cardiac disease, will have to think about sleep apnoea (SA).*"

THE SERVE-HF TRIAL

Sleep apnoea (SA) is a common comorbidity of heart failure (HF); it is estimated that 50-75% of the 15 million HF patients in Europe suffer from SA. Although it is one of the most common comorbidities, it is one of the least recognised and diagnosed. "*[SA] was always seen as something that you could find in patients with HF but until recently there was no way of specifically treating it,*" highlighted Prof Cowie.

The trial has enrolled 1,325 patients and is taking place in 80 centres across Europe and Australia, with an average patient follow-up of 54 months (24-84 months). The key areas of focus in SERVE-HF include: time to death, unplanned HF-related hospitalisation, and impact on health economics, quality of life (QoL), cardiac function, and exercise capacity.

Therefore, while assessing patients with HF who are on the best medical treatment, the aim of this particular trial is to answer the following question: "*If you actually specifically treat SA with a mask and ventilator do you actually improve the outcome for that patient? That is what the trial will tell us.*" In addition to this, another sub-study is being conducted, as Prof Cowie told us: "*We will be able to tell you what happens to the heart, what happens to the blood hormones, what happens to sleep quality, what happens to their QoL, and what happens to their cognitive functions... we will be able to give a narrative as to why patients do better in terms of the effect on the heart, breathing, and brain function.*"

Is the Field Going to Open Up for Cardiologists and Wake them up to this Condition?

"*Yes, it is not really thought about by cardiologists; it is very much thought of to be a sleep or a respiratory physician who would be interested in that,*" stated Prof Cowie. If the results of the trial are positive then: "*It will be a real wake-up call and people will have to get with it and understand what it is, how you diagnose it, and what the form of treatments might be; so indeed, it will be a big change if it is positive,*" explained Prof Cowie.

Although the trial is only based in HF patients, it is hoped that the results will raise awareness about SA much more widely. Moreover, if the results of the trial are positive then, as Prof Cowie claimed: "*It really will change practice for cardiologists and sleep physicians right across the world.*"

PAST TRIALS, FUTURE TECHNOLOGIES

A Canadian trial, the CANPAP study, which used constant positive airway pressure (CPAP) in HF patients with SA, is the only other trial of this type. It was closed early because there were some concerns over the safety of ventilating these patients with CPAP, although there were some signs that some patients may benefit from this treatment. "*The CANPAP study was neutral and did not show any overall benefit,*" indicated Prof Cowie, "*there has been no positive study for SA as yet; this will be the first one if it is positive.*"

"*Most people feel that this [CPAP therapy] is not a very sophisticated treatment and, certainly for HF patients with central SA, there is a much better way of ventilating a patient called servo assisted ventilation... it is better tolerated, it is more physiological, and certainly controls central SA much better than CPAP... CANPAP was interesting, it was the first trial in the area, but it was neutral.*

"*We think we have a better technology that is more appropriate for HF patients and we are trialling it in a much larger and much longer term follow-up study,*" highlighted Prof Cowie.

Will other Technologies Follow this One?

Prof Cowie replied: "*It is always moving on, the whole sleep and ventilation field is moving on. The machines are much smaller than they used to be, they are much quieter, so less obtrusive; there are also a huge variety of masks, they are much more comfortable, and smaller than before. Cardiologists should be aware that the technology has moved on a lot, and they need to be familiar with what modern technology is like: which is much lighter, much quieter, and much better tolerated by patients.*"

To ensure that cardiologists are aware of the condition, and to ensure that patients are receiving the best treatment, a collaboration of specialists is needed in the future. "*There will have to be a lot of cross talk between cardiologists and lung specialists, and also... with industry because they are the people who provide the equipment and have a lot of experience with it. ResMed is working hard to raise awareness of itself as a company amongst cardiologists and also helping them to start screening for the condition,*" expressed Prof Cowie.

FUTURE PERSPECTIVES

When conducting these trials, cost is one point which should be considered. Therefore, a health economic study is also being conducted to show people how much they will have to spend to achieve the required benefit.

Although cardiologists will want this to move quickly if the results are positive, getting new therapies implemented is yet another hurdle which needs to be overcome. Prof Cowie mentioned: "*I do think it will be a problem here yes, because it is across different demarcation lines – cardiologists, respiratory physicians,*" he added; however, "*I think healthcare systems are getting a bit better and quicker, that if the evidence is strong they then open up access to their citizens to these therapies, but generally they try and do it in a ramp sort of way, rather than a sudden overnight change because that just does not happen.*"

"*Myself and my co-investigators are working very hard in each of the European countries to work out what the best system might be, and to prepare the ground in case our study is positive so we can come up with solutions to cardiologists [so] that when we present the trial results we can suggest what they need to be doing in their practice and how it might work, and we can present examples from around Europe of how to do it.*

"*In effect, trials, evidence-base, and guidelines are all fine but you have to help people implement otherwise nothing happens,*" said Prof Cowie. Although people may be aware of this very remarkable, game-changing trial, the implication for cardiologists may not be clear, "*I am hoping that the whole area will become more familiar to cardiologists and they start doing what they should be doing,*" Prof Cowie concluded.

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ESC GOLD MEDALLISTS 2014

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Prof Alain Carpentier, France

Prof Petr Widimský, Czech Republic

YOUNG INVESTIGATOR AWARDS

Anne-Marie Schjerning Olsen
Denmark

Impact of NSAID treatment on bleeding risk after myocardial infarction in patients treated with different combinations of aspirin, clopidogrel, or vitamin k antagonist - a Nationwide study.

Francesco Paneni
Sweden

Prolyl-isomerase-1 (Pin1) causes endothelial dysfunction and vascular inflammation in diabetes: a study in mice and humans.

Pierluigi Costanzo
UK

Impact of change of body mass index on long-term cardiovascular events and all-cause mortality in patients with Type 2 Diabetes Mellitus.

Kaleab Asrress
UK

Performance of novel adenosine-free and established indices of coronary lesion severity using invasive and non-invasive techniques, as well as absolute quantification of myocardial blood flow.

Andreas Mangold
Austria

CD4+CD28null T cells are enriched at the culprit lesion site in STE-ACS and promote NET production.

EMERGING OPTIONS FOR PATIENTS WITH ATRIAL FIBRILLATION

Summary of Presentations from the Daiichi Sankyo Satellite Symposium, held at the Annual ESC Congress, Barcelona, Spain, on 31st August 2014

Co-Chairs

Jeffrey Weitz,[1] John Camm[2]

Speakers

Christian Ruff,[3] Andreas Goette,[4] Jack Ansell[5]

1. McMaster University, Hamilton, Ontario, Canada
2. St George's Healthcare NHS Trust, London, UK
3. Brigham & Women's Hospital, Boston, Massachusetts, USA
4. St Vincenz-Hospital, Paderborn, Germany
5. New York City, New York, USA

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MEETING SUMMARY

Dr Jeffrey Weitz chaired the symposium and welcomed Dr Christian Ruff, who discussed and summarised recent results from key trials of new oral anticoagulants (NOACs) in atrial fibrillation (AF) with a focus on edoxaban. Prof Andreas Goette then evaluated the current guidelines for the use of cardioversion in AF treatment and recent findings from NOAC trials. Dr Jack Ansell described the current management strategies for NOACs and the limitations therein, as well as novel reversal strategies for NOACs currently under development. Finally Prof John Camm, co-chair, summed up the use of NOACs as an alternative to warfarin in the prevention of stroke in patients with AF, and closed the meeting.

New Insights from ENGAGE AF-TIMI 48

Doctor Christian Ruff

Effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction study 48 (ENGAGE AF-TIMI 48)[1,2] is the largest trial of a NOAC in AF, having enrolled 21,105 patients to one of three treatment strategies: higher-dose edoxaban (60 mg QD), lower-dose edoxaban (30 mg QD), or warfarin titrated to an international normalised ratio (INR) of 2.0–3.0.[1] The primary endpoint was stroke or systemic embolism, whilst the safety endpoint was

major bleeding, as per the International Society on Thrombosis and Haemostasis definition. An important aspect of the trial design included a 50% dose reduction of edoxaban (60-30 mg or 30-15 mg) for high-risk patients with clinical features anticipated to significantly increase drug exposure and risk of bleeding, defined as a creatinine clearance of 30–50 mL/min, weight ≤60 kg, or receiving a strong P-glycoprotein (P-gp) inhibitor (verapamil, quinidine, or dronedarone).

This trial found that both edoxaban regimens had comparable efficacy to warfarin with regard to reducing stroke or systemic embolism (annualised rate of stroke or systemic embolism was 1.50% in the warfarin group, and 1.18% [p<0.001 non-inferiority], and 1.61% [p=0.005 non-inferiority] in the higher and lower-dose edoxaban arms, respectively). In addition, during the overall study period of 2.8 years, cardiovascular mortality was reduced by ~14–15%.[2] Importantly, both edoxaban regimens were associated with a significant reduction in major (p<0.001), clinically-relevant non-major (p<0.001), and minor bleeding (p=0.002 for higher-dose and p<0.001 for lower dose) compared with warfarin. However, although the rates of ischaemic stroke were comparable between higher-dose edoxaban and warfarin, a higher incidence was observed in patients receiving the lower-dose regimen.

Important insights gained from previous trials influenced the trial design for ENGAGE AF-TIMI 48;[1] for example, the safety issues that occurred when patients were transitioned from rivaroxaban to a vitamin K antagonist (VKA) upon completion of the rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF) trial.[3] 1 month post-trial, fewer than half of the rivaroxaban patients had INR values within the therapeutic range and subsequently had an increased risk of stroke compared with patients who were given warfarin throughout the trial.[3,4] To minimise this effect during ENGAGE AF-TIMI 48,[5] patients who were given a VKA had their INR checked frequently within the first 2 weeks and the dose was aggressively titrated to achieve a therapeutic range. In addition, treatment with a VKA was overlapped with a modified edoxaban dose. This strategy was successful in preventing the excess number of strokes seen previously, as ~85% and ~99% of patients were within the therapeutic range 2 weeks and 1 month after transition, respectively.[5]

Another recent analysis from the ENGAGE AF-TIMI 48 study evaluated the mortality benefit of edoxaban compared with warfarin with regard to bleeding.[6] Compared with the higher and lower-dose edoxaban groups, there were 66 and 102 excess deaths in the warfarin group. Of these, 39–45% were due to fatal bleeds and approximately 90% of the total excess deaths in the warfarin group were preceded by a major bleed. Thus, lower rates of fatal bleeding and major bleeding contributing to death accounted for over half the reduction in mortality observed in the edoxaban groups.

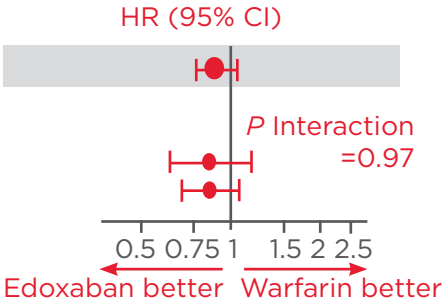
Prescription of anticoagulants is a balance of risks, with increased thrombosis or bleeding occurring if therapy is not adjusted correctly.[7] Emerging data from the randomised evaluation of long-term anticoagulation therapy (RE-LY) study[8] reported that higher dabigatran concentrations had a stronger correlation with bleeding events than stroke reduction. Investigators also observed that age impacted bleeding and stroke risk at a given dabigatran concentration. Due to the risks involved with anticoagulants, it would be beneficial if drug dosages could be modified according to patient risk factors. The ENGAGE AF-TIMI 48 trial[1,9] subsequently assessed whether the dose of edoxaban could be adjusted using clinical factors alone, such as low body weight (≤60 kg), reduced renal function (creatinine clearance 30–50 mL/min), or concomitant treatment with a strong P-gp inhibitor. The study found that, compared with warfarin, the efficacy of edoxaban was maintained when the dose was reduced by half in high-risk populations (60-30 mg or 30-15 mg).[2] Interestingly, while efficacy was maintained, the risk of bleeding was further reduced, as shown in Figure 1. The reason for this appears to be the prevention of excess edoxaban exposure, resulting in lower anti-Xa activity and a better balance of risk for the patient.

In conclusion, recent analyses of ENGAGE AF-TIMI 48 have demonstrated the comparable efficacy of edoxaban compared with warfarin, in conjunction with a lower incidence of bleeding events. Using the patient's clinical features to adjust the edoxaban dose was sufficient to prevent excess edoxaban levels and also optimise the balance between ischaemic and bleeding events, without having to measure prospectively the drug levels or anticoagulant activity.

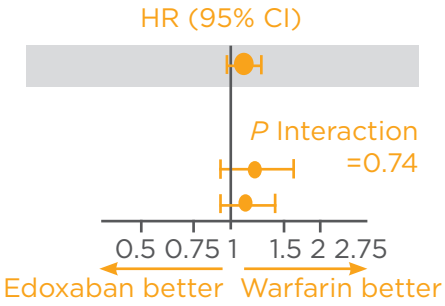
A

ENGAGE Dose Reduction: Preserved Efficacy

	Patients	Edoxaban 60/DR30 mg	Warfarin
All patients	21,105	1.57	1.80
Patient-specific dose reduction			
Yes	5,356	2.32	2.68
No	15,749	1.33	1.53



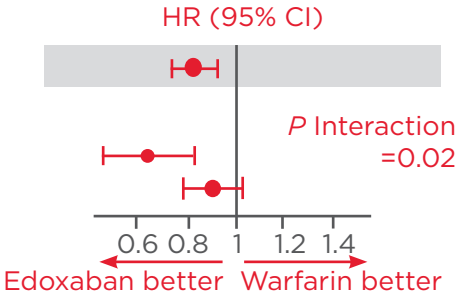
	Patients	Edoxaban 60/DR15 mg	Warfarin
All patients	14,070	2.04	1.80
Patient-specific dose reduction			
Yes	3,572	3.14	2.68
No	10,498	1.69	1.53



B

ENGAGE Dose Reduction: Better Safety

	Patients	Edoxaban 60/DR30 mg	Warfarin
All patients	21,026	2.75	3.43
Patient-specific dose reduction			
Yes	5,330	3.05	4.85
No	15,696	2.66	3.02



	Patients	Edoxaban 60/DR15 mg	Warfarin
All patients	14,014	1.61	3.43
Patient-specific dose reduction			
Yes	3,550	1.50	4.85
No	10,464	1.65	3.02

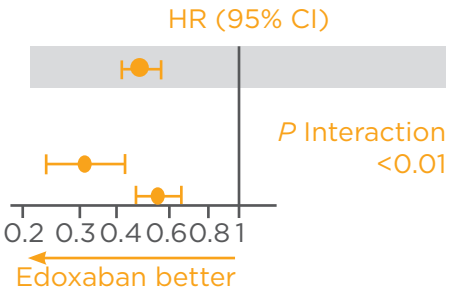


Figure 1: A) Hazard ratio (HR) of the primary efficacy outcome of stroke or systemic embolism with edoxaban versus warfarin; B) HR of the principal safety outcome of major bleeding with edoxaban versus warfarin.

CI: confidence interval.

Adapted from Giugliano RP et al.[2]

Future Direction of Anticoagulation Therapy

Professor Andreas Goette

Clot formation occurs in the presence of haemodynamic changes and endothelial injury as described by Virchow's triad.[10] Patients with AF have a higher likelihood of developing a clot and subsequent stroke than patients without AF.[11] Indeed, it has been shown that periods of AF as short as 5 minutes can increase the rate of stroke (Figure 2).[12]

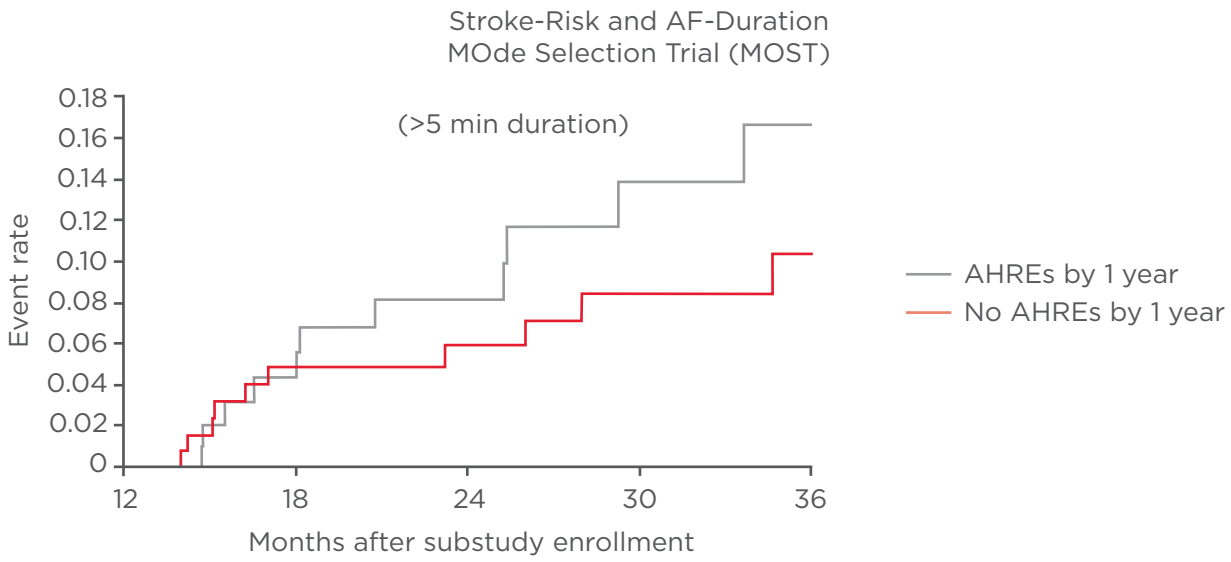


Figure 2: Kaplan–Meier plot of death or nonfatal stroke after 1 year of ancillary study follow-up in patients with AHREs versus those without AHREs.[12]

AF: atrial fibrillation; AHRE: atrial high rate episode.

Reprinted from Circulation, 107, Glotzer TV et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST), 1614–9 Copyright (2014), with permission from Wolters Kluwer Health.

Cardioversion is when an attempt is made to revert AF back to sinus rhythm, either by using drugs (pharmacologic cardioversion) or electric current (electric cardioversion). There is a risk of thromboembolism following cardioversion, so current guidelines recommend anticoagulant therapy prior to initiation of the procedure.[13] VKAs are the main anticoagulants used for cardioversion because although NOACs are available for patients with AF, few data are available regarding their efficacy and safety in the cardioversion setting.

Sub-analyses of the key NOAC trials (RE-LY,[14] ROCKET AF,[3] and apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation [ARISTOTLE])[15] confirmed no differences in the incidence of stroke between the NOACs and warfarin in patients undergoing cardioversion. However, the number of patients included in these sub-analyses was small and the studies were not sufficiently powered to fully elucidate the effect of NOACs during cardioversion.[14] Therefore, prospective studies such as the XVERT trial[16] are still required to establish efficacy.

The edoxaban versus warfarin in subjects undergoing cardioversion of atrial fibrillation (ENSURE in AF) study is the largest trial that will assess electrical cardioversion, recruiting at approximately 300 sites and enrolling >2,000 patients across 20 countries (Daiichi Sankyo, data on file). Patients with AF lasting >48 hours within the past year, who are indicated for electrical cardioversion, will be primarily assessed for safety, and events such as major and non-major bleeds will be evaluated. Efficacy will also be monitored, although it may be limited due to the number of cardioversions required for statistical significance.

Patients may, or may not, undergo transoesophageal echocardiography (TEE) during the ENSURE in AF trial, after which warfarin (INR 2.0–3.0) or edoxaban (60 mg QD) will be given. Non-TEE guided approaches will have a pretreatment phase of 21 days so that full anticoagulant coverage is assured. While the standard edoxaban dose will be 60 mg, high-risk patients with a low body weight (≤60 kg), reduced creatinine clearance (15–50 mL/min), or concomitant use of a potent P-gp inhibitor (except amiodarone) will be given 30 mg edoxaban QD.

In summary, it is hoped that the ENSURE in AF trial, in conjunction with other prospective clinical trials, will provide robust data that can inform guidelines for patient care. Further prospective trials that assess cardioversion and catheter ablation are required in order to confirm the potential role of NOACs in all AF-associated procedures.

Table 1: Suggestions for reversal of target-specific oral anticoagulants.

Parameter	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
3-factor PCC	Unclear	Unclear	Unclear	Unclear
4-factor PCC	Possible (activated)	Possible	Possible	Possible
Activated factor VIIa	No	No	No	No
FFP	No	No	No	No
Haemodialysis	Yes	No	No	No
Hemoperfusion with activated charcoal	Yes	Possible	Possible	N/A
Oral activated charcoal	Yes	Yes	Yes	N/A

FFP: fresh frozen plasma; PCC: prothrombin complex concentrate.
Updated after Kaatz et al.[24]

Clinical Management of Treatment with NOACs

Doctor Jack Ansell

Until recently, VKAs were the only oral anticoagulant available for AF patients, and these required complex management. However, several NOACs have now been introduced that, while less complex than VKAs, may still require management. Although it is currently believed that the benefits of NOACs include a low requirement for management by physicians, there are a number of considerations to be assessed when prescribing these therapies.

Aspects to consider when prescribing the new anticoagulants include dosing strategies, possible drug interactions, peri-procedural management, adherence, monitoring, and follow-up.[17] Available NOACs include dabigatran, rivaroxaban, and apixaban, while edoxaban is still under investigation. Each NOAC has both standard dosing and available modifications that can be given depending on patient risk factors, which can lead to complex requirements regarding which NOAC to use, and at which dose.[18]

Monitoring drug levels or drug effects during the course of anticoagulant treatment is not necessary, but even if it were desired, deciding the appropriate method and time-point for monitoring can be difficult. Compared with warfarin and other VKAs, NOACs produce sharp peaks and troughs of drug concentration and drug effect. Thus, one must consider that if the NOACs are to be monitored, should the blood samples be taken at the top, middle, or bottom of the peaks and should repeat monitoring be done at the same time? Recent data have suggested that monitoring trough levels of dabigatran and maintaining an adjusted level may lead to less bleeding.[8] However, despite the inherent limitations of monitoring, assessing drug level or drug effect under special circumstances, such as major bleeding and emergency situations, may be desired.

Further to this, available monitoring tests include prothrombin or thrombin time (TT) (presence of drug), chromogenic anti-factor Xa or dilute TT (amount of drug present), or the activated partial thromboplastin time (aPTT).[19–23] TT (dabigatran) is a widely available test but its high sensitivity to dabigatran can be a disadvantage. A normal TT essentially rules out any meaningful presence of dabigatran. Dilute TT tests, although not available everywhere, can provide a quantitative determination of dabigatran. For factor Xa inhibitors, the prothrombin time has variable sensitivity, and only certain reagents are suitable for dose-effect monitoring. The chromogenic anti-factor Xa assay provides a good quantitative measure, but it is not yet globally available.

On occasion, patients who are on anticoagulants require reversal strategies, such as when major bleeding events occur, or emergency procedures are necessary (Table 1).[17] While it is important to note that only animal studies and anecdotal reports have been reported for NOAC reversal strategies so far,[24] haemodialysis can be used for dabigatran-related events, but may not be feasible under emergency situations, whilst fresh frozen

plasma (FFP) or activated factor VIIa should not be used for NOACs. Four factor prothrombin complex concentrates have been reported for Xa inhibitors and the activated form could be used for dabigatran-related major bleeding; however, the efficacy evidence is limited. Interestingly, a recent analysis compared the bleeding outcomes from five Phase III clinical trials involving dabigatran. While the dabigatran group received significantly more red cell transfusions and fewer FFP transfusions compared with the warfarin arms, there were no significant differences found regarding the number of patients who were hospitalised or died within 30 days.[25] Similar results were also found in the ROCKET AF trial.[26]

Reversal therapies currently under investigation include an anti-dabigatran antibody (aDabi-Fab), which is in Phase III trials in healthy volunteers.[27] aDabi-Fab immediately reverses the effects of dabigatran for 24 hours and is renally eliminated. Promisingly, no detectable immunogenicity against the antibody was noted. Andexanet alfa is a modified, inactive, recombinant Xa reversal agent that binds to Xa inhibitors and prevents their binding to endogenous Xa in the coagulation cascade. It is currently under assessment in Phase III trials by Portola. This recombinant protein was found to be safe, effective, and well tolerated in a Phase I trial of 32 healthy volunteers, and has been shown to reverse anticoagulation within 5 minutes with the effects lasting for 3 hours.[28] Finally, aripazine (PER977) is a small molecule that binds by charge effects to NOACs. Phase I trial results reported the reversal of edoxaban effects within ~10 minutes after an intravenous injection of aripazine, the effect of which lasted for 24 hours.[29,30] The effect of aripazine was dose dependent and the drug was well tolerated.

In summary, although NOACs are more convenient than VKAs, active management is still required, and physicians should be aware of the multiple doses available per indication. Challenges of NOACs include the limited number of appropriate monitoring assays to measure the drug effect and the absence of a currently approved antidote, even though there is controversy over the necessity of such therapies.

Closing Remarks

Professor John Camm

Recent data indicate that NOACs provide a convenient alternative to warfarin in patients with AF, and may provide an alternative to warfarin for patients undergoing cardioversion, although more prospective data are required. However, while therapy with NOACs is simpler, some active management is still required under certain circumstances, although drug monitoring is rarely required. In particular, analyses of the ENGAGE AF-TIMI 48 trial have shown that modification of the edoxaban dose, based upon clinical characteristics, can prevent bleeding events in patients for whom the anticipated plasma concentration of edoxaban would be higher.

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MEETING THE CHALLENGES IN ATRIAL FIBRILLATION MANAGEMENT: THE ROLE OF NEW ANTICOAGULANTS

Summary of Presentations from the Daiichi Sankyo Satellite Symposium, held at the Annual ESC Congress, Barcelona, Spain, on 1st September 2014

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MEETING SUMMARY

Prof Gregory Lip opened the symposium with a discussion on determining stroke and bleeding risk in atrial fibrillation (AF) patients and their management. Prof Raffaele De Caterina presented data from the PREFER in AF registry and trends in the management of AF across Europe. Dr Robert Giugliano concluded with a presentation of the latest data from the ENGAGE AF-TIMI 48 trial.

Balancing the Risk of Stroke and Bleeding in the Treatment of Patients with AF

Professor Gregory Lip

The management of AF patients involves a careful balance of the risk of stroke and bleeding. Therefore, it is important that the risk assessment of both these factors is determined as accurately as possible. Traditionally the older $CHADS_2$ score has been used to assess high-risk patients who would benefit from vitamin K antagonist (VKA) (including warfarin) therapy.[1] The $CHADS_2$ score is calculated by adding one point for each of the following conditions: recent congestive heart failure, hypertension, aged ≥75 years, diabetes mellitus, and two points for stroke or transient ischaemic attack (TIA).[1] The higher the $CHADS_2$ score, the greater the risk of stroke. However, there are limitations to the $CHADS_2$ scoring system as many common risk factors are not accounted for within the $CHADS_2$ score. This has been demonstrated by several large observational

cohort studies. For example, a Swedish AF cohort study that assessed >182,000 patients showed that age is a very powerful driver of stroke risk, where those aged 65–74 years have nearly a 3-fold increase in the risk of stroke and those aged 75 years and above have a 5-fold increase.[2] Other factors that confer an increased risk of stroke include female gender (HR 1.17; 95% CI 1.11–1.22), prior stroke (HR 2.87; 95% CI 2.74–3.01), hypertension (HR 1.17; 95% CI 1.11–1.22), and diabetes (HR 1.19; 95% CI 1.13–1.26).[2]

The CHA_2DS_2-VASc score, which is now the recommended risk score in many guidelines, is more accurate than the $CHADS_2$ score at determining low-risk patients.[3-5] Olesen et al.[5] showed that patients with a $CHADS_2$ score of 0 have an annual stroke rate in the region of 1.67% per year. However, based on the CHA_2DS_2-VASc score, the 'low-risk' patients have a stroke rate of 0.78% per year, which is almost that of the general population.[5] In relation to high-risk patients, the C-statistic gave a value of 0.72 for the $CHADS_2$ score but a value of 0.85 for the CHA_2DS_2-VASc, indicating that the CHA_2DS_2-VASc was more discriminating.[5] In addition, a Danish nationwide cohort assessed >17,000 patients with a $CHADS_2$ score of 0.[6] Applying the CHA_2DS_2-VASc score to this population gives a stroke rate ranging from 0.8% per year to as high as 3.2% per year.[6] This shows that a $CHADS_2$ score of 0 does not guarantee that a patient is at low risk as there may be some patients with a stroke risk as high as 3%, thereby potentially putting patients at risk of experiencing a stroke.

The risk of bleeding in patients can also be estimated by analysing bleeding risk factors in a fashion similar to the assessment of stroke risk. In 2010, the HAS-BLED score was proposed[7] and features in the European guidelines as well as other national guidelines.[8] The HAS-BLED score takes into account hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio (INR), old age, and drugs/alcohol.[7,9] A high HAS-BLED score corresponds to a high bleeding risk. However, current guidelines recommend that a high HAS-BLED score is not a contraindication to anticoagulant therapy, but rather highlights that a patient may be at potential risk of increased bleeding and require careful review and follow-up. A comparison of the HAS-BLED score with other bleeding risk schemas show that the HAS-BLED score is more accurate than the $HEMORR_2HAGES$ and ATRIA scores in terms of predicting the risk of serious bleeding.[10] In fact, the HAS-BLED score is the only bleeding risk score that reliably predicts intracranial bleeding.[10]

Can the $CHADS_2$ or the CHA_2DS_2-VASc scores be used to predict bleeding? As the $CHADS_2$ or the CHA_2DS2-VASc score increases, the bleeding rate also increases, but not significantly so.[11] The C-statistic shows that HAS-BLED outperforms both $CHADS_2$ and CHA_2DS_2-VASc to predict serious bleeding.[11] Thus, the prediction of serious bleeding should be assessed using a specific bleeding score such as HAS-BLED; similarly, stroke risk should be measured using a specific stroke risk score, such as CHA_2DS_2-VASc.[11]

The 2012 ESC guidelines for the management of AF emphasise identifying truly low-risk patients, instead of focusing on the identification of high-risk patients.[8] They also include recommendations that male patients with a CHA_2DS_2-VASc score of 0, and women with a score of 0 or 1, do not receive any antithrombotic therapy. For those that do receive antithrombotic therapy, the ESC guidelines recommend the use of non-VKA oral anticoagulants (NOACs) compared with VKAs.[8] Similarly, the NICE guidelines clearly state to use the CHA_2DS_2-VASc score to assess stroke risk and the HAS-BLED score to assess bleeding risk.[12] Anticoagulation therapy should be offered to patients with AF and additional stroke risk factors. Aspirin monotherapy is not recommended for stroke prevention or people with AF, as evidence indicates that aspirin is virtually ineffective for stroke prevention.[8]

The use of warfarin requires extensive monitoring and effective anticoagulant control. In fact, patients who spend ≥70% of time in therapeutic range (TTR) have been found to have a 79% reduced risk of stroke compared with patients with a TTR of ≤30%.[13] The use of warfarin or VKAs is acceptable providing that TTR remains above 70%, as recommended in the ESC guidelines.[8] However, maintaining patients at this level of TTR is challenging as shown by a national study in the USA that reported an overall mean TTR of 53%.[14]

In order to avoid the limitations of long-term anticoagulation therapy with VKAs, the NOACs were developed and studied in extensive clinical trial programmes. A meta-analysis of Phase III trials compared all four NOACs with warfarin.[15] This analysis showed that the NOACs have a favourable risk–benefit profile and were non-

inferior to warfarin for the prevention of stroke and systemic embolism (Figure 1).[15] The NOACs were also associated with a lower rate of major bleeding (Figure 1).[15]

Patient attitudes towards any chronic treatment are very important. A recent study investigated patient attitudes towards stroke prevention and bleeding and found that the majority of patients would like to avoid a stroke and were willing to sustain approximately four major bleeds rather than endure the potential long-term effects of a stroke episode such as disability, incontinence, and the need to be looked after continuously.[16]

In conclusion, patients with AF are now assessed for both stroke and bleeding risk, and the landscape for stroke prevention in AF is rapidly changing. The HAS-BLED score may be used to identify those at risk of bleeding, whereas the CHA_2DS_2-VASc score may be applied to identify 'truly low-risk' patients.

Implementing Treatment Guidelines in Clinical Practice: Insights from the PREFER in AF Registry

Professor Raffaele De Caterina

As the landscape in oral anticoagulation for stroke prevention in AF is changing, it is important to understand how treatment guidelines are being implemented in clinical practice. The current ESC guidelines for the management of AF recommend a NOAC for the prevention of thromboembolism in non-valvular AF.[8] Prevention of thromboembolic events – European Registry (PREFER) in AF was a prospective, observational, multicentre study which was designed to determine how patients with AF are currently managed in Europe.[17] The study was conducted in seven European countries (Spain, France, UK, Italy, Germany, Switzerland, and Austria). A total of 7,243 consecutive patients were enrolled from January 2012 to January 2013. Subjects had to be >18 years of age and have a history of AF.

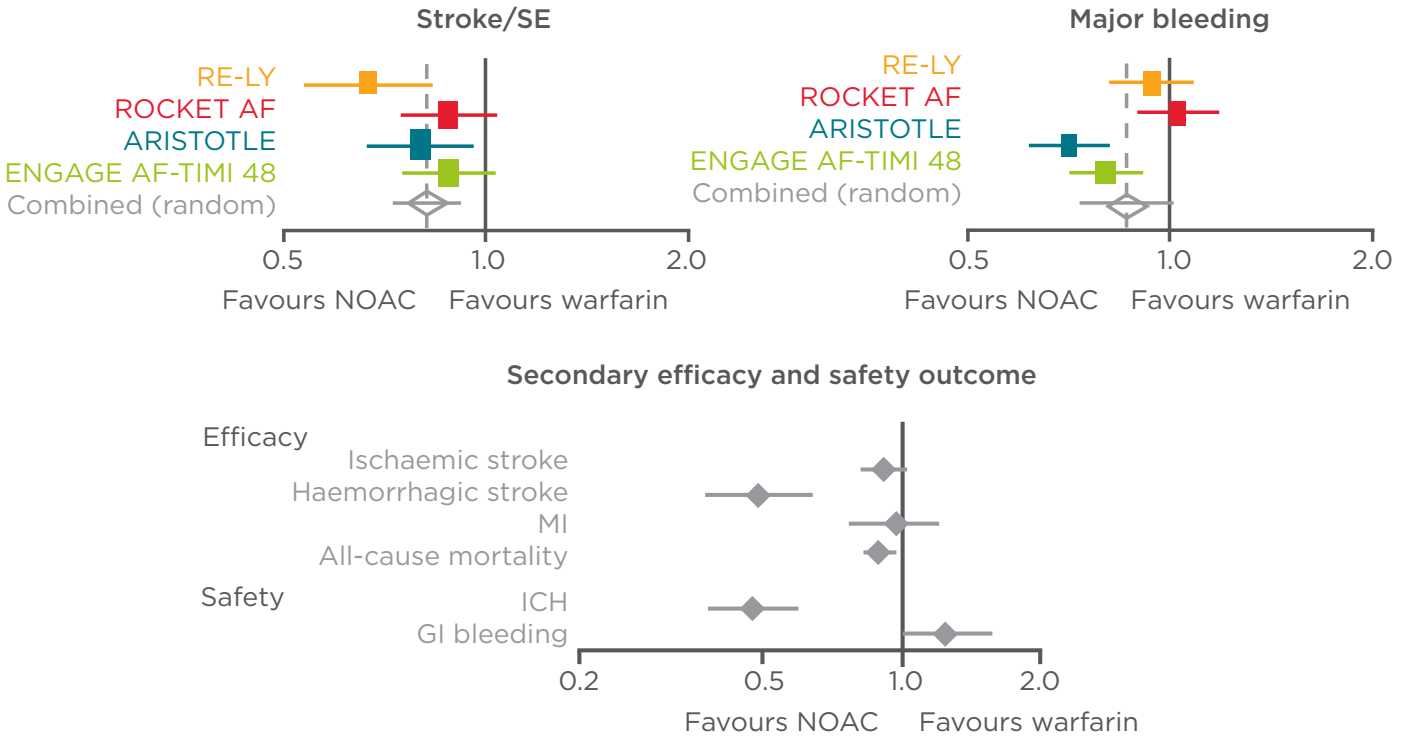

Figure 1: Efficacy and safety of 4 high-dose NOACs versus warfarin: meta-analysis of Phase III trials. Ruff CT et al.[15]

GI: gastrointestinal; ICH: intracranial haemorrhage; MI: myocardial infarction; NOAC: new oral anticoagulant; SE: systemic embolism.

Reprinted from The Lancet, 383, Ruff CT et al. Comparison of the Efficacy and Safety of New Oral Anticoagulants with Warfarin in Patients with Atrial Fibrillation: a Meta-analysis of Randomised Trials, 955–62. Copyright (2014), with permission from Elsevier.

Patients were assessed at baseline and at a 1-year follow-up visit.[17] Enrolled patients had similar stroke and bleeding risks at baseline.

In order to assess whether there had been a change in the pattern of the management of AF, the results of the PREFER in AF registry were compared with the EuroHeart survey, a registry that was conducted before the introduction of the ESC 2010 guidelines.[18] The results show that since the introduction of the ESC guidelines, there is an increased use of NOACs as well as VKAs, especially in high-risk patients, which is in accordance with the new guidelines (Figure 2).[17,18] The results also showed that with increasing CHA_2DS_2-VASc score, more patients received a VKA or a VKA with an antiplatelet agent.[19] However, a higher HAS-BLED score was associated with fewer patients who received VKAs alone, and an increasing proportion received a VKA with an antiplatelet agent or an antiplatelet agent alone. This analysis showed that physicians may prescribe oral anticoagulants (OACs) less frequently in patients with a very high risk of bleeding.

In the PREFER in AF registry, approximately 10% of patients received combined therapy at baseline,[20] despite combination treatment with an antiplatelet and antithrombotic agent not being recommended in the ESC guidelines, due to the increased risk of bleeding events.[8,20] Furthermore, in the PREFER trial, out of 660 patients who received an antiplatelet plus OAC, as many as 95.3% were estimated to be inappropriately treated with this combination treatment.[20] Similarly, 63.8% of inappropriate prescribing was found in 105 patients who received triple therapy with an OAC, aspirin, and clopidogrel.[20] These findings indicate that not all physicians currently follow the recommended guidelines which state that vascular disease and AF can be treated with OACs alone in most patients. The reason is that OACs are not only effective at preventing stroke in AF, but also myocardial infarction (MI) and vascular disease.[8]

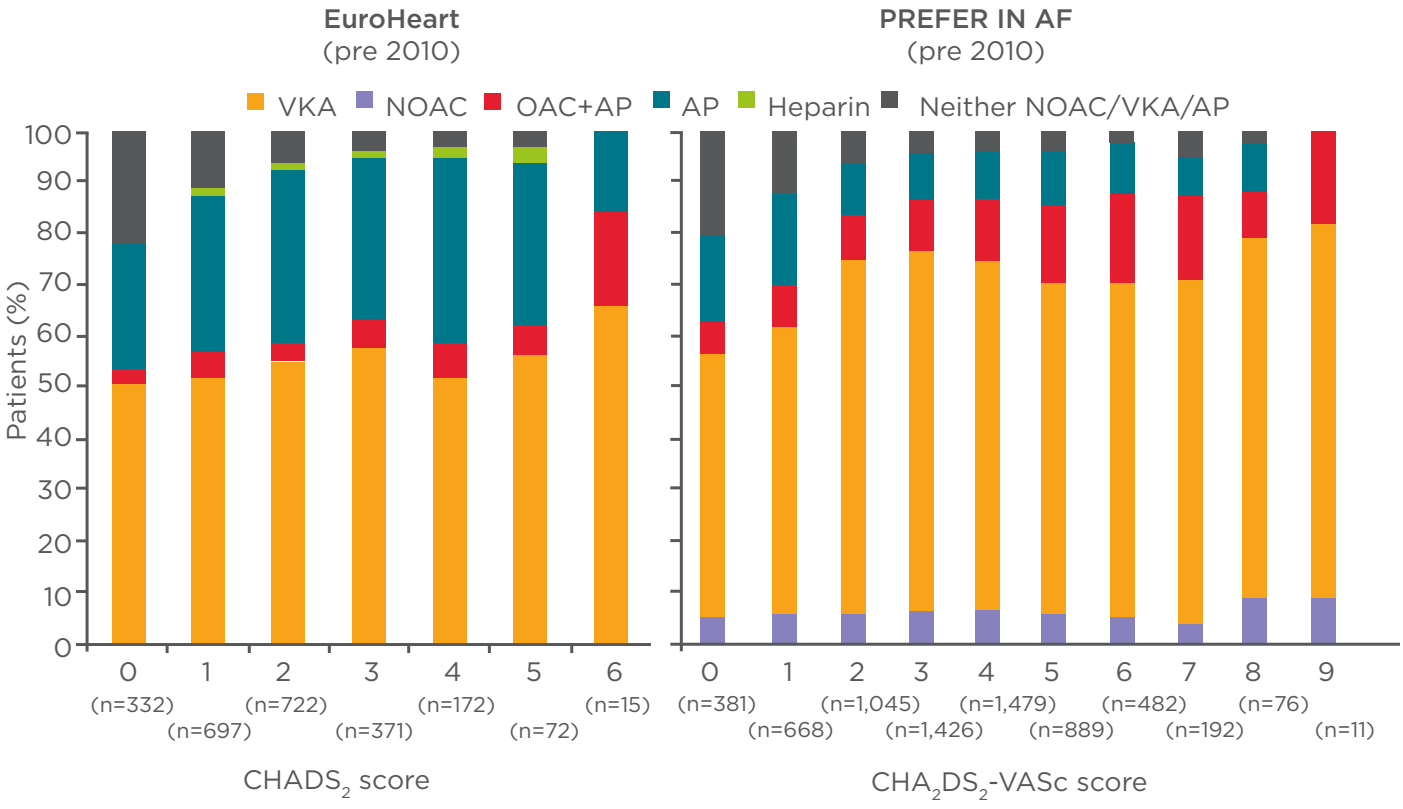

Figure 2: EuroHeart and PREFER in AF: Improved anticoagulation by CHADS2/CHA2DS2-VASc over time.[17,18]

AP: antiplatelet; NOAC: new oral anticoagulant; OAC: oral anticoagulant; VKA: vitamin K antagonist.

Nieuwlaat et al. Antithrombotic Treatment in Real-life Atrial Fibrillation Patients: A Report from the Euro Heart Survey on Atrial Fibrillation. European Heart Journal. 2006;27:3018-26. By permission of Oxford University Press.

There is evidence that combination treatment can also result in an increased risk of bleeding.[21] The latest analyses from the PREFER in AF registry indicate that combination treatment is prescribed less frequently since the 2012 ESC guidelines.[21] Other trends include a slight decline in the prescription of VKAs and a rise in the prescription of NOACs.[21] It is expected that these trends may continue for several years.

The patterns of prescription of OACs and their management are inconsistent across Europe as different OACs are used in different countries. For example, phenprocoumon is frequently used in Germany, Austria, and Switzerland, fluindione is common in France, acenocoumarol is largely used in Spain, and warfarin is commonly used in the UK and Italy.[17] Importantly, the INR control appears to be better in Western Europe than other parts of the world.[22] Despite this, the perception of physicians towards the quality of anticoagulation treatment does not correspond with recommendations, as it was found in the PREFER in AF study that they have a tendency to overestimate the quality of anticoagulation.[23]

The PREFER in AF registry also assessed quality of life in terms of patient satisfaction with, and convenience of, treatment using the Perception of Anticoagulant Treatment Questionnaire (PACT-Q). In general, treatment satisfaction was reasonably good (63.4±15.9).[24] NOACs were preferred to VKAs for both treatment satisfaction (NOACs versus VKAs; 66.1±16.6% versus 63.2±15.9%) and convenience (NOACs versus VKAs; 88.1 versus 82.1%).[24] There was also very little difference in satisfaction between OACs and antiplatelet agents.[24] Treatment satisfaction and quality of life factors were the main reason for patients to switch from one treatment modality to another.

These results show that treatment guidelines have shaped the way OACs are used to help prevent stroke in AF, with a clear trend towards greater use of OACs in those at higher risk of stroke. NOAC uptake has also increased since 2012, and it is likely that this trend will continue for the next few years.

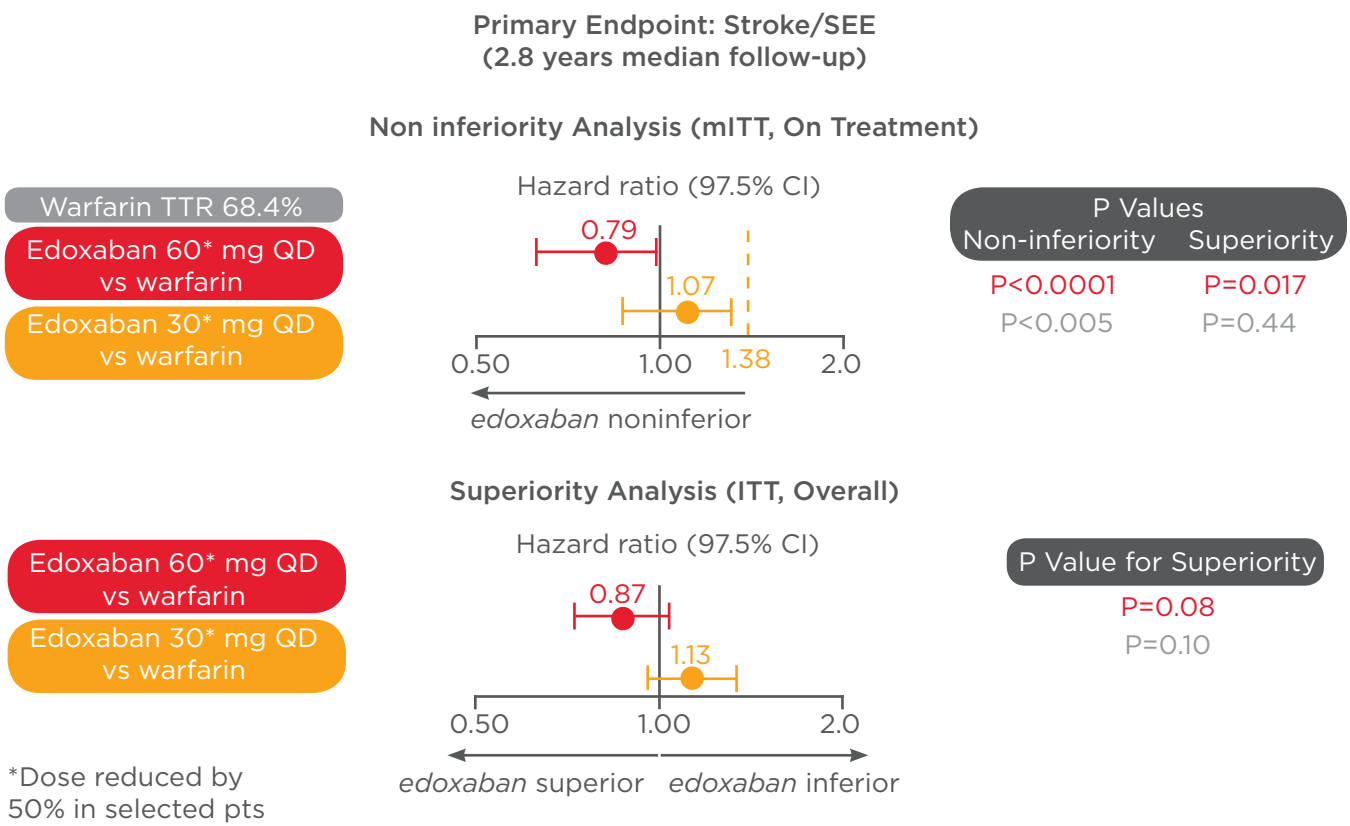

Figure 3: Non-inferiority and superiority analysis for the primary endpoint of stroke or systemic embolism.
CI: confidence interval; ITT: intention to treat; SEE: systemic embolic event; QD: once-daily.
Data taken from Giugliano RP et al.[26]

What does ENGAGE AF-TIMI 48 add to the Management of Patients with AF?

Professor Robert Giugliano

The ENGAGE AF-TIMI 48 trial was conducted in almost 1,400 centres in 46 countries worldwide.[25] The trial was a randomised, double-blind, double-dummy study comparing two once-daily regimens of edoxaban with warfarin in 21,105 patients with AF and a $CHADS_2$ score of ≥2.[25] Subjects were randomised to one of three treatment arms; either warfarin, high-dose edoxaban (60 mg once-daily [QD]), or low-dose edoxaban (30 mg QD). Patients in both edoxaban groups were dose reduced by 50% if they were at risk of overexposure and satisfied one of the following criteria: creatinine clearance of 30–50 mL/min, ≤60 kg in weight, or taking a strong P-glycoprotein inhibitor.[25] Each edoxaban regimen was tested for non-inferiority to warfarin during the treatment period.[25] The primary efficacy endpoint was stroke or systemic embolism, and composites of ischaemic events were also assessed. The principal safety endpoint was major bleeding as defined by the International Society on Thrombosis and Haemostasis criteria.[25]

Of the patients enrolled, 99.6% received the study drug with follow-up completed in 99.5%.[26] <9% of patients per year came off the study drug and <1% withdrew consent.[26] Median follow-up was 2.8 years. In the warfarin comparator arm, a median TTR of 68.4% was achieved with one-quarter of the patients achieving a TTR above 77%, showing that the patients were well controlled on warfarin in this trial.[26] Both doses of edoxaban were shown to be non-inferior to warfarin for the primary endpoint of stroke or systemic embolism (60 mg: p<0.0001; 30 mg: p=0.005).[26] In the superiority analysis, the high-dose regimen of edoxaban had a HR of 0.87 (p=0.08), whereas the lower-dose regimen had a HR of 1.13 (p=0.10) (Figure 3).[26]

In terms of the secondary endpoints, haemorrhagic stroke was reduced with the higher-dose regimen and markedly reduced with the lower-dose regimen, compared with warfarin.[26] Protection against ischaemic stroke was the same between the high-dose group and warfarin, whereas the lower-dose group was less effective than warfarin.[26] The rates of all three prespecified secondary composite outcomes were significantly lower with high-dose edoxaban than with warfarin.[26] There was no difference in MI rates between either dose regimen of edoxaban and warfarin.[26] Major bleeding, which was the primary safety outcome, was reduced by 20% and 50% in the higher-dose and lower-dose regimen, compared with warfarin, respectively.[26] Similarly, both dose regimens were associated with a reduction in fatal bleeding and intracranial haemorrhage in comparison with warfarin.[26] Although the lower-dose edoxaban regimen had a lower rate of gastrointestinal bleeding than warfarin, a 23% relative increase was observed in the high-dose group, compared with warfarin.[26]

An analysis of net clinical outcomes was also conducted, where efficacy and safety were combined with mortality outcomes.[26] The primary net clinical outcome of stroke, systemic embolic event (SEE), death, and major bleeding, was reduced by 11% and 17% in comparison to warfarin for the high and low-dose regimen, respectively.[26] Other composites, including disabling stroke, life-threatening bleeding, or death, as well as stroke, SEE, life-threatening bleeds, or all-cause mortality were similarly reduced for both dose regimens of edoxaban.[26]

Since the initial publication of ENGAGE AF-TIMI 48, there have been additional analyses of stroke and intracranial haemorrhage, as well as preliminary findings on the relationship between edoxaban drug concentration, factor Xa levels, and outcomes. With regard to haemorrhagic stroke, there is a marked reduction in risk with both dose regimens of edoxaban in comparison with warfarin. This reduction was observed as quickly as 6 months from treatment initiation, and the reduction in risk was maintained over 3 years.[27] Further analyses also showed that both dose regimens of edoxaban reduced different subtypes of intracranial haemorrhage compared with warfarin.[27] A small number of haemorrhagic transformations and micro-haemorrhages were observed; however, these are less likely to result in death compared with other intracranial haemorrhages.[27]

The rate of ischaemic stroke was similar with high-dose edoxaban and warfarin; however, the lower-dose edoxaban group had a higher rate of ischaemic stroke.[27] Notably, within the first 30 days, during which patients are deemed to be at higher risk, there is no difference between the three treatment arms.[27] Annualised rates of stroke and TIAs showed that the higher-dose regimen of edoxaban was non-inferior to warfarin in the prevention of ischaemic stroke plus TIA, and that the lower-dose regimen was less effective

than warfarin.[27] The same result was found when applying an updated definition of stroke, which incorporated both clinical and tissue criteria.[27]

Additional findings were also available for anti-factor Xa activity and edoxaban drug concentration. Although there were two dosing regimens, four doses of edoxaban were actually studied (15 mg reduced from 30 mg or 30 mg reduced from 60 mg in patients at increased bleeding risk, 30 mg and 60 mg). Anti-factor Xa activity gradually increased from lower to higher doses of edoxaban.[28] The effects of these dose reductions on stroke or SEE and major bleeding were assessed. In the non-dose reduced group, high-dose edoxaban was more effective at preventing stroke or a SEE than warfarin. In contrast, lower-dose edoxaban was less effective than warfarin.[28] In the population who were dose reduced, the event rates were higher in each of the three arms, including an increase from 1.5-2.9% per year in the warfarin group. However, the relationship remained the same, with the high-dose edoxaban group associated with the lowest risk of primary events, compared with the other two treatment arms.[28]

In terms of major bleeding, a stepwise reduction was observed in the non-dose reduced group from warfarin to high-dose to low-dose edoxaban, with the low-dose group exhibiting a significant reduction in major bleeding ($p<0.001$).[28] The dose-reduced group displayed a higher risk of bleeding overall; the warfarin group showed an increase in major bleeding events from 3.02-4.85% per year.[28] However, both the higher and lower-dose groups displayed a significant protective effect compared with warfarin (high dose versus low dose; 3.05 versus 1.5%).[28]

The results from ENGAGE AF-TIMI 48 showed that in comparison with well-managed warfarin (TTR ≥68%), once-daily edoxaban is non-inferior for the prevention of stroke and systemic embolism. Both edoxaban regimens significantly reduced major bleeding, intracranial haemorrhage, haemorrhagic stroke, and cardiovascular death, with both doses of edoxaban also achieving superior net clinical outcomes.

Summary

Treatment of AF patients requires a careful balance between the risk of stroke and bleeding, with guidelines recommending the use of scores to help in assessing the risk–benefit ratio. The updated ESC guidelines also recommend the use of OACs, and increased uptake has been observed across Europe, although VKAs still remain the most commonly used antithrombotic treatment. Recent data from the ENGAGE AF-TIMI 48 trial have also shown both once-daily regimens of edoxaban were non-inferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

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PREMATURE HEART ATTACKS: BAD LIFESTYLE, BAD LUCK, OR BAD GENES?

Summary of Presentations from the Aegerion Pharmaceuticals-Supported Symposium, held at the Annual ESC Congress, Barcelona, Spain, on 1st September 2014

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ABSTRACT

Homozygous familial hypercholesterolaemia (HoFH), a rare inherited lipid disorder usually caused by bi-allelic defects in the *LDLR* gene, is characterised by marked elevation in low-density lipoprotein -cholesterol (LDL-C). Aggressive, early intervention with lipid-lowering therapy is warranted in patients with HoFH, and the recent introduction of new drug treatments including lomitapide and mipomersen has enabled physicians and their patients to achieve lower LDL-C levels than previously possible in this hard-to-treat condition. Understanding the overall impact of new interventions in HoFH requires a correct assessment of the true prevalence of the disease. Although it is rare, emerging studies suggest that HoFH may be more common than previously thought. We have reviewed data on the epidemiology and management of HoFH, with a focus on raising awareness on this condition so that clinicians can be made aware of the potential for genetic causes for presentation with premature cardiovascular disease. As classic clinical characteristics may be absent in HoFH patients, genetic status and/or family history should be part of the assessment of patients with significantly elevated LDL-C and premature atherosclerosis with a premature heart attack or clinical complications. As direct outcomes data for new treatments for HoFH are not yet available, intermediate phenotypes of arterial structure and function are being studied as endpoints in clinical trials. Novel therapies which enable lowering of LDL-C to levels that were, until recently, unachievable, have the potential to alter cardiovascular morbidity and mortality in this high-risk group of patients.

Keywords: Homozygous familial hypercholesterolaemia, prevalence, incidence, myocardial infarction, cardiovascular outcomes, premature mortality, lipid-lowering therapy, lomitapide, mipomersen.

INTRODUCTION

Patients with homozygous familial hypercholesterolaemia (HoFH) have extremely high cholesterol levels, and without treatment these patients often die from clinical complications of early atherosclerosis (AS) by the second decade of life.[1] Lifetime exposure to elevated levels of low-density lipoprotein cholesterol (LDL-C) drives premature AS and increases the likelihood of clinical events which can manifest in childhood or adulthood.[2,3] In addition to cardiac disease, aortic root disease with supravalvular aortic stenosis is a particularly feared complication.[2] Aggressive, early intervention with lipid-lowering therapy is warranted in patients with HoFH, and the introduction of new treatment options has led to the achievement of lower LDL-C levels. Although direct outcomes data for novel licensed therapies or agents in development are not yet available, intermediate phenotypes of arterial structure and function are being studied as endpoints in clinical trials.

Understanding the overall impact of new interventions in HoFH requires an appreciation of the real prevalence of the disease. Although it is rare, there is now evidence that HoFH may be more common than once thought. At the recent European Society of Cardiology (ESC) annual meeting in Barcelona, Spain, Aegerion Pharmaceuticals - a company that commercialises a product for HoFH (lomitapide) and is active in the research into the treatment of HoFH - sponsored a satellite symposium. The session was well attended by cardiologists, yet there remains a need to spread the message of this rare disease throughout the clinical community. In this article, we will reiterate the themes from the session at ESC and explore current thoughts on the epidemiology and management of HoFH, considering whether, for some patients with premature cardiac disease, there may be an underlying genetic cause.

WHAT IS THE TRUE PREVALENCE OF HOFH?

Although the incidence of sudden death in young people is relatively low, the majority of these deaths have been found to be of cardiac origin. In people aged <40 years, the incidence of sudden death in the general population has been estimated to be 2.07 per 100,000 person-years, and the incidence of sudden cardiac death to be 1.62 per 100,000 person-years.[4] These estimates were determined from death certificate data recorded by Statistics Netherlands from 1996-2006. From the reported data, it appears that AS may be the underlying pathology in approximately 40% of sudden deaths (Figure 1). As there is no dedicated International Classification of Diseases (ICD) code for 'sudden death', the authors first performed a literature analysis of causes of sudden death in the young, and from this they selected ICD-10 codes that could be used as a proxy for sudden death.

The question for cardiologists is clear: why are these young people developing cardiac conditions so early in life? To answer this question, a number of factors need to be considered. Sudden death may result from arrhythmia rather than myocardial infarction (MI). MI can be caused by a number of underlying conditions, of which atherosclerotic coronary disease is the most common. In young patients alternative conditions such as hypercoagulable states, recreational drug use, congenital coronary abnormalities, and coronary vasculitis all need to be considered.[5]

The aetiology of coronary heart disease (CHD) in young patients is generally different to that in older individuals. Importantly, there are genetic disorders that predispose young people to AS and consequent cardiac risk. A study of 200 patients (100 with premature CHD and 100 with late-onset CHD) revealed that while risk factors of smoking, hypertension, and diabetes were present in both groups, the largest proportional difference was for family history, which was evident in 39 of the younger patients versus only 11 of the older patients ($p<0.001$).[6] This study used a cut-off age of 45 years to define early versus late onset of CHD, and the findings provide a clue to the possible contribution of genetic abnormalities in LDL metabolism to death.

MI is a heritable phenotype and inheritance plays the greatest role in early-onset MI. Early-onset MI is associated with rare mutations in key

genes controlling lipid metabolism.[7,8] Deleterious mutations in the LDL-receptor and apolipoprotein A-V genes (*LDLR* and *APOA5*, respectively) occur significantly more frequently in early-onset MI patients than in non-MI controls.[6] The mutations in these genes are associated with elevations in LDL-C and triglycerides, respectively.[6] Among the diseases of lipid metabolism that can arise from genetic aberrations, heterozygous familial hypercholesterolaemia (HeFH) is the most prevalent, and is actually the most common autosomal dominant disease in man. It occurs when a mutation (usually in the *LDLR* gene) is inherited from one parent. HeFH can usually be managed adequately with statins (with or without ezetimibe), dietary modifications, and lifestyle changes.[9] However, HeFH has a sister condition, HoFH, in which defective genes controlling lipid metabolism are inherited from both parents. The genetic defect is usually, but not always, in the *LDLR* gene, and can also affect other genes controlling the LDLR pathway, such as *ApoB* and *PCSK9*.[2]

HoFH is a very severe disease characterised by extremely elevated LDL-C levels, xanthomas, and evidence of atherosclerotic valvular disease.[2] Historically, the incidence of HoFH in the general population has been estimated at 1:1,000,000.[2] However, these estimates were calculated from a 1973 study, which estimated the prevalence of HeFH based on the frequency of autosomal dominant hypercholesterolaemia among relatives of a small cohort of MI survivors.[10] Emerging studies suggest that the prevalence of HeFH, and consequently HoFH, may be higher than previously thought. For example, in a Dutch study that examined 104,682 medical records in the Netherlands' autosomal dominant hypercholesterolaemia database, 49 patients (0.05%) were identified as having HoFH.[9] Although mean lipid levels in these patients with molecularly defined disease were lower than generally assumed in HoFH patients, with mean (±SD) LDL-C level prior to lipid-lowering therapy of 12.9±5.1 mmol/L. These data place the estimation of the incidence of HoFH in the Dutch population at 1:300,000, and there are no logical reasons to suggest that this figure would not apply to the rest of Western Europe. In founder populations with little genetic admixture the incidence of HoFH is thought to be even higher.

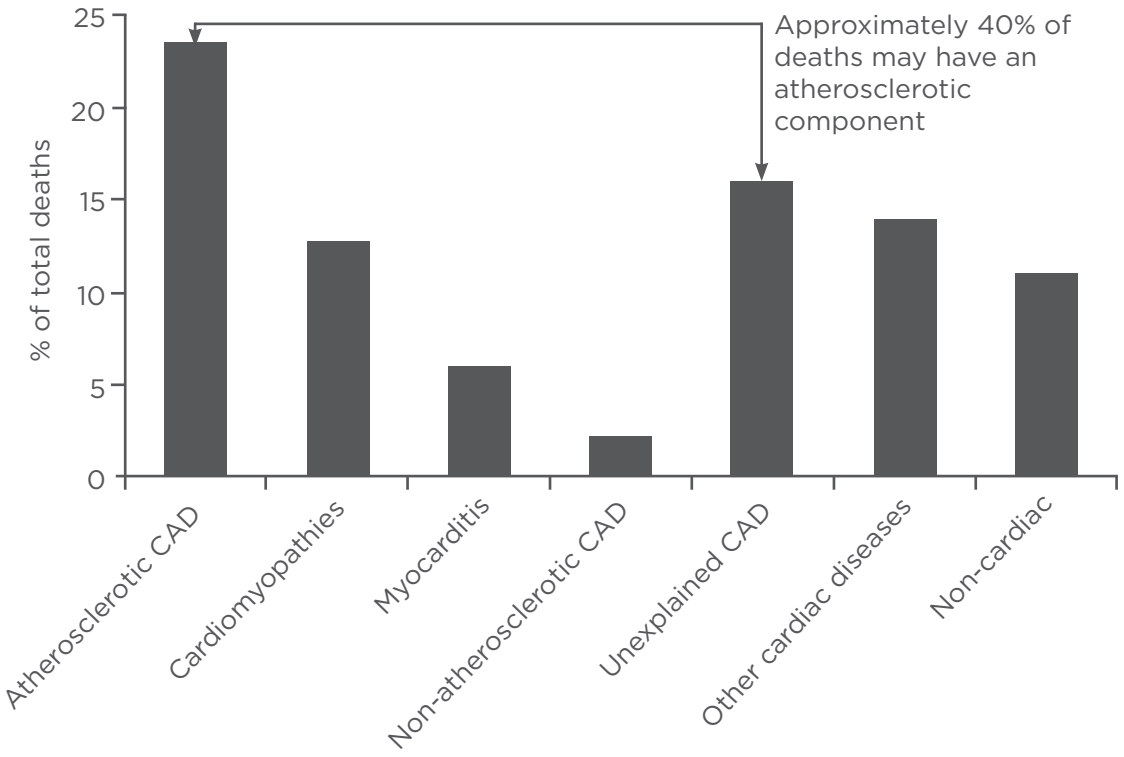

Figure 1: Incidence of SCD in a literature analysis of 17 publications, including 3,150 SCD victims <40 years old.

SCD: sudden cardiac death; CAD: coronary artery disease.

Adapted from Vaartjes I et al. Eur J Cardiovasc Prev Rehabil. 2009;16:592-96.[4]

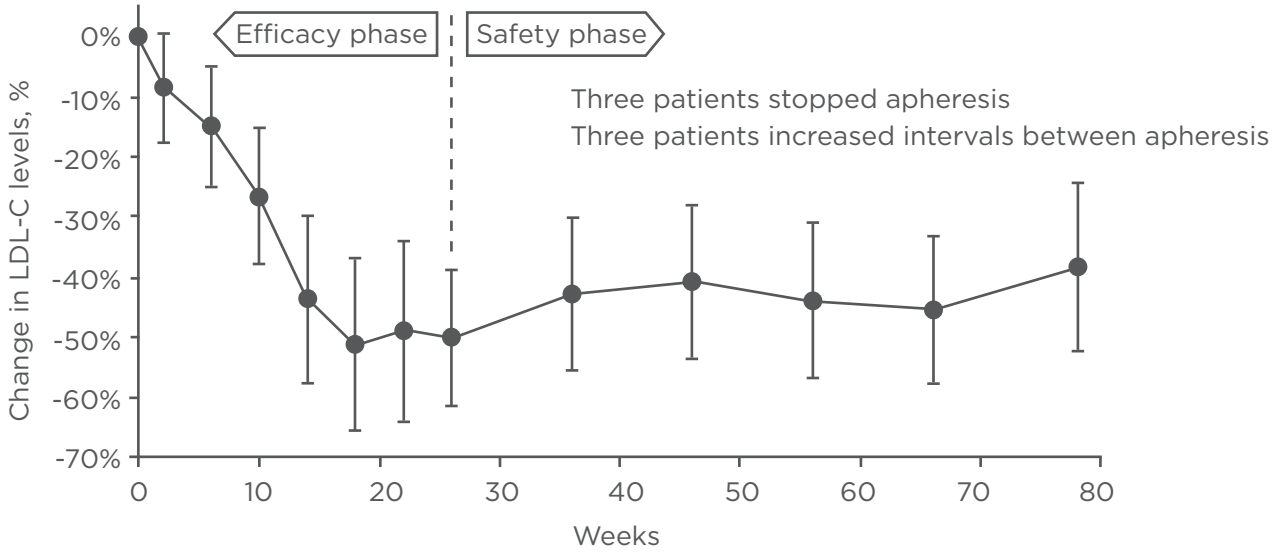

Figure 2: Mean change in low-density lipoprotein-C (LDL-C) from baseline (%) in lomitapide Phase III study.

Given that the global incidence of HoFH is likely to have been underestimated, it is ever more important to ask the right questions when a patient with significantly elevated LDL-C presents with a premature atherosclerotic disease or MI. Genetic status and/or family history should be part of the examination and workup. Classic features of HoFH may be absent in the patient phenotype, thus making genetic assessment even more important. LDL-C levels are classically >300 mg/dL, but examination of baseline characteristics of clinical trials in HoFH have revealed a much wider variation from 150–500 mg/dL.[11]

AFTER DIAGNOSIS OF HOFH, WHAT ARE THE TREATMENT OPTIONS?

Early and aggressive reduction of LDL-C is the foundation of the successful management of HoFH.[3,12] Prompt intervention with effective lipid-lowering therapies will reduce the lifelong exposure to elevated LDL-C, and thereby has the potential to improve outcomes. Treatment should be started immediately after diagnosis in infancy, but treatments that rely on a functioning LDL receptor may be of limited efficacy in HoFH patients.[13] Such treatments, which are frequently used with success in other forms of hypercholesterolaemia, include statins, ezetimibe, and bile acid sequestrants.[14] The limited success of pharmacotherapy for HoFH has established LDL apheresis as standard treatment; however, this mode of therapy is complex and expensive, and access is not universal.[15] The treatment challenges in HoFH have been highlighted by Raal et al.,[16] who reported findings in 149 patients with HoFH in clinics in Cape Town and Johannesburg. Although treatment with modern lipid-lowering therapies, available in 1990s, resulted in a 26% reduction in LDL-C and prolonged survival, lipid levels were still considerably higher than currently recommended targets, with life expectancy remaining considerably shortened.[3,16] A number of novel therapeutic approaches are being explored to fulfil the unmet medical need for additional HoFH treatments, including reduction of lipoprotein synthesis (lomitapide, mipomersen), upregulating LDL-receptor function (monoclonal antibodies against proprotein convertase subtilisin/kexin Type 9 [PCSK9]), and inhibiting cholesterol ester transfer protein (anacetrapib). Evacetrapib, lomitapide, and mipomersen have been approved by the US FDA for use in patients with HoFH,[17,18] and additionally lomitapide has received approval from the European Commission.[19]

Lomitapide

Lomitapide, an oral agent indicated for the treatment of adults with HoFH as an adjunct to low-fat diets and other lipid-lowering therapies (with or without apheresis), inhibits microsomal triglyceride transfer protein in enterocytes and hepatocytes and reduces synthesis of chylomicrons and very low-density lipoproteins (VLDL). In a Phase III, open-label, single-arm dose-escalation

study involving 29 patients with HoFH receiving lomitapide (median dose 40 mg/day), the mean LDL-C reduction at 26 weeks was 40% in the intent-to-treat analysis, and 50% in the patients who completed the first 26 weeks of the study (range 20-90%) and was maintained out to the end of the Phase III trial at 78 weeks (Figure 2).[17,19,20] The statistically significant reduction from baseline in LDL-C levels was maintained after 126 weeks of lomitapide treatment in 17 patients who participated in a long-term extension phase of the study.[20]

Lomitapide is active in the liver and intestine, and most prevalent adverse effects of lomitapide relate to its mechanism of action. High fat meals can provoke bloating, diarrhoea, and other gastrointestinal tract symptoms, and these can often be ameliorated by restricting dietary fat/triglyceride intake and dose titration.[17,19] Patients should receive dietary counselling before starting treatment with lomitapide. Adverse hepatic effects include altered liver function tests (such as increased plasma levels of transaminases) and liver fat accumulation. Altered liver function tests can generally be managed with dose interruption/reduction while hepatic fat content, as measured by nuclear magnetic resonance spectroscopy, generally stabilises over time.[17,19,20] In the Phase III study, four patients had alanine aminotransferase more than 5-times the upper limit of normal - all elevations were managed either by dose reduction or temporary interruption of lomitapide - and high alcohol intake was a contributory factor in three of the four cases.[20] It is also important for patients and healthcare professionals to be vigilant for potential drug-drug interactions and to follow liver monitoring recommendations.[17,19]

A worldwide observational registry study of lomitapide (Lomitapide Observational Worldwide Evaluation Registry; LOWER) is currently recruiting patients, and will document the real-world efficacy and safety of lomitapide. LOWER is now established in the US, Europe, Canada, Taiwan, Brazil, and Argentina. As of the time this manuscript was finalised, 54 patients were enrolled; 300 enrolled patients are expected by March 2018. A vascular imaging sub-study of the LOWER registry (CAPTUre) will evaluate aortic and carotid AS by magnetic resonance imaging (MRI) at baseline and years 1, 2, and 5. Lomitapide is currently only licensed for use in adults,[17,19] but a study involving children and adolescents is expected to commence recruitment in late 2014. In common with the adult Phase III trial, the study will have an efficacy and a safety phase; however, in contrast with the pivotal trial, the efficacy phase of the paediatric study will be placebo-controlled, with all patients switching to lomitapide in the safety phase. Also, importantly, the paediatric study will include the results of vascular imaging procedures as surrogate outcomes endpoints.

Mipomersen

Mipomersen is an antisense oligonucleotide that inhibits the transcription of apoB100 mRNA, thereby reducing VLDL synthesis. In the Phase III trial of mipomersen, the mean LDL-C reduction at week 26 achieved by HoFH patients treated with mipomersen 200 mg/week subcutaneously was 24.7% (range 2–82%).[21] Data from the long-term extension study showed that these reductions were sustained for up to 104 weeks.[22] The most common side-effects of mipomersen are injection site reactions, flu-like reactions, elevations in transaminases, and hepatic steatosis.[18] In common with lomitapide, mipomersen is being studied in a long-term patient registry. Mipomersen is only approved for use in the US. In the US, access to both lomitapide and mipomersen are covered by a Risk Evaluation and Mitigation Strategy (REMS) programme, which recognises the potential for drug-induced toxicity.

Therapies Currently in Development

Evolocumab, a monoclonal antibody directed against PCSK9, was evaluated in the TESLA trial,[23] which randomised 49 patients with HoFH to evolocumab (n=33) or placebo (n=16). Evolocumab resulted in a 23.1% reduction in LDL-C from baseline at week 12, which was a 30.9% reduction over placebo. Another PCSK9 inhibitor (alirocumab) has been studied as an agent to lower elevated LDL-C,[24] but has not been specifically evaluated in HoFH. A Phase III study evaluating the cholesteryl ester transfer protein inhibitor anacetrapib in HoFH (NCT01841684) was planned but never started.

Current Position and Future Direction

Significant therapeutic advances have been achieved for patients with HoFH, with mechanisms of action that decrease LDL production and increase LDL catabolism. Novel treatments may improve outcomes but currently there are no cardiovascular (CV) outcome data for novel therapies. The availability of outcomes data in HoFH will be hindered by the rarity of the disease,

and physicians should not wait for these data, but treat patients promptly with the current therapeutic armamentarium. Looking to the future, optimal management of HoFH may require multi-agent combinations, involving multiple lipid-lowering mechanisms at low doses, which will also hopefully minimise off-target toxicity.

WHAT WILL EFFECTIVE TREATMENT MEAN FOR THE HOFH PATIENT POPULATION?

An improved understanding of the molecular pathophysiology of HoFH has led to the development of promising new therapies in a disease that has been historically difficult to treat. Although there are as yet no direct data on CV outcomes and survival for any of the novel therapies, better management of LDL-C is anticipated to translate into improved CV outcomes. The lomitapide and mipomersen registries should provide additional information of this type.

Evidence from a South African cohort of 149 HoFH subjects has shown that cholesterol lowering with statins is associated with markedly improved survival.[16] However, assessing the benefits of treatments on outcomes in this way is challenging in such a rare disorder. Early intervention is required to maximise lifetime gains,[12] and intermediate phenotypes of arterial structure and function are therefore valuable as endpoints in clinical trials. Endothelial dysfunction is an early event in the process of atherogenesis, and endothelial function can be measured non-invasively from childhood. In children with FH, impairment of endothelial function has been found from the age of 7.[25] In HeFH, the rate of increase of carotid intima-media thickness, a measure of structure arterial disease, is also accelerated from the first decade of life. In children with HeFH, statin therapy has been shown to improve endothelial function and to slow or even reverse progressive arterial wall thickening.[26] More recently, the size, composition, and morphology of carotid plaques have been evaluated non-invasively using MRI.[27] Novel therapies that substantially lower LDL-C levels in addition to statins are being evaluated in terms of their effects on these endpoints. Patients receiving lomitapide who are enrolled in CAPTure, the vascular imaging sub-study of the LOWER registry, will be evaluated for aortic and carotid AS by MRI at baseline and at years 1, 2, and 5. Global recruitment is planned from Q1 2015, and the estimated sample size is 60.

In non-FH patients, a prospective meta-analysis of data conducted by the Cholesterol Treatment Trialists' (CTT) Collaborators concluded that, overall, for each mmol/L reduction in LDL-C achieved with statin therapy the 5-year incidence of major coronary events, coronary revascularisation, and stroke was reduced by about one-fifth.[28]

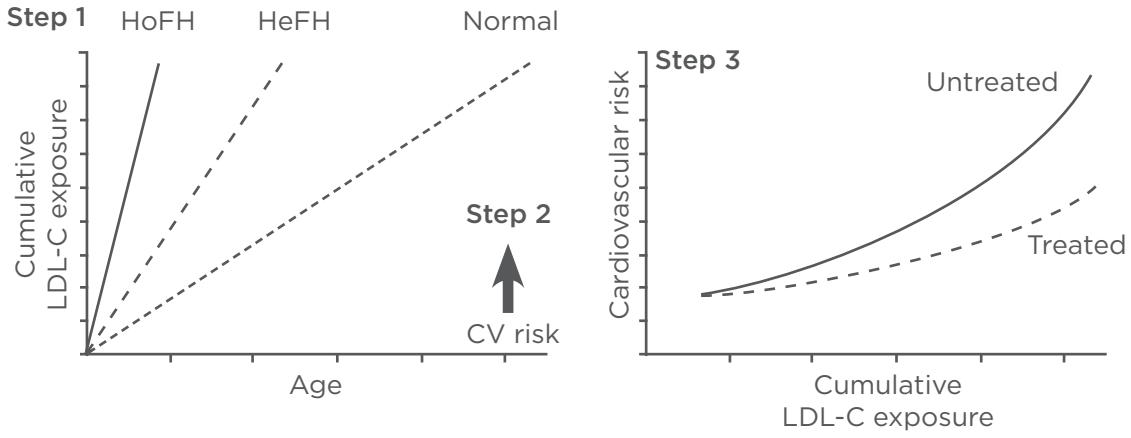

Figure 3: Development of a cumulative exposure model to predict survival benefits.
Step 1: Calculate cumulative LDL-C exposure as a function of age; Step 2: use the relationship between cardiovascular risk and cumulative LDL-C exposure to calculate cardiovascular risks as a function of age; Step 3: use the cardiovascular risks as a function of age to construct survival curves for untreated and treated scenarios.
HoFH: homozygous familial hypercholesterolaemia; HeFH: heterozygous familial hypercholesterolaemia; LDL-C: low-density lipoprotein-C; CV: cardiovascular.

Overall, statin therapy also produced a clear reduction in all-cause mortality. However, the CTT data underestimate survival benefits of cholesterol lowering in populations with genetic diseases such as FH. Exposure to risk factors over time is key, and in FH risk is driven by exposure to LDL-C. Thus, early intervention may prevent or delay the progression of atherosclerotic disease and improve the clinical benefit that is achievable with lipid-lowering therapies. In a meta-analysis of data from 312,321 participants, naturally random allocation to prolonged exposure to lower LDL-C levels beginning early in life was associated with a reduction in CHD risk of 54.5% per mmol/L (38.7 mg/dL) of LDL-C lowering.[29] This represents a 3-fold greater reduction in risk of CHD for each unit of LDL-C lowering than that observed with statin treatment started later in life.[29] This concept of 'cumulative exposure' and the leveraged lifetime gains from early risk factor lowering has been incorporated into the new UK JBS3 guidelines,[30] which provide CV prevention recommendations for the general population.

Although survival data are lacking, especially for the latest novel treatment approaches (lomitapide and mipomersen), modelling could be used to estimate the potential benefits of lipid-lowering therapy from an early age in rare diseases such as HoFH. A cumulative exposure model can be developed to try to predict the survival benefits of a new treatment; Figure 3 is an example of one possible way to do this. It would work as follows: first, cumulative LDL-C exposure as a function of age is calculated, and the relationship between CV risk and cumulative LDL-C exposure is used to calculate CV risks as a function of age. The CV risks as a function of age are then used to construct survival curves for untreated and treated scenarios.

In this new era, the development of novel therapeutic approaches has meant that lower LDL-C levels are becoming achievable. In many heterozygous patients with FH, combination therapy with statins and newer lipid-lowering therapies can result for the first time in normalisation of LDL-C levels. The impact of this approach in HoFH is currently being evaluated, and results of this research are so far very encouraging.

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IMAGING DURING TRANSCATHETER INTERVENTIONS FOR VALVULAR HEART DISEASE

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ABSTRACT

Valvular heart disease is a growing field, and the number of new approaches for percutaneous treatment is increasing rapidly. These procedures usually cannot be performed with fluoroscopy alone; allowing echocardiography to be an essential role inside the Cath Lab. Three-dimensional echocardiography, and the introduction of a novel imaging modality that integrates live echocardiography and live fluoroscopy imaging, has potential in facilitating procedure guidance and increasing procedure efficiency.

Keywords: Valvular heart disease, transcatheter aortic valve implantation (TAVI), percutaneous mitral valve repair, paravalvular leakage, 3D echocardiography, EchoNavigator.

INTRODUCTION

The prevalence of valvular heart disease (VHD) is increasing with the ageing of the population. Transcatheter interventions have merged as an option for patients who, due to comorbidities or high surgical risk, would have otherwise suffered untreatable conditions. Nowadays we can perform heart valve interventions such as transcatheter aortic valve implantation (TAVI), percutaneous mitral valve (MV) repair, or percutaneous closure of paravalvular leakages (PVL). Catheter-based approaches for patients with regurgitant as well as stenotic valvular disease have shown excellent procedural success and clinical outcomes.[1-4]

Echocardiography plays an important role not only in identifying patients suitable for these interventions, but in providing intra-procedural monitoring. This is necessary because for VHD interventions continuous soft tissue imaging is required, which cannot be achieved with fluoroscopy alone. Moreover, echocardiography is a non-radiation, non-contrast, and real-time technique. These features have turned echocardiography into an essential tool inside the Cath Lab.

Transoesophageal echocardiography (TEE) provides more detailed images of anatomy and lesions than transthoracic echocardiography (TTE) and does not interfere with the procedure´s sterile field; therefore, it is the most commonly used technique. The use of only two-dimensional (2D) TEE is limited in that it only provides two spatial dimensions having to mentally reconstruct the anatomical setting and is limited in knowing the relation of the lesion to be treated, catheters, and wires with its surrounding structures. Nowadays, 3D echocardiography (3DE) complements 2D echocardiography (2DE).[5-7] With 3DE, an anatomical structure can be seen from different perspectives in real-time, providing a better understanding of morphology and spatial relation of intracardiac structures.[8,9]

During VHD interventions, fluoroscopy for catheter and device visualisation and echocardiography for anatomy and soft tissue imaging are most frequently used. Recently, a new navigation system (EchoNavigator, Philips Healthcare, Best, the Netherlands) has been introduced which synchronises echocardiography and fluoroscopy in real-time. The system places the two imaging modalities in the same co-ordinate system and is based on the localisation and tracking of the TEE probe. After synchronisation of TEE and fluoroscopy images, the system automatically tracks and follows the movements of the c-arm gantry.

When the c-arm is moved, echocardiography images will be updated and reconstructed with the same orientation as the c-arm.

It allows the visualisation on one screen of an X-ray view and up to three echocardiography views simultaneously and in real-time: an echocardiography image in the same orientation as the c-arm gantry, the standard TEE echocardiography view as on the echocardiographer's screen, and a free image that can be rotated or cropped. The system also allows the placing of markers in real-time on specific points of interest on echocardiography images; these markers will be automatically displayed on the fluoroscopy image in real-time and can be used for guidance during the procedure.[10,11]

In this review we will describe the role of imaging during transcatheter interventions on VHD in the Cath Lab, focusing on 3DE and the new navigation system that integrates live 3D and live fluoroscopy images.

TAVI

The treatment of patients with aortic stenosis has been transformed after the introduction of TAVI, since it has shown to be an effective treatment for patients with severe aortic stenosis deemed high-risk for conventional surgery.[1] Detailed knowledge about the anatomy of the aortic root and its surrounding is crucial for a safe and precise procedure. Accurate pre-procedural aortic annular dimension measurements are important for the selection of an appropriate valve prosthesis size. Although 2DE seems to underestimate the size of the ellipsoid-shaped annulus,[12] 3D TEE has shown to be accurate in sizing the annulus, presenting the true annulus, and enabling assessment of its circularity and the measurement of its diameters.[13,14]

TEE imaging is useful for procedural guidance. During balloon valvuloplasty, TEE can guide positioning of the balloon relative to the aortic valve and confirm stable position during inflation, since the balloon may migrate during inflation, particularly in patients with significant septal hypertrophy. The behaviour of the calcified aortic cusps that are pushed into the sinuses and towards the coronary ostia during inflation may also be monitored using TEE. Visualisation of the guidewire into the left ventricle (LV) and around the MV subvalvular apparatus is facilitated with 3DE, reducing the likelihood of valvular disruption and regurgitation.

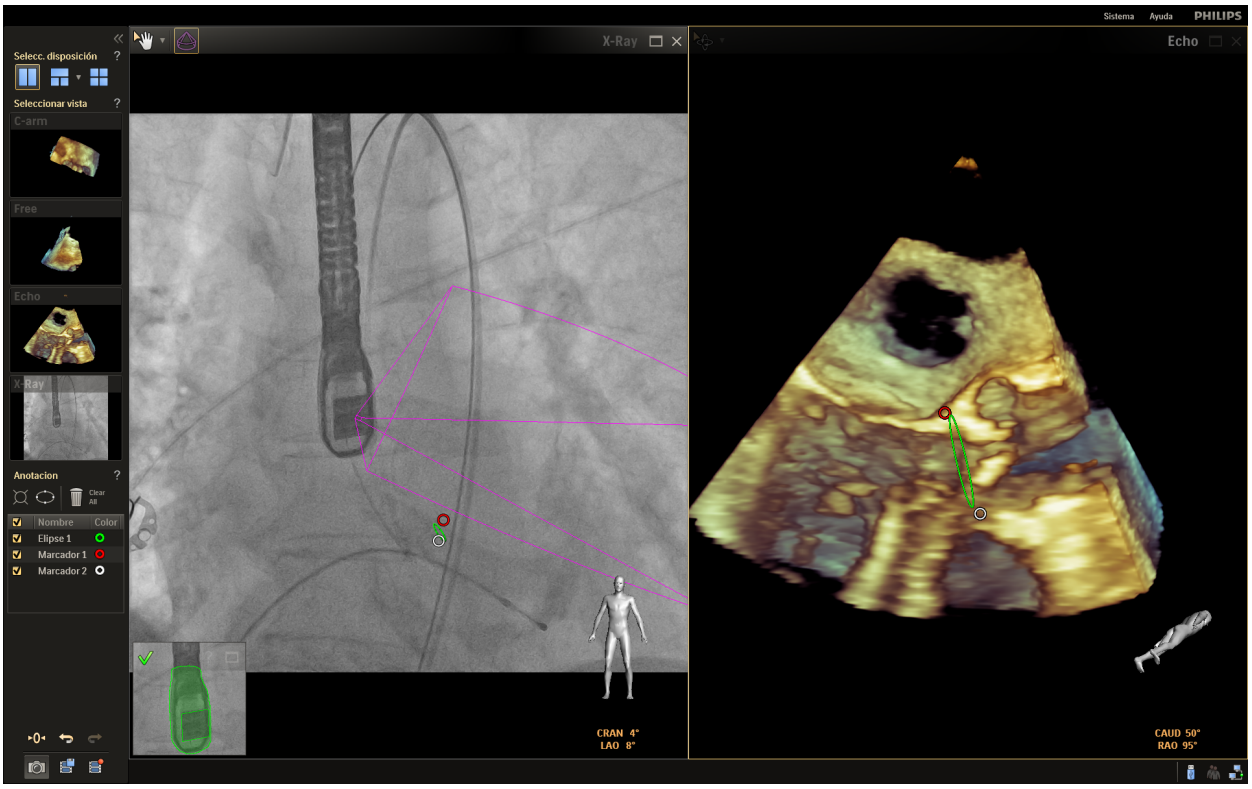

Figure 1: Transcatheter aortic valve implantation.
The level of the aortic annulus has been marked using EchoNavigator for procedure guidance.

During deployment of the prosthesis, TEE is very helpful in confirming the correct position of the valve and is usually used in conjunction with fluoroscopy for this purpose. Especially in patients with less calcified valves, where visualising the aortic annulus in fluoroscopy may be more challenging, the EchoNavigator system seems especially useful as the level of the annulus can be marked in an echocardiography image. These markers will be automatically transposed and set in the fluoroscopy image, allowing the use of this reference for catheter guidance and evaluation of prosthesis implantation depth (Figure 1).

Following deployment, the echocardiographer must rapidly and accurately assess the position and function of the prosthesis. The 3DE depth perspective allows better visualisation of the position of the prosthesis relative to the native valve annulus and surrounding structures.[15] It is important to confirm adequate movement of prosthetic cusps and that the valve stent has assumed a circular configuration. The presence of immediate complications such as pericardial effusion or aortic regurgitation must be identified. 3DE can be useful in the detection and quantification of paravalvular aortic regurgitation.[16,17]

PERCUTANEOUS MV REPAIR

MV repair using a percutaneous approach is currently performed using the MitraClip system (Abbott Laboratories, Abbott Park, IL, USA). This technique is able to alter the MV morphology, and reduce mitral regurgitation (MR). This catheter-based technique is similar to the Alfieri technique since it implants a Clip that holds the free edges of the mid portions of the anterior and posterior mitral leaflets together, reducing the degree of MR.[18] The MitraClip procedure has shown to be a feasible and safe alternative for patients ineligible for surgery.[19]

Echocardiography is the essential imaging modality, not only for selection of patients, but also during the intervention. The procedure is technically demanding, and fluoroscopy alone is not enough to guide the procedure as the MV leaflets are not seen, and continuous echocardiography imaging is required. 3DE complements 2DE in different steps of the procedure, providing valuable additional information, and should be used when available.[20]

The transseptal puncture is the first of the main procedural steps for MitraClip implantation. It is one of the most important steps because a correct puncture site is crucial for the normal development of the rest of the procedure. The transseptal puncture must be performed in a specific site that allows manipulation of the system inside the left atrium (LA) and grasping of leaflets. It should be performed in a posterior and superior location in the interatrial septum and at a certain distance from the valvular plane. 2D TEE imaging planes using a short axis view at the base for anterior-posterior orientation (30-45˚), a bicaval view for superior-inferior orientation (90-120˚), and a four-chamber view to identify the height above the MV are used. A persistent foramen oval should be avoided for transseptal puncture as it is too anterior. 3DE is very convenient because it allows us to visualise the whole interatrial septum in one view, without needing to shift from one plane to another for localisation of the correct puncture site.

The EchoNavigator system that allows image integration of fluoroscopy and echocardiography in real-time can be used during the transseptal puncture. Since a specific puncture site is needed, this system allows marking on 2DE or 3DE of the exact puncture site. This marker will be automatically transposed to the fluoroscopy image and can be used as a guide for interventionalists, facilitating targeting (Figure 2).

After the puncture has been performed, the Steerable Guide Catheter with the dilator is introduced into the LA. Once placed in the LA, the dilator is retrieved and the Clip Delivery System is advanced into the LA. In both steps, continuous monitoring of the catheter is necessary to avoid injuring the free LA wall. We also have to ensure that the tip of the Steerable Guide Catheter remains across the interatrial septum. 3DE can be particularly helpful in this setting as it allows better definition of catheters and, therefore, evaluation of their distance to the LA wall.

The MitraClip system should be placed above the MV in its mid portion, and perpendicular to the line of coaptation, directed towards the largest proximal isovelocity surface area (PISA). Instead of changing from 2D midoesophageal intercommissural view to midoesophageal long axis view for alignment, a 3DE en face view of the MV from the LA perspective allows visualisation in one image of the whole MV for precise and correct orientation (Figure 3). With the use of EchoNavigator, the origin of the largest PISA can be marked on echocardiography, and the device targeted towards this marker in the fluoroscopy images.

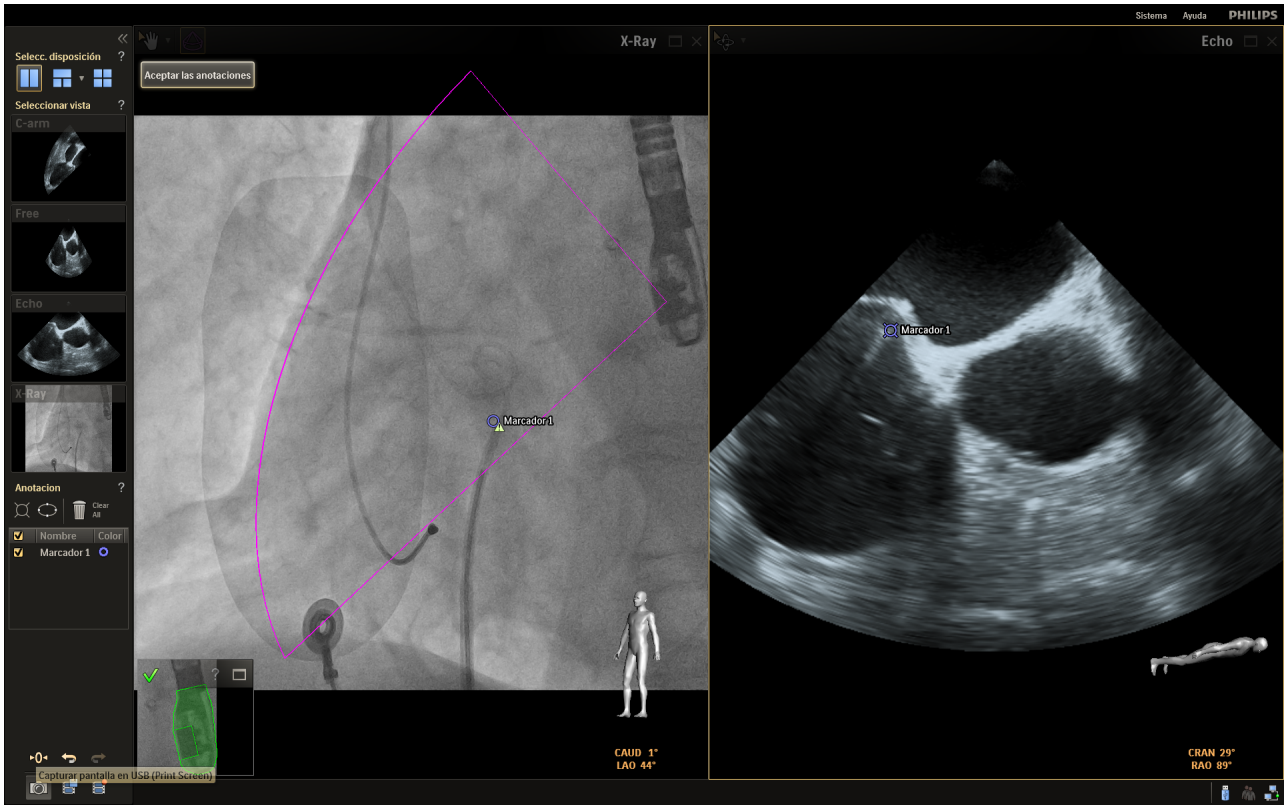

Figure 2: Transseptal puncture site has been marked using EchoNavigator system at the beginning of a MitraClip implant procedure to ensure correct location of the puncture.

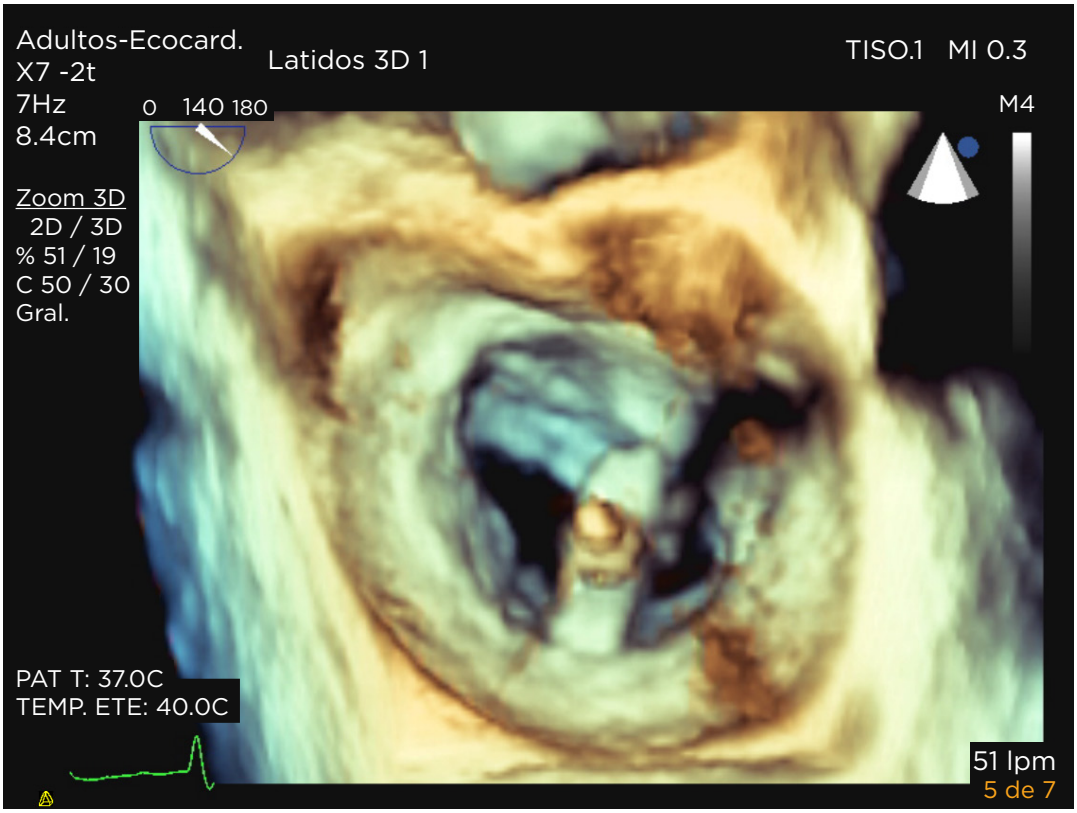

Figure 3: A 3DE en face view of the MV from the LA perspective allows visualisation in one image of the whole MV for precise and correct orientation of the MitraClip device.

3DE: 3D echocardiography; MV: mitral valve; LA: left atrium.

After crossing the MV, the orientation of the Clip and the delivery system should be confirmed, since the Clip may rotate during translation into the LV. 3DE allows a rapid check from the LV perspective to confirm that the arms of the MitraClip device are still perpendicular to the line of coaptation; alternatively 2DE transgastric short-axis view may be used. Once the MitraClip is satisfactorily positioned, grasping of the mitral leaflets between the Clip arms and the grippers is monitored using LV outflow tract view (where the insertion of the posterior leaflet is commonly best seen), four-chamber view (where the insertion of the anterior leaflet is best seen), and intercommissural view (60-70˚), adding information in the evaluation of chordae tendineae. Once grasping has been achieved, 3D TEE helps confirm correct bridging between the valves and the Clip.

Before release, assessment of residual MR with Colour Doppler should be performed. It is also essential to exclude mitral stenosis. This can be accomplished by measuring the transvalvular gradient with continuous-wave Doppler and planimetering the two orifices using 3DE. It is important to ensure that all periprocedural measurements of MR are made under similar haemodynamic conditions since these influence MR severity. There are currently no consensus guidelines on how to evaluate the degree of MR in the presence of a double orifice, and a multi-modal analysis is recommended. 3DE can also be used for quantification of MR. Direct measurements of vena contracta area using 3DE have potential for the quantification of MR with irregular vena contracta areas.[21] In the absence of aortic regurgitation and ventricular septal defects, using 3D acquisition of LV volumes, the regurgitant volume can be calculated.

MV gradient should be evaluated before Clip release; a mean gradient of up to 5 mmHg is considered acceptable. Using 3D TEE, if the sum of the planimetered orifices gives an area of <1.5 cm^2 it is considered criteria for significant mitral stenosis.[18]

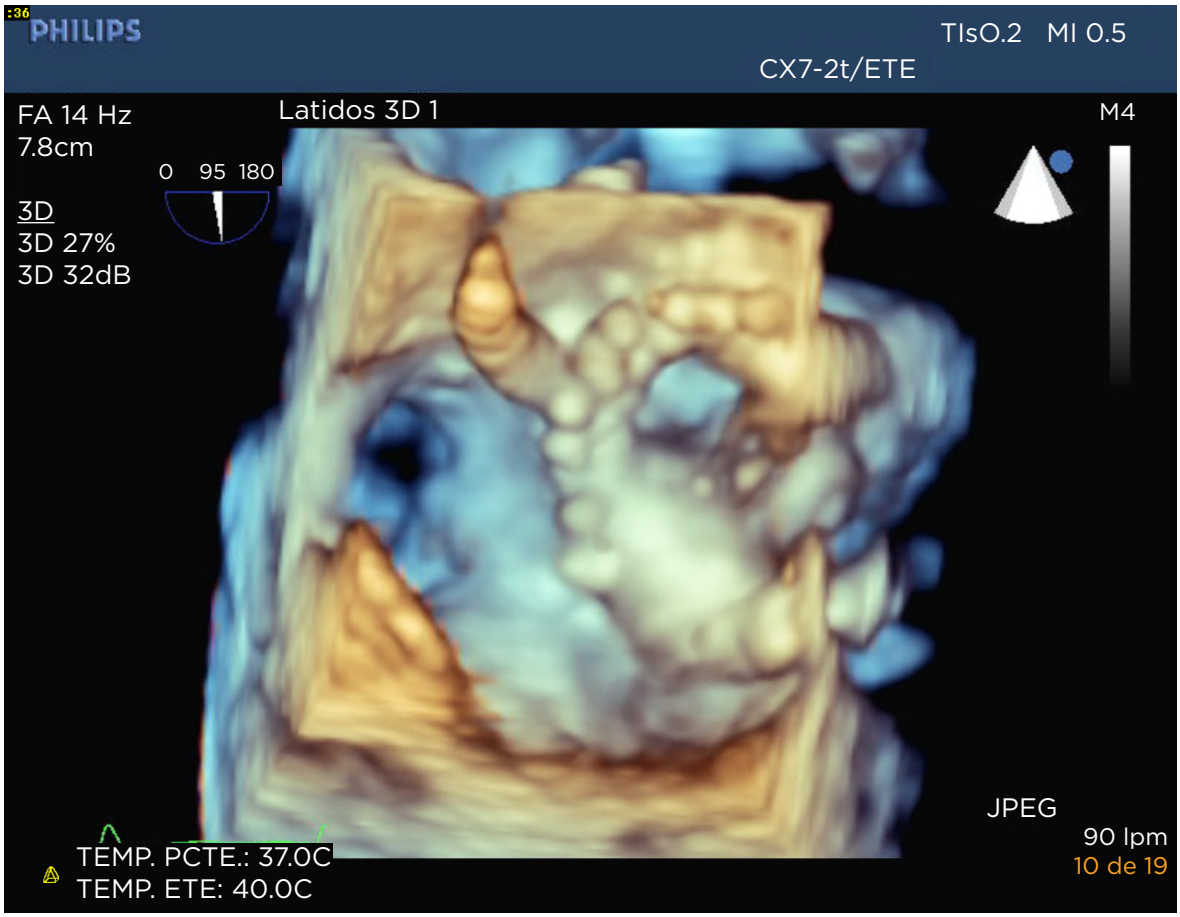

Figure 4: MV prosthesis paravalvular leak closure.
Real-time 3D TEE allows assessment during catheter navigation, determining whether it is located through the defect as seen in the figure or through the prosthetic valve leaflets.
MV: mitral valve; TEE: transoesophageal echocardiography.

In cases of unsatisfactory MR reduction, repositioning of the Clip or the implant of a second Clip may be considered. After deployment, the residual degree of MR should be reassessed.[22]

PERCUTANEOUS CLOSURE OF PVLS

Prosthetic PVLs are a potential complication of surgical valve replacements that can have significant clinical consequences, such as haemolytic anaemia or congestive heart failure. In cases where a second surgery is deemed high-risk, percutaneous treatment of this disorder is advisable if possible, having shown good clinical results and rates of procedural success.[23]

Percutaneous closure of a PVL is a challenging and time-consuming intervention, usually leading to long procedure times with high levels of ionising radiation. The optimal technique for planning the intervention is 3D TEE because 2DE shows limitations due to acoustic shadowing and difficulties in orientation. Real-time 3DE provides an en face view of the mitral prosthesis, allowing accurate assessment of the number, localisation, size, and shape of the paravalvular dehiscence. The location and orientation of the jets can be delineated using 3D Colour Doppler. A prosthesis in an aortic position is usually less optimally imaged than the mitral prosthesis due to its more anterior position, making it further away from the TEE probe and the fact that a proper short axis en face view may be difficult to obtain.[24]

Due to the difficulties in location and intubation of the defect in a 2D image-like fluoroscopy, EchoNavigator is very helpful in cases of PVL closure; since the defect can be marked in the echocardiography image, this marker is transposed to the fluoroscopy image and can be used to facilitate targeting of the lesion. Real-time 3D TEE allows assessment during catheter navigation, determining whether it is located through the defect or through the prosthetic valve leaflets (Figure 4). After device positioning and before deployment, 3D TEE can confirm adequate positioning and absence of interaction between the occluder and the prosthesis as well as residual paravalvular regurgitation. Repositioning or implantation of another device can be performed, but results are not considered optimal.

CONCLUSIONS

VHD is a growing field, with a significant increase in the number of patients that can be treated percutaneously. However, percutaneous treatment of these diseases is challenging and fluoroscopy alone is usually not enough, having turned echo cardiography into an essential tool inside the Cath Lab. 3DE has given access to high resolution images in real-time, allowing continuous and detailed imaging of anatomy and surrounding. Moreover, the actual integration of different imaging modalities, such as live echocardiography and live X-ray, and future fusion has added value, increasing anatomical awareness and confidence during procedure guidance.

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RED CELL DISTRIBUTION WIDTH FOR PREDICTING CARDIOVASCULAR DISEASE: A LITERATURE REVIEW

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ABSTRACT

Although the classical risk factors for cardiovascular disease (CVD) are very important, identification of potential novel risk factors could help clarify CVD pathophysiology, offer novel targets for intervention, and lead to improved risk stratification. Erythrocytes, or red blood cells (RBCs), are constituents of clots and thrombi formed *in vivo* but little is known about whether inherent properties of RBCs could affect the risk for CVD. The red cell distribution width (RDW) is a measure of the size variation and an index of the heterogeneity of erythrocytes, i.e. anisocytosis. Recently, a large number of studies have found an independent association beyond traditional risk factors between increased RDW (anisocytosis) and CVD. For instance, increased RDW has been associated with different CVDs such as coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, pulmonary arterial hypertension, and venous thromboembolism. RDW has also been associated with overall and cardiovascular mortality in different populations. RDW is influenced by many factors including traditional risk factors for CVDs, and it remains to be determined whether RDW is only a biomarker or also a pathogenic mediator for certain CVDs. Future Mendelian randomisation studies may provide a method for assessing the causal nature of increased RDW. Still, RDW is an inexpensive test measured routinely by automated blood cell counters and could be a useful predictor for CVD. In this article we present an overview of the literature about RDW and its association with CVDs.

Keywords: Cardiovascular disease, coronary heart disease, stroke, venous thromboembolism, red cell distribution width (RDW), biomarker, risk factor.

INTRODUCTION

Classical *in vitro* studies of the function of the coagulation system are performed in plasma, i.e. without erythrocytes or red blood cells (RBCs).[1] Few studies have therefore investigated the prothrombotic potential of RBCs. However, RBCs are constituents of clots and thrombi formed *in vivo*.[2-6] RBCs may play a prothrombotic role in blood coagulation by increasing blood viscosity and forcing platelets towards the vessel wall.[2-6] Incorporation of RBCs into a fibrin clot affects clot structure and mechanical properties. Even small structural differences in RBCs may have a large influence on pathophysiology.[2-6] Moreover, RBCs may actively participate in thrombin generation.[7] An increased focus on RBCs may therefore be justified, and may reveal novel mechanisms and risk factors for cardiovascular disease (CVD).

Mean corpuscular volume (MCV) is an index of RBC size.[8-12] Red cell distribution width (RDW) is a measure of the size variation and an index of the heterogeneity of erythrocytes (i.e. anisocytosis).[8-10] MCV and RDW are part of routine haematology laboratory tests and are used for classification of anaemia.[8-10] Recent studies have shown that RDW is associated with several CVDs such as coronary heart

disease (CHD), stroke, peripheral artery disease (PAD), heart failure (HF), venous thromboembolism (VTE), and pulmonary arterial hypertension (PAH).[11] The cause of these associations is still unclear. In this article we present an overview of the literature about RDW and its association with CVDs.

LABORATORY MEASUREMENT OF RDW

Modern automated blood cell counters calculate RDW from the RBC volume histogram as an index of heterogeneity.[12] RDW is often expressed as a percentage coefficient of variation (CV), and is calculated by dividing the standard deviation (SD) of the RBC volume by the MCV.[11] The result is multiplied by 100 in order to express it as a percentage.[12] The situation is complicated by there being RDW indices that are expressed in different ways. For several manufacturers, RDW is expressed as CV percentage.[12] RDW may also be expressed as a direct measurement of the width of the distribution, which gives a measure (in fL) that is independent of mean MCV.[12,13] The reference intervals differ between different manufacturers and may even vary between different instruments from the same manufacturer.[12-14] The lower reference limit for five different instruments varied between 10.7% and 12.9%, and the upper reference limit between 13.8% and 15.3%.[12,13] This is because different instruments use different algorithms to truncate the distribution in order to eliminate extreme values, which are often due to artefacts. The International Council for Standardization in Haematology has suggested a standardised statistical method for the analysis of RDW.[12,15,16] At present, any clinical use of RDW must be evaluated by comparison with reference values established for each model of analyser.

DETERMINANTS OF RDW

A number of haematological and non-haematological diseases have been associated with increased RDW (Table 1). Increased RDW (i.e. anisocytosis) is common in patients with deficiencies of iron, folate, and vitamin B12.[12,14] RDW has been used for differential diagnosis of anaemia. RDW is usually normal in thalassaemia traits and increased in iron deficiency anaemia.[12,14] Increased RDW is present in megaloblastic anaemia but RDW is usually normal in macrocytosis due to other causes.[12,14] However, there is a wide distribution of RDW values within a given disease, which has diminished its usefulness in differential diagnosis.[14] Increased RDW may be seen in other haematological disorders such as haemolytic anaemia, transfusion, sickle cell/beta thalassaemia, anaemia of chronic disorders, hereditary spherocytosis, and sickle cell anaemia,[11] and has also been associated with non-haematological diseases such as chronic hepatobiliary disease,[11] hypothyreosis,[17] hyperthyreosis,[17] Behçet's disease,[18] systemic lupus erythematosus,[19] and inflammatory bowel disease.[20]

Table 1: Haematological and non-haematological diseases associated with increased red cell distribution width.

Haematologic disorders	Non-haematological disorders
Iron deficiency anaemia[12,14]	Chronic hepatobiliary disease[11]
Megaloblastic anaemia (folate and vitamin B12 deficiency)[12,14]	Hypothyreosis[17]
Haemolytic anaemia[11]	Hyperthyreosis[17]
Sickle cell/beta thalassaemia[11]	Behçet's disease[18]
Transfusion[11]	Systemic lupus erythematosus[19]
Anaemia of chronic disorders[11]	Inflammatory bowel disease[20]
Hereditary spherocytosis[11]	Peripheral artery disease[48-51]
Sickle cell anaemia[11]	Stroke[52-57]
	Coronary heart disease[58-73]
	Heart failure[74-88]
	Atrial fibrillation[89-91]
	Pulmonary arterial hypertension[92-93]
	Venous thromboembolism[94-101]
	Hypertension[36-39]

It is, therefore, unsurprising that RDW correlates with inflammatory markers such as high-sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate, interleukin-6, soluble transferrin receptor, soluble tumour necrosis factor (TNF) receptor I, and soluble TNF receptor II (Table 2).[21-25] Increased levels of cytokines in inflammatory states promote anisocytosis by desensitising bone marrow erythroid progenitor cells and inhibiting RBC maturation.[11] In a study of patients with CHD, RDW did not correlate with hsCRP.[26] Instead, elevated levels of brain natriuretic peptide (BNP) were associated with increased RDW.[26] Increased RDW has also been associated with a number of other biomarkers (Table 2). In a study by Lippi et al.[27] RDW was independently associated with kidney function (estimated glomerular filtration rate). RDW has also been associated with microalbuminuria.[28] Among patients with HF, an association has been found between increased RDW and elevated troponin T levels.[29]

RDW has been associated with acquired and lifestyle factors such as increasing age, obesity, low cardiorespiratory fitness, smoking, being unmarried, and high alcohol consumption (Table 2).[30-34] It is also associated with obstructive sleep apnoea syndrome.[35] Hypertension has been associated with increased RDW.[36] RDW is especially increased in non-dipper hypertension patients.[37,38] An inverse relationship between lung function and RDW has been found.[39] An association has also been found between RDW and an unfavourable lipid profile, especially amongst women.[40] In another study, high RDW was associated with increased cholesterol content of the erythrocyte membrane.[41] An association has also been found between increased RDW and shorter telomere length.[42] Thus, RDW is associated with conditions, lifestyle factors, and biomarkers that are risk factors for CVDs and ageing (Table 2). Increased RDW may therefore be determined by epigenetic changes. The correlation between telomere length and RDW further suggests that the epigenetic changes associated with increased RDW reflect increased ageing, as shortened telomeres do.[42-44] It is possible that genetic factors affect RDW. Recently, a genome-wide association study of African Americans identified two variants (rs1050828 and rs10493739) on chromosomes Xq28 (*G6pD* gene) and 1p31.1, respectively, that are associated with RDW.[45]

Even though high RDW has been associated with increased incidence of several CVDs, this does not seem to be the case for incidence of diabetes.[46] A recent analysis by Engström et al.[46] of 26,709 nondiabetic participants from the population-based Malmö Diet and Cancer (MDC) Study showed that incidence of diabetes over a 14-year follow-up was substantially lower in subjects with high RDW. Thus, high RDW was a protective factor for new-onset diabetes. Low RDW was also associated with significantly higher waist circumference and glucose, insulin, and triglyceride concentrations.[46] By contrast, RDW was significantly and positively associated with HbA1c, with HbA1c increasing by 0.1% per 1 SD increase in RDW,[46] in accordance with recent data from nondiabetic participants in the National Health and Nutrition Examination Survey (NHANES) study.[47] A possible explanation for the positive association between HbA1c and RDW is that the RBC survival rates are on average higher in subjects with high RDW, leading to higher HbA1c due to increased duration of glucose exposure.[46]

Table 2: Laboratory markers and acquired and lifestyle-related factors associated with increased red cell distribution width.

Laboratory markers	Acquired and lifestyle-related factors
Inflammatory markers[21-25]	Age[33,34]
Brain natriuretic peptide[26]	Obesity[30]
Estimated glomerular filtration rate[27]	Low cardiorespiratory fitness[31]
Microalbuminuria[28]	Smoking[32,33]
Troponin T[29]	High alcohol consumption[33]
Unfavourable lipid profile[40]	Being unmarried[33]
HbA1c[46,47]	Obstructive sleep apnoea syndrome[35]
Short telomere length[42]	Lung function[39]
rs1050828 and rs10493739 variants[45]	

Table 3: Summary of published case-control studies, cohort-studies, and prognostic (mortality) studies showing associations of high red cell distribution width with risk of cardiovascular diseases and mortality.

Disease	Type of association (positive/negative)		
	Case-control studies	Cohort studies	Prognosis (mortality)
Peripheral artery disease	Positive[48]	-	Positive[51]
Stroke	Positive[52]	Positive[53]	Positive[55,56]
Coronary heart disease	-	Positive[60,73]	Positive[58,59,61-72]
Heart failure	-	Positive[33]	Positive[74-88]
Atrial fibrillation	Positive[90]	Positive[89,91]	-
Pulmonary arterial hypertension	-	-	Positive[92,93]
Venous thromboembolism	Positive[99,100]	Positive[101]	Positive[94-96]
Mortality among non-CVD patients and in the general population			
The general population	-	-	Positive[103-106]
Hospitalised patients	-	-	Positive[107]
Trauma and critically ill patients	-	-	Positive[108-113]
Sepsis	-	-	Positive[114]
Pancreatitis	-	-	Positive[115]
Hip fracture	-	-	Positive[116]
Kidney transplant recipients	-	-	Positive[117]

CVD AND INCREASED RDW

Increased RDW has been associated with an increased risk of a wide spectrum of CVDs in a large number of studies (Table 1).[33,48-102] Though initially quite unexpected, it is now unsurprising as studies have shown that increased RDW is associated with a large number of biomarkers and lifestyle factors associated with CVD (Table 2). As well as arterial CVDs, VTE[94-102] has been linked to increased RDW (Table 3).

PAD

In a cross-sectional study (the NHANES study), higher RDW values were independently associated with a higher risk of PAD.[48] Moreover, RDW significantly improved the risk prediction beyond that estimated by the American College of Cardiology/American Heart Association-defined PAD screening criteria.[48] In another study, RDW was found to be associated with the severity of atherosclerotic disease in patients with PAD.[49] However, Magri and Fava[50] found no association between RDW and PAD in diabetes patients. In a follow-up study of 13,039 outpatients with PAD at the Mayo Clinic, increased RDW was associated with mortality.[51] A 1% increment in RDW was associated with a 10% greater risk of all-cause mortality (HR 1.10, 95% CI 1.08-1.12, p<0.0001).

Stroke

In a case-control study, increased RDW was associated with ischaemic stroke.[52] Patients in the highest RDW quartile were significantly more likely to have a stroke compared with patients in the lowest quartile (OR 4.50, p<0.0001).[52] RDW was also a predictor for stroke in a follow-up study of 153 patients with HF.[53] Chen et al.[54] found that RDW was associated with all-cause mortality, but not with CVD (i.e. stroke and/or CHD). Increased RDW was also associated with poor prognosis or mortality among stroke patients in two studies,[55,56] though no association between RDW and stroke severity and functional outcome was observed in another study.[57]

CHD

In 2007, Anderson et al.[58] studied 29,536 consecutive patients undergoing coronary angiography. The highest RDW quartile compared with the lowest quartile had an increased risk of 30-day mortality (HR=1.8). Tonelli et al.[59] performed a *post hoc* analysis of data from the Cholesterol and Recurrent

Events study of patients with prior myocardial infarction (MI). Baseline RDW was measured in 4,111 participants who were randomised to receive pravastatin (40 mg, daily) or placebo and followed for a median of 59.7 months. A significant association was observed between baseline RDW and all-cause mortality (HR 1.14 per 1% increase in RDW).[59] The highest RDW quartile had an adjusted HR for death of 1.78 compared with the lowest quartile. Higher RDW was also associated with increased risk of coronary death/nonfatal MI, new symptomatic HF, and stroke.[59] A recent population-based study of 26,820 men and women reported that RDW was associated with an incidence of fatal acute coronary events.[60] However, no relationship was observed between RDW and nonfatal coronary events.[60] A large number of other studies have confirmed that RDW is a predictor for mortality in patients with CHD.[61-72] RDW was also found to be a predictor for incident CHD in healthy individuals in the NHANES study.[73]

HF

In 2007, Felker et al.[74] found that RDW was a prognostic factor regarding morbidity and mortality in the North American Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity study. An adjusted HR of 1.17 per 1 SD increase was found (p<0.001). This finding was replicated in a cohort of 2,140 HF patients from the Duke Databank, in which higher RDW was strongly associated with all-cause mortality (adjusted HR 1.29 per 1 SD, p<0.001). A large number of studies have confirmed that RDW is a predictor for poor prognosis in patients with acute and chronic HF.[33,74-88] In a large prospective study of 26,784 individuals, Borné et al.[33] found that RDW was an independent risk factor for incident HF in the MDC Study cohort. The HR for HF was 1.47 (95% CI 1.14-1.89) in the highest compared with the lowest RDW quartile.[33]

Atrial Fibrillation (AF)

In a study of 132 patients undergoing non-emergency coronary artery bypass grafting, preoperative RDW levels were significantly higher in patients who developed AF than in those who did not (13.9% versus 13.3%, p=0.03).[89] RDW was also associated with paroxysmal AF in a case-control study.[90] In a large prospective study of 26,124 individuals, Adamsson Eryd et al.[91] found that RDW was an independent risk factor for incident AF in the MDC Study cohort. The HR for AF was 1.33 (95% CI 1.16-1.53) in the highest compared with the lowest RDW quartile.[91]

PAH

Hampole et al.[92] found that RDW is independently associated with death in patients with PAH and performs better as a prognostic indicator than N-terminal pro-BNP. This was confirmed by Rhodes et al.[93] who found that RDW is a better predictor for mortality than other biomarkers in PAH.

VTE

Three studies have determined RDW in patients with pulmonary embolism (PE).[94-96] These studies found that high RDW was an independent predictor of PE-related mortality.[94-96] Two studies found an association between high RDW and chronic thromboembolic pulmonary hypertension.[97,98] RDW was also associated with VTE in two case-control studies,[99,100] but these case-control studies cannot exclude the possibility that anisocytosis was the result of the thrombotic event itself. A prospective cohort study by Zöller et al.[101] showed a graded independent association between RDW and risk of first VTE event among middle-aged subjects. After adjustment for potential confounding factors, the HRs for VTE for the second, third, and fourth RDW quartiles were 1.15 (95% CI 0.94-1.41), 1.41 (1.14-1.73), and 1.74 (1.38-2.21), respectively, compared with the lowest RDW quartile. In the multivariate model, subjects with the top 5% of RDW values had an even higher risk compared with the lowest quartile (HR 2.51, 95% CI 1.78-2.54).[101]

RDW was also associated with cerebral venous sinus thrombosis (CVST) in a diagnostic study of 138 patients referred to emergency services with complaints of headache.[102] Diagnosis of CVST was established by magnetic resonance venography. Diagnostic validity of RDW was found to be excellent in differentiating patients with CVST and primary headache, with a sensitivity of 91.9% and a specificity of 99%.

OVERALL MORTALITY

RDW has been shown to be a predictor for overall mortality in the general population.[103] Patel et al.[103] studied overall mortality among 8,175 adults 45 years or older who participated in the NHANES study. Compared with the lowest quintile of RDW, the adjusted HR for all-cause mortality was 1.1 (95% CI 0.9-1.3) in the second quintile, 1.2 (95% CI 1.0-1.4)

in the third quintile, 1.4 (95% CI 1.2-1.8) in the fourth quintile, and 2.1 (95% CI 1.7-2.6) in the fifth quintile.[103] Similar results have been found in other studies, including a meta-analysis.[104-106] Perlstein et al.[104] found a strong association between RDW and all-cause mortality in 15,852 adult participants in the NHANES III study. RDW was found to be a stronger risk factor for mortality in blacks and men compared to whites and women.[105] RDW is also a risk factor for mortality among older adults.[106] RDW has been shown to be a predictor for mortality in hospitalised patients (Table 3),[107] including patients with trauma and critical illness, sepsis and shock, acute pancreatitis, and hip fracture, as well as kidney transplant recipients.[108-117]

DISCUSSION

RDW is emerging as a potential biomarker not only for CVDs but also for predicting mortality in different patient groups and in the general population (Table 3). The methods for determining RDW are nowadays easily accessible and routinely performed using automated blood cell counters.[118] The mechanisms of the associations between CVDs and RDW are unclear. It is unlikely that only one mechanism is responsible because increased RDW is associated with several CVDs with different aetiologies. Still, it is possible that inherent properties of the RBC related to RDW may contribute to certain CVDs as RBCs are an important constituent of clots and thrombi formed *in vivo*.[2-6] Prospective studies show that high RDW, even after long-term follow-up, is a predictor for incident CVD.[33,60,73,91,101] Still, high RDW might not be the cause of CVD; it might just be a simple epiphenomenon due to conditions such as inflammation, impaired kidney function, malnutrition, or oxidative damage.[11] Clarification of the mechanisms behind the associations between high RDW and CVD may lead to new therapeutic opportunities. Recently, a genome-wide association study has found two gene variants associated with RDW. This indicates that RDW may also be affected by genetic factors. Mendelian randomisation studies may therefore be an important option for generating estimates for causal effects of RDW in different CVDs.[119]

Pros and Cons

RDW is a robust universal predictor for poor outcome for several CVDs (Table 3). On the other hand, this lack of specificity might become problematic if RDW is used for risk prediction in the clinic. Moreover, as we do not yet know why high RDW predicts CVD, we have no possibility for intervention regarding the cause of high RDW. The strength of RDW may be if it adds information to risk scores such as the Framingham Risk Score (FRS).[120] For instance, the FRS identifies only 70% of individuals at risk of CVD events and there is great interest in adding novel risk factors to improve its predictive capacity.[120,121] An important advantage is the low cost. Moreover, the analysis is quick and may easily be done in all laboratories on a modern automated blood cell counter. However, the method is not yet standardised, which is a major limitation that must be solved before the method can be introduced in the clinic.[12-14] Moreover, spurious RDW measurements may result from biases in determination of MCV, and a high-quality laboratory standard is necessary.[11,122]

Future Opportunities

An important issue for future research is the inclusion of RDW in risk score models such as the FRS. RDW has been shown to improve the Simplified Acute Physiology Score in critically ill patients.[123] RDW has also been included in other risk score models,[124,125] suggesting that this might be a possible avenue of clinical research. Due to the lack of standardisation it is important to develop a standardised method for RDW determination that will give results which are comparable between different manufacturers and laboratories.[12-16] Otherwise the clinical use of RDW will be limited. Perhaps the most important issue for future research is to elucidate the cause of the association between increased RDW and CVD. This might lead to the identification of new disease mechanisms and new treatments. For instance, although RBCs are constituents of clots and thrombi formed *in vivo*,[2-6] little is known about how different properties of RBCs affect arterial and VTE disorders. A special intriguing issue is why low RDW is associated with increased incidence of diabetes,[46] and at the same time HbAc1 is positively correlated with RDW.[46,47]

CONCLUSIONS

RDW is a novel and universal predictor for CVD and mortality. Clarification of the mechanisms underlying the association between RDW and CVDs may reveal new pathogenic mechanisms. There is an urgent need for standardisation before RDW can be used in clinical praxis as a novel risk factor that adds information beyond traditional CV risk factors.

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CASE REPORT: DOUBLE ORIFICE MITRAL VALVE WITH CLEFT IN ANTERIOR LEAFLET OF DOMINANT VALVE IN AN AFRO-CARIBBEAN

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ABSTRACT

Double orifice mitral valve (DOMV) is a rare congenital mitral valve (MV) disorder. It is associated with other types of congenital heart disease in 45% of patients, but it has been documented to be isolated with or without noncompaction of the left ventricle. The focused features of this case report are the transthoracic echocardiographic images of an isolated case of DOMV, with an additional rare association of a cleft in the anterior leaflet of the dominant MV presenting as mitral regurgitation in a 13-year-old Afro-Caribbean female.

Keywords: Double orifice mitral valve, noncompaction, tensor apparatus, rheumatic heart disease.

INTRODUCTION

In 1876 Greenfield[1] described the first case of double orifice mitral valve (DOMV). There have been >200 cases documented of all types of DOMV[2,3] via autopsy, transthoracic, and transoesophageal echocardiography (TTE and TOE), with anatomy more clearly defined by three-dimensional (3D) echocardiogram.[3-5] Banerjee et al.[6] indicates that there is an incidence rate of <0.05% in the population. Isolated cases are a rare occurrence in the DOMV group and the true incidence of this specific type is not known. There are >40% of DOMV cases that are associated with other types of cardiovascular disease, the most common of which are atrioventricular septal and ventricular septal defects, comprising 56% to 17%, in post mortem series. There can be up to 39% with left sided obstructive lesions, such as coarctation of the aorta, interrupted aortic arch, or right-sided obstructive lesion such as pulmonary stenosis. The list of associated conditions include: atrioventricular septal defect, primum atrial septal defect, ventricular septal defect, atrial septal defect, truncus arteriosus, coarctation of the aorta, interruption of the aortic arch, tetralogy of Fallot, corrected transposition, bicuspid aortic valve, pulmonary stenosis, Ebstein's anomaly of the tricuspid valve, dysplastic tricuspid valve, double orifice tricuspid valve, tricuspid atresia, parachute mitral valve, marfanoid features, left ventricular noncompaction, atrial tachycardia, congenital complete heart block, and cardiomyopathy.[1-14]

Presentation may not occur, hence being totally asymptomatic with competent DOMV.[4] Mitral regurgitation (MR) occurs in the majority of cases (45%) and mitral stenosis (MS) in 11%, in either or both MVs to varying degrees of severity. MR and MS can be masked by concomitant cardiac lesions such as interatrial communications of primum atrial septal defect and secundum atrial septal defect, and also tetralogy of Fallot,[9] which reduces left ventricular inflow. There are varied abnormalities of the MV annulus, the tensor apparatus and papillary muscles which may be duplicated, with each MV having its own complete subvalvular attachments to the left ventricle (LV).[1-8]

DOMV may occur with or without noncompaction of the LV.[5] They are then classified into three main groups anatomically by Trowitzsch et al.[2] as Type 1, having a complete bridge going between the valves

as in the index case, Type 2, an incomplete bridge with connections at the edge of the leaflets of the MVs, and Type 3, a hole in the lateral commissure. The TTE findings, the focused features of the index case, are of an isolated DOMV with severe MR in both MVs, in which the index developing country was mistaken initially for rheumatic heart disease (RHD) affecting the MV, and the patient was placed on a 28-day prophylactic penicillin therapy.

CASE REPORT OF TTE FEATURES OF THE INDEX CASE

The index case is a 13-year-old teenager with clinical signs of MR, being reevaluated with TTE. There was situs solitus, atrioventricular concordance, and ventriculoarterial concordance. Figure 1 shows normal off-setting atrioventricular valves (AV) ruling out atrioventricular septal defect structural morphology. A large left atrium (LA) with an intact interatrial septum (IAS) deviated to the right, indicating a relative increase in left atrial pressure. There are dilated pulmonary veins (PV), indicative of raised left atrial pressures. Relative large LV with LV end diastolic diameter of 4.2 cm with low fractional shortening of 27% and ejection fraction of 53%. The right ventricle (RV) has a prominent moderator band. In this image the MVs are closed (dominant MV1 and smaller MV2) with their tendon apparatus noted.

Figure 2 shows both the MVs, the dominant MV1, and smaller MV2 open. As in Figure 1, it also shows large LA with IAS deviated to the right, dilated PVs, relative large LV, and the RV with prominent moderator band. Figure 3 shows forward, diastolic flow across dominant MV1 and to the left of this flow, a smaller red colour Doppler flow across MV2. Figure 4 shows regurgitant flow of dominant MV1 deviated to the left and posteriorly with reversal of flow in dilated left PV. Figure 5 shows pulsed Doppler regurgitant flow of MV1 of 4 m/s. Figure 6 shows, in rotated four chamber view, smaller MV2 open. This figure also depicts, as previous figures, large LA with IAS deviated to the right, dilated PV, large LV, and in this view, relative large RV with prominent moderator band. Figure 7 shows with colour Doppler regurgitant flow in MV2 which was directed posteriorly and to the lateral aspect of the LA. Figure 8 with posterior angulation in four chamber view, shows colour Doppler guided continuous wave (CW) regurgitant flow MV2 of CW 6.5 m/s. There is reversal of flow in left PVs.

Figure 9 shows dilated LA and aorta (AO). The AO:LA ratio 1:3 where the normal ratio is 1:1.1 confirms a markedly dilated LA. Dilated PV is also noted. Left atrial volumes were not necessary to confirm markedly enlarged LA, in this specific case. Figure 10 parasternal short axis view, shows two unequal MVs with the medial valve being the larger dominant valve and an anterior lateral inferior smaller valve with abnormal tensor apparatus for both valves. There is marked left atrial enlargement. Figure 10 shows dominant valve closed, whereas Figure 2 shows dominant valve open. Figure 11 shows short axis view of LV with MV1 with open cleft in anterior leaflet (MV1) which is partially open and MV2. Figure 12 shows short axis view of LV with both MV1 cleft and MV2 fully open.

The dominant MV had a cleft in anterior leaflet with severe MR extending to PVs which were dilated. The smaller MV also had a moderate-to-severe form of MR. The two valves were not seen concomitantly in the same four chamber view plane. Hence, the use of separate four chamber views showed severe MR of the medial dominant MV and moderate-to-severe MR in the smaller anterior lateral MV.

The directions of the regurgitant flow from both MV1 and MV2 were to the left and posterior, with far-field beam widening and also attenuation closer to the back of the LA, and hence were not parallel to the beam and were most likely underestimated. The peak E velocities for MV1 and MV2 did not exceed 1.5 m/s, ruling out a concomitant MS. It was not possible to clearly differentiate E and A waves in the absence of atrial fibrillation. Because of the direction of regurgitant flow and the eccentric orifices of MV1 and MV2, the presence of multiple jets from the MV1, the cleft of MV1, and MV2 makes the calculation of vena contracta, jet area, and proximal isovelocity surface area invalid in the assessment of severity of MR. No A waves with poor left ventricular function implies some diastolic dysfunction.

The parasternal long axis view showed dilated LA with an AO to LA ratio (i.e. AO:LA) greater than 1:3 (normal 1:1.1, Figure 5). Hence, direct and indirect assessment of MV regurgitant severity was shown by the regurgitant flow hitting the back of the dilated LA with reversal of flow in dilated PVs and bowing of the intact IAS to the right in the apical four chamber view. The presence of markedly dilated right and left PVs demonstrated markedly increased left atrial pressures. The LV was also enlarged. 3D echocardiography, cardiac

magnetic resonance imaging, and computed tomography are not available in the index country.

DISCUSSION

The embryological development of the MVs occurs with the merging of the endocardial cushion and the myocardial ridge by the 40th day of gestation, connecting the final MV to the tensor apparatus and papillary muscle on the left ventricular wall. DOMV is believed to occur when merging is abnormal. The MV abnormality is believed to be secondary to genetic mutations affecting the regulatory proteins in the myocytes.[8]

A familial case involving a brother and sister has been described, indicating an underlying chromosomal or genetic cause;[11] however, the index case had no family history of congenital heart disease or MV disease. 85% of DOMV patients have a dominant orifice and smaller vestigial one as in the index case. Two equal valves occur in 15% of cases, or a third duplication of the MV with each its own tensor apparatus.

The varied structural anatomy of the MV, their competence, tensor apparatus, papillary muscle, and noncompaction determines the final clinical presentation; DOMV patients with competent valves would be asymptomatic and diagnosed as an incidental echocardiographic[4] or autopsy finding,[1,2] comparing the patients who present signs of severe pulmonary hypertension (PH) with Eisenmenger's syndrome to the ones presenting with mitral stenotic symptoms and signs. The presentation can be dilated cardiomyopathy when noncompaction is predominant.[14]

All the aforementioned symptoms and signs are well documented.[3-14] Hence the management of DOMV is based on the patient's individual anatomy and physiology. This is usually only needed when there is significant MR and MS.[3,14]

This case confirms that complex structural cardiac anatomy can be clearly defined in expert hands. Surgical intervention with prosthetic MV replacement was recommended to avoid use of anticoagulants until after child bearing because of the documented potential teratogenic effects of these drugs; mechanical valves could be used thereafter.

CONCLUSION

This paper reviewed an index case of DOMV with cleft in anterior leaflet of dominant valve with severe MR. In a developing country it is important to note that all mitral regurgitant signs are not due to RHD. Isolated DOMV is a rare congenital cardiac malformation, which can cause irreversible cardiac disease and PH if not detected early, and requires a high index of suspicion.

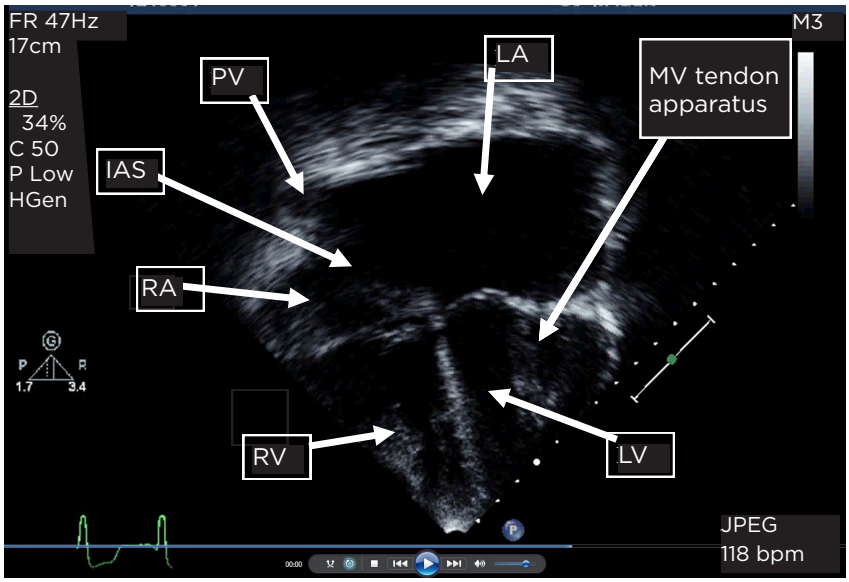

Figure 1: Normal off-setting atrioventricular valves (AV) valves. Large left atrium (LA) with inter atrial septum (IAS) to the right. Dilated pulmonary veins (PV). Large left ventricle (LV). Large right ventricle (RV) with prominent moderator band. Mitral valves (MV1 & 2 tendon apparatus closed).

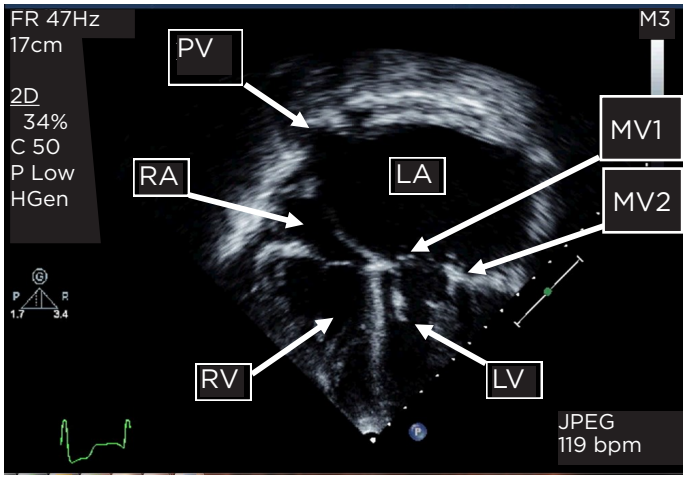

Figure 2: Normal off-setting atrioventricular valves. Large left atrium (LA) with inter atrial septum to the right. Dilated pulmonary veins (PV). Large left ventricle (LV). Large right ventricle (RV) with prominent moderator band. Mitral valves (MV1 & 2 open).

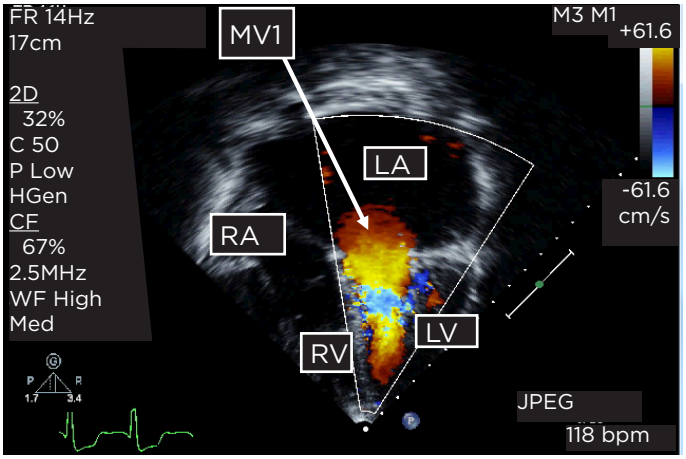

Figure 3: Diastolic flow mitral valve 1 (MV1).
L/RV: left/right ventricle; L/RA: left/right atrium.

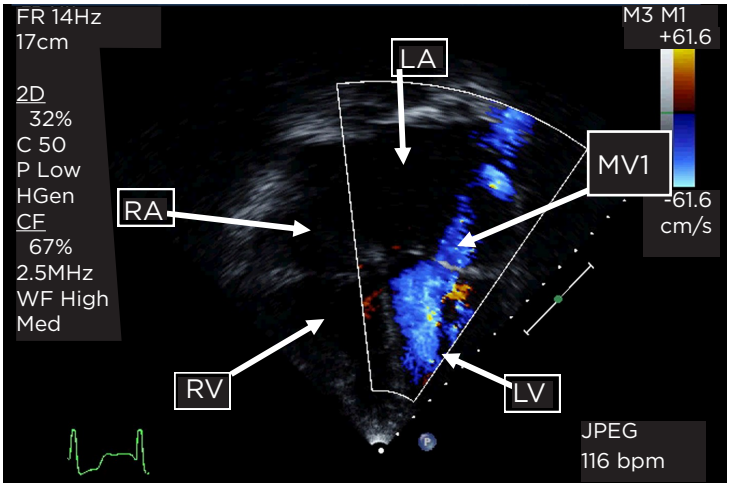

Figure 4: Regurgitant flow mitral valve 1 (MV1) with reversal of flow in left pulmonary vein.
L/RV: left/right ventricle; L/RA: left/right atrium.

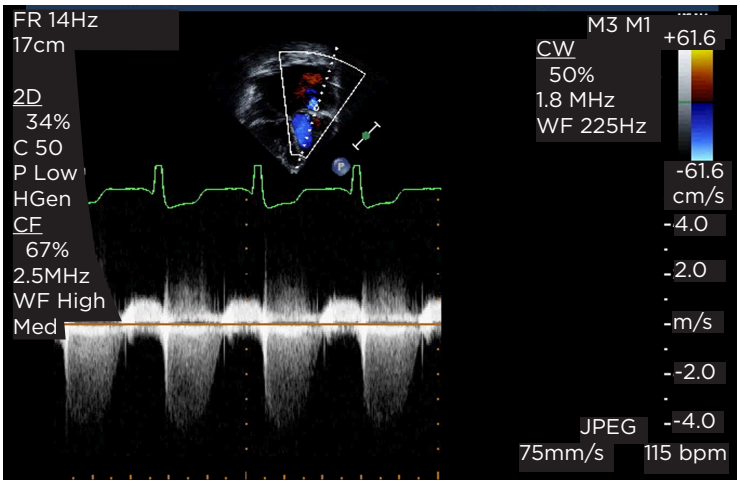

Figure 5: Doppler regurgitant flow mitral valve 1 pulsed wave 4 m/s.

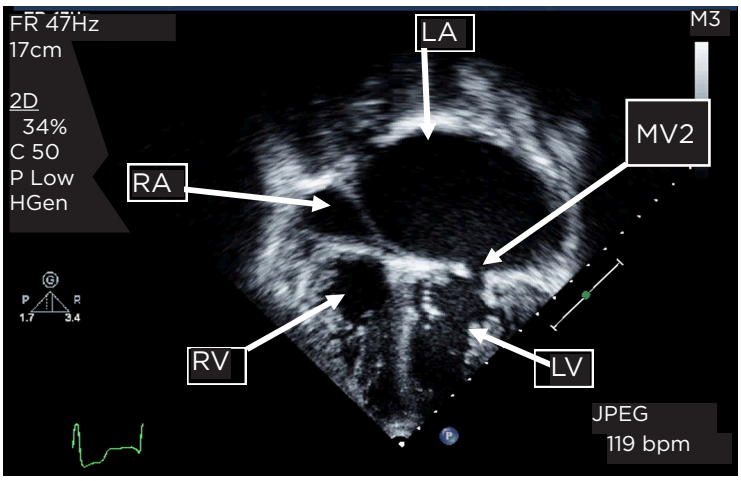

Figure 6: Mitral valves (MV2 open). Large left atrium (LA) with interatrial septum to the right. Dilated pulmonary veins (PV). Large left ventricle (LV). Large right ventricle (RV) with prominent moderator band.

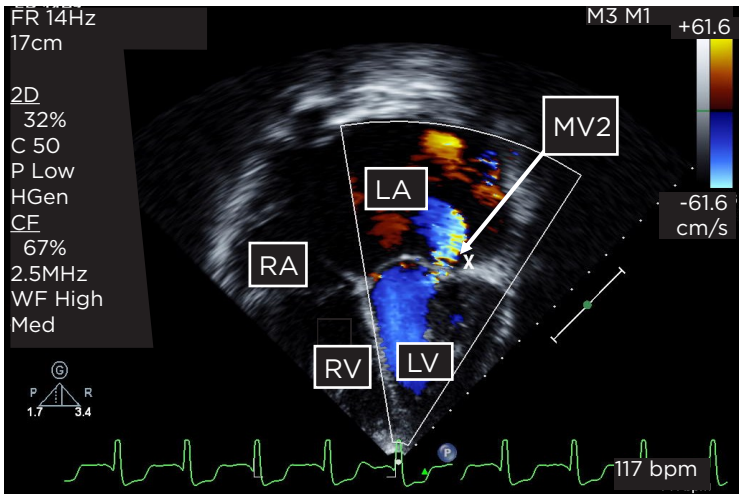

Figure 7: Regurgitant flow in mitral valve 2 (MV2).
L/RV: left/right ventricle; L/RA: left/right atrium.

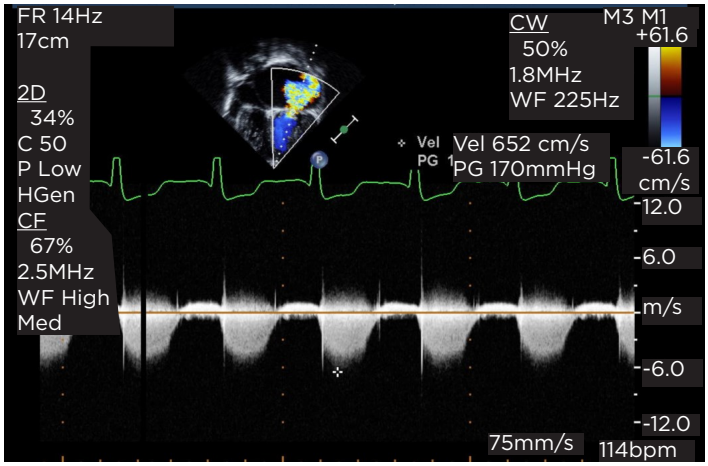

Figure 8: Doppler regurgitant flow mitral valve 2 (MV2) continuous wave 6.5m/s. Reversal of flow in left pulmonary veins.

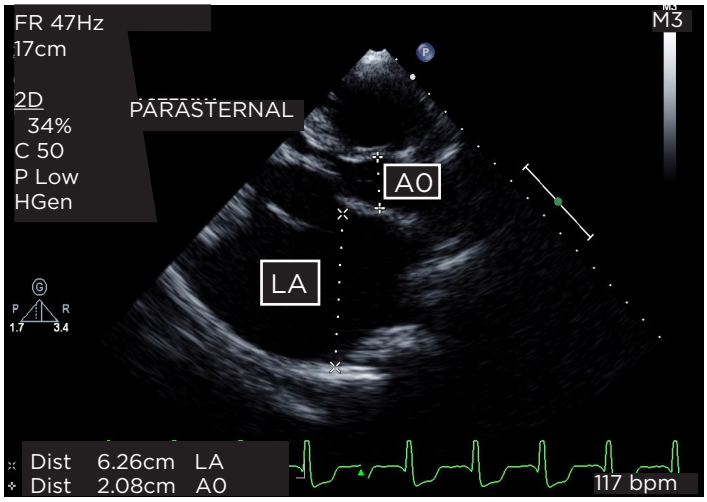

Figure 9: Dilated left atrium (LA), aorta (AO). AO: LA ratio 1:3. Dilated pulmonary veins.

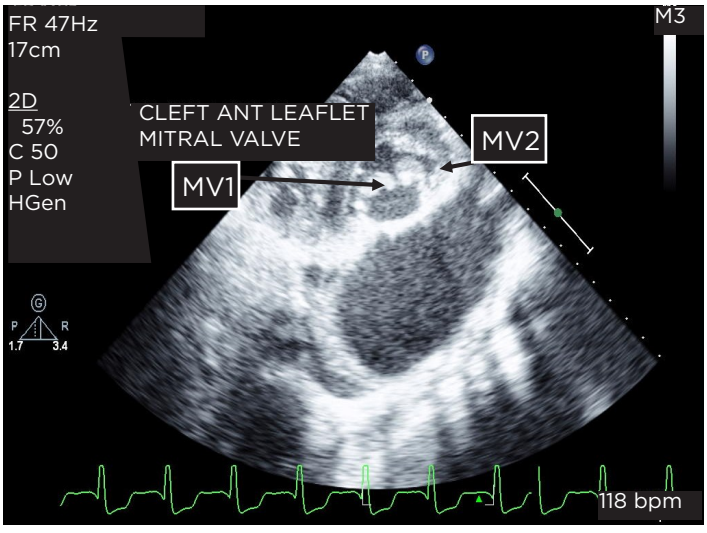

Figure 10: Short axis view of left ventricle with mitral valve 1 (MV1) with cleft closed and mitral valve 2 (MV2).

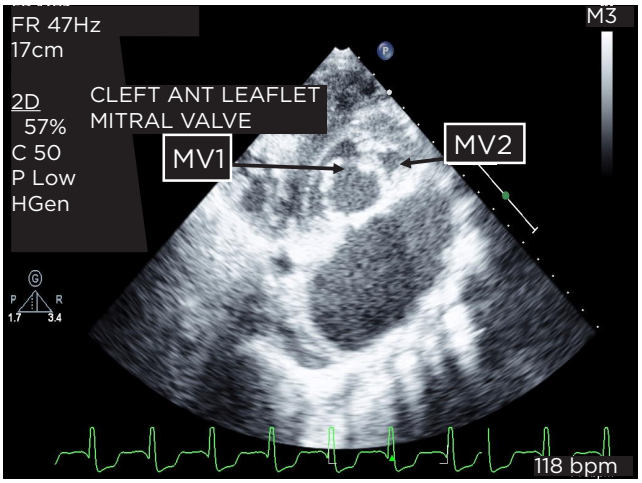

Figure 11: Short axis view of left ventricle with mitral valve 1 (MV1) with open cleft in anterior leaflet partially open and mitral valve 2 (MV2).

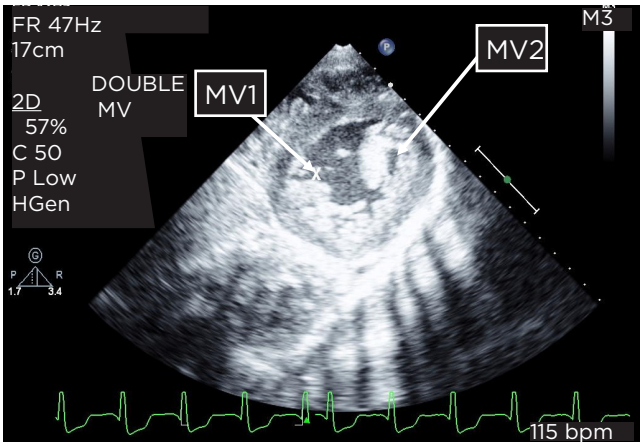

Figure 12: Short axis view of left ventricle with mitral valve I (MV1) cleft fully open and mitral valve 2 (MV2).

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THE QUEST FOR A MEDICAL TREATMENT OF AORTIC STENOSIS: PUTATIVE THERAPEUTIC TARGETS

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ABSTRACT

Aortic stenosis (AS), i.e. calcification and obstruction of the aortic valve (AV), is the most common type of valvular heart disease. The therapeutic options for AS are currently limited to either AV replacement surgery or transcatheter AV implantation. In contrast, no medical treatment has proven effective in slowing the process of valve calcification. The molecular and cellular pathophysiology of AS is an active and complex process, with components of inflammation, lipid accumulation, valvular remodelling, dystrophic calcification, oxidative stress, apoptosis, and heterotopic ossification. These pathways contain several potential targets for medical treatment, which are discussed in the present review. These include the targeting of lipids and lipoproteins, inflammation, and calcification pathways, which have been explored in experimental, epidemiological, and prospective studies. However, further mechanistic studies and prospective trials are needed to better understand the pathophysiology of AS and to lead to new therapeutic strategies for the prevention, or at least the delay, of either surgical or transcatheter valve implantations.

Keywords: Aortic stenosis, echocardiography, inflammation, leukotrienes, valvular heart disease.

INTRODUCTION

Aortic stenosis (AS), i.e. calcification and obstruction of the aortic valve (AV), is the most common type of valvular heart disease. The therapeutic options for AS are currently limited to invasive procedures, such as aortic valve replacement surgery (AVRS) or transcatheter aortic valve implantation (TAVI). In contrast, no medical treatment has proven to be effective in slowing the process of AV calcification.

Based on the original histological description of AV calcification in 1904 by Mönckeberg,[1] calcified AS was for a long time considered as a purely degenerative process associated with aging and being the consequence of calcium deposits on the surface of the valve. Nowadays however, and over the last two decades, the aspect of AS as a chronic inflammatory disease has emerged, and supplanted other theories.[2,3] This inflammatory theory has radically changed the view of AS pathophysiology into an active process of remodelling and valvular calcification, and opened up the quest for a medical treatment of this disease.

Indeed, several key phenomena have been identified as part of the calcification process, with potential therapeutic interest. Examples of such potential medical strategies include targeting lipids and lipoproteins, osteogenic pathways, inflammatory mediators, and proteases. The poor prognosis and increased mortality associated with AS after the onset of symptoms in the absence of either AVRS or TAVI[4] stresses the importance of seeking medical treatments which would slow down the progression of the disease. This article will review the molecular and cellular pathophysiology as well as potential new therapeutic targets of AS.

CELLULAR AND MOLECULAR MECHANISMS OF AS

Based on the histological examinations of the human explanted AV with different degrees of

stenosis, a continuum of pathophysiological changes has been identified,[2] as indicated in Figure 1. Put simply, these processes can be divided into an early initiating stage which is characterised by subendothelial thickening at the aortic side of the valvular leaflets and the presence of lipids; followed by a progression of the disease characterised by inflammation, valvular remodelling, and dystrophic calcification, and finally the end-stage disease with altered valvular structure and heterotopic bone formation (Figure 1).

Early-Stage Disease Processes

The mechanical stress on the AV[5] in combination with hyperlipidaemia and other proatherogenic factors induce endothelial cell activation, which may serve as a starting point for the transition from a normal valve towards a thickened structure (Figure 1). This early stage of AS is also characterised by the recruitment of inflammatory cells, such as macrophages and T cells, which have been detected in valvular lesions.[2,3] Activated leukocytes are a source of proteases, e.g. matrix metalloproteinases (MMP), which induce a degradation of the extracellular matrix (ECM), resulting in valve remodelling and structural alterations as depicted in Figure 1. The resulting thickening and hardening of the AV are, in turn, associated with valvular dysfunction, and as a consequence, further negative alterations of the mechanical stress on the AV.[5] Collectively, this results in a vicious circle of increased inflammation and a narrowing of the AV. Valvular remodelling ranges from simple thickening of the valve to severe calcification, resulting in a significant limitation of the cusp opening. In this process, there may be a potentially vulnerable and reversible disease phase, characterised by increased inflammation which may involve several inflammatory mediators, including transforming growth factor beta (TGF β), interleukin-1 beta (IL-1 β), and tumour necrosis factor-alpha (TNF-α) (Figure 1).

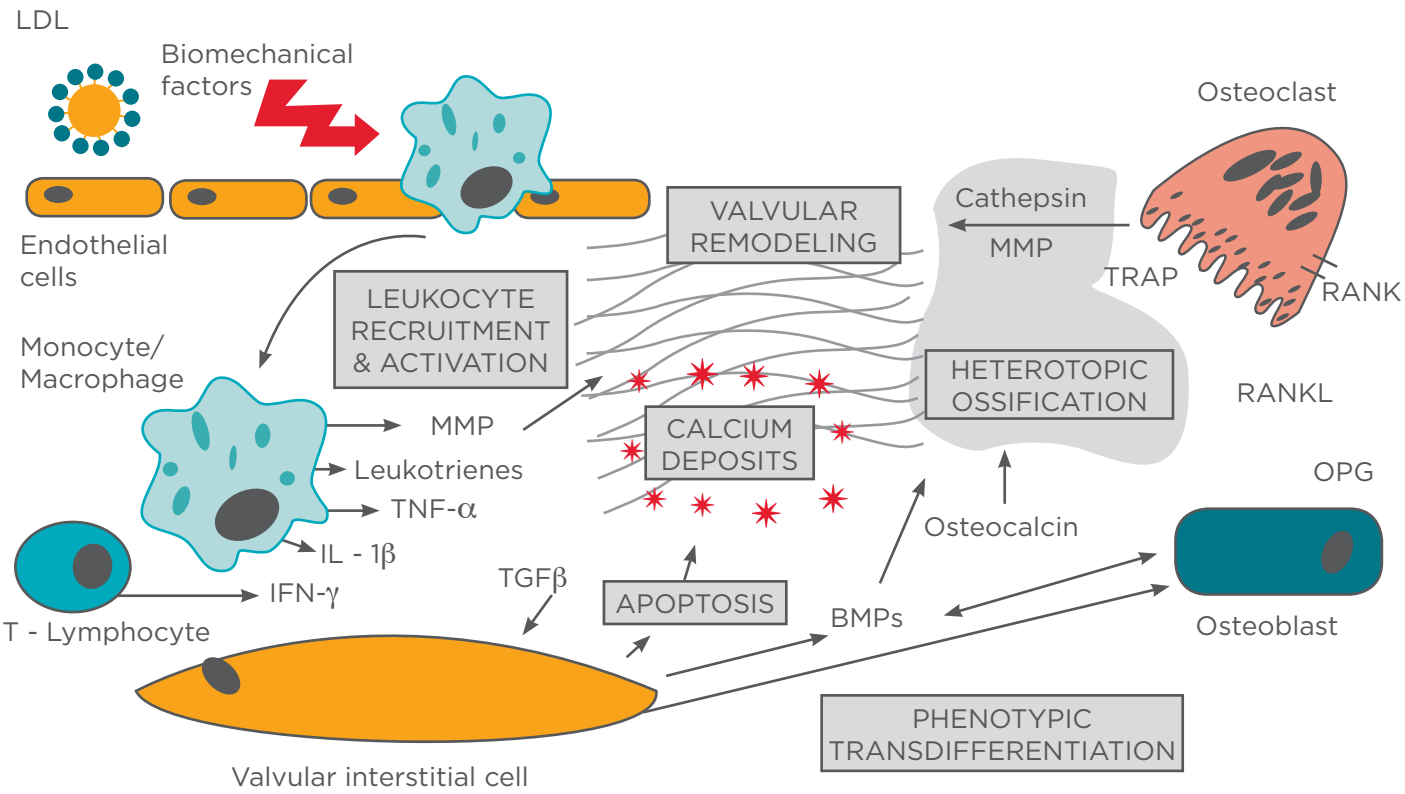

Figure 1: Cellular and molecular mechanisms of aortic stenosis.
The figure shows an overview of some of the early, intermediate, and late processes associated with the development of AS, with examples of cells and mediators involved in valvular remodelling, dystrophic calcification, and heterotopic bone formation within the AV.
AS: aortic stenosis; AV: aortic valve; LDL: low density lipoprotein; MMP: matrix metalloproteinase; TNF: tumour necrosis factor; IL: interleukin; IFN: interferon; BMP: bone morphogenic protein; OPG: osteoprotegerin; RANK: receptor activator of nuclear factor kappa B; RANKL: RANK ligand; TRAP: tartrate-resistant acid phosphatase; TGF β: transforming growth factor beta.

Table 1: Studies of statins in aortic stenosis.

Study	N	Treatment	Follow-up	Baseline Characteristics (Placebo/treated)	AS progression
SALTIRE[16]	155	Atorvastatin 80 mg	2.1 years	Age 68/68 years Female 32/28 years TAV 97/96% V_{max} 3.45/3.39 m/s LDL 3.54/3.45 mol/L	V_{max} ↑ 0.199 m/s/year (placebo) ↑ 0.203 m/s/year (atorvastatin) Calcification ↑ 21.7%/year (placebo) ↑ 22.3%/year (atorvastatin)
SEAS[17]	1,873	Simvastatin 40 mg + Ezetimibe 10 mg	4.4 years	Age 67/68 years Female 39/39% TAV 94/95% V_{max} 3.1/3.1 m/s LDL 3.59/3.62 mmol/L	V_{max} ↑ 0.16 m/s/year (placebo) ↑ 0.15 m/s/year (E+S) P_{mean} ↑ 2.8 mmHg/year (placebo) ↑ 2.7 mmHg/year (E+S)
ASTRONOMER[18]	269	Rosuvastatin 40 mg	3.5 years	Age 58/58 years Female 19/15% TAV 46/55% V_{max} 3.16/3.19 m/s LDL 3.18/3.12 mmol/L	P_{mean} ↑ 6.1 mm Hg/year (placebo) ↑ 6.3 mm Hg/year (rosuvastatin) AVA ↓ 0.08 cm^2/year (placebo) ↓ 0.07cm^2/year (rosuvastatin)

AS: aortic stenosis; Vmax: maximum velocity; LDL: low density lipoprotein; TAV: transcatheter aortic valve; Pmean: mean aortic valve gradient.

Disease Progression

Thickened portions of the AV without macroscopically apparent calcification histologically present spots of mineralisation at this stage, as initially described by Otto et al.[2] and illustrated in Figure 1. The presence of these small calcifications reflects the deposition of hydroxyapatite and other calcium phosphates and is referred to as dystrophic calcification. One of the initiators of dystrophic calcification in the valve is the elastin degradation by gelatinases, and MMP-9 expression and activity is increased in AS.[6,7]

The biomechanical and biochemical environment of the structurally altered AV may have unfavourable effects on the survival of valvular interstitial cells (VIC), and apoptotic VICs have been described as a locus for calcium deposits (Figure 1).

End-Stage Disease Processes

The VICs are at the same time characterised by a high phenotypic plasticity and can undergo transdifferentiation in the AV to an osteoblast phenotype associated with an expression of osteogenic proteins (Figure 1).[8] Although the exact mechanism today remains largely unknown, the evolution towards osteoblasts is facilitated by the transcription factor RUNX2/Cbfa1. In addition, transdifferentiation of VIC may involve epigenetic changes in terms of promoter hypomethylation.[9]

Valvular osteoblasts secrete osteogenic proteins, such as bone morphogenetic proteins (BMP), which signal through the Wnt/β-catenin pathway to induce active osteogenesis, referred to as heterotopic ossification.[10] In addition, osteocalcin, which participates in bone calcification, also represents a factor specific to osteoblasts in AS (Figure 1). Biomechanical stresses can induce microfractures in the heterotopic ossification of the AV.[5] At this time point, osteoclasts are formed by the fusion of mononuclear circulating precursors, and participate in a process of bone remodelling, which may further aggravate the valve calcification, which is discussed below.[11] It should also be mentioned that inflammation is not limited to the early stage of AS, but also appears to remain active in the calcified valve tissue, suggesting that inflammation also plays an active role in heterotopic ossification.

TARGETING LIPIDS AND LIPOPROTEINS

Parallels Between AS and Atherosclerosis

AS pathophysiology shares several of the above-described processes with the arterial calcification encountered in atherosclerosis, such as inflammatory infiltration, lipid accumulation, biomechanical factors, ECM remodelling, and deposition of calcium. In addition, there is a parallel between the epidemiology of AS and atherosclerosis. Among the risk factors for AS (ageing aside) hyperlipidaemia, hypertension, kidney failure, and diabetes can also be included. Nevertheless, in almost half of the cases, patients with AS present no underlying atherosclerotic lesions in their coronary arteries.[12] These findings suggests that, despite morphological and epidemiological similarities, the pathophysiology of AS and that of atherosclerosis are not identical.

Statins in AS

These similarities in terms of atherosclerotic vessel disease and AV stenosis raised the hypothesis that lipid-lowering therapy would retard stenosis progression, similar to its effects on atherosclerosis and its ischaemic complications. This notion received support from the promising effect of statins on the process of calcification *in vitro*.[13] In addition, several observational retrospective studies supported the concept of decreased haemodynamic progression of AS in statin-treated patients.[14,15] In addition, a non-randomised and open-label trial of 121 subjects who had indication for statin treatment (because of elevated low-density lipoprotein [LDL]) showed a decreased echocardiographic progression of AS severity by rosuvastatin treatment.[16] However, prospective studies have not provided support for the treatment of AS with cholesterol lowering drugs. The results of the three major randomised controlled trials (RCTs) evaluating the effects of different lipid lowering therapies on AS progression[17-19] are presented in Table 1. Although there are several differences between the study populations in terms of, for example, age, sex-distribution, and the proportion of bicuspid and tricuspid valves, the subjects shared LDL cholesterol levels below those that may motivate statin treatment as primary prevention (Table 1).

Importantly, the subjects included in the three RCTs listed in Table 1 exhibited similar haemodynamic parameters on echocardiography, with a maximum velocity (V_{max}) over the AV between 3 and 4 m/s, indicative of a moderate AS at the start of the treatment. The follow-up time ranged from 2-4 years, and the yearly progression was ≈0.2 m/s for V_{max} (Table 1). None of the studies showed any significant differences between placebo and treated groups for the echocardiographic parameters of AS progression studied (Table 1). It has been suggested that the failure of these clinical trials was due to a recruitment of patients at a too-late stage of AS. A medical intervention at an earlier stage, in a potentially reversible phase of valvular remodelling, could have been more appropriate than at an established moderate stenosis, which may represent an already non-modifiable phase of the disease. However, a recent *post hoc* analysis of 23,508 participants from three RCTs comparing high (80 mg) and lower doses of atorvastatin did not reveal a dose-dependent effect of atorvastatin treatment on the incidence of clinically diagnosed AS during the median follow-up time of 4.9 years.[20] Even though the last word of the story of statins in AS is probably not yet told, currently the treatment of AS by statins cannot be anticipated in the absence of other indications.

Lipoprotein(a)

In a genome-wide association study of 6,942 participants derived from three different cohorts, a single nucleotide polymorphism in the gene encoding lipoprotein(a) (Lp[a]) was significantly associated with AV calcification (as determined by computed tomography [CT]), as well as with incident AS.[21] Lp(a) is a LDL-like lipoprotein

containing apolipoprotein B-100, which can be linked to a lipoprotein-associated phospholipase (Lp-pLA$_2$), an enzyme which hydrolyses oxidised phospholipids (Figure 2).[22] Both Lp(a) and Lp-PLA$_2$ have previously been identified as risk markers for atherosclerosis, and inhibitors of Lp-PLA$_2$ were developed for the treatment of coronary artery disease (CAD).[22] However, in a recent large multicentre RCT of patients with stable coronary disease, the Lp-PLA$_2$ inhibitor darapladib did not show any significant beneficial effects in preventing the primary end-point of cardiovascular (CV) death, myocardial infarction, or stroke.[23] Interestingly, the above-mentioned association of the Lp(a) polymorphism with AV calcification was independent of coronary artery calcification and clinical CAD,[21] lending additional support to a differential pathophysiology between atherosclerosis and AS. Furthermore, a recent study has strengthened the implication of the Lp(a)/Lp-PLA$_2$ pathway in AS by showing that either Lp-PLA$_2$ expression or activity in human stenotic AVs correlated with valve weight, stenosis severity, and valvular calcium content.[24] In the latter study, lysophosphatidylcholine, which is a product of oxidised phospholipid metabolism by Lp-PLA$_2$, induced mineralisation of VICs, an *in vitro* model of valvular calcification.[24] Although an appealing perspective, the potential impact of Lp-PLA$_2$ inhibitors on AS currently remains to be established.

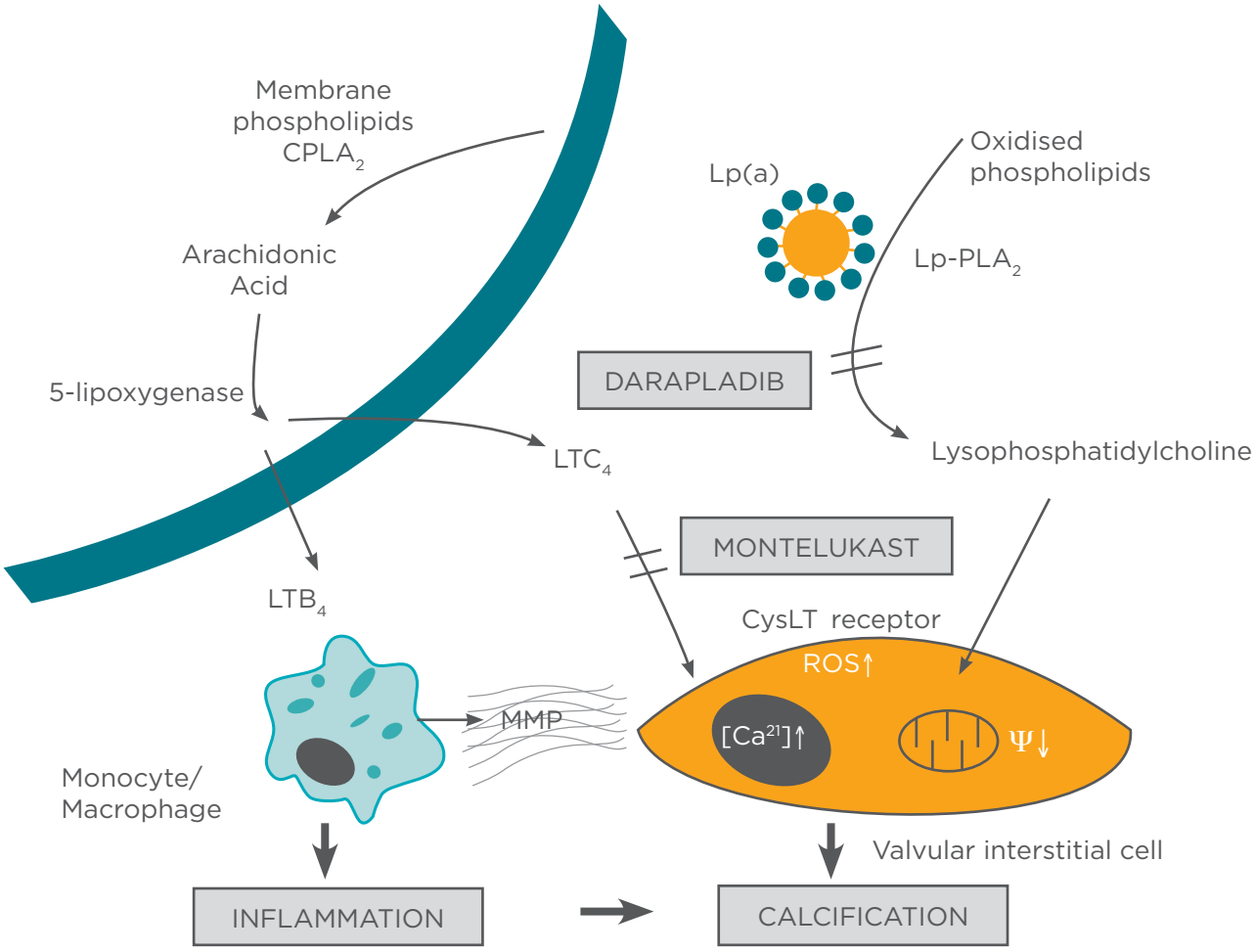

Figure 2: Lp(a), phospholipases and lipid mediators of inflammation in AS.
Membrane phospholipids are metabolised by cytosolic PLA$_2$ into lipid mediators of inflammation, such as leukotrienes, which induce recruitment and activation of inflammatory cells, and activate intracellular pathways in valvular interstitial cells associated with calcification. On the other hand, oxidised phospholipids hydrolysed by Lp-PLA$_2$ yield lysophosphatidyl choline, which also stimulates a calcification process through similar pathways in valvular interstitial cells. The effects of leukotrienes can be blocked by leukotriene receptor antagonists, such as montelukast, whereas darapladib is an Lp-PLA$_2$ inhibitor.
AS: aortic stenosis; Lp: lipoprotein; c: cytosolic; PLA$_2$: phospholipase A$_2$; LT: leukotriene; MMP: matrix metalloproteinase; ROS: reactive oxygen species; Ca: calcium; Ψ: mitochondrial membrane potential.

TARGETING INFLAMMATION

Also intracellular metabolism of phospholipids by means of another phospholipase, namely the cytosolic Group 4A phospholipase A2, ($cPLA_2$) may represent key pro-inflammatory stimuli in AS (Figure 2). Arachidonic acid, which is released from cell membrane phospholipids by means of $cPLA_2$ metabolism, serves as the substrate for the production of potent lipid mediators of inflammation. Arachidonic acid metabolism leads to the production of prostaglandins and thromboxanes through the cyclooxygenase pathway, whereas the 5-lipoxygenase enzyme catalyses the formation of leukotrienes, as depicted in Figure 2. Interestingly, the expression levels of the leukotriene synthesising enzyme 5-lipoxygenase in the thickened portion of human stenotic AVs are significantly associated with the severity of AS, as determined by echocardiographic criteria.[6] This overexpression results in an increased leukotriene production in AVs,[6] which was recently shown to correlate with valvular calcium content.[25] The role of leukotrienes in recruitment and activation of inflammatory cells is well established, and is linked to chemotaxis, protease release, as well as activation of proinflammatory pathways, such as NF- κB induction, which are all hallmarks of AS.[26] In addition, human VICs express the $CysLT_1$ subtype of leukotriene receptors, and leukotriene C_4 induces nuclear calcium signalling, increased production of reactive oxygen species, and a reduction of the mitochondrial membrane potential in these cells (Figure 2).[6,27] The latter processes may be of importance for the concomitant induction of osteogenic proteins and increased calcification observed *in vitro* after leukotriene stimulation.[6]

Given the important role of inflammation in the pathophysiology of AS, anti-inflammatory treatment could represent a potential therapeutic avenue to explore in search of medical treatments of AS. To obtain a rapid transfer of knowledge from bench to bedside, it is of particular interest that anti-leukotrienes today are in clinical use for the treatment of asthma. We recently extrapolated the anti-inflammatory effect exerted in asthma by the leukotriene receptor antagonist montelukast, to CV disease. In a phamacoepidemiological study of a population-based cohort, montelukast was associated with decreased CV risk, preventing the recurrence of either myocardial infarction or stroke.[28] Taken together, these observations suggested a generalisability of the anti-inflammatory effects of leukotriene modifiers beyond pulmonary disease. To test the applicability of the hypothesis that anti-leukotrienes have the potential to be protective for the development of AS, we have analysed the incidence of AS in relation to the use of montelukast in a nationwide population-based cohort of approximately 7 million subjects. With the limitations of integrating only administrative registry data and a short follow-up time (3.5 years), this analysis indicated a trend towards reduced incidence of AS associated with montelukast use, which however, did not reach statistical significance.[29] However, these results could potentially open up the design of future interventional studies targeting the leukotriene pathway in AS.

BISPHOSPHONATES (BPS)

Osteoclasts in AS

As mentioned above, valvular osteoclasts were recently identified in human AS.[11] Activation of RANK (receptor activator of nuclear factor kappa B) which is expressed on the surface of osteoclasts (Figure 1) by the RANK ligand (RANKL) causes release of proteases such as MMP-9, cathepsin K, and tartrate-resistant acid phosphatase. In contrast, osteoprotegerin (OPG), a soluble receptor which is part of the TNF receptor family, binds to RANKL, and hence, blocks its interaction with the RANK (Figure 1). The expression of the RANKL/RANK/OPG pathway has been demonstrated in AVs[10] which reinforces the notion of osteoclast activation in AS. Paradoxically, these osteoclasts do not seem to reduce valvular calcifications, but are rather associated with the progression of calcification.[11] This is radically opposed to other inflammatory diseases, such as periodontal bone loss due to a stimulation of osteoclasts by inflammatory mediators. Nevertheless, there may be a disjunction or malfunction of bone resorption, while the release of proteolytic enzymes from osteoclasts remains intact. The net effects of a stimulation of the osteoclasts would, in that case, be an increase in valve remodelling and an accelerated calcification.

Observational Studies of BPS in AS

BPS are analogues of pyrophosphate prescribed to prevent and treat osteoporosis. Their mechanisms of action are complex and not completely understood, but involve direct inhibition of osteoclasts. Since activation of osteoclasts may be deleterious in AS, BPS could potentially have

beneficial effects on AS progression. A number of retrospective studies have been reported in which the echocardiographic progression of AS has been followed according to BPS exposure, as shown in Table 2. Although the initial studies indicated that BPS use was associated with a decrease in AS progression (measured as either aortic valve area [AVA] or mean pressure gradient; Table 2),[30-32] the most recent and largest cohort did not reveal any significant differences in echocardiographic AS progression (AVA, P_{mean} [mean AV gradient], P_{max} [maximal pressure gradient]), valve replacement surgery or overall survival between BPS-treated and non-treated subjects with mild-to-moderate AS.[33] There are several differences between the studied populations, in terms of age, sex, and the proportion of BPS-treated subjects, which may account for the differential results reported (Table 2). In line with the above discussion on statin treatment in AS, the degree of AS at inclusion may have been decisive also in these studies for the possibility of detecting differences in stenosis progression (Table 2). The latter notion is supported by the results reported in the study by Sterbakova et al.[31] in which the annualised mean gradient change was lower in BPS-treated compared with the untreated patients with mild AS, whereas no effects of BPS treatment were observed in patients with moderate-to-severe AS.

Adding even more complexity to the role of BPS in this context, a CT study of 3,710 women from the community-based Multi-Ethnic Study of Atherosclerosis (MESA) reported that BPS exhibited age-dependent effects on CV calcification. First, AV calcification, defined as any calcified lesion within the AV leaflets, was more prevalent in BPS users compared with unexposed subjects.[34] Second, whereas BPS use was associated with increased AV calcification in women <65 years of age, a trend towards lower prevalence of AV calcification was reported in women ≥65 years.[34]

Table 2: Studies of BPS in AS.

Reference	Study population	Results
Skolnick et al.[29]	N=55 AVA 1.4 cm^2 2.4 years follow up Mean age 82 years 75% women	22% on BPS AVA ↓ 0.2 cm^2 (NT) AVA ↓ 0.1 cm^2 (Osteoporosis treatment; p=0.025)
Sterbakova et al.[30]	N=103 P_{mean} 33 mmHg 2.4 years follow up Mean age~70 years 51% women	27% on BPS P_{mean} ↑ 2 mmHg (NT) P_{mean} ↓ 0.3 mmHg (BPS; p=0.007)
Innasimuthu et al.[31]	N=76 AVA 0.6–2 cm^2 1.9 years follow up Mean age≈80 years 42% women	11% on BPS AVA ↓ 0.2cm^2 (NT) AVA ↑ 0.1 cm^2 (BPS; p=0.001)
Aksoy et al.[32]	N=801 AVA 1.0-2.0 cm^2 Mean age 76 years 100% women	39% on BPS No significant difference between BPS and NT in the rate of change in AVA, P_{mean} or P_{max}
Elmariah et al.[33]	N=3,710 CVD-free community cohort Mean age 63 years 100% women	5.8% on NC-BPS <65 years AC ↑ by NC-BPS ≥65 years AC ↓ by NC-BPS

AS: aortic stenosis; BPS: bisphosphonates; AVA: aortic valve area; P_{mean}: mean aortic valve gradient; NT: non-treated; P_{max}: maximal pressure gradient; CVD: cardiovascular disease; NC-BPS: nitrogen-containing bisphosphonates; AC: aortic calcification.

CONCLUSION

The molecular and cellular pathophysiology of AS is an active and complex process with components of inflammation, valvular remodelling, dystrophic calcification, oxidative stress, apoptosis, and heterotopic ossification (Figure 1). These pathways contain several potential targets for medical treatment, as has been exemplified above. For example, although statins appear to prevent calcification *in vitro*, the notion of targeting atherogenic lipids by means of statin treatment in AS has been challenged by the negative results of RCTs (Table 1). However, other lipid pathways, such as Lp(a) and Lp-PLA_2 have recently emerged in the context of AV calcification and AS (Figure 2). Furthermore, lipid mediators of inflammation, such as leukotrienes (Figure 2) may be interesting targets for future studies, as is also other anti-inflammatory treatments. Finally, whereas results of studies with BPS have generated contradictory results (Table 2), more specific targeting of calcification pathways activated in the AV could potentially be anticipated. Possible synergies between these pathways should also be considered in view of evaluating combination therapies. In conclusion, further mechanistic studies are needed to better understand the pathophysiology of AS and to lead to new therapeutic strategies for the prevention, or at least the delay, of either surgical or transcatheter valve implantations.

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FACTORS AFFECTING SERUM PARAOXONASE 1 ACTIVITY IN MIGRANT AND RESIDENT GUJARATI SOUTH ASIANS

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ABSTRACT

Paraoxonase 1 (PON1) protects against the development of atherosclerosis by hydrolysing damaging lipid peroxides formed in low-density lipoprotein (LDL) and cell membranes. The effect of migration on PON1 activity is unknown. We have investigated the effect of migration on serum PON1 activity by comparing an Indian Gujarati community who had migrated to Sandwell (West Midlands, UK) with people still living in their villages of origin around the town of Navsari (Gujarat, North-West India) and determined biochemical and nutritional parameters which may correlate with PON1 activity. PON1 activity was almost double in men and women living in Sandwell compared to those in Navsari. In the Spearman's Rank correlation analysis, PON1 activity was significantly negatively correlated with fasting glucose and C-reactive protein, and positively with fasting non-esterified fatty acids, homeostasis model assessment (HOMA)-insulin sensitivity, and high-density lipoprotein (HDL) in rural Indian men, positively with HDL and apolipoprotein A1 (apo A1) in migrant Indian men, negatively with HOMA-β-cell activity and apo A1. It was positively correlated with HDL cholesterol, mean LDL particle diameter, and oxidised-LDL (ox-LDL) in rural Indian women and positively with HDL cholesterol, apo A1, and ox-LDL in migrant Indian women. Multivariate analysis with PON1 as the dependent variable indicated significant relationships with migrant status and HDL cholesterol only (both $p<0.001$). In conclusion, in the South Asian populations studied here, PON1 activity significantly correlated with measures of insulin sensitivity and the metabolic syndrome; however, by far the strongest determinant of PON1 activity was migration, or at least environmental and dietary changes which accompany migration. We also found an as yet unexplained lack of gender difference in HDL cholesterol, which requires further investigation.

Keywords: Paraoxonase 1, migration, South Asians, coronary heart disease (CHD).

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of mortality amongst Indian migrants. High CHD rates are consistently reported for populations of Indian origin across the world.[1,2] Men and women in Britain whose families originated on the Indian sub-continent have approximately 40% higher morbidity and mortality from CHD than the British population of European descent.[3,4] In India, CHD

prevalence in cities reaches similar levels to that in migrants; however, CHD rates are believed to remain low in rural India.[5]

Established risk factors such as diabetes, serum cholesterol, smoking, hypertension, and obesity are major contributors to CHD in Indian populations.[2,5] However, most previous studies attempting to explain their increase in CHD on migration have compared them with populations in the locality to which they had moved. We hypothesised that migration would adversely affect established, and perhaps reveal, novel risk factors amongst migrants to Britain when compared with contemporaries from an identical cultural and genetic background, still resident in their villages of origin in rural India.[2] To this end we compared CHD risk factors in Gujarati Indians who had migrated to Sandwell, UK, with contemporaries still living in their villages of origin in the Gujarat. We found that increased fat intake and obesity in Sandwell migrants explained the much higher prevalence of established and novel CHD risk factors found in this population.[2]

The paraoxonase (PON) multigene family comprises three members: PON1, PON2, and PON3.[6] The genes for all three members of the family are widely expressed in mammalian tissues;[7] however, PON1 and PON3 are predominantly located in the plasma associated with high-density lipoprotein (HDL) while PON2 is not found in the plasma but has a wide cellular distribution.[8] PON1, PON2, and PON3 all retard the proatherogenic oxidative modification of low-density lipoprotein (LDL) and cell membranes, and are therefore considered to be antiatherogenic.[9] PON1 is now considered to be a major factor in the antioxidative activity of HDL.[10]

The transgenic expression of human PON1, PON2, or PON3 in various mouse models of atherosclerosis (AS) has been shown to retard or reverse AS by mechanisms which include a reduction in circulating and aortic oxidised-LDL (ox-LDL), a reduction in macrophage oxidative stress and foam cell formation, an increase in reverse cholesterol transport, and a normalisation of endothelial function.[11-15]

Several studies have previously shown prospectively that PON1 activity is a risk factor for CHD development independently of HDL concentration,[16-19] although the finding is not universal.[20,21] Several case control studies have shown low PON1 to be a risk factor for CHD in various Indian populations resident on the sub-continent;[22-24] however, nothing is known regarding the effect of migration on serum PON1. The purpose of the present investigation was therefore to determine the effect of migration on serum PON1 and its relationship to other CHD risk factors in migrant and resident Gujaratis.

MATERIALS AND METHODS

Study Design, Setting, and Participants

This was a cross-sectional study of an Indian Gujarati community who had migrated to Sandwell (West Midlands, UK) from rural villages around the town of Navsari (Gujarat, North-West India) with age, gender, and caste matched contemporaries still living in those villages in India, as previously described in detail.[2] Prospective participants were contacted by letter. Clinic sessions in the UK and India ran between September 1998 and September 2001. All participants in the study gave informed consent. Ethical approval for the study was obtained both in Sandwell and Gujarat by the respective local research ethics committees.

Variables

Participants were invited to attend clinics fasting (from 10:00 pm the previous evening); trained fieldworkers administered standard, pretested questionnaires on lifestyle (including smoking and drinking habit), medical history, and place of origin. Venous blood was collected from all participants. Serum and plasma were obtained within 1 hour by centrifugation and snap-frozen to be stored at -70 °C. Venous blood samples were collected fasting and at 120 minutes after the administration of a 75 g oral glucose challenge. Waist measurements were taken (after removing upper clothing) as the narrowest circumference above the umbilicus and below the rib. The hip was measured over light clothing as the widest circumference around the buttocks. Waist and hip measurements were taken non-consecutively in duplicate (repeated where there were differences >2%). Body mass was measured on Seca 870 solar scales (Seca Ltd., Birmingham, UK). A Leicester standard rule (Seca Ltd.) was used to determine the height of the subject. Blood pressure (BP) was measured three times (using the mean of the last two for analysis), with the validated semi-automatic Omron HEM-705CP (Omron Healthcare Europe, Mannheim, Germany) with appropriate cuff sizes, after more than 5 minutes seated.

Laboratory Analyses

Venous blood was collected in EDTA from all participants and was analysed for a full blood count using haematology analysers at either the clinical haematology department, Sandwell Hospital, UK (STAK S, Beckman Coulter Corp., Hialeah, FL, USA), or the Mankodi Laboratory, India (Bayer Advia, Bayer Diagnostics, Baroda, India). Plasma glucose was determined by a glucose oxidase method using automated biochemistry analysers at Sandwell and Navsari.

Plasma and serum aliquots were stored at -70 °C and transported by air, frozen in liquid nitrogen or dry ice, from India to the UK, and analysed as a single batch for serum cholesterol (CHOD-PAP method), triglycerides (GPO-PAP method), HDL cholesterol (direct method) (ABX diagnostics, Montpellier, France), and apolipoproteins (apo) A1 and B by turbidimetry and nephelometry respectively (ABX diagnostics), all on a Cobas Mira autoanalyser (Roche, Welwyn Garden City, UK). Serum non-esterified fatty acids (NEFA) were measured by enzymatic colorimetry (WAKO chemicals, Alpha Laboratories, Eastleigh, UK). Ox-LDL was determined using a sandwich enzyme-linked immunosorbent assay technique involving a two-site immunoassay (Mercodia, Uppsala, Sweden).[25] Plasma fibrinogen and C-reactive protein (CRP) were measured by immunonephelometry on a Dade Behring BNII autoanalyser (Milton Keynes, UK). Serum B12 and homocysteine were measured by chemiluminescent immunoassay using the Access immunoassay system (Beckman Instrument Inc., Fullerton, CA, USA). Insulin was measured by immunoassay using charcoal extraction, and pancreatic β cell function and insulin sensitivity were calculated by the homeostasis model assessment (HOMA). In young, lean, and healthy reference subjects, β cell function (HOMA B) is 100% and insulin sensitivity (HOMA S) equals 1. LDL particle subclasses were determined using nondenaturing gradient gel electrophoresis.[26] Paraoxonase activity - determined by the rate of generation of *p*-nitrophenol - was determined at 405 nm, 25 °C, with the use of a continuously recording spectrophotometer (described in detail elsewhere).[27]

PON1 analysis and other biochemical analyses on frozen plasma and serum were performed in 'batch' following the recruitment of the final subjects (India and the UK) and the associated transportation of plasma samples to our UK laboratory in December 2002. Batch analysis was conducted over a period of 3 months.

Study Size, Bias, and Confounding

Of a total of 814 eligible subjects invited for the original study, 242 were recruited from the UK (67% response rate) and 294 from India (65% response rate). The required number of subjects to observe a statistically significant ($p<0.05$) correlation coefficient of at least 0.35, using a two-sided test with a power of 90%, was 81. To control for confounding variables, subsets by gender and site were developed.

Statistical Analysis

Data were analysed in SPSS v14 (SPSS Inc., Chicago, IL, USA.) using standard and non-parametric tests and Kolmogorov-Smirnov normality plots. Parametric data are presented as mean (standard deviation [SD]) and non-parametric data as medians (interquartile range [IQR]). Comparisons were made by T-test or Mann-Whitney test, as appropriate. Univariate analysis of correlations was reported with Spearman's rank correlation coefficients. Linear regression models were calculated to test the strength of association - beta (95% CI) from independent predictors. The standardised beta coefficients presented allowed a direct comparison (along a scale of 0-1) of the strength of each association within the model.

RESULTS

The demographic and biochemical characteristics of the study populations are given in Tables 1 and 2. Men and women living in Sandwell had increased body mass index (by 6 [4.5–7.4] kg/m^2 mean [95% CI]), waist circumference, systolic and diastolic blood pressure, and hypertension compared to those living in Navsari but smoked less and drank more. The prevalence of CHD presented in Table 1 also shows non-significantly higher levels in migrants compared to rural contemporaries; men and women living in Sandwell had significantly higher total cholesterol, triglyceride, apo B, apo A1, haemoglobin, fibrinogen, folate, vitamin B12, insulin, and HOMA B than those living in Navsari, but significantly lower homocysteine and HOMA S. Women in Sandwell had significantly higher HDL, iron, NEFA, and CRP than women in Navsari, but lower fasting plasma glucose and ox-LDL. PON1 activity was almost double in Sandwell men and women (Table 2).

Table 1: Demographic details of the study populations (data are mean [SD] or number [percentage]).

Characteristics of Indian Gujaratis	Men				Women				p
	Navsari (n=139)		Sandwell (n=119)		Navsari (n=155)		Sandwell (n=123)		
Age (Years)	49.1	(14.6)	49.0	(12.8)	48.5	(14.0)	49.2	(11.5)	0.18
BMI (kg/m^2)	21.0	(3.9)	25.9	(3.9)	20.8	(4.1)	26.6	(4.9)	<0.001
Waist circumference (cm)	80.0	(11.5)	91.3	(12.8)	72.9	(11.1)	82.3	(10.6)	<0.001
Systolic BP (mmHg)	121	(20)	135	(20)	111	(22)	121	(21)	<0.001
Diastolic BP (mmHg)	74.8	(11.7)	83.7	(10.5)	68.9	(10.6)	75.6	(10.5)	<0.001
Alcohol use	81	(58.3)	93	(78.2)	1	(0.6)	37	(30.1)	<0.001
Ever smoker	81	(58.3)	28	(23.5)	7	(4.5)	1	(0.8)	<0.001
Diabetes	24	(17.4)	19	(16.7)	17	(10.8)	18	(16.1)	0.36
OHT	13	(9.4)	10	(8.4)	5	(3.2)	4	(3.25)	0.005
Insulin therapy	1	(0.7)	1	(0.8)	2	(1.3)	0		0.09
Hypertension	33	(23.6)	53	(44.2)	28	(18.0)	39	(31.7)	<0.001
AHT	12	(8.6)	16	(13.4)	11	(7.1)	16	(13.1)	0.21
CHD	13	(3.4)	13	(10.9)	9	(5.8)	11	(8.9)	0.29
Stroke	1	(0.7)	2	(1.6)	0		3	(2.4)	0.02
Statin therapy	0		14	(11.8)	1	(0.6)	4	(3.3)	<0.001

SD: standard deviation; p: probability; BMI: body mass index; BP: blood pressure; OHT: oral hypoglycaemic therapy; AHT: antihypertensive therapy; CHD: coronary heart disease.

In Spearman's correlation analysis (Table 3) PON1 activity had a significant negative correlation with fasting glucose and CRP, and positive with fasting NEFA, HOMA S, and HDL in rural Indian men; positively with HDL and apo A1 in migrant Indian men; negatively with HOMA B and apo A1, and positively with HDL, mean LDL particle diameter, and ox-LDL in rural Indian women; and positively with HDL, apo A1, and ox-LDL in migrant Indian women.

Spearman's analysis of correlations of ox-LDL indicated a plethora of correlations; however, on multivariate analysis, only total cholesterol (p<0.001), haemoglobin (p=0.012), and HDL (p=0.02) remained significant (Table 4). Multivariate analysis with PON1 as the dependent variable indicated significant relationships with migrant status and HDL only (both p<0.001). Variables included in the multivariate models were repeated with an exclusion of known diabetics and statin therapy, where PON1 remained independently related to HDL and migrant status (p<0.001).

DISCUSSION

In this population of South Asians, PON1 activity correlated with a number of parameters related to insulin resistance (IR) and the metabolic syndrome (MetS), as has been described previously.[28] Recently it has been shown that human PON1 can prevent diabetes mellitus development in mice through its antioxidant properties and the stimulation of beta-cell insulin release, suggesting a possible role for PON1 in insulin biosynthesis.[29,30] PON2 also has an important role in hepatic insulin signalling[31] which may suggest a role for the PON family in energy metabolism that requires further investigation. PON1 activity in Type 1 diabetes is inversely correlated with blood glucose levels; also PON1 is lower in subjects with MetS, suggesting modulation of PON1 by factors associated with IR.[32] Similar results have recently been reported in Type 2 diabetes adding further support to this theory, but which requires more detailed molecular analysis. *In vitro* studies have indicated that the

PON1 gene is upregulated by high glucose concentrations in HepG2 hepatocytes.[33] However, PON1 is extremely susceptible to oxidative inactivation,[34] and the high levels of oxidative stress which accompany hyperglycaemia[35] may well counteract increased hepatic PON1 production. The association of PON1 with duration of diabetes, which has been reported in T2DM,[28] may also be explained by this mechanism.

The negative relationship between PON1 activity and IR offers interesting possibilities. The relationship between IR, MetS, and the subsequent progression to Type 2 diabetes could indicate that the measurement of PON1 activity may provide an early indicator of metabolic disturbances before the onset of measurable arterial changes. Further work in this area is warranted.

Table 2: Biochemical parameters of the study populations (data are mean [SD] or median and interquartile range).

	Rural Indian men	Migrant Indian men	*Differences between men (p)*	Rural Indian women	Migrant Indian women	*Differences between women (p)*
Plasma glucose (mmol/l)	5.81	-2.38	5.6	-1.8	0.81	5.41
Plasma insulin (mU/l)	8.73	(5.95, 14.10)	10.3	(7.61, 14.66)	<0.001	9.05
HOMA B (%)	103	-59,167	124	-90,198	<0.001	111
HOMA S (0-1)	0.481	(0.277, 0.809)	0.402	(0.282, 0.571)	0.002	0.521
NEFAs (mmol/l)	0.358	-0.271	0.438	(0.220)	0.027	0.269
Serum cholesterol (mmol/l)	4.84	-1.03	5.34	-1.01	<0.001	4.87
Serum triglycerides (mmol/l)	0.82	(0.64, 1.19)	1.15	(0.93, 1.57)	<0.001	0.78
HDL cholesterol (mmol/l)	1.17	-0.41	1.23	-0.31	0.51	1.15
Apo B (g/l)	0.98	-0.3	1.15	-0.29	<0.001	0.95
Apo A1 (g/l)	1.42	-0.41	1.55	-0.33	<0.001	1.48
Homocysteine (µmol/l)	15.8	(11.1, 21.9)	10.4	(7.9, 13.6)	<0.001	12.8
Serum folate (mg/l)	3.1	(2.50, 4.90)	4.9	(3.75, 6.00)	<0.001	4.15
Serum vitamin B12 (µg/ml)	148	-112, 195	181	-144, 234	0.001	142
hs-CRP (g/l)	1.17	(0.56, 2.86)	1.06	(0.69, 2.50)	0.65	0.83
PON-1 (nmol/min/ml)	140	(88, 180)	229	(186, 293)	<0.001	123
Oxidised LDL (U/l)	39	(29.0, 51.0)	41.9	(29.0, 52.0)	0.54	33

SD: standard deviation; HOMA: homeostasis model assessment; HOMA B: β-cell function; HOMA S: insulin sensitivity; NEFA: non-esterified fatty acid; HDL: high-density lipoprotein; Apo: apolipoprotein; hs-CRP: high-sensitivity C-reactive protein; PON1: paraoxonase 1 activity; LDL: low-density lipoprotein.

Table 3: Spearman's rank correlation analysis of paraoxonase 1 activity.

	Rural Indian men		Migrant Indian men		Rural Indian women		Migrant Indian women	
	R	p	R	p	R	p	R	p
Fasting glucose	-0.279	0.001						
2 hr PCG	-0.308	0.005						
Fasting NEFA	0.318	0.002						
2 hr post-challenge NEFA								
HOMA S	0.393	0.001						
HOMA B						-0.213	0.033	
HDL cholesterol	0.261	0.014	0.236		0.027	0.308	0.001	0.322
ApoB								
Apo A1			0.262	0.014		-0.269	0.003	0.37
Mean LDL particle diameter						0.221	0.017	
Ox LDL						0.182	0.05	0.272
hs-CRP	-0.295	0.005						

R: Spearman's rank correlation coefficient; PCG: post-challenge glucose; NEFA: non-esterified fatty acid; HOMA: homeostasis model assessment; HOMA S: insulin sensitivity; HOMA B: β-cell function; HDL: high-density lipoprotein; Apo: apolipoprotein; LDL: low-density lipoprotein; Ox: oxidised; hs-CRP: high-sensitivity C-reactive protein.

Table 4: Multivariate analysis of paraoxonase 1 activity and oxidised low-density lipoprotein.

Multivariate models	β (95% CI)			p
1. Dependent variable: Ox LDL (U/l)				
Serum cholesterol (mmol/l)	8	5.3	10.7	<0.001
Haemoglobin (μmol/l)	1.7	0.38	3.02	0.012
HDL cholesterol (mmol/l)	-10.8	-19.9	-1.7	0.02
2. Dependent variable: PON1 (nmol/min/ml)				
Migrant status	0.563	0.405	0.721	<0.001
HDL cholesterol (mmol/l)	0.489	0.259	0.72	<0.001

Ox: oxidised; LDL: low-density lipoprotein; HDL: high-density lipoprotein; PON1: paraoxonase-1 activity.

The increase in HDL-cholesterol (C) on migration, which we have reported previously,[2] is most probably due to the shift from a high carbohydrate diet in India to a high fat diet in the UK, leading to increased energy in the diet.[2] There was also a lack of gender differences in HDL-C concentration in either Navsari or Sandwell (and apo A1 in Sandwell). This is unusual as it is generally accepted that women have higher HDL-C than men, at least until the menopause.[36] Only 48% of the female study participants answered the question as to whether they were menopausal or not. Of those that did, 85 answered yes and 49 no. The expected differences in HDL-C were found: 1.11±0.26 mmol/l with menopause and 1.28±0.33 mmol/l without (p<0.001). It would, therefore, appear that the

lack of gender differences is due to higher than expected HDL-C in the males. The lack of gender differences in HDL-C are not explained by plasma testosterone or sex hormone binding globulin levels and require further investigation and confirmation.

Perhaps the most striking observation from this study is the relationship between PON1 activity and migrant status. PON1 activity was almost double in the Sandwell population compared to those in Navsari in both men (229 [186, 293] versus 140 [88, 180] nmol/minute/ml p<0.001) and women (216 [169, 229] versus 123 [75, 172] nmol/minute/ml p<0.001). Activity levels in Sandwell were more comparable to those reported in other European-based populations.[37] The most likely explanation for this rise in PON1 activity on migration, given that neither HDL-C or apo A1 increased to the same proportion, is that the rise in PON1 is a response to the increased blood glucose and the rise in lipids which, in turn, is likely to be due to the increase in fat and energy in the diet. This response may be to protect against an increase in oxidation and glycation due to the increased serum lipids and glucose. These findings suggest environmental rather than genetic factors to be responsible. However, as the samples were not able to be PON1 genotyped, we cannot exclude genetic differences between the two populations.

It has been found that paraoxonase functional activity is partially dependent on genotype.[38] The PON1 gene at 7q21.3 encodes both paraoxonase and arylesterase activity, and is subject to a number of polymorphisms.[39,40] Two alleles, the PON1-192 Q-isoform and PON1-192 R-isoform, have been identified as the chief determinants of paraoxonase activity.[41,42] This results in the inheritance of two PON1-192R high-activity alleles, two PON1-192Q low-activity alleles or heterozygous codominant inheritance of both, and consequently three distinct phenotypes for paraoxonase activity.[43,44] Although encoded for and by the same gene, there is no significant evidence demonstrating that arylesterase activity is affected by the PON1 genotype. It could be suggested that measurement of arylesterase activity would, therefore, produce more reliable results; however, it is not yet fully understood whether the rate of paraoxon hydrolysis affects the rate of phenyl acetate hydrolysis by a single enzymatic molecule. It was neither possible to genotype the sample populations of this study, nor to measure arylesterase activity. A further study to analyse phenotypes is needed, given that data on paraoxon as substrate alone places an important limitation on our conclusions.

Furthermore, a number of inflammatory cytokines, oxidative stress (downregulators), hypolipaemic drugs, and polyphenols such as quercetin, resveratrol, and punicalagins (upregulators) are also known to affect PON1 gene expression. This is through a variety of mechanisms including sterol regulatory element binding protein 2 and Sp1 binding to the PON1 promoter, peroxisome proliferator-activated receptor α and γ activation, stimulation of the aryl hydrocarbon receptor, and activation of c-Jun N-terminal kinase and cAMP protein kinase A signalling cascades.[45] Differences in any of these effectors in the Navsari and Sandwell populations could be responsible for the activity of differences found.

Differences in oxidative stress, a known inhibitor of PON1 activity, could also contribute.[34] The Navsari population was deficient in folate and vitamin B12 leading to increased plasma homocysteine. Homocysteine is further metabolised to homocysteine thiolactone (HTL) a potent inducer of cardiovascular disease and a natural substrate of PON1.[46] PON1 is pivotal in preventing the proatherogenicity of HTL, but HTL can also modify PON1 by N-homocysteinylation[46] inhibiting its activity, and it is conceivable that in the Navsari population, this has happened.

More recently, patients with anaemia, caused by vitamin B12 deficiency, were found to have significantly lower PON1 activity than healthy controls, or than in patients with iron deficient anaemia.[47] There was a statistically significant correlation between serum vitamin B12 concentration and PON1 activity (which was not the case in our study). PON1 activity was restored to the levels found in healthy controls after vitamin B12 therapy. Therefore, the lower PON1 activity found in the Navsari population could be secondary to the vitamin B12 deficiency found in this population. Further studies in this area are warranted.

In conclusion, in the South Asian populations studied here, PON1 activity significantly correlated with measures of insulin sensitivity and the MetS; however, by far the strongest determinant of PON1 activity was migration, or at least environmental and dietary changes which accompany migration. To reinforce our findings, a study incorporating

genotyping the PON1 gene will need to be conducted. We also found higher levels of HDL amongst migrant females relative to rural contemporaries, which could be due to alcohol intake, and also an (as yet) unexplained lack of gender difference in HDL-C, which requires further investigation.

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RATIONALE FOR PROMISING NOVEL THERAPEUTIC APPROACH FOCUSED ON ENDOTHELIN PATHWAY FOR PERIPHERAL ARTERIAL DISEASE

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ABSTRACT

There is evidence to suggest that endothelin (ET-1) is involved in the pathophysiology of peripheral arterial disease (PAD), contributing to atherosclerotic narrowing of the lower limb arteries as well as microvascular dysfunction. This paper summarises the evidence and discusses the potential role of a promising novel therapeutic strategy for PAD focused on ET-1 pathway modification. ET-1 pathway is involved in PAD with raised plasma levels and local sources of ET-1. More recent evidence of a potential role of ET-1 in ischaemia-induced skeletal muscle damage suggests that this may be a useful target for treatment. ET antagonism may play an adjunctive role in improving endothelial function and reducing oxidative tissue damage within the affected vessels. However, in patients with advanced atherosclerotic lesions, manipulation of the ET-1 pathway is unlikely to be of a significant benefit in terms of lesion regression and improving blood flow. Results from small clinical studies support data from promising initial pilot and basic research. Considering the potentially important role of ET-1 in the development of vascular dysfunction reviewed in the present article – conditions with increased inflammatory activity, oxidative stress, and vascular tone such as atherosclerosis, and PAD – larger clinical trials using ET receptor antagonists are encouraged and needed.

Keywords: Peripheral arterial disease, endothelin, cause-based treatment.

INTRODUCTION

Peripheral arterial disease (PAD) is defined as the set of vascular diseases caused primarily by atherosclerosis (AS) and thromboembolic pathophysiological processes that alter the normal structure and function of the aorta, its visceral branches, and arteries of the lower limbs.[1] In Western society, >20% of the population over the age of 55 are affected by this condition.[2] One-third of patients with PAD have intermittent claudication (IC),[3] defined as leg pain during exercise caused by arterial occlusive disease, which leads the patient to stop, and decreases with rest. In severe PAD, critical limb ischaemia (CLI) occurs, where viability of the limb is threatened, and 20% of patients face limb loss within a year.[4] There is evidence to suggest that endothelin (ET-1) is involved in the pathophysiology of PAD, contributing to atherosclerotic narrowing of the lower limb arteries as well as microvascular dysfunction. This paper summarises this evidence and discusses the potential role of a promising novel therapeutic strategy for PAD focused on ET-1 pathway modification.

ET-1 Pathway

ET-1 production and secretion are primarily controlled at the gene transcriptional level (Figure 1). ET-1 gene expression is regulated by a number of transcription factors, including activator protein 1, hypoxia inducible factor-1, nuclear factor κB (NF-κB), vascular endothelial zinc finger 1, GATA binding protein 2 (GATA-2), and GATA-4, nuclear factor of activated T cells among others that are of relevance for AS and diabetes. The transcription factors are, in turn, activated by several inducers such as angiotensin II, cytokines, glucose, insulin,

and hypoxia. Mature ET-1 is formed from pre-pro-ET-1 via a 39-amino acid intermediate, big ET-1.[5] Big ET-1 is processed to ET-1 by a family of ET converting enzymes (ECEs) and other enzymes such as chymases, non-ECE metalloproteinases, and endopeptidases.[5,6] Under physiological conditions, ET-1 is produced in small amounts mainly in endothelial cells, primarily acting as an autocrine and/or paracrine mediator. Under pathophysiological conditions, however, the production is stimulated in several cell types such as endothelial cells, vascular smooth muscle (VSM) cells, cardiac myocytes,[7] and inflammatory cells.[8,9] Increased expression of ET-1 has been demonstrated in AS animal models[10,11] as well as in human coronary artery disease (CAD)[12,13] and PAD.[14] This results in enhanced vasoconstrictor tone, increased inflammatory activity, and elevated oxidative stress. The effect of ET-1 is mediated via activation of its two distinct receptors, the ET Type A and B (ETA and ETB) receptors. In the vascular wall the ETA receptor is localised to the smooth muscle cell and mediates the major part of the vasoconstrictor effect of ET-1 under physiological conditions. The ETB receptor is localised to the endothelial cells and mediates vasodilatation via release of nitric oxide (NO). ETB receptors are also located on VSM cells and mediate vasoconstriction.

ENDOTHELIAL DYSFUNCTION AND INFLAMMATION AT THE PATHOPHYSIOLOGY OF PAD

Endothelial dysfunction is considered to occur early during the development of cardiovascular disease (CVD) including AS and vascular complications associated with diabetes mellitus. A key event in endothelial dysfunction is the reduction in bioavailability and biological activity of NO. Reduced levels of NO contribute to increased vascular tone, inflammation, platelet aggregation, and oxidative stress, which all are central features of AS and diabetic vasculopathies.[15] Development of endothelial dysfunction involves several biological mediators including increased expression of ET-1 and altered expression of ET receptors.[16] Considering the prominent biological actions mediated by ET-1, such as potent vasoconstriction, pro-inflammatory actions, and mitogenic properties, overproduction of ET-1 may be of significant pathological importance in CVD (Figure 2).

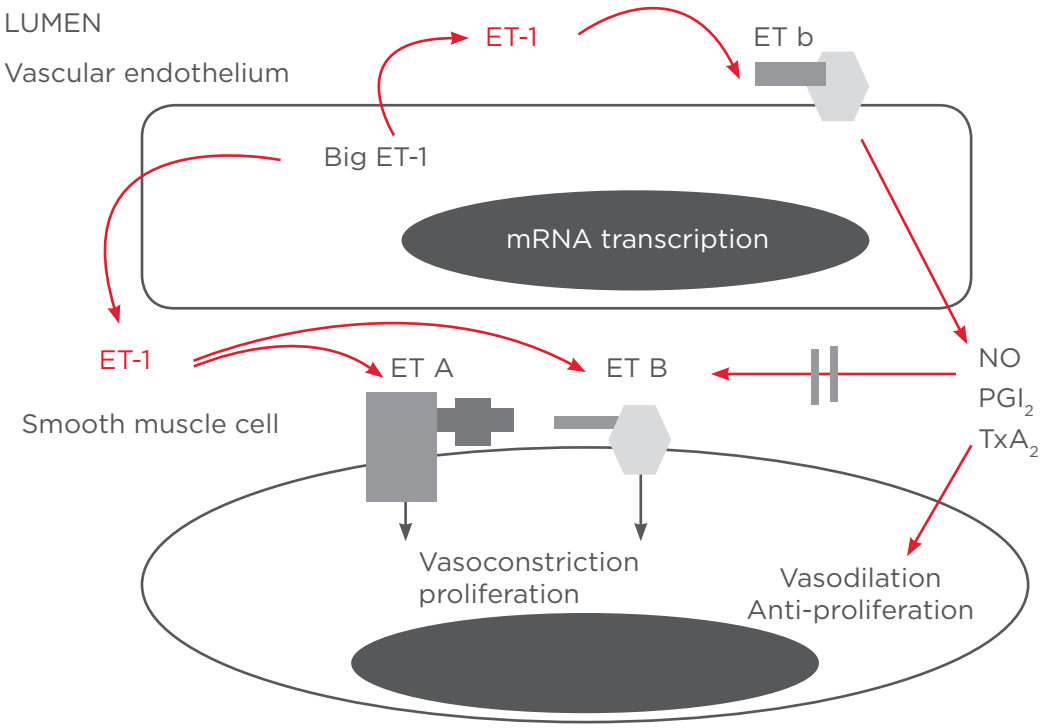

Figure 1: Endothelin pathway in the vessel wall.
ET-1: endothelin; ET A/B: endothelin receptor type A/B; NO: nitric oxide; PGI_2: prostacyclin; TxA_2; thromboxane A2.

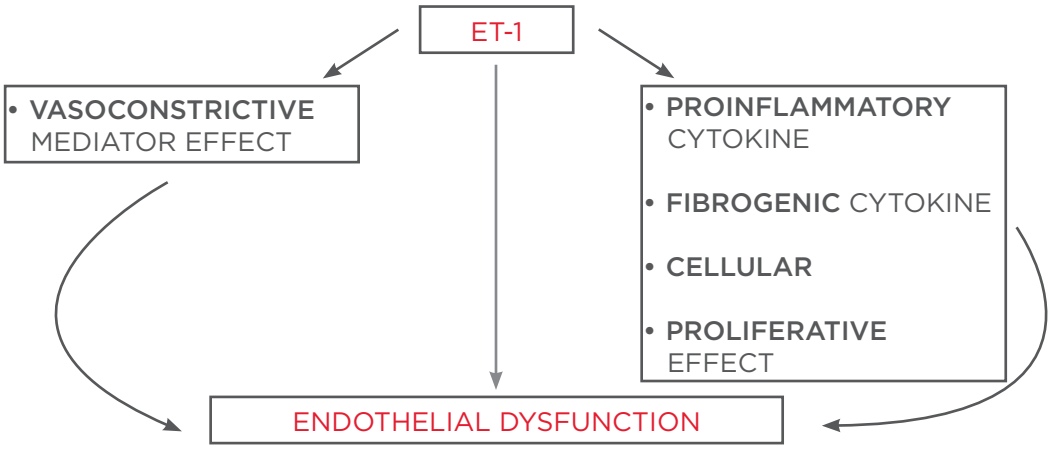

Figure 2: Endothelin (ET-1) biological actions.

The endothelium seems to be responsible for the balanced relationships involved in the functioning of the vascular wall. When this balance is upset, the regulation of vascular homeostasis is lost, causing endothelial dysfunction, defined as functional deterioration of the endothelium characterised by vasospasm, vasoconstriction, abnormal coagulation mechanisms, abnormal fibrinolysis, and an increase in vascular cell proliferation. A reduction in the brachial arterial flow mediated dilation (BAFMD), a surrogate of endothelium function, has been demonstrated in patients with PAD[17] with no significant differences according to the severity of the disease,[18,19] supporting the hypothesis that endothelial dysfunction is a process which begins in the early stages of PAD. Moreover, elevated high-sensitivity C-reactive protein (hsCRP) seems to be an independent predictor of cardiovascular (CV) events in patients with PAD.[17]

The endothelium homeostasis is, in part, mediated by NO levels. There is an inducible isoform of nitric oxide synthase (iNOS), which is stimulated by cytokines and produces much larger quantities of NO than the other isoforms.[20] In order to work, these enzymes require cofactors, including tetrahydrobiopterin (BH4) and nicotinamide adenine dinucleotide phosphate (NADPH). The importance of NO in atherogenesis was suggested after studies in mice with an apolipoprotein E (apoE) deficiency found that the atherosclerotic lesions developed spontaneously when endothelial nitric oxide synthase (eNOS) was eliminated. However, in studies with apoE and iNOS double-knockout mice, there was a reduction in the formation of the atherosclerotic plaque. These findings suggest that eNOS-derived NO may 'protect' the vascular wall from AS, while the NO deriving from iNOS may promote the formation of atherosclerotic lesions.[20,21]

Once released into the lumen of the vessel, the NO deriving from the endothelium is oxidised or participates in nitrosylation reactions. The NO activity is the result of the balance between its production by NOS and its inactivation by oxygen free radicals. We know that ET-1 and its receptors are involved in the expression of such NOS and in the NO levels. Therefore, ETA inhibits NO synthesis, whereas ETB increases NO production and release (Figure 1).[22] However, there is a substantial change in the expression and function of the ET receptors in various pathophysiological conditions as AS, resulting in an altered biological response.[16]

Oxidised low-density lipoprotein (LDL) also increases the production of ET-1.[23] High levels of ET-1 have been found in patients with arteriosclerosis, both in coronary disease[24,25] and PAD.[26] In a previous study, as occurred with BAFMD, we found no relationship between the nitrite levels in plasma, as estimator of NO production, and the severity of the PAD.[27] This leads us to think that the loss of the physiological function of NO as a homeostatic signal by which the endothelium acts, occurs in the first stages of PAD and that this is perpetuated through a vicious circle (self-feedback), which leads to a reduction in BAFMD as estimator of endothelial dysfunction. Otherwise, we have seen that elevated hsCRP has a linear association to the clinical severity with which PAD presents.[28] We not only found this linear

association between clinical severity and elevated hsCRP, but we also found that, although weak, there seems to be a reverse correlation between hsCRP levels and BAFMD values in these patients.

Therefore, the CRP stimulates the production of NO by NOS, increasing NO oxidation and nitrosylation and reducing the levels of BH4, encouraging the formation of free radicals. These free radicals, in turn, inactivate the NO which has been produced and destroy the BH4, resulting in endothelial dysfunction. In fact, it has been demonstrated in *in vitro* studies, that CRP is capable of stimulating the production of NO, independent of iNOS stimulation.[29] We observed increased levels of hsCRP in the patients with PAD and also a linear correlation between these levels and the clinical severity degree.[27] This finding suggests the existence of an inflammatory substrate in the aetiopathogenesis of PAD. Both CRP, as principal indicator of systemic inflammation, and other cytokines (interleukin [IL]-6, tumour necrosis factor [TNF-α] etc.), may be responsible for the loss of balance in the endothelial NO system and the subsequent endothelial dysfunction. The reverse correlation between BAFMD and the hsCRP levels found in this study, although weak, implies a relationship between inflammation and endothelial dysfunction in the aetiopathogenesis of PAD, with the loss of the homeostatic function of NO as a key step in the origins of the disease, but not in its progression.

Summarising, when BAFMD is used as a surrogate measure of endothelial dysfunction, our observations suggest that endothelial function during the initial stages of PAD may not progressively deteriorate with disease severity.[19] Concentrations of the inflammatory marker CRP, however, exhibited a great correlation with PAD progression. These observations support the previously documented role of inflammation in the maintenance and progression of PAD.[28]

These findings highlight the potential importance of early intervention during the initial stages of PAD in order to delay disease progression. As a prototypical target for therapeutic intervention, patients with early PAD may benefit from reduced concentrations of ET-1. Concentrations of ET-1 can be decreased using renin-angiotensin inhibitors, which indirectly block ET-1 production, and statins, which reduce ET gene expression irrespective of their lipid-lowering effects.[30,31] Treatment with dual and single ET receptor antagonists (i.e. bosentan, zibotentan) may also confer benefits in the future and merit evaluation, either alone or in combination with other drugs that delay PAD progression.

POTENTIAL ROLE OF ET-1 IN PAD

In PAD, raised ET-1 levels have been demonstrated in both patients with claudication and CLI.[32] Mangiafico et al.[32,33] found that whilst no correlation between plasma ET-1 levels and pain-free walking distance in patients with claudication was found, treating claudicants with prostaglandin E1 resulted in improved walking distances, which was associated with decreases in ET-1 plasma levels. Recently, our group confirmed that raised ET-1 plasma levels occurred in patients with PAD compared to controls. Our study found higher ET-1 plasma levels in patients with claudication compared to those with CLI.[34] This suggests that in very advanced disease, as vessel damage progresses, potential sources of ET-1 such as endothelial cells may be lost, leading to reduced ET-1 secretion. Newton et al.[35] studied markers of endothelial function in patients with CLI before and after lower limb amputation and found that ET-1 plasma levels, unlike those of vascular endothelial growth factor and von Willebrand factor, did not reduce following amputation.[10] Moreover, higher levels of ET-1 in these patients were associated with poorer prognosis in terms of all-cause mortality and CV mortality.

ET-1 immunoreactivity, mRNA levels,[36] and ET receptor binding[37] have been found in atherosclerotic plaques and diseased coronary arteries where ET-1 was associated with medial VSM cells and luminal endothelial cells. Indeed, VSM cells could be a potential source of ET-1 in AS, which would explain that the development of the disease is associated with increased production of ET-1 even if there is loss of ET-1 production by endothelial cells, except in the advanced stages of the disease. Meanwhile, ETA receptors were found predominantly on smooth muscle cells and ETB receptors on microvascular endothelial cells.[38]

In diseased femoral and popliteal arteries obtained from patients with CLI, a similar pattern has been shown with ET-1 binding to ETA and ETB receptors on medial VSM cells and further ETB receptors located on microvessels and vascular nerves.[39] These atherosclerotic lesions are significant sources of ET-1. Whilst ET-1 is known to be a paracrine

factor, being released abluminally to act on ET receptor bearing cells locally, overspill of the peptide into the systemic circulation are likely to contribute to raised plasma levels and enables the peptide to also exert its effect further downstream. The effects of ET-1 on vessels and blood flow are well established. Infusion of ET-1 into femoral arteries in dogs resulted in an initial increase followed by a gradual decrease in femoral blood flow.[40,41] In humans, ET-1 infusion reduced blood flow in the legs of young healthy volunteers.[42] In older subjects, ET antagonism resulted in greater increases in blood flow than in younger subjects, suggesting that ET-1 may play a role in the age-related raised baseline vascular tone.[43] However there is currently little evidence on the direct effect of ET-1 on femoral blood flow in patients with PAD.

PAD is characterised by endothelial dysfunction and AS in the lower limb arteries,[44] and ET-1 is likely to contribute to both of these processes. ET-1 activation is associated with atherogenic risk factors such as hypertension, hyperlipidaemia,[45] and diabetes[46] where, as a potent vasoconstrictor, it acts to antagonise endothelium-derived vasodilators such as nitric oxide contributing to endothelial dysfunction.[47-49] Endothelial dysfunction in turn, promotes leucocyte adhesion, thrombosis, inflammation, and cell proliferation leading to the development of atherosclerotic plaques. Once developed, these lesions provide further sources of ET-1 which acts, in a paracrine fashion, to contribute to the progression of the disease.[50] As the atherosclerotic lesions progress, flow-limiting stenoses or even occlusions occur, compromising perfusion to the distal tissue.

INCREASED OXIDATIVE STRESS BY ET-1

Several reports support a role for ET-1 in the formation of reactive oxygen species (ROS). Formation of superoxide (O_2-) will result in decreased bioactivity of NO and formation of peroxynitrite. ET-1 stimulates ROS production in human endothelial and VSM cell cultures,[51,52] as well as in isolated vessels.[53-55] Mainly ETA receptors seem to mediate ROS production stimulated by ET-1 although ETB receptors have been suggested to contribute to O_2- production.[51,52] ET-1 has been shown to increase the expression of NOX2, the rate-limiting subunit of NADPH oxidase.[56] The stimulating effect of ET-1 on O_2- production may also be coupled to the NADPH oxidase subunit p22phox.[56,57] These data are in agreement with the *in vivo* observations in transgenic mice over expressing ET-1.[58] These mice exhibit endothelial dysfunction, increased NADPH oxidase activity, and increased expression of NOX2. A recent report shows that ET-1 increases expression and activity of p47phox in rat aortic rings via the ETA receptor which would suggest that ET-1 is involved in the activation of NADPH oxidase.[59] It was recently demonstrated that the selective ETA antagonist avosentan significantly reduces aortic plaque formation in diabetic apoE−/− mice, independently of effects on blood pressure, lipid, or glucose levels. The anti-atherosclerotic effect of avosentan was associated with a significant reduction in macrophage infiltration and reduced nitrotyrosine levels, reflecting a parallel decrease in oxidative stress and AS.[60] This observation supports the notion that ET-1-mediated stimulation of oxidative stress is of importance, although the link between increased oxidative stress and AS is complex, as exemplified by the observation that genetic deletion of p47phox, an essential component of NADPH oxidase, did not affect the progression of AS in apoE−/− mouse model.[61] On the other hand, O_2− generation may increase AS by activating mitogenic signalling pathways in VSM cells.[62]

The vasoconstrictor effects of ET-1 may be more pronounced in states of reduced bioavailability of the eNOS co-factor tetrahydrobiopterin (BH4).[63] Recent data demonstrate that ET-1 mediates O_2- production and vasoconstriction through activation of NADPH oxidase and uncoupled NOS in the rat aorta.[54] The uncoupling of NOS means that NOS generates O_2- instead of NO in states of BH4 deficiency. These effects could be inhibited by BH4 and by dual ET receptor blockade, but not by selective ETA receptor blockade.[54] ET-1 may also promote BH4 deficiency in a rat model of hypertension via an ETA-mediated NADPH oxidase pathway, which contributes to impaired endothelium-dependent relaxation.[64]

ET-1 has been demonstrated to be associated with increased oxidative stress and endothelial dysfunction in humans. ET-1 mediates a marked increase in O_2- production in internal mammary arteries and saphenous veins from patients with CAD via a mechanism involving a flavin-dependent enzyme which is likely to be NADPH oxidase also in humans.[65] ET-1 also stimulates O_2- formation and impairs endothelium-dependent vasodilatation

in human venous bypass conduits from patients with CAD and diabetes.[66] The impairment in endothelium-dependent vasodilatation *in vivo* induced by ET-1 in healthy humans can be prevented by administration of the anti-oxidant vitamin C.[67] Conversely, ET-1 is increased in human CAD by oxygen-derived radicals *ex vivo* and *in vivo*,[68] indicating a vicious circle of oxidative stress leading to increased expression of ET-1 which, in turn, increases oxidative stress. Taken together, these data suggest that increased oxidative stress induced by ET-1 in the vessel wall contributes to endothelial dysfunction that, together with pro-inflammatory effects, may be important mechanisms behind development of AS.

PRO-INFLAMMATORY EFFECTS OF ET-1

Apart from its direct vasomotor activity, ET-1 has been implicated in the inflammatory processes within the vascular wall. Specifically, ET-1 activates macrophages, resulting in the release of pro-inflammatory and chemotactic mediators, including TNF-α, IL-1, IL-6, and IL-8.[69-71] Cardiac overexpression of ET-1 in mice is associated with an inflammatory response involving increased activation of the pro-inflammatory transcription factor NF-κB and expression of several pro-inflammatory cytokines including TNF-α, IL-1, and IL-6.[72] In turn, transcription factors and pro-inflammatory cytokines such as NF-κB, TNF-α, and IL-6 stimulate ET-1 production.[73] ET-1 enhances the expression of adhesion molecules on TNF-α stimulated vascular endothelial cells[74] suggesting an involvement of ETB receptors. Furthermore, ET-1 stimulates aggregation of polymorphonuclear neutrophils.[75] Conversely, ET receptor blockade attenuates the accumulation of neutrophils and myeloperoxidase activity in the ischaemic myocardium.[76] Although not a true AS model, it has been shown that vascular inflammation and neointima formation following vascular injury by carotid artery ligation is attenuated in endothelial cell ET-1 knockout mice.[77]

IL-6 has been implicated in the development of AS[78] and endothelial dysfunction in humans.[79] As noted above, ET-1 stimulates IL-6 release *in vitro* and *in vivo*. The release of IL-6 induced by ET-1 from human VSM involves activation of NF-κB. Possibly, release of IL-6 may further increase oxidative stress as suggested by the *in vitro* observation that IL-6 induces production of ROS.[80]

ET-1 RECEPTOR ANTAGONISM THERAPEUTIC APPROACH

Need for a Cause-Based Therapeutic Strategy

It has been shown that it is essential to focus and act on the risk factors associated with PAD, since PAD patients are at high-risk of CV morbidity and mortality. Between 2-4% of patients with IC present a non-fatal CV event during the first year of diagnosis, and approximately 60% will die from various CV causes.[81,82] For patients with critical ischaemia, the prognosis is even worse, with higher rates of limb loss and mortality from CV causes. Therefore, treatments for this condition must be directed, on one hand, towards treating the CV risk factors and, on the other hand, to treat localised symptoms caused by the disease.

25% of IC patients progressively deteriorate, requiring intervention in 5% of all cases in the form of revascularisation of the lower limbs, with 1-2% requiring a major amputation.[83,84] Current treatment options in this regard include smoking cessation - a dose-dependent relationship between smoking and the severity of PAD has already been demonstrated[85] - and the promotion of exercise programs for patients with IC, since exercise, in addition to attenuating CV risk factors, has also been shown to relieve the symptoms of the disease.[86,87] On the other hand, structured supervised exercise programmes have been shown to be effective in improving a patient's walking ability.[88] However, these programmes are not available in most health systems as their high cost and low compliance rate make them prohibitive and difficult to implement. Intermittent pneumatic compression therapy has also been shown to be effective in alleviating disease symptoms.[85]

With respect to surgery, endovascular revascularisation, open surgery, and other techniques have proven effective, and remain the best options when trying to save a limb and improve quality of life (QoL) in critical ischaemia. It should be noted, however, that there is still much controversy surrounding the relevance of surgical indications in patients with claudication, with some contending that surgery should be reserved for cases of critical ischaemia. The results of revascularisation techniques depend on the location and morphology of the lesion, but in a significant percentage of cases it cannot be carried out due to an associated comorbidity or a recurrence

of the symptomatology over time as a result of vessel restenosis. Thus, percutaneous transluminal angioplasty (PTA) has been shown to improve QoL at 3 months in patients with IC.[89] However, up to 60% of patients develop restenosis, with a non-negligible recurrence-of-symptoms ratio. On the other hand, applied pharmacological therapies have shown controversial benefits. While such therapies are generally employed to manage limb pain and improve QoL for patients, none has shown any convincing efficacy in preventing amputation.[82] Clinical trials have evaluated numerous drug therapies, such as naftidrofuryl, pentoxifylline, L-carnitine, levocarnitine, garlic, testosterone, cilostazol, and chelation therapy, but none have proven effective or less effective than standard treatments.[90,91]

At present, ET receptor antagonists are approved for the treatment of pulmonary arterial hypertension and for the prevention of new digital ulcers in systemic sclerosis. Accumulating evidence suggest that ET-1 is of pathophysiological importance in the development of several CV diseases including AS, PAD, and diabetic angiopathy. The expression of ET-1 and its receptors are markedly altered during disease progression, resulting in increased biological importance of the ET-1 system. Results from small randomised clinical studies support data from promising initial pilot studies. Considering the potentially important role of ET-1 in the development of vascular dysfunction reviewed in the present article – conditions with increased inflammatory activity, oxidative stress, and vascular tone such as AS and PAD – larger clinical trials using ET receptor antagonists are encouraged and needed.

Preclinical Studies with ET Receptor Antagonists

A dual ETA/ETB receptor antagonist reduced foam cell formation in macrophages exposed to oxidised LDL.[92] In the same study, Babaei et al.[92] showed that the ET receptor antagonist significantly inhibited the development of AS in LDL receptor knockout mice. These data clearly suggest that ET-1 is involved in the development of AS and that ET receptor blockade exerts anti-atherogenic effects.

CONCLUSION

In summary, there is evidence that the ET-1 pathway is involved in PAD with raised plasma levels and local sources of ET-1. In the diseased arteries, ET-1 is likely to play a role in atherogenesis. More recent evidence of a potential role of ET-1 in ischaemia-induced skeletal muscle damage suggests that this may be a more useful target for treatment. ET antagonism may play an adjunctive role in improving microvessel function and reducing tissue damage within the affected muscle. However, in patients with advanced atherosclerotic lesions, manipulation of the ET-1 pathway is unlikely to be of significant benefit in terms of lesion regression and improving blood flow. Results from small randomised clinical studies support data from promising initial pilot studies. Considering the potentially important role of ET-1 in the development of vascular dysfunction reviewed in the present article — conditions with increased inflammatory activity, oxidative stress, and vascular tone such as AS and PAD — larger clinical trials using ET receptor antagonists are encouraged and needed.

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CURRENT CONTROVERSIES IN INFECTIVE ENDOCARDITIS

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ABSTRACT

Infective endocarditis (IE) remains a devastating disease with a high mortality. Its microbiology is changing with increasing incidence of *Staphylococcus aureus* infection, which often does not present with the typical signs that are incorporated into diagnostic criteria. With expanding indications for the implantation of cardiac devices, such as cardiac resynchronisation pacemakers and defibrillators, the incidence of device-related endocarditis is also increasing rapidly. The European Society of Cardiology (ESC) provides evidence-based guidelines regarding prophylaxis, diagnosis, and management of IE, the most recent of which were published in 2009. The aim of this review is to identify topical areas of controversy, where new research developments have shed some light since the last publication of these guidelines. The review focuses on antibiotic prophylaxis, investigating potential IE in *S. aureus* bacteraemia, and management of cardiac device-related IE. It is notable that not 1 in over 80 recommendations in the latest ESC guidelines is backed by data that are level of evidence A. Whilst it is clearly unethical to perform trials in this area of medicine against placebo, treatment algorithms and approaches to management can readily be compared with each other in a randomised way, and data using this approach are emerging. Increasing the quantity and quality of evidence when it comes to IE remains a significant challenge.

Keywords: Infective endocarditis, *Staphylococcus aureus*, prophylaxis, cardiac devices, guidelines.

INTRODUCTION

Infective endocarditis (IE) is a devastating disease with an incidence estimated between 30-100 episodes per million patient-years.[1-4] Since its first description by the case series from Sir William Osler in 1885, the epidemiology of IE has evolved from predominantly a disease of young adults with rheumatic valve disease, to a disease also affecting the elderly (aged between 70-80), and those with prosthetic valves and intra-cardiac devices. A smaller group of challenging patients also exists who are on long-term renal dialysis, are intravenous drug abusers, HIV positive, or have complex congenital heart disease.[5-7] There have also been changes in the microbiology of IE with increasing incidence of *Staphylococcus aureus* infection and multi-drug resistant bacteria. In the latest cohort study from 2,781 inpatients across 52 different hospitals around the world (ICE-PCS), 42% of IE cases were caused by *Staphylococcus*, of which 31% were *S. aureus*.[8] These changes in demographics and epidemiology of IE likely contribute to the persistently high inpatient mortality (around 20%) with the worst outcomes in elderly patients, *S. aureus* infection, prosthetic valve involvement, and those at high operative risk.[6,8] The European Society of Cardiology (ESC) provides evidence-based guidelines regarding prophylaxis, diagnosis, and management of IE, the most recent of which were published in 2009.[9] Many controversial areas remain in the management of IE and it is clearly impossible to touch on all of these. The aim of this review is to identify topical areas of controversy, where new research developments have shed some light since the last publication of these guidelines.

PROPHYLAXIS

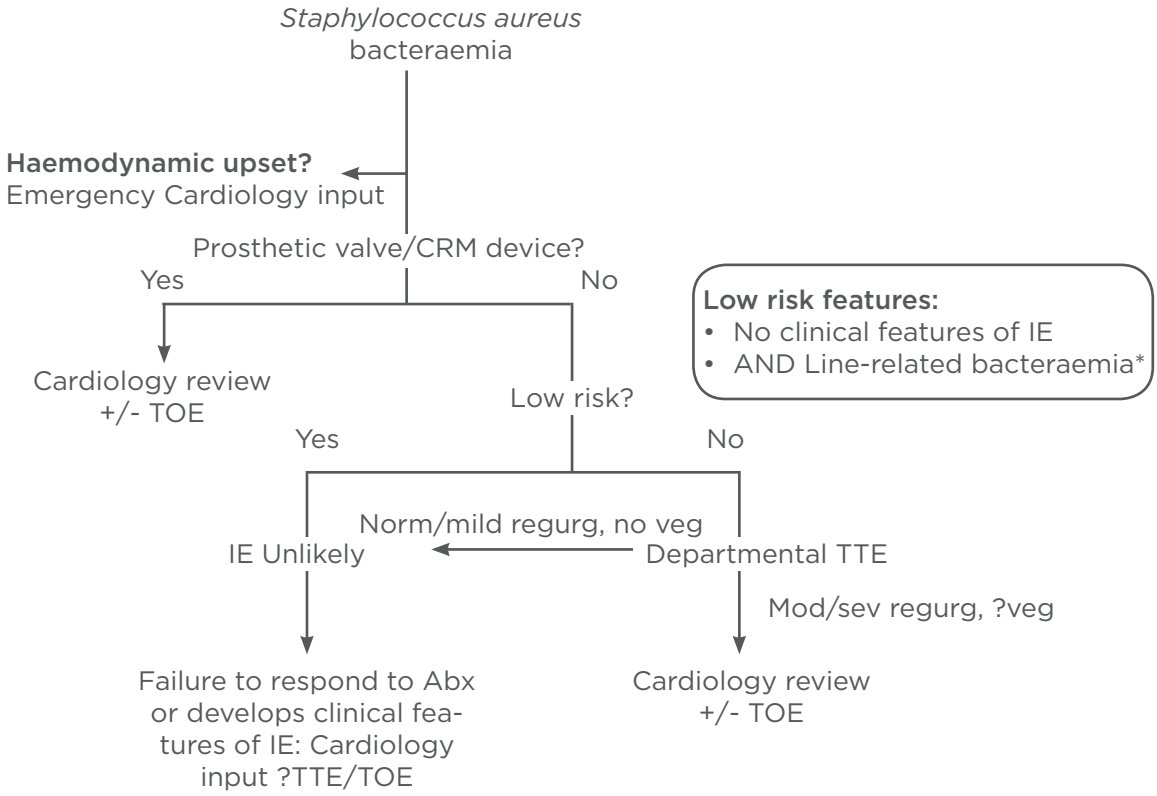
Prophylaxis for the prevention of IE following invasive or dental procedures has been under intense debate for >50 years and remains standard practice in many parts of the world. Evidence for bacterial prophylaxis to prevent IE came from early observational studies which showed bacteraemia following dental procedures,[10] and animal studies where prophylaxis with amoxicillin prevented development of IE in animals inoculated with *Streptococcus*.[11] Later evidence demonstrated that bacteraemia was more common following routine dental brushing, and therefore, far more frequent than that of dental procedures (particularly in those with periodontal disease and prolonged brushing),[12,13] and that the risk of IE from dental procedures was extremely low at 1:14,000,000.[14] Furthermore, the existing evidence has failed to demonstrate any efficacy of widespread antibiotic prophylaxis in the prevention of IE. Following comprehensive reviews, three professional bodies, the ESC, the American Heart Association (AHA), and the British Society for Antimicrobial Chemotherapy (BSAC) have recommended restricting antibiotic prophylaxis to use in high-risk patients. (Table 1).[4,15,16] For patients in the highest risk groups, in particular those with prosthetic valves, there is evidence for the use of antibiotic prophylaxis. It should be noted though that common native valve diseases including bicuspid valve, mitral valve prolapse, and calcific aortic stenosis are not considered high risk.

A recent review by the UK National Institute of Health and Clinical Excellence (NICE) took the matter further and recommended stopping antibiotic prophylaxis for all patients.[17] NICE did recognise the high-risk patient groups as suggested by the other guidelines, but chose not to separate the groups in the interest of simplicity and population economics. The published recommendations from NICE were received with mixed reactions from clinicians addressing risk-benefit considerations of individual patients, and a call was made for both national and international monitoring of IE outcomes.[18] A questionnaire sent in 2012 to cardiologists, cardiothoracic surgeons, infection specialists, and dentists showed 39% of cardiologists and cardiothoracic surgeons did not follow the NICE guidelines; even amongst dentists with the highest rate of acceptance (87%), 36% still prescribed antibiotic prophylaxis following the guideline publication.[19] Similar trends were observed in North America where despite 75% satisfaction with AHA guidelines, 70% of dentists still had patients on antibiotics before dental procedures.[20] Studies are now also emerging on the impact of the new guidelines on IE admission and complications. In one North American study of 1,157 paediatric IE admissions (age <18), there was no significant change in either admission trends or incidence of oral streptococci IE.[21] Similar findings were observed in another North American study where no perceivable increase was observed in the incidence of viridans group streptococci.[22]

Table 1: Cardiac conditions of patients at highest risk of infective endocarditis (IE) and recommendations for antibiotic prophylaxis.

Recommendations	Class	Level
Antibiotic prophylaxis should only be recommended for patients at highest risk of IE.	IIa	C
1. Patients with a prosthetic valve or any prosthetic material used for cardiac valve repair,		
2. Patients with previous IE,		
3. Patients with congenital heart disease (CHD): a. Cyanotic CHD with or without previous interventions, b. CHD with complete repair (surgical or percutaneous) for the next 6 months, c. When a residual defect persists after cardiac surgery or percutaneous technique.		
Antibiotic prophylaxis is no longer recommended in other forms of valvular or CHD.	III	C

Modified from Habib G et al.[44]



Definition of line-related bacteraemia
- Bacteraemia due to *S. aureus*, absence of another obvious source and any of the following:
  - Isolation of *S. aureus* with the same susceptibility profile from:
    - purulent exudate in catheter insertion site, or
    - the catheter tip without any other obvious source.
  - Temporal resolution of signs and symptoms of infection after removing the catheter without active antibiotics (all cases will receive active antibiotics once bacteraemia is diagnosed).

Figure 1: Proposed algorithm for prioritisation of echocardiography in the setting of *Staphylococcus aureus* bacteraemia.
CRM: cardiac rhythm management; TOE: transoesophageal echocardiography; IE: infective endocarditis; TTE: transthoracic echocardiography; Abx: antibiotics.
Modified from Joseph et al.[32]

In the UK, a recent study that examined all patients admitted with IE did not show a significant increase in the incidence of IE cases or deaths from IE 2 years after implementation of the NICE guidelines, despite 78.6% reduction in the prescription of antibiotic prophylaxis.[19] These studies suggest that reducing antibiotic prophylaxis had no adverse impact on IE although all are limited by inclusion of patients, including those at high-risk. All guidelines agree that regular dental surveillance to promote good oral hygiene and reduce the need for invasive procedures is important, and the lack of access in many countries, including the UK, remains a significant problem.[23]

IMAGING IN *S. AUREUS* BACTERAEMIA (SAB)

S. aureus is an increasingly common cause of IE and associated with significantly higher mortality due to its propensity to cause deep-seated and metastatic infections.[6,8] IE is a frequent complication of SAB,[24] and recent BSAC guidelines have recommended echocardiography as a routine investigation for all cases of SAB.[25] Evidence to support routine screening of patients with SAB for associated IE came first from a study by Fowler et al.[26] which found 25% of 103 patients with SAB had echocardiographic evidence of IE despite the presence of clinical features in only

7% of the patients. Subsequent studies using echocardiography in patients with SAB found similar results.[27,28] Guidelines, however, differ on the timing and modality of echocardiography that should be used. Transthoracic echocardiography (TTE) has the advantage of being widely accessible with no risk to the patient but, despite advances in imaging technology, good quality TTE remains less sensitive (82-89%) when compared to transoesophageal echocardiography (TOE).[29] The quality of TTE can also vary depending on patient factors such as body mass index and concurrent lung disease, and identifying vegetations in patients with metallic valves and intra-cardiac devices is difficult with TTE due to imaging artefact. Imaging can also identify coincidental pathology, such as minor aortic valve thickening, which can confuse the diagnostic process and lead to further investigations. TOE on the other hand is a limited resource, costly, and poses a small procedural risk to the patient. If imaging is carried out very early in the course of the illness, it is also possible that small vegetations could be missed, and no guidance exists on whether repeated imaging is beneficial. Some clinicians are reluctant to perform TOE in patients with SAB and have no features of IE, who show prompt clinical response to antimicrobial treatment, and have the focus of infection (e.g. a central intravenous catheter) promptly removed.

Several studies in the last few years have identified groups of patients who are at high or very low-risk of having echocardiographic evidence of IE. Those patients with intra-cardiac material, such as prosthetic valves or cardiac rhythm management devices, have up to a 5-fold higher risk of IE,[26,30-32] and patients with community acquired compared to hospital acquired SAB infection have up to a 3-fold higher risk of IE.[28,31-33] Those patients with prolonged bacteraemia on repeated blood cultures of >4 days are also at higher risk of developing IE.[30] Conversely, patients with strictly defined line-related infections have a particularly low risk of IE,[31] particularly when the high-risk features described above are also absent.[32] Those patients with a TTE which demonstrates no or mild valvular regurgitation only, and no evidence of IE, are also at low risk of developing IE.[32,33] A recent publication has suggested a diagnostic approach incorporating these features, suggesting that imaging can be prioritised appropriately in patients with SAB; we summarise this approach in Figure 1. This algorithm relies on early and continued input from a specialist infectious disease/microbiology and cardiology multidisciplinary team.[34] Imaging should be of the best quality and performed by an experienced operator, with guidance and interpretation overseen by the cardiology team in the context of the individual clinical case.

TIMING OF SURGERY

Almost half of patients with IE need surgical treatment due to complications.[5,8,35] The three main indications for surgery are heart failure, uncontrolled infection, and prevention of embolic events (Table 2). It is not clear, however, when surgery should be performed, and this remains a hotly contended topic. The benefits of early surgery may also depend on the point at which it is measured, as there is an initial increase in mortality due to the operation itself before the longer term advantages become apparent. A recent meta-analysis by Chatterjee et al.[36] included 10 studies totalling 3,758 patients who had early surgery compared to conventional medical treatment and showed significantly less long-term all-cause mortality in the early surgical cohort compared to conventional treatment (OR 0.53, 95% CI 0.37-0.75, p=0.0004). However, the studies were heterogeneous - with the definition of early surgery ranging from within 48 hours to up to 60 days - included both native valve and prosthetic valve infection, and excluded the large recent cohort study from ICE-PCS.[37] In order to provide a more accurate overview of the role of early surgery we have separated native from prosthetic valve IE (PVE).

Native valve IE remains the most common presentation, accounting for two-thirds of all IE admissions.[8] Most of the observational studies, to date, favour early surgery (Figure 1). This is supported by a randomised controlled trial (RCT) from Kang et al.[38] where patients with native valve endocarditis were randomised to either surgery within 48 hours of admission (37 patients) or to conventional medical treatment (39 patients). The study demonstrated a significant reduction in the primary end-point of in-hospital death and new embolic events in patients who underwent early surgery (3%) compared to conventional treatment (23%). This important difference persisted at 6-month follow-up. Furthermore, in a recent observational study of 212 patients (73 had surgery within 2 weeks and 139 had medical therapy), survival at a median of 5.5-years follow-up was significantly higher in the early surgery group when

compared to medical therapy (94% versus 82%) with reduced cardiac events (12% versus 32%).[39] Altogether, these data suggest that early surgery is beneficial for patients with native valve IE; whether surgery should be performed within 48 hours of admission as suggested by Kang et al.[38] or later is still under debate. It is also important to note that in the study by Kang et al.[38] all patients undergoing early surgery had severe valvular disease, so results may not apply to other groups (such as those with embolic disease only). The organisms in their cohort were also not typical of those seen at other centres and the timing of embolic events not clear.

PVE accounts for 21% of all IE and is associated with significantly greater mortality.[8] Given the greater and more severe complications of PVE, one could reasonably suspect that early surgery would be beneficial in these patients. Evidence for the role of early surgery in PVE is sadly limited to three observational studies (Figure 2). The largest study (1,025 patients: 490 early surgery [median 8 days], 535 medical therapy alone), ICE-PCS, showed significantly lower mortality in patients treated with early surgery compared to medical therapy but only in the highest risk quintile. In the overall cohort there was no survival benefit associated with early surgery, either in-hospital (HR 0.9, 95% CI 0.76-1.07) or at 1-year follow-up (HR 1.04, 95% CI 0.89-1.23). The two smaller studies showed similar findings (Figure 2). The apparent difference for early surgery in native and PVE is difficult to explain, but the greater complexity and frequency of complications associated with PVE surgery may be contributory. In addition, organisms vary between endocarditis contracted soon after valve implantation compared to those contracted later. The presence of local and distant complications as well as the level of co-morbidities also adds to the risk of undertaking surgery.

Table 2: Indications and timings of surgery in left-sided native valve infective endocarditis (IE).

Recommendations: Indications for surgery	Timing	Class	Level
A. HEART FAILURE (HF)			
Aortic or mitral IE with severe acute regurgitation or valve obstruction causing refractory pulmonary oedema or cardiogenic shock.	Emergency	I	B
Aortic or mitral IE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or cardiogenic shock.	Emergency	I	B
Aortic or mitral IE with severe acute regurgitation and persisting HF or echocardiographic signs of poor haemodynamic tolerance (early mitral closure or pulmonary hypertension).	Urgent	I	B
Aortic or mitral IE with severe acute regurgitation and no HF.	Elective	IIa	B
B. UNCONTROLLED INFECTION			
Locally uncontrolled infection.	Urgent	I	B
Persisting fever and positive blood culture >7-10 days.	Urgent	I	B
Infection caused by fungi or multiresistant organisms.	Urgent/elective	I	B
C. PREVENTION OF EMBOLISM			
Aortic or mitral IE with large vegetations (>10mm) following one or more embolic episodes, despite appropriate antibiotic treatment.	Urgent	I	B
Aortic or mitral IE with large vegetations (10mm) and other predictors of complicated course (HF, persistent infection, abscess).	Urgent	I	C
Isolated very large vegetations (>15mm)	Urgent	IIb	C

Modified from Habib G et al.[44]

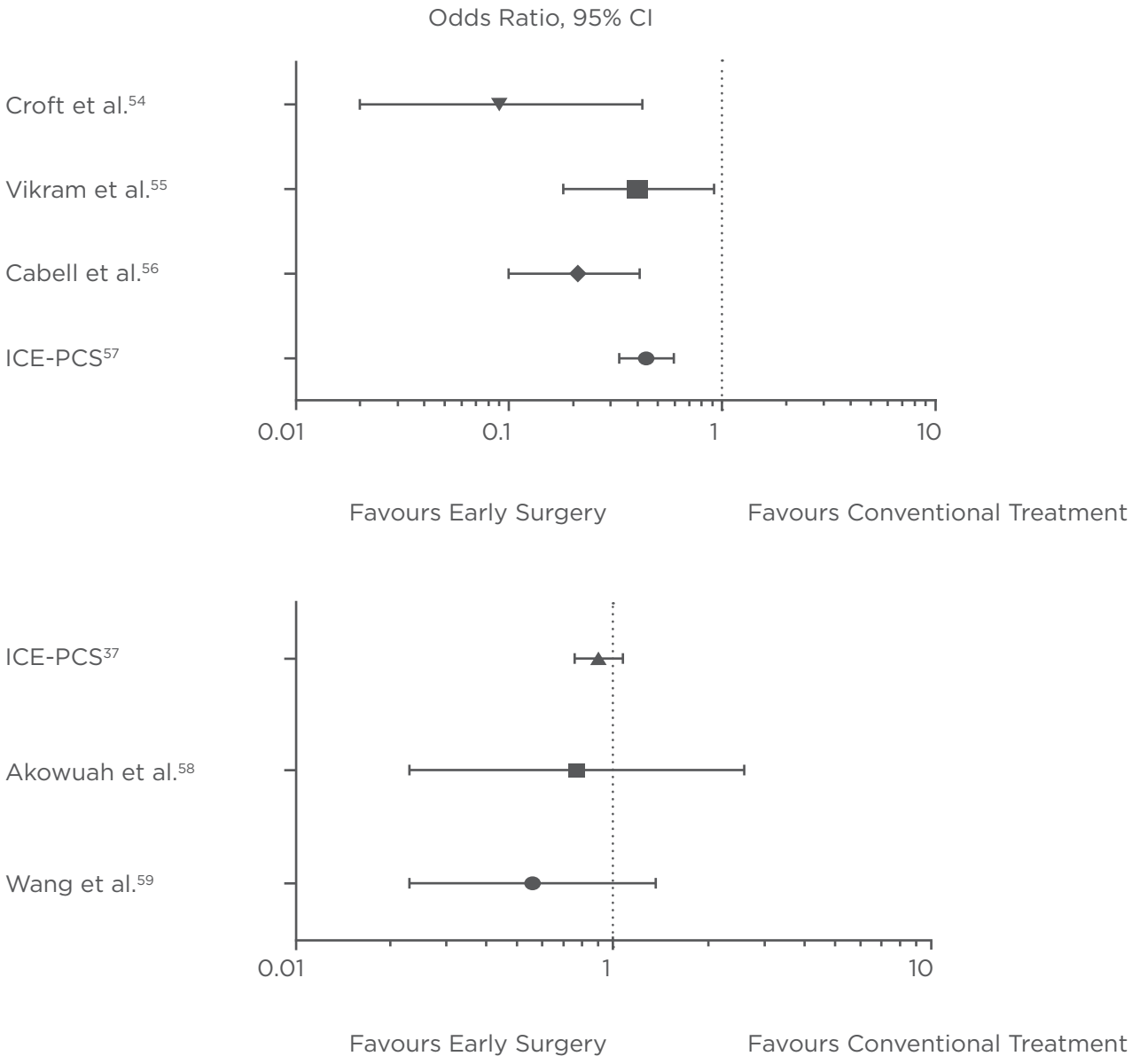


Figure 2: All-cause mortality odds ratio with 95% confidence interval (CI) for A) patients with native valve infective endocarditis (IE) comparing early surgery versus conventional therapy;[54-57] B) patients with prosthetic valve infective IE comparing early surgery versus conventional therapy.[37,58,59]

Future RCTs are needed before we conclusively know the benefit of early surgery in PVE.

CARDIAC DEVICE-RELATED ENDOCARDITIS (CDE)

CDE is a serious complication of bacteraemia in patients with permanent pacemakers or implantable cardioverter defibrillators (ICDs), and is associated with high mortality.[40] The number of implantable devices continues to increase substantially with the advent of primary prevention indications for ICDs and the expanding indications for implantation of cardiac resynchronisation devices as a treatment for heart failure. With infection rates of 1.9 per 1,000 device years, CDE now accounts for 7% of all IE and this is expected to rise substantially further.[41] In a recent study 177 patients from a cohort of 2,760 patients with IE were diagnosed with CDE with in-hospital mortality of 14.7% and 24% at 1 year.[42] This was similar to a previous study from Michigan, which found mortality of 18% in patients with CDE.[43] The diagnosis of CDE is made using a combination of clinical symptoms, echocardiography, and blood cultures. Once diagnosed, the current guidelines recommend prolonged antibiotic treatment and total device extraction.[44] This can be distinguished

from generator/pocket infections, although in most cases infection here also involves the leads and so device extraction is routinely carried out.[45] Superficial skin wound infection is often treated with antibiotics alone, but with a low threshold for pocket exploration/extraction if the infection does not resolve.

The evidence for treatment of CDE is mostly extrapolated from cardiac device infection studies, and for CDE there are only two recently published studies that report the mortality of device extraction and antibiotic treatment compared to antibiotic treatment alone.[40,43] These studies confirmed the guideline recommendations, demonstrating reduced mortality (HR 0.44, 95% CI 0.2-0.96;[46] HR 0.42, 95% CI 0.22-0.8240) in patients treated with device extraction and antibiotics compared to antibiotic therapy alone. A further study from Spain that examined 33 patients with CDE showed that failure to undertake device extraction was significantly correlated with treatment failure ($p<0.0001$).[47] Current ESC guidelines recommend that for vegetations of <25 mm in diameter, especially when there is no destruction of the tricuspid valve, transvenous lead extraction can be attempted without need for thoracotomy. A recent observational single centre study incorporating 1,838 lead extractions over a 16-year period suggested that 21% of patients had lead associated vegetations detected on TOE.[48] All leads were removed percutaneously despite some vegetations being as large as 40 mm (mean diameter 16 mm). Only two vegetations embolised and these were both >20 mm.

Transvenous lead extraction still carries a significant risk, with major life-threatening complications occurring in up to 3.5% of patients and operative mortality in up to 0.8%.[49] The 30-day mortality in patients with lead associated vegetations has been reported as being as high as 10%.[48] Extraction should therefore be carried out in a specialist centre by experienced operators, with appropriate monitoring and cardiothoracic surgical support within the facility. The European Heart Rhythm Association (EHRA) has recently produced guidelines on training and accreditation for this procedure.[49]

Other areas of uncertainty in the management of these difficult cases relate to the duration of antibiotic treatment length and the timing of new device re-implantation. 6 weeks of anti-microbial treatment have been suggested by several previous studies,[42,50,51] but a 4-week duration has been advocated recently.[52] The current guidelines from the AHA and ESC suggest 4-6 weeks depending on patient characteristics and clinical response to treatment.[44,53] The question of when to re-implant the new device is based on expert opinion: current advice is to wait for 14 days after the first negative blood culture.[52] It is important to remember that the original indications for device implantation may no longer be relevant and re-implantation may therefore not be required. However, for those patients who require a device, the new system is usually inserted via the contralateral side. With the continual increase in cardiac device implantation, it is important that further studies and databases are established to evaluate approaches to treatment. The prospective European Lead Extraction ConTRolled (ELECTRa) Registry involves 100 centres in 25 countries, and aims to evaluate the short and long-term safety of transvenous lead extraction and provide a mechanism for verification and potential adjustment of standards for lead extraction procedures.

CONCLUSION

IE remains a deadly disease with high mortality and many areas of its management remain controversial. New methods and treatments are emerging, which aim to accelerate diagnosis, reduce delays, optimise treatment, and improve multi-disciplinary specialist involvement. Delay in diagnosis and involvement of specialist centres is still a leading cause of morbidity. Moreover, it is notable that not 1 in over 80 recommendations within the latest ESC guidelines is backed by data that are level of evidence A (i.e. from multiple randomised clinical trials). Whilst it is clearly unethical to perform trials in this area of medicine against placebo, treatment algorithms and approaches to management can readily be compared with each other in a randomised way, and data using this approach are emerging. It would be particularly useful to initiate studies in areas such as: the use of new molecular techniques for microbiological diagnosis; the choice and duration of antibiotic therapy; identifying appropriate groups for outpatient intravenous antibiotic therapy; imaging and treatment of IE in complex congenital heart disease; and the timing of surgery in prosthetic valve endocarditis and following cerebral events. Increasing the quantity and quality of the evidence base when it comes to IE remains a significant challenge.

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A happy marriage makes for a happy heart

"The contribution of this study is in showing that these sorts of links [between marital interactions and CVD] may be observed even during the earliest stages of plaque development, and that these observations may be rooted not just in the way that we evaluate our relationships in general but in the quality of specific social interactions with our partners as they unfold during our daily lives."

Prof Thomas Kamarck, Kenneth P. Dietrich School of Arts and Sciences, University of Pittsburgh, Pittsburgh, USA

MARRIAGE and marital-type relationships have the potential to reduce a person's risk of cardiovascular disease (CVD), recent research has shown.

According to a study by Prof Thomas Kamarck, Professor of Psychology, Kenneth P. Dietrich School of Arts and Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, new evidence suggests that the quality of an individual's personal relationships, and in particular their marriage, can determine a variety of different health results in later life.

Researchers studied 281 healthy adult participants who were living in a marital or marital-like relationship (cohabiting with a partner) and interactions between these couples were observed every hour for 4 days; participants were asked to label these communications as either positive or negative. As well as this, the dimensions of the subjects' carotid arteries were also measured; a thickening of these can lead to the build-up of fatty plaques, and thus increase one's risk of CVD.

The study found that participants who reported positive interactions with their partner had significantly thinner carotid arteries than those who recorded communications that were negative. These findings were consistent across all groups including age, race, gender, and level of education, and remained so even after other factors that may have influenced the risk of CVD (such as diet) had been accounted for.

Regarding the results, Prof Kamark said: "The contribution of this study is in showing that these sorts of links [between marital interactions and CVD] may be observed even during the earliest stages of plaque development, and that these observations may be rooted not just in the way that we evaluate our relationships in general but in the quality of specific social interactions with our partners as they unfold during our daily lives."

Athletes set the pace for endurance training


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DISTURBANCES in heart rhythm (also known as arrhythmias) may be experienced by elderly athletes who have an extensive history of endurance training for marathons, triathlons, and iron man challenges, new research demonstrates.

A study using rats has found that molecular changes in the heart's natural pacemaker occur in response to pervasive exercise, contrary to previous understanding that increased activity of the automatic nervous system causes such a reaction.

According to past research, the hearts of endurance athletes can beat only 30 times per minute in comparison to normal adults, whose heart rates (HRs) range from between 60 and 100 beats per minute.

The study suggests that the heart's pacemaker changes in response to physical training; specifically that a decrease in the protein HCN4 is responsible for lowering HR. This could be useful in helping medical professionals understand heart rhythm disturbances and even loss of consciousness in athletes.

Dr Alicia D'Souza, Institute of Cardiovascular Sciences, University of Manchester, Manchester, UK, said: "The HR is set by the heart's pacemaker, but this is controlled by the nervous system. The 'vagal' nerves lower the HR and therefore it was assumed the low HR of athletes is the result of over activity of the vagal nerves.

"But our research shows this is not the case. Actually the heart's pacemaker changes in response to training and, in particular, there is a decrease in an important pacemaker protein, known as HCN4, and this is responsible for the low HR."

Prof Mark Boyett, Professor of Cardiac Electrophysiology at the Institute of Cardiovascular Sciences, insists that the benefits of physical training far outweigh the costs in maintaining a healthy lifestyle, even if the effects of this may mean that elderly athletes require the assistance of an artificial electronic pacemaker in later life.

"Actually the heart's pacemaker changes in response to training and, in particular, there is a decrease in an important pacemaker protein, known as HCN4, and this is responsible for the low HR."

Dr Alicia D'Souza,
University of Manchester,
Manchester, UK

Promising biomarker test may reduce death in pregnant women

BIOMARKERS have recently been discovered which could potentially screen for peripartum cardiomyopathy (PPCM) – a detrimental disorder which is the one of the two main causes of death in pregnant women and those who have just given birth.

"There's an urgent need for biomarkers of PPCM since the condition can be hard to differentiate from the normal symptoms of pregnancy that include dyspnoea, oedema, and palpitations," said Prof Karen Sliwa, co-author and Director, Hatter Institute for Cardiovascular Research in Africa, Department of Medicine, University of Cape Town, Cape Town, South Africa.

PPCM is a form of dilated cardiomyopathy, which presents with heart failure (HF) secondary to left ventricular systolic dysfunction, where patients have no prior history of heart disease and no other known causes of HF. This condition is prevalent in developing countries, in particular, Haiti, South Africa, and Egypt.

The study comprised of 77 PPCM patients, 75 healthy peripartum women, 25 breastfeeding mothers, and 65 non-pregnant acute HF patients, and plasma was taken and tested for levels of cardiovascular (N-terminal pro-brain natriuretic peptide [NT-proBNP]), anti (sFlt-1) and angiogenic (placental [PIGF]), or vascular endothelial (VEGF) growth factors.

Both the angiogenesis and the relaxin-2 pathways were the main focus of the investigation since these are altered in PPCM. To discriminate PPCM among peripartum women, the biomarkers ratio of these pathways, PIGF and its receptor Flt-1 along with relaxin-2, can be used.

It was found that PPCM patients had significantly higher levels of NT-proBNP, lower levels of plasma relaxin-2, and the sFlt-1/PIGF ratio and sFLT-1/VEGF ratio were statistically lower.

"The next step will be to confirm our findings in a larger cohort and if they hold we could go on to develop a bedside test similar to NT-proBNP in HF," commented Prof Sliwa.

> "There's an urgent need for biomarkers of PPCM since the condition can be hard to differentiate from the normal symptoms of pregnancy that include dyspnoea, oedema, and palpitations."
>
> *Prof Karen Sliwa, Hatter Institute for Cardiovascular Research in Africa, University of Cape Town, Cape Town, South Africa*

Remote monitoring lowers risk of mortality in cardiac device patients

"Although the mechanisms of these associations require further investigation, our data suggest a need to ensure enrolment and high RM use in device patients."

Dr Suneet Mittal, Director of Electrophysiology, The Valley Health System of New York and New Jersey, Ridgewood, USA

REMOTE monitoring (RM) has the potential to improve clinical results in patients who rely on implanted cardiac devices, observational studies reveal.

In each of the studies, patients were fitted with a range of cardiac devices: Boston Scientific implantable cardioverter-defibrillators (ICDs), St. Jude Medical pacemakers, cardiac resynchronisation (CRT) pacemakers, and CRT defibrillators.

Participants were monitored over the course of 3 and 4 years; their adherence to RM was defined by a percentage of follow-up weeks and a status transmission from the device itself.

In both cases, results showed that adherence to RM reduced risks of mortality and rehospitalisation (patients using Boston ICDs were at the least risk in the second investigation); even low adherence demonstrated an improved survival rate when compared to participants who showed no adherence at all. Patients with pacemakers showed the highest survival rate, followed by those with ICDs, CRT pacemakers, and CRT defibrillators.

Yet despite the apparent success of the studies, the fact that patients were not randomised makes it difficult to establish causality and, at present, RM is used by only a small percentage of patients with cardiac devices in the USA; a lack of proof that it actually improves medical outcomes could be the reason for this.

Dr Suneet Mittal, Director of Electrophysiology, The Valley Health System of New York and New Jersey, Ridgewood, New Jersey, USA, commented: "Although the mechanisms of these associations require further investigation, our data suggest a need to ensure enrolment and high RM use in device patients."

However, a significant benefit of using RM is that the method is unobtrusive to patients, and both studies can serve as models for future research with the potential to inform medical guidelines and provide greater standards of patient care.

New parameter assesses acute heart failure survival

"Our study shows that deranged iron status is common in AHF. Mortality in the patients with NIB was high during the 12-month follow-up, whereas all of the patients with no iron abnormalities survived to 1 year."

Prof Ewa Jankowaka, Laboratory for Applied Research on Cardiovascular System, Wroclaw Medical University, Wroclaw, Poland

SURVIVAL prediction in patients with acute heart failure (AHF) are assessed using, what the investigators call, the negative iron balance (NIB), which is considered superior to standard iron deficiency measures (i.e. serum ferritin and transferrin saturation [TSAT]).

Recent research has investigated the depletion of iron stores and unmet iron needs by measuring circulating hepcidin, and soluble transferrin receptors.

Severe forms of iron deficiency are due to the occurrence of both receptor overexpression and low hepcidin, thus, investigators have named this manifestation the NIB.

Prof Piotr Ponikowski, last author, Head of Department of Heart Diseases, Head of Cardiology Department, Department for Heart Diseases, Wroclaw Medical University, Wroclaw, Poland, commented: "We have data showing that iron may be important for clinical outcomes in chronic heart failure and correction of iron deficiency in these patients is beneficial. This is the first study of iron status in AHF."

To assess the prevalence of NIB and its impact on 12-month mortality, a prospective, observational study involving 165 patients hospitalised for AHF was carried out. The results of the investigation revealed that NIB led to a poorer prognosis in AHF patients regardless of whether they were anaemic or not; serum ferritin and TSAT could not compare to NIB in the 12-month mortality prediction.

Commenting on the findings, Prof Ewa Jankowska, primary author, Associate Professor, Laboratory for Applied Research on Cardiovascular System, Department of Heart Diseases, said: "Our study shows that deranged iron status is common in AHF. Mortality in the patients with NIB was high during the 12-month follow-up, whereas all of the patients with no iron abnormalities survived to 1 year."

Together, both authors concluded: "Iron supplementation may reverse NIB and improve survival in AHF patients but this needs to be tested in a randomised clinical trial. We hope to initiate such [a] trial soon."

The latest accessory to lower blood pressure

REVOLUTIONARY electronic neck cuffs which lower high blood pressure (BP) without side-effects have been developed to fulfil the needs of patients who are unsuccessful under prescribed therapy.

According to the World Health Organization (WHO), high BP is estimated to cause 7.5 million deaths, accounting for 12.8% of the total number of all deaths worldwide. In the UK, a staggering 5 million people are undiagnosed due to the lack of obvious symptoms. The possibility of stroke or heart attack is increased if high blood pressure is left untreated and, due to the systemic nature of the condition, the additional pressure can damage other organs, such as eyes, kidneys, the heart, and central nervous system.

The cuff, which is fitted with 24 electrodes, is implanted in the so-called vagal nerve on the neck, and the closest electrode to the nerve fibres which transmit the BP signal is overwritten via the act of electrostimulation. This process is so precise that other bundles of nerve fibres and other functions are not affected; this procedure is dubbed 'BaroLoopTM' based on the individual analysis, selection, and stimulation that is carried out by the device.

The device was first tested on rodent models and was successful in reducing the mean BP by 30%; no side-effects, such as reduced heart rate or radical decrease in respiratory rate, were detected.

The development of the neck cuff was a collaborative research project, carried out at the University of Freiburg, Freiburg, Germany, between Dr Dennis Plachta and Prof Thomas Stieglitz and neurosurgeons Dr Mortimer Gierthmühlen and Prof Josef Zentner.

The development of a completely implantable system is next on the investigators' agenda. The device could potentially be classed as an active implant which must adhere to the highest level of safety standards; therefore, it could take at least a decade for the development of a fully licensed product.

According to the World Health Organization (WHO), high BP is estimated to cause 7.5 million deaths, accounting for 12.8% of the total number of all deaths worldwide.

Eplerenone: a new hope for acute myocardial infarction patients

"This study suggests that eplerenone can be used early in the course of MI without safety issues. The long-term benefit on remodelling and secondary HF is possible but will deserve further studies."

Prof Gilles Montalescot, Pitié-Salpêtrière University Hospital, Paris, France

EARLY administration of eplerenone – a known mineralocorticoid receptor antagonist drug used to reduce the mortality rate in heart failure (HF) patients – has shown to be significantly effective in patients after an acute myocardial infarction (MI).

1,012 acute ST-segment elevation myocardial infarction (STEMI) patients who had no history of HF participated in a multicentre placebo-controlled trial to evaluate the drug's effectiveness following an MI. The participants were randomised into either an eplerenone (25/50 mg per day) or a placebo group, initiated within 24 hours of symptoms onset, and in addition to standard therapy.

The primary endpoints of the study included cardiovascular mortality, re-hospitalisation or extended initial hospital stay due to diagnosed HF, sustained ventricular tachycardia or fibrillation, and definite signs of HF.

After a mean follow-up of 10.5 months, the primary endpoint had occurred in 93 patients in the eplerenone group (18.4%), while in the placebo group 150 patients (29.6%) were affected. This statistically significant difference was driven by fluctuations in brain natriuretic peptide (BNP)/N-terminal portion of proBNP (NT-proBNP). It was observed that there were lower levels of BNP and NT-proBNP in the eplerenone group; high levels in the blood suggested the worsening of HF symptoms.

Due to the small size of the study there was no statistically significant change with regards to other components of the primary endpoint and, in particular, cardiovascular event rates.

In another trial it was shown that eplerenone was more effective during early administration than late, as in the latter situation, there were relative safety concerns (hyperkalaemia) about its use.

"This study suggests that eplerenone can be used early in the course of MI without safety issues. The long-term benefit on remodelling and secondary HF is possible but will deserve further studies," said Prof Gilles Montalescot, principal investigator and Director, Cardiac Care Unit, Institute of Cardiology, Pitié-Salpêtrière University Hospital, Paris, France.

EVERY AF PATIENT IS DIFFERENT.
ORAL ANTICOAGULANTS NEED TO ADDRESS THIS.

Treatment of AF should be tailored to the particular patient's needs.[1] Every patient presents with their own individual factors that need to be considered when initiating them on oral anticoagulation

References:
1. Basu Ray I. Atrial Fibrillation: present treatment protocols by drugs and interventions. *JIACM* 2003;4(3):213–227.
2. Ogilvie IM *et al.* Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med* 2010;123(7):638–645.

AF= Atrial fibrillation
Date of preparation: July 2014. DSC/14/0015

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Featured Suppliers

Cardiology

A fast-growing biopharmaceutical firm based in Massachusetts, USA, Aegerion has centred its efforts on researching, developing, and commercialising numerous novel life-changing therapeutics for the treatment of potentially deadly orphan diseases. This includes lomitapide, a potentially revolutionary drug designed to combat homozygous familial hypercholesterolaemia (HoFH) - the most severe form. The management team, board, and scientific advisors at Aegerion are all leaders in their fields, and are currently aiming to implement clinical development activities in support of a marketing authorisation application for lomitapide in HoFH in Japan.

Daiichi Sankyo is a globally established pharmaceutical company that has origins in Japan and now provides a range of innovative products and services across more than 50 countries worldwide. Daiichi has built up its scientific expertise for more than 100 years, and has a rich legacy of innovation to draw from, as well as a continuous supply of groundbreaking new treatments for patients. Having built a 30,000-strong workforce possessing great knowledge and work ethic, the company is able to create new innovative medicines, as well as new methods of drug discovery and delivery.

At JenaValve Technology GmbH, quality is of the utmost importance; it lingers on every aspect of the company's technological development, design processes, and device engineering. JenaValve is extremely proud of its German roots, and in 2011 the transapical JenaValve system™ was CE-marked for approval in the European market. Transcatheter aortic valve transplantation (TAVI) has become an established therapeutic alternative to surgical aortic valve replacement over the years for high-risk patients suffering from aortic heart valve stenosis. JenaValve is looking to further expand the advancement of TAVI technology in the years ahead in order to meet growing patient needs.

Philips Healthcare has managed to combine clinical prowess and a unique insight to develop innovative products that are aimed at improving the health and quality of life of customers across the world. The company's influence is fast-growing in clinical areas including oncology, cardiology, and women's health. Philips is using this enhanced knowledge to treat serious conditions, which affect millions of people worldwide, including congestive heart failure, lung and breast cancers, and coronary artery disease. Philips aims to provide state-of-the-art care, ranging from disease prevention, screening, and diagnosis to treatment, monitoring, and health management.

Simbionix is a world-leading provider of a wide range of innovative training and education solutions for the healthcare industry. Founded in 1997, Simbionix combines innovative research and development, cutting-edge technology, and strong clinical relationships to promote adoption of the best medical practices, leading to the advancement of clinical performance and the optimisation of procedural outcomes. The company's comprehensive education solutions include top-of-the-line medical simulators and learning management systems, which can be found in simulation centres, hospitals, colleges, and other educational facilities in more than 60 countries.

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Cardiology

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British Society for Heart Failure (BSH) 17th Annual Autumn Meeting

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London, United Kingdom

This meeting will focus on the many issues surrounding the management of heart failure patients. It will take a multidisciplinary approach, bringing together all levels of clinicians. The meeting will aim to consolidate, support, and increase the knowledge of all those attending, giving them greater confidence in their day-to-day practice. There will be a number of presentations focusing on the most current topics in the field of heart failure.

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3rd-6th December 2014

Vienna, Austria

This event will aim to cover the main themes discussed in cardiology this year, including three-dimensional imaging and imaging in acute cardiac care. It will include more than 150 scientific sessions and over 30 hands-on interactive sessions, with a focus on education, training, and scientific initiatives. The event will aim to reflect the importance of moving from a technology-focused approach to a more patient-centric one.

A Year in Cardiology

12th December 2014

London, United Kingdom

This 1-day event aims to provide a succinct review of the hot topics of 2014, with a particular emphasis on areas relevant to clinical practice. It aims to bring together all those looking to be kept abreast of the year's major advances in cardiology, including consultants and cardiology trainees. A number of leading experts within the UK will attend, many of whom will discuss key developments in all of the subspecialties within cardiology.

Asian Pacific Society of Cardiology Congress 2015

29th April–2nd May 2015

Abu Dhabi, United Arab Emirates

This Congress invites cardiovascular surgeons and physicians, as well as nurses, physician assistants, and other allied health professionals involved in the care of cardiovascular patients. Well-renowned opinion leaders and experts within the field of cardiology and cardiovascular care are likely to attend. The Congress seeks to present the latest cutting-edge research, with the aim of updating attendees with the latest findings.

Nuclear Cardiology and Cardiac Computed Tomography (CT)

3rd-6th May 2015

Glasgow, United Kingdom

This event is a key scientific occasion in nuclear cardiology and cardiac CT. Over the 3 days the event will provide attendees with an exciting and diverse scientific programme. It will aim to offer a full spectrum of educational opportunities, ranging from continuing education to cutting-edge presentations of new and original scientific research. The event will also represent a collaboration between all cardiovascular imaging modalities.

General Meeting of the Association for European Paediatric Cardiology (AEPC) 2015

20th-23rd May 2015

Prague, Czech Republic

This meeting will present a variety of presentations focusing on the hot topics in this specialty. Attendees will have the opportunity to update and exchange the latest knowledge in paediatric and congenital cardiology as well as cardiac surgery, while new scientific findings will be presented during abstract sessions. The event will act as a networking platform, and will provide experts with the chance to exchange experiences.

European Heart Rhythm Association (EHRA) EUROPACE 2015

21st-24th June 2015

Milan, Italy

This conference aims to attract key opinion leaders, well-recognised scientists, and physicians within the field of cardiology. The growing attendance rate of this event is reflected in its increasing importance within the scientific community. There is a multidisciplinary and translational approach throughout the conference towards modern electrophysiology, in the diagnosis and therapy of arrhythmias, and in conduction disturbance.

European Society of Cardiology (ESC) Congress 2015

29th August–2nd September 2015

London, United Kingdom

The ESC is one of the largest cardiology meetings in the world. It strives to be unique and diverse, not only through the quality of the science on display but also in the diversity of attendees and the ensuing networking opportunities. As cardiology is a rapidly evolving field, it is important to keep up-to-date not only in areas of special interests, but also in what is happening elsewhere across the spectrum of cardiovascular disease.