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"This edition brings you the very best of 2018's developments, with highlights from Europe's premier cardiology event..."

Spencer Gore, CEO

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Aims and Scope

The European Medical Journal (EMJ) is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

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

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

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

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- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
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Front cover and contents photograph: Munich, Germany, home of the ESC 2018. © bloodua / 123rf.com

EMJ Cardiol.

EMJ Innovations 2.1

The European Medical Journal is bringing the New Year in with a bang with the publication of *EMJ Innovations 2.1*. This edition is packed with all the most exciting upcoming...

VIEW ALL JOURNALS ←

Welcome

Hello and welcome to the latest edition of *EMJ Cardiology*, wherein we celebrate yet another excellent year of cardiological advances. This edition brings you the very best of 2018's developments, with highlights from Europe's premier cardiology event: the indomitable European Society of Cardiology (ESC) Congress.

Held in the Bavarian capital, Munich, this year's ESC Congress certainly lived up to the society's motto of 'Our Diversity is Our Strength'. Almost 33,000 attendees flocked to the international congress centre from >150 countries to attend the mammoth event and take part in its enormous programme of top-quality research, including thousands of unique abstracts and hundreds of scheduled presentations. Whether you experienced ESC 2018 or sadly missed the event this year, *EMJ Cardiology 6.1*'s Congress Review section brings you all of the latest breakthroughs for you to enjoy.

Complementing this thorough review, we also bring you a selection of abstract reviews, presented at the ESC Congress and summarised by the study authors themselves. Topics here range from the prevention of thoracic aortic aneurysm progression to the latest studies in transcatheter aortic valve implantation; this section is full of inspiration and innovation.

We are also privileged to include Editorial Board interviews with two of the cardiological world's most prominent minds: Prof Denilson Campos de Albuquerque and Dr Sazzli Kasim. They discuss the importance of societal and international collaboration in nurturing this ever-growing field, as well as their hopes and predictions for the future.

Finally, a selection of the finest peer-reviewed articles is available for your enjoyment. Topics here include intracoronary imaging in percutaneous coronary intervention, cardioprotective approaches to patients with breast cancer, an overview of treatment options for chronic Chagasic patients, and more.

This year has been incredible for the sphere of cardiology, with a variety of key breakthroughs that are poised to greatly improve the standard of care. It is my pleasure to bring you this issue of *EMJ Cardiology* and I would like to express my heartfelt thanks to all those who helped in its creation. I hope this issue sparks great debate and we look forward to hearing all about it at next year's ESC Congress in Paris, France.

Spencer Gore

Spencer Gore

Chief Executive Officer, European Medical Group

Foreword

Dear friends,

It is with great pleasure that I present to you the 2018 edition of *EMJ Cardiology*: *EMJ Cardiology 6.1*.

I feel that the past year has been alight with innovation and advances, providing opportunities that should be grasped and built upon for the future of cardiology research, and these have been perfectly captured within the pages of this striking eJournal.

This year's European Society of Cardiology (ESC) Congress summarised these magnificent moments and provided healthcare professionals and researchers with the ideal platform to develop, engage, and network with peers and colleagues from around the world. Knowledge was gained and new collaborations formed at this fantastic event. *EMJ Cardiology*, I am proud to declare, is the perfect next step for the field of cardiology, as it provides an opportunity to re-live the ESC Congress and inspires continuation of inspiring new research and innovation.

I encourage you to read on to discover the latest information surrounding cardioprotective approaches in breast cancer patients, the most pertinent insights into intracoronary imaging in percutaneous coronary intervention, and much, much more in the peer-reviewed articles section of this journal. My Editor's Pick for this edition, which I truly believe is well worth a read, is that by Li Kam Wa and Gerber. Intracoronary imaging is very important for interventional cardiologists and, therefore, a discussion on the increasing availability and presence of such a variety of imaging technologies is vital.

I hope you agree that this edition of *EMJ Cardiology* is a special one and should be read by all. So, join me in sharing and revelling in this fantastic information as we thank all of those involved in its creation and enjoy the content within. I look forward to the upcoming year, with even more cardiology updates, the 2019 ESC Congress, and of course *EMJ Cardiology 7.1*.

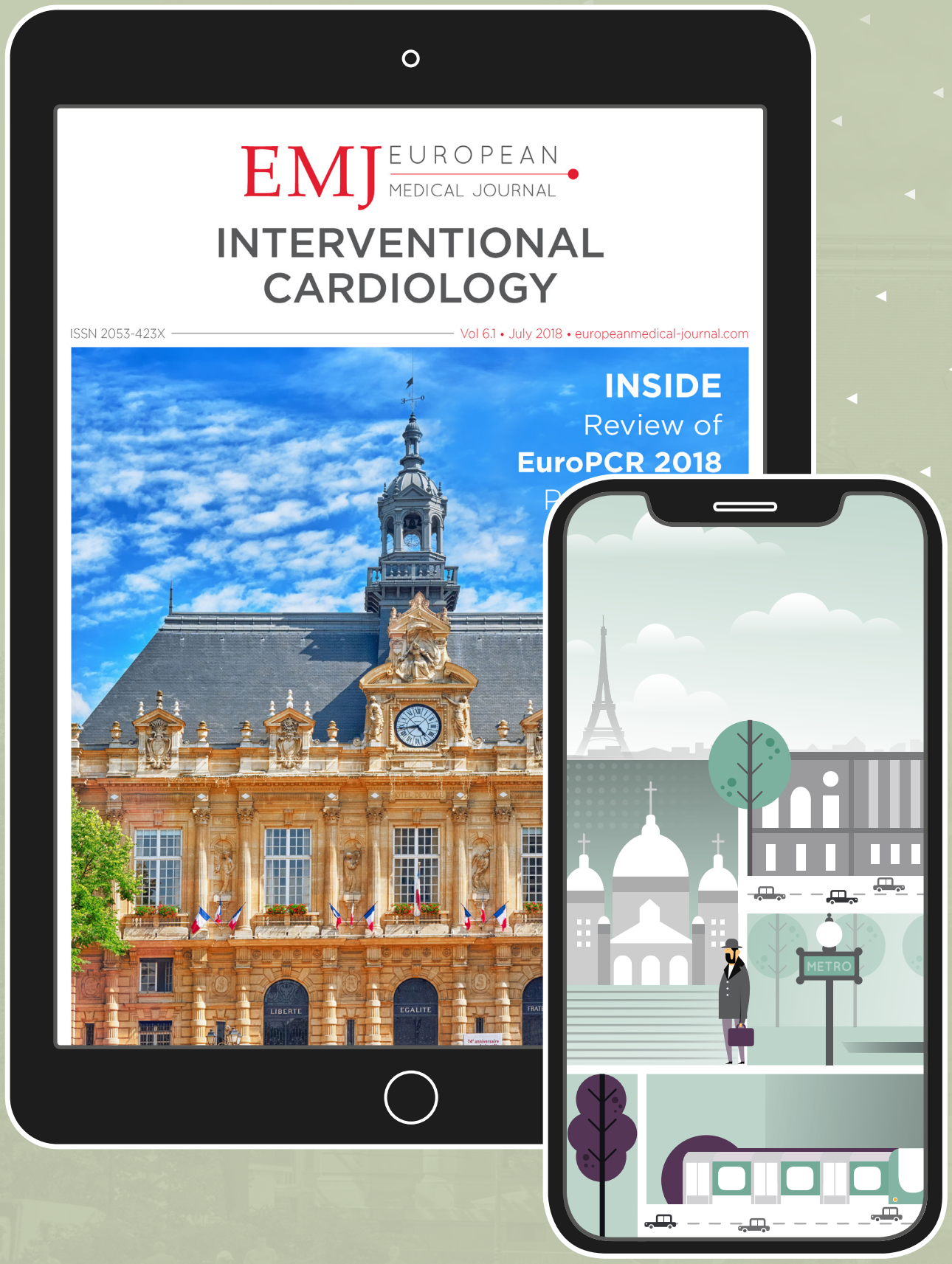
Enjoy.

With best wishes,

Dr Çetin Erol

Ankara University, Turkey

Available now.



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+ Congress Awards

And even more...

EMJ Interventional Cardiology 6.1 provides an in-depth review of EuroPCR 2018, and a look into the history of interventional cardiology, all inside 6.1.

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Congress Review

Review of the European Society of Cardiology (ESC) Congress 2018

Location: Munich, Germany – Internationales Congress Center München (ICM)

Date: 25.08.18–29.08.18

Citation: EMJ Cardiol. 2018;6[1]:12-31. Congress Review.

Known as the largest cardiovascular conference in the world, it was apt that the high standards of the European Society of Cardiology (ESC) were matched by this year's ESC Congress host city of Munich, Germany, where the event returned for the fourth time. During the 5-day meeting, from 25th–29th August 2018, the Internationales Congress Center München (ICM) was brought to life by an impressive total of >32,000 healthcare professionals passing through its doors, ready to hear the breaking news from cardiovascular researchers.

Although great demands were placed on the city, Munich's pride in hosting this prestigious event was clear on arrival, with ESC branding displayed throughout Munich International Airport to welcome delegates from a record-breaking 156 countries. The city's unique marketing activities fostered feelings of unity and empowerment, which were strengthened as attendees arrived in their masses at the main auditorium for the 2018 Inaugural Session at the end of Day 1. After an innovative, futuristic welcome from ESC President Prof Jeroen Bax, a very special guest addressed the audience in an exclusive video interview: Barbra Streisand. Proving the great work of the ESC reaches far and wide, the music legend explained why she is a passionate advocate for heart health and how she established the Barbra Streisand Women's Heart Center. From one inspiring figure to another, distinguished cardiology researcher Prof Eugene Braunweld took to the stage to highlight some of the momentous cardiology events that have taken place during his long career, to rapturous applause from the crowd. Following the presentation of the ESC Gold Medals to worthy winners Marc Pfeffer, Ottavio Alfieri, and Evgeny Shlyakhto and the naming of the newly elected fellows of the ESC, Prof Bax announced the official opening of this year's ESC Congress to the sound of traditional Bavarian music.

With such a momentous opening ceremony, it was clear that the following 4 days were going to be packed full of inspiring, field-changing advances from the cardiology sphere. Living up to the ESC motto of 'Our Diversity is Our Strength', attendees from across the globe were offered sessions on every cardiology subspeciality in the form of 92 late-breaking science studies and 4,500 abstracts presented in 500 expert sessions. Some major studies presented at this year's congress, including the MARINER, CAMELLIA-TIMI, and High-STEACS investigations, are set to revolutionise the treatment and lifestyle management of cardiovascular patients; continue reading for more details of these studies and many more. "The major clinical trials presented at ESC Congress 2018 reflect the growing reputation of our meeting as 'the' place to be to receive the latest updates in cardiology," reflected Prof Stephen Achenbach, Chair of the Congress Programme Committee.

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Devoting much attention to this year's congress spotlight of valvular heart disease, many new features were introduced at the 2018 event to enhance learning, including a 'Cardiology in 4 Days' track, a dedicated 'Library Room' lecture hall, and two 'Science Boxes' for oral presentations. Continuous development was also key for the congress organisers, with four sessions devoted to updates on Clinical Practice Guidelines on syncope, myocardial revascularisation, cardiovascular disease in pregnancy, and arterial hypertension. As well as three large exhibition halls displaying the very latest opportunities from industry and digital health, delegates were appreciative of the ESC-branded deckchairs where they could take some time to reflect, network, and enjoy Munich's last weekend of summer.

As the hugely successful ESC Congress 2018 drew to a close, Prof Bax reflected on his time as ESC President during the General Assembly and thanked the 2016–2018 ESC Board members, before handing his title to Prof Barbara Casadei. Now ESC President for 2018–2020, Prof Casadei described her vision for the society, stating: "To maintain high standards and the legacy of the present, we must continually evolve to be fit for the future." Whether you were unable to attend this year's ESC Congress or you would simply like to re-live the momentous occasions from the event, *EMJ Cardiology 6.1* provides a comprehensive overview of the annual meeting and shows that the future of cardiology is bright for clinicians, researchers, and, most importantly, patients. Continue reading for detailed congress highlights, late-breaking trial results, and abstract reviews to enhance your daily work and set the scene for the ESC Congress 2019. With a spotlight on Global Health, we are already looking forward to next year's annual meeting and hope to see you all there in Europe's largest conference complex in Paris, France.

Findings from the MARINER Trial: Oral Anticoagulant Use

RESULTS from the hotly anticipated MARINER trial were presented at the ESC Congress 2018 during a Hot Line Session and reported in a ESC press release dated 26th August 2018. Conducted at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New York City, New York, USA, the MARINER trial was designed to investigate the effects of an anticoagulant regimen post hospital discharge on the formation of blood clots. Patients were randomly allocated in a 1:1 ratio[1] to a 45-day course of either oral rivaroxaban 10 mg once per day (7.5 mg for patients with a reduced kidney function) or placebo upon leaving the hospital.

"...the usefulness of extended thromboprophylaxis remains uncertain."

The primary safety outcome of the trial was major bleeding and the primary efficacy outcome was a composite measure of any symptomatic venous thromboembolism and death related to venous thromboembolism. The two components of the primary efficacy outcomes were the prespecified secondary efficacy outcomes, which were analysed separately.

The primary efficacy outcome occurred in 0.83% of 6,007 patients in the treatment arm and 1.10% of patients in the placebo arm (hazard ratio [HR]: 0.76; 95% confidence interval [CI]: 0.52–1.09; p=0.14). As the primary efficacy outcome was not achieved, the subsequent efficacy analyses of the secondary outcomes were exploratory. Symptomatic venous thromboembolism occurred in 0.18% of patients in the treatment arm and 0.42% of patients in the placebo arm (HR: 0.44; 95% CI: 0.22–0.89) and venous thromboembolism-related death occurred in 0.72% of patients in the treatment arm and 0.77% of patients in the placebo arm (HR: 0.93; 95% CI: 0.62–1.42). The primary safety outcome, major bleeding, occurred in 0.28% of patients in the treatment arm and 0.15% of patients in the placebo arm (HR: 1.88; 95% CI: 0.84–4.23; p=0.124).[1]

The researchers concluded that the MARINER trial did not show a significant benefit associated with the post-discharge rivaroxaban treatment regimen and noted: "...the usefulness of extended thromboprophylaxis remains uncertain." They recommended that future studies focus on the highest-risk patients, as they are the most likely to benefit from anticoagulant prophylaxis.

References

1. Spyropoulos AC et al.; MARINER Investigators. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. N Engl J Med. 2018. [Epub ahead of print].

Daily Aspirin Prevents Heart Attack

DAILY aspirin has long been associated with beneficial effects for individuals who have had a heart attack or stroke, preventing a second adverse cardiac event; however, the prophylactic use of aspirin in patients who have not had a heart attack is still debated. The results of the hotly anticipated ARRIVE study, aimed at settling this argument, were presented in a ESC press release dated 26th August 2018.

The use of aspirin to prevent first adverse cardiac events is still unclear; with conflicting results published across the different clinical trials, critics highlight the increased risk of major bleeding following aspirin administration. With a primary endpoint of occurrence of composite cardiovascular death, myocardial infarction, unstable angina, stroke, and transient ischaemic heart attack, the ARRIVE study, led by Prof J. Michael Gaziano, Brigham and Women's Hospital, Boston, Massachusetts, USA, recruited 12,546 patients (average age: 63.9 years, 29.7% female) with no prior history of vascular events but a moderate risk of cardiovascular events in 10 years, from the USA, Poland, UK, Germany, Italy, Ireland, and Spain. The patients were split into two groups, one receiving 100 mg aspirin daily and the other a placebo.

"Participants who took aspirin tended to have fewer heart attacks, particularly those aged 50–59 years..."

Intention-to-treat analysis showed that the primary endpoint occurred in 4.29% of the aspirin group compared with 4.48% of the placebo group (hazard ratio [HR]: 0.96; 95% confidence interval [CI]: 0.81–1.13; p=0.60), while per-protocol analysis identified the primary endpoint occurred in 3.40% of the aspirin group and 4.19% of the control group (HR: 0.81; 95%; CI: 0.64–1.02; p=0.0756). Further per-protocol investigation revealed that daily aspirin reduced the risk of total and nonfatal myocardial infarction (HR: 0.53, 95% CI: 0.36–0.79; p=0.0014; HR: 0.55, 95% CI: 0.36–0.84; p=0.0056, respectively).

Intention-to-treat analysis of the risks of the aspirin regimen showed that, while the incidence of most adverse effects was similar between the two groups, gastrointestinal bleeds occurred more frequently in individuals in the aspirin group compared to the control group (61 versus 29, respectively; HR: 2.11; 95% CI: 1.36–3.28; p=0.0007).

"Participants who took aspirin tended to have fewer heart attacks, particularly those aged 50–59 years, but there was no effect on stroke," summarised Prof Gaziano. He concluded: "The decision on whether to use aspirin for protection against cardiovascular disease should be made in consultation with a doctor, considering all the potential risks and benefits."

Novel Heart Attack Identification Assay Causes Change in Diagnosis

RETHINKING the Universal Definition of Myocardial Infarction (MI) could be on the horizon after the first randomised trial testing the criteria used to diagnose heart attacks suggests that regulation needs to move away from the traditional binary threshold. The pioneering High-STEACS trial set out to understand whether implementation of a high-sensitivity cardiac troponin I assay along with a sex-specific 99th percentile diagnostic threshold would reduce subsequent MI or cardiovascular death at 1 year in patients with suspected acute coronary syndrome.

Reported in a ESC press release dated 28th August 2018, a total of 48,282 consecutive patients suspected of having acute coronary syndrome were enrolled from 10 hospitals in Scotland. A validation period over the first 6 months of the study used the traditional assay, after which hospitals were randomly allocated to carry out either early (at 6 months) or late (at 12 months) implementation of the high-sensitivity assay to guide clinical decisions using the 99th percentile as the diagnostic threshold. Patients were followed-up for 18–27 months and then for the following year.

These results suggest that clinicians were more confident ruling out MI when using the high-sensitivity assay.

Results showed that the implementation of the high-sensitivity cardiac troponin test increased the frequency of identification of patients with myocardial injury, but only one-third had a diagnosis of MI. These results suggest that clinicians were more confident ruling out MI when using the high-sensitivity assay. Length of stay was doubled in MI patients but halved in those without myocardial injury, and was reduced by one-third across the trial population. Follow-up results showed that at 1 year there was no improvement in recurrence rates of MI or cardiovascular death.

Principal investigator Prof Nicholas Mills, University of Edinburgh, Edinburgh, UK, summarised the results: "The findings were surprising and initially disappointing. But it was encouraging that there was no evidence of misdiagnosis, inappropriate treatment, excess bleeding, or harm." The study results question the current guidelines for diagnosing MI and definitely warrant further investigation.

Lorcaserin Does Not Increase Risk of Cardiovascular Events

WEIGHT LOSS drug lorcaserin can be used by high-risk cardiovascular patients without increasing their risk of major adverse cardiovascular events (MACE), according to newly released results of the CAMELLIA-TIMI 61 trial. Announced at the ESC Congress 2018 and reported in a ESC press release dated 26th August 2018, this is the first dedicated cardiovascular outcomes trial to demonstrate cardiovascular safety of any weight loss agent.

To examine the safety and efficacy of lorcaserin, the trial enrolled 12,000 adults (64% male) from 473 centres across eight countries who had a BMI ≥27 kg/m^2 and either cardiovascular disease or diabetes with at least one other cardiovascular risk factor. The participants, who had an average age of 64 years, were randomised in a 1:1 ratio to 10 mg lorcaserin twice daily or placebo.

Internationales Congress Center München (ICM)

Venue of ESC 2018

The primary safety endpoint of the trial was non-inferiority of lorcaserin compared to placebo for MACE and was successfully achieved, with MACE occurring in 6.1% of lorcaserin patients versus 6.2% of those on placebo ($p<0.001$). However, lorcaserin was not shown to be superior to placebo in terms of MACE plus hospitalisation for heart failure, unstable angina, or coronary revascularisation. With regard to its efficacy in assisting weight loss, 39% of lorcaserin patients had lost ≥5% of their body weight at Year 1 compared to 17% of the placebo group ($p<0.001$), and this statistically significant difference remained for 3.3 years of follow-up.

"We have been able to show for the first time that this weight loss drug does what it is intended to do. It helps people lose weight without causing an increase in MACE in a population at higher risk for heart attacks and strokes."

Commenting on these promising results, trial investigator Dr Erin Bohula, Brigham and Women's Hospital, Massachusetts, Boston, USA, explained: "We have been able to show for the first time that this weight loss drug does what it is intended to do. It helps people lose weight without causing an increase in MACE in a population at higher risk for heart attacks and strokes." Compared to placebo, the drug also reduced the conversion rate from pre-diabetes to diabetes and led to small improvements in blood pressure, heart rate, and blood glucose and triglyceride levels; however, while cardiovascular risk was reduced, there was no substantial cardiovascular benefit shown.

Although approved by the U.S. Food and Drug Administration (FDA) in 2012 for aiding weight loss in certain high-risk cardiovascular patients, lorcaserin is not approved in Europe due to concerns regarding malignancy, heart valve problems, and psychiatric disorders. However, CAMELLIA-TIMI 61 showed no significant difference in tumours or valvular disease at 1 year between lorcaserin and placebo, providing hope for European approval of lorcaserin in the near future.

High-Density Lipoprotein: Not as Good as it Seems?

HIGH-DENSITY lipoprotein (HDL) cholesterol, known to be the 'good' form of cholesterol, may be dangerous to health when present in very high levels. According to research reported in a ESC press release dated 25th August 2018, high levels of HDL cholesterol may be linked to an increased risk of heart attacks and death.

Researchers from the Emory University School of Medicine, Atlanta, Georgia, USA, recruited 5,965 patients, most of whom had heart disease, with an average age of 63 years and a split of 65% males and 35% females. The participants were separated into five groups based on their HDL levels: <30 mg/dL, 31–40 mg/dL, 41–50 mg/dL, 51–60 mg/dL, and >60 mg/dL.

"One thing is certain: the mantra of HDL cholesterol as the 'good' cholesterol may no longer be the case for everyone."

At a median follow-up of 4 years, it was found that 769 (13%) of the study participants had experienced a heart attack or had died from a cardiovascular event. Individuals in the 41–50 mg/dL and the 51–60 mg/dL groups had the lowest risk of a heart attack or death. Risk of heart attack or death was increased in both the low HDL level groups (<41 mg/dL) and the very high HDL level group (>60 mg/dL), with those in the very high HDL level group having an almost 50% increased risk of heart attack or death compared to those with HDL levels of 41–60 mg/dL.

When taking into account other risk factors for heart disease, such as low-density lipoprotein, smoking, and diabetes, and factors associated with high HDL levels, such as race, sex, and alcohol intake, it was found that the results remained consistent.

In addition, the results supported those studies testing the same theory. Study author Dr Marc Allard-Ratick, Emory University School of Medicine, said: "Our results are important because they contribute to a steadily growing body of evidence that very high HDL cholesterol levels may not be protective, and because unlike much of the other data available at this time, this study was conducted primarily in patients with established heart disease."

Dr Allard-Ratick also highlighted that further research is needed in order to establish the mechanisms behind the increased risk of heart attacks, other cardiovascular events, and death with higher HDL levels, but concluded: "One thing is certain: the mantra of HDL cholesterol as the 'good' cholesterol may no longer be the case for everyone."

New Data in the Debate Over Low Carbohydrate Diets

CHALLENGING conventional wisdom was the topic of discussion at a ESC press conference in which the results of the NHANES trial were presented, detailing the findings that a long-term low carbohydrate diet is in fact linked to a greater risk of all-cause death, as well as death

caused by a number of cardiovascular and other chronic conditions. Reported in a ESC press release dated 28th August 2018, the study has added new data to the conflicting results that have been produced by earlier studies about this controversial diet.

This prospective study assessed a nationally representative sample of 24,825 patients from 1999–2010 to evaluate the link between low carbohydrate diets, all-cause death, and deaths from coronary heart disease, cerebrovascular disease (such as stroke), and cancer. Participants were divided into quartiles based on carbohydrate intake; they had an average age of 47.6 years and 51% were female. Results indicated that, over an average 6.4-year follow-up, the risk of all-cause death was 32% higher in the quartile with the lowest intake compared to the quartile with the highest intake of carbohydrates. The risk of death from coronary heart disease, cerebrovascular disease, and cancer increased in the lowest quartile by 51%, 50%, and 35%, respectively. In addition to these findings, researchers reported a rise in the risk of each type of death with each drop in carbohydrate intake, which remained significant following adjustment for potentially contributary factors.

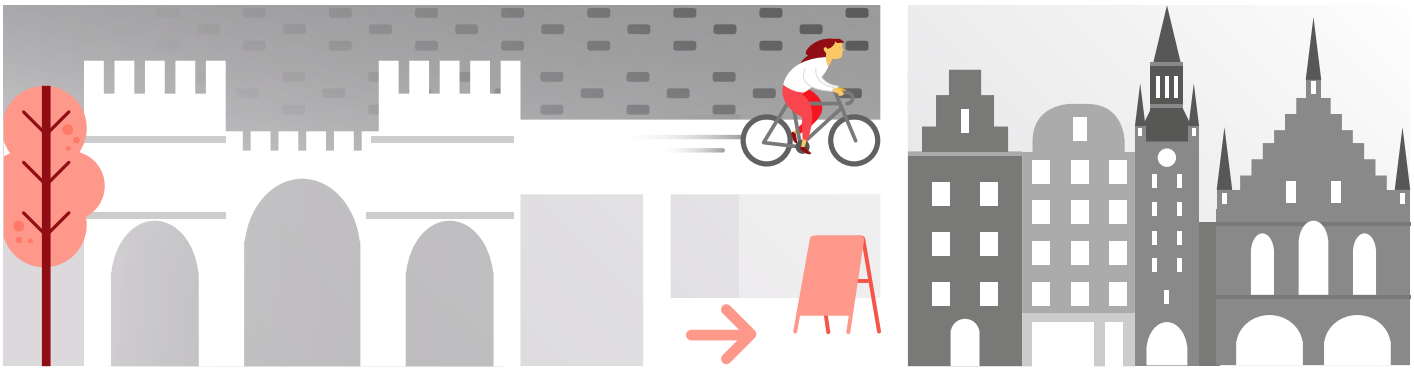
The results of this study are certain to help advise and improve education for those hoping to pursue a low carbohydrate diet...

Furthermore, the data were confirmed by the results of a meta-analysis of seven prospective cohort studies enrolling 447,506 patients for an average follow-up of 15.6 years. This demonstrated that risk of total, cardiovascular, and cancer mortality increased by 15%, 13%, and 8% in the lower compared to the higher carbohydrate intakes, respectively.

Prof Maciej Banach, Medical University of Lodz, Lodz, Poland, commented: "Low carbohydrate diets might be useful in the short term to lose weight, lower blood pressure, and improve blood glucose control, but our study suggests that in the long-term they are linked with an increased risk of death from any cause, and deaths due to cardiovascular disease, cerebrovascular disease, and cancer." He also specified that the results of the study highlighted "an unfavourable association between low carbohydrate diets and total and cause-specific death, based on individual data and pooled results of previous studies." The results of this study are certain to help advise and improve education for those hoping to pursue a low carbohydrate diet, balancing the short-term benefits with the longer-term risks.

Large Data Analysis Challenges Previous Conclusions About Healthy Heart Diet

"THINKING on what constitutes a high-quality diet for a global population needs to be reconsidered," argued Prof Salim Yusuf, senior author and director of the Population Health Research Institute (PHRI) at McMaster University, Hamilton, Canada in a ESC press release dated 28th August 2018. Recommendations regarding healthy diets for heart disease are largely outdated, being based on studies conducted many years ago, which are no longer representative of the global diet. Now, a new study has shown that previous conceptions about a healthy heart diet may be untrue.



The observational Prospective Urban Rural Epidemiological (PURE) study examined participants from five studies, totalling >218,000 people from >50 countries. A scoring system for dietary quality was developed, with points allocated according to the prevalence of foods associated with lower risk of death in previous studies, including fruit, vegetables, nuts, legumes, fish, dairy, and meat. Participants were then stratified into five groups based on these scores, and the risks of cardiovascular disease and death were compared in those with a high-quality diet (≥18 points) or low-quality diet (≤11 points).

"People who consumed a diet emphasising fruit, vegetables, nuts, legumes, fish, dairy products, and meat had the lowest risks of cardiovascular disease and early death."

After a median follow-up of 9.1 years, there had been 6,821 deaths and 5,466 major cardiovascular events. Once adjusted for confounding factors, the results of the study showed that the high-quality diet group was associated with markedly lower risks of major cardiovascular events (hazard ratio [HR]: 0.89; 95% confidence interval [CI]: 0.80–1.00; p=0.0193), stroke (HR: 0.83; 95% CI: 0.71–0.97; p=0.0402), cardiovascular death (HR: 0.71; 95% CI: 0.59–0.85; p<0.0001), non-cardiovascular death (HR: 0.74; 95% CI: 0.66–0.84; p<0.0001), and total deaths (HR: 0.75; 95% CI: 0.68–0.83; p<0.0001).

"People who consumed a diet emphasising fruit, vegetables, nuts, legumes, fish, dairy products, and meat had the lowest risks of cardiovascular disease and early death," explained co-principal investigator Dr Andrew Mente, PHRI. Notably, Dr Mente also pointed out that "we found that unprocessed meat is associated with benefit."

Further study is needed to verify the results of this extensive study, but it is clear that previous assumptions about a healthy diet should be re-evaluated. Furthermore, the scale of these results means that they are more universally applicable, as Dr Mahshid Dehghan, PHRI, explained: "Our results appeared to apply to people from different parts of the world and so the findings are globally applicable."

Drug-Coated Balloons Compared to Drug-Eluting Stents

SPEAKING at the ESC Congress 2018 about the late-breaking results of the BASKET-SMALL 2 trial, the study's principal investigator Prof Raban Jeger, University Hospital Basel, Basel, Switzerland, declared: "The BASKET-SMALL 2 trial met its primary endpoint of non-inferiority for major adverse cardiac events (MACE) at 12 months. This is a long-awaited milestone in clinical evidence for the drug-coated balloon technique, which so far has primarily been used for the treatment of in-stent restenosis." The trial was discussed in a ESC press release dated 28th August 2018.

"The results of this trial move us a step closer towards treating small blocked arteries without having to insert a permanent implant."

Currently, drug-coated balloons are approved in Europe for the reopening of stented arteries that have become blocked for a second time. The BASKET-SMALL 2 trial was the largest randomised trial to investigate the non-inferiority of drug-coated balloons in comparison with drug-eluting stents, with the trial's primary objective to demonstrate non-inferiority in regard to MACE after 12 months.

From 2012–2017, 758 patients were enrolled. The patients had an average age of 68 years and all presented with a first-time lesion in an artery that was <3 mm in diameter. The patients were then randomised on a 1:1 basis to receive angioplasty utilising a balloon coated with iopromide and paclitaxel (n=382) or implantation of a second-generation drug-eluting stent that was covered with everolimus or paclitaxel (n=376).

At 12 months, the MACE rate in the drug-coated balloon group was 7.6% and the rate in the drug-eluting stent group was 7.5%, with no difference in the two rates being shown (p=0.918); thus, non-inferiority of the primary endpoint was demonstrated. Prof Jeger commented: "The results of this trial move us a step closer towards treating small blocked arteries without having to insert a permanent implant."

A Smartphone App to Screen for Atrial Fibrillation

A STUDY presented at the ESC Congress 2018 and reported in a ESC press release dated 25th August 2018 has shown positive results after initial evaluation of a smartphone app used to measure heart rhythm and detect atrial fibrillation (AF). All that is required for someone to measure their heart rhythm with the app is a smartphone with a camera, offering a low-cost method to screen thousands of people for AF.

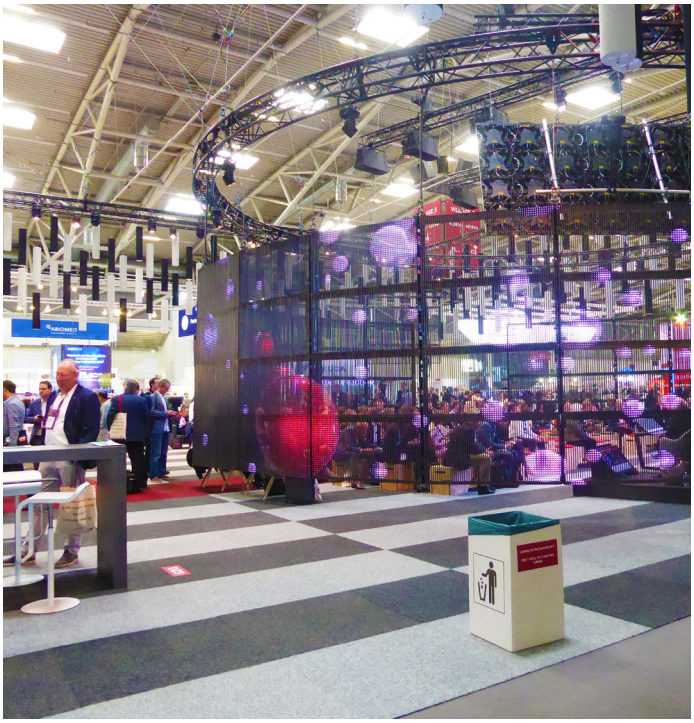
AF is the most common heart rhythm disorder; with 25% of middle-aged adults in Europe and the USA anticipated to develop the disorder, and 20–30% of strokes caused by AF, screening as many people as possible for this potentially life-threatening disorder is paramount. The smartphone app, certified in the European Union (EU) to detect AF, was made freely available to the public, and within 48 hours of its release 12,328 adults had downloaded the app and enrolled in the study.

Participants were instructed to measure their heart rhythm twice a day for 1 week. Symptoms including heart palpitations, shortness of breath, and fatigue were all advised to be added to the app. Participants held their left index finger in front of the phone's camera for 1 minute while photoplethysmography measured their heart rhythm. Rhythm results

were classified as regular (80%), possible AF (1%), other irregular rhythm (17%), or insufficient quality (2%); those patients with results indicating AF or other irregular rhythms were reviewed by medical technicians who were experienced in analysing photoplethysmography signals under the supervision of cardiologists and were then advised to see their doctor. All participants received a report on their phones with a copy of their rhythm trace and interpretation. After 4 months, those with AF and abnormal readings received follow-up questionnaires by email about the actions they had taken as a result of the screening.

"The verification of diagnoses by medical technicians showed that interpretations by the app were very accurate, suggesting that this step could be significantly downsized and possibly omitted from a screening programme."

The follow-up questionnaire was completed by 73.5% (100) of the AF patients. Results showed that 60 of the patients had previously been diagnosed with AF and after consulting their doctors 17 of these patients had their treatment adjusted. For the remaining 40 patients, AF was a new diagnosis, of whom 21 consulted their doctor for confirmation.



Prof Pieter Vandervoort, University of Hasselt, Hasselt, Germany, summarised the implications of the study results in relation to future investigations: "The verification of diagnoses by medical technicians showed that interpretations by the app were very accurate, suggesting that this step could be significantly downsized and possibly omitted from a screening programme. According to our study, approximately 225 people would need to be screened to detect one new AF diagnosis. This is an acceptable return, given the low cost."

Security Body Scanners Safe for Cardiac Device Patients

BODY SCANNERS, often used for security checks at airports and public buildings, are safe to be used by patients with implanted cardiac devices. As reported in a ESC press release dated 26th August 2018, results of late-breaking research show full body scanners do not interfere with or lead to the malfunction of pacemakers or defibrillators, providing reassurance to the >4 million people across the globe with heart failure or cardiac arrhythmias who rely on the devices to survive.

Using a multicentre survey of 800 cardiac device patients, 80% of whom would refuse to use security body scanners due to concerns about their safety, the study assessed the safety of such scanners for these patients. Led by Dr Carsten Lennerz, German Heart Centre Munich, Technical University of Munich, Munich and German Centre for Cardiovascular Research (DZHK), Berlin, Germany, the research

team studied 300 patients with a cardiac resynchronisation therapy (CRT) device, implantable cardioverter defibrillator (ICD), or pacemaker who were routinely checked at the German Heart Centre Munich. All patients underwent a body scan that mimicked the scanners used in airport security checks, which emit millimetre waves that bounce off the skin and create an image of the body and any concealed objects.

"The study suggests that millimetre wave body scanners pose no threat to patients with pacemakers, ICD, and CRT devices..."

While it was thought that a scanner's electromagnetic field could be mistaken by cardiac devices for heart signals, the team found no evidence of pacemaker or defibrillator errors or interruption to device programming, which is tailored to a specific patient. "The study suggests that millimetre wave body scanners pose no threat to patients with pacemakers, ICD, and CRT devices and there is no need for specific protocols or restrictions on their use," summarised Dr Lennerz. The team noted that the high-frequency signals produced by body scanners have limited penetration into the body and are filtered out by pacemakers and defibrillators; therefore, there is no risk of incorrect pace setting or unnecessary delivery of shock therapy when security scans are required, successfully reassuring many cardiac device patients.

Oral Treatment for Endocarditis Could Reduce Patients' Hospitalisation Time

ENDOCARDITIS is a serious infection that affects the endocardium and one or more of the heart valves; the infection has a mortality rate of 15–30%. Treatment of this condition requires intensive care and is often accompanied by an extensive hospital stay while the patient receives antibiotics intravenously. However, a recent study by researchers at Copenhagen University Hospital, Copenhagen, Denmark, which was reported in a ESC press release dated 28th August 2018, has revealed that stable patients may be able to switch to oral antibiotics, thus drastically reducing the time they spend in the hospital.

The nationwide POET trial examined 400 patients with endocarditis who had received intravenous antibiotics for at least 10 days; these patients were randomly allocated to continue treatment intravenously or switch to oral antibiotics. The oral antibiotic group was offered the treatment as outpatients. The patients received their respective treatments for a median of 18 days and all patients were followed for 6 months after their treatment had finished. The combined primary endpoint of the study was defined as all-cause death, unplanned cardiac surgery, embolic events, and reinfection.

"These novel findings may have a significant impact on future clinical practice for the management of patients who are stable."

The results showed little difference between the oral and intravenously treated groups, with the primary endpoint occurring in 10.5% of patients. "Shifting to oral antibiotic treatment in stabilised patients with endocarditis was as effective and safe as continued intravenous antibiotic treatment and was given during half the antibiotic treatment period," explained principal investigator Prof Henning Bundgaard, Copenhagen University Hospital. "These novel findings may have a significant impact on future clinical practice for the management of patients who are stable."

Eliminating lengthy hospital stays has been shown to be beneficial for a number of conditions and the same is likely true for endocarditis, for which stable patients remain in hospital primarily to receive intravenous treatment as per guidelines. "It is a huge challenge for patients to stay in hospital for up to 6 weeks receiving intravenous treatment, which is associated with an increased risk of complications," explained Prof Bundgaard. "Reducing the length of hospital stay has improved outcomes in other diseases and oral antibiotics could be a safe way to achieve this," he added.

Eight Hours a Night Keeps the Cardiologist Out of Sight

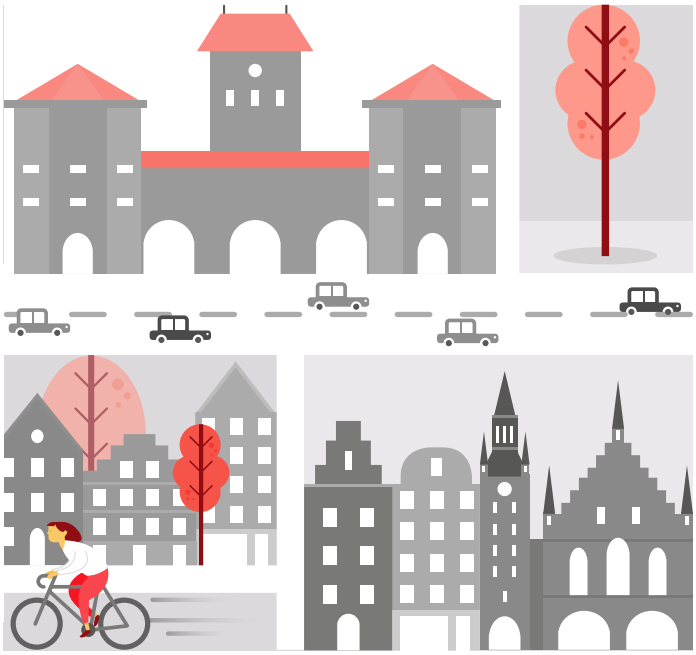
Six to eight hours has been identified as the optimal time period to spend sleeping every night to avert the development of cardiovascular disease, according to new research presented in a ESC press release dated 26th August 2018.

"We spend one-third of our lives asleep, yet we know little about the impact of this biological need on the cardiovascular system," explained study author Dr Epameinondas Fountas, Onassis Cardiac Surgery Centre, Athens, Greece. The researchers investigated the relationship between sleep duration and cardiovascular disease by conducting a meta-analysis of 1,000,541 individuals. The study compared patients with short sleep durations (<6 hours) and patients with long sleep durations (>8 hours) to the reference group (6–8-hour sleep duration).

Analysis of the results revealed that patients who had a short sleep duration and those with a long sleep duration both had an increased risk of developing cardiovascular disease. With an average follow-up of 9.3 years, it was identified that short-duration sleepers had an 11% and long-duration sleepers a 33% greater risk of developing or dying from coronary artery disease or stroke.

"Our findings suggest that too much or too little sleep may be bad for the heart," Dr Fountas concluded. While an occasional lie-in or a night staring at the ceiling is not likely to be harmful, data are accumulating that suggest that prolonged periods of extended and truncated sleeping periods will be detrimental to the patient's health. The link between sleep duration and the development of cardiovascular disease is unclear, and while it is understood that sleep has a key role in biological processes such as glucose metabolism, blood pressure, and inflammation, which all impact upon the cardiovascular system, further work is needed to elucidate the connection between sleep and heart disease.

"Our findings suggest that too much or too little sleep may be bad for the heart."



Endurance Sports Associated with Increased Atrial Fibrosis

LEFT ATRIAL FIBROSIS may be the link between endurance training and increased atrial fibrillation risk. This is according to the results of a study presented at the ESC Congress 2018 and reported in a ESC press release dated 27th August 2018.

Atrial fibrillation is already known to be increased in individuals who undertake intensive endurance sports training (>1,500 hours of training).[1] The researchers hypothesised that those who partake in intensive endurance training might present with an increased incidence of left atrial fibrosis, which has been previously associated with atrial fibrillation, when compared with non-athletes.

"The next step in our research is to see whether the degree of left atrial fibrosis is related to the amount of endurance training."

In order to investigate this hypothesis, two study groups were set up: the endurance athletes group comprised 16 endurance athletes >35 years old who had competed in endurance sports for ≥10 years and trained for ≥10 hours a week. For the purposes of the study, endurance sports included running, cycling, Nordic skiing, and rowing. The control group consisted of 20 healthy controls who did not compete in endurance sports.

Late gadolinium enhancement MRI was used to assess atrial fibrillation. It was found that the mean left atrial fibrosis score was 13.7%±5.4 in the endurance athlete group and 11.8%±7.3 in the control group. After controlling for BMI and age, which are both factors that influence left atrial fibrosis, there was a 6% greater incidence of left atrial fibrosis in the endurance athlete group (p=0.05).

Lead author, Dr David Peritz, University of Utah, Salt Lake City, Utah, USA, was careful to highlight the limitations of the study, noting: "This was a small study and the clinical significance deserves further investigation...". He went on to discuss the next stages of research based on this finding of association, stating: "The next step in our research is to see whether the degree of left atrial fibrosis is related to the amount of endurance training."

References

1. Kirchhof P et al.; ESC Scientific Document Group. European 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893-962.

Pregnancy with Heart Disease

PREGNANCY in patients with heart disease is usually safe for both mother and child, according to a ESC press release dated 28th August 2018. Researchers from the Netherlands confirmed this hypothesis after assessing the outcomes of pregnancy in women with heart disease; 57% of the study population had congenital heart disease, 29% had valvular heart disease, 8% had cardiomyopathy, 4% had aortic disease, 2% had ischaemic heart disease, and 1% had pulmonary arterial hypertension.

Of the 5,739 women enrolled into the study from 138 centres in 53 countries from 2007–2018, <1% of women died during pregnancy and women with pulmonary arterial hypertension had the highest rates of death (9%). Fetal and neonatal death rates were both 1%. Caesarean section deliveries were carried out in 44% of the studied women, of which over one-third were for cardiac reasons, equating to 16% of all deliveries. Heart failure, supraventricular, and ventricular arrhythmia complications occurred in 11%, 2%, and 2% of women, respectively. Researchers also found that women who had heart failure, diminished exercise capacity, decreased pump function of the heart, or used anticoagulant medication before becoming pregnant were more at risk of experiencing complications.

With heart disease being the leading cause of death during pregnancy in developed countries, the more clinicians and researchers can understand about the correlation the better the chances women with heart disease who become pregnant will have of having a safe gestation and birth. Prof Jolien Roos-Hesselink, Erasmus Medical Centre, Rotterdam, Netherlands, stated: "After an initial increase in maternal mortality and new diagnoses of heart failure during pregnancy between 2007 and 2010, these rates have been declining. This occurred despite the presence of more very high-risk women with heart disease being included in our registry as time went by." Prof Roos-Hesselink also commented that the fall in adverse outcomes over the years might indicate greater awareness of the specific problems and better management of pregnant women with heart disease.

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Congress Interview

Dr Çetin Erol

Ankara University, Turkey

During the ESC 2018 Congress, we met with *EMJ Cardiology's* Editor-in-Chief, Dr Çetin Erol, to ask about his experience of this year's event and his general thoughts, including the main focus of the congress, important sessions to attend, and a look at the 2019 meeting.

The focus of this year's ESC Congress is valvular heart disease. Why do you believe this topic was chosen?

This topic was chosen because the population is getting older and the elderly are commonly diagnosed with aortic valve disease, which can be very dangerous if it is not treated when the symptoms begin. In addition, atherosclerotic heart disease includes myocardial infarction and can cause mitral regurgitation, either functional or organic, which is another important problem in our time. That is why I think they chose this topic. Of course, rheumatic heart disease is less of a problem for developed countries but is a significant problem in underdeveloped countries.

"Of course, ESC is the best meeting because it is the largest, most famous, and is attended by >31,000 people from around the world; we are very proud of our society."

What other diseases, techniques, and therapies are currently under the spotlight in cardiology research?

Aspirin is a topic of great interest this year and has always been a problem for patients and doctors, especially in regard to primary prevention and whether it is useful. I think this problem will be solved at this meeting, as study results will be revealed and strict European guidelines will be announced on aspirin use for primary prevention.

Are there any other scientific meetings you attend in addition to ESC?

Of course, ESC is the best meeting because it is the largest, most famous, and is attended by >31,000 people from around the world; we are very proud of our society. However, I try to attend American College of Cardiology (ACC) meetings as well as ESC because I want to be aware of what the Americans do in their field. Furthermore, because it is a clinical meeting, I prefer to go to ACC rather than American Heart Association (AHA) meetings.

"Aspirin is a topic of great interest this year and has always been a problem for patients and doctors, especially in regard to primary prevention and whether it is useful."

Also, if I have time, I would like to go to the European Association of Cardiovascular Imaging (EACVI) meeting because I am principally an echocardiographer; I became an invasive cardiologist later in my career.

Before arriving in Munich, what part of this year's congress programme were you most looking forward to?

Of course, there are many late-breaking trials and hotlines at this year's congress but unfortunately so far I haven't been to any of these sessions. However, it is easy to follow-up with the results on the ESC website where all the details are available, so we will look at all of the results when we return home. In this meeting I have many jobs to do because I am a chairperson of some sessions, a member of the ESC jury, and an Editorial Board member, so I am very busy. If I find time then I will attend extra sessions, but most I will read about when I am home.

For your colleagues who have not been in attendance at this year's congress, what are your key take-home messages from the event?

A key message is to always put the patient first and that we have to be careful when considering new drugs or treatments; we have to wait for long-term results and more information.

Finally, are there any additional sessions that you would like to see added to the 2019 ESC Congress programme in Paris?

Next year the topic is global health and the focus will be on prevention, which is the most important thing in cardiology. We have to prevent the diseases because it is easier to prevent than to treat. We must look at risk factors and deal with these factors. The first thing to consider should be lifestyle interventions, including stopping smoking, losing weight, and maintaining a healthy diet.

"A key message is to always put the patient first and that we have to be careful when considering new drugs or treatments..."

OUR EXCLUSIVE INTERVIEWS CONTINUE ON THE NEXT PAGE, CLICK HERE TO VIEW ←

Interviews

Hear from the experts as two esteemed members of our Editorial Board give their opinions on today's hot topics in cardiology

Featuring: Prof Denilson Campos de Albuquerque and Dr Sazzli Kasim

Prof Denilson Campos de Albuquerque

State University of Rio de Janeiro, Brazil

What inspired you to follow a career in cardiology, and specifically your specialism in cardiac failure?

As a matter of fact, I always liked the variety of options presented by cardiology. One can finish a residency in cardiology and choose between specialities as different as interventional cardiology, cardiac imaging, ambulatory patients, or even intensive cardiac care. This multifaceted approach, along with the prevalence of cardiology patients, makes the discipline inspiring to be a part of.

You were the co-ordinator of the BREATHE registry study. Could you give us a brief insight into both the aims of the study and the conclusions drawn from this observational investigation?

BREATHE was the first, and remains the only, Brazilian registry for heart failure patients nationwide. I think it is paramount to know the specifics of heart failure treatment in Brazil and compare it both internally (between different regions) and externally (with other international registries). With this information, it was possible to develop specific public health policies.

We included 1,263 patients from 57 different centres across Brazil and they were followed for 1 year. Interestingly, when compared to EUROSCORE (Europe) and ADHERE (USA), BREATHE included the most female patients (25.4%, 60.0%, and 70.1%, respectively). The prevalence of comorbid conditions was higher in patients in BREATHE, with almost 90% presenting with, for example, atrial fibrillation, but fewer with ischaemic cardiomyopathy (around 30%; almost half that of EUROSCORE and ADHERE). Internally, it was possible to detect the differences between Brazil's richer and poorer areas. Lastly, the findings of 54.8% readmission rates and 39.5% mortality in 12 months indicate the challenges currently facing Brazilian cardiologists.

We understand that you have an interest in the genetic components surrounding heart failure. What do you find most interesting about this field, and why?

We have three different ongoing projects at the State University of Rio de Janeiro that address this relationship. I believe that it is possible to identify several genetic markers that predispose patients to the development of heart failure. Going even further, it will be possible to recognise, through one patient's DNA, how he or she will respond to specific drugs (angiotensin-converting-enzyme inhibitors or betablockers, for instance). Maybe it will even be possible to prioritise some patients over others. Imagine the possibility of predicting, early in the course of heart failure, a worse prognosis in the long term and preparing for it, implementing advanced care before the establishment of end-stage complications.

You have previously conducted research on gene polymorphism frequency variations within ancestries. How will the knowledge of these polymorphisms affect the way we diagnose and treat heart failure?

We were able to prove the Brazilian population's multiethnic nature by mapping ancestry genes, and we observed that >85% had some level of African American DNA. With this in mind, Brazilian cardiologists can expand the use of the combination of nitrates and hydralazine to almost all of Brazil's population, with no regard for skin colour.

Sarcopenia in advanced heart failure is a growing concern. What is the impact of the skeletal muscle wasting disorder on the heart, and what therapeutic strategies have you and your team used to combat this disorder?

Sarcopenia is a definitive marker of the end stage of heart failure; in our clinic, we have a nutritionist who works simultaneously with the physicians to address this and other nutritional issues. The focus is on prevention since once the condition is established it is hard to revert. The heart failure patients receive multidisciplinary care that includes not only medical treatment, but also a nurse and nutritionist at the very least.

As an academic involved in the Optimize Heart Failure Care Program, what impact do you think the introduction of the programme has had on clinical practice?

Every single programme that draws attention to the epidemic nature of heart failure is important. I think the Optimize Heart Failure Care Program is a great opportunity for every physician to realise how big the problem is and what it will take to manage the causes. One thing about the programme that is very interesting is the participation of the patients; the programme was created to impact as much the patients as the doctors through specific tools, such as a mobile app.

"Imagine the possibility of predicting, early in the course of heart failure, a worse prognosis in the long term and preparing for it, implementing advanced care before the establishment of end-stage complications."

How far has our understanding advanced with regard to risk factors for heart failure since your career began? What do you think are the most significant developments you have seen during this time?

We have had known risk factors for cardiovascular disease for decades, including hypertension, diabetes, smoking, obesity, and sedentarism; however, we are now able to identify new factors, such genetics, amyloidosis, and chemotherapy especially. The way we are dealing with these new factors is changing annually, with new drugs or with new knowledge. I think we are more capable of diagnosing specific causes of heart failure with genetic tests and this diagnostic field will continue to widen.

What do you believe the primary focus of research into cardiac failure should be over the next 5 years?

Genetics and heart failure. I do believe that pharmacogenomics is the future of cardiology.

You have attended a large number of congresses during your academic career; why do you think congresses are so important to the medical community?

In one word: networking. It is relatively simple to have access to this ocean of medical information over the web, but you cannot overestimate how important is to feel the impact of the 'stars' of a meeting as soon as the late breaking clinical trial ends and the backstage talks begin. I have initiated several partnerships following unpretentious talks during lunchtime, for example. A lot of ideas are generated and feedback given, which is only possible in the direct presence of one another.

What advice would you give to medical students hoping to specialise in cardiology?

Never underestimate the power of knowledge. Cardiology is one of the top specialities in terms of the number of abstracts. But, equally as important as the information itself is putting it into practice, which will determine how well you will use it. The process of repetition will lead you as close to perfection as possible.

"It is relatively simple to have access to this ocean of medical information over the web, but you cannot overestimate how important is to feel the impact of the 'stars' of a meeting as soon as the late breaking clinical trial ends and the backstage talks begin."

Dr Sazzli Kasim @sazzlikasim

Universiti Teknologi MARA, Malaysia

To begin, what initially inspired you to specialise in cardiology?

Cardiology has always been fascinating as it allows me to apply my medical skills as a physician by thinking through the pathophysiology affecting patients, as well as proceeding to treat them using surgical precision to achieve wellness via a multidisciplinary team approach. Not many specialities allow for this type of practice.

Could you give us a brief understanding of your roles and responsibilities at the Universiti Teknologi MARA?

Being a university staff member, I am an educator, researcher, clinician, and administrator, and I am part of the medical faculty teaching staff. We run the largest undergraduate medical degree programme in the country, with up to 240 students per annum. We have postgraduate Master's and several PhD students within our department looking at areas of cardiac biomarkers, imaging, and lipidology. Our unit is actively running several clinical trials in the field of heart failure as well as lipid research. Our cardiac service has involved an accredited training centre since 2015 and includes an active ST-elevation myocardial infarction (STEMI) programme. Of note, our unit was established in late 2011 and became fully functional in 2013. Since 2016, I have been directly involved in the planning and construction of our future academic health centre in the north of Kuala Lumpur, Malaysia. This 400-bed public hospital will have womb-to-tomb services, e.g., mother and child health, minimally invasive and robotic

surgery, advanced rehabilitation medicine, and elderly care, alongside general medical service. We foresee our doors opening for patients in the second quarter of 2020.

Since you began your work in clinical practice, what key changes in the types and prevalence of cardiac conditions have you experienced?

I trained in Europe and returned to Malaysia in 2012 to practice. The widespread adoption of guideline-mandated treatment for primary and secondary prevention is a success story in many parts of the world, with reducing trends in ischaemic heart disease. The high prevalence of hypertension, diabetes, and obesity in Malaysia is a challenge for us and we aim to replicate the successes seen in many developed parts of the world. Coronary disease in Malaysia appears to be more aggressive, affecting younger males and females, as well as having a more complex anatomy. Percutaneous coronary intervention has evolved with thinner strut stents, drug-eluting balloons, and antiplatelet agents with greater potency, allowing it to be more effective in tackling the high disease burden in this region. The incidence of hypertensive cardiomyopathy is frightening, with many young patients undiagnosed until their first heart failure event. We still see sequelae of rheumatic heart disease in abundance here in Malaysia, which is not a scene many of my European counterparts would be used to seeing. Certain diseases, such as pulmonary hypertension and aortic stenosis, require greater education and awareness since they are underdiagnosed in Malaysia.

You have previously published manuscripts on the use of high-sensitivity troponin assays in acute coronary syndrome diagnosis. Can you briefly explain this technique and the key benefits of these assays in the assessment and treatment of cardiology disorders?

This particular assay is highly relevant. Many patients with myocardial infarction are missed during diagnosis due to the inability of currently available assays to discriminate the presence of infarction. The ability of high-sensitivity troponin assays to detect cell death as early as 1 hour after infarction allows them to be used in the emergency setting to rule out heart attacks. We have developed a position paper to address logistical issues faced by many of our Association of Southeast Asian Nations (ASEAN) counterparts. Nationally, we are about to embark on implementing a guideline on the use of cardiac biomarkers to make them cost effective and efficient. We hope to get this work published later this year.

Are there any developments soon to be revealed in the field of cardiology that you believe will have a great impact on the field?

Despite the falling number of drug breakthroughs within the field, cardiovascular research, especially in the field of genetics, holds much promise. Currently, we practice precision medicine without realisation. Drugs targeting specific pathways in heart failure, arrhythmias, and atherosclerotic processes are prescribed in the millions, simply due the high prevalence of disease globally. Cancer therapy may be more ligand-specific, but it provides nowhere near the magnitude of benefit cardiovascular science therapy has to offer. In the near future, achieving mortality reduction using sodium–glucose linked transporter inhibitors in diabetics may provide insights to better heart failure treatment. From a population point of view, drug therapy with the poly-pill approach may save millions of lives worldwide by treating the silent intermediate risk factors affecting half of the world's population.

What challenges, in respect to patient outcomes, does the field of cardiology currently face, and what advances do you hope to see in the next 5 years for the management of life-threatening heart conditions?

Advanced heart failure remains associated with a poor prognosis for many, and readmissions, high disability-adjusted life years, and sudden cardiac deaths still affect many patients everywhere. Stem cell therapy promised so much but has yet to deliver; whereas, resynchronisation therapy and ventricular assist devices may

improve quality of life but require an expensive and complex technology. I would like to see the regeneration of cardiac myocytes, halting the apoptosis process, as well as painless prevention of sudden death becoming a reality in the next 5 years.

You are currently a council member of the National Heart Association of Malaysia (NHAM). Could you tell us more about the aims of the society and how it has impacted cardiology practices in Malaysia?

NHAM aims to improve cardiovascular care in Malaysia. It addresses disease burden by having a national database on acute coronary syndromes and percutaneous interventions, thus allowing greater insight on fallacies missed by policies. It initiated nationwide adoption of STEMI programmes, as well as continuing to educate the public, physicians, and healthcare providers alike by having a compact yet enjoyable annual scientific meeting in April. This is the largest scientific meeting in the country, attracting some 1,800 participants in 2017. Translating advancement in technology to clinical practice is done via the annual live intervention meeting (MyLIVE) held in July annually. With the work of its sister societies, NHAM has produced many clinical practice guidelines adopted by the Ministry of Health Malaysia to provide evidence-based care nationwide.

As a clinician, researcher, and educator, how do you manage your time and balance these roles? Do you have any advice for colleagues who also have multiple responsibilities?

I don't. Balance is my utopian dream on the 31st of December every year, but it rarely comes in a wrapped package. In my opinion, having a vision of what is achievable is extremely important. Achieving goals should be a balance between several quick wins and working on a longer-term prospect. It is important to focus on what matters most, i.e., family and colleagues, but at the same time to envelop others with your enthusiasm. Make sure your goals are realistic and many will follow. I find that once goals are aligned, keeping others on the right track is a matter of routine and even remote supervision.

Finally, what do you believe is your proudest achievement from your career thus far?

My proudest achievement would surely be being where I am today: surrounded by my wife and four children, along with the rest of my family. That is a feat on its own.

"Balance is my utopian dream on the 31st of December every year, but it rarely comes in a wrapped package. In my opinion, having a vision of what is achievable is extremely important."

Guidelines, Clinical Evidence, and Real-Life Practice: How to Find Your Way in Managing Hypercholesterolaemia

This satellite symposium took place on 28th August 2018, as part of the European Society of Cardiology (ESC) Congress in Munich, Germany

Chairperson: Erik Stroes[1,2]

Speakers: Lluis Masana,[3] Michel Farnier[4]

1. Faculty of Medicine, University of Amsterdam, Amsterdam, Netherlands
2. AMC Medical Research BV, Amsterdam, Netherlands
3. Vascular Medicine and Metabolism Unit, Sant Joan University Hospital, Institut d'Investigació Sanitaria Pere Virgili (IISPV), Centre in Diabetes and Associated Metabolic Disorders (CIBERDEM), Universitat Rovira i Virgili, Reus, Spain
4. Lipid Clinic, Point Médical and Department of Cardiology, Centre Hospitalier Universitaire (CHU) Dijon-Bourgogne, Dijon, France

Disclosure: Prof Stroes has received fees to his institution for lectures and advisory boards for Amgen, Sanofi, Novartis, Athera, Mylan, Akcea, and Regeneron. Prof Masana received fees for lectures and advisory boards from Amgen, Sanofi, MSD, and Mylan. Prof Farnier has research contracts with Amgen, Sanofi/Regeneron; has undertaken consulting work for Abbott, Akcea/Ionis, Amarin, Amgen, AstraZeneca, Eli Lilly, Kowa, Merck and Co., Mylan, Pfizer, Sanofi/Regeneron, and Servier; and has participated in clinical trials including ODYSSEY (Sanofi/Regeneron), TESLA/TAUSSIG (Amgen), and Anacetrapib (Merck and Co.).

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Meeting Summary

Prof Masana presented evidence that low-density lipoprotein (LDL) cholesterol is a causal factor for atherosclerosis and that cardiovascular disease (CVD)-relative risk (RR) is reduced proportionally to LDL reductions, regardless of the type of monotherapy used. Combination therapy offers the advantage of increased lipid-lowering efficacy and a reduction in the side effects associated with high-intensity statins. The rationale thus exists for replacing high-intensity statin therapy with high-intensity cholesterol-lowering therapy.

Prof Farnier gave an in-depth description of the results of the IMPROVE-IT, FOURIER, and ODYSSEY-Outcomes trials, demonstrating that the magnitude of clinical benefit is independent of whether it is achieved by statins, ezetimibe, or PCSK9 inhibitors. The IMPROVE-IT study also showed that the magnitude of benefit is proportionate to the absolute decrease in LDL cholesterol. This is consistent with the conclusions of a meta-analysis of randomised controlled statin trials, showing that patients achieving very low LDL cholesterol levels have a reduced risk of major cardiovascular (CV) events compared with those achieving moderately low levels. The greatest benefits for reductions in major adverse CV events from lowering LDL cholesterol occur in patients with diabetes.

The above studies have led the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) taskforce on PCSK9 inhibitors to outline a strategy for additional treatment, with patients on maximally-tolerated statin doses failing to achieve LDL cholesterol goals at 4 weeks being considered for ezetimibe treatment, and those failing to achieve goals after a further 4 weeks being considered for PCSK9 inhibitors.

Votes from the audience, collected at the start and end of each presentation, showed that the speakers convinced delegates that the lower the LDL cholesterol level achieved the better the outcome for patients would be, that combination therapy is as effective as single dose high-intensity statins, and that statins plus ezetimibe should be considered as standard treatment in high-risk patients, particularly in Type II diabetes mellitus (T2DM) patients.

From Guidelines to Real Life: Practical Considerations for Patients with Hypercholesterolaemia. Combination Therapy

Professor Lluis Masana

The audience were asked to consider the case of a 71-year-old ex-smoker with hypertension treated with angiotensin-converting-enzyme inhibitors, calcium inhibitors, and hydrochlorothiazide, who was admitted to hospital with acute myocardial infarction (MI). The patient had untreated moderate hypercholesterolaemia (total cholesterol: 213 mg/dL; high-density lipoprotein [HDL] cholesterol: 43 mg/dL; LDL cholesterol: 140 mg/dL; and triglycerides [TG]: 150 mg/dL) and had been prescribed omeprazole.

In the first vote, 62%, 4%, and 6% of delegates said LDL cholesterol therapy targets should be <70 mg/dL, <50 mg/dL, and <30 mg/dL, respectively (NB. 1 mg/dL cholesterol=0.02586 mmol/L). Eight percent said that a 50% reduction should be achieved, 8% indicated that no target was necessary if a high-intensity statin was used, and 11% said that the lowest possible LDL cholesterol level should be aimed for. The LDL cholesterol target for such a patient is <70 mg/dL.[1]

In the second vote, 51% and 23% of delegates indicated that the patient should be started on atorvastatin 80 mg or rosuvastatin 20 mg, respectively. Fourteen percent said they would start on atorvastatin 40 mg/ezetimibe 10 mg, 3% voted for atorvastatin 80 mg/ezetimibe 10 mg, 1% decided on rosuvastatin 10 mg/ezetimibe 10 mg, and 7% chose rosuvastatin 20 mg/ezetimibe 10 mg.

Such responses demonstrated that three-quarters of the audience were aware of the ESC/EAS and the American College of Cardiology (ACC)/American Heart Association (AHA) 2013 guidelines on blood cholesterol treatment recommending that hypercholesterolaemic patients who have experienced a MI should receive high-intensity statins before being considered for combination therapy. For patients at higher risk for side effects, moderate-intensity statins can be started and, if this fails, statins should be increased to the highest intensity tolerable; only if this approach does not work should combination therapy be considered.[1,2]

Guidelines were developed after several trials showed no CV benefits for non-statin lipid-modifying agents used in combination with statins versus statin monotherapy. Negative trials included ILLUMINATE (torcetrapib),[3] HPS2-THRIVE (niacin),[4] DAL-OUTCOMES (dalcetrapib),[5] AIM-HIGH (niacin),[6] and ACCELERATE (evacetrapib).[7] Positive outcomes were observed in two studies, FIELD[8] and ACCORD,[9] for the fenofibrate/statin combination in patient subsets with high TG and low HDL cholesterol but not in overall diabetic subjects. Following these findings, the AHA and ACC 2013 cholesterol treatment guidelines recommended high-intensity statins as the preferred option for established CVD or hyperlipidaemia.[2]

Notably, in 2017, a EAS comprehensive review of scientific studies concluded that LDL cholesterol is not just a CV risk biomarker but also an aetiological factor in atherosclerosis.[10]

The LDL cholesterol level associated with CV outcomes has been established by a meta-

regression analysis for statin and non-statin therapies.[11] The analysis included statins (25 trials), fibrates (9 trials), ezetimibe (1 trial), niacin (3 trials), cholesteryl ester transfer protein inhibitors (3 trials), diet (4 trials), bile acid sequestrants (2 trials), ileal bypass surgery (1 trial), and PCSK9 inhibitors (2 trials). The analysis found a 23% reduction in CV events for each mmol/L reduction in LDL cholesterol when patients were treated with statins (RR: 0.77; 95% confidence interval [CI]: 0.71–0.84; p<0.001). A similar RR was reported for five non-statin therapies, including diet, bile acid sequestrant, ileal bypass, and ezetimibe (RR: 0.77; 95% CI: 0.75–0.79; p<0.001). The findings indicated that the relationship between CV event risk and LDL cholesterol levels achieved exists for both statins and certain non-statin therapies.

The IMPROVE-IT study demonstrated a relationship between incremental lowering of LDL cholesterol and improved CV outcomes when the non-statin lipid-modifying agent ezetimibe was added to simvastatin.[12] This suggests that, regardless of the mechanism of action, all reductions in LDL levels are of equivalent benefit and that a high-intensity cholesterol-lowering strategy should replace high-intensity statin therapy.[13]

Current cholesterol-lowering drugs include statins, ezetimibe, PCSK9 inhibitors, and resins/colesevelam. TG-lowering drugs include fibrates and omega-3 fatty acids. In addition to each agent reducing CV events as a monotherapy, there is now evidence supporting the effectiveness of combining statins with ezetimibe and PCSK9 inhibitors. There is also evidence supported by post-hoc analyses that statins and fenofibrate may be useful in patients with diabetes and atherogenic dyslipidaemia. Negative results have been reported for statin–omega 3 combinations, although high-dose omega 3 fatty acids with fibrates are used to treat patients with very high TG levels.[1]

Cholesterol-lowering therapies are classified into four groups according to LDL cholesterol reduction intensity, with low, mild, high, and very-high-intensity cholesterol-lowering therapies reducing LDL cholesterol by <30%, 30–49%, 50–60%, and >60%, respectively.[13]

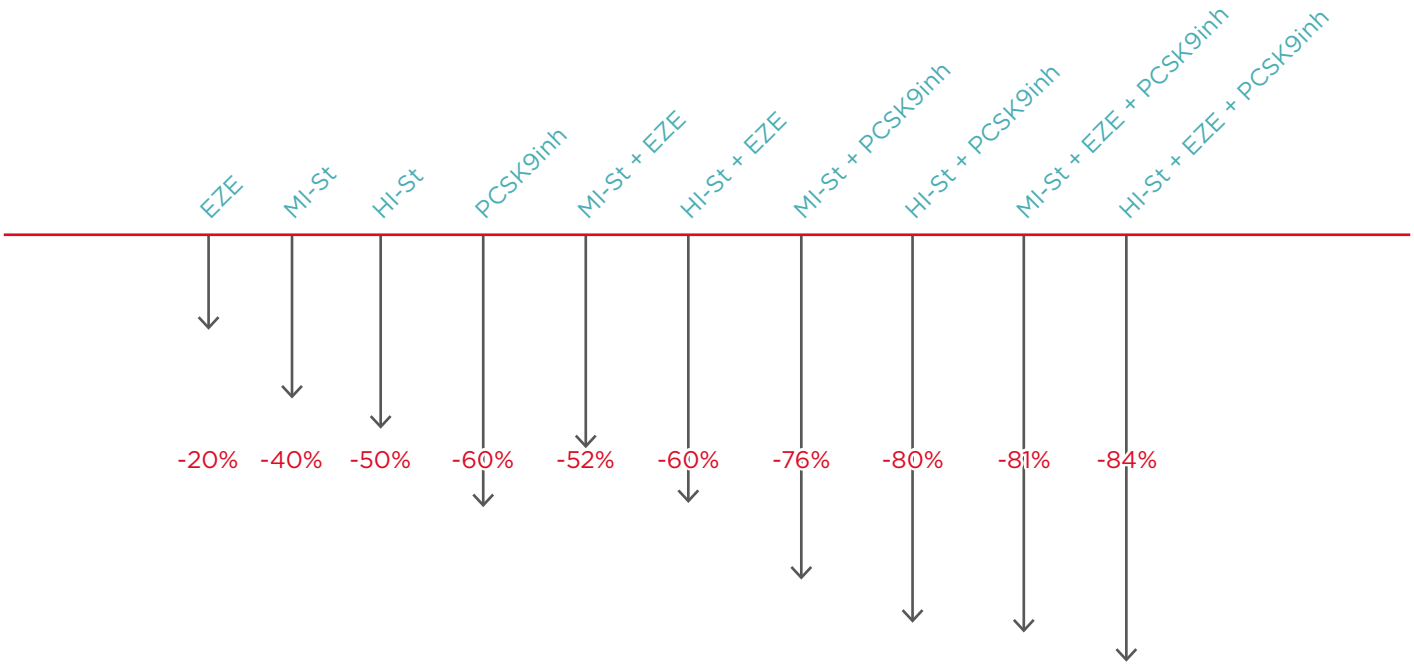

Figure 1: The lipid-lowering difference between high-intensity and moderate-intensity statins when combined with ezetimibe and PCSK9 is 3%.

EZE: ezetimibe; HI-St: high-intensity statin; inh: inhibitor; MI-St: moderate-intensity statin.

Adapted from Masana et al.[19]

Very-high-intensity combinations include atorvastatin 40–80 mg/ezetimibe 10 mg and rosuvastatin 20–40 mg/ezetimibe 10 mg.[12]

Since 1984, randomised controlled trials have achieved progressively lower LDL cholesterol concentrations. For example, the latest FOURIER study reported LDL levels of 30 mg/dL.[14] A pre-specified secondary analysis of this study demonstrated that such a concentration is more favourable, in terms of CV outcomes, than concentrations of 90 mg/dL or 70 mg/dL.[15]

While these data suggest that CV prevention is improved with lower LDL cholesterol levels, only 28.1% of CVD patients reach LDL cholesterol targets, according to the DYSIS targets.[16]

DYSIS furthermore found that, in patients at very high CV risk, the mean difference between actual levels and target levels was roughly 1 mmol/L, and that for populations failing to achieve LDL cholesterol targets the mean starting dose was equivalent to 35 mg/day of simvastatin, and only 7% received combination therapy. Such data suggests the need to address undertreatment.

Treatment options for patients taking medium or standard doses of statins who are not exhibiting the desired response include doubling their dose, switching to a more powerful statin, and starting combination therapy.[1]

A study that compared LDL cholesterol reductions for a range of statins (e.g., atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin) and a second study looking at pitavastatin found that only atorvastatin and rosuvastatin at daily doses of ≥20 mg produced reductions >40%.[17,18] Furthermore, when the atorvastatin dose was doubled, from 40 mg to 80 mg, the LDL lipid-lowering effect increased by only 6%, from 44% to 50%. Reductions in LDL cholesterol achieved from doubling doses are less pronounced than those observed following the addition of other agents. Combining two different lipid-lowering drugs provides a greater LDL cholesterol decrease; however, this does not simply correspond to the addition of each individual drug effect. For example, rosuvastatin 20 mg/day and ezetimibe 10 mg/day lowered LDL by 50% and 20%, respectively, but the two agents combined lower LDL cholesterol by 60%.[19]

Generally, the following LDL cholesterol reductions can be achieved with therapy: ezetimibe: -20%; moderate-intensity statin: -40%; high-intensity statin: -50%; PCSK9 inhibitor: -60%; high-intensity statin plus ezetimibe: -60%; moderate intensity statin plus PCSK9 inhibitor: -76%; high-intensity statin plus PCSK9 inhibitor: -80%; moderate-intensity statin plus ezetimibe plus PCSK9 inhibitor: -81%; and high-intensity statin plus ezetimibe plus PCSK9 inhibitor: -84%.[20] Thus, maximum LCL cholesterol lipid lowering can be achieved with combinations of high intensity statins plus ezetimibe plus PCSK9 inhibitors. Notably, the difference between high-intensity and moderate-intensity statins when combined with ezetimibe and PCSK9 inhibitors is just 3% (Figure 1).[19]

Benefits of statins, including CVD reduction and increased survival, need to be balanced against risks such as developing muscle symptoms, T2DM, and transaminases elevation. Evidence from studies, including PROVE-IT, A-Z, TNT, IDEAL, and SEARCH, suggests that the diabetogenic effects of statins are dose-related.[21] According to a EAS panel, factors influencing the risk of statin-associated muscle symptoms include pre-existing risk factors and comorbidities, high-dose statin therapy, polypharmacy, and drug–drug interactions (including concomitant use of gemfibrozil, macrolides, azole antifungal agents, protease inhibitors, and immunosuppressive drugs such as cyclosporine and inhibitors of CYP450 isoenzymes).[22]

To conclude, LDL cholesterol can be considered a causal factor for atherosclerosis, with the RR of CVD reduced proportionally to LDL cholesterol decreases regardless of the therapy used. The benefits of combination therapy, such as statins plus ezetimibe and statins plus PCSK9 inhibitors, have a scientific evidence base. Combination therapy increases lipid-lowering efficacy and reduces side effects associated with high-intensity statins, improving adherence and CV event reduction. Thus, the rationale exists for replacing high-intensity statin therapy with high-intensity cholesterol-lowering therapy.

In a repeat of the original vote, 39%, 4%, and 0% of the audience said LDL cholesterol therapy targets should be <70 mg/dL, <50 mg/dL,

and <30 mg/dL, respectively. Eleven percent said that a 50% reduction should be achieved, 17% indicated there is no target when high intensity statins are used, and 29% that the lowest possible level should be aimed for.

Regarding the second vote on treatments, 51% choose atorvastatin 80 mg, 14% voted for rosuvastatin 20 mg, 20% for atorvastatin 40 mg plus ezetimibe, 10% for atorvastatin 80 mg plus ezetimibe, 5% for rosuvastatin 10 mg plus ezetimibe, and 15% for rosuvastatin 20 mg plus ezetimibe.

The feedback from the audience demonstrated that the presentation had been successful in convincing delegates that the lower the LDL cholesterol level achieved the more favourable the outcome for patients and that use of combination therapy was as effective as single-dose high-intensity statins.

Interpretation of Recent Trial Outcomes and Considerations for Daily Practice

Professor Michel Farnier

At the start of Prof Farnier's presentation, the audience was asked to consider the case of a 62-year-old male with T2DM treated with coronary artery bypass graft who had a lipid profile on rosuvastatin 20 mg of an LDL cholesterol level of 81 mg/dL, TG levels of 180 mg/dL, and HDL-C levels of 40 mg/dL.

In the first vote, 6% of the delegates opted for no change to treatment, 27% for increasing the dose of rosuvastatin to 40 mg, 55% for adding ezetimibe, 4% for adding a PCSK9 inhibitor, and 7% for adding fenofibrate.

A number of trials have shown benefits from adding LDL therapies to statins, including IMPROVE-IT (ezetimibe),[12] REVEAL (anacetrapib), FOURIER (evolocumab),[15] SPIRE-1 and 2 (bococizumab),[23] and ODYSSEY-Outcomes (alirocumab).[24] Bococizumab and anacetrapib have since been withdrawn due to antidrug antibodies, which caused the LDL-lowering effect to wear off in bococizumab trials and accumulation in adipose tissue with anacetrapib.

In the IMPROVE-IT study, 18,144 patients with post-acute coronary syndrome for <10 days with LDL cholesterol of 50–100 mg/dL (on lipid-lowering therapy) or 50–125 mg/dL (without lipid-lowering therapy) were randomised to simvastatin 40 mg plus ezetimibe 10 mg or simvastatin 40 mg plus placebo.[12] Results at a median follow-up of 6 years showed that the primary endpoint (CV death, MI, documented unstable angina requiring rehospitalisation, coronary revascularisation for >30 days, or stroke) occurred in 32.7% of patients in the simvastatin plus ezetimibe group versus 34.7% in the simvastatin plus placebo group (hazard ratio [HR]: 0.936; 95% CI: 0.89–0.99; p=0.016).[12]

In the FOURIER trial,[25] 27,564 stable patients with established CVD (prior MI [81%], prior stroke [19%], or symptomatic peripheral artery disease [PAD] [13%]), 69% of whom were on high-intensity statins, who had either LDL cholesterol >70 mg/dL or non-HDL cholesterol >100 mg/dL were randomised to evolocumab every 2 weeks (or every 4 weeks) versus placebo. At a median follow-up of 2.2 years the primary efficacy endpoint (CV death, MI, stroke, hospitalisation for unstable angina, or coronary revascularisation) occurred in 11.3% of patients taking placebo versus 9.8% taking evolocumab (HR: 0.85; 95% CI: 0.79–0.92; p<0.001). The RR reduction was 15% and absolute risk reduction 1.5%.

Finally, in the ODYSSEY Outcomes trial, 18,924 patients were randomised to alirocumab or placebo plus background high-intensity statins starting 1–12 months after acute coronary syndrome. All participants had baseline LDL cholesterol levels of ≥70 mg/dL despite intensive statin treatment. The specific strategy was to obtain LDL cholesterol targets between 25 and 50 mg/dL, with some subjects needing up-titration of alirocumab, others down-titration of alirocumab, and a few switching to placebo when cholesterol became too low (<15 mg/dL).

Results at a median of 2.8 years showed the primary endpoint (a composite of coronary heart disease death, nonfatal MI, ischaemic stroke, or unstable angina requiring hospitalisation) occurred in 9.5% of alirocumab patients versus 11.1% of placebo patients (HR: 0.85; 95% CI: 0.78–0.93; p=0.0003). The study was presented by Prof Gabriel Steg at the 2018 ACC meeting.[24]

Taking the IMPROVE-IT, FOURIER, and ODYSSEY-Outcomes studies together, the magnitude of LDL cholesterol lowering benefit is independent of whether it is achieved by statins, PCSK9 inhibitors, or ezetimibe. This conclusion is in alignment with studies showing genetic mutations affecting LDL metabolism that decrease LDL cholesterol results in dose-dependent decreases in atherosclerotic cardiovascular disease (ASCVD) risk.[10] The magnitude of benefit is proportional to the absolute decrease in LDL cholesterol, which is demonstrated by the IMPROVE-IT study showing that reductions in LDL cholesterol are directly related to reductions in event rates.[12] When the same durations of follow-up were used to compare PCSK9 inhibitors in the FOURIER and SPIRE trials with statin treatment in the Cholesterol Treatment Trialists meta-analysis of statin trials, a similar magnitude of risk reduction was obtained. At 1 year of treatment, for every 1 mmol/L of LDL cholesterol reduction, the RR reduction of major vascular events was 14% in SPIRE 2 and 12% in CTT with statins. At 2 years of treatment, for every 1 mmol/L of LDL cholesterol reduction, the RR reduction of major vascular events was 17% in FOURIER versus 17% in CTT with statins.[26] Together with the genetic evidence, this demonstrates that therapies reduce CV event risks proportionally to absolute achieved reductions in LDL cholesterol and total durations of therapy. For non-statin therapies used for ASCVD, cost-effectiveness analyses are essential to determine whether, how, and when PCSK9 inhibitor treatment meets accepted value for financial metrics.[27] The higher the risk, the higher the benefit, and this raises a key question of how to identify statin therapy patients at highest risk of recurrent disease for additional treatments.

A meta-analysis of eight randomised controlled statin trials demonstrated that patients achieving very low LDL cholesterol levels had lower risks of major CV events than those achieving moderately low levels. Compared to patients achieving LDL cholesterol >175 mg/dL, those reaching LDL cholesterol 75–100 mg/dL, 50–75 mg/dL, and <50 mg/dL had adjusted HR for major CV events of 0.56, 0.51, and 0.44, respectively.[28]

Similar relationships hold for events when the placebo arms in FOURIER and ODYSSEY-Outcomes were analysed. In FOURIER, 13.6% of patients with LDL cholesterol <80 mg/dL had a CV event versus 16.2% with LDL cholesterol >109 mg/dL. In the ODYSSEY-Outcomes trial, 9.5% of patients with LDL cholesterol <80 mg/dL experienced an event versus 14.9% with LDL cholesterol >100 mg/dL.

For the FOURIER placebo group, the risk of CV death, MI, or stroke was 10.8% for patients <2 years from qualifying MI versus 9.3% for patients >2 years from qualifying MI (HR: 1.19; 95% CI: 1.04–1.37; p=0.01). The risk changes to 15.0% for patients having over two prior MI versus 8.2% for patients having one prior MI (HR: 2.04; 95% CI: 1.78–2.35; p<0.001), and 12.6% for patients having multivessel disease versus 8.9% for single vessel disease (HR: 1.47; 95% CI: 1.27–1.70; p<0.001). Analysis of FOURIER placebo data showed that the risk of CV, MI, or stroke was 13.0% in patients with PAD versus 7.6% in patients without PAD (adjusted HR: 1.81; 95% CI: 1.53–2.14; p<0.001).

Among the categories of highest risk ASCVD on statin therapy (defined as around or above a benchmark of 30% of a 10-year risk) are patients with clinical atherosclerotic CVD and T2DM.[29]

When IMPROVE-IT was analysed according to diabetic status, in non-diabetic patients the probability of the primary endpoint at 7 years was 30.2% for patients taking simvastatin or ezetimibe versus 30.8% for patients taking simvastatin alone (HR: 0.98; 95% CI: 0.91–1.04; p=0.526). For diabetic patients it was 40.0% for patients taking simvastatin or ezetimibe versus 45.5% for patients taking simvastatin alone (HR: 0.85; 95% CI: 0.78–0.94; p<0.001).[30] Such data demonstrate that patients with diabetes derived significantly greater relative and absolute benefits from the addition of ezetimibe than patients without diabetes.

A recent meta-analysis of seven trials showed the ezetimibe plus statin combination therapy was associated with a greater reduction in major adverse CV events in diabetic patients than those without diabetes (pooled RR: 0.84 versus 0.93; $p_{heterogeneity}$=0.012).[31] Such data raise questions about why ezetimibe delivers greater benefits to patients with T2DM. The benefit

was shown in IMPROVE-IT, where there was a 3 mg/dL greater reduction in LDL cholesterol for patients with diabetes compared to those without (p=0.03).[30] Furthermore, a pooled analysis of 27 clinical trials of patients with and without diabetes receiving ezetimibe plus statin or statin alone showed patients with diabetes achieved significantly larger reductions in LDL cholesterol with the combination therapy (difference of 2.5%; p<0.0001).[32]

Reductions in cholesterol do not fully explain the magnitude of the effect in diabetic patients, leading to suggestions that other beneficial effects may also occur, including influencing postprandial lipaemia (a condition in which TG-rich chylomicron remnants are increased during the postprandial period).[33]

The ESC and EAS recently updated their practical clinical guidance for the use of PCSK9 inhibitors in patients with ASCVD.[34] The new guidelines recommend that in patients with clinical ASCVD, ezetimibe should be given according to clinical judgement and local guidance, and that for patients with LDL cholesterol >140 mg/dL or patients with LDL-C >100 mg/dL and additional indices of risk, a PCSK9 inhibitor should be considered. Additional risk categories include familial hypercholesterolaemia, diabetes with target organ damage or marked hypertension, severe or extensive ASCVD, and rapid progression of ASCVD.

The taskforce additionally provided a decision algorithm for PCSK9 inhibitors in familial hypercholesterolaemia in primary prevention, with patients who have no additional indices being considered for PCSK9 inhibitors when they have LDL cholesterol levels >180 mg/dL and for patients with additional indices of risk severity being considered with LDL cholesterol levels >140 mg/dL. Here, additional risk indices are defined as diabetes with target organ damage, lipoprotein (a) >50 mg/dL, major risk factors such as smoking, marked hypertension, >40 years of age without treatment, and premature ASCVD (<55 years in males and <60 years in females) in first-degree relatives and imaging indicators.

The taskforce recommendation is to first place patients on the maximally tolerated statin doses and assess their response at 4 weeks. Those failing to achieve LDL cholesterol goals should be considered for ezetimibe, with their response assessed again after 4 weeks. Those found to be above LDL cholesterol thresholds should then be considered for a PCSK9 inhibitor. Patients prescribed the PCSK9 inhibitors should have their LDL cholesterol-lowering response assessed 2 weeks after the first injection.

A recent analysis of the DYSIS II study found that, among 631 Italian patients with coronary heart disease receiving lipid lowering treatment, 64.6% had LDL cholesterol levels >70 mg/dL and 25.1% had LDL cholesterol levels >100 mg/dL. In a model, the addition of ezetimibe reduced the percentage of patients with LDL cholesterol >70 mg/dL and >100 mg/dL from 64.6–37.9% and from 25.1–11.8%, respectively.[35]

A simulation model involving a cohort of 105,269 patients was undertaken to estimate the percentage of patients with ASCVD that would require a PCSK9 inhibitor.[36] The USA database revealed that only 25.2% achieved LDL cholesterol levels <70 mg/dL, with 51.5% of the database using statin monotherapy and 1.7% statins plus ezetimibe. The model showed that following treatment intensification, 99.3% could achieve LDL cholesterol levels <70 mg/dL including 67.3% with statin monotherapy, 18.7% with statins plus ezetimibe, and 14% with add-on PCSK9 inhibitors. In conclusion, combining statins with ezetimibe represents the logical first choice of therapy when LDL cholesterol is uncontrolled by statin monotherapy, with PCSK9 inhibitors considered for the highest risk categories on maximally tolerated statin plus ezetimibe therapies.

When the vote was returned to the audience, 2% said they would not change the treatment, 9% would use rosuvastatin 40 mg, 85% would add ezetimibe, 3% would add a PCSK9 inhibitor, and 2% would add a fibrate. The second vote showed that the vast majority of the audience agreed with the rationale given in the presentation to add ezetimibe and consider statin plus ezetimibe in secondary prevention of high-risk patients with T2DM.

Conclusion

In summary, the symposium's take-home messages are that clinicians should move away from thinking about high-intensity statin therapy and instead consider high-intensity lipid-lowering therapy. Furthermore, patients that do not achieve the LDL cholesterol target with residual LDL cholesterol burden and high absolute risk require combination therapy, preferably with high-intensity statin and ezetimibe.

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Reversal of Apixaban and Rivaroxaban Anticoagulation by Andexanet Alfa in ANNEXA-A and ANNEXA-R as Assessed by Non-Tissue Factor-Initiated Thrombin Generation Independent of Tissue Factor Pathway Inhibitor

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Abstract

Andexanet alfa is a modified factor Xa (FXa) drug designed to bind and sequester FXa inhibitors and thus reverse anticoagulation. The oral presentation reviewed in this article, presented by Dr Genmin Lu at the European Society of Cardiology (ESC) Congress 2018, provides new insights into the effect of the interaction between andexanet alfa and tissue factor (TF) pathway inhibitors on the restoration of thrombin generation (TG) in the TF (extrinsic) and non-TF (intrinsic) coagulation pathways.

INTRODUCTION

Andexanet alfa is a recombinant modified FXa protein with no enzymatic activity, designed to bind and sequester FXa inhibitors and thus reverse anticoagulation (Figure 1).[1] Phase III studies have shown that andexanet alfa reverses the anticoagulation effects of the FXa inhibitors apixaban and rivaroxaban in older (aged 50–75 years), healthy volunteers.[2] The ongoing ANNEXA-4 study in patients who had acute major bleeding after the administration of an FXa inhibitor showed 79–83% haemostatic efficacy.[3,4] In 2018, andexanet alfa was approved by the U.S. Food and Drug Administration (FDA) for patients treated with rivaroxaban and

apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.[5] At the time of this oral presentation, andexanet alfa was under review for this indication in Europe.

ANDEXANET ALFA REVERSES THE ANTICOAGULATION EFFECTS OF APIXABAN AND RIVAROXABAN

The Phase III ANNEXA-A (apixaban) and ANNEXA-R (rivaroxaban) studies evaluated the effects of andexanet alfa versus placebo on healthy, older volunteers treated with 5 mg of apixaban twice daily or 20 mg of rivaroxaban daily, respectively. In Part 1 of the studies, subjects received andexanet alfa as a 400 mg (ANNEXA-A) or 800 mg (ANNEXA-R) bolus, whereas subjects in Part 2 received the same bolus plus a 480 mg (4 mg/min, ANNEXA-A) or 960 mg (8 mg/min, ANNEXA-R) infusion of andexanet alfa.[2]

When administered as a bolus or a bolus plus 2-hour infusion in subjects receiving anticoagulation for 4 days, andexanet alfa immediately and significantly reversed apixaban or rivaroxaban-associated anti-FXa activity. The reversal effect was sustained throughout the infusion and for approximately 2 hours following the end of infusion compared with placebo. Andexanet alfa treatment also reduced unbound, pharmacologically active concentrations of both FXa inhibitors and restored TF-initiated TG (TF-TG) compared with placebo. No serious adverse or thrombotic events were reported.[2]

AN ANDEXANET ALFA-TISSUE FACTOR PATHWAY INHIBITOR INTERACTION CONTRIBUTES TO THE SUSTAINED REVERSAL OF TISSUE FACTOR-INITIATED, BUT NOT NON-TISSUE FACTOR-INITIATED, THROMBIN GENERATION

As a modified FXa protein, andexanet alfa has no known major interactions with any other coagulation factors except for TF pathway inhibitor (TFPI), an endogenous, reversible inhibitor of the TF pathway. The interaction between andexanet alfa and TFPI may affect TF-TG (Figure 1), which is a secondary pharmacodynamic endpoint used in andexanet alfa clinical studies.[2]

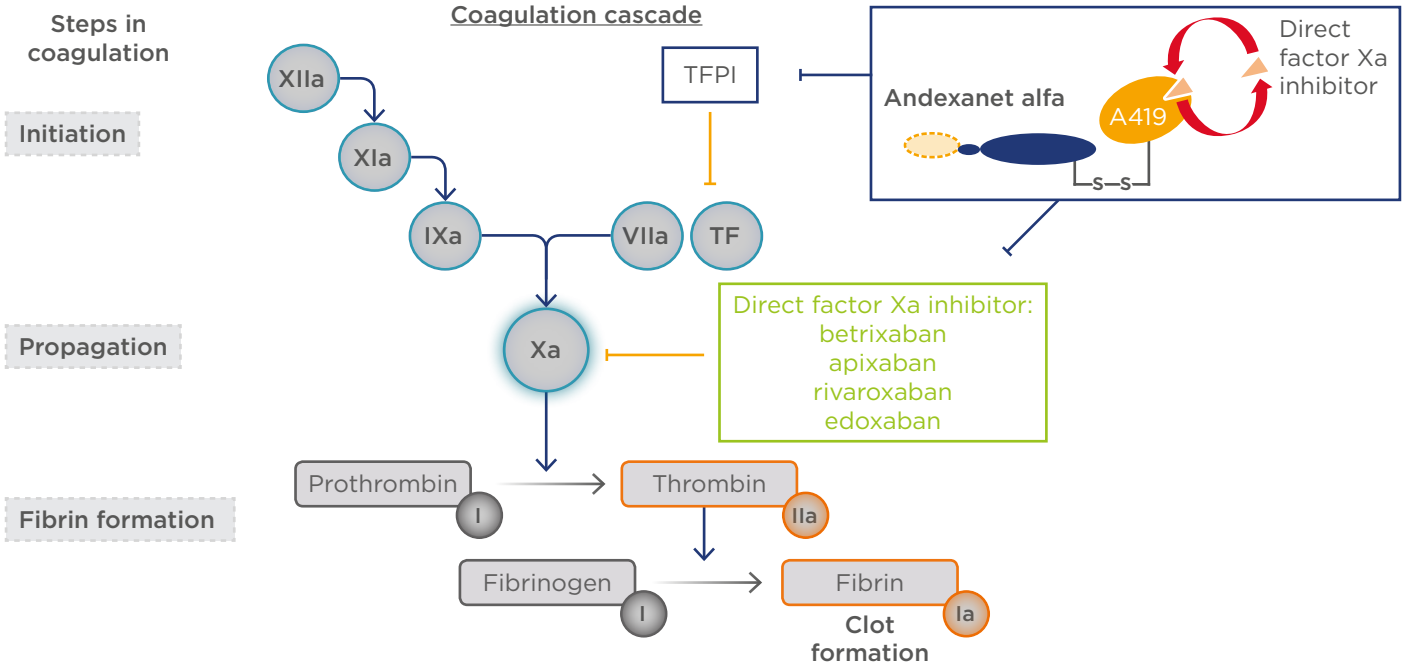

Figure 1: Andexanet alfa mechanism of action.

TF: tissue factor; TFPI: tissue factor pathway inhibitor.

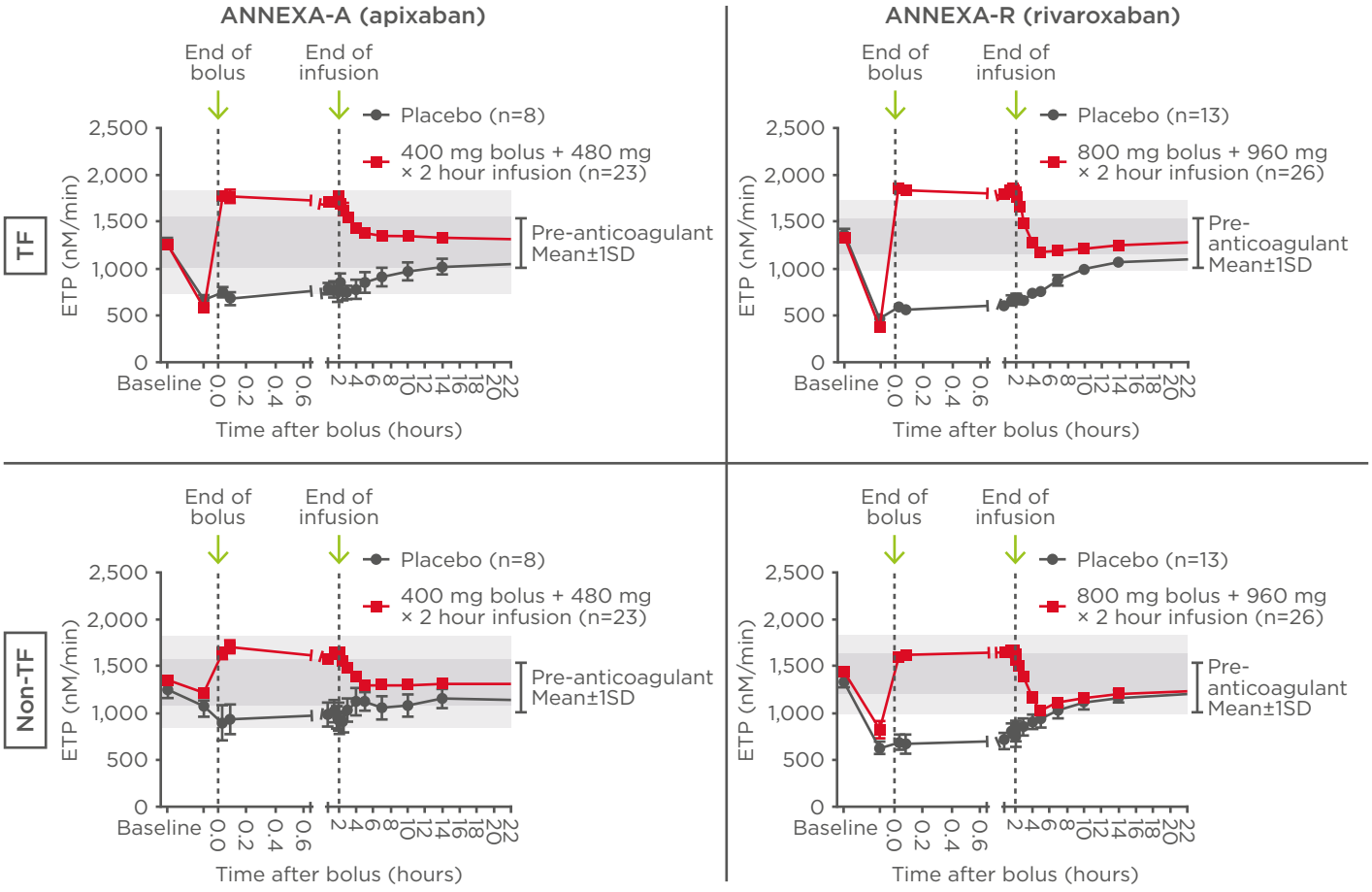

Figure 2: Time courses of tissue factor and non-tissue factor-initiated thrombin generation before and after administration of andexanet.

Andexanet versus placebo p values: TF: p<0.0001; non-TF: p<0.001. The shaded areas represent Day 1 pre-anticoagulant baseline ranges shown as mean±1SD (dark grey) and mean±2SD (light grey).

ETP: endogenous thrombin potential; SD: standard deviation; TF: tissue factor.

The objective of the current study was to compare the effect of the andexanet alfa–TFPI interaction on restoration of TG in the TF (extrinsic) versus non-TF (intrinsic) pathways in the Phase III studies ANNEXA-A and ANNEXA-R.[6,7]

Retained plasma samples from subjects who received the andexanet alfa bolus plus 2-hour infusion were analysed using a validated non-TF-TG assay; this was similar to the TF-TG assay but instead used an activated partial thromboplastin time reagent (Actin FS; Siemens, Munich, Germany) as an activator. Restoration of TG was assessed by endogenous thrombin potential (ETP) and other TG parameters, including lag time, peak thrombin, time-to-peak, and velocity index.[6,7] Following anticoagulation for 4 days, andexanet alfa significantly reduced apixaban and rivaroxaban-induced inhibition of both TF-TG and non-TF-TG versus placebo, as assessed by ETP and all other TG parameters (TF all p<0.0001; non-TF all p<0.001; Figure 2).[6,7]

In apixaban-treated subjects, andexanet alfa restored TG to pre-anticoagulant levels under both TF and non-TF conditions, as assessed by ETP. It restored non-TF-TG in 100.0% of subjects (n=23) versus 37.5% of subjects who received placebo (n=8; p=0.0003).[6] During administration of andexanet alfa, non-TF-TG had less of an increase in ETP above the pre-anticoagulant baseline level used to define the normal range compared with TF-TG. Following the end of the andexanet alfa infusion, there was a significant difference in TF-TG ETP between andexanet and placebo-treated subjects for at least 12 hours; however, for

non-TF-TG, the ETP for andexanet-treated subjects decreased to that of the placebo-treated group within 2 hours after infusion and stayed within the pre-anticoagulant baseline range (mean±1 standard deviation).[7]

The results were similar in rivaroxaban-treated subjects. Andexanet alfa restored non-TF-TG in 100.0% of subjects treated with andexanet alfa (n=26) versus 15.4% of subjects who received placebo (n=13; p<0.0001).[6] Non-TF-TG in the andexanet group had less of an increase in ETP above the pre-anticoagulant baseline level compared with TF-TG. Also, there was a significant difference in TF-TG ETP between andexanet and placebo-treated subjects for at least 12 hours after infusion; whereas for non-TF-TG, the ETP in the andexanet group decreased to that of placebo within 2 hours and gradually returned to the pre-anticoagulant baseline range (mean±1 standard deviation).[6,7]

CONCLUSION

Sequestration of the FXa inhibitors apixaban and rivaroxaban is the major contributor in restoring TG both during and immediately after the administration of andexanet alfa. The interaction between andexanet alfa and TFPI may contribute to the duration of the sustained reversal of TF-TG but does not contribute to non-TF-TG. Importantly, andexanet alfa restored TG to pre-anticoagulant levels under both conditions, whether TG was initiated via the extrinsic or intrinsic pathways. Overall, these data from studies in healthy volunteers suggest that the major function of andexanet alfa is to bind and reverse the anticoagulant activity of FXa inhibitors.

QUESTION AND ANSWER SESSION

A clinical concern for anticoagulant antidotes is 'rebound' when treatment is stopped. Have you experienced any rebound anticoagulation activity when treatment with andexanet alfa is stopped?

Andexanet alfa had an immediate and sustained effect on FXa inhibitors throughout and for approximately 2 hours following the end of infusion compared with placebo. The time course profile for the reversal of anti-FXa activity is consistent with the mechanism of action (binding and sequestering FXa inhibitors) and the effective half-life of andexanet alfa (~1 hour). However, as andexanet is cleared after the end of the infusion, the anticoagulant anti-FXa levels return to that of the placebo group. The andexanet alfa bolus followed by a 2-hour infusion was sufficient to completely reverse the anticoagulant effect, as previously demonstrated by TG and clinical efficacy in the ANNEXA-4 study in bleeding patients.

Following administration of the andexanet alfa bolus, what is the recommended period of treatment for the maintenance infusion? Is it until the bleeding clinically stops or do you use a prespecified timeframe?

We have evaluated an andexanet alfa bolus and bolus followed by infusion in Phase II and III studies in healthy volunteers. The two dose regimens shown here were sufficient for reversal of FXa inhibitors based on PD markers. Based on our data from animal models and ongoing Phase IV studies in bleeding patients, a 2-hour infusion is sufficient to stop bleeding in most patients.

The andexanet doses were different for the two inhibitors, apixaban and rivaroxaban. Was this due to the difference in plasma protein binding?

The different protein binding of apixaban and rivaroxaban is a minor factor when determining the doses of andexanet. The major difference is their volume of distribution. As andexanet binds to the inhibitor with high affinity in a 1:1 molar ratio, administration of andexanet causes redistribution of the inhibitor from the extravascular compartment into the plasma compartment. Rivaroxaban has an approximately 3-fold higher volume of distribution versus apixaban, hence the need for higher dosing to bind and sequester the total anticoagulant activity in the plasma.

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Abstract Reviews

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Fibre-Optic Contact Force Catheter Efficiency and Effectiveness in Paroxysmal Atrial Fibrillation Ablation from a Large, Multinational, Prospective Registry (ABLATOR)

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Keywords: Atrial fibrillation, catheter ablation, contact force (CF).

Citation: EMJ Cardiol. 2018;6[1]:52-53. Abstract Review No. AR1.

Over recent years, in response to the widespread use of contact force (CF) ablation catheters for the treatment of atrial fibrillation, numerous studies have sought to assess their performance, effectiveness, and safety.

Randomised trials have proven the non-inferiority of CF catheters compared to non-CF catheters in terms of safety and long-term efficacy and have shown a correlation between the use of optimal force and higher success rates. However, whether these results can be extrapolated to a real-world setting with operators of varied experience levels across centres with diverse volumes remains unknown. This study is a subset analysis of the ABLATOR registry, which is a prospective, multicentre, international registry that included 2,035 patients who were indicated for an atrial fibrillation ablation using different St. Jude Medical technologies. Patient enrolment took place from December 2014–June 2016. The purpose of this sub-study was to evaluate the performance of CF ablation catheters, specifically the TactiCath™ Quartz catheter (Abbott, Lake Bluff, Illinois, USA), in patients undergoing *de novo* paroxysmal atrial fibrillation ablation. From the overall population of the ABLATOR registry, 473 subjects were included in this subanalysis and 460 completed the follow-up (approximately 3% lost to follow-up).

The results of this study are comparable to, or better than, the success rates reported in randomised trials investigating the use of other CF ablation catheters, such SMART-AF (66%),[1] FIRE and ICE (64%),[2] and TOCCASTAR (68%).[3] The clinically relevant freedom from recurrence at 1-year follow-up was 76.9%, which decreased to 71.6% when patients on antiarrhythmic drugs were excluded. Serious adverse events affected 3.2% of this registry. Only 1 oesophageal fistula was reported (0.2%), 1 vascular complication (0.2%), and 9 patients had pericardial effusion, 7 of whom had cardiac tamponade (1.5%). These results are in keeping with the SMART-AF results, which reported that cardiac tamponade occurred in 2.5% of the subjects.[1] Despite similarity to the SMART-AF trial, these results are higher than expected based on the current clinical experience. Most of the previous studies enrolled patients during the initial years of CF catheter use, when the optimal CF to achieve durable lesions for successful isolation of the pulmonary veins had not yet been defined and the safety profile had not been optimised.

Mansour et al.[4] recently reported on a registry of 41,709 patients who underwent atrial fibrillation using the TactiCath Quartz catheter. The overall rate of complications was reported as 0.481% and cardiac perforations were reported in 0.281% of the subjects. This progressive reduction in the complication rates was comparable with the initial SMART-AF and TOCCASTAR studies; however, the discrete improvement in success rates may be attributed to an increase in operator experience and a better understanding of the use of these technologies.

In conclusion, real-world efficiency, effectiveness, and safety of the TactiCath Quartz catheter for paroxysmal atrial fibrillation ablation has been clearly proven in this registry, beyond the results of randomised trials. The importance of registries in opposition to randomised trials is based on the need to know the real-world outcomes in varied centres with different levels of operator expertise.

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Impact of a Cardiac Rehabilitation Programme After a Myocardial Infarction in Individuals Not Undergoing Revascularisation: New Horizons for a Time-Tested Intervention

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Keywords: Acute coronary syndromes, cardiac rehabilitation (CR), myocardial infarction (MI), secondary prevention.

Citation: EMJ Cardiol. 2018;6[1]:53-55. Abstract Review No. AR2.

Cardiac rehabilitation (CR) plays a pivotal role in the contemporary management of myocardial infarction (MI) patients[1] and several studies have documented the significant benefits on cardiovascular outcomes, both in terms of morbidity and mortality.[2,3] CR has greatly evolved since its introduction and this has been reflected by the expanding indications for this holistic intervention.[1,3] Exercise training exerts several physiological effects via both cardiac and extracardiac mechanisms,[3,4] and has become one of the mainstays of CR programmes.[3] Despite these positive data, certain patient subgroups tend to be referred to CR less often.[3,5] Of these, patients not undergoing revascularisation present a particularly complex challenge given their suboptimal referral[5] and higher risk status.[6]

A study by our group assessed the impact of a Phase II CR programme among MI survivors not undergoing revascularisation during hospitalisation, in terms of functional parameters assessed by cardiopulmonary exercise testing using a treadmill.[7] A total of 349 patients from a single tertiary centre were included in this retrospective cohort study and the study population was mainly composed of male individuals (81.2%), with a mean age of 59.0±10.5 years. Of these, 12.6% had not been submitted to revascularisation during hospitalisation. Significant differences were present in terms of age, sex, history of coronary artery disease, prevalence of arterial hypertension, and smoking status. After the CR programme (mean number of sessions: 21.1±6.7), patients presented with significant improvements in cardiorespiratory fitness, as assessed by peak oxygen consumption (pVO_2). Importantly, although patients not undergoing revascularisation during hospitalisation had a significantly lower pVO_2 than the remaining patients (both at the beginning and at the end of the CR programme), there were no differences between these groups in terms of the benefit derived from the CR programme. This finding was maintained after adjusting for age and sex. Additionally, no differences were present between the groups in terms of the respiratory exchange ratio.

Previous data from patients with incomplete revascularisation have showed that a CR programme could be beneficial.[8] In a study of 190 patients after an acute coronary syndrome (49 with incomplete revascularisation), a CR programme was well tolerated and presented significant increases in workload capacity, which did not differ between the study groups. Additionally, it should be noted that patients who did not undergo revascularisation tended to present with different risk profiles, namely in terms of a higher prevalence of comorbidities.[6,9] As a result, the global scope of CR makes this intervention especially attractive for this subgroup of MI patients. The improvement in cardiorespiratory fitness (as assessed by pVO_2) should also be highlighted since exercise capacity has been described as an important predictor of cardiovascular events in different groups of individuals.[10]

In conclusion, the results of the present study highlight the importance of CR programmes in MI survivors, namely in those who do not undergo revascularisation during hospitalisation. Future research should further explore this issue to fully ascertain the overall impact of CR on this higher-risk population, whose unmet needs in terms of secondary prevention still need to be improved.

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The Effect of Renin-Angiotensin System Blockade on Long-Term Outcomes Following Transcatheter Aortic Valve Implantation

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Keywords: Aortic stenosis, bradykinin system, renin-angiotensin system (RAS), transcatheter aortic valve implantation (TAVI).

Citation: EMJ Cardiol. 2018;6[1]:55-57. Abstract Review No. AR3.

BACKGROUND

Several studies have demonstrated the benefits of transcatheter aortic valve implantation (TAVI) in high and intermediate-risk patients, but there is still a gap in the evidence regarding the long-term outcomes related to pharmacological therapies.[1-3] In particular, the presence of fibrosis and myocardial hypertrophy in patients with aortic stenosis has been related to worse prognosis.[4,5] Therefore, better outcomes might be achieved with the use of strategies that improve cardiac remodelling by reversing fibrosis and hypertrophy.[6,7] In this regard, renin-angiotensin system (RAS) blockade has been shown to have a positive impact on remodelling and major clinical outcomes in previous studies.[8-10] In this study, we aimed to determine the effects of RAS blockade following successful TAVI procedures.

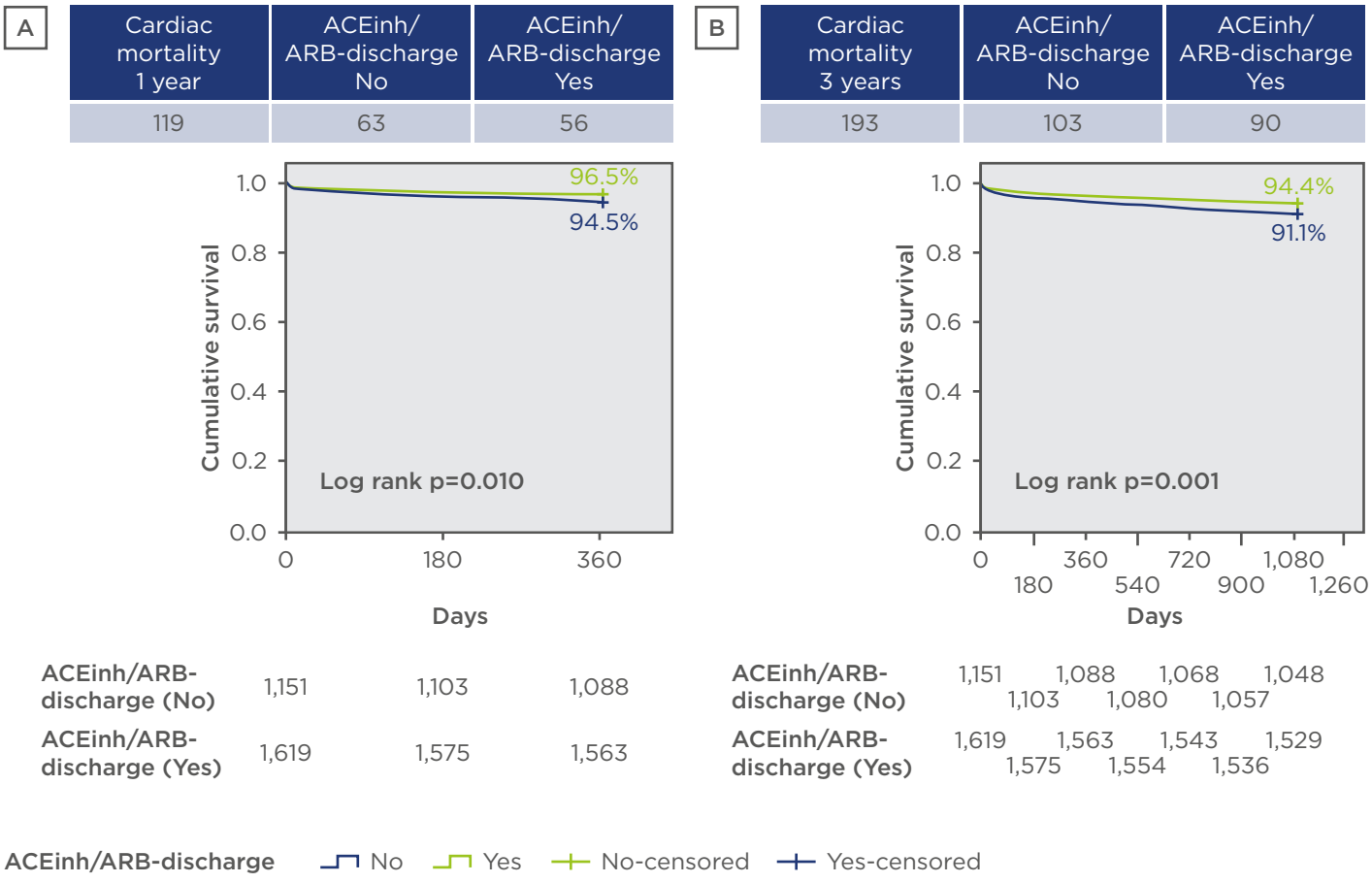

Figure 1: Cardiac mortality at A) 1 and B) 3-year follow-up following transcatheter aortic valve implantation with and without renin-angiotensin system blockade.

ACEinh: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

METHODS

Patients with severe aortic stenosis who underwent TAVI between August 2007 and August 2017 were included from nine institutions. All baseline clinical, echocardiographic, and procedural data were prospectively recorded in a dedicated database and prespecified follow-up was performed. Dose and type of RAS blockade therapy were also recorded. Patients were compared according to the prescription of RAS blockade (or lack of) at discharge. Only those patients who survived the in-hospital period and who had been on continuous RAS blockade therapy for at least 1 month after TAVI were included in the treatment group. A matched comparison was performed according to baseline and procedural differences.

RESULTS

A total of 2,866 patients were included and the final study population consisted of 2,715 patients who were alive at discharge. The mean age of the study population was 80.8±7.1 years and 53.7% of the patients were female. A total of 1,622 patients (59.7%) received RAS blockade therapy after the procedure and at a median follow-up of 3 years post-TAVI, the RAS blockade group had significantly lower cumulative mortality than the non-RAS blockade group (9.5% versus 16.5%; p=0.001, log rank test). Matched adjustment by main baseline and procedural differences, including hypertension, diabetes, chronic kidney disease, chronic pulmonary disease, baseline New York Heart Association (NYHA) class, and baseline left ventricular ejection fraction, was performed. No differences existed between the use of

other medications, the degree of residual aortic regurgitation, or the TAVI approach. RAS blockade therapy was still associated with significantly lower cardiac mortality (hazard ratio: 0.581; 95% confidence interval: 0.310–0.893; p=0.002) both at 1 and 3-year follow-up (Figure 1). In addition, the rates of myocardial infarction, cerebrovascular events, and hospital readmission due to heart failure remained lower in the RAS blockade group than the non-RAS blockade patients.

DISCUSSION

While a positive effect of RAS blockade was expected, the marked cardiovascular protective effect irrespective of other conditions is a major finding from this study. Although some authors suggest that many post-TAVI patients are already prescribed cardioprotective treatments, we found that up to 40% of patients were not. Confirmation of such effects and analysis of the cardioprotective mechanisms of RAS blockade are warranted and will be conducted through the RASTAVI clinical trial,[11] which will investigate the use of ramipril for RAS blockade after TAVI for severe aortic stenosis.

CONCLUSION

This retrospective cohort of the randomised RASTAVI study suggests that post-TAVI RAS blockade therapy is associated with lower cardiac mortality at 3-year follow-up and results in a cardiovascular protective effect irrespective of the left ventricular ejection fraction or residual aortic regurgitation. The RASTAVI randomised trial will help to determine the accuracy of these findings.

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Effect of Renin-Angiotensin System Blockade in the Prevention of Thoracic Aortic Aneurysm Progression

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Keywords: Medial degeneration, renin-angiotensin system blockade, thoracic aortic aneurysm (TAA).

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Abstract Review No. AR4.

INTRODUCTION

Data are limited on the efficacy of medical therapies for non-syndromic thoracic aortic aneurysms (TAA), with expression of disease-causing genes restricted to vascular smooth muscle cells (VSMC) and disease manifestations restricted to the aorta, in contrast to syndromic TAA, which is associated with abnormalities of multiple organ systems (particularly in Marfan syndrome).[1,2] However, accumulating evidence has demonstrated that renin-angiotensin system activity through the VSMC is strongly associated with the formation and progression of TAA.[3,4]

The aim of this study was to evaluate the effect of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy on ascending aortic diameter progression in patients with non-syndromic TAA.

METHODS

Fifty consecutive patients (mean age: 57.9±14.9 years) with TAA were enrolled in our retrospective, non-randomised, single centre study after aortic surgery (with or without valve sparring). Preoperatively, in addition to beta-blockers, 17 patients (34%) received ACEI (perindopril, enalapril, or fosinopril), 18 patients (36%) were treated with an ARB regimen (losartan or valsartan), and 15 patients (30%) did not receive any ACEI or ARB medications. Repeated (in 2.39±1.73 years) preoperative CT with three-dimensional reconstruction was used to evaluate aortic diameters and aortic dilatation rate. Left ventricular function and dimensions were examined during preoperative transthoracic echocardiography. Histopathological analysis of resected aortic tissue specimens was conducted after surgery of the ascending aorta.

RESULTS

The mean ascending aortic diameter in the overall group did not change significantly during the preoperative follow-up (from 44.6±7.2 mm to 44.9±6.3 mm; p=0.86). The aortic growth was 0.17±1.33 mm/year in patients receiving ARB but significantly higher, 2.0±0.81 mm/year, in ACEI patients (p=0.04) and 3.0±1.58 mm/year (p=0.01) in patients who did not receive ARB or ACEI therapy.

Global systolic left ventricular function (ejection fraction measured by the Simpson methodology) was slightly depressed in all subgroups: 53.1±10.3% in ACEI, 55.5±10.2% in ARB (ACEI versus ARB; p=0.49), and 58.6±8.0% in control patients (p=0.35 and p=0.10; versus ACEI and ARB, respectively).

No interaction was found between aortic valve morphology and aortic dilatation rate. Bicuspid aortic valve was identified in 18 patients (37.5%), while tricuspid valve interaction was identified in 32 patients (62.5%). Bicuspid aortic valve patients were younger than their tricuspid aortic valve counterparts (47.2±12.2 versus 60.0±10.8 years, respectively; p<0.0001), but aortic root dilatation rate did not vary between bicuspid aortic valve and tricuspid aortic valve patients (1.0±2.9 versus 1.85±1.2 mm/year; p=0.50).

Patients with medial degeneration in tissue samples, including elastic fibre fragmentation, cystic medial change, and smooth muscle cell necrosis (Figure 1), and had lower preoperative ascending aortic dilatation rates compared with patients with histological features of atherosclerosis (0.8±1.03 versus 3.1±2.26 mm/year; p=0.007) in the ARB group.

CONCLUSION

Blockade of the renin-angiotensin system pathway by ARB may have a beneficial effect on aortic growth in patients with non-syndromic TAA irrespective of aortic valve morphology. Medial degeneration with smooth muscle cell necrosis, which plays a crucial role in the pathogenesis of ascending TAA, is likely to be the main predictor of the response to ARB therapy.

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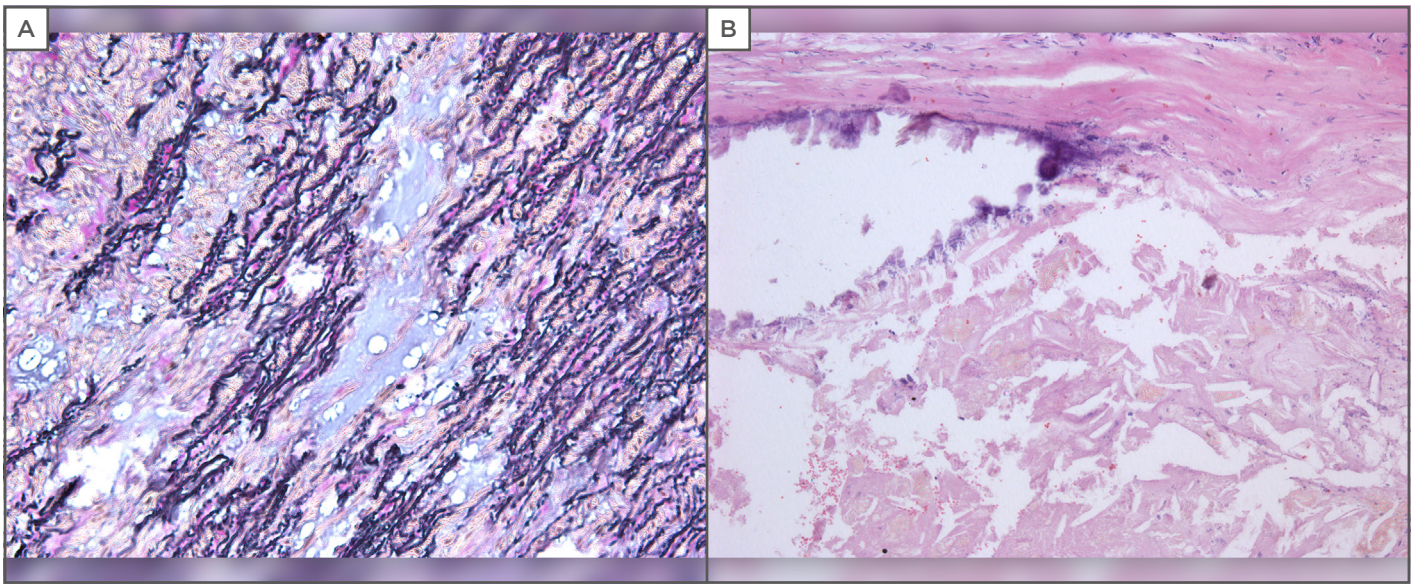

Figure 1: Histologic examination of resected aortic tissue specimens after aortic surgery.

A) Medial degeneration of the thoracic aorta, elastic fibre fragmentation, and cystic medial change; B) An aortic plaque formed through the accumulation of lipids in the intima-media layer of the aorta.

High Cardiovascular Risk is Associated with the Degree of Fibrosis in Nonalcoholic Liver Disease

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Keywords: Cardiovascular disease, cardiovascular risk, cirrhosis, fibrosis, fibrosis score, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis, risk score, screening.

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Cardiovascular diseases remain the leading cause of death worldwide.[1] Nonalcoholic fatty liver disease (NAFLD), encompassing steatosis, nonalcoholic steatohepatitis, and cirrhosis, has a

global prevalence of 25% and is associated with increased liver-specific and cardiovascular mortality.[2,3] Both groups of diseases have been associated with risk factors from the metabolic syndrome spectrum.[4]

In our study, we analysed a cohort of 2,138 asymptomatic subjects from the SAKKOPI registry (Salzburg Colon Cancer Prevention Initiative). From this cohort, subjects with a non-invasive diagnosis of NAFLD were selected. Subsequently, the correlation between two scores of 10-year cardiovascular risk, the Framingham Risk Score (FRS) and European Society of Cardiology (ESC) HeartScore (HS), and two scores estimating the degree of fibrosis in NAFLD based on risk factors and laboratory parameters, the NAFLD Fibrosis Score (NFS) and Fibrosis 4 Score (Fib4), was assessed in this subgroup.

While an association between NAFLD and cardiovascular morbidity and mortality has been shown previously, this study not only showed an increased cardiovascular risk in subjects diagnosed with NAFLD (no NAFLD: FRS: 5.5±5.2%, HS: 2.9±3.8%; NAFLD: FRS: 8.8±6.5%, HS: 3.7±4.1%; p<0.001) but also pointed to a progressive increase in cardiovascular risk with higher degrees of estimated liver fibrosis.

The FRS was 8.0±6.1%, 11.5±5.2%, and 10.8±6.4% in patients with a NFS F0–F2, NFS F3–F4, and indifferent NFS, respectively. HS showed a similar pattern: NFS F0–F2: 3.0±3.4%, NFS F3–F4: 7.0±5.7%, and indifferent NFS: 5.4±4.5%. NFS correlated significantly with FRS (r=0.18; p<0.001) and HS (r=0.27; p<0.001). Also, the Fib4 estimation of the degree of fibrosis correlated with FRS (r=0.25; p<0.001); in patients with F0–F1 according to Fib4, the FRS was 7.3±5.8%, while the FRS was 11.1±6.9% and 11.1±6.7% in patients with F3–F4 (Fib4) and indifferent Fib4, respectively. However, there was no correlation between Fib4 and the HS (r=0.02; p=0.55); the HS values, assessing cardiovascular risk, were F0–F1 (Fib4): 3.2±3.6%, F3–F4 (Fib4): 2.9±3.9%, and indifferent Fib4: 3.3±3.8%.

These results show the need for a high clinical suspicion for cardiovascular disease and a multidisciplinary approach to patients with NAFLD, especially those with a high degree of fibrosis. Furthermore, routine cardiovascular screening in this cohort of cardiovascular asymptomatic NAFLD patients should be considered. Screening strategies, including assessment of coexisting risk factors, physical examination, laboratory testing, cardiovascular risk scoring, and ultrasound imaging of the carotid arteries or CT coronary artery calcium scoring, have been proposed.[5] However, the impact of such an approach on hard endpoints, as well as cost-effectiveness, needs further investigation in prospective studies. The symmetrical increase in cardiovascular risk and estimated liver fibrosis could also illustrate the systemic interactions underlying both diseases, including the traditional risk factors as well as other metabolic, inflammatory, vasoactive, and thrombogenic processes.[5] This raises the question of whether emerging pharmacological treatment strategies for NAFLD or nonalcoholic steatohepatitis, which include antifibrotic agents,[6] could result in the reduction of the cardiovascular burden in this significant patient population.

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Prognostic Role of Cardiac Power Index in Patients with Biopsy-Proven Inflammatory Cardiomyopathy

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BACKGROUND

Most patients with acute myocarditis and mild cardiac involvement recover without long-term sequelae. However, those patients with advanced cardiac involvement may have a more varied outlook. Of these, at least one-third of patients will have residual ventricular dysfunction, around 25% will progress to transplantation or death, and the remainder will recover and have normal ventricular function.[1,2]

Various diagnostic tests are used to assess heart function, but a test that predicts the prognosis of heart failure and thereafter helps clinicians to intervene earlier in those patients with a poor prognosis is still lacking.[3] Cardiac power index (CPI) (mean arterial blood pressure x cardiac index x 0.0022) has been demonstrated to be an important haemodynamic predictor of mortality and adverse events in patients with various cardiac diseases.[4-9] However, its prognostic impact on patients with inflammatory cardiomyopathy is less well investigated.

METHODS

All patients with biopsy-proven inflammatory cardiomyopathy undergoing invasive haemodynamic assessment with longitudinal follow-up were retrospectively analysed and classified into two groups. Group 1 represented patients with a normal CPI (≥0.5 W/m^2) and Group 2 represented patients with a diminished CPI (<0.5 W/m^2). The combined primary endpoint was cardiac death, aborted sudden cardiac death, heart transplantation, and left ventricular assist device implantation.

RESULTS

One hundred and sixty-seven patients (mean age: 60±11 years; 71% male) were available for analysis and the mean CPI was 0.43±0.14 W/m^2 (Group 1: 0.62±0.12 W/m^2 versus Group 2: 0.37±0.083 W/m^2; p<0.001). At presentation, a lower CPI was associated with lower systolic, diastolic, and mean blood pressure; lower ejection fraction; lower cardiac output; higher pulmonary vascular resistance; and higher right ventricular pressure.

Over a mean of 3.6±2.4 years of follow-up, there were 7 deaths, 12 incidences of aborted sudden cardiac death, 3 transplants, and 2 left ventricular assist device placements. Diminished CPI was associated with an increased incidence of the combined primary endpoint (hazard ratio: 3.4; 95% confidence interval: 1.29–8.98). Event-free survival by Kaplan–Meier estimate was significantly lower in Group 2 than Group 1 (80.1% versus 97.4%, respectively; p<0.01).

CONCLUSION

In conclusion, patients with inflammatory cardiomyopathy and a low CPI had an increased incidence of the combined primary endpoint during long-term follow-up compared to patients with a normal CPI.

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Risk Stratification and Age-Adjusted D-Dimer Test: Are They Satisfactory in Acute Pulmonary Embolism?

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Keywords: European Society of Cardiology (ESC) Guidelines 2014, pulmonary embolism (PE), risk stratification, Wells' score.

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BACKGROUND AND AIMS

Pulmonary embolism (PE) is associated with high morbidity and mortality and often has a nonspecific clinical presentation; thus, prognostic assessment is important for the management of patients with PE. The use of diagnostic testing to reduce the risk of missing a potentially life-threatening diagnosis increases both the cost of care and the use of medical resources. Various score systems exist to evaluate the probability of PE, which can also be used for risk stratification to obtain the most accurate diagnosis. The aim of our study was to review the evidence for existing prognostic models in acute PE and determine their validity and usefulness for predicting patient outcomes. We also determined the accuracy of an age-adjusted D-dimer threshold to detect PE.

MATERIALS AND METHODS

The study involved the retrospective application of an age-dependent D-dimer cut-off (age/100 in patients aged >50 years) in 659 consecutive patients, both in and outpatients, aged ≥18 years who had undergone CT pulmonary angiogram for suspected PE according to the European Society of Cardiology (ESC) guidelines. We included individuals who presented to an emergency department with a suspicion of PE and who were then referred for objective testing; all participants included were capable of providing informed consent. This study was performed in three emergency departments in Hungary between January 2016 and September 2017. We retrospectively collected information regarding symptoms (dyspnoea, unilateral leg swelling, and haemoptysis), vital signs, and medical and social history (cancer, recent surgery, medication, history of deep vein thrombosis or

PE, and chronic obstructive pulmonary disease). We calculated test characteristics, including sensitivity and specificity. We applied three different D-dimer approaches to the low and moderate-probability patients.

The primary outcome was exclusion of PE with each D-dimer approach, while the secondary objective was to estimate the negative predictive value for each rule. Data were analysed using SPSS 20.0 statistical software (SPSS Inc., Chicago, Illinois, USA) and a chi-squared test, Independent Samples T Test, analysis of variance (ANOVA), and correlation interpretation were performed; p values <0.05 were considered statistically significant.

RESULTS

In the 659 cases (407 women and 252 men), a total of 105 D-dimer assays, 51 CT angiograms, and 212 chest X-ray examinations were carried out redundantly; if these procedures were not carried out, it could have saved money for the hospitals and reduced radiation exposure for patients. The age-adjusted D-dimer threshold was more specific (70% versus 60%) but less sensitive (95% versus 98%) than risk stratification. The sensitivity of the combined technique (risk stratification and age-adjusted D-dimer test) was 100%.

CONCLUSION

Our study showed that Geneva score (which was calculated from the patients' complaints, medical history, and physical examination) had the closest correlation with the true diagnosis. An age-adjusted D-dimer limit has the potential to reduce the need for diagnostic imaging and is more accurate than the standard threshold of 500 ng/dL. The combination of risk stratification and age-adjusted D-dimer can be used to safety diagnose PE. Finally, we can conclude that risk evaluation in acute PE is indispensable and the appropriate use of guidelines results in lower healthcare costs. Our data support the use of age-adjustment and perhaps adjustment for other factors also seen in patients evaluated for PE.

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Contemporary Use of Intracoronary Imaging in Percutaneous Coronary Intervention

EDITOR'S PICK

This informative paper by Li Kam Wa and Gerber provides a case-based overview of intravascular ultrasound and optical coherence tomography that is applicable for all members of the intravascular imaging community. Modern-day interventional cardiologists must effectively evaluate their work in the coronary arteries, and therefore intracoronary imaging is very important. The increasing availability and presence of such a variety of imaging technology in the cathlab must be discussed in detail. This paper will provide interventionalists with useful, practical insights to enhance contemporary clinical practice.

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Abstract

Since the first balloon angioplasty in 1977, remarkable advances in catheter-based technology have been achieved with the use of stents and intracoronary devices. However, despite these developments, visual assessment of a 2-dimensional lumenogram of the coronary vessels remains the predominant method of assessing coronary disease and guiding angioplasty worldwide. It is an enigma that there is still such a low uptake in the use of intravascular imaging, whether in the form of intravascular ultrasound (IVUS) or optical coherence tomography (OCT), with both techniques providing cross-sectional imaging of the coronary vessels with a resolution at the microscopic scale. The intracoronary imaging community tends to focus on the academic aspects of IVUS and OCT, often highlighting the evidence-based benefits in lesion subsets, such as left main stem or bifurcation percutaneous coronary intervention. However, this does not impart crucial practical-related aspects pertaining to IVUS or OCT, which can improve outcomes and achieve optimal results for operators and patients. Here, the authors present a case-based approach to IVUS and OCT use in contemporary clinical practice, with the hope of providing useful, practical insights for the busy interventionalist and prompting the consideration of intracoronary imaging catheters as an essential part of their percutaneous coronary intervention toolbox.

INTRODUCTION

For >50 years, coronary angiography has been the gold standard for the assessment of coronary anatomy; however, as an isolated technique to guide the management of ischaemic heart disease, its limitations are well known. Cardiologists are now able to move beyond a simple 2-dimensional visual assessment of the vessel lumen, using complementary techniques that deliver cross-sectional imaging of the entire coronary vessel and provide essential information to guide coronary intervention.

Intracoronary imaging is not a recent innovation; it first led to a paradigm shift in stent implantation and optimisation in 1995 when the switch from an anticoagulation to an antiplatelet strategy in percutaneous coronary intervention (PCI) with the aid of intravascular ultrasound (IVUS) was first described. This switch led to reduced bleeding rates that are still seen during antiplatelet therapy today.[1]

Of the imaging technologies that are widely available, IVUS is the most well established; however, more recently, optical coherence tomography (OCT) has also progressed into day-to-day clinical practice. Both techniques deliver additional information that a lumenogram of coronary angiography alone cannot provide, although the use of these techniques varies widely across the world.[2] In the UK, IVUS is used in 7% of PCI cases and OCT in 2%,[3] compared to IVUS use in >80% of cases in Japan.[4]

Traditionally, reviews of intracoronary imaging tend to focus on the academic and technical aspects related to IVUS or OCT use. Here, a case-based approach to understanding intracoronary imaging use is presented from the practical perspective, using clinical situations that will be familiar to any interventional cardiologist in 2018.

THE TECHNOLOGY

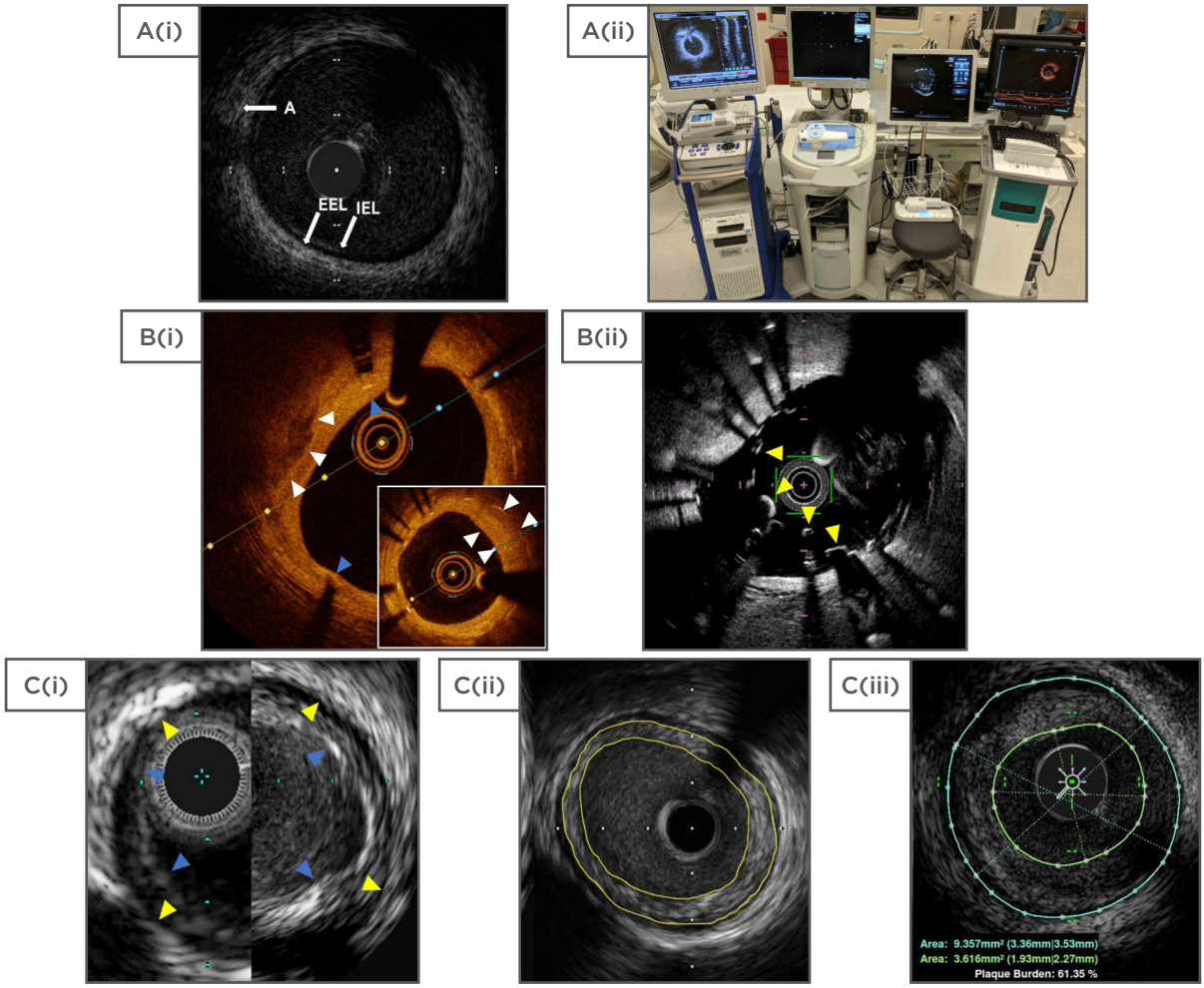
Both IVUS and OCT rely on a probe mounted on a catheter, which is advanced over a standard 0.014-inch angioplasty wire and then withdrawn mechanically or manually by operator pullback across the area of interest. The probe emits ultrasound waves during IVUS or near-infrared light during OCT, and the reflected waves are used to construct a cross-sectional image of the vessel. Ultrasound, with a frequency of 20–60 Hz, depending on the commercial device, allows an axial resolution of 40–150 µm (Figure 1D) with a penetration of 4–8 mm.[5] In contrast, OCT provides a higher axial resolution of 10–20 µm, at the expense of a reduced penetration of 1.0–2.5 mm.[6] Advancements in technology now allow co-registration of images (IVUS-angiography or OCT-angiography), removing any operator error in translating the cross-sectional imaging to a location on angiography. Tri-registration with instantaneous wave-free ratio, IVUS, and angiography is also available, allowing true multimodality anatomical and physiological assessment of coronary lesions.

Intravascular Ultrasound

IVUS catheters are compatible with ≥5 Fr guide catheters and are either mechanical rotating or phased array in design. In a rotating design, the transducer rapidly rotates to produce higher resolution images, whereas for a phased array device the transducer is fixed. Automated pullback is available for most devices at a speed of up to 10 mm/s. The generated greyscale image allows assessment of the entire vessel wall and identification of the internal elastic lamina, external elastic lamina, and adventia (Figure 1A).

To overcome the limitations of greyscale IVUS, complementary technologies have been developed to further analyse atherosclerotic plaques. Near-infrared spectroscopy in combination with IVUS is available as a single catheter (Infraredx, Inc., Burlington, Massachusetts, USA) and uses near-infrared light to determine plaque composition. The chemogram generated can be displayed as a colour-coded ring around the standard IVUS image to indicate areas with a high concentration of lipids. Dedicated device software automatically calculates a lipid core burden index, with higher values reflecting lipid-rich plaques.

Radiofrequency IVUS also combines greyscale IVUS with further analysis to provide information about coronary plaque composition. Proprietary software is available from Volcano, San Diego, California, USA (virtual histology, VH-IVUS); Terumo Medical Corporation, Tokyo, Japan (integrated backscatter-IVUS); and Boston Scientific, Marlborough, Massachusetts, USA (iMAP™).[7]



D

Device	Guide (Fr)	Frequency and axial resolution	Pullback speed	Notes
Eagle Eye Platinum (Philips, Amsterdam, Netherlands)	5	20 MHz, 170 µm	1 mm/s	Short tip with high penetration suited to OCT.
Revolution (Philips)	6	45 MHz, 50 µm	0.5 mm/s	
Opticross (Boston Scientific, Marlborough, Massachusetts, USA)	5	40 MHz, 38 µm	0.5 mm/s	Highest resolution 5 Fr-compatible system.
Atlantis SR Pro (Boston Scientific)	6	40 MHz, 43 µm	0.5 mm/s	
HD IVUS (ACIST, Eden Prairie, Minnesota, USA)	6	60 MHz, <40 µm	10 mm/s	First 'high definition' IVUS device to market.
Dragonfly OPTIS (Abbott, Chicago, Illinois, USA)	6	10 µm	20 mm/s	54–75 mm pullback range.
Fastview (Terumo, Tokyo, Japan)	6	10 µm	40 mm/s	150 mm pullback range, second-generation OFDI OCT.

Figure 1: Comparison of intravascular ultrasound and optical coherence tomography technologies.

A(i): Normal coronary vessel by HD IVUS (ASCIST). A(ii): Stand-alone intracoronary imaging consoles, left to right: Philips (formerly Volcano), Boston Scientific, ACIST HDI, Abbot (formerly St Jude Medical). B(i): OCT (OPTIS) view of calcified plaque (white arrows) with overlying stent struts and stent shadows (blue arrows). The distal vessel shows significant neointimal formation (insert, white arrows). B(ii): OCT (Fastview) view of an underexpanded stent (yellow arrows) that was not apparent at angiography. C(i): Comparison between Philips Eagle Eye Platinum (20 MHz, left) and Revolution (45 MHz, right). EEL as yellow arrows and IEL as blue arrows. C(ii): Concentric plaque outlined in yellow (Boston, Atlantis SR Pro). C(iii): Concentric plaque by IVUS outlined in green and blue (ACIST, HD IVUS). D: Currently available IVUS/OCT catheters in Europe.

A: adventitia; CTO: chronic total occlusion; EEL: external elastic lamina; HD: high definition; IEL: internal elastic lamina; IVUS: intravascular ultrasound; OCT: optical coherence tomography; OFDI: optical frequency domain imaging.

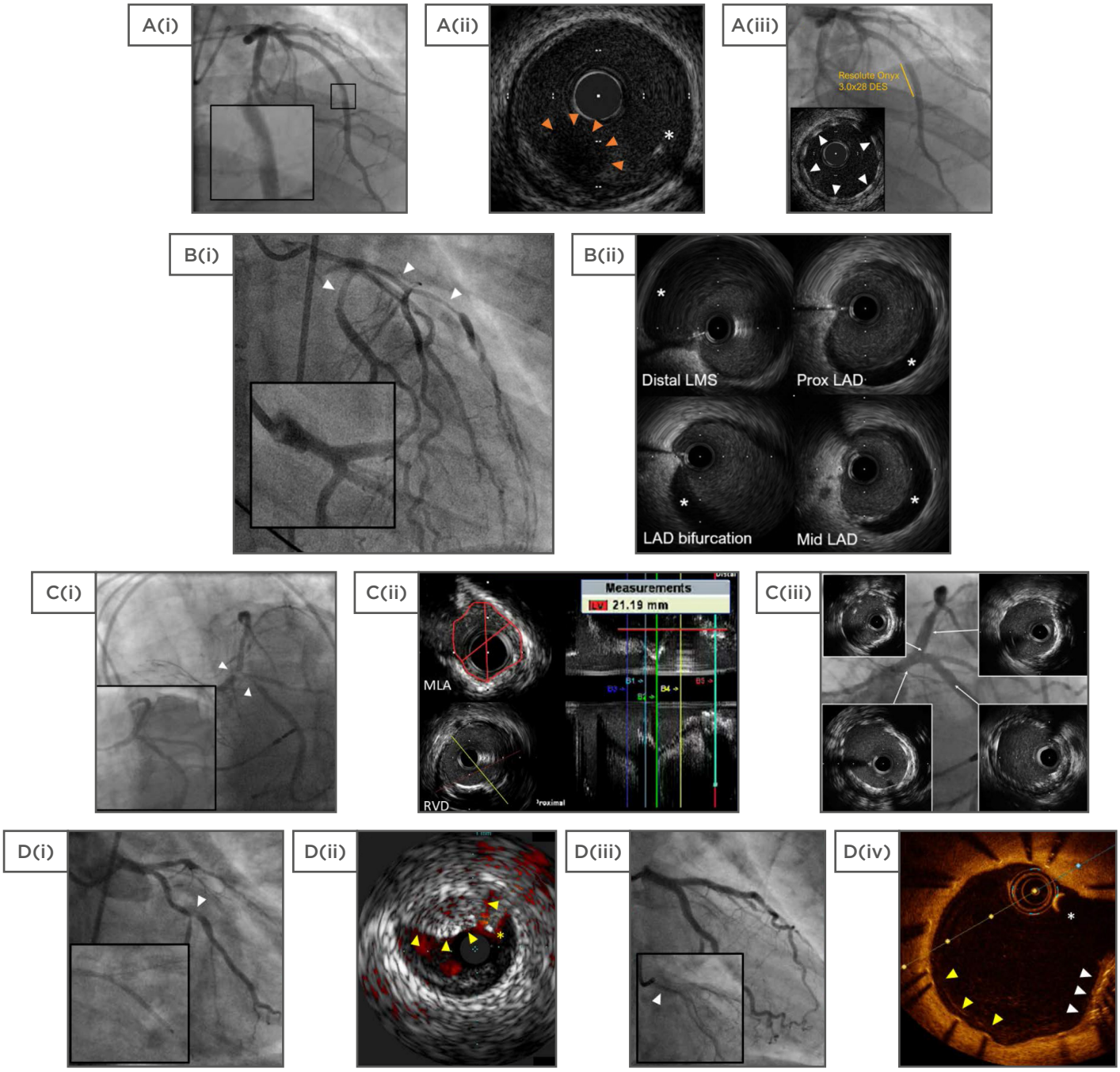


Figure 2: Selected cases using intravascular ultrasound and optical coherence tomography.

A: Plaque rupture; A(i): Hazy mid LAD magnified; A(ii): 60 MHz HD IVUS showing plaque rupture with thrombus (hypoechoic with red arrows) and guidewire (asterisk); A(iii): Final result with well-expanded struts (arrows). B: Spontaneous coronary artery dissection; B(i): Impaired flow angiographically (arrows), with the distal left main stem suggestive of dissection (magnified); B(ii): 40 MHz IVUS (Atlantis SR Pro) images with the false lumen (hypoechoic, asterisks). C: LMS intervention; C(i): Severe LMS disease (arrows) compared to previous angiography (insert); C(ii): MLA and RVD measurements with automated pullback; C(iii): Final angiographic result with IVUS (inserts). D: Stent failure; D(i): LCx bifurcation disease (arrow) with failure to advance the stent (magnified); D(ii): IVUS with coregistered ChromaFlo highlighting blood red (Eagle Eye, Philips), used to guide wire placement. Unexpanded stent (yellow arrows) and guidewire (asterisk); D(iii): Final result with the crushed stent (magnified, arrow); D(iv): Surveillance OCT showing the guidewire (asterisk), crushed stent (white arrows), and adequate stent coverage (yellow arrows).

HD: high definition; IVUS: intravascular ultrasound; LMS: left main-stem; MLA: minimum lumen area; OCT: optical coherence tomography; Prox: proximal; RVD: reference vessel diameter.

Optical Coherence Tomography

An OCT catheter contains a single fibre optic core rotating within a transparent sheath that emits light across a range of wavelengths. OCT offers high spatial resolution and clear images, offset by reduced tissue penetration compared to IVUS. In addition, there are technical differences that must be taken into consideration with the use of OCT; for example, red blood cells scatter the light emitted by the probe and therefore OCT requires the artery to be clear of blood. Typically, this is achieved by flushing the vessel with contrast, which can be of concern in patients with renal impairment. Rapid automated pullback is available, allowing imaging of the vessel up to a speed of 40 mm/s, which is faster than IVUS catheters (10 mm/s). In addition, the high-contrast images of OCT (Figure 1B) show reduced interobserver and intraobserver variability compared to greyscale IVUS.[8]

CLINICAL CASES

For any patient who comes to the catheter laboratory, the operator must ask themselves: 'Does this patient have a mandate for intervention?'. Once this decision has been made, they must consider a wealth of information before deciding on the revascularisation strategy. Identifying the lesions that require treatment; whether the lesion requires preparation; the type, length, and number of balloons and/or stents; and how to optimise stent deployment can be made possible with the aid of intracoronary imaging. The following four cases illustrate instances when the use of intracoronary imaging has proved key in diagnosis and management.

Case 1

A 35-year-old male smoker who works as a local chef presented with a 2-hour history of central chest pain. Prehospital 12-lead ECG showed lateral ST-elevation and the patient was brought directly to the cathlab. The right coronary artery was unobstructed; however, angiography of the left system revealed a hazy lesion within the mid left anterior descending artery (LAD) (Figure 2A(i)).

At this stage, the diagnosis by angiography alone was uncertain. The differential diagnosis included coronary embolisation, spontaneous coronary artery dissection (SCAD), and plaque disease, though one would suspect atherosclerotic disease to be less likely given the patient's age and absence of ischaemic risk factors. An IVUS catheter was advanced, followed by manual pullback across the lesion; this showed normal coronary arteries distally and proximally, with plaque rupture and adherent fresh coronary thrombus at the site of angiographic abnormality (Figure 2A(ii)) in the mid vessel. An Export aspiration catheter (Medtronic, Minneapolis, Minnesota, USA) was passed, followed by stenting with a RESOLUTE ONYX™ (Medtronic) 3.5x22.0 mm stent and post dilation (the final result of which can be seen in Figure 2A(iii)). The patient was treated with dual antiplatelet and statin therapy, and was discharged 4 days later.

Case 2

A 32-year-old female with no past medical history presented with 1 hour of central chest pain. Prehospital 12-lead ECG showed anterolateral ST-elevation with reciprocal ST-depression and she was brought directly to the cathlab for angiography. The right coronary system was free of any disease. The left coronary system showed an abnormal proximal circumflex (LCx) and abnormal proximal LAD involving the first diagonal (Figure 2B(i)). The patient's pain and ECG changes resolved with the administration of intracoronary nitrates.

Possible diagnoses at this stage included coronary spasm, given the response to nitrates, or a recanalised infarct. Transthoracic echocardiography showed anterolateral hypokinesia with preserved left ventricular systolic function, and her initial troponin T was 1,100 ng/L (reference: <14 ng/L). The patient was treated with dual antiplatelet therapy and abciximab. Further review of the images suggested distal left main-stem (LMS) dissection flap (Figure 2B(i), magnified).

IVUS re-study confirmed SCAD involving the distal LMS, proximal LAD, and first diagonal (Figure 2B(ii)). The patient was managed medically with dual antiplatelet therapy and discharged 5 days later. Surveillance angiography at 10 weeks confirmed complete resolution of the dissection.

Culprit Lesion Identification and Characterisation

The majority of myocardial infarction cases are due to atherosclerotic plaque rupture or plaque erosion, the site of which may not be apparent following coronary angiography. In those with unremarkable coronary arteries, occult plaque rupture was identified as the cause of myocardial infarction in 38% of patients, but only after the use of IVUS.[9] These are patients who may otherwise have been managed for myocarditis or thrombophilia, treated for coronary spasm, and/or denied the benefits of dual antiplatelet and statin therapy. In Cases 1 and 2, intracoronary imaging clearly identified the aetiology as atherosclerotic plaque rupture and SCAD, respectively.

OCT has been shown to be superior to both IVUS and coronary angioscopy in identifying plaque rupture, erosion, and coronary thrombus.[10] This ability to differentiate between plaque erosion and plaque rupture may provide future opportunities for risk stratification and targeted therapy in acute coronary syndrome (ACS).[11,12] Indeed, it has been suggested that in ACS patients with plaque erosion identified by OCT, antithrombotic therapy alone may be a viable alternative to stenting.[13] Finally, OCT also provides a good alternative to IVUS for the detection of dissection. OCT was not used in these cases due to concerns regarding propagating a SCAD false lumen. However, it should be noted that guidelines suggest that the use of OCT is safe in this situation.[14]

Case 3

An 80-year-old female with a background of transcatheter aortic valve replacement and permanent pacemaker implantation 2 years prior, PCI to LAD 7 years prior, chronic kidney disease stage 4, and peripheral vascular disease presented with exertional chest pain. Coronary angiography revealed severe distal LMS, severe ostial LAD disease, and severe ostial LCx disease; this was a significant progression from the coronary angiography conducted 3 years prior (Figure 2C(i)). The initial revascularisation strategy pursued was PCI of the LMS into the LAD with the T and protrusion technique, and a provisional T stent for the obtuse marginal branch. IVUS revealed a ring of fibrocalcific disease not evident on angiography. Measurements showed a reference vessel diameter of 5.5 mm, minimum lumen area (MLA) of 3.08 mm^2, and lesion length of 21 mm. After preparation with compliant and cutting balloons, a Xience Prime 3.5x23.0 mm stent (Abbott, Lake Bluff, Illinois, USA) was inserted. The LCx was stented without complication followed by usual kissing balloon inflation. The result is shown in Figure 2C(iii), with IVUS demonstrating well-expanded stents throughout.

Case 4

A 49-year-old transgender female with a history of hypertension and smoking presented with several hours of intermittent chest pain. The initial 12-lead ECG showed anterolateral ST-elevation and the patient was brought directly to the cathlab; on arrival, she was in cardiogenic shock.

The LAD was occluded at the level of the first diagonal with Thrombolysis in Myocardial Infarction (TIMI) 0 grade flow (Figure 2D(i)). The LCx had severe ostial disease, as well as severe disease at the bifurcation with a large marginal branch. Following thrombus aspiration, the LAD was predilated and stented from the mid vessel to ostium without difficulty. The patient's anterior ST-elevation resolved; however, she still had persistent lateral ST segment elevation at this stage.

An attempt was made to direct stent the LCx and marginal branch with a 3.5x38.0 mm Ultimaster® stent (Terumo Medical Corporation). However, the stent could not be advanced into the LCx and on withdrawal of the device, the stent came free from the balloon; an attempt to readvance the balloon and inflate the stent in a suboptimal position was unsuccessful. Rewiring the stent with a Fielder XT (Asahi Intecc, Nagoya, Japan) wire under IVUS guidance was also unsuccessful (Figure 2D(ii)). Therefore, the trapped stent was crushed into the adventitia using sequential balloon inflation, followed by stenting from the marginal back into the LMS. IVUS showed underexpansion in the LMS and proximal LCx; therefore, proximal optimisation was carried out with a 4.0x12.0 mm noncompliant balloon at 25 atm. The patient was discharged from hospital after 3 days and surveillance OCT at 3 months showed good stent coverage throughout (Figure 2D(iv)).

Table 1: Selected meta-analyses of intravascular ultrasound and optical coherence tomography-guided angioplasty.

	Population	Trials	MACE	Cardiac death	Myocardial infarction	Stent thrombosis	TLR	Notes
IVUS versus angiography								
Buccheri et al.,[17] 2017	14,587	RCT 14 Obs 10	0.79 (0.67–0.91)	0.47 (0.32–0.66)	0.72 (0.52–0.93)	0.42 (0.20–0.70)	0.74 (0.58–0.90)	Also reduced all-cause death.
Shin et al.,[18] 2016	2,345	RCT 3	0.36 (0.13–0.99)	0.38 (0.10–1.42)	N/A	0.50 (0.13–2.01)	N/A	Second-generation DES only, patient level data.
Parise et al.,[19] 2011	2,193	RCT 7	0.81 (0.65–0.99)	N/A	0.86 (0.54–1.36)	N/A	0.65 (0.51–0.83)	BMS only.
OCT versus angiography								
Buccheri et al.,[17] 2017	2,396	RCT 2 Obs 3	0.68 (0.49–0.97)	0.31 (0.13–0.66)	0.79 (0.44–1.40)	0.39 (0.10–1.20)	0.66 (0.35–1.20)	
Kuku et al.,[20] 2018	1,753	RCT 2 Obs 2	0.70 (0.49–1.00)	0.40 (0.18–0.90)	0.70 (0.42–1.16)	1.17 (0.40–3.43)	1.07 (0.48–2.38)	50% BMS use.
OCT versus IVUS								
Buccheri et al.[17] 2017	1,349	RCT 2 Obs 1	0.87 (0.61–1.30)	0.66 (0.27–1.50)	1.10 (0.60–2.10)	0.93 (0.24–3.40)	0.88 (0.47–1.60)	

Green indicates significantly reduced risk versus comparator. All results as odds ratio (95% confidence interval), unless specified, for IVUS or OCT versus comparator.

BMS: bare metal stent; DES: drug-eluting stent; IVUS: intravascular ultrasound; MACE: major adverse cardiovascular events; N/A: not available; OCT: optical coherence tomography; Obs: observational; RCT: randomised controlled trial; TLR: target lesion revascularisation.

Stent Optimisation

The most common use of intracoronary imaging is for stent optimisation. Cases 3 and 4 illustrate the benefit of intracoronary imaging in lesion preparation and ensuring adequate stent expansion. Although a somewhat unusual situation, Case 4 also highlights the application of IVUS in directing guidewire passage, though this is more often seen in the context of chronic total occlusion recannalisation.

While several criteria to define optimal stent deployment by intracoronary imaging have been published, including by the authors of this review,[15] no consensus currently exists. All criteria aim to reduce the known predictors of adverse events: stent underexpansion, incomplete stent apposition, and geographical miss (failing to completely cover the lesion or edge dissection). When used for this indication, intracoronary imaging modifies the revascularisation strategy in over one-third of patients versus angiographic guidance alone.[16] In addition, this use of intracoronary imaging is also associated with reduced hard clinical endpoints of stent thrombosis, target lesion revascularisation, myocardial infarction, and cardiac death versus an angiography-only strategy (Table 1).[17-20] This has been demonstrated best in patients with left main disease, long lesions, or chronic total occlusion, rather than by routine use in all cases.[18,21]

Though the use of IVUS is well established for stent optimisation, OCT provides an attractive alternative given its enhanced resolution and that its main limitation (reduced penetration) is of less concern. Results from increasing numbers of trials involving OCT are becoming available, with ILUMIEN III[22] and OPINION[16] published in the last 2 years. Both studies showed the non-inferiority of OCT versus IVUS-guided PCI with regard to minimal lumen area and clinical target vessel failure, respectively. However, OPINION lacked an angiography-only arm and large, long-term studies powered to demonstrate a difference in clinical outcomes are lacking. This may change with ILUMIEN IV,[23] which is currently recruiting to compare OCT versus angiography in up to 3,650 patients with coronary artery disease and high-risk or complex lesions, who possibly stand to benefit the most from the high-resolution imaging that OCT offers.

Stent Surveillance

The higher resolution of OCT is particularly suited to evaluation of stents after implantation, as in Case 4 (Figure 2D(iv)), with the assumption that stent coverage represents neoendothelialisation. In addition, OCT is appropriate for evaluating the mechanisms behind stent failure. It has been suggested that OCT-defined features, such as tissue heterogeneity, tissue backscatter, and visibility of microvessels, may provide a histological correlation of the vascular response to stenting,[24] though this may not be true outside the setting of stent restenosis.[25]

OTHER APPLICATIONS

Left Main Stem Assessment

Much effort has been made to assess lesion haemodynamic severity by intracoronary imaging. However, the potential disparity between lesion anatomy and ischaemia means assessment of haemodynamic significance remains firmly in the domain of physiological indices, such as fractional flow reserve (FFR) and the instantaneous wave-free ratio.[26-30]

Neither IVUS nor OCT have shown any binary cut-off measurements suitable for justifying coronary intervention. The exception to this is LMS disease, for which there is a reasonable correlation between MLA by IVUS and FFR.[31] The proposed MLA threshold for intervention has decreased in recent years, with the suggestion that a MLA as low as 4.5 mm^2 in the right population may correlate well with a FFR ≤0.8.[32] Nonetheless, current guidelines recommend a cut-off of 6 mm^2 for intervention, which has shown acceptable sensitivity for significant LMS disease in outcome-driven studies.[33,34]

IVUS may be used in LMS and bifurcation stenting to ensure adequate stent expansion. In Case 4, underexpansion was only apparent with the use of IVUS. Ensuring a MLA >5 mm^2 at the ostium of the LCx, >6.3 mm^2 at the ostium of the LAD, and >8.2 mm^2 in the main body of the LMS has been associated with reduced rates of in-stent restenosis and major adverse events.[35] Similar cut-off values in determining LMS significance and stent optimisation were also recently used in a large trial of contemporary PCI versus coronary artery bypass surgery.[36]

By comparison, while assessment of the LMS by OCT is technically feasible,[37] there are some specific challenges. The low penetration of OCT limits assessment of plaque burden, and, in ostial LMS lesions, precise positioning of the guide catheter to achieve an adequate blood-free field can be difficult.[38] No data currently support the use of OCT in determining LMS (or any other epicardial vessel) lesion significance, and IVUS is likely to remain the modality of choice for this indication for the foreseeable future.

High-Risk Plaque

Intracoronary imaging allows analysis of atherosclerotic plaques on a lesion-by-lesion basis, and the arterial remodelling process in response to the stresses of atherosclerosis may provide an indicator of high-risk lesions. Outward growth of the external elastic membrane with preservation of the luminal area (positive remodelling) in the early stages of atherosclerosis leads to increased plaque vulnerability and may explain why positive remodelling and only modest stenoses are often evident in ACS. In comparison, vessel shrinkage and loss of luminal area (negative remodelling) are more common in more stenotic yet stable lesions.[39]

Although intracoronary imaging has been extensively studied with regard to identifying a 'vulnerable plaque' (particularly VH-IVUS) and supported by data from the PROSPECT trial,[40] it has not progressed to day-to-day clinical use. The main reason for this is that sufficient information about plaque characteristics can often be obtained from correct interpretation of the greyscale IVUS images; therefore, the addition of VH-IVUS may not alter the treatment strategy. In the PROSPECT trial,[40] which investigated lesion-related risk factors, the strongest predictor of future lesion events was a plaque burden of ≥70% (odds ratio: 4.99; 95% confidence interval: 2.54–9.79). VH-IVUS-identified thin-capped fibroatheroma and a MLA ≤4.0 mm^2 were also reasonable predictors (odds ratio: 3.00 and 2.77, respectively). The follow-up event rate at a median of 3.4 years was 10% when there was a plaque burden ≥70% and MLA ≤4.0 mm^2.

The addition of VH-IVUS-identified thin-capped fibroatheroma increased this rate to 17%.[40]

Despite this, it is suspected that most interventionalists are not confident enough to correctly identify thin-capped fibroatheroma on VH-IVUS given the infrequent use of this technique. As a result, from a practical standpoint, measurement of the greyscale plaque burden, symmetry index, and MLA at various points along the vessel lumen may suffice. Indeed, no lesion events occurred in PROSPECT trial patients with <40% plaque area involvement.[41]

Zero-Contrast Angiography

Given the limitations of angiography, with a maximum of two orthogonal views using biplane imaging per contrast injection, intracoronary imaging offers the potential to reduce or eliminate the use of radiocontrast. This is an attractive proposal for those with renal insufficiency or severe contrast allergy and has been performed successfully with IVUS.[42,43] Case reports show that this may also be possible with OCT, though problems with colloid nephrotoxicity remain.[44,45]

GUIDELINES

Guidelines and consensus statements have been published by the major European and American societies for the use of IVUS and OCT during revascularisation.[34,46-48] The use of IVUS to optimise stent implantation in selected patients, as well as in the assessment and optimisation of LMS treatment, both carry IIa recommendations from the European Society of Cardiology (ESC). American and European guidelines advise that IVUS and OCT should be considered to detect the mechanisms behind stent failure; however, these guidelines are now several years old and updated ESC guidelines are due for publication in 2018.

CONCLUSION

Intracoronary imaging is a widely available and essential adjunct to angiography, allowing cardiologists to deliver the best possible outcomes for their patients. While there are monetary and healthcare system barriers to the widespread adoption of intracoronary imaging worldwide, the authors hope that this review will help interventional cardiologists recognise the proven benefits of intracoronary imaging and encourage them to reach for the IVUS or OCT catheter more often in day-to-day clinical practice.

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A Comparison of Different Doses of Dexmedetomidine for Myocardial Protection in Percutaneous Coronary Interventional Patients

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Abstract

Introduction: Dexmedetomidine has been shown to have a myocardial protective effect in off-pump coronary artery bypass patients. However, the same dosage of dexmedetomidine could not elicit a myocardial protective effect in percutaneous coronary intervention patients. The aim of this study was to assess the effect of different doses of dexmedetomidine when used for myocardial protection in percutaneous coronary interventional patients.

Methodology: 240 patients (Group D1, treated with dexmedetomidine [n=80]; Group D2, treated with dexmedetomidine [n=80]; and the control group [C; n=80]) were enrolled in the study. Dexmedetomidine was administered over 15 minutes in the respective doses in Groups D1 and D2 at the start of the procedure, while normal saline was given to patients in Group C. Maintenance of dexmedetomidine/NS was started at 0.5 µg/kg/hour in the groups until 30 minutes post-procedure. Creatine phosphokinase (CPK) and CPK-MB, heart rate (HR), mean blood pressure (MAP), and sedation score were noted at baseline (T0), 6 hours (T1), 12 hours (T2), and 24 hours (T3) after the loading dose.

Results: MAP and HR significantly decreased in D1 and D2 compared to C ($p<0.05$). None of the patients in D1 had a reduction in MAP <20% and HR <50 bpm; however, 3 patients in D2 had a clinically significant reduction in MAP, and 5 patients had HR <50 bpm. The patients in D2 were more sedated compared to patients in D1 and C. The difference in CPK and CPK-MB was significant at 6 hours, 12 hours, and 24 hours in D2.

Conclusion: Dexmedetomidine 2 µg/kg provides myocardial protection compared to 1 µg/kg, but at the cost of a clinically significant decrease in MAP and HR. Patients who received dexmedetomidine 2 µg/kg were more sedated compared to patients receiving 1 µg/kg, warranting greater care during and post-procedure.

INTRODUCTION

Acute myocardial infarction (MI) is a major cause of death and disability worldwide. Myocardial injury in acute MI is due to both ischaemic as well as reperfusion injury. Reperfusion injury is defined as damage to the tissue caused when blood supply is restored to the ischaemic area after a certain period. A similar type of injury occurs in the myocardium after acute MI is treated with percutaneous coronary intervention (PCI) or fibrinolytic therapy.[1-3] This suggests that the process of reperfusion can itself induce cardiomyocyte death, known as myocardial reperfusion injury.

Various mechanisms have been postulated for reperfusion injury. Reperfusion is associated with microvascular injury, particularly due to increased permeability of capillaries and arterioles. Following reperfusion, there is an imbalance between vasoconstrictors and vasodilators; the activated endothelial cells produce more reactive oxygen radicals but less nitric oxide due to a decrease in endothelial nitric oxide synthase and increase in superoxide. Also, there are increased concentrations of vasoconstrictors such as endothelin I and angiotensin II. This imbalance causes an inflammatory response that is partially responsible for the damage caused by reperfusion injury.[4]

White blood cells are carried to the reperfused area as a result of the restoration of blood flow, which causes a release of inflammatory factors, such as interleukins (IL) and free radicals.[5] Inflammatory mediators cause damage to cellular proteins, DNA, and the plasma membrane, which can cause further release of free radicals. These mediators may also act indirectly through redox signalling to initiate apoptosis. White blood cells may also obstruct small capillaries by binding to the endothelium, worsening the ischaemia.[5] The ischaemic tissue has a reduced number of free radical scavengers, which results in further tissue damage after reperfusion. Other mechanisms suggested in reperfusion injury include calcium overload and depletion of high energy phosphate stores.[6-8] Reperfusion can cause hyperkalaemia,[9] arrhythmias,[10] and a rise in cardiac enzymes (Troponin I and T and creatinine phosphokinase [CPK]-MB).[11] Thus, identification of these conditions can aid in the diagnosis of reperfusion.

A number of strategies have been used to prevent lethal myocardial reperfusion injury in patients undergoing PCI. Mechanical interventions include remote ischaemic preconditioning, therapeutic hypothermia, and therapeutic hyperoxaemia, whereas pharmacological interventions include adenosine, anti-inflammatory agents, atrial natriuretic peptide, atorvastatin, erythropoietin, glucose-insulin-potassium therapy, and sodium nitrite.[12] Despite so many available interventions, there is still no effective therapy to prevent myocardial reperfusion injury. A number of new therapeutic strategies thought to have the potential to improve clinical outcomes in patients with acute MI treated with PCI are currently under investigation for preventing myocardial reperfusion injury; one such therapeutic strategy is dexmedetomidine.

Dexmedetomidine is an α2-adrenergic receptor agonist used for conscious sedation. It has a relatively high ratio of α-2:α-1 activity (1620:1) and is considered a more selective α2 receptor agonist, being 8-fold more selective for the α2 receptor than clonidine.[13] Its use is increasing both inside and outside operation theatres because of its unique property of providing sedation without causing respiratory depression.[14] The recommended dosing for adults is 1 µg/kg over 10 minutes (loading dose for procedural sedation), with doses ranging from 0.2–1.0 µg/kg/hour (maintenance dosing for procedural sedation). Besides being useful as a sedative agent, dexmedetomidine has also been shown to have a protective effect on many organs in various experimental studies.[15-17] Dexmedetomidine has been shown to have a protective effect on myocardial ischaemia-reperfusion injury in rats;[18,19] however, there is limited literature detailing the effect of dexmedetomidine during ischaemia-reperfusion injury in PCI patients. Dexmedetomidine has also been shown to have a myocardial protective effect in off-pump coronary artery bypass patients.[20,21] However, the same dosage of dexmedetomidine could not elicit a myocardial protective effect in PCI patients as far as a decrease in myocardial enzymes was concerned.[22]

The aim of this study was to assess the effect of different doses of dexmedetomidine when used for myocardial protection in PCI patients. It was hypothesised that a dose of

dexmedetomidine higher than that routinely used may elicit a myocardial protective effect in patients undergoing PCI.

METHODOLOGY

After approval from the institutional ethics committee was obtained, a prospective double-blind randomised controlled trial was conducted over 6 months, from February–July 2017, in a tertiary cardiac care institute. In total, 240 patients undergoing elective PCI for single vessel disease were recruited. Patients with an ejection fraction (EF) of <40%, in cardiogenic shock, and undergoing emergency procedures were excluded from the study. The sample size was calculated as per a previous study, keeping the value of α-error as 0.05 and the power of the study as 80%.[23] Patients were randomised using a computer-generated randomisation table. The subjects were randomised into Group D1 (n=80), Group D2 (n=80), and a control group (C; n=80). The groups' dosing regimens were:

- D1: Injection of dexmedetomidine 1 µg/kg was administered over 15 minutes as a loading dose, followed by 0.5 µg/kg/hour as a maintenance infusion.
- D2: Injection of dexmedetomidine 2 µg/kg was administered over 15 minutes as a loading dose, followed by 0.5 µg/kg/hour as a maintenance infusion.
- C: Injection of 0.9% sodium chloride started and maintained at the same rate as for D1 and D2.

An anaesthesia technician not related to the study prepared the drug in an unlabelled syringe and passed it to the on-duty anaesthesiologist.

Table 1: Modified Ramsay Sedation Scale.

Grade	Patient response
1	Anxious, agitated, and restless
2	Co-operative, oriented, and tranquil
3	Responds to commands only
4	Brisk response to light glabellar tap or loud noise
5	Sluggish response to light glabellar tap or loud noise
6	No response

For D1, 200 µg of dexmedetomidine was added to 50 cc normal saline (NS) (4 µg/cc). For D2, 400 µg of dexmedetomidine was added to 50 cc NS (8 µg/cc). For C, the unlabelled syringe only contained NS. The attending anaesthesiologist was blinded to the drug and dose administered and considered each unlabelled syringe as containing dexmedetomidine 4 µg/cc, calculating the volume to be infused via a syringe pump accordingly, with a routine dose of 1 µg/kg bolus followed by maintenance infusion of 0.5 µg/kg/hour. Thus, the infusate was given at the same rate in all three groups as if the patient were being given dexmedetomidine routinely.

Immediately before the procedure, baseline (T0) CPK and CPK-MB was measured; dexmedetomidine 1 µg/kg, dexmedetomidine 2 µg/kg, or 0.9% sodium chloride infusion was then started. After the loading dose, maintenance infusion of dexmedetomidine or NS was started and continued until 30 minutes post-procedure. CPK and CPK-MB were measured at 6 hours (T1), 12 hours (T2), and 24 hours (T3) after the loading dose.

Heart rate (HR), blood pressure (BP), peripheral oxygen saturation, and sedation score were monitored every 5 minutes during the procedure and every 10 minutes post-procedure for 2 hours. Sedation score was assessed as a per modified Ramsay Sedation Scale (RSS), shown in Table 1.

It was decided to stop the infusion of the unlabelled syringe if mean arterial pressure (MAP) decreased to <20% of baseline or HR decreased to <50 bpm. Rescue drugs, in the form of injected mephentermine in 6 mg boluses intravenously and atropine 0.6 mg injected intravenously, were given for hypotension and bradycardia, respectively. In cases of persistent hypotension, dopamine was injected at a dose of 5–10 µg/kg/min.

An electrocardiogram (ECG) was performed pre and post-procedurally, at 24 hours and 72 hours, for arrhythmias and new ECG changes. As per institutional protocol, oxygen supplementation was given to all patients undergoing PCI with a simple oxygen mask with oxygen at 4 L/min.

At the end of the study, the on-duty anaesthesiologist gave the filled proforma to the primary investigator. Statistical analysis was

performed using Medcalc software. Analysis was completed using analysis of variance (ANOVA) followed by a post-hoc test. Haemodynamic variables and CPK and CPK-MB values were expressed as mean ± standard deviation. A p value <0.05 was considered significant.

RESULTS

Each of the three groups included 80 patients. In D1 there were 48 males and 32 females, in D2 there were 40 males and 40 females, and in C there were 43 males and 37 females. All patients were aged between 40 and 60 years. An EF between 40% and 50% was observed in 67, 60, and 61 patients in groups D1, D2, and C, respectively; an EF between 51% and 60% was observed in 13, 20, and 19 patients in groups D1, D2, and C, respectively.

HR decreased significantly, by around 15%, after the loading dose of dexmedetomidine 1 µg/kg infusion was administered in D1 (p=0.02). HR decreased by approximately 19% after the loading dose of dexmedetomidine 2 µg/kg infusion was administered in D2 (p<0.01) (Table 2). There was a statistically significant decrease in MAP by around 12% after the dexmedetomidine 1 µg/kg loading dose was administered. The decrease was greater, approximately 15%, after the administration of the 2 µg/kg dexmedetomidine loading dose (Table 2).

While none of the patients in D1 had a decrease in MAP by <20% and a HR <50 bpm, three patients in D2 had a clinically significant decrease in MAP and five patients had HR <50 bpm, requiring administration of rescue drugs (mephentermine and atropine, respectively).

There was no statistically significant difference in the CPK and CPK-MB values at T0, T1, T2, and T3 between the D1 and C groups (Table 2). However, there was a statistically significant difference in the CPK and CPK-MB values at T1, T2, and T3 between the D2 and C groups (Table 2). Five patients in C had arrhythmias during and post-procedure. In comparison, two D1 patients had arrhythmias and none were reported for D2 patients. All patients in D1 had a modified RSS of either 3 or 4, while patients in D2 had a modified RSS of either 4 or 5. No patient in either group had a reduction in blood oxygen saturation.

DISCUSSION

Dexmedetomidine has been proven to have various advantages in addition to its sedative and analgesic properties. Dexmedetomidine has anti-inflammatory effects when used as an adjunct to general anaesthesia and leads to a significant reduction in serum IL-6, IL-8, and tumour necrosis factor-α levels within a 24-hour period postoperatively.[24] Dexmedetomidine protects cardiomyocytes against hypoxia/reoxygenation injury by suppressing TLR4-MyD88-NFκB signalling.[25] Studies have shown that dexmedetomidine protects against oxygen-glucose deprivation/reoxygenation injury-induced apoptosis via the p38 MAPK/ERK signalling pathway.[26] However, few studies have failed to demonstrate the myocardial protective effect of dexmedetomidine in the usual recommended doses as far as cardiac enzymes are concerned.[22,27]

The authors earlier postulated that dexmedetomidine 1 µg/kg loading dose may have a beneficial effect by maintaining the supply:demand ratio, although no beneficial effect was seen on the cardiac enzymes. Dexmedetomidine has been shown to decrease the coronary vessel diameter, at the same time it decreased the heart rate, thus maintaining a balance in the supply and demand of oxygen.[22]

In the present study, it was observed that a 2 µg/kg dexmedetomidine loading dose has a myocardial protective effect when compared to a 1 µg/kg dexmedetomidine loading dose, with regard to myocardial enzymes. This myocardial protective effect comes at a cost of a greater reduction in HR and MAP, along with a higher sedation score seen in the D2 patients.

Many studies regarding the myocardial protective effect of dexmedetomidine have been carried out in animal models. In one such study in anaesthetised pigs by Yoshitomi et al.,[28] it was shown that a high dose of dexmedetomidine (100 ng/mL of coronary blood flow) had a favourable subendocardial:subepicardial blood flow ratio, resulting in better functional recovery from myocardial stunning. In a rat study by Okada et al.,[29] dexmedetomidine was shown to have a direct dose-dependent cardioprotective effect on reperfusion injury.

Table 2: Comparison of haemodynamics (heart rate and mean blood pressure), creatine phosphokinase, and creatine phosphokinase-muscle/brain in three groups at four time intervals.

	D1	D2	C	p value	Post-hoc analysis (p value)	
					D1 versus C	D2 versus C
Baseline heart rate	89.98±16.76	91.76±15.56	88.62±20.22	0.53	0.88	0.50
Post-loading dose heart rate	76.13±16.52	74.68±18.28	83.56±16.66	<0.01 (highly significant)	0.02	<0.01
Baseline MAP	78.62±10.28	77.88±9.88	79.64±11.18	0.57	0.81	0.54
Post-loading dose MAP	69.52±9.24	66.48±10.12	75.44±12.26	<0.01 (highly significant)	<0.01	<0.01
CPK baseline (T0)	144.46±16.88	146.78±18.62	148.82±16.42	0.28	0.25	0.74
CPK-MB baseline (T0)	29.25±7.68	28.16±8.42	26.62±7.88	0.12	0.10	0.44
CPK at 6 hours (T1)	193.98±22.66	168.84±18.26	200.42±25.54	<0.01 (highly significant)	0.16	<0.01
CPK-MB at 6 hours (T1)	36.22±8.66	29.98±6.24	38.44±9.62	<0.01 (highly significant)	0.21	<0.01
CPK at 12 hours (T2)	183.56±15.42	148.24±14.48	190.02±25.24	<0.01 (highly significant)	0.08	<0.01
CPK-MB at 12 hours (T2)	31.66±8.42	29.12±5.86	33.82±7.48	<0.01 (highly significant)	0.15	<0.01
CPK at 24 hours (T3)	169.82±28.26	147.76±15.52	177.24±20.02	<0.01 (highly significant)	0.08	<0.01
CPK-MB at 24 hours (T3)	30.88±8.66	28.66±6.42	31.42±6.48	0.04	0.89	0.04

C: control; CPK: creatine phosphokinase; CPK-MB: creatine phosphokinase-muscle/brain; D1: dexmedetomidine 1 µg/kg; D2: dexmedetomidine 2 µg/kg; MAP: mean blood pressure; T: timepoint.

Dexmedetomidine improved the infarct size and exhibited a cardioprotective effect on global ischaemia; thus, it was thought that a dose higher than the routinely used 1 µg/kg loading dose is required to elicit a myocardial protective effect in patients undergoing PCI.

Chi et al.[21] observed that a 1 µg/kg dexmedetomidine dose reduced myocardial damage in patients undergoing off-pump coronary artery bypass graft surgery, as noted by a decrease in the myocardial enzymes in the dexmedetomidine group when compared to the control group. Analysis was carried out to uncover the possible reasons as to why the same dose of dexmedetomidine could not replicate the results in PCI patients. Firstly, the subgroup of patients in this study were conscious, coming from the ward or intensive care unit with different anxiety levels compared to the anaesthetised surgical patients. Secondly, the dosage required in PCI patients may be different because of the shorter duration of the procedure; the total duration of the procedure was less than the time for normal cardiac surgery. The total dosage of dexmedetomidine infused into the patient was, therefore, reduced in PCI patients compared to the cardiac surgical patients, even though the same maintenance dosing regime was used. Thirdly, the sample size was calculated based on previous surgical studies: a larger sample size may be required in PCI patients. Further study with a different dexmedetomidine dose and with a larger sample size is required to validate the myocardial protective effect in ischaemia reperfusion injury.

Although a myocardial protective effect was elicited by a loading dose of 2 µg/kg dexmedetomidine, it was also associated with a greater number of side effects. In the present study, HR decreased by 15% in D1 and decreased by 19% in D2. Similarly, MAP decreased by 12% in D1 but decreased by 15% in D2. None of the patients in D1 had a decline in MAP <20% and HR <50 bpm, but three D2 patients had a clinically significant decrease in MAP, and five patients had a HR <50 bpm, requiring

administration of rescue drugs (mephentermine and atropine, respectively).

Dexmedetomidine caused conscious sedation from which the patient could be woken up easily when stimulated in D1. However, the patients in D2 were more sedated than in D1, warranting greater care in the recovery room. Thus, it is beneficial to use dexmedetomidine 2 μg/kg for myocardial protection in PCI patients, but the beneficial effects come at the cost of requiring greater vigilance by the nursing staff during and post-procedure.

In the present study, five control patients had arrhythmias during or post-procedure compared to two in D1 and none in the D2. There is a probability that dexmedetomidine could have prevented the arrhythmias caused by ischaemia/reperfusion in the D1 and D2 patients in a dose-dependent manner, but the sample size may not be adequate to conclusively prove that.

One of the limitations of the present study was that troponin was not used as a marker of myocardial ischaemia-reperfusion injury. This was because troponin is a paid investigation in the present study institute. In view of the large sample size and the paucity of funds, it was decided to use another marker of myocardial injury, i.e., CPK-MB, which has also been used in previous studies.[20,21,23] Another limitation was that long-term patient follow-up was not done in the present study.

CONCLUSION

Dexmedetomidine 2 μg/kg provides a myocardial protective effect as compared to 1 μg/kg, but at the cost of a greater fall in HR and MAP and with a higher sedation score, warranting careful monitoring in the post-procedure recovery room. Large-scale clinical outcome trials are needed before recommending use of a higher dose of dexmedetomidine to confirm its safety and myocardial protective efficacy.

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Cardioprotective Approaches to the Management of Patients with Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Do We Need Increased Surveillance in Elderly Women on Trastuzumab?

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Abstract

Cardiotoxic effects in patients with breast cancer may present as asymptomatic left ventricular (LV) dysfunction or symptomatic LV decline, which can progress to overt heart failure (HF). Trastuzumab is a monoclonal antibody against human epidermal growth factor receptor (HER)2 and is a recommended targeted treatment for patients with overexpression of this receptor. However, the use of trastuzumab is associated with cardiotoxicity, manifested as LV dysfunction or HF. This review addresses the key issues related to individualised cardioprotection and surveillance, especially in elderly patients with HER2-positive breast cancer, based on the current cardio-oncology literature. Cardiac imaging techniques (e.g., echocardiography or multiple-gated acquisition scan) and biomarkers (e.g., cardiac troponins) that play a crucial role in the detection and monitoring of cardiotoxicity related to systemic therapies for breast cancer are briefly described. This review presents cardioprotective approaches, including interruption or termination of trastuzumab therapy, and treatment with an angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, or beta-blocker, which have been recommended for the reduction of cardiac adverse effects. Since the data relevant to cardiotoxicity of trastuzumab among real-world older women with breast cancer and cardiovascular diseases are still limited, this article focusses on improvements to the cardiac safety of trastuzumab-based regimens. In particular, this review emphasises the importance of intense surveillance in the elderly female population.

INTRODUCTION

Due to recent advances in antineoplastic treatment for breast cancer, cancer-related mortality has substantially decreased. However, several systemic therapies have contributed to cardiac complications that adversely influence patient outcomes.[1] In patients with human epidermal growth factor receptor (HER)2-positive breast cancer, treatment with trastuzumab and anthracyclines has been associated with short and long-term cardiotoxicity. Therefore, reducing the negative impact of these antineoplastic agents on the cardiac condition, via early detection, immediate treatment, and regular monitoring, is a key objective in breast cancer management, particularly among elderly patients who often present with pre-existing cardiovascular disease (CVD). In a real-world hospital setting, female patients aged ≥65 years diagnosed with breast cancer have been considered to be candidates for systemic therapy if the expected advantages of such a therapy would outweigh the risks (e.g., cardiac adverse effects).[1] It has been estimated that approximately 15–25% of breast cancers consist of HER2-positive tumours.[1] Trastuzumab (Herceptin®; Roche Holding AG, Basel, Switzerland) is a humanised monoclonal antibody that binds to the extracellular domain of HER2 and targets the HER2 signalling pathway.[1,2] Herceptin is a targeted anticancer therapy that was approved for clinical use in 1998 and can be used concurrently or sequentially with systemic chemotherapy (CHT), leading to the improvement of disease-free survival and overall survival of women with HER2-positive breast cancer, both in early and metastatic stages.[2]

However, trastuzumab can also cause treatment-induced cardiotoxicity, which manifests mostly as a decline in left ventricular ejection fraction (LVEF) (often asymptomatic) or abnormal cardiac function that may progress to overt heart failure (HF).[2] For instance, according to some clinical studies, cardiotoxic side effects occurred in up to 27% of patients who received trastuzumab concurrently with anthracyclines, which are highly cardiotoxic agents, but in <13% of those who received trastuzumab with paclitaxel.[3] Cardiotoxicity related to trastuzumab and anthracyclines, as well as to other anticancer therapies, remains a serious concern.[4] Therefore, the key goal is to improve the cardiac safety of trastuzumab. This may require a more intense surveillance in elderly patients compared with their younger counterparts. For this reason, in older women (who often present with multiple morbidities and have a greater incidence of cardiomyopathy and HF), routine surveillance should be optimised (e.g., via a vigilant diagnostic approach and the implementation of more aggressive cardioprotective measures, including pharmacologic and non-pharmacologic modalities, such as dietary, educational, or lifestyle-related strategies).[1,4] This is consistent with recent findings from the HERA trial,[5] which have shown that cardiotoxicity events associated with trastuzumab were less severe when patients were screened in a very strict manner for pre-existing cardiac conditions.[5] Furthermore, the final analysis of the HERA trial, including 11 years of follow-up of trastuzumab after adjuvant CHT in patients with HER2-positive early breast cancer, revealed that 1 year of adjuvant trastuzumab treatment after CHT significantly improved long-term disease-free survival, while 2 years of trastuzumab treatment had no additional benefit.[5]

MECHANISMS UNDERLYING TRASTUZUMAB-INDUCED CARDIOTOXICITY

The mechanism underlying trastuzumab-induced cardiotoxicity remains unclear. Oxidative stress and the production of highly toxic free radical molecules are thought to be the main culprits for the induction of myocyte injury. In addition, it has been suggested that blockage of HER2 receptors can contribute to trastuzumab-induced cardiotoxicity because HER2 receptors are expressed on cardiac myocytes and play a crucial role in embryonic cardiac development, as well as growth and repair of the heart muscle in adult life.[4] Cardiotoxicity due to trastuzumab is mostly reversible and not dose dependent. The effects of trastuzumab are characterised as type 2 CHT-related cardiac dysfunction. In contrast, drugs commonly used in therapy with anthracyclines, such as doxorubicin, represent a type 1 CHT-related cardiac dysfunction, manifested as an irreversible, dose-dependent myocardial damage.[4] It should be highlighted

that the highest risk of cardiotoxicity induced by trastuzumab occurs in cases of concurrent treatment with anthracycline-based regimens in patients presenting with advanced age, Type 2 diabetes mellitus, decreased glomerular filtration rate, low baseline LVEF, arterial hypertension, or pre-existing CVD.[2-4]

Trastuzumab-induced cardiotoxicity can negatively interfere with a recommended course of anticancer treatment. Under these circumstances, it has been recommended to monitor LVEF before starting trastuzumab therapy (at baseline), every 3 months during the treatment course, and then 6 months after treatment completion.[1] While the risk of overt HF during treatment with trastuzumab is rather low (1–4% of patients), asymptomatic decline of LVEF is much more frequent (7–19% of patients) according to the results of recent clinical trials.[2,5] It should be underscored that in the hospital setting the rates of cardiac side effects are even higher, especially in elderly women with CVD or risk factors for such cardiovascular comorbidities.[1,3,6] In daily clinical practice, this discrepancy can be even more aggravated because such patients have often been excluded from participation in randomised clinical trials (RCT).

Moreover, it should be underscored that the cardiotoxicity secondary to trastuzumab exposure is dose-independent, meaning that it can unpredictably escalate to HF. However, if promptly detected and adequately treated, this condition is usually reversible.[7] Additionally, it has been found that after the resolution of trastuzumab-induced cardiac adverse effects, trastuzumab therapy can be restarted following the implementation of a standard therapy for HF under close supervision of a consulting cardiologist.[7] In addition, since a commonly used CHT regimen containing anthracyclines predisposes a patient to trastuzumab-induced cardiotoxicity, the incidence of adverse cardiac effects is highest when anthracyclines and trastuzumab are administered concurrently. In contrast, cardiotoxicity declines as the time period between anthracycline and trastuzumab administration increases and, when trastuzumab is used in sequence (after completing a course of CHT with anthracyclines).[8]

CARDIOTOXICITY OF TRASTUZUMAB IN ELDERLY PATIENTS: IMPORTANT CONSIDERATIONS

In general, in the older population (>65 years of age), biological characteristics of breast cancer, including hormone receptor (HR) positivity, low mitotic rate, low nuclear grade, rare *p53* gene mutations, and relatively infrequent overexpression of epidermal growth factor receptor or HER2, are often more favourable than in younger patients.[9,10] However, in spite of that, mortality rate remains higher in older versus younger women,[11] and this can be due to the different behaviour of tumours in elderly patients or a possible risk of death from comorbid diseases.[9,10]

Trastuzumab therapy should be considered for elderly patients with early-stage breast cancer (e.g., HER2-positive and HR-negative or HER2-positive and HR-positive with lymph node invasion) and with more advanced malignancy, but the cardiotoxicity of the treatment must always be paramount.[12-14] According to a study that assessed standard CHT with or without trastuzumab in patients with metastatic breast cancer, it was revealed that cardiac dysfunction (New York Heart Association [NYHA] Class III or IV) was recorded in 16% of patients using anthracycline, cyclophosphamide, and trastuzumab, compared to 3% of those who were treated only with anthracycline and cyclophosphamide. In addition, in this trial, NYHA Class III or IV was reported in 2% of female patients receiving paclitaxel and trastuzumab, compared to 1% of those who were treated with paclitaxel alone.[15]

In the landmark study NSABP B-31,[16] which compared anthracycline and cyclophosphamide, followed by paclitaxel with anthracycline and cyclophosphamide, followed by trastuzumab and paclitaxel, the participants had HER2-positive and node-positive breast cancer, and normal post-CHT LVEF (as per multiple-gated acquisition [MUGA] scan evaluation). In this study population, the incidence of adverse cardiac events was 4.1% in the trastuzumab group compared to 0.8% in the control group after 3 years, and 4.0% versus 1.3%, respectively, at 7 years of follow-up.[16] Similarly, in the NCCTG N9831 trial,[17] which also evaluated the efficacy

and safety of trastuzumab in addition to paclitaxel after anthracycline (doxorubicin) and cyclophosphamide CHT, the rates of HF in the trastuzumab versus control groups were 3.8% versus 1.3%, and 2.3% versus 0.9%, respectively.

According to the results of a meta-analysis of eight RCT, which addressed the use of trastuzumab for non-metastatic or locally advanced breast cancer, the incidence of symptomatic HF ranged from 0.8–14.2% among trastuzumab-treated patients, compared to 0.2–4.1% in the control group.[18] Based on data from a European cancer registry, in which 32.6% of patients were ≥60 years of age, the cumulative risk of trastuzumab-related cardiotoxicity for the females >70 years old compared with the younger patients was 6.4% versus 1.3% after 1 year, 9.8% versus 2.0% after 2 years, and 9.8% versus 2.2% after 3 years of treatment, respectively.[19] This is concurrent with the USA cancer registry that included trastuzumab-treated HER2-positive metastatic breast cancer patients, in which the incidence of HF for women >75 years old was 3.2%, between 65 and 74 years was 1.9%, and <65 years of age was 1.5%.[20] Convergent with these results, in a group of German females who were taking trastuzumab in an adjuvant setting, the frequency of decline in LVEF or an overt HF was 3.7% in the subgroup of women <65 years of age, 3.9% in the patients between 65 and 69 years of age, and 5.7% in the women ≥70 years of age.[21]

In general, several studies have revealed that trastuzumab, with or without anthracyclines, contributed to a risk of acquiring HF that can be estimated as two-fold higher than that occurring in patients who did not receive trastuzumab therapy.[22] It should be underscored that the hospital-based studies take into consideration many elderly patients, treated daily in clinical practice, who otherwise would have been excluded from RCT. Since the mortality rate 5 years after diagnosis of HF is about 50% in patients >65 years, a close surveillance of early HF symptoms and LV function in this elderly breast cancer population treated with trastuzumab is critically important.[22]

ADVANTAGES OF USING CARDIAC BIOMARKERS FOR EARLY IDENTIFICATION OF MYOCARDIAL INJURY IN PATIENTS WITH HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-POSITIVE BREAST CANCER TREATED WITH TRASTUZUMAB OR ANTHRACYCLINES

Recently, cardiac biomarkers have been investigated for their potential as early detectors of anticancer therapy-induced cardiotoxicity. While the role of biomarkers in monitoring anthracycline toxicity is generally well understood, substantial uncertainty remains regarding their role in monitoring targeted HER2 anticancer treatments. Cardiac troponins and N-terminal pro-B-type natriuretic peptide (BNP) are gaining interest in monitoring cardiac toxicity with trastuzumab.[23] There is some variability among biomarker studies, especially regarding the sensitivity or specificity of the biomarker assays and reference ranges for normal versus abnormal results. However, despite these issues, there is an agreement that troponin I predicts early, but not late, cardiac events induced following trastuzumab administration after anticancer regimens that contain anthracyclines. Moreover, troponin increases may illustrate cardiac damage due to anthracyclines rather than trastuzumab-induced myocardial injury.[23] Therefore, troponin levels can serve as biomarkers of susceptibility to cardiotoxicity during the early period of trastuzumab therapy, especially in patients with HER2-positive breast cancer who have recently received CHT regimens with anthracyclines.[23] In addition, elevation of the troponin levels would enable an immediate introduction of preventive measures before the onset of functional LVEF deterioration. For this reason, cardiac troponin I (cTnI) and T (cTnT) can be used as biomarkers of myocardial injury in a population with HER2-positive breast cancer,[23] as illustrated in recent research trials. For instance, in a study by Cardinale et al.,[23] the plasma levels of cTnI patients with different types of neoplasms who received high doses of CHT were measured after each CHT cycle. The study participants were divided into troponin positive (cTnI+) and troponin negative

(cTnI-) subgroups. In the cTnI- subgroup, there was a transient decline of LVEF post CHT (with a nadir after 3 months from baseline), followed by a subsequent recovery. In contrast, participants in the cTnI+ subgroup had bigger declines in their LVEF, which persisted for up to 7 months of monitoring.[23]

The impact of persistent elevations of cTnI was assessed in another trial, and the results showed that the patients who received high-dose CHT and had persistent increases in cTnI had a higher incidence of cardiotoxicity (85%) compared to the patients with only transient increases of cTnI (37%) or to patients that had no elevation of cTnI (1%).[24] It should be noted that BNP represents a biomarker of volume overload, and persistent N-terminal pro-BNP increase after administration of CHT has been correlated with a significant drop of LVEF.[25] However, further studies are required to reveal whether N-terminal pro-BNP may serve as a predictive marker of trastuzumab and/or CHT-induced LV dysfunction. The role of high-sensitivity C-reactive protein is still controversial; however, it has been reported that high-sensitivity C-reactive protein can be a valid biomarker of trastuzumab-induced cardiotoxicity.[26] Due to the heterogeneity of the examined populations, these findings have to be considered with caution. Furthermore, more research trials in this area are certainly merited.

CARDIAC IMAGING FOR DETECTION AND MONITORING OF TRASTUZUMAB-INDUCED CARDIOTOXICITY

Current techniques for detecting cardiotoxicity predominantly rely on assessment of LVEF via echocardiography (ECHO) or MUGA scan. However, in some patients, by the time a decline in LVEF is detected, there has already been subclinical myocardial injury. Therefore, there is a necessity to design and implement biomarkers that will facilitate the early detection of myocardial damage.[22,27,28]

Unquestionably, cardiac function should be monitored during trastuzumab treatment, and a decrease in LVEF of ≥10–<55% (often asymptomatic) has been found to be clinically relevant.[27] LVEF has most usually been measured via conventional two-dimensional (2D) transthoracic ECHO or radionuclide ventriculography (MUGA scan). However, these methods lack precision and have been reported to miss some subclinical cardiac abnormalities.[27]

On the other hand, prompt detection of trastuzumab-induced cardiotoxicity followed by immediate administration of cardioprotective medications prior to any further decrease in cardiac function or appearance of HF symptoms is critical for both the patient and the treating team (especially for a cardiologist and an oncologist).

Regarding the cardiac imaging tools, some modern ECHO techniques, as well as cardiac MRI, have shown promise for more accurate diagnosis of LV dysfunction, which is relevant to trastuzumab. For instance, three-dimensional (3D) ECHO was indicated as a better tool than 2D ECHO for precise measurements of LVEF.[29] According to the recommendations of the European Association of Cardiovascular Imaging (EACVI),[30] standard parasternal long axis and apical view recordings should be carried out in the end-expiratory phase, with the patients in the supine left lateral position. An average of three cycle recordings should be used for standard measurements of cardiac dimensions and function. Biplanar apical 2 and 4-chamber views should be used to measure left atrial volume. All measurements need to be performed in end systole. In addition, specific 3D loops recorded from the apical view by storing four heart cycles allows for the analysis of LV volumes.[30]

AN INTEGRATIVE DIAGNOSTIC APPROACH: A COMBINATION OF CARDIAC IMAGING AND BIOMARKERS IN SURVEILLANCE OF CARDIOTOXIC EFFECTS RELATED TO TRASTUZUMAB AND ANTHRACYCLINES

According to the Society for Cardiovascular Magnetic Resonance (SCMR) guidelines, in cardiac MRI analysis, which can be performed using dedicated software, the epicardial and endocardial contours can be traced in end diastole and end systole. Simultaneously, calculation of ventricular volumes, LVEF percentage, and LV mass are being performed. Moreover, 3D ECHO was demonstrated to be more reproducible over a long period of

monitoring and more consistent between different cardiologists performing serial ECHO exams, since both intra-observer and inter-observer variability for LVEF are minimised.[29,30]

A recent study by Kang et al.[31] investigated whether changes of myocardial strain and high-sensitive cTnT may predict future cardiac dysfunction among patients who were previously exposed to anthracycline (e.g., epirubicin). In this study, the patients were examined using 2D speckle tracking ECHO (2D-STE) at baseline and then again during follow-up. Calculated global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) were performed using 2D-STE, while LVEF was evaluated by real-time 3D ECHO.[31] In this trial, in which cardiotoxicity criteria included a decrease of the LVEF of ≥5–<55% with symptomatic HF or an asymptomatic LVEF decline of ≥10–55%, the decrease of GLS was an independent predictor of cardiotoxicity.[31] In addition, GLS combined with cTnT could provide a reliable way to predict cardiac dysfunction in patients receiving anthracycline-based chemotherapy.[31] Similarly, the clinical value of 2D-STE, combined with high-sensitive cTnT in early detection of the cardiotoxicity induced by anthracyclines and trastuzumab, was also investigated in a study by Ho et al.[32] The long-term effects of standard CHT on myocardial function in asymptomatic breast cancer survivors were examined using 2D-STE. According to this trial, some subclinical systolic and diastolic myocardial dysfunctions were reported in asymptomatic survivors of breast cancer (up to 6 years post standard CHT).[32]

In summary, an integrative approach that uses both cardiac imaging and biomarkers to identify cardiotoxicity of anticancer medications has beenhelpful regarding trastuzumab and anthracycline CHT, but this methodology requires further study in various therapeutic contexts, especially in theelderly patient population.[28]

AN OPPORTUNITY FOR PREVENTION AND TREATMENT OF TRASTUZUMAB AND ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Trastuzumab-induced cardiotoxicity is reversible and discontinuation of this agent may be needed in up to 19% of patients.[33] Some studies report that angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers (BB) have protective effects in CHT-induced cardiotoxicity. Cardinale et al.[34] reported prevention of AC-induced cardiomyopathy using the ACEI enalapril. Likewise, Kalay et al.[35] reported a beneficial effect of carvedilol (a BB) use for prevention of cardiotoxicity. The MANTICORE trial was designed to assess the effectiveness of an ACEI (perindopril) and BB (bisoprolol) in primary prevention of trastuzumab-induced cardiotoxicity (Table 1).[36,37] Results of the MANTICORE trial have revealed that bisoprolol and perindopril did not prevent LV remodeling; however, the two drugs had beneficial effects on LVEF among patients with HER2-positive, invasive, early breast cancer treated with trastuzumab.[37] Furthermore, the PRADA trial showed that the angiotensin-receptor blocker candesartan, but not the BB metoprolol, resulted in less early LVEF deterioration compared to placebo during anthracycline-containing CHT with or without trastuzumab and radiation therapy (Table 1).[38,39] Moreover, in the PRADA study, an anticancer treatment was associated with a modest, short-term decline in LV function. However, a long-term assessment is necessary and, if sustained (meaning that the long-term effect of early angiotensin inhibition can be confirmed), preventative therapy with angiotensin-receptor blocker may be recommended as a standard of care. Therefore, in patients treated for early, HER2-positive breast cancer, concomitant therapy with candesartan may provide protection against early decline in LV function.[39] There is a growing need to adequately assess cardiac safety during anticancer therapy, especially among elderly patients and cancer survivors regardless of their age. At this point, cardio-oncology, as an emerging medical speciality, requires organisational and educational training support, research infrastructure, and well equipped clinical facilities. This is in accordance with an international consensus, under the auspices of the International CardioOncology Society and the Canadian Cardiac Oncology Network (CCON); both regional and international collaborative efforts in clinical research and practice are essential for real progress in this new interdisciplinary speciality.[40]

Table 1: Pharmacotherapy for prevention of trastuzumab-induced cardiotoxicity in patients with human epidermal growth factor receptor 2-positive breast cancer based on two major randomised controlled trials.

Study	Study details › Number of patients › Cancer characteristics › Follow-up duration	Main anticancer treatment	Cardio-protective medications	Trial results and cardiac outcomes	Clinical implications
MANTICORE RCT;[36] placebo-controlled, double-blind. Pituskin et al.,[37] 2011.	› 99 women › HER2-positive, early invasive breast cancer therapy › 12 months	Trastuzumab	ACEI (perindopril) BB (bisoprolol)	The first RCT testing cardiac medications in prevention of trastuzumab-induced cardiotoxicity. 12-month change in LV end-diastolic volume (evaluated via ECHO, cMRI).	Guidelines will be developed for the use of ACEI and BB in HER2-positive breast cancer treated with trastuzumab.
PRADA RCT;[38] placebo-controlled, double-blind. Gulati et al.,[39] 2016.	› 120 women › HER2-positive, early stage breast cancer › 12 months	Anthracycline-containing CHT with or without trastuzumab and RT	ARB (candesartan) BB (metoprolol)	Change in LVEF (evaluated via ECHO, MUGA scans, or cMRI) from baseline to completion of adjuvant anticancer therapy.	Treatment with candesartan (but not with metoprolol) provides protection against LVEF decline in breast cancer patients. Further RCT are needed to investigate the protective role of ARB long-term.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; BB: beta-blocker; cMRI: cardiac magnetic resonance imaging; CHT: chemotherapy; ECHO: echocardiography; HER2: human epidermal growth factor receptor 2; LV: left ventricle; LVEF: left ventricular ejection fraction; MUGA: multiple-gated acquisition scan; RT: radiotherapy; RCT: randomised controlled trial.

In general, for elderly patients, the treatment teams should agree that numerical age is not so important for treatment decision-making. In contrast, individual cardiovascular risk factors, CVD or other comorbidities, overall life expectancy, quality of life, and patient preferences should play a main role in the multidisciplinary management of such patients.[41,42]

CONCLUSION

Targeted anticancer therapy, such as treatment with trastuzumab, has shown a 50% reduction in cancer recurrence rates and >30% improvement in survival outcomes of patients with HER2-overexpressing breast cancer. However, trastuzumab has contributed to various cardiotoxic effects (e.g., asymptomatic LVEF decline or overt HF onset), especially among elderly patients. In a real-world hospital setting, an appropriate assessment of patients by a multidisciplinary team prior to the initiation of trastuzumab is necessary to minimise the risk of potential cardiac adverse effects. Furthermore, using cardiac biomarkers (e.g., troponin I) for screening can be helpful for the early detection of myocardial injury among the most vulnerable patients. Both physicians and patients should keep in mind that advanced age and pre-existing CVD augment the probability of trastuzumab-induced cardiotoxicity and, thus, regular monitoring combined with prompt treatment are of utmost importance. Consequently, serial assessment of LVEF (via ECHO or other cardiac imaging tests)

and measurement of specific cardiac biomarkers, as well as the use of medication, such as ACEI, angiotensin-receptor blockers, or BB, should be considered, together with a close follow-up (e.g., HF symptoms, arterial blood pressure, heart rate, LVEF, and renal function parameters). Such a proactive approach will hopefully prevent several unnecessary cardiovascular complications.

Future studies are needed to determine whether the selected cardiac biomarkers, novel imaging techniques, or their combination can be successfully employed in the older population for early detection; timely treatment; and regular, long-term follow-up of trastuzumab-induced cardiac adverse effects. There is the necessity to switch the thinking pattern regarding cardiotoxicity from 'responding to a problem' to 'preventing and successfully solving problems'. Finally, a future challenge is the establishment of relevant practice guidelines focussed on preventive and therapeutic strategies against cardiotoxicity at the dynamic 'intersection' of cardiology and oncology, with particular attention to a growing population of elderly patients.

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The Cardiomyopathy of Iron Deficiency Anaemia

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Abstract

Anaemia is a huge global health challenge. Iron deficiency (ID) is the most prevalent, preventable, and treatable cause of anaemia worldwide. ID anaemia (IDA) is frequent in patients with heart failure. ID is an important factor in the development of heart failure but is also considered a separate condition with unfavourable clinical and prognostic consequences. In this review, the authors narrate how IDA affects the myocardium, and the possible mechanisms surrounding this impact are described. The review summarises the pathological changes seen in ID cardiomyopathy via ECG, videography, and laboratory tests. Using these tests, the early changes in the myocardium of patients with IDA have been recognised, resulting in the identification of pivotal and developmental targets for improving the morbidity and mortality of patients with IDA. Some of the progress in treatment of IDA patients has also been described. Although IDA patients experience myocardium remodelling, patients can recover heart function through iron supplementation, such as using ferric carboxymaltose. In addition, this paper includes a discussion surrounding the sex differences of the disease; however, research on this aspect is limited and should form the focus of future investigations. The authors focus on myocardial changes in adults with acute or chronic IDA.

BACKGROUND

Anaemia is a significant challenge in global health; it is characterised by lower than normal levels of red blood cells and haemoglobin per unit volume of blood and is mainly caused by genetic traits, malnutrition, and loss of trace elements. The main types of anaemia identified by studies of the global burden of diseases are iron deficiency anaemias (IDA), thalassaemias, sickle cell disease, and infection-related anaemias.[1,2] Among the main causes, iron deficiency (ID) is the most prevalent, preventable, and treatable cause of anaemia worldwide.[3]

IDA is a condition in which iron stores in the body are insufficient to meet the needs of the patient to produce red blood cells, resulting in a lower than normal red blood cell count.

ID is the most common nutritional deficiency in various regions around the world. IDA accounts for 50% of all anaemia cases worldwide,[4] making it the most acknowledged consequence of persisting ID. Moreover, anaemia has been confirmed as one of the top 20 risk factors associated with the global burden of disease by the World Health Organization (WHO).[5]

METHODS

For this review, the authors applied a search strategy using a combination of the keywords 'anemias', 'systematic review', 'heart', 'IDA', and 'cardiomyopathy'. No language restrictions were applied and publications before March 2018 were screened.

The initial round of paper selection included both meta-analyses and individual studies on IDA with information on cardiomyopathy, as well as any general review for further studies containing these relationships. The present review focusses on myocardial changes in adults with acute or chronic IDA and excluded myocardial changes in IDA in infants and children.

DEFINITION

The diagnosis of IDA is defined as a haemoglobin level <12 g/dL in women and <13 g/dL in men; serum ferritin level <12 ng/mL; and mean corpuscular volume and mean corpuscular haemoglobin concentration values below the normal range (i.e., 32–36 g/dL for mean corpuscular haemoglobin concentration).[6]

Adequate iron reserves are required for many important processes in the body, including oxygen transport as part of the haemoglobin molecule, enzymatic reactions in the cytochrome system, and electron transport and energy metabolism in the body.[7] Serum ferritin levels may also be a significant determinant of myocardial ischaemia burden during an ischaemic attack.[8] ID in the adult general population is defined by the WHO as plasma ferritin <15 mg/L. In chronic heart failure, the criteria for diagnosing ID are not uniform but generally include an absolute ferritin level <100 µg/L and a functional ferritin level 100–300 µg/L in combination with a transferrin saturation <20%.[9-11] Using these criteria, a study published in 2010 showed that ID was present in 37% of all patients with heart failure.[12]

Recent research has shown that male patients with anaemia have a higher incidence of cardiovascular diseases and a worse life expectancy than female patients with anaemia,[13] which was partially due to the younger age of female patients with anaemia in this study. Among young people, the prevalence of anaemia in women is higher than in men, mainly due to the high prevalence of microcytic anaemia in women.[14] In addition, anaemia may influence the mortality in patients of both sexes with chronic heart failure, but this effect is reduced in women because of a sex difference in the oxygen affinity of haemoglobin.[15]

SIGNS AND SYMPTOMS

Individuals with anaemia generally have a significantly decreased ability to work and reduced quality of life. They often experience fatigue, dizziness, headache, pica, palpitations, shortness of breath, and an increased heart rate.[16]

The initial signs and symptoms of anaemia are caused by tissue hypoxia and physiological compensatory mechanisms. Anaemia can cause left ventricular dilation, systolic dysfunction, diastolic dysfunction, and even chronic heart failure.[17-19] Anaemia has been recognised as one of the independent risk factors for heart failure,[20] and it has been confirmed that IDA is strongly associated with heart failure.[11] Recent data have shown that patients with chronic heart failure complicated with ID have a higher rate of hospital readmission compared to patients without ID.[2] One study found that up to 73% of patients with advanced heart failure also had IDA, which was confirmed by bone marrow biopsy.[21] In nonischaemic cardiac failure, IDA is a well-defined adverse prognostic factor.[4,12,22,23] These study findings indicate that IDA plays a significant role in the function of the heart. In addition, the myocardium is a key factor in the pathophysiology of heart failure.[24,25]

Anaemia and ID are common causes of heart failure, both separately and in combination.[22] Honda et al.[14] showed that anaemia was an independent predictor of myocardial damage or subclinical myocardial damage and cardiovascular mortality in the general population. Current evidence suggests that ID and anaemia are more prevalent in patients with heart failure and reduced ejection fraction, as well as in those with heart failure and preserved ejection fraction.[26] Cho et al.[27] reported that anaemia was associated with larger cardiac chambers, increased left ventricle (LV) mass, and higher LV filling pressure. The oral

administration and intravenous injection of iron can help to improve the quality of life of patients with heart failure.[28-30] Paying attention to early myocardial motion changes in patients with IDA can help clinicians and researchers to understand the changes in ejection fraction and ventricular function.

MECHANISMS OF IRON DEFICIENCY ANAEMIA CARDIOMYOPATHY

Anaemia is one of the many consequences of long-term ID and compensatory changes occur in the circulatory system. Researchers have long been concerned about the effect of ID on cardiomyopathy. Patients with IDA develop changes in levels of cardiac muscle as well as remodelling of cardiac muscle molecules.[31] In the early stages, the cardiac output increases and forms a high-power cycle. Long-lasting hyperdynamic circulation increases the load on the heart, causing myocardial ischaemia and hypoxia, and may cause ventricular hypertrophy. If IDA is not corrected, the myocardium cannot withstand the high workload, leading to contraction and fatigue, cardiac remodelling, expansion of the ventricles, normal or thin wall thickness, and, eventually, heart failure.[32] Turner et al.[33] induced ID in mice and found that the increased cardiac output and sympathetic activation resulted in left ventricular hypertrophy. Yokusoglu et al.[34] demonstrated an altered autonomic balance in patients with IDA. Anaemia may cause abnormalities in sympathetic nerve activity through the perception of hypoxia in the carotid body. It is now believed that this hypoxia-linked inhibition of the mitochondrial respiratory chain or potassium channels leads to intracellular calcium accumulation, which, in turn, can lead to myocyte dysfunction. The relationship between ID and the development of left ventricular hypertrophy has been verified by several studies.[33,35-37]

Naito et al.[38] described how increased erythropoietin concentration and cardiac STAT3 phosphorylation were associated with the compensatory, beneficial cardiac remodelling associated with chronic IDA; following this, they speculated that a corresponding decrease in these factors might initiate cardiac dysfunction in long-term IDA. This experiment also showed that progressive cardiac fibrosis is a result of ID in an animal model. In a mouse experiment, erythropoietin receptor signalling played an important role in cardiac remodelling following chronic ID through the p53 pathway.[39] Dong et al.[37] reported left ventricular hypertrophy and dilatation in ID rats due to mitochondrial swelling and irregular sarcomere organisation, increased mitochondrial cytochrome c release, and reactive nitrogen species in cardiomyocytes.

Iron is an essential element in the synthesis of collagen,[40] which is an important component of the cardiovascular system due to its role in supporting and sustaining the hardness of the vascular wall. In ID, the content of collagen in heart tissue is decreased,[41] which results in the decreased elasticity of the myocardium and vascular wall, as well as changes in the normal pressure–volume relationship. Iron is also an important component of the enzymatic system of cardiomyocytes. Without iron, the biological enzyme system is destroyed, and mitochondrial cytochrome c release is increased. This condition is often accompanied by mitochondrial swelling, irregular deformation of sarcomeres, and increased presence of reactive nitrogen species in cardiomyocytes, eventually leading to muscle cell damage.[42] IDA increases the production of brain natriuretic peptide and oxygen free radicals, increases platelet aggregation, accelerates atherosclerosis progression, and increases the risk of thrombosis in coronary arteries with underlying lesions, causing coronary artery occlusion.[43] In addition, ID promotes lipid peroxidation and increases the levels of endothelial cells and reactive oxygen species.[44] Increased oxidative stress counteracts the vascular endothelial cells and impairs their function.[45]

DIAGNOSTIC STUDIES

In ongoing IDA, the patient develops cardiac hypertrophy and cardiac chamber enlargement, eventually leading to heart failure.[38] Various auxiliary examinations can be used to identify changes in the myocardium of IDA patients. ECG have been used to show that IDA may be associated with prolonged P-wave duration and dispersion.[19] In an IDA study of pregnant women in their second trimester, a significant decrease in QRS duration and increase in QTc

were observed.[46] Another group of researchers observed a shortened QTc in nonpregnant women with severe IDA. The authors believed that this finding was due to hyperactivity of the sympathetic nerves secondary to the hyperdynamic circulation.[47] T-wave abnormalities, including flat and negative T-waves in lead II, III, avF, and V2–V4, were more frequent in these patients and 90% of subjects in the study group had tachycardia and ECG abnormalities. There was a negative correlation between haemoglobin and serum ferritin levels, and tachycardia and electrocardiogram abnormalities.[46]

A number of studies have used echocardiography to confirm changes in the myocardium. Two-dimensional echocardiography has revealed changes in the intraventricular diameter parameters. The left ventricular end-diastolic and left ventricular end-systolic diameters, left ventricular posterior wall thickness, and left ventricular mass index were significantly elevated in patients with anaemia.[27] In addition, the LV ejection fraction did not differ significantly between groups and the left atrial volume index was increased in patients with anaemia.[27] Doppler measurements have shown that the peak E velocity (Ve), peak A velocity (Va), ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/E' ratio), stroke volume, and cardiac index were elevated significantly in the anaemia group. There was no significant difference in the deceleration time of mitral inflow velocity, peak E' velocity, or peak A' velocity.[27] Goncharova and Govorin[3] reported alterations in diastolic function in the majority of LV segments with myocardial tissue, including decreased Ve, increased Va, and decreased Ve/Va during the dynamic observation of patients with severe IDA. In a previous study,[48] the global longitudinal strain, global area strain, global radial strain, and global circumferential strain of the LV by three-dimensional speckle-tracking echocardiography were measured. Results showed LV remodelling and LV systolic dysfunction in patients with haemoglobin levels in the range of 6–9 g/dL.[48]

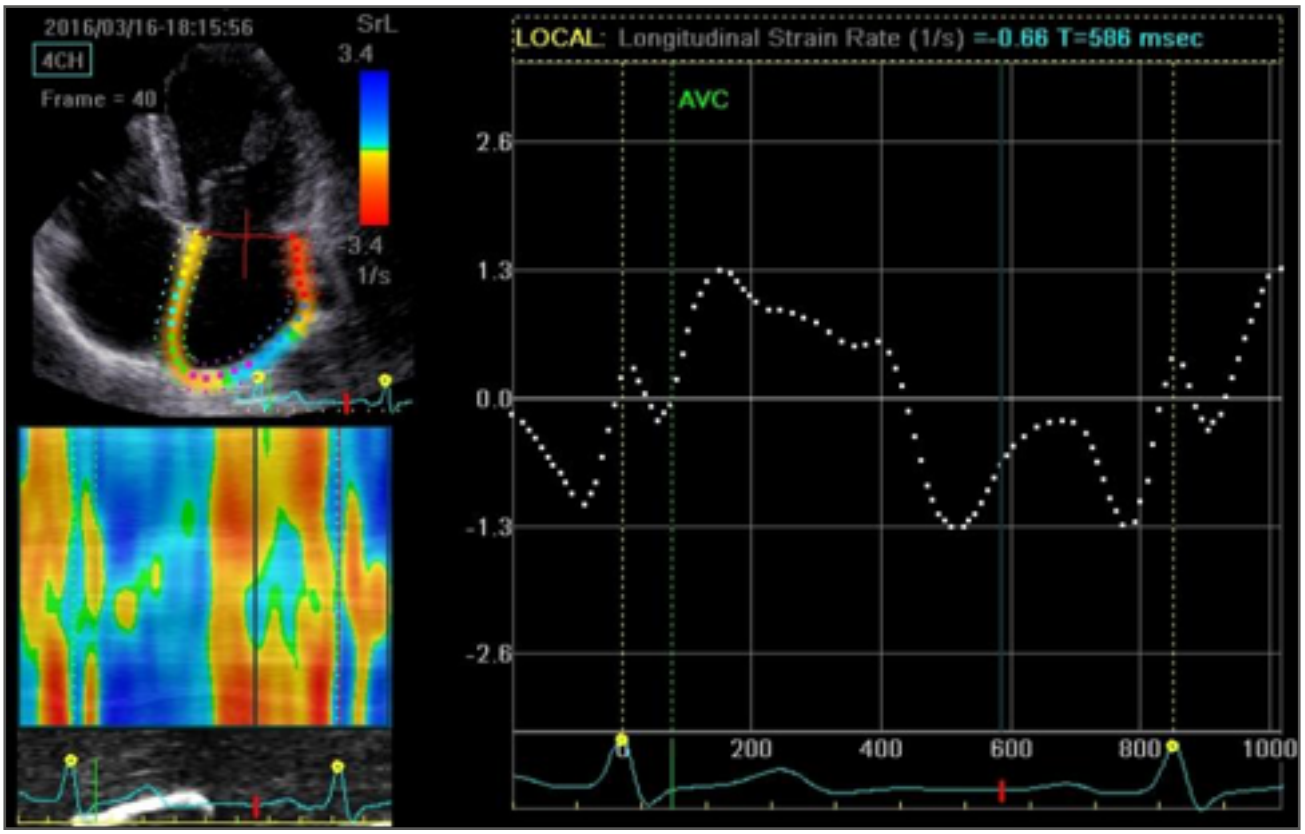

Figure 1: Global longitudinal left atrial strain rate from an apical four-chamber view of a severe iron deficiency anaemia patient.

In another study, researchers evaluated the left atrium (LA) function in patients with IDA using two-dimensional speckle-tracking echocardiography (Figure 1).[49] The new LA function parameters, global peak atrial longitudinal strain, and strain rate of the systolic LV, as well as the early and late diastolic LV strain rate curves of the LA, exerted better potential for the accurate assessment of LA dysfunction in patients with IDA.[49] The left atrial reservoir function and pipeline function have been shown to decline, while the booster pump function has been shown to increase.[49]

Nagao et al.[50] demonstrated the robust relationship between myocardial ID and nonischaemic heart failure by T2* cardiac MRI. Kurisu et al.[51] assessed the effects of haemoglobin level on the myocardial washout rate of thallium-201 (Tl-201) in patients with normal myocardial perfusion assessed by myocardial perfusion single-photon emission CT (SPECT). The haemoglobin level was inversely associated with myocardial washout rate of Tl-201 in patients with normal myocardial perfusion on SPECT. Furthermore, the myocardial washout rate of Tl-201 was in accordance with haemoglobin-regulated coronary blood flow.[51] These findings provide a new way to reveal the effects of anaemia on the myocardium.

Bellotto et al.[52] examined the relationship between haemoglobin and the risk of myocardial injury, reporting increased cardiac troponin I levels in patients with anaemia secondary to upper gastrointestinal bleeding and no other clinical signs or symptoms of coronary insufficiency on enrolment. In the context of these studies, it can be inferred that myocardial injury in patients with acute or chronic IDA can be detected and monitored early by measuring troponin I levels. This indicator is more sensitive than other indicators of myocardial damage.

TREATMENT

The cardiomyopathy of IDA may be completely reversible.[53] Sohn et al.[54] used chest electrocardiographic and radiographic images in a 66-year-old woman with cardiac hypertrophy who developed severe chronic anaemia due to long-term bloodletting with cupping. After 3 months of iron supplementation, the patient's cardiac hypertrophy improved remarkably. In another study, low haemoglobin level was associated with larger cardiac chambers, increased LV mass, and higher LV filling pressure.[27] Appropriate correction of anaemia decreased LV mass, LA volume, and E/E'. Furthermore, ferric carboxymaltose may alleviate IDA in patients for whom oral iron supplementation is ineffective.[55] A large study also found that ferric carboxymaltose was suitable for those patients who could not tolerate oral iron and effectively improved the symptoms of IDA.[56]

CONCLUSION

The present review focussed on several possible mechanisms for the development of IDA cardiomyopathy. IDA-related myocardial changes are caused by both ID and anaemia, as well as the combined effects of the two factors.[31] The myocardial changes of IDA cardiomyopathy can be detected by echocardiography and laboratory examinations. In addition, three and two-dimensional speckle-tracking echocardiography can be used to detect early changes in the LV myocardium in patients with IDA.[48,49] The laboratory index of cardiac troponin I can be used to assess myocardium damage in early IDA cardiomyopathy, which may be reversed by treatment. Ferric carboxymaltose may be a better method to supplement iron in patients with IDA. In summary, awareness of the myocardial effects in patients with IDA should be improved to help preclinical diagnosis and treatment, which have pivotal and developmental prospects in reducing morbidity and mortality. Further studies on the sex differences in the impact of IDA on cardiomyopathy are warranted.

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Treatment of Chronic Chagasic Patients: Is Killing the Parasite the Only Option?

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Abstract

Chagas disease is a tropical illness characterised by arrhythmias, heart failure, and eventually death. In approximately 10–30% of patients, chronic disease appears 10–30 years after infection onset. One of the biggest challenges for treatment is how to manage disease progression during the non-symptomatic phase to avoid the most life-threatening consequences of Chagas disease. The aim of this review is to evaluate the empirical rationale for an alternative therapy based on pathophysiological mechanisms that lead to chronic cardiac pathology and that have the possibility of evaluation through serological markers. The author identifies L-arginine serum levels, IL-2, and short-form Cha autoantibodies as possible markers for Chagas disease and discusses the reports regarding the therapeutic potential of amiodarone and angiotensin-converting enzyme inhibitors to modulate the electrophysiological, inflammatory, and vascular disturbances that lead to symptomatic Chagas disease. This review considers this discussion to improve the comprehension of therapeutic alternatives based on the vast literature detailing Chagas disease's pathophysiology.

INTRODUCTION

Chronic Chagasic cardiomyopathy (CCC) is one of the principal challenges for clinicians treating asymptomatic Chagasic patients. Only benznidazole (BZ), a DNA destabiliser, is approved by the U.S. Food and Drug Administration (FDA) for Chagas disease treatment. The drug is most prominently used in Europe for the treatment of Latin-American immigrants infected with *Trypanosoma cruzi*. There is controversy regarding the treatment of chronic phase Chagasic patients, especially considering the potential side effects associated with BZ, including granulocytopenia, rash, and digestive alterations. Additionally, in a large trial published in 2015, BZ treatment did not show a significant improvement in the outcome of Chagas disease in chronic patients.[1] Similarly, combination therapy using posaconazole and BZ in another study had no effect.[2] A study by Sguassero et al.[3] has suggested a long-term trypanocidal effect after BZ treatment but with an imprecise relationship with improvement of clinical condition.

Alternatively, non-trypanocidal therapy, implemented to avoid the symptomatic and

structural alterations associated with Chagas disease, has been suggested as a possible factor that helps control Chagasic cardiomyopathy. In this case, amiodarone, a drug used to control malignant arrhythmias in Chagas disease, was associated with the best clinical outcome when combined with BZ in the BENEFIT trial.[1] This represented an interesting finding due to the previously reported trypanocidal potential of amiodarone[4] and the possible immunomodulatory effects of these drugs.[5] In experimental models, dipyridamole (coronary vasodilator agent) and captopril (angiotensin-converting enzyme [ACE] antihypertensive agent), among others, have been associated with an amelioration of Chagasic cardiomyopathy,[6,7] which suggests their use together with trypanocidal therapy to palliate the inflammation induced by *T. cruzi* and thereby obtain clinical improvement of Chagasic patients, especially before the establishment of cardiac pathology.

This review will analyse the pathophysiological causes associated with trypanocidal effects and improvement of clinical outcome in chronic patients. In addition, an approach using adjuvant therapies that could be implemented in the early phases of infection will be proposed. Finally, the authors highlight the necessity of more clinical trials to evaluate treatment schemes for patients with concomitant cardiovascular pathology.

CHRONIC CHAGASIC CARDIOMYOPATHY: THE HOLY GRAIL OF RESEARCH IN THERAPEUTICS

Chagas disease progresses to the chronic phase in approximately one-third of infected patients; this is often 10–30 years after the first infection. CCC is the most severe consequence of chronic infection and has a deep economic impact on the healthcare system. For instance, lifetime costs per patient have been calculated at $11,619.00 per patient in Colombia[8] and global costs have been estimated at $7.19 billion per year and $188.80 billion across the total lifetime of all patients.[9] Additionally, the same study calculated the disability-adjusted life-years to be 3.57 years for Chagasic patients, which suggests a considerable loss in quality of life and work capacity as a result of this infection. Therefore, it is important to design a rational approach that allows for the avoidance of CCC development. However, this design supposes comprehension of the pathophysiological determinants of evolution to CCC, which is a goal far from being reached.

CCC is a complex condition that involves an unbalanced inflammatory process which impacts cardiac remodelling, electrical conduction, and vascular integrity, which, in turn, leads to a complex cardiomyopathy with mixed pathophysiological mechanisms normally associated with different cardiomyopathies (dilated, ischaemic, and/or hypertensive). Macroscopically, CCC is characterised by thickening of the ventricular walls and cardiomegaly, the development of small nodules around the epicardium, and intracavitary thrombus.[10] Furthermore, Suárez[10] classified the progression of CCC into four phases: normal, ambiguous, type 1, and type 2. The type 2 stage is characterised by global chamber dilatation, cavitary thrombosis with coronary sclerosis, endocardial engrossment, and apical aneurism; patients with type 2 phase CCC often die as a result of of heart failure and/or malignant arrhythmias.

The pathophysiological mechanisms driving CCC may be divided into four categories: vascular, autoimmune, oxidative, and parasite-derived.

Vascular Involvement in Chronic Chagasic Cardiomyopathy Development

The role of vasculature in Chagas disease pathology has been documented since the 1980s. Early studies reported myocardial vascular occlusion in experimental models of chronic Chagas disease.[11] Later studies demonstrated sub-epicardial and endocardial ischaemic foci,[12] coronary circulation disturbances with areas of focal vascular constriction, microaneurysm formation, vessel dilatation, and proliferation of microvessels.[13] Other work has associated endothelial infection with the activation of the NFκB pathway and the upregulation of vascular cell adhesion molecule 1 and E-selectin.[14] Additionally, endothelin 1, a potent vasoconstrictor, was secreted during parasite infection. The protein was identified in the supernatants of *T. cruzi*-infected human

umbilical vein endothelial cells.[15] Furthermore, COX-2, thromboxane synthase, inducible nitric oxide (NO) synthase, the p65 NFκB subunit, serum TNF-α, and p22 of NAD(P)H oxidase subunit expressions were increased in the vessels of Chagasic animals.[16] Moreover, *T. cruzi* promotes a systemic increase in TNF-α, which stimulates inducible NO synthase expression in vessels promoting nitrosative stress[16] and the production of IL-6 and TNF-α, which was evident in the inflammatory infiltrate in the endothelial and smooth muscle layers.[17]

Pathological changes are reflected in Chagasic patients' outcome. Vascular disorders, especially thromboembolism, have been reported for >60 years.[18] More recently, Chagasic cardiomyopathy has been associated with increased risk of ischaemic stroke.[19] CCC is often under-considered in the clinical practice, even though the prevalence of apical aneurysm and mural thrombus in Chagas disease-related stroke patients has been estimated at 37.0% and 11.7%, respectively.[20] However, stroke may be the initial manifestation of Chagas disease for many patients. Additionally, microcirculation abnormalities have been described in patients with normal coronary images. Thinning of the ventricular wall in CCC patients is related to ischaemic lesions in the peripheral territory irrigated by the right coronary artery.[21] Studies of Chagasic patients with angiographically normal coronary arteries revealed myocardial perfusion abnormalities, which are thought to be associated with microcirculatory disturbances.[22] More recently, impairment in coronary reserve was described in non-symptomatic Chagasic patients.[23] Finally, endothelial adhesion markers have been investigated for an association with CCC. Increased levels of soluble platelet-selectin, a well-known endothelial marker,[24] have been reported in CCC, reinforcing the idea that vascular dysfunction plays a key role in the development of chronic cardiomyopathy.

Oxidative Alterations in Chagasic Hearts

Mitochondrial Damage and Hypoxia

Oxidative reactions are well known mediators of cardiac disturbances during CCC. Beyond the fact that inflammation generates reactive oxygen species, the impact of infection itself regarding ischaemia and the generation of oxidative damage in cardiac cells and the possible impact of this phenomena in the evolution of CCC is further outlined below.

One of the most important organelles in cardiac functioning are the mitochondria. Different respiratory chain complexes have demonstrated increased activity in skeletal muscle mitochondria during chronic experimental infection.[25] In cardiac cells of a CCC experimental model, increases in citrate synthase activity and changes in mitochondrial structure were detected.[26] Another study has shown that there are subpatent mitochondrial changes in the evolution of indeterminate to symptomatic phase.[27] Additionally, *T. cruzi* invasion elicits Ca^{2+} overload, mitochondrial membrane electrical potential transition,[28] and a decline in the oxidative phosphorylation ability of the myocardium in a chronically infected mouse model.[29]

Mitochondrial dysfunction is closely linked to heart failure. Different pathophysiological mechanisms are associated with cardiac cell disturbances during heart failure. Intrinsic apoptotic pathways, reactive oxygen species-induced cellular damage, intracellular acidosis for anaerobic glycolysis, and ATP deficiency associated with contractility dysfunctions have been proposed as pathophysiological explanations of mitochondrial involvement in heart disease.[30] Ongoing research should shed light on the possible cause and effect mechanisms involved in Chagas disease.

Autoimmunity in Chagas Disease

Independently of mechanisms involved in parasite persistence, the chronic stimulation of the immune system generates a proinflammatory state that predisposes to autoimmunity. Over 30 years ago, the link between autoimmunity and chronic Chagas disease, especially to arrhythmias, was made. This raised the question of whether the release of intracellular autoantigens during myocytolysis originating from a parasite invasion might generate an autoimmune response and produce cardiac dysfunction. Humoral autoimmune response has been associated with cardiac pathology in chronic Chagas disease.[30] β1-adrenergic autoimmune responses have been associated with *T. cruzi* ribosomal P0 cross-reactivity[31]

and autoantibodies were shown to bind to the extracellular loop of this receptor and modulate calcium ion channels in cardiac cells[32] and have since been associated with Chagasic cardiomyopathy progression.[33] Moreover, antimuscarinic autoantibodies have been implicated in allosteric positive regulation of heart muscarinic 2 receptors.[34] This modulation altered the vagal nerve function in Chagasic patients,[35] which was postulated as a treatment response marker in children with Chagas disease,[36] although the relationship of these antibodies to ventricular dysfunction is controversial.[37] Additionally, myosin,[36,38] galectin-1,[39] cardiolipin,[40] and troponin T[41] have been reported in chronic Chagas disease, reflecting the complexity of the autoimmune response and the necessity of discriminating the role of each one in the pathology.

On the other hand, cytotoxic autoimmunity may have a role in chronic Chagasic cardiomyopathy. Autoreactive T cells, isolated from chronically infected mice, may generate unspecific alterations in heart repolarisation, cardiac inflammatory infiltration, and tissue damage when transferred to uninfected mice.[42] *T. cruzi* antigens, such as B13, cruzipain, and Cha, cross-react with host antigens at the B or T cell level.[43] These autoreactive cells can produce IFNγ and TNF-α; this characteristic may be linked to *T. cruzi*-induced IL-12 production.[31] Inflammation linked to IL-2 response, a powerful T cell mitogen, has been implicated in the genesis of malignant arrhythmias and postulated as a prognostic factor and as a possible drug marker,[5] relating for the first time in a direct way to arrhythmias and inflammation in Chagas disease. This array of autoimmune responses, in addition to proarrhythmogenic parasite secretory factors,[44] microvascular angiopathy in the brain[45] and in coronary circulation,[46] continuous parasite invasion,[47] and chronic oxidative damage to heart tissue,[48] may generate chronic cardiac dysfunction, which leads to heart failure as well as valvular and hypertrophic cardiac pathology.

Parasite Involvement in Cardiac Electrical Disturbances and Remodelling

It is well known that *T. cruzi* secretes and sheds a wide variety of glycoproteins during cellular invasion and the differences among strain secretomes have been suggested to correlate with virulence.[49] Previous work by the authors described that immunogenic proteins obtained from the secretome of *T. cruzi*, mainly of high molecular weight, were able to induce arrhythmias in an *ex vivo* isolated beating heart.[50] Calcium overload associated with parasite invasion[51] is one of the most plausible ionic mechanisms that explains the increasing action potential duration reported in cardiac cells infected with *T. cruzi*.[52] Additionally, preliminary results recently published by the authors have shown evidence of overexpression of hydrogen cyanide 1 and 4 channels in the atria and ventricles of mice during acute infection.[53]

On the other hand, since the early 2000s, *T. cruzi* persistence in cardiac tissue from endomyocardial biopsies have been linked to inflammation, necrosis, and fibrosis. *T. cruzi* infection in a three-dimensional cardiac culture model induced fibrosis through activation of the TGF-β pathway.[54] Additionally, genes associated with the immune response, inflammation, cytoskeleton organisation, cell-to-cell and cell-to-matrix interactions, apoptosis, cell cycle, and oxidative stress were among those affected during the infection of cardiac cells by *T. cruzi*.[55] Taken together, these results suggest that parasite persistence may contribute to the pathophysiology of fibrosis and inflammation in chronically infected mice.

Neurohumoral and Autonomic Pathogenic Mechanisms

Chagas disease pathophysiology is a complex mix of mechanisms that lead to severe consequences in a portion of chronically diseased patients. One of the oldest theories regarding the generation of CCC is the imbalance of the autonomic nervous system.[56] In the following years, parasitism in the sympathetic ganglionic chain was described in experimental models,[57] which was associated with heart rate dysregulation in Chagasic patients[58] and autoimmunity directed against neuronal tissue.[59] More recently, control of orthosympathetic dysfunction has been linked to the improvement of arrhythmogenesis[60] and chronic heart remodelling.[61]

A RATIONAL APPROACH FOR THE TREATMENT OF CHRONIC CHAGASIC CARDIOMYOPATHY

One of the principal challenges facing physicians treating patients with Chagasic disease is how to explain the diagnosis to the patient, which is especially difficult if they are not symptomatic. With a 10–30% probability of sudden death or developing heart failure over the long-term, toxicity is an important factor to consider when analysing the efficacy of conventional therapies.

Prognosis Factors in Chronic Chagasic Cardiomyopathy

One of the most challenging issues for the treatment of CCC patients is discriminating which patients are at risk of developing heart failure and/or dying suddenly and which are not. Several authors have contributed to the identification of markers that are associated with clinical outcome. Left ventricular systolic dysfunction and non-sustained ventricular tachycardia have been identified as principal predictors of myocardial damage in CCC.[62] Additionally, heart rate turbulence, turbulence onset, and turbulence slope are strong risk predictors of sudden death.[63] Alternatively, another paper has proposed QT-interval dispersion, syncope, ventricular extrasystoles, and severe dysfunction of the left ventricle as the strongest indicators of sudden death.[64]

Left atrial volume has been shown to provide powerful prognostic information incrementally and independently of clinical data and conventional ECG parameters, allowing for the prediction of chronic Chagasic disease patient survival.[65] Moreover, determination of ACE2 activity provided a new and important diagnostic and prognostic marker for patients with Chagas disease.[66]

One of the principal problems of the aforementioned prediction factors is their relative complexity for a large-scale survey of Chagasic patients at risk of sudden death/heart failure. The authors have proposed several markers to identify patients at risk of heart failure and/or Chagas disease. Based on the pathophysiological model, the authors have explored serological markers of sudden death and heart failure.

Autoimmunity and Inflammation as Predictive Markers of Sudden Death

Sudden death is the principal cause of death for Chagas disease patients, which is especially concerning because most cases are asymptomatic. A key issue for physicians is identifying and monitoring a marker that can orientate the treatment of asymptomatic patients. Based on recent work, the Cha transcription factor is an interesting candidate for a prognostic marker. Cha is a ubiquitously expressed member of the class C basic helix-loop-helix family; expression of the protein and its binding to the CD2 promoter region negatively correlated with CD2 expression in T cells after mitogenic stimulation, whereas overexpression of Cha inhibited CD2 expression.[67] It has been reported that *T. cruzi*-infected mice contain autoreactive T cells that can cross-react with Cha and the shed acute-phase antigen homologous peptides. Transfer of T cells from infected mice into noninfected counterparts triggered anti-Cha antibody (with an epitope targeting residues 120–129) production in naïve recipients, causing cardiac pathology similar to *T. cruzi*-infected mice.[68] The authors have demonstrated that higher anti-short form Cha antibodies levels are present in Chagasic patients from Colombia and Venezuela with a higher risk of sudden death.[69] Measurement of anti-short form Cha antibodies levels, through an conventional ELISA assay, may help to identify non-symptomatic patients at risk of sudden death.

Furthermore, the role of inflammation in arrhythmias was explored using a mathematical model. A multiplex array of cytokines was developed (IL-2, IL-6, IL-4, IL-10, IL-17, TNF, and IFN-γ) to identify discriminant variables to clinical and treatment evolution. IL-2 was identified as the principal discriminatory variable to evaluate sudden death risk and amiodarone treatment response.[5] Interestingly, IL-2 release induced stretching of the tissue, which led to the appearance of abnormal bioelectrical activity, causing an increase in action potential duration at the levels of 90% repolarisation.[70] Additionally, IL-2 has been associated with an upregulation of SCN3B expression and a resultant increase in sodium current density.[71] Myocarditis and near fatal arrhythmias during high dose IL-2

therapy for metastatic renal cancer were recently reported,[72] which reinforces the potential use of IL-2 levels as a marker for arrhythmias in Chagasic patients.

Markers of Vascular Function in Chronic Chagasic Cardiomyopathy

CCC evolution must be addressed to identify non-symptomatic patients. A key tool for the assessment of vascular function is L-arginine plasmatic levels. Plasmatic levels of L-arginine and the asymmetric dimethylarginine (ADMA), a competitive inhibitor of NO synthase, have been associated with heart failure, demonstrating that the lower L-arginine to ADMA ratio indicates less available NO and suggesting that NO-related endothelial dysfunction may play a role in the adverse risk of heart failure progression.[73] Additionally, the use of the L-arginine to ADMA ratio for evaluating postoperative outcome in patients after heart transplant has been reported.[74] For Chagas disease, Carbajosa et al.[75] demonstrated reduced plasmatic levels of L-arginine in mice during acute infection and increased survival rates when the mice were supplemented with 3.75 mg/kg of L-arginine in drinking water.[75] Based on this previous work, the role of the L-arginine to ADMA ratio as indicator of heart failure in Chagasic patients has been proposed. Some preliminary, unpublished results support this perspective. Based on pathophysiology, Figure 1 and Table 1[1,4,74-80] summarise the possible serological markers for identification of potential candidates for treatment during Chagas disease.

EMPIRICAL RATIONALE FOR AN APPROACH FOR INDETERMINATE AND CHRONIC CHAGASIC CARDIOMYOPATHY PATIENTS

Based on the pathophysiology of Chagas disease and recent work, possible therapeutic alternatives to current treatments that may help to alleviate the effects of Chagas disease are outlined in the following sections.

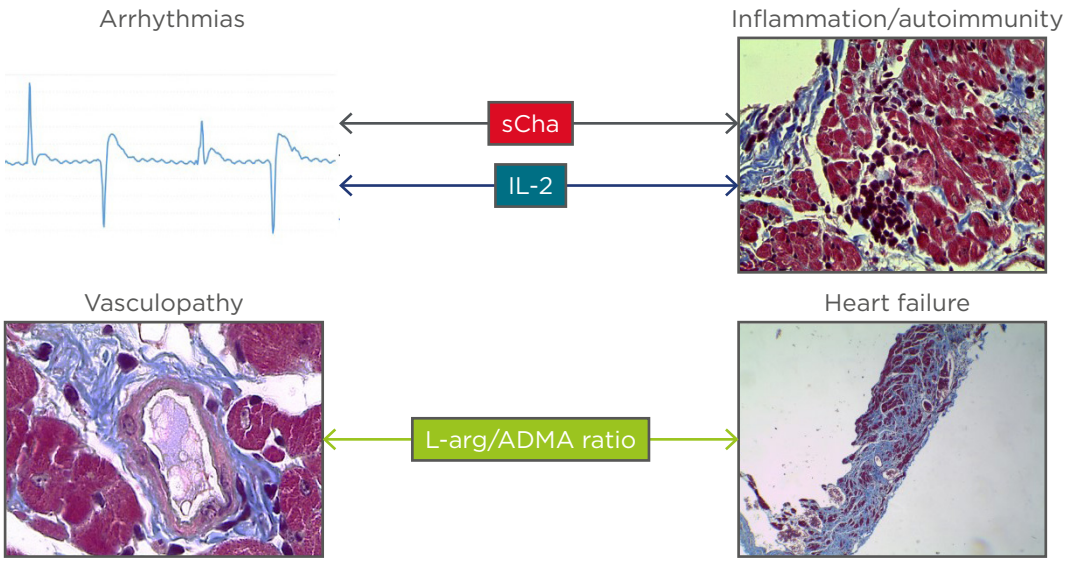

Figure 1: Short form Cha, IL-2, and L-arginine/asymmetric dimethylarginine ratio are proposed as evolution markers for non-symptomatic Chagasic patients.

As described in the main text, sCha (a T cell transcription factor) autoantibodies have been associated with autoreactive T cell infiltration and high sudden death risk in Chagasic patients, being considered a potential prognosis marker for malignant arrhythmias in Chagas disease. On the other hand, IL-2, a potent mitogen of T cells, has been associated with sudden death and atrial fibrillation in Chagasic patients and other cardiac pathologies, suggesting that this cytokine is an inflammatory marker that may be detected during the non-symptomatic phase. These facts are summarised by the arrows connecting markers to the relevant pathophysiological processes. Finally, L-arginine/ADMA ratio is proposed as a marker of endothelial function and may indicate heart failure risk in Chagasic patients.

ADMA: asymmetric dimethylarginine; L-arg: L-arginine; sCha: short form Cha.

Table 1: Summary of listed evolution markers for chronic Chagas disease.

Study	Marker	Pathophysiological process involved	Outcome targeted
Lundgren et al.,[74] 2018; Carbajosa et al.,[75] 2018; Rajão et al.,[76] 2015	sCha	Cellular autoimmunity	Arrhythmias, sudden death
Adesse et al.,[4] 2011; Santeliz et al.,[7] 2017; Kratz et al.,[77] 2018; Benaim et al.,[78] 2006	IL-2	Cellular	Amiodarone efficacy, sudden death
Morillo et al.,[1] 2015; Adesse et al.,[4] 2011; Carmo et al.,[79] 2015; Matsumori et al.,[80] 1997	L-arginine	Endothelial activation	Heart failure, myocardial ischaemia
Morillo et al.,[1] 2015; Adesse et al.,[4] 2011; Carmo et al.,[79] 2015; Matsumori et al.,[80] 1997	Asymmetric dimethylarginine	Endothelial activation	Heart failure, myocardial ischaemia

sCha: short form Cha.

Benznidazole and Nifurtimox: Old-Fashioned Therapy with a New Approach

BZ and nifurtimox are the standard treatment for Chagas disease. Both therapeutics exploit free-radical generation to generate nitrosative damage in the developing parasite. BZ induces oxidation, mainly in the nucleotide pool, and catalyses the generation of double-stranded breaks in the parasite DNA, caused by the induction of extensive heterochromatin unpacking of the parasite genome. Finally, it has been reported that BZ induces lesions in the mitochondrial DNA.[76] As previously stated, one of the most limiting factors preventing BZ use is the high rate of treatment discontinuation due to side effects; furthermore, the therapeutic efficacy of BZ in chronic Chagasic patients is still a matter of debate. As a result, shorter or intermittent dosing regimens of BZ treatment or combining BZ and nifurtimox with new chemical entities have been proposed.[77] What follows is a short summary of possible therapeutic alternatives to improve the efficacy of BZ during the treatment of non-symptomatic Chagas disease.

Amiodarone: A Polyvalent Tool for Treatment a Variable Pathology

Amiodarone is considered a 'dirty' drug in virtue of the multiple mechanisms of action the drug exhibits. Reported amiodarone actions include a) the inhibition of inward sodium and calcium currents, b) blockage of voltage and ligand-gated potassium channel currents, c) downregulation of Kv1.5 messenger ribonucleic acid (mRNA), and d) nonselective downregulation of β adrenoceptors during chronic administration. Moreover, amiodarone has been postulated as a trypanocidal drug[76] with a profound effect on intracellular amastigotes, including mitochondrial swelling and disorganisation of reservosomes and the kinetoplast and a blockade of amastigote-trypomastigote differentiation.[4] Statistical differences in parasitaemia were not detected in Chagasic patients treated with amiodarone.[80] However, in a large-scale study,[1] BZ administration combined with amiodarone appeared to benefit the patient.

Amiodarone is associated with anti-inflammatory effects. Matsumori et al.[80] conducted one of the first reports that linked amiodarone and inflammation, showing amiodarone triggered the reduction of TNF release by peripheral blood mononuclear cells.[80] This was followed by the

proposal that amiodarone dose-dependently exerts a powerful anti-inflammatory activity, possibly due to the activation of NO as a result of calcium channel antagonism, to the inhibition of phospholipase A2, and/or a reduction in neutrophil movement and activation, which is thought to reduce free radical production and proteolytic enzyme release.[81] More recently, it was proposed that, through regulation of AP-1 and NFκB signalling, amiodarone inhibits the production of IL-2, TNF, and IFN-γ, and prevents T cell activation.[82] This last result is closely associated with the role of IL-2 as an indicator of amiodarone treatment as reported in Chagasic patients,[5] and it strongly suggests a possible role of amiodarone treatment beyond channel modulation capacity. The findings make the drug an important tool to consider in the prevention of cardiac remodelling and sudden death because of Chagas disease. The determination of an amiodarone treatment pattern to avoid the chronic toxicity associated with amiodarone treatment is yet to be confirmed.

Angiotensin-Converting Inhibitors: A Cheap Weapon for an Elusive Enemy

The ACE inhibitor (ACEI) family of antihypertensive agents are among those most widely used in antihypertensive therapy. ACEI are particularly effective when reducing proteinuria and improving outcomes in chronic heart failure.[83] Beyond their classically reported effects, ACEI have a range of action mechanisms, more of which have been expanded upon in recent years. It has been shown that captopril induces a dose-dependent reduction of total and differential white blood cell counts, while it improved serum oxidant/antioxidant biomarkers and histopathological changes in lipopolysaccharide-treated rats.[84] However, there has been doubt cast on the evidence indicating that ACE reduces the plasma level of major inflammatory markers in hypertension models.[85]

The most promising data have been described for the use of ACEI for Chagas disease. In an experimental approach, it was proposed that a combination treatment of BZ plus enalapril was able to increase the IL-10 levels and reduce the cardiac inflammation while BZ inhibited collagen neogenesis at the infection site[86] and reduced cardiac leukocyte recruitment, total collagen in the cardiac tissue, chemokines, creatine kinase, creatine kinase muscle to brain ratio, and C-reactive protein levels in an experimental model of chronic phase disease.[87] Conversely enalapril alone treatment alone a reduction in serum levels of IFN-γ, TNF-α, CCL5/RANTES, and NO, but not in that of IL-10.[88] However, in contradiction to other work, Coelho dos Santos et al.[89] reported that captopril interferes with the host-parasite equilibrium by enhancing infection of monocytes and decreasing the expression of the modulatory cytokine IL-10, while guiding development of the proinflammatory Th17 subset.

In Chagasic patients, it has been proposed that treatment with enalapril, spironolactone, and the subsequent addition of carvedilol is safe and associated with beneficial effects on cardiac function and clinical status.[90] This finding is closely related with results that associate plasma ACE2 activity with their clinical severity and echocardiographic parameters, resulting in a significantly increase in Chagas diseased patients with heart failure but not in patients without systolic dysfunction.[66] With these data in mind, it is plausible to propose ACEI treatment, especially in hypertensive patients, in order to control the endothelial dysfunction in indeterminate risk patients and reduce the risk of developing CCC. Figure 2 shows the summary of the treatment proposed to indeterminate Chagas diseased patients.

Beta-Blockers and Mineralocorticoids Receptor Antagonists

Beta-blockers and mineralocorticoids are widely used to treat heart failure and cardiac remodelling. These drugs show a wide range of action mechanisms and therapeutic uses and are therefore interesting candidates to be considered for CCC treatment.

Beta-blockers available for clinical treatments have variable affinity for β1 and β2 receptors, and in some cases exclusively for β3, although there is an overall emphasis on the β1 receptor, the most prevalent subtype of adrenergic receptors in the heart. Carvedilol is a nonselective beta-blocker indicated in the treatment of mild-to-moderate congestive heart failure. It blocks β1 and β2-adrenergic receptors as well as the α1-adrenergic receptors. In experimental models, carvedilol did not attenuate cardiac

remodelling or mortality in this model of Chagas cardiomyopathy, but the treatment did improve survival during the acute phase of the disease.[91] Moreover, in a c57bl/6 mouse model of infection, carvedilol therapy did not alter the levels of circulating parasites. Instead, the drug modulated the pattern of CCL2 and IL-10 mediators.[92] An extensive meta-analysis, however, concluded that there were no conclusive data to support or reject the use of either carvedilol for treating Chagas cardiomyopathy,[93] although individual clinical trials suggest beneficial effects.[94,95] Interestingly, carvedilol alone and in combination with vitamins C and E was effective at attenuating the systemic oxidative stress in patients with Chagas heart disease, especially those less severely affected, thus suggesting the possibility of synergism between these compounds[96] and opening a window for future explorations.

Propranolol is a widely used noncardioselective β-adrenergic receptor antagonist used in the treatment and prevention of many disorders, including acute myocardial infarction, arrhythmias, angina pectoris, hypertension, hypertensive emergencies, hyperthyroidism, migraine, pheochromocytoma, menopause, and anxiety. Recently, propranolol has been linked to the impairment of lysosome spreading and prevention of *T. cruzi* invasion in HeLa cells.[97] However, despite this evidence, the development of a sufficiently extensive clinical programme that allows for the establishment of beta-blockers' clinical efficacy in treating CCC remains elusive.

Finally, mineralocorticoid receptor antagonists (MRA) are often used as potassium preserving diuretics in the treatment of heart failure and ascites. However, there are few reports about the use of MRA for treating CCC. In experimental models, it has been proposed that spironolactone attenuated myocardial remodelling in Chagas cardiomyopathy, reduced mortality during the chronic phase, and reduced inflammatory infiltration in a Sirius hamster model.[98] Interestingly, a report that suggested the improvement of cardiac function in CCC patients cotreated with spironolactone[90] and ACE inhibitors was highlighted, suggesting MRA as adjuvant therapy in CCC heart failure. It is necessary to generate more evidence to determine the efficacy of MRA in treatment of CCC.

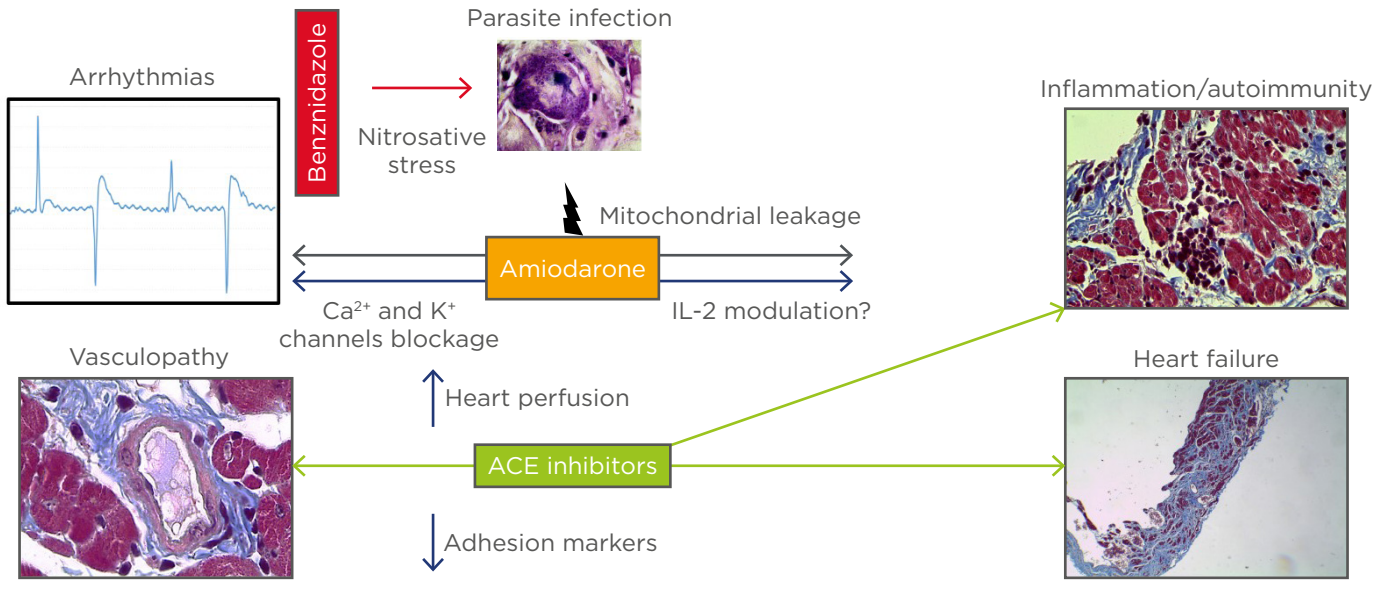

Figure 2: Therapeutic alternative proposed for chronic Chagasic patients.

In addition to parasite replication control with benznidazole, amiodarone treatment may provide a parasiticidal synergistic effect, together with the well-known anti-arrhythmic activity and the recently proposed anti-IL-2 effect. ACE inhibitors have also been associated with a reduction in inflammation, probably due to endothelial transmigration blocking, additional to these effects in preventing cardiac remodelling and heart failure.

ACE: angiotensin converting hormone.

CONCLUSION

Treatment of indeterminate patients is one of the most complex issues in Chagas disease and represents a challenge for clinicians. This review explored an approach for treating Chagasic patients during indeterminate phase considering several variables: a) pathophysiology of CCC, b) experimental and clinical reports, and c) accessibility of treatment for CCC. It is especially important to consider the fact that, in the longest clinical trial to date (BENEFIT),[1] BZ treatment alone was not able to improve clinical outcome, supporting the proposal of combination parasiticide therapy with drugs that allow for the improvement of vascular function, the modulation of the immune response, electrophysiological alteration in CCC, and, importantly, that are associated with putative serological markers for evaluating drug efficacy. In this review, alternative therapeutics (amiodarone and ACEI) that may be considered as first-line treatment when the clinical indication for their original usage exists were highlighted. Amiodarone, in particular, is a plausible option for patients with reduced ejection fraction and/or symptomatic arrhythmias, when clinically indicated,[99] and, when feasible, therapy should be combined with ACEI agents to reduce cardiac remodelling through immunomodulation or inclusive parasite replication control. The currently available data may allow for the introduction of these new approaches without expensive trials. However, it may be necessary to conduct more extensive research in order to define treatment strategies, possible adverse effects, and, if it is necessary, to develop different therapeutic schemes for the mixed clinical presentations (gastrointestinal or cardiac forms) or for patients with concomitant cardiovascular pathologies (diabetes, atherosclerosis, or hypertension).

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