EMJ EUROPEAN MEDICAL JOURNAL

CARDIOLOGY

ISSN 2053-4213 — Vol 7.1 • October 2019 • europeanmedical-journal.com

+ Review of ESC 2019

Paris, France

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"Cardiovascular diseases are the world's biggest killer, and despite the rapid and continued advancement in the field, there is still a significant patient need."

Spencer Gore, CEO

Editorial Board

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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.

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European Medical Journal Cardiology is published once a year. For subscription details please visit: www.europeanmedical-journal.com

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EMJ Cardiol. 7.1

EMJ Interventional Cardiology 2019

This eJournal focusses on the key findings from the congress, with a range of reviews and highlights, as well as some special features that delve deeper into EuroPCR.

VIEW ALL JOURNALS ←

Welcome

It is with great pleasure that I welcome all our readers, collaborators, and friends to *EMJ Cardiology 7.1*, an anticipated addition to our growing list of 2019 publications that features a comprehensive review of the European Society of Cardiology (ESC) meeting held in Paris, France. Boasting an enormous attendance and an equally diverse range of sessions, this was an event replete with ground-breaking findings, which we are immeasurably pleased to present to you in these pages.

Throughout our review, you will find out more about some of the most exciting breakthroughs presented at the meeting, including evidence of how microbes may contribute to the destabilisation of coronary plaques, and an update on the ESC guidelines on environmental and psychosocial impacts on heart disease. Also included is an informative interview with ESC Publications Committee Chairperson Thomas F. Lüscher, who provides expert insight into the role of society-affiliated journals and how this landscape is changing in modern times. We have also included our in-house feature on the potential of digital technology to help transform cardiovascular care.

As always, we have included a selection of abstract summaries from the congress which we believe deserve special mention. Hsu et al. present data from their nationwide cohort study revealing the effect of de-escalated switching dual antiplatelet therapy after acute myocardial infarction in patients undergoing percutaneous coronary intervention, and Hewitt et al. provide a summary of artificial intelligence in echocardiography for standard clinical metrics: both summaries I am certain the cardiovascular community will be eager to read.

A varied range of peer-reviewed articles aptly complement our congress review. Gheorghe et al. delve into the topic of tricuspid regurgitation, commenting on its new recognition as an important predictor of mortality in patients with left-side valvular or myocardial disease. Berezin provides an in-depth analysis of circulating cardiac biomarkers in heart failure and their application in biomarker-guided therapy, whilst Kosmas et al. investigate the role of lipoprotein(a) in calcific aortic valve stenosis, an important paper which aims to emphasise the need for better understanding of the complex molecular processes implicated in the disease.

Cardiovascular diseases are the world's biggest killer, and despite the rapid and continued advancement in the field, there is still a significant patient need. We hope that this publication goes some way to contributing to the global effort to advance cardiovascular understanding, and that you, as our readers, manage to take something from this edition and implement it into your daily research or clinical practice. Enjoy!

Spencer Gore

Chief Executive Officer, European Medical Group

Foreword

Dear colleagues,

The European Society of Cardiology (ESC) Congress was held in collaboration with the World Congress of Cardiology (WCC) in Paris, France, spotlighting global cardiovascular health and the differences in prevention, diagnosis, and management of cardiovascular disease worldwide. It has been an exciting year for scientific developments in cardiology, and without further ado, I proudly present to you *EMJ Cardiology 7.1*.

For those of you who were unable to attend ESC, or would like to relive the highlights, in this issue we present congress stories and features from this year's event, and an interview with the Chairperson of the ESC Publications Committee. A host of late-breaking research was presented at the congress, such as the study detailing decreased levels of sports-related cardiac-deaths due to increased bystander resuscitation. For more highlights of ESC, I recommend the abstract review summaries, which include the utility of artificial intelligence in echocardiography and the genetic reprogramming of cardiac fibroblast into induced cardiomyocyte precursor cells.

In the following pages, you will also find an immersive array of peer-reviewed articles that focus on the hot topics and advances within cardiology. For the interventional cardiologists among you, Salazar et al. provide a case of an angiography guidewire fracture within the left anterior descending artery and explores the options for management of the rare, yet serious, complication to avoid future guidewire associated complications.

My Editor's Pick for this edition by Kosmas et al. examines the scientific and clinical evidence of lipoprotein(a) in calcific aortic valve stenosis. As the only monogenetic risk factor for aortic valve calcification and stenosis, lipoprotein(a) has received increased attention and improved understanding of its clinical relevance could significantly reduce the risk of aortic valve stenosis progression.

Another valued addition is the informative review by Tucker and Patel which focusses on the role of specific chemokines in plaque regulation. The prevalence of atherosclerotic diseases is increasing globally; therefore, a discussion on the potential of manipulation chemokine pathways as prospective therapeutic targets for plaque stabilisation is vital.

I hope you all enjoy reading *EMJ Cardiology 7.1,* which will prove an informative and inspiring read and a source of information to assist in daily practice.

Dr Çetin Erol

Ankara University, Turkey

Congress Review

Review of the European Society of Cardiology (ESC) Congress 2019 with the World Congress of Cardiology (WCC) 2019

Location: Paris Expo Porte de Versailles – Paris, France

Date: 31st August – 4th September 2019

Citation: EMJ Cardiol. 2019;7[1]:10-23. Congress Review.

The beating heart of France, complete with an abundance of unmistakably Parisian architecture, created the beautiful backdrop to this year's European Society of Cardiology (ESC) congress, as they were joined by the World Congress of Cardiology (WCC). Amongst the eclectic array of art, history, and culture, Paris in the height of summer is an image synonymous with romance, creating the perfect setting for an influx of attendees with a vested interest in affairs of the heart.

This year, the ESC congress was, as always, an incomparable event for cardiologists around the world. As the world's biggest cardiology event, they had to open with a bang: featuring instruments from across the world, playing to the rhythm of cardiovascular health. They shone a spotlight on global cardiovascular health at the event, with particular focus on differences in prevalence, strategies for prevention, clinical manifestations, diagnostic modalities, and cardiovascular disease management across the globe.

The EMJ team, along with the 30,000 attendees at the event, were spoilt for choice, with >500 sessions on offer across the 5-day event. For those who were unable to attend the event, and those who did attend and want to re-experience the highlights from ESC, we have selected a range of late-breaking research stories, abstract presentations, and congress sessions to cover in our annual review of ESC.

A host of late-breaking research was presented at ESC: from a decline in sport-related cardiac arrest death due to increased incidence of bystander resuscitation to a link between microbes and the destabilisation of coronary placques. Caregivers were also a hot topic at the event, with research presented on depression in this group as a predicter of health problems in the future. Another study of interest explored the use of ticagrelor and aspirin in the reduction of ischaemic events in patients with stable coronary artery disease and diabetes.

Our hand-picked selection of abstracts from ESC have been written up in summaries, penned by the authors themselves to provide a first-hand account of the research. These explore a range of cardiovascular topics including antiplatelet therapy and oral anticoagulation in transcatheter aortic valve replacement; artificial intelligence in echocardiography; and the regulation of a catecholamine-dependent altered cAMP signalling in a patient-specific induced pluripotent stem cell Takotsubo-model.

ESC's spotlight on global cardiovascular health was a big focus of the Congress, further exploring the worrying statistic that eight out of ten cardiovascular disease deaths occur in low and middle-income countries. This is an important area for focus for ESC, and they are actively working to improve cardiovascular health worldwide: they are uniting 57 national cardiac societies, 28 sub-speciality communities, and >100,000 individual members.

As the digital era seemingly takes over every aspect of our lives, health is no exception; consequently, digital health was an extremely hot topic at ESC this year, with particular focus on wearable devices, data protection and ethics,

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and implementation of digital health into daily practice. This topic forms one of our congress features, as we consider the impact of an increasingly digital world on healthcare.

2019 saw ESC updating five sets of their guidelines, and these were a prominent focus at the congress. Their guidelines on chronic coronary syndromes were published on the 31st August, covered in our congress review. The baleful impact of pollution and noise on patients with coronary syndromes were exemplified: a first for the guidelines.

ESC, along with the WCC, put on a fantastic event this year and we really were spoilt for choice in choosing the content for our review of the congress. Looking ahead to next year, Amsterdam, the Netherlands, will play host to ESC 2020, which is sure to be another unmissable event on the calendar of anyone with a keen interest in cardiology. But for now, without further ado, we present our review of ESC 2019.

ESC 2019 REVIEWED →

Additional Non-Culprit Lesion Intervention Offers Greater Cardiovascular Outcomes

RESULTS from the COMPLETE trial presented in an ESC press release dated 1st September 2019 concluded that complete revascularisation reduced clinical events in patients with ST-segment elevation myocardial infarction (STEMI) compared to patients that did not receive additional revascularisation of non-culprit lesions.

Multivessel coronary artery disease is defined as the presence of multiple narrowed arteries, non-culprit arteries, following myocardial infarction (MI), in addition to the causative artery, known as the culprit artery. Percutaneous coronary intervention (PCI) is used to widen the culprit artery to reduce adverse clinical outcomes such as cardiovascular death or MI. As many as 50% of STEMI patients are afflicted by multivessel coronary artery disease; this trial ascertained the preventative effect of additional non-culprit lesion PCI against major cardiovascular events, the results of which had not yet been explored in any single, large study.

The trial enrolled 4,041 patients from 31 countries with STEMI and multivessel coronary artery disease who were randomly allocated to one of two groups: complete revascularisation with PCI of angiographically significant non-culprit lesions, or revascularisation alone. Random allocation was organised by proposed timings of non-culprit lesion PCI as before or after primary hospitalisation. The first co-primary outcome was cardiovascular death or MI and the second co-primary outcome encompassed ischaemia-driven revascularisation.

After a median of 3 years, the follow-up indicated that 158 patients (7.8%) in the group who received complete vascularisation of both culprit and non-culprit lesion PCI exhibited first co-primary outcomes compared to 213 patients (10.5%) in the culprit-lesion only group (hazard ratio 0.74; 95% confidence interval: 0.60–0.91; p=0.004). Furthermore, the second co-primary outcome occurred in 179 patients (8.9%) in the complete revascularisation group and in 399 patients in the group that did not receive complete vascularisation (hazard ratio 0.77; 95% confidence interval: 0.59–1.00).

"COMPLETE is the first randomised trial to show that complete revascularisation reduces hard cardiovascular events compared to culprit-lesion only PCI in patients with STEMI and multivessel coronary artery disease," commented principal investigator of the study Prof Shamir R. Mehta, Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada. "These findings are likely to have a large impact on clinical practice and prevent many thousands of recurrent heart attacks globally every year," Prof Mehta reflected.

"These findings are likely to have a large impact on clinical practice and prevent many thousands of recurrent heart attacks globally every year,"

Microbes may Contribute to the Destabilisation of Coronary Plaques

ACCORDING to the results presented at ESC, in a press release dated the 31st of August, micro-organisms in the body may contribute to the destabilisation of coronary plaques and subsequent heart attack.

Previous research indicates that factors such as age, diet, medications, smoking, and pollution have an adverse impact on cell physiology, the immune system, and metabolism and that these effects are mediated by micro-organism in the intestinal tract. Therefore, the study, which took place at the Catholic University of Sacred Heart, Rome, Italy, investigated the impact of the microbiota to the instability of coronary plaques.

"The varying chemicals emitted by these bacteria might affect plaque destabilisation and consequent heart attack."

In the study, 30 patients with acute coronary syndrome and 10 patients with stable angina were enrolled. Isolated gut bacteria from faeces samples and coronary plague bacteria extracted from angioplasty balloons were compared and revealed a difference in the microbiota between the two sites. While faecal bacteria showed a heterogeneous composition and a noticeable presence of *Bacteroidetes* and *Firmicutes*, the composition of coronary plaques primarily consisted of microbes with proinflammatory characteristics belonging to *Proteobacteria* and *Actinobacteria*. These findings suggest a selective retention of proinflammatory retention in atherosclerotic plaque that could provoke an inflammatory response and plaque rupture.

Further discovered in the analyses was a difference in gut microbiota between the two patient groups. *Firmicutes*, *Fusobacteria*, and *Actinobacteria* were primarily present in those with acute coronary syndrome, while *Bacteroidetes* and *Proteobacteria* were predominant in those with stable angina. Dr Eugenia Pisano, Catholic University of Sacred Heart, noted: "we found a different make-up of the gut microbiome in acute and stable patients. The varying chemicals emitted by these bacteria might affect plaque destabilisation and consequent heart attack. Studies are needed to examine whether these metabolites do influence plaque instability."

Dr Pisano concluded that, while this was a small study, the results proved valuable because they implicate that microbiota in the gut and coronary plaque might have pathogenetic functions in the plaque destabilisation process and may become potential therapeutic targets.

"air pollution and environmental noise increase the risk of heart attack and stroke, so policies and regulations are needed to minimise both."

Environmental and Psychosocial Aspects of Heart Disease and Pollution and Noise Reduction Advised in ESC Guidelines

THE ESC guidelines on chronic coronary syndromes were published on the 31st August. For the first time, the baleful impact of pollution and noise on patients with coronary syndromes were exemplified.

Chairperson of the Guidelines Task Force and director of the Turku PET centre, Turku, Finland, Prof Juhani Knuuti said "air pollution and environmental noise increase the risk of heart attack and stroke, so policies and regulations are needed to minimise both." Compared to the previous document, lifestyle changes have a bigger focus to prevent worsening of chronic coronary syndromes because unhealthy behaviours will have contributed to the development of coronary artery disease (CAD).

As a continuation of the preceding stable CAD guidelines, the document further covers chronic coronary syndromes. Patients are advised to quit smoking, avoid passive smoking, and eat a vegetable, fruit, and whole grain rich diet and limit saturated fat and alcohol consumption. Furthermore, because CAD patients have a 2-fold higher risk of mood and anxiety disorders, improvements in lifestyle and adherence to medications presents as a challenge. For this reason, counselling is encouraged for those with depression, anxiety, or stress. Prof Knuuti also states that "patients need to take medications as prescribed even if they have no symptoms. Promoting behaviour change and medication adherence should be part of each appointment with general practitioners or specialists including nurses and cardiologists."

As the diagnosis of chronic coronary syndromes has significantly advanced since the release of the previous guidelines, the most encountered clinical scenarios were also outlined. Fellow Chairperson of the Guidelines Task Force and professor in interventional cardiology at the Lambe Institute for Translational Medicine, Galway, Ireland, Prof William Wijns stated that "each of these scenarios requires different diagnostic and therapeutic approaches. But in general, treatment of a chronic coronary syndrome demands long-lasting healthy habits, medication adherence, and interventions in selected patients."

Hospitalisations of Atrial Fibrillation Patients Reduced Through Home-Based Education

AN AGEING population, accompanied by the acquisition of lifestyle-related comorbidities such as sleep apnoea and obesity, has led to an increased prevalence of atrial fibrillation (AF) to which healthcare services must tackle. Accounting for more hospitalisations than either heart attack or heart failure, there has been a shift in focus towards managing the disease through the provision of home-based education as a means of lessening the patient and clinician burden. Now, findings presented in a press release, on the 1st September, at ESC, attest to the effectiveness of this approach.

In the HELP-AF study, 627 AF patients from 6 hospitals from Adelaide, Australia, were enrolled and allocated the HELP-AF programme or usual care within 2 months of their emergency presentation. The intervention arm received two educational home visits by a pharmacist or nurse: the first 2 weeks after enrolment, and the second 6 weeks after that. The sessions revolved around education into:

1. Management of future AF episodes.
2. Optimal medicine use to manage symptoms and stroke risk.
3. The role of personalised lifestyle modification.

Over 24 months, the HELP-AF group presented with 233 unplanned hospitalisations compared to 323 in the usual care group, with an incident ratio of 0.74 (95% confidence interval: 0.62–0.89; p=0.001). Following adjustments for multi-variables, the education programme reduced total unplanned hospitalisations by 26%, cardiovascular hospitalisations by 49%, and AF-related hospitalisations by 31%.

Principal investigator Prof Prash Sanders from the University of Adelaide, Adelaide, said: "the study shows that education delivered in a structured and individualised way within the patient's home has a dramatic impact not only on hospitalisations for AF, but on all cardiovascular hospitalisations."

The standardised design of the protocol and its prospectively easy replication in other countries and settings holds great promise for helping provide the personalised therapeutic attention that this patient demographic clearly needs.

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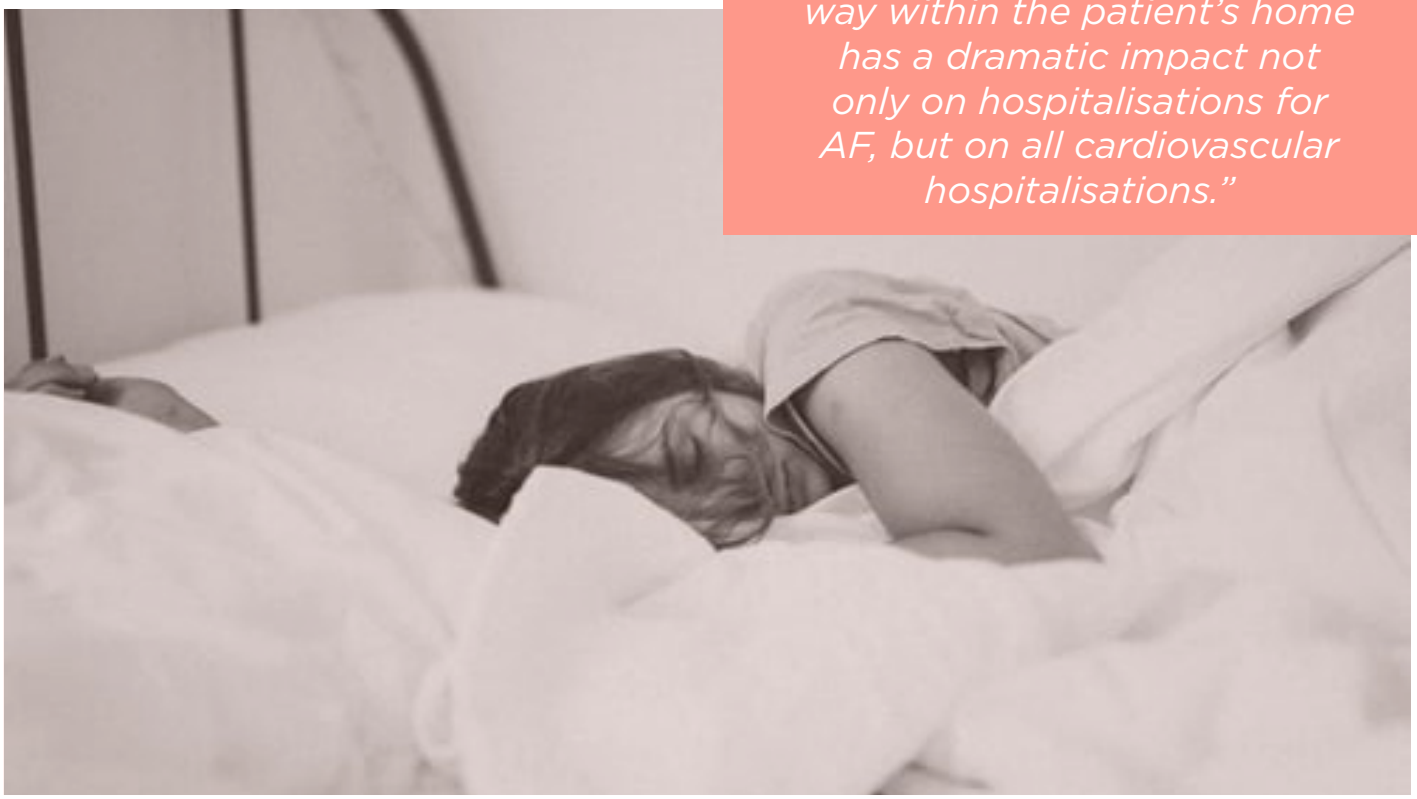

Ticagrelor and Aspirin Combination Reduces Ischaemic Events in Diabetics with Stable Coronary Artery Disease

"In addition to heart attack and stroke, acute limb ischaemia and major amputations were also reduced with ticagrelor"

MILLIONS of patients worldwide are at high risk for heart attack, stroke, and amputations as a result of their diabetes and stable coronary artery disease, a common development seen in diabetic patients. Usually, aspirin is prescribed to reduce risk, but cardiovascular events still occur at a high rate; however, in late-breaking results from the THEMIS trial reported in a ESC press release dated 1st September 2019, reduced ischaemic events were seen in patients given a combination of ticagrelor and aspirin.

The THEMIS trial took place at 1,315 sites across 42 countries worldwide and involved 19,220 participants aged ≥50 who had Type 2 diabetes mellitus and stable coronary artery disease. The risk of thrombotic events was compared in those randomly given aspirin and placebo to those given the combination of aspirin and ticagrelor.

"There was a significant reduction in the primary endpoint of cardiovascular death, heart attack, and stroke with ticagrelor versus placebo. In addition to heart attack and stroke, acute limb ischaemia and major amputations were also reduced with ticagrelor. Major bleeding was significantly increased," commented senior author Prof Deepak Bhatt of Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA.

In patients that received ticagrelor, the incidence of primary efficacy outcome was lower (7.7% versus 8.5%; hazard ratio 0.90; 95% confidence interval: 0.81–0.99; p=0.038). However, the primary safety outcome of thrombolysis in myocardial infarction major bleeding was increased in the ticagrelor group (2.2% versus 1.0%; hazard ratio 2.32; 95% confidence interval: 1.82–2.94; p<0.001).

Prof Bhatt concluded that it is crucial to define subgroups that would benefit from ticagrelor plus aspirin, of whom are patients at high ischaemic rick, but low bleeding risk. Furthermore, substantial gains for the reduction of a full spectrum of coronary, cerebral, and peripheral ischaemic events was seen in ticagrelor plus aspirin.

Depressive Symptoms can be Predictive of Health Problems in Caregivers

SIGNS of depression in caregivers of stroke patients may be predictive of future health problems, as shown in a study presented at the ESC Congress, with the WCC, in Paris, France, and reported in a ESC press release dated 1st September 2019. The research brings to light the importance of recognising and addressing caregivers' mental health.

Caregivers of stroke survivors can undergo a heavy emotional and physical burden, as stroke can often leave patients with long-term disability. "More attention needs to be paid, especially early on, to managing depressive symptoms in caregivers. They must realise that self-care is not selfish," explained study author Prof Misook L. Chung, University of Kentucky College of Nursing, Lexington, Kentucky, USA.

This study comprised 102 participants who were caring for a stroke survivor. The sample had a mean age of 58 years, were two-thirds female, and around 70% were spouses of the patient. Questionnaires were answered on two occasions: 6–10 weeks after hospital discharge and 1 year later.

Depressive symptoms, such as trouble focussing and diminished appetite, were reported less frequently over the period of the study: 32.4% compared to 30.4%. A total of 57.8% of the participants reported no mental distress, while 20.6% experienced persistent symptoms of depression over their first year of caregiving. One-third of the participants marked their physical health as either fair or poor after 1 year; additionally, 43% reported feeling that they had experienced a deterioration of their health.

Caregivers experiencing symptoms of depression were seven times more likely to have health problems following 1 year of care-giving than those who did not have depressive symptoms. Poor family functioning, lack of interpersonal support, and heavier care duties were all reported by those with persistent depressive symptoms.

As this study relied on self-reporting techniques, the findings are limited and further research is needed to identify a concrete link; however, the research does suggest earlier interventions and longer-term follow up are needed. Prof Chung concluded: "Self-care intervention programmes should include depressive symptom management for caregivers."

"More attention needs to be paid, especially early on, to managing depressive symptoms in caregivers. They must realise that self-care is not selfish,"

Patients with Heart Failure have a Similar Risk of Dementia-Type Lesions to Stroke Patients

COGNITIVE impairment is experienced by 50% of older patients with heart failure. Also associated with dementia, this type of brain damage, called white matter lesions (WML), is just as common in those with heart failure as it is in patients with a history of stroke. These results from the LIFE-Adult-Study were reported in a ESC press release on the 2nd September 2019.

Conducted in Leipzig, Germany, between 2011 and 2014, the population-based cohort study involved 10,000 randomly selected residents aged 18–80. Information on health conditions, including heart failure and stroke, was obtained through health assessments and physical examinations of the participants. Further investigation of the brain with the use of MRI was performed in 2,490 participants.

In the majority of the subgroup, 87% had no or mild WML, and 13% had moderate or severe WML; the latter is associated with cognitive impairment and dementia. A 2.5-times greater risk of WML was observed in heart failure compared to those without. There was a similar trend in stroke patients, who had a 2-times greater risk compared with participants with no history of stroke.

Furthermore, the duration of heart failure was linked with the severity of the lesions: more lesions were present in the brains of patients with a long-standing heart failure diagnosis compared to those who were newly diagnosed. The risk of WML increased from 1.3 for those with a diagnosis of <3 years to a risk of 2.9 for a diagnosis >6 years.

Despite this association, study author Dr Tina Stegmann of Leipzig University Hospital, Leipzig, Germany, commented: "It is still unclear what the pathological pathways are. Some investigators have identified changes in brain structure in patients with heart failure and cognitive dysfunction, but the findings are inconsistent." She concluded that "studies are needed to see if WML could be a therapeutic target for treating cognitive decline in patients with heart failure."

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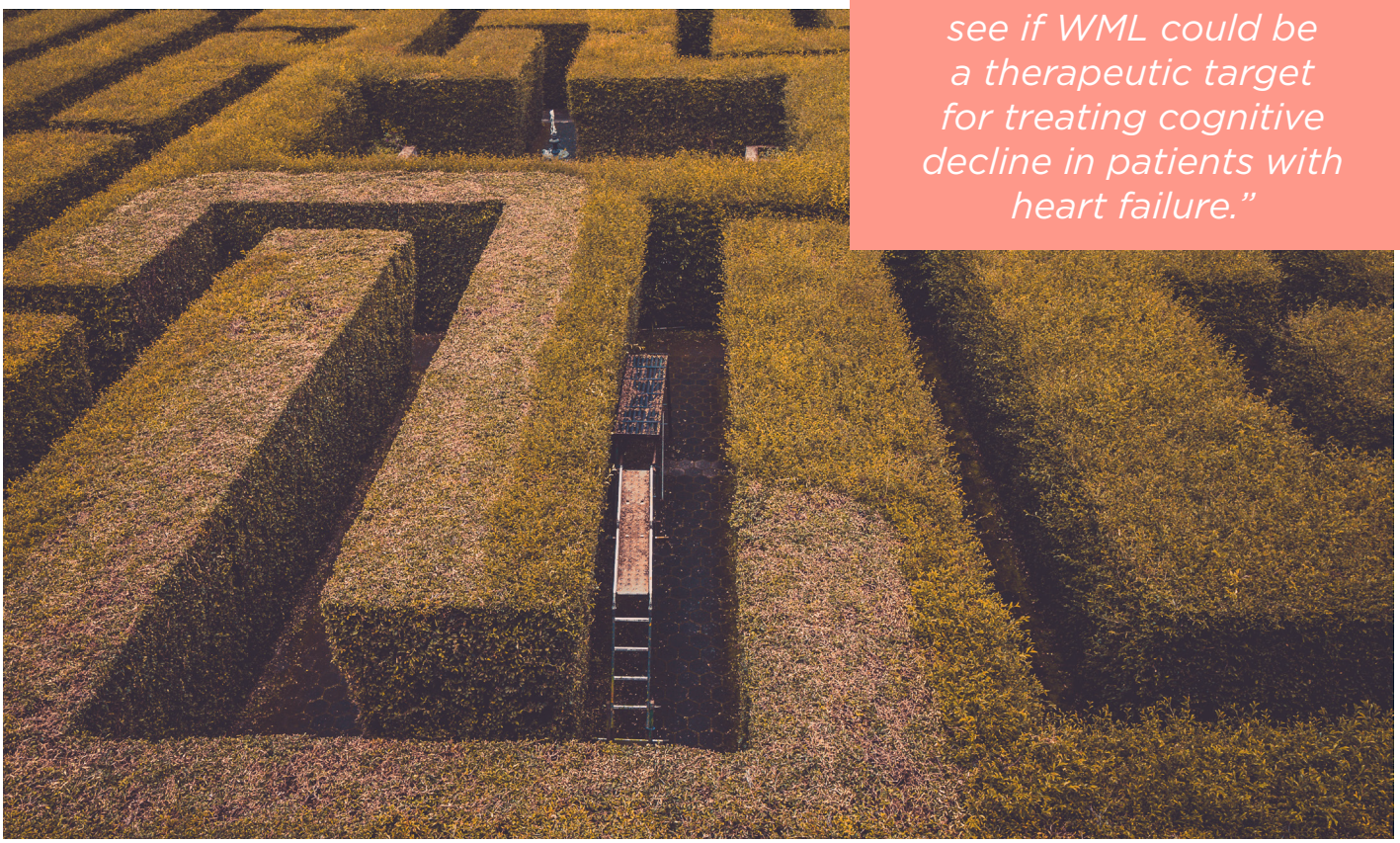


HOPE-ful Results for Patients with Hypertension

"Adopting the HOPE 4 strategy to better control hypertension and reduce other risk factors could help achieve the United Nations' target for a one-third reduction in premature cardiovascular mortality by 2030."

LATE-BREAKING results from the HOPE 4 trial were reported in a ESC press release dated 2nd September, showing that an intervention programme targeted at patients with hypertension in Colombia and Malaysia successfully reduced cardiovascular risk over 1 year.

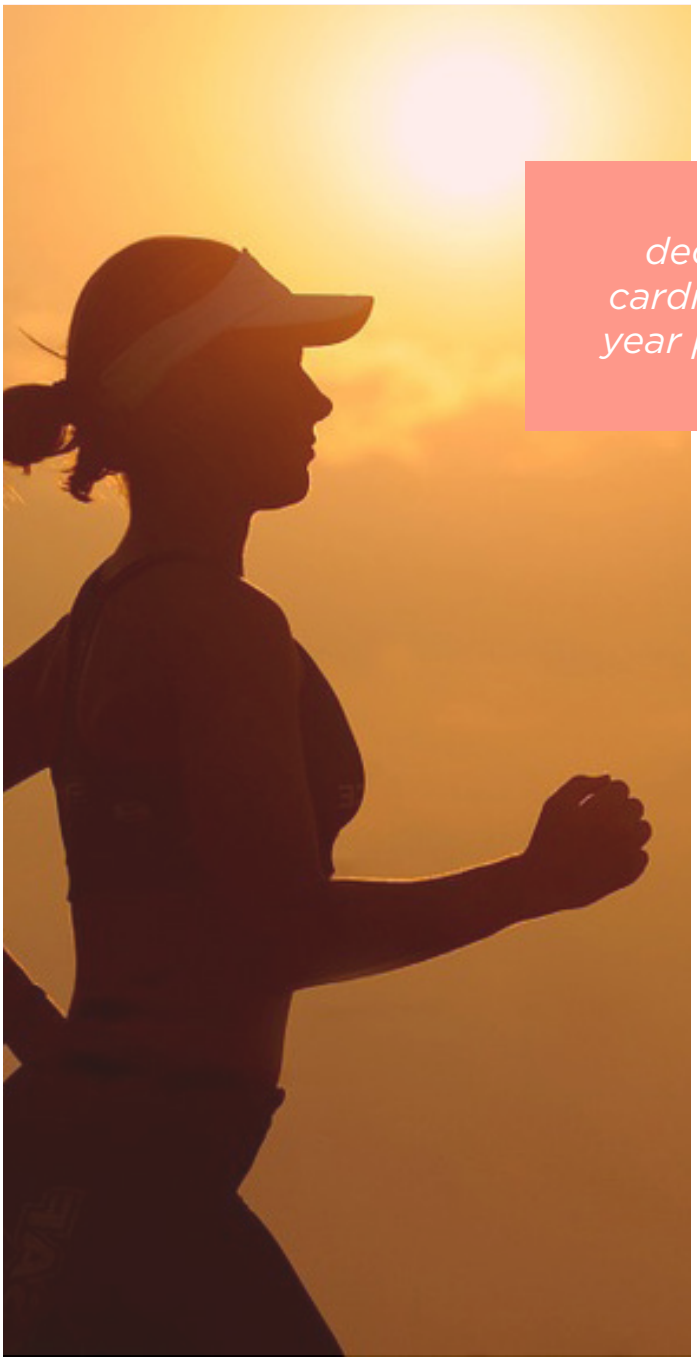
The trial enrolled 1,371 patients aged ≥50 years from across the 2 countries. The patients all had new or poorly controlled hypertension. There were 30 separate communities involved, 16 of which were randomised to receive standard of care as a control group, and 14 that took part in the intervention programme for 1 year. This included undergoing screening to detect eligible patients, implementation and monitoring of treatments, as well as control of risk factors by non-physician health workers using tablet-based management algorithms and counselling, free statins and antihypertensive medications (overseen by physicians), and partnering with a treatment supporter, such as a friend or relative to assist with adherence to medications and lifestyle changes. Treatment supporters attended 74% of visits to the health workers or physicians while also giving ongoing support outside of these visits.

The Framingham Risk Score was the measure used to determine the effectiveness of the intervention, specifically the change in this score from baseline to 12 months. In the intervention group, this score was reduced by an absolute 11.2% in that time, a 75.0% greater reduction than that seen in the control arm. Furthermore, systolic blood pressure saw an absolute 11.5 mmHg greater reduction and serum low-density lipoprotein was reduced by 0.4 mmol/L more in the intervention versus the control group.

Prof Salim Yusuf, Executive Director of the Population Health Research Institute of McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada, and Principal Investigator of the study, commented: "This strategy is pragmatic, effective, and scalable, and has the potential to substantially reduce cardiovascular disease globally, compared to current methods that are solely physicians based." He added: "Adopting the HOPE 4 strategy to better control hypertension and reduce other risk factors could help achieve the United Nations' target for a one-third reduction in premature cardiovascular mortality by 2030."

Bystander Resuscitation Increase Leads to Fewer Sports-Related Cardiac Deaths

DECREASED rates of death due to sports-related sudden cardiac arrest has been attributed to an increase in bystander cardiopulmonary resuscitation (CPR), as found by research reported in a ESC press release dated 2nd September 2019 in Paris, France.



The study considered two registries initiated by the Paris-Sudden Death Expertise Centre. Cases of individuals who had experienced cardiac arrest, during or immediately following sport in Paris (and surrounding suburbs), from the time periods 2005–2010 (n=158) and 2011–2016 (n=162), were included in the analysis.

Incidence was stable across the 2 time periods: an estimated 6.9 cases per 1 million inhabitants. Average age was not significantly different between the periods (from 49 to 52 years of age), nor was percentage of men (from 94% to 96%) or prevalence of known heart disease (from 14% to 17%). In the later time period, bystander CPR increased to 81%, significantly higher than in 2005–2010 at a rate of 46%. Similarly, automated external defibrillator use was up from 1.3% to 11.9%. Athlete cardiac arrest survival rates increased from 20% to 60%.

"We observed an important decrease in deaths due to sudden cardiac arrest during sports over a 12-year period which was related to more frequent CPR."

Death, as a result of cardiac arrest from sport, decreased from 4.3 to 3.4 deaths in every 1 million inhabitants. Prof Xavier Jouven, Paris-Sudden Death Expertise Centre, Paris, discussed the findings: "We observed an important decrease in deaths due to sudden cardiac arrest during sports over a 12-year period which was related to more frequent CPR. The static incidence is probably caused by difficulties in early identification of individuals at high risk for sudden cardiac arrest during sports."

"To further improve survival from cardiac arrest, CPR should be taught to the general public and particularly to sports medicine practitioners," concluded Prof Jouven. "An AED should be available in all sports venues. Preventing sudden cardiac arrest remains the ideal goal – in the future, smartwatches and internet-connected T-shirts may alert us to warning signs occurring minutes or hours before, allowing early resuscitation and prevention."

Antithrombotic Regimen Following Coronary Stenting Optimised Through Genotyping

FOR HEART attack patients undergoing coronary stent implantation, bleeding and clotting risks can be simultaneously reduced following oral $P2Y_{12}$ inhibition through use of genotype guidance. This message was delivered in a ESC press release dated 3rd September 2019, and has potentially wider implications for the field.

ESC guidelines advise dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor for 1 year in patients following primary percutaneous coronary intervention (PCI) with ST-segment elevation myocardial infarction (STEMI). Ticagrelor, prasugrel, and clopidogrel and are the most common inhibitors prescribed; however, they are subject to differing costs and availability, and the former two exhibit safety constraints in regard to propensity to bleeding events, a major concern in the treatment of these patients.

CYP2C19 gene functionality has been linked to clopidogrel effectiveness. Investigators from St. Antonius Hospital, Nieuwegein, the Netherlands, hypothesised that genotyping would allow identification of patients better suited for clopidogrel treatment (i.e., *1/*1 noncarriers), and those better suited for ticagrelor/prasugrel treatment (i.e., *2 and *3 loss-of-function allele carriers), in regard to thrombotic complication reduction.

The POPular Genetics trial involved 2,488 STEMI patients being randomly allocated to standard treatment or genotype-guided arms.

"This study demonstrated that a CYP2C19 genotype-guided strategy benefits patients with STEMI undergoing primary PCI by reducing the risk of bleeding without increasing the risk of thrombotic events,"

The former was treated with ticagrelor or prasugrel for 1 year, whereas the latter had genotype testing performed as soon as possible after PCI through blood sample testing. Patients without loss-of-function mutations (*1/*1) received clopidogrel for 1 year.

Patients in the genotype-guided arm experienced significantly fewer bleeding events (9.8%) than those in the standard treatment arm (12.5%) (hazard ratio: 0.78; 95% confidence interval: 0.61–0.98; p=0.04). Similar clinical endpoints were achieved in both arms (5.1% in the genotype-guided arm, and 5.9% in the standard treatment arm), meaning noninferiority was proven.

"This study demonstrated that a *CYP2C19* genotype-guided strategy benefits patients with STEMI undergoing primary PCI by reducing the risk of bleeding without increasing the risk of thrombotic events," commented first author Dr Danny Classens, St. Antonius Hospital.

Digital Ripples in the Cardiovascular Pond

Michael Dodsworth
Editorial Administrator

An acceptance has slowly emerged within the healthcare community that limitations exist in its ability to efficiently, and most importantly sustainably, deliver effective therapies to patients who need them. These challenges are often complex and multifactorial in nature, arising from factors such as an ageing population, increased prevalence of chronic diseases, financial pressures on healthcare systems, and a demand for better patient engagement. Not one to shy away from these unique obstacles, the healthcare community have instead opted to look outward to the digital technology sector in order to harness the brilliant potential it presents, helping provide a patient-centric and efficient service. The result is a partnership that has taken the clinical community, and indeed general population, by storm.

Digital health encompasses the use of information and communication technologies to conduct research, inform healthcare professionals, treat patients, track diseases, and monitor public health. This can be through a variety of means, including, but not limited to:

- **Telemedicine and telecare:** the provision of services such as remote patient monitoring and homecare.
- **Big data:** the acquisition and analysis of large, heterogenous sets of data. This can allow the delineation of important environmental and social factors that can impact on public health.
- **Mobile health:** the use of mobile technologies to provide information and facilitate decision making on a population level.
- **Personalised health:** Implantable or wearable nanotechnologies that can monitor health in real-time (e.g., fall detectors, insulin pumps).

These examples show just some of the ways in which digital innovation has, or can, change the way in which healthcare can be facilitated: a diverse selection of approaches to meet an equally diverse selection of challenges. Expanding rapidly since its introduction, digital health has become the third largest industry in the European health sector, following pharmaceuticals and medical devices.[1] The European Society of Cardiology (ESC), as one of the largest representative bodies of cardiologists in the world, has understandably given increased attention to digital health as a means to provide support to its various members in their daily practice, be it clinical, research-focussed, or legislative.

An ESC working group has recently published a position paper on the society's stance on digital health.[2] In the paper, the group identify how the treatments employed to tackle cardiovascular disease, whilst available and guidance-based,

often offer disappointing long-term benefits due to reasons such as non-adherence. Cardiac telerehabilitation and other types of monitoring are proposed to allow the opportunity for practitioners in the field to redesign and improve care and diagnosis for these patients.

Heart failure is an ideal example of a cardiovascular pathology benefiting from this digital revolution. Heart failure is a chronic condition often requiring patients to modify their lifestyle habits and behaviours in order to best optimise their recovery and improve life-quality. Invasive telemonitoring could potentially be used to report on the progression of heart failure in real time, be it worsening or improving, and better inform healthcare professionals of important decisions to be made regarding the patient's ongoing treatment. The monitoring has an added benefit of giving the patient comprehensive and personalised information, enabling them to play a more active role in the management of their condition. Contrary to invasive intervention, a recent meta-analysis on noninvasive telemonitoring was able to show that structured telephone support reduced all-cause mortality and heart failure-related hospitalisations compared to standard of care,[3] suggesting different applications for digital technology in heart failure. Other examples of digital technology application in the field include means for primary prevention of cardiovascular disease (home blood pressure monitoring for controlling hypertension)[4] or secondary prevention of ischaemic heart disease (noninvasive telemonitoring for arrhythmia detection).[5]

Prof Martin Cowie, Professor of Cardiology, National Health and Lung Institute, Imperial College London, London, UK, is optimistic about the possibilities that digital health allows: "Digital Health is disrupting the usual way patients and healthcare professionals interact. It could potentially transform healthcare so that care is delivered more remotely, and patients can access advice from wherever they are, rather than having to physically attend a hospital or office facility."

It would be naïve to assume that the possibilities digital health allow are not accompanied by certain disadvantages. Ethical, legal, and data protection constraints can hamper the digital innovation of cardiovascular healthcare, as well as aversion by practitioners themselves; often the use of certain technologies can be seen as forced or in search of a problem that doesn't exist, and evidence for their effectiveness can be circumstantial at best, and lacking in robustness at worst. The difficulties that regulatory bodies have in reacting quickly to the 'disruption' that digital innovation brings is an ongoing challenge, but one that most parties involved would agree is a challenge worth facing.

"The clinical community has quite a high bar. If we want to use a new drug, or a new device, we want really strong evidence: we want this also for electronic technologies," chimed Prof Cowie. "Some of these are no-brainers like electronic prescribing; you don't need to do a trial to show that's good [...] but for some of the other things that are interfering in work flow and changing the data we are looking at, you really do have to show that that makes a meaningful difference."

The adoption of digital technology across the cardiovascular field, and indeed all disciplines of healthcare, is clearly not a straightforward process. Undeniable benefits are often accompanied by constraints, and the cardiovascular community are still trying to determine the best application of the tools available to them. However, the innovation of ideas, technologies, and practice is of the utmost importance in the digital era in which we live today. The global burden of cardiovascular disease is being met with a new arsenal of weapons for its management, surely a promising sign for years to come.

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Congress Interview

Prof Thomas F. Lüscher, MD, FRCP, FESC

Professor of Cardiology, Imperial College London, National Heart and Lung Institute, London, UK
Chairperson of the ESC Publications Committee

Q1 Can you please briefly describe the main duties and responsibilities of the European Society of Cardiology's (ESC) Publications Committee?

The ESC Publications Committee co-ordinates and oversees all scientific journals as well as books of the ESC. The committee is chaired by myself and Prof John A. Camm (Vice-Chair) from London, UK, and involves all the ESC Journal editors, as well as their editorial managers. For some items on the agenda for the publications committee meeting, publishers are also welcomed to discuss common issues. The ESC Publications Committee meets three times a year, i.e., at the ESC Annual Congress, in January, and in summer. At these meetings the Publications Committee discuss issues of common interest such as the changing publication landscape, the performance of each of the journals, strategic measures to improve visibility and impact, as well as quality of the journals among other issues.

Q2 The ESC publishes the European Heart Journal and 11 other periodicals detailing cardiovascular medicine and research. How does the committee identify areas of research to which increased awareness is, in your opinion, deserved?

Indeed, the ESC Journal family has grown over the last few years and now covers the entire field of cardiovascular medicine and research. The topics of each of the speciality journals have been selected carefully and reflect the increasing specialisation of cardiovascular medicine into larger and smaller areas. Personally, I am convinced that we currently have reached saturation and should not consider any other journals, otherwise some of the titles may compete amongst each other for manuscripts. A new area that has been discussed is congenital heart disease; however, we decided that such articles should be covered by the European Journal of Heart Failure, European Journal of Preventive Cardiology, or Europace. An evolving area that has not been yet covered is valvular heart disease, but this is currently centre stage and therefore mostly published in the European Heart Journal or in parts of the EuroIntervention publication.

Q3 Complementary to their other publications, the ESC produces an eJournal titled EuroIntervention. Are we witnessing a shift in the way medical publishers operate towards providing content through a predominately digital medium?

Indeed, EuroIntervention is published by Europa, a French based company, that also runs the EuroPCR Annual Congress in Paris, France. Nevertheless, we strongly interact with EuroIntervention and transfer many manuscripts to this journal. The journal is not only electronic, but also in print, like all other journals that we publish except for ESC Heart Failure. We have investigated the issue of print versus digital and there is clearly an age factor involved; older readers tend to prefer print, while the younger generation prefer digital. It is a question of time until most journals may only be available in digital form.

"It is a question of time until most journals may only be available in digital form."

Q4 How important is communication with other ESC committees towards achieving the goals that you set yourself?

The most important interaction we have with other ESC committees is with the ESC Guidelines Committee because we publish all our guidelines in the European Heart Journal. Furthermore, the ESC Textbook of Cardiovascular Medicine and its electronic database ESC CardioMed interact very intensively with the newly developing guidelines of the ESC. As such, we aim to shorten the ESC guidelines and print, or make available, background information, epidemiology, mechanisms, and so forth in the ESC Textbook of Cardiovascular Medicine and ESC CardioMed, respectively.

Q5 Does the Publications Committee liaise with presenters and contributors at each ESC Congress in order to promote their respective content and find potential contributors?

No, this is left to the individual editors. As the editor of the European Heart Journal, I contact all presenters of Hotline Sessions at the ESC and its affiliated congresses. The manuscript is submitted as a Fast Track with online presentations at the time of the congress, for instance in Paris later this month.

Q6 The ESC is one of the largest bodies of cardiologists in the World, with >95,000 members. What are some of the advantages and disadvantages, from a publication standpoint, of providing content to this many people?

Unlike the American College of Cardiology (ACC) or the American Heart Association (AHA), which mainly serve native English-speaking members, readers, and contributors, the ESC involves numerous countries where English is the second language and, in some instances, not widely spoken. The healthcare systems in all these member states are quite different, as is the economic level or gross national product; therefore, many recommendations published by the ESC are not affordable in certain countries and in others they are immediately adopted. Nevertheless, the more successful that the ESC has been, the more it has been able to bring together cardiologists and physicians interested in cardiovascular medicine and research from all over the world, and to provide high quality educational programmes, textbooks, and scientific journals.

Q7 'Plan S', an initiative to enforce mandatory open-access content across the European medical publication landscape, is garnering increased attention in the media. What are your thoughts on the implications this could have for the ESC, and the industry as a whole?

I have published about Plan S on several occasions, and I do consider it as a big threat in regard to the way it is implemented. I welcome open-access in principle, although I am convinced that the hybrid model of publishing, incorporating income from subscriptions with the option of buying or to be selected as open-access, is currently the best model, allowing for an effective and professional editorial system. Unfortunately, Plan S does not allow for this, and this creates difficulties for many of the top journals, especially as American companies do

"the more successful that the ESC has been, the more it has been able to bring together cardiologists and physicians interested in cardiovascular medicine and research from all over the world"

not currently seem to consider Plan S as a viable option. This may cause significant issues for the European community. I believe that Plan S is quite ideological as it currently stands, and we should allow hybrid journals as well as open-access journals in the future, rather than having a strict open-access only policy.

The financial implications for scientific societies are quite significant; most medical societies offer their journal as a benefit of membership, and this would fall apart with Plan S and endanger their financial structure. Even for the ESC, Plan S would be financially disadvantageous. Most of all, a split of the scientific community, with some funding bodies requiring Plan S while others do not, specifically the highly competitive American bodies, would create a big threat to the scientific journals publishing with the hybrid structure.

Q8 Finally, what advice would you give to other Congress-affiliated Publication Committees that are looking to provide similarly high-quality content?

There are not many other congress-affiliated publications committees like the one of the ESC. The AHA also has a journal family and the ACC has built a smaller, but significant journal family as well. I am sure in other large scientific societies, for example, oncology, similar issues may arise. Any journal family needs a strong publications committee where efforts can be co-ordinated, strategy is discussed, the pros/cons and strengths/weaknesses evaluated, and the appropriate measures taken.

The Bigger Picture in Stroke Prevention and Anticoagulation: Think Beyond Atrial Fibrillation

This symposium took place on 31st August 2019, as part of the European Society of Cardiology (ESC) Congress in Paris, France

Chairpeople: Gilbert Deray,[1] Christian Ruff[2,3]

Speakers: Hendrik Bonnemeier,[4] Reinhold Kreutz,[5] Manesh Patel,[6] Peter Rossing[7,8]

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7. Steno Diabetes Center Copenhagen, Gentofte, Denmark
8. University of Copenhagen, Copenhagen, Denmark

Disclosure: Dr Deray has received honoraria for speaking and support for research (Xareno) from Bayer. Dr Ruff has received research grants from Boehringer Ingelheim, Daiichi Sankyo, MedImmune, and National Institutes of Health; and honoraria for scientific advisory boards and consulting from Bayer, Bristol–Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Janssen, MedImmune, Pfizer, Portola, and Anthos. Dr Bonnemeier has received advisory board and speaker fees from Advanced Circulatory Systems, Bayer, Berlin Chemie, Biotronik, Boehringer, Boston Scientific, BMS, Cardiome, Daiichi Sankyo, Impulse Dynamics, Jolife, NayaMed, Medtronic, Lilly, LivaNova, MSD, OmniaMed, Physiocontrol, Pfizer, Sanofi, Servier, Sorin, St. Jude Medical, and Zoll; and honoraria for consultancy, lectures, and support for research from Bayer, Berlin-Chemie, Menarini, Daiichi Sankyo, and Servier. Dr Kreutz has received honoraria for consultancy, lectures, and support for research from Bayer, Berlin-Chemie Menarini, Daiichi Sankyo, Ferrer, Sanofi, and Servier. Dr Patel has received research funding from Janssen, AstraZeneca, Bayer, Cardiovascular Systems Inc, HeartFlow, Maquet, NHLBI; and been a consultant or advisor for AstraZeneca, Genzyme, and Janssen. Dr Rossing has received research funding from AstraZeneca and Novo Nordisk; and consultancy/speaker fees (to his institution) from AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol–Myers Squibb, Eli Lilly, Gilead, MSD, Mundi, Novo Nordisk, and Sanofi.

Acknowledgements: Medical writing assistance was provided by Jennie James, Surrey, UK.

Support: The publication of this article was funded by Bayer. The views and opinions expressed are those of the presenters. Content was reviewed by Bayer for medical accuracy.

Citation: EMJ Cardiol. 2019;7[1]:30-37

Meeting Summary

This symposium brought together experts in cardiology, nephrology, diabetology, and clinical pharmacology to discuss best practice when caring for patients with atrial fibrillation (AF) and

comorbidities. They urged delegates to not only consider the issue of AF but also to think about protection in a broader sense, including comorbidities to improve outcomes for patients when it comes to stroke prevention. Dr Ruff spoke of the tremendous opportunity to reduce the burden of stroke by addressing important modifiable risk factors for stroke, focussing on AF and diabetes, and their link to chronic kidney disease (CKD). Dr Bonnemeier and Dr Kreutz discussed patients with AF and renal dysfunction, noting that CKD is a frequent comorbidity associated with increased risk of stroke and bleeding among patients with AF. The associated patient case study inspired debate about the challenges of oral anticoagulant (OAC) therapy in this patient group and highlighted that while decline in renal function is common in AF patients treated with OAC, the extent of decline may depend on which anticoagulant is used. Furthermore, available data from randomised control trials and recent retrospective analyses were shared which showed differences in the progression of CKD associated with vitamin K antagonists (VKA) versus the novel OAC (NOAC), such as rivaroxaban. Dr Patel and Dr Rossing focussed on diabetes and AF, stating that their frequent coexistence is a bad combination associated with substantially increased risks of death and cardiovascular (CV) events. Exploring the link between diabetes and CKD, they demonstrated the significant impact renal dysfunction has on the prognosis of Type 2 diabetes mellitus (T2DM). They additionally presented recent evidence from retrospective analyses comparing renal outcomes in patients with AF and diabetes treated with NOAC or VKA, noting that choice of anticoagulation may impact risk for renal outcomes.

Introduction: What is the Bigger Picture?

Doctor Gilbert Deray and Doctor Christian Ruff

Dr Deray introduced a multidisciplinary panel of speakers from cardiology, nephrology, diabetology, and clinical pharmacology, providing a comprehensive look at how to improve outcomes in patients with AF and comorbidities, striving for protection beyond stroke risk. While tremendous advances in both stroke prevention and treatment have improved patient outcomes, stroke remains the second most common cause of death globally after ischaemic heart disease; yet up to 80% of strokes can be avoided.[1]

Dr Ruff acknowledged that physicians are providing anticoagulants to AF patients to prevent strokes but questioned if more could be done to protect patients with comorbidities. He pointed out that approximately 90% of the population-attributable risk factors of stroke are caused by potentially modifiable risk factors,[2] and stated that this provides a "tremendous opportunity" to greatly reduce the stroke burden around the world.

Explaining that the panel would focus on two of these modifiable risk factors, diabetes and AF (including renal dysfunction), Dr Ruff noted that AF is associated with a 5-fold increase in risk of stroke[3] and diabetes, and with a 2-fold increase in the risk of stroke.[4] Furthermore, diabetes is a risk factor for AF and a common cause of CKD, which is associated with a 30–60% increase in ischaemic stroke (IS) risk.[5]

Dr Ruff stated that the reason for focussing on prevention of AF-associated stroke is because the related outcomes are worse than for non-AF strokes.[6] One in four patients that are admitted with IS associated with AF will die within 30 days, making AF stroke almost twice as likely to be fatal than non-AF stroke. Furthermore, 30% of the patients who survive an AF-related stroke have severe dependence at 12 months compared with 11% for non-AF stroke.[6]

Registry data suggest that the use of OAC therapy remains suboptimal across the world,[7] and according to Dr Ruff, physicians are still on a journey to optimise the therapies available to better protect patients when it comes to stroke prevention. He added: "We need to take a step back and look at the bigger picture and investigate the comorbidities and complex patients we see in practice."

Think about the Kidneys: Why does Renal Function Matter in Patients with Atrial Fibrillation?

Doctor Hendrik Bonnemeier and Doctor Reinhold Kreutz

Reiterating the need to look beyond AF, Dr Bonnemeier described how he sees AF patients with comorbidities such as arterial hypertension, coronary artery disease (CAD), obesity, diabetes, and CKD, and noted that these diseases overlap and interact. He outlined a 'typical' patient case, a 66-year-old male presenting with palpitations.

The patient had arterial hypertension (blood pressure: 150/90 mmHg), diabetes (receiving dietetic therapy), and was overweight (BMI: 29). He had persistent nonvalvular AF (NVAF) and had undergone external cardioversion twice. His electrocardiogram showed AF with a heart rate of around 100 beats per minute.

After around 20 hours, the patient spontaneously converted into sinus rhythm. He had undergone a heart procedure 2 years before, with exclusion of significant CAD, and echocardiography revealed good left ventricle function and left ventricular hypertrophy as a result of hypertension.

The patient was on rivaroxaban 20 mg once daily (od), verapamil 120 mg twice daily, ramipril 5 mg twice daily, torasemide 5 mg od, and pantoprazole 20 mg od.

The lab findings showed creatinine 1.89 mg/dL, estimated glomerular filtration rate (eGFR) 46 mL/min, mild increase in c-Troponin T (0.2 ng/mL), and mild increase in N-terminal pro-B-type natriuretic peptide (198 pg/mL), probably due to the AF.

Dr Bonnemeier and Dr Kreutz agreed that there are several issues to consider when thinking about anticoagulation to manage thromboembolic risk in a multimorbid patient such as this case, not least the impact of CKD. They noted several issues to consider in patients with AF and CKD including the need to balance the risks of both IS and bleeding, the need to monitor renal function and to select appropriate dosing based on the level of renal function, and how choice of anticoagulant therapy can affect renal outcomes.

The 2018 European Heart Rhythm Association (EHRA) Practical Guide on the use of NOAC in patients with AF advises on the optimal use of NOAC according to renal function.[8] Dr Kreutz outlined the guidance for rivaroxaban, noting that it is evidence based[9] and straightforward: 20 mg od for patients with a creatinine clearance (CrCl) of ≥50 mL/min, and 15 mg od for patients with a CrCl of 30–49 mL/min. Cautionary use of 15 mg od is recommended for patients with severe renal impairment (CrCl: 15–29 mL/min) and in Europe, no NOAC is recommended for patients with end stage renal disease (ESRD; CrCl: <15 mL/min) undergoing dialysis.

The Phase III ROCKET AF trial, which compared the efficacy and safety of rivaroxaban to warfarin in 14,264 AF patients, studied a specific renal dose of rivaroxaban to support safety, and 1,474 patients with moderate renal impairment received the reduced dose of 15 mg od.[9]

Atrial Fibrillation and Chronic Kidney Disease: Knowing the Risks

CKD is a frequent comorbidity in patients with AF and is associated with adverse outcomes.[10,11] A large Danish cohort study (N=132,372) showed that CKD was associated with an increased risk of stroke or systemic thromboembolism (SE) and bleeding among patients with AF.[11]

Dr Kreutz touched upon the interaction between vascular calcification and CKD, noting that medial vascular calcification is highly prevalent in patients with CKD.[12] Research suggests that vascular calcification affecting the kidneys is a possible side effect of VKA treatment. It is further hypothesised that VKA, such as warfarin, promote vascular calcification because the effect of VKA is not limited to coagulation, but affects all vitamin K-dependent proteins including matrix G1 protein, which plays a major inhibitory role in the development of vascular calcification.[13] Dr Kreutz suggested that treatment with a VKA, which inhibits the activation of matrix G1 protein and thereby abolishes its protective effect against calcification, may contribute to worsening renal function and accelerate progression of kidney disease.

Supporting this concept, post-trial analyses of the RE-LY (comparing the efficacy and safety of dabigatran to warfarin) and ROCKET AF trials

showed that AF patients treated with warfarin had a significantly greater decline in renal function over the course of the study compared to the NOAC arms.[14,15]

Differences in Progression of Chronic Kidney Disease

A retrospective analysis of a large USA administrative database suggested decline in renal function is common in AF patients treated with OAC, but the extent may depend on which anticoagulant is used. It found NOAC, including rivaroxaban, were associated with lower risks of adverse renal outcomes over time compared to warfarin. The study compared three NOAC (apixaban, dabigatran, and rivaroxaban) to warfarin for their effects on four renal outcomes: ≥30% decline in eGFR, doubling of the serum creatinine level, acute kidney injury (AKI), and kidney failure. When comparing each NOAC with warfarin, rivaroxaban was associated with lower risks of ≥30% decline in eGFR, doubling of serum creatinine, and AKI; dabigatran was associated with lower risks of ≥30% decline in eGFR and AKI; however, apixaban did not have a statistically significant relationship with any of the renal outcomes.[16]

Recent real-world data from a subgroup analysis of the retrospective cohort study RELOAD, which compared the effectiveness and safety of rivaroxaban to phenprocoumon (a VKA widely used in Germany) in patients with NVAF and renal impairment, showed that when using the 'one tablet per day' definition of estimating drug exposure time, the incidence of the primary endpoint of IS was significantly lower in patients (without evidence of cancer at baseline) receiving rivaroxaban 15 mg or 20 mg od compared with those receiving phenprocoumon (2.40 versus 3.51 events per 100 patient-years, respectively; p=0.015). There was also a trend towards lower risk of the primary safety outcome of intracranial haemorrhage (ICH) for rivaroxaban versus phenprocoumon (0.57 versus 0.89 events per 100 patient-years; p=0.14).[17]

Furthermore, new findings from RELOADeD, an observational study in the European Union (EU), comparing rivaroxaban, apixaban, and edoxaban to phenprocoumon in patients with NVAF and renal disease revealed a comparable risk of IS/SE for all NOAC compared to phenprocoumon, and a beneficial effect for both rivaroxaban and apixaban with regards to ICH. Results showed significant risk reductions related to ESRD/dialysis for rivaroxaban (73%) and apixaban (57%) compared to phenprocoumon, while for the risk of AKI, this trend was only seen for rivaroxaban (Figure 1).[18]

Rivaroxaban was also associated with lower risk of AKI or progression to Stage 5 CKD compared with warfarin in the RIVAL study, which used USA Truven MarketScan claims data to compare the impact on renal outcomes in NVAF patients (Stage 5 CKD or haemodialysis excluded). Rivaroxaban was additionally associated with a 19% risk reduction in AKI and an 18% reduction in progression to Stage 5 CKD or haemodialysis compared to warfarin.[19]

To further investigate the observed lower risks of renal adverse events with rivaroxaban compared to VKA, the prospective XARENO (Factor XA -inhibition in RENal patients with non-valvular atrial fibrillation Observational registry) study is ongoing. The multicentre study will collect data from ≥2,500 patients with NVAF and eGFR/CrCl 15–49 mL/min and compare progression of CKD and clinical outcomes in patients receiving rivaroxaban, VKA, or no anticoagulation therapy for ≥3 months. The first results are expected at the end of 2020.[20]

Panel Discussion Highlights

- Delegates and the panel discussed the lack of clear evidence on the efficacy and safety of NOAC in patients with ESRD or on dialysis, and the need for further studies, noting that the use of NOAC in patients with severe renal function impairment (CrCl <15 mL/min) or those on dialysis is not recommended by the EHRA Guidelines, nor by the respective EU labels for each drug; dabigatran is contraindicated in CrCl <30 mL/min.
- The panel suggested that helping to reduce the need for dialysis through preservation of renal function was critical and stated this is a "key point" when making decisions about anticoagulation.

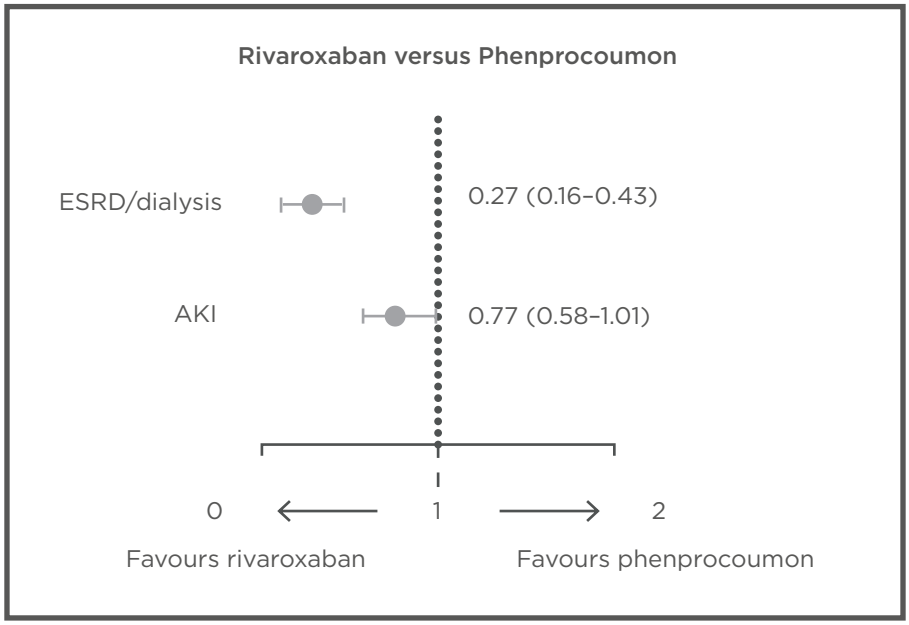

Figure 1: Confounder-adjusted hazard ratios of renal safety outcomes with 95% confidence intervals for rivaroxaban versus phenprocoumon in patients with NVAF and renal disease.

A multiple Cox-regression was performed to calculate confounder-adjusted hazard ratios for the risk of ESRD and AKI in new users of NOAC versus new users of phenprocoumon. Results indicated a beneficial effect of NOAC in renal function worsening over time when compared to phenprocoumon in patients with NVAF and renal disease.[18]

AF: atrial fibrillation; AKI: acute kidney injury; ESRD: end-stage renal disease.

Adapted from Bonnemeier et al.[18]

Think About Diabetes: More than just a Thromboembolic Risk Factor in Patients with Atrial Fibrillation?

Doctor Manesh Patel and Doctor Peter Rossing

Dr Patel began by sharing a patient case study of a 68-year-old female with AF, hypertension, and diabetes, describing diabetes as "the 21st century plague."

- The patient had some peripheral neuropathy and her family was concerned about some unsteadiness. She also experienced pain in her legs when walking, but it is unclear if this was because of peripheral neuropathy or peripheral arterial disease (PAD).
- She denied any congestive heart failure symptoms and upon examination had chronic AF with a heart rate of 73 beats per minute and an eGFR of 43 mL/min.
- Current medications include metformin, amlodipine, atorvastatin, and multivitamins.
- The patient and her family were interested in determining if she should be on an OAC.

Dr Patel handed over to diabetologist Dr Rossing to discuss his thoughts on the presented case. After thanking delegates for having a diabetologist at the European Society of Cardiology (ESC) meeting, Dr Rossing said this patient case illustrated a big overlap between diabetes and cardiology, and also with CKD because a significant percentage of patients with diabetes have CKD.[21] The United States Renal Data System (USRDS) 2017 report showed that among National Health and Nutrition Examination Survey (NHANES) participants with diabetes, 28.7% had increased albuminuria, 20.7% had impaired renal function, and 10.0% had both.[21]

Diabetes and hypertension are the most common causes of CKD.[22] Dr Rossing explained that diabetes and hypertension increase the risk of

kidney disease through a variety of pathways, including inappropriate activation of the renin–angiotensin–aldosterone system, impaired insulin-mediated vasodilatation, augmented sympathetic nervous system activation, altered innate and adaptive immunity, and abnormal sodium processing by the kidney.[23] Kidney disease has a significant impact on the prognosis of T2DM. Patients with T2DM and albuminuria or impaired renal function had an increased risk of mortality compared with T2DM patients with healthy kidneys, and the risk was further increased in patients with both albuminuria or impaired renal function.[24]

Diabetes also increases the risk of developing AF.[25,26] The Framingham Heart Study showed that having diabetes increased the odds of developing AF by 40% for men and 60% for women.[25] In another large cohort study, diabetes was identified as a strong independent risk factor for AF.[26] Dr Rossing noted that AF and T2DM frequently coexist and described them as a "bad combination" associated with substantially increased risks of death and CV events.[27] The large ADVANCE study including 11,140 patients with T2DM, of whom 7.6% had AF at baseline, showed that AF is associated with 61% greater risk of all-cause mortality and 68% increased risk of major cerebrovascular events in patients with diabetes.[27] He said physicians taking care of patients with diabetes and CKD need to look out for AF, and screen and intervene not only for glucose but all the relevant risk factors in this population.

Less Risk of Renal Adverse Events

The RELOADeD study was revisited, with a focus on patients with NVAF and diabetes initiating rivaroxaban, apixaban, edoxaban, or phenprocoumon. Dr Patel shared recent results indicating the NOAC, particularly rivaroxaban and apixaban, are associated with less renal adverse effects over time compared to phenprocoumon. A comparable risk of IS/SE was seen for each NOAC compared to phenprocoumon, with a trend towards better effectiveness for rivaroxaban. There was a numerical benefit for NOAC over phenprocoumon for the risk of ICH and significant risk reductions related to ESRD for rivaroxaban (68%) and apixaban (40%). For the risk of AKI, only rivaroxaban showed a risk reduction (28%).[28]

Furthermore, recent findings from a retrospective analysis of USA claims data for patients with NVAF and diabetes also suggest that rivaroxaban is associated with lower risks of renal adverse effects than warfarin. Rivaroxaban was associated with a 17% lower risk of AKI and an 18% lower risk of progression to Stage 5 CKD or haemodialysis compared to warfarin (Figure 2).[29]

Diabetes, Chronic Kidney Disease, and Cardiovascular Disease Risk

There is a strong correlation between diabetes and CV disease. Macrovascular complications, namely CAD, PAD, and stroke, are a consequence of the injurious effects of hyperglycaemia, along with microvascular complications including diabetic nephropathy, neuropathy, and retinopathy.[30] Diabetes has been identified as a strong and consistent independent risk factor for stroke in patients with AF,[31] and is also independently associated with an increased risk of AF.[32] Furthermore, diabetes is a significant CV risk factor in patients with PAD or CAD.[33]

Evidence from a large population-level cohort study (N=1,268,029) showed that patients with both diabetes and renal impairment have an even greater CV risk than those with either diabetes or renal impairment alone. The study found that patients with a previous myocardial infarction represent a very high-risk group; patients with both diabetes and CKD were shown to be at similar or even higher risk of CV events and all-cause mortality.[34]

Dr Patel noted that rivaroxaban has been shown to be effective in patients with NVAF and diabetes in both randomised control trials[35] and real-world[36] studies, with consistent results. The ROCKET AF Phase III trial, which compared the effectiveness and safety of rivaroxaban and warfarin, enrolled 39.9% of patients with both NVAF and diabetes (n=5,695). A subanalysis of this cohort showed the efficacy and safety of rivaroxaban compared to warfarin was similar in patients with and without diabetes, supporting use of rivaroxaban as an alternative to warfarin in patients with these coexisting conditions.[35]

Similarly, results from a USA administrative claims database analysis showed that the effectiveness and safety of rivaroxaban was at least as good as warfarin in patients with NVAF and diabetes (n=11,034) treated in routine clinical practice.

	Rate per 100 PY		HR (95% CI)	HR (95% CI)
	Rivaroxaban	Warfarin		
AKI	7.70	13.45		0.83 (0.74–0.92)
Stage 5 CKD or haemodialysis	3.74	6.03		0.82 (0.70–0.96)

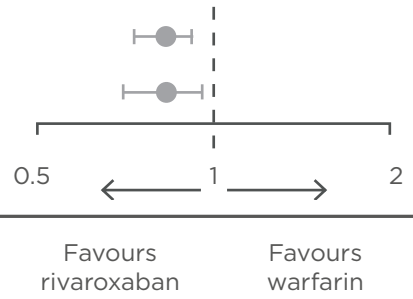

Figure 2: Risk of major adverse renal outcomes with rivaroxaban versus warfarin.

Retrospective analysis of US MarketScan claims data for patients with NVAF and diabetes, newly initiating therapy with rivaroxaban (n=10,017) or warfarin (n=11,665).

Patients with CKD Stage 5 or on haemodialysis were excluded.

Rivaroxaban was associated with lower risks of AKI and progression to Stage 5 CKD or haemodialysis versus warfarin in patients with NVAF and diabetes.

Sensitivity analysis using an intention-to-treat approach, excluding patients with AKI at baseline and limited to patients with >365 days of follow-up, yielded consistent results.

AKI: acute kidney injury; CI: confidence interval; CKD: chronic kidney disease; NVAF: nonvalvular atrial fibrillation; PY: patient years.

Adapted from Hernandez et al.[29]

Rivaroxaban was associated with nonsignificant reductions in stroke or SE compared to warfarin (0.87 versus 1.35 events per 100 patient-years), with no differences in major bleeding. Reduced-dose rivaroxaban (15 mg od) was associated with a significantly decreased hazard of stroke or SE and IS, without an increase in major bleeding risk.[36]

Dr Patel shared results from a retrospective claims database analysis of patients with NVAF and diabetes investigating the effectiveness and safety of rivaroxaban and warfarin for prevention of major adverse CV events or major adverse limb events. Rivaroxaban use was associated with a lower risk of both major adverse CV events and major adverse limb events, with no difference in major bleeding.[37]

Returning to the patient case outlined previously, Dr Patel reminded delegates that it is important to determine what the patient is most concerned about, noting that most patients worry about being a burden to their family. He suggested that if there is concern about mobility, stroke reduction, and the kidneys, there could be an argument to proceed with anticoagulants for the patient. He added: "Although we've been talking about AF-related stroke prevention for 10 years there's still so much to learn and progress we have to make to better optimally care for these multimorbid patients."

Panel Discussion Highlights

The panel noted that CV risk management for patients recently diagnosed with T2DM includes glycaemic control, smoking cessation, blood pressure control, reduction in serum lipid with a statin, diet, exercise, and weight loss or maintenance, but does not include decisions about anticoagulation. Prof Rossing emphasised that the choice of an anticoagulant is an important consideration and should perhaps be part of this conversation since it can impact renal outcomes and thereby plays an important role in a patient's progression down the line.

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European Society of Cardiology Chronic Coronary Syndromes Guidelines Review

These sessions took place on 2nd–3rd September 2019, as part of the European Society of Cardiology (ESC) Congress in Paris, France

Speakers: Keith Fox,[1] John Eikelboom,[2] Gilles Montalescot,[3] Dirk Sibbing[4]

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Disclosure: Prof Dr Med Sibbing has served on advisory boards for AstraZeneca, Bayer, Daiichi Sankyo, Ferrer, Sanofi Aventis, as a lecturer for AstraZeneca, Bayer, Daiichi Sankyo, Pfizer, Roche Diagnostics, and Sanofi Aventis, and has received research funding from Roche Diagnostics. Prof Montalescot reports research grants to the institution or consulting/lecture fees from Abbott, Amgen, Actelion, American College of Cardiology Foundation, AstraZeneca, Axis-Santé, Bayer, Boston Scientific, Boehringer Ingelheim, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Brigham Women's Hospital, China Heart House, Daiichi Sankyo, Idorsia, Elsevier, Europa, Fédération Française de Cardiologie, ICAN, Lead-Up, Medtronic, Menarini, MSD, Novo Nordisk, Partners, Pfizer, Quantum Genomics, Sanofi, Servier, and WebMD. Prof Eikelboom has received grants and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Janssen, AstraZeneca, Eli Lilly, GlaxoSmithKline and Sanofi Aventis. Prof Fox has received research grants from AstraZeneca and Bayer/Janssen, and consulting fees from AstraZeneca, Bayer/Janssen, Sanofi/Regeneron, and Verseon.

Acknowledgements: Writing assistance was provided by Dr Samantha Stanbury, Stockport, UK.

Support: The publication of this article was funded by Bayer AG. The congress sessions covered in the article were funded and organised by Bayer AG.

Citation: EMJ Cardiol. 2019;7[1]:38-45.

Meeting Summary

New guidelines for the diagnosis and management of chronic coronary syndromes (CCS)[1] were released during the 2019 European Society of Cardiology (ESC) Congress. The new guidelines were discussed in multiple sessions with different formats across the congress; this review summarises some of the discussion among experts at the congress around what the new guidelines mean for the way they manage their patients with respect to antithrombotic treatment.

A significant change in the new guidelines versus previous guidelines published in 2013[2] is an update in nomenclature from 'stable' coronary artery disease (CAD) to chronic coronary syndromes, to reflect the fact that patients with CCS are at continuous risk of heart attacks, strokes, and death. This highlights the need for effective preventive therapy to protect against these thrombotic events and maintain a state of relative stability in patients with CCS. To this end, a new recommendation in the 2019 guidelines is to consider intensification of antithrombotic therapy, using aspirin plus another antithrombotic agent, to provide enhanced long-term protection for patients with CCS at high risk

of ischaemic events. This review places the new guideline recommendations in clinical perspective, including thorough presentations of case studies to illustrate how patients at greatest risk of ischaemic events can be identified, and treatment stratified accordingly. These case studies highlight the role of dual pathway inhibition (DPI) in managing CCS patients with the greatest need for cardiovascular protection, who are likely to derive the greatest benefit from this treatment strategy.

Vascular Protection: When Do Patients Need More? Guideline Update

Professor Keith Fox

Prof Fox began the session by highlighting key issues in CCS and discussed how the new guidelines address these issues. Firstly, the previous standard of care was inadequate. Secondly, the concept of stable CAD is outdated: it is now recognised that there is a spectrum of risk in CCS, and a long-term risk of recurrent events persists even in periods of relative stability.

In the past, standard long-term treatment for stable CAD was aspirin monotherapy. New guidelines for CCS recommend considering adding a second antithrombotic agent to aspirin for long-term secondary prevention, for patients without high bleeding risk who are at high or moderate risk of further ischaemic events (Figure 1).[1] This is a Class IIa recommendation that should be considered for high-risk patients, and may also be considered for moderate-risk patients (Class IIb recommendation). High-risk patients are defined as those with diffuse multivessel CAD with at least one additional risk factor (diabetes requiring medication, recurrent myocardial infarction [MI], peripheral artery disease [PAD], or chronic kidney disease with estimated glomerular filtration rate [eGFR] 15–59 mL/min/1.73m^2); moderate risk is defined as multivessel/diffuse CAD and/or at least one other risk factor from the above list, or heart failure (HF) (Figure 1). These risk factors have been identified based largely on a risk stratification analysis of the COMPASS study population, which identified high-risk groups as patients with ≥2 vascular beds affected, HF, renal insufficiency, or diabetes, and provided clear evidence for heightened benefits of a dual treatment strategy in these patient groups (Figure 2).[3]

The ESC guidelines present four antithrombotic agents as possible partners to use in combination with aspirin: clopidogrel, prasugrel, ticagrelor, and rivaroxaban (Table 1).[1] The first three are antiplatelet agents, acting via inhibition of the $P2Y_{12}$ receptor; their combination with aspirin constitutes dual antiplatelet therapy (DAPT). Rivaroxaban targets a different pathway, acting as an anticoagulant via inhibition of Factor Xa, and therefore provides dual pathway inhibition (DPI) when combined with the antiplatelet activity of aspirin. It is difficult to select a preferred treatment option in the absence of head-to-head trials (the guidelines simply list the treatments in alphabetical order), and individual factors make different treatments more suitable for different patients (discussed further later in this report). However, while results from separate studies with different agents cannot be directly compared, Prof Fox considered how convincing the evidence is for each option. Clopidogrel plus aspirin was investigated in the CHARISMA study, which was overall a negative trial (no significant effect on major adverse cardiovascular events, or cardiovascular or all-cause mortality), although there was a marginal benefit in a subgroup of patients with documented cardiovascular disease (as opposed to asymptomatic patients with atherosclerotic risk factors).[4] Prasugrel has some evidence for benefits in the first year of treatment (including new data presented at ESC 2019[5]) but long-term evidence is lacking. Ticagrelor showed evidence of improved outcomes in the long-term treatment setting (1–3 years post-MI) in PEGASUS;[6] however, there was no significant impact on overall mortality, and a considerable increase in risk of major bleeding. The COMPASS study (the pivotal trial demonstrating efficacy of rivaroxaban 2.5 mg twice daily [bid] plus aspirin in patients with CAD and/or PAD)[7] provides the most convincing evidence of improvements in cardiovascular outcomes and overall mortality in this setting; indeed, the effect was so marked that the trial was terminated early, after an interim analysis revealed an excess of events in the aspirin-only arm compared with the rivaroxaban plus aspirin arm.

Recommendations for antithrombotic therapy in patients with CCS and in sinus rhythm	Class*	Evidence level*
Adding a **second antithrombotic** drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk of ischaemic events** and without high bleeding risk	IIa	A
Adding a **second antithrombotic** drug to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk of ischaemic events** and without high bleeding risk	IIb	A

High ischaemic risk defined as:

- Diffuse multivessel CAD with **at least one** of the following:
  - Diabetes requiring medication
  - Recurrent MI
  - PAD
  - CKD with eGFR 15–59 mL/min/1.73m^2

Moderate ischaemic risk defined as:

- **At least one** of the following:
  - Multivessel/diffuse CAD
  - Diabetes requiring medication
  - Recurrent MI
  - PAD
  - HF
  - CKD with eGFR 15–59 ml/min/1.73m^2

Figure 1: 2019 guidelines for the management of CCS: Recommendations for event prevention[1]

*A Class IIa recommendation is given if there is a divergence of opinion about the usefulness/efficacy of the given treatment but the weight of evidence/opinion is in favour of usefulness/efficacy; a Class IIb recommendation is given if usefulness/efficacy is less well established by evidence/opinion. Level of evidence A reflects data derived from multiple randomised clinical trials or meta-analyses.

CAD: coronary artery disease; CCS: chronic coronary syndromes; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; MI: myocardial infarction; PAD: peripheral artery disease.

All trials of dual antithrombotic therapy showed an increased risk of bleeding compared with monotherapy. The guideline recommendation for addition of a second antithrombotic agent therefore applies to patients without a high underlying risk of bleeding (defined as a history of intracerebral haemorrhage; ischaemic stroke, or other intracranial pathology; recent gastrointestinal [GI] bleeding; anaemia due to possible GI blood loss, or other GI pathology associated with increased bleeding risk; renal failure requiring dialysis or eGFR <15 mL/min/1.73m^2; liver failure; bleeding diathesis or coagulopathy; or extreme old age or frailty). For all patients, it is necessary to weigh up potential treatment benefits versus bleeding risk. However, while ischaemic risk increases with accumulation of risk factors, bleeding risk increases at a much slower rate (based on analysis of data from the REACH registry)[8] leading to a more favourable benefit–risk balance for patients with high ischaemic risk.

Prof Fox closed the session by summarising key take-home messages: for patients with no elevated bleeding risk, there are now several options for long-term management. DAPT is well established in the setting of short-term treatment following acute coronary syndromes (ACS); guidelines now advocate extending this to long-term management of CCS for high-risk patients. DPI, adding an anticoagulant instead of a second antiplatelet agent, represents a new treatment paradigm, with compelling data from the COMPASS trial to support this approach. Speaking in a separate interview, Prof Jan Steffel, University Heart Center, Zurich, Switzerland, noted that although the COMPASS data are recognised by the cardiology community, formalising clinical practice recommendations based on those data in these guidelines should boost awareness of the need for 'aggressive' diagnosis and treatment for high-risk patients to reduce morbidity and mortality.

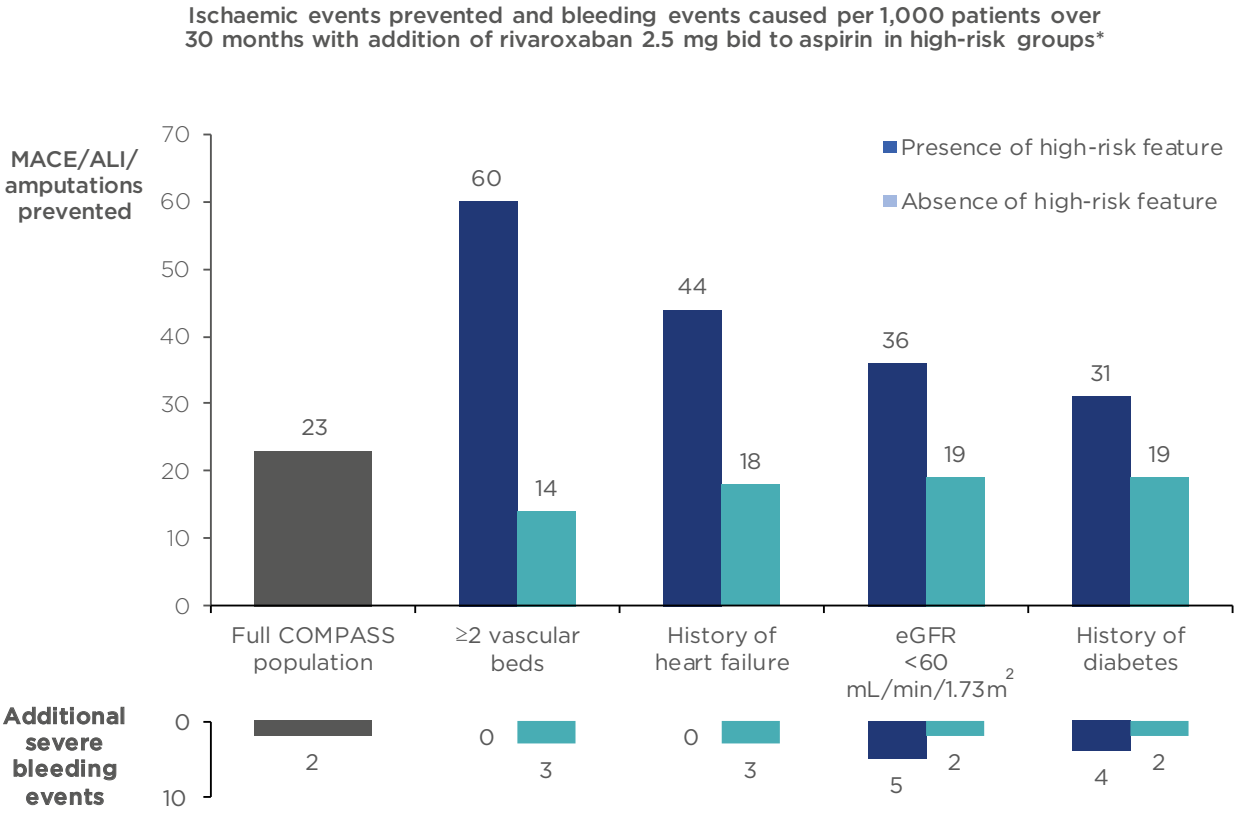

Figure 2: Identifying high-benefit patients for dual pathway inhibition: Risk-stratification analysis of COMPASS data[3]

*Identified through two independent methods (a modified REACH score and a CART analysis).

ALI: acute limb ischaemia; bid: twice daily; CART: classification and regression tree; eGFR: estimated glomerular filtration rate; MACE: major adverse cardiac events; REACH: REduction of Atherothrombosis for Continued Health.

Drug option	Dose	Indication	Additional cautions
Clopidogrel	75 mg od	◆ Post-MI in patients who have tolerated DAPT for 1 year	
Prasugrel	10 mg od†	◆ Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age >75 years
Ticagrelor	60 mg bid	◆ Post-MI in patients who have tolerated DAPT for 1 year	
Rivaroxaban	2.5 mg bid	◆ Post-MI >1 year ***or*** ◆ Multivessel CAD‡	CrCl 15–29 mL/min

Table 1: Treatment options for dual antithrombotic therapy in combination with aspirin 75–100 mg once daily*[1]

*In patients with high or moderate risk of ischaemic events who do not have high bleeding risk

†5 mg od if body weight <60kg or age >75 years

‡Rivaroxaban is the only option for dual antithrombotic therapy indicated in patients with CCS at high ischaemic risk with or without a prior MI

bid: twice daily; CAD: coronary artery disease; CrCl: creatinine clearance; DAPT: dual anti-platelet therapy; MI: myocardial infarction; od: once daily; PCI: percutaneous coronary intervention.

Guidelines in Perspective

Professor John Eikelboom

One challenge in CCS is the number of therapies that may be required to address all aspects of cardiovascular risk. Lifestyle modification is the foundation on which to build secondary prevention through medication, including treatments to lower lipids, and control blood pressure. Antithrombotic medication is an important part of the overall picture. Historically, aspirin has been the mainstay of antithrombotic treatment. Now, guidelines recommend considering intensification of antithrombotic therapy for patients at high risk of ischaemic events by adding a second antithrombotic agent for long-term secondary prevention.[1]

The new ESC guidelines do not distinguish between DAPT and DPI in the approach to intensifying antithrombotic treatment. Prof Eikelboom gave his perspective on the selection of a second antithrombotic agent. DAPT has been tested primarily in the post MI setting and is standard treatment for the first year following MI, and the first few months to 1 year following percutaneous coronary intervention (PCI). At that point, the need for intensified antiplatelet treatment should be re-evaluated. If the patient is no longer considered to be at high ischaemic risk, they can revert to single antiplatelet therapy (SAPT). If ischaemic risk remains high, the preferred course of action depends on what is driving that risk. If the primary concern is stent-related risk (e.g., multiple stents, long stent, or bifurcation stent), continued DAPT may be appropriate. However, if the main driver of ischaemic risk is atherosclerotic disease, then a dual pathway approach (using rivaroxaban in combination with aspirin) is likely to be more appropriate.

Prof Eikelboom noted that rivaroxaban 2.5 mg bid also reduced stent thrombosis in patients with ACS in the ATLAS study;[9] so, the DPI approach should not be ruled out in patients with stent-related risk, particularly if they also have additional risk factors relating to atherosclerotic risk. Rivaroxaban has the broadest indication of all options for dual antithrombotic therapy listed in the new ESC guidelines, as it's the only option for which the indication is not restricted to the post-MI setting (Table 1). The guidelines support its use in patients who have been shown to derive the greatest benefit from the DPI approach, as identified in a risk stratification analysis of patients in the COMPASS study.[3] Indeed, the definition for high-risk patients provided in the new guidelines (described above in the *Guideline Update* section) was based largely on this analysis. Therefore, while the guidelines do not distinguish between DPI and DAPT in the recommendations for dual antithrombotic therapy, much of the direct evidence supporting dual antithrombotic therapy in high-risk patients is for DPI with rivaroxaban plus aspirin.

A query arose as to whether it was worth considering adjusting treatment, in light of the new guidelines, for patients who had been stable on SAPT for a long period. Prof Eikelboom confirmed that he would consider adding rivaroxaban for CCS patients with underlying atherosclerotic disease, even if they had been stable for many years. Speaking in a separate interview, Prof Jan Steffel noted that CCS patients are stable only in relative, but not absolute, terms, as reflected by the change in nomenclature in the new guidelines. Prof Martin Cowie, Imperial College London, London, UK, (interviewed separately) also highlighted this as an important aspect of the guidelines update, stating that there is "no such thing as *stable* CAD," and emphasising the importance of assessing risk at each interaction with the patient to guide consideration as to whether they require amplified antithrombotic therapy.

FROM TRIAL TO TREATMENT IN TREATMENT IN VASCULAR PROTECTION: WHICH HIGH-RISK CORONARY ARTERY DISEASE PATIENTS BENEFIT THE MOST?

Case studies on clinical implementation of dual pathway inhibition in light of current guidelines.

Diabetes

Professor Gilles Montalescot

Prof Montalescot described the case of a 70-year-old woman with a long-standing history of hypertension and diabetes, managed using

angiotensin converting enzyme (ACE) inhibitors and metformin. She had undergone PCI following MI, after which she received DAPT with aspirin plus ticagrelor, as well as lipid-lowering treatment with a statin. She was seen as an outpatient 13 months post PCI and was doing well. Her ECG was normal, and low-density lipoprotein controlled to 0.62 g/L, although there was some evidence of renal dysfunction, with creatinine clearance 54 mL/min. This appeared to be a relatively straightforward case, but Prof Montalescot addressed particular considerations in light of the new guidelines. He presented five options for continued management of this patient:

a) Stop ticagrelor (moving to aspirin monotherapy would have been the standard approach under the old guidelines for stable CAD).

b) Stop aspirin (ticagrelor monotherapy).

c) Continue aspirin plus ticagrelor (a regimen of ticagrelor plus aspirin was investigated in patients with diabetes and CAD in the THEMIS study).[10]

d) Switch to SAPT with clopidogrel.

e) Replace ticagrelor with rivaroxaban 2.5 mg bid (switch to DPI).

The audience were split between options (c) and (e). Prof Montalescot outlined a possible clinical decision-making pathway taking several factors into consideration:

1. Bleeding risk; if bleeding risk is high, monotherapy would be more appropriate than combined therapy.
2. Ischaemic risk.
    - **i)** Stent-related risk; elevated risk of stent thrombosis (which may be present if the patient has, for example, multiple stents, long stents, small-diameter stents in a small artery, or a prior history of stent thrombosis) may indicate continuation of DAPT.
    - **ii)** Clinical risk; several clinical risk factors, including polyvascular disease (≥2 diseased vascular beds), HF, diabetes, and renal dysfunction, place patients at increased risk of an ischaemic event. COMPASS data show a substantial benefit of DPI with rivaroxaban plus aspirin in these patient groups.
    - **iii)** For patients with low ischaemic risk, dual antithrombotic therapy may not be necessary, and the guideline recommendation to use a second antithrombotic agent in addition to aspirin does not apply to this group.

The patient featured in the case study did not have high bleeding risk or high stent-related risk but did have three identified clinical risk factors: age >65 years, diabetes, and renal dysfunction. According to an analysis of cumulative risk using REACH registry data for a subset of patients with ≥1 risk factor (consistent with enrolment criteria for COMPASS), a patient with three such risk factors would have approximately 17% increase in risk of an event over 4 years.[8] Therefore, Prof Montalescot considered her a suitable candidate for DPI with rivaroxaban plus aspirin. This is further supported by the COMPASS risk-stratification analysis, which showed that either diabetes or renal function alone would confer a greater benefit of the rivaroxaban plus aspirin regimen (compared with the average reduction in events seen in the overall study population);[3] combined, these risk factors suggest the patient stands to gain considerable benefit from this treatment strategy.

It was noted that many factors drive cardiovascular risk, and it is important to consider all sources of risk, including optimal control of blood pressure and lipids. The patient described in the case study was well controlled on ACE inhibitors and statins, but that is not always the case for many patients presenting in the clinic. It was suggested that she might benefit from a switch from metformin to a sodium-glucose co-transporter 2 (SGLT2) inhibitor to optimise glycaemic control. She did not have documented PAD; however, PAD is common in patients with diabetes, and the ESC recently published updated guidelines for diabetes[11] which recommend rivaroxaban (2.5 mg bid) plus low-dose aspirin for diabetes patients with lower extremity arterial disease.

Polyvascular Disease (Coronary Artery Disease/ Peripheral Artery Disease)

Professor Dirk Sibbing

Prof Sibbing presented a case study featuring a 58-year-old male with multiple cardiovascular risk factors, including hyperlipidaemia, hypertension, and continued smoking. The patient had diffuse multivessel CAD and had undergone a coronary artery bypass graft several years previously, and multiple PCI in the intervening years, with a history of stent thrombosis and restenosis. He also had PAD affecting the bifurcations of the femoral arteries and carotid arteries bilaterally. He presented to the clinic with chest pain (angina pectoris) on exertion; angiography confirmed progression of the patient's CAD on his existing SAPT treatment regimen (aspirin only), with stenosis requiring a further PCI (the patient's sixth such procedure). He was prescribed atorvastatin and candesartan to manage his lipids and blood pressure. Prof Sibbing outlined options for antithrombotic treatment: initial treatment following PCI would be 6 months' DAPT (aspirin plus clopidogrel or ticagrelor); options for long-term treatment included SAPT (revert to aspirin only), continued DAPT (e.g., aspirin plus ticagrelor), or DPI with aspirin plus rivaroxaban. This patient could have been considered a candidate for continued DAPT, given his history of stent thrombosis and restenosis (as discussed by Prof Eikelboom and Prof Montalescot); however, Prof Sibbing noted that CAD patients who also have PAD are at substantially increased atherosclerotic risk versus those with CAD only,[12] so this was a prominent concern. He revealed that he had chosen to treat the patient with aspirin plus rivaroxaban, switching to DPI for long-term secondary prevention. This treatment decision was taken prior to the recent release of the new ECS guidelines for CCS, and was based on convincing data from the COMPASS study demonstrating an enhanced benefit of aspirin plus rivaroxaban in patients with CAD+PAD, greater than that seen in patients with CAD only.[13] Risk of bleeding was similar in both patient subgroups, indicating a particularly favourable benefit–risk balance for patients with CAD+PAD.

Patients with polyvascular disease were among several subgroups identified in the COMPASS study population as being high-risk patients for whom DPI provided enhanced protection.[3] These data are now reflected in the new ESC guidelines for CCS,[1] supporting a Class IIa recommendation for addition of a second antithrombotic agent such as rivaroxaban for the long-term treatment of patients with high ischaemic risk.

Heart Failure

Professor Gilles Montalescot

Prof Montalescot's second case study featured a 68-year old patient, a heavy smoker, who had undergone PCI following MI, and presented 16 months later with signs of HF. The patient improved on furosemide; he also remained on aspirin and prasugrel (initiated following PCI), as well as statins, ACE inhibitors, and beta-blockers.

Prof Montalescot considered options for continued management of this patient (based on the factors outlined when discussing his diabetes case study, above). The patient did not have an elevated risk of bleeding, so dual antithrombotic was not contraindicated. A patient with HF meets the criteria for moderate ischaemic risk according to the guideline's definition; other risk factors such as smoking and age >65 years add to the patient's overall risk profile.[8] Therefore, consideration of dual antithrombotic therapy was warranted. The patient was already on DAPT (aspirin plus prasugrel), so it was queried whether there was any need to change their treatment regimen. Prof Montalescot discussed circumstances in which a cardiologist might consider switching away from DAPT, namely when there are other risk factors besides stent-related risk to consider. The risk-stratification analysis from the COMPASS trial identified patients with polyvascular disease, HF, renal insufficiency, and diabetes as groups that derived the greatest benefit from DPI with aspirin plus rivaroxaban (Figure 2).[3] This provides an evidence-based rationale for considering a switch to DPI (replacing prasugrel with rivaroxaban) for this patient with HF.

Conclusion

Together, these case studies demonstrate several scenarios in which the availability of a new treatment option, DPI with rivaroxaban plus aspirin, can improve the management of patients with CCS who require additional cardiovascular protection. This is now supported by the new guidelines published by ESC.

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Hypercholesterolaemia Management: What Will Be Our Options After Tomorrow?

This symposium took place on 1st September 2019 as part of the European Society of Cardiology (ESC) Annual Congress in Paris, France

Chairpeople: Lale Tokgozoglu[1]

Speakers: Lale Tokgozoglu,[1] Philippe Gabriel Steg,[2,3] Brian Ference,[4] Erik Stroes[5]

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Disclosure: Prof Tokgozoglu has been a speaker and/or advisor for Abbott, Actelion, Amgen, Bayer, MSD, Mylan, Novartis, Novo Nordisk, Pfizer, Recordati, Sanofi, Sanovel, and Servier. Prof Steg has received research grants from Bayer, Merck, Sanofi, and Servier; has clinical trial contracts with Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Pfizer, Sanofi, and Servier; and has spoken and/or advised for Amgen, Novo Nordisk, and Regeneron. Prof Ference has received research grants from Merck, Novartis, Amgen, Esperion Therapeutics, and Ionis Pharmaceuticals and has consulted and/or advised for Amgen, Regeneron, Sanofi, Novartis, Pfizer, Eli Lily, Novo Nordisk, Ionis Pharmaceuticals, dalCOR, The Medicines Co., Mylan, CiVi Pharma, KrKa Pharmaceuticals, American College of Cardiology (ACC), European Atherosclerosis Society (EAS), and European Society of Cardiology (ESC). Prof Stroes has advised and/or spoken for Amgen, Sanofi-Regeneron, Merck, Chiesi, Akcea, IONIS, AstraZeneca, Athera, and Mylan.

Acknowledgements: Writing assistance was provided by Stephen Jeffreys and Stefan Amisten on behalf of the European Medical Journal.

Support: The publication of this article was funded by Mylan Pharma. The views and opinions expressed are those of the presenters. Content was reviewed by Mylan and the speakers for medical accuracy.

Citation: EMJ Cardiol. 2019;7[1]:46-55.

Meeting Summary

Prof Tokgozoglu opened the seminar by reviewing the evidence for atherosclerotic cardiovascular disease (ASCVD) management and suggested that in very high-risk patients, a further reduction in low density lipoprotein cholesterol (LDL-C) further reduces cardiovascular (CV) events. More stringent LDL-C goals are needed for very high-risk patients, and a treatment algorithm may allow for the identification of such patients and for optimal personalised therapies.

Prof Steg reviewed the use of statins in LDL-C and CV risk management and highlighted the benefits of a combination therapy consisting of the cholesterol absorption inhibitor ezetimibe with traditional

statins for stable CV disease (CVD) patients and for acute coronary syndrome (ACS) event survivors. The identification of patients with the greatest baseline CV risk, who would benefit most from the addition of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, was also outlined.

Prof Ference explained how genetic segmentation of patient cohorts may be used to optimise the profiling of patient groups, and how Mendelian randomisation studies have demonstrated CV risk reductions on par with the three main LDL-C reducing agents: statins, ezetimibe, and PCSK9 inhibitors.

Prof Stroes discussed the evidence to support LDL-C eradication for optimal CV risk control which points clearly toward starting with an affordable statin-ezetimibe combination therapy approach. However, for patients with very high, absolute CV risk, and residual LDL-C burden, PCSK9 inhibition could be added to the regimen. The effect of medication stacking on reduced treatment adherence and increased incidence of adverse events was also explored, as well as the need for decision support tools to optimise patient-centred therapies tailored to individual needs, and novel therapies that improve both physician capability and patient adherence are needed to improve treatment outcomes and adherence.

To Be or Not to Be... But at Which Goal?

Professor Lale Tokgozoglu

Prof Tokgozoglu opened the meeting by providing an overview of the advances in the management of dyslipidaemia over recent years. CVD is a major cause of morbidity for all regions of the world.[1] A recent study from Swedish national registries on CV event rates in a high-risk ASCVD population found that in a real-world setting, CV event rates were high in cohorts with incident ischaemic stroke or incident myocardial infarction (MI), with major adverse cardiovascular event composite rates two to three times higher than those reported in the FOURIER clinical trial, which indicates a substantial disease burden in this patient group despite treatment with moderate or high-intensity statins.[2] This registry providing real-world evidence suggests that there is more to be done to reduce adverse CV outcomes in these high-risk patients.

There is consistent evidence from randomised controlled trials, prospective cohort series, and Mendelian randomisation trials that the plasma LDL-C concentration is strongly and log-linearly associated with a dose-dependent increase in the risk of incident ASCVD events.[3] The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL-C has both a causal and a cumulative effect.

In a meta-analysis of eight statin trials, major CV events were decreased as the achieved LDL-C decreased on statin therapy. However, there were large inter-individual variability in the reductions of LDL-C, non-high density lipoprotein-cholesterol, and apolipoprotein B (apoB) achieved with a fixed statin dose, and >40% of trial participants assigned to high-dose statin therapy did not reach an LDL-C target of <70 mg/dL.[4]

Evidence for benefit from further lowering of LDL-C in hyperlipidaemia has come from two large prospective PCSK9 inhibitor studies, the FOURIER and the ODYSSEY studies, which established the efficacy of evolocumab and alirocumab, respectively. Both studies demonstrated continued risk reduction even at very low LDL-C levels, without any LDL-C concentration threshold.[5, 6]

The safety and efficacy of PCSK9 inhibitors were also evaluated in a meta-analysis of 39 randomised clinical trials with >66,000 patients. The study authors concluded that PCSK9 inhibitors are associated with lower risk of MI, ischaemic stroke, and coronary revascularisation, and that the PCSK9 inhibitors alirocumab and evolocumab have a favourable safety profile.[7]

Furthermore, a meta-analysis based on Cholesterol Treatment Trialists' Collaboration (CTTC) patient data examined the efficacy and safety of further lowering of LDL-C in patients starting with very low LDL-C levels. This study reported a consistent relative risk reduction in major vascular events per change in LDL-C in patient populations, starting as low as a LDL-C

median of 1.6 mmol/L (63 mg/dL) and achieved levels as low as a LDL-C median of 0.5 mmol/L (21 mg/dL), without any offsetting adverse effects. The results from this study suggest that further lowering of LDL-C, beyond the lowest current targets, would further reduce CV risk.[8]

Although LDL-C goals are attained with monotherapy in many patients, a significant proportion of patients either at high risk, or with very high LDL-C levels, need additional treatment. New European Society of Cardiology (ESC) guidelines provide advice on how this can be approached.[9]

To follow a stratified treatment approach, a definition is needed for patients who are at 'highest risk', (i.e., those with the highest baseline event rate). Highest risk categories include polyvascular disease; ASCVD with comorbidities, such as chronic kidney disease or diabetes with end-organ damage; or familial hypercholesterolaemia (FH) patients with a CVD event.[10] A simple nine-point risk stratification tool has been developed by the Thrombolysis In Myocardial Infarction (TIMI) group to predict recurrent CV events in a large population of stable patients with previous MI. The risk score for secondary prevention incorporates the following readily available clinical characteristics: older age, diabetes, hypertension, smoking, peripheral artery disease, previous stroke, previous coronary artery bypass graft, history of heart failure, and renal dysfunction.[11] Recently, there has been interest in developing genetic risk scores by combining multiple variants with small effects. The effect of these scores on outcomes are being tested in different populations. One group has developed genetic risk scores to identify individuals at increased risk for both incident and recurrent coronary heart disease events, and reported that people with the highest burden of genetic risk derived the largest relative and absolute clinical benefit from statin therapy.[12]

Combination Therapy in Cardiovascular Risk Reduction: What are we Waiting for in Dyslipidaemia Management?

Professor Philippe Gabriel Steg

LDL-C reduction with statins is the cornerstone of lipid therapy to reduce CV risk. The MRFIT study demonstrated a clear curvilinear relationship, thus establishing that there is no threshold effect.[13] Lowering LDL-C with statins is very effective in decreasing CV risk, as coronary heart disease (CHD) event rates in primary and secondary prevention trials are directly proportional to the on-treatment LDL-C levels.[14,15] Statin CV outcomes trials show that the magnitude of CV events reduction is related to the LDL-C reduction, and that there is a direct relationship of 22% risk reduction in CV events per 1 mmol/L reduction in LDL-C.[16]

Additional LDL-C reduction with ezetimibe further reduces LDL-C and CV risk, as reported by the IMPROVE-IT study, which randomised patients to receive either simvastatin monotherapy or simvastatin plus ezetimibe combination therapy. The event rate for the primary end point at 7 years was 32.7% in the simvastatin plus ezetimibe group, compared with 34.7% in the simvastatin monotherapy group.[17] Furthermore, in patients whose conditions were stabilised after an ACS, a strong gradient of risk for recurrent CV events was identified, as well as an increasingly favourable relative and absolute benefit from the addition of ezetimibe to simvastatin therapy with increasing risk profile.[11] A similar study found that dual inhibition of cholesterol absorption and synthesis through co-administration of ezetimibe plus simvastatin was more efficacious than respective monotherapies at achieving target LDL-C levels compared with respective monotherapy.[18]

In a comparative efficacy and safety study of rosuvastatin versus atorvastatin, simvastatin, and pravastatin (the STELLAR trial),[19] rosuvastatin reduced total cholesterol significantly more ($p<0.001$) than all comparators, and triglycerides significantly more ($p<0.001$) than simvastatin and pravastatin.[19]

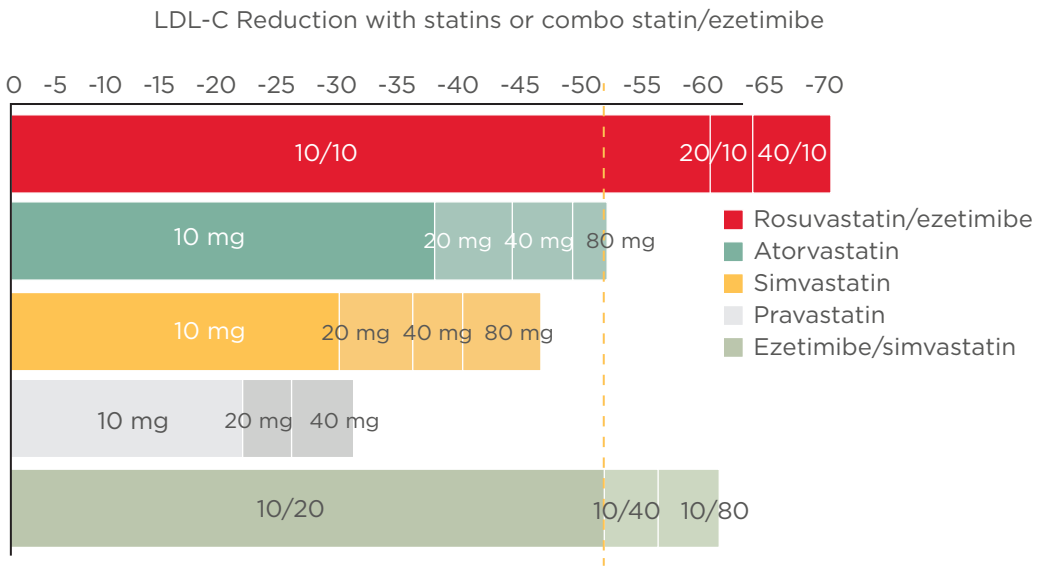

Figure 1: Comparison of three efficacy studies evaluating low-density lipoprotein cholesterol reduction with statins and statin/ezetimibe.

Adapted from Goldberg et al.,[18] Jones et al.,[19] Ballantyne et al., [20] and Ballantyne et al.[21]

LDL-C: low density lipoprotein cholesterol.

The GRAVITY[20] study compared the efficacy and safety of rosuvastatin plus ezetimibe versus simvastatin plus ezetimibe and reported that co-administration of rosuvastatin 10 and 20 mg plus ezetimibe achieved significantly greater ($p<0.05$) reductions in LDL-C and other atherogenic lipids in high-risk patients compared with simvastatin 40 and 80 mg plus ezetimibe co-administration, respectively. The EXPLORER[21] study investigated the efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg (Figure 1).

Lower LDL-C levels can be achieved with CV benefits in patients with stable CV disease, as demonstrated in the FOURIER study.[5] Lower LDL-C levels can also be achieved in post ACS patients, as was demonstrated in the meta-analysis by Boekholdt et al.[4] However, statins do not completely abolish the risk of CV events, although intensive lipid-lowering statin regimen provides greater protection against death or major CV events than a standard regimen.[22]

Patients who have had an ACS are at high risk for recurrent ischaemic CV events, and the ODYSSEY[6] study demonstrated that the monoclonal PCSK9 inhibitor antibody alirocumab further reduced the risk of recurrent ischaemic CV events compared with placebo in ACS patients receiving high-intensity statin therapy.[6] The effects of treatment on all-cause death and its components, CV and non-CV death, were further examined in a post-trial analysis, which reported that the risk of death declined with lower achieved LDL-C, down to an LDL-C level of approximately 30 mg/dL.[23]

In conclusion, the evidence shows that statins should be the first-line therapy to reduce LDL-C and CV risk. Furthermore reductions in LDL produce additional clinical benefits, even though there is a risk of myopathy and elevated liver enzymes when high dose statins are further increased. Importantly, the LDL-lowering efficacy of increasing statin dosing is modest due to the rule of six.[24] Prof Steg suggested that if LDL goals are not achieved by statin therapy, then a combination of statin plus ezetimibe, with proven benefits in post ACS patients, should be considered. For high-risk patients, there is evidence that lower LDL targets are associated with clinical benefits. Finding the patients with the greatest baseline risk and the greatest relative and absolute benefit will be important in order to maximise the cost-effectiveness of new agents such as PCSK9 inhibitors.

Low Density Lipoprotein Cholesterol Reducing Agents: What Genetics Tells Us

Professor Brian Ference

In 2003, the ninth member of the proprotein convertase gene, *PCSK9*, was mapped. In the same year, a study reported that two mutations in *PCSK9* were causing autosomal dominant hypercholesterolaemia in two French families through a gain-of-function expression mechanism.[25] Another study reported on sequence variations in *PCSK9* and low LDL resulting in protection from CHD due to loss-of-function mutations in the *PCSK9* gene.[26]

When the first reports emerged of the large-scale studies for the *PCSK9* inhibitor monoclonal antibodies evolocumab and alirocumab, there was much excitement due to the reported ~60% reduction in LDL-C compared with baseline.[27, 28] However, as the FOURIER[5] and ODYSSEY[6] Outcomes trials reported, the longer term results did not live up to these early reports of very efficacious LDL-C reductions.

Mendelian randomisation enables the trialist to use genetic epidemiology for screening for the most appropriate allele in the treatment arm and allow other alleles to be represented in the 'usual care' arm. In a recent study, genetic scores were used, consisting of independently inherited variants in the genes encoding PCSK9 and 3-hydroxy-3-methylglutaryl–coenzyme A reductase (*HMGCR*, the statin target gene) as instruments to randomly assign 112,772 participants from 14 studies to groups according to the number of LDL cholesterol-lowering alleles they had inherited. The effects of lower LDL-C levels mediated by variants in *PCSK9*, *HMGCR*, or both, on the risk of CV events and the risk of diabetes were compared, and gene variants in *PCSK9* and *HMGCR* were associated with nearly identical protective effects on the risk of CV events per decrease of 10 mg/dL (0.26 mmol/L) LDL-C. When present together, *PCSK9* and *HMGCR* variants had additive effects on the risk of both CV events and diabetes.[29]

LDL has both a causal and a cumulative effect on CHD risk. A study conducted to evaluate the effect of naturally random allocation to lower LDL-C mediated by polymorphisms in the *NPC1L1* gene (the ezetimibe target), the *HMGCR* gene, or both, on the risk of CHD found that compared to the reference group, the *NPC1L1* polymorphism group had 2.4 mg/dL lower LDL-C and 4.8% lower risk of CHD while the *HMGCR* polymorphism group had 2.9 mg/dL lower LDL-C and 5.3% lower risk of CHD. Additionally, the group with lower LDL-C mediated by both *NPC1L1* and *HMGCR* polymorphisms had 5.8 mg/dL additively lower LDL-C and a 10.8% lower risk of CHD.[30]

Mendelian randomisation studies introduce an element of chance into an observational study designed specifically to assess whether an observed association between an exposure and an outcome is likely to be causal. Numerous variants in multiple genes have been reported to be associated with lower LDL-C levels. Each of these variants is inherited randomly at the time of conception in a process sometimes referred to as Mendelian randomisation.[3]

Therefore, inheriting an LDL-C-lowering allele in one of these genes is analogous to being allocated indiscriminately to treatment with an LDL-C-lowering therapy, while inheriting the other allele is analogous to being randomly allocated to 'usual care.' If the variant under study is associated solely with LDL-C and not with other lipid or non-lipid pleiotropic effects, and if allocation is indeed random, then comparing the risk of ASCVD among persons with and without such a variant should provide an unconfounded estimate of the causal effect of lower LDL-C levels on the risk of ASCVD in a manner similar to a long-term, randomised trial.[3]

Mendelian randomisation studies have consistently demonstrated that variants in >50 genes, which are associated with lower LDL-C levels (but not with other potential predictors or intermediates for ASCVD), are also associated with a correspondingly lower risk of CHD. This provides powerful evidence that LDL is causally associated with the risk of CHD.[3]

Indeed, when the effect of each LDL-C variant is plotted against its effect on CHD, there is a continuous, dose-dependent, and log-linear causal association between the magnitude of the absolute change in LDL-C level and the lifetime risk of CHD. When adjusted for a standard reduction in LDL-C, each of the genetic variants associated

with LDL-C has a remarkably similar effect on the risk of CHD per unit lower LDL-C, including variants in the genes that encode the targets of pharmacological agents commonly used to lower LDL-C (*HMGCR*, *NPC1L1,* and *PCSK9*), with no evidence of any heterogeneity of effect. This observation strongly implies that the causal effect of these variants on the risk of CHD is mediated essentially entirely through LDL-C. Taken together, meta-analyses of Mendelian randomisation studies involving >300,000 participants and 80,000 CHD cases provide compelling evidence that LDL-C is causally associated with the risk of ASCVD and the causal effect of LDL-C on ASCVD is largely independent of the mechanism by which LDL-C is reduced.[3]

In conclusion, genetic variants in the genes *HMGGR*, *PCSK9,* and *NPC1L1* all have the same effect on the risk of ASCVD per unit change in LDL-C, implying that lowering LDL-C by inhibiting HMG-CoA reductase, PCSK9, or NPC1L1 have biologically equivalent effects on the risk of ASCVD. Randomised trials demonstrate that lowering LDL-C with statins, PCSK9 inhibitors, and ezetimibe is associated with the reduction in CV events per mmol/L reduction in LDL-C. This shows that lowering LDL-C by inhibiting HMG-CoA reductase, PCSK9, or NPC1L1 have biologically therapeutically equivalent effects on the risk of ASCVD.

More generally, both Mendelian randomisation and randomised trials demonstrate that any therapy that lowers LDL-C by reducing LDL particles through the LDL receptor should have the same clinical benefit proportional to the absolute reduction in LDL-C, alone or in combination. The effect of genetic variants and therapies that reduce LDL-C other than through the LDL receptor, or reduce both LDL-C and triglycerides, will be proportional to the absolute change in apoB; indeed, the clinical benefit of any lipid-lowering therapy will be proportional to the absolute reduction in apoB.

Getting to Goals Cost Effectively: How Can we Make a Difference?

Professor Erik Stroes

There have been major advances in addressing atherosclerosis in this last decade. Not only have there been initiatives to reduce lifestyle and environmental impacts, such as smoking, diet choice, exercise, and avoiding environmental risk factors, but medical advances have also seen the advent of lipoprotein targeting, improved blood pressure control, antidiabetic therapies, antithrombotics, and anti-inflammatory therapies all impacting on this important area. There is still a requirement to address the residual risk.

Patient stratification to develop patient treatment pathways relevant to the absolute risk is critical to positive clinical outcomes. As the risk of likely CV event rate increases, the requirement for more forthright interventions are required. A recent study on CV risk factors and prevention looking at individual lifetime benefit from *PCSK9* inhibition in statin-treated patients with coronary artery disease found that the individual estimated lifetime benefit from *PCSK9* inhibition in patients with stable coronary artery disease on high-dose statin varied from 6–12 months free of stroke or MI. Highest benefit is expected in younger patients (age 40–60 years) with high risk factor burden and relatively high LDL-C levels.[31]

A recent review predicted therapy-benefit for individualised CVD prevention and reported that findings in both primary and secondary CVD prevention have shown that the degree of variation in individualised therapy benefit is large. Individualised therapy-benefits are estimated by combining prediction algorithms and clinical trial data, and lifetime estimates (e.g., gain in healthy life expectancy) look at therapy-benefit over the course of an individual's life, and are influenced by short-term estimates (e.g., 10-year absolute risk reduction), rather than age alone.[32]

A model to explore the efficacy of conventional and novel lipid-lowering therapies in a large cohort of heterozygous FH patients reported that with maximal dose statin, 8.3% and 48.1% of patients with and without CHD would reach their recommended LDL-C targets, respectively.

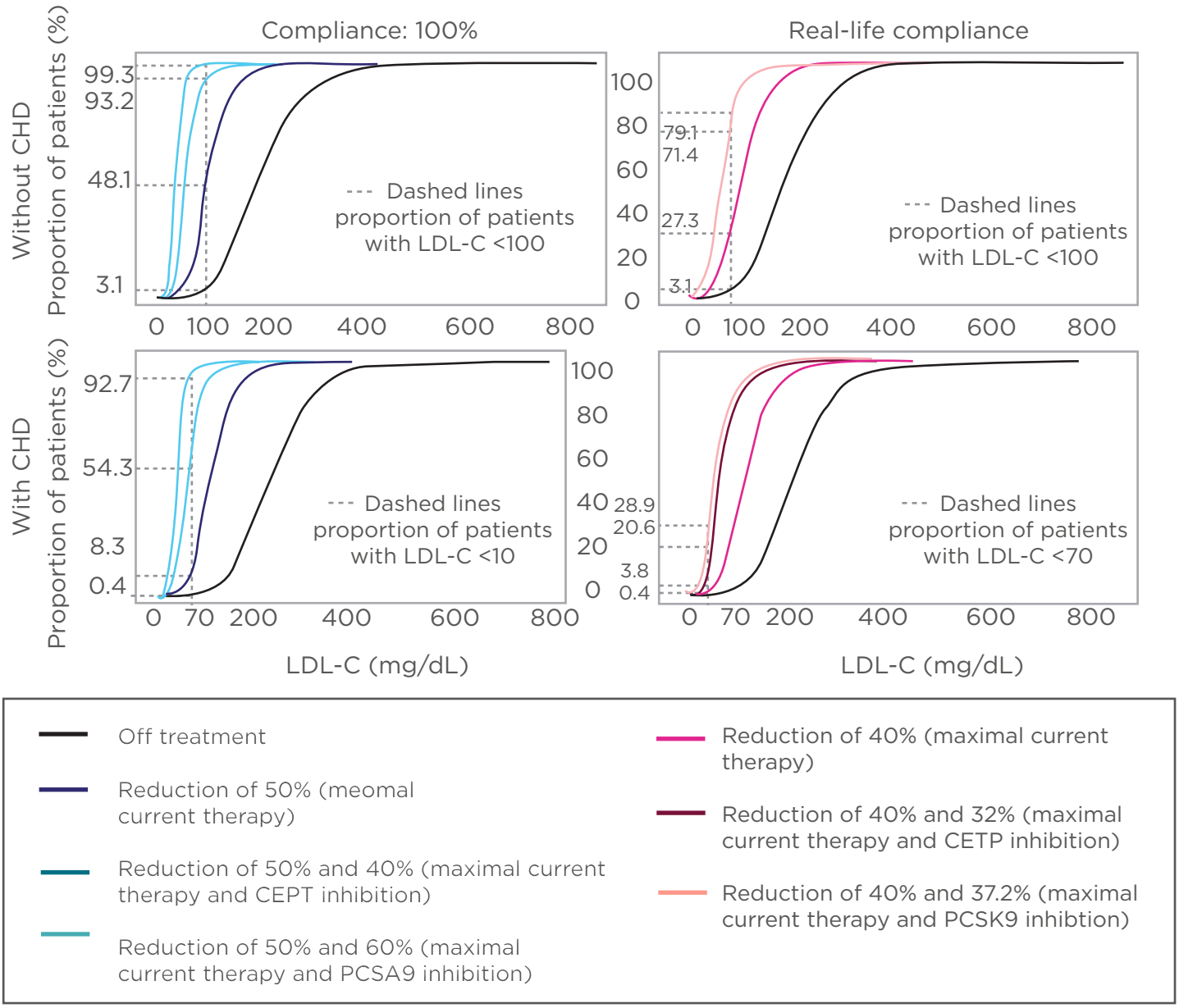

Figure 2: Proportion of patients on LDL-C target in different treatment regimens stratified by history of CHD, with 100% adherence for all treatment scenarios, or 80% adherence for statin therapy with or without ezetimibe, 80% for cholesteryl ester transfer protein inhibitors and 62% for PCSK9 inhibitors.

CHD: coronary heart disease; CETP: cholesteryl ester transfer protein; LDL-C: low density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin-kexin type 9.

This increases to 54.3% and 93.2% when ezetimibe is added, and by adding *PCSK9* inhibitors, this could result in 99.8% and 100.0% treatment goal attainment. However, using literature-based adherence rates, these numbers could be significantly reduced, and it could be argued that patients with heterozygous FH with high untreated LDL-C levels should experience reasonable or high value from the addition of more advanced LDL-C lowering agents such as *PCSK9* inhibitors (Figure 2).[33]

Work towards a tailored medicine approach for high-risk patients requires a multifactorial approach embracing lifestyle interventions, evaluating appropriate guidelines to recommend medical therapy and carry out an absolute risk assessment to develop the most active patient treatment pathway. However, the issue of affordability will also have to be addressed. A cost-effectiveness analysis of evolocumab therapy for reducing CV events in very high-risk patients with atherosclerotic CV disease

according to the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines has just been completed, and demonstrates that at current list price, evolocumab provides high value across a range of CV events in very high-risk patients.[34]

However, the advocacy for such a treatment regime will only come from the physician group familiar with this therapeutic approach. With a broad choice of approaches coming from a range of specialists such as cardiologists, neurologists, vascular internists, endocrinologists, and vascular surgeons, there is a need for harmonisation in the CVD therapy arena, with a harmonised targeted medicine approach for the patient.

The advent of decision-support tools will be a step-change for reducing complexity and managing risk in this setting.

The next challenge is loss of adherence. It is estimated that a substantial proportion of patients adhere inadequately to CV medications, and the prevalence of suboptimal adherence is similar across all individual CVD medications. Risk assessments demonstrate that a considerable proportion of all CVD events (~9% in Europe) could be attributed to poor adherence to vascular medications alone, and that the level of optimal adherence confers a significant inverse association with subsequent adverse outcomes. Measures to enhance adherence to help maximise the potentials of effective CV therapies in the clinical setting are therefore urgently required.[35]

Increased adherence may be achieved through novel treatment modalities such as small interference RNA (siRNA) therapies. The RNA interference pathway regulates messenger RNA (mRNA) stability and translation in nearly all human cells.[36] siRNA constitute a form of RNA interference that selectively and catalytically inhibit the translation of their complementary target mRNA in a sequence-specific manner.[37] Inclisiran is an investigational, chemically synthesised siRNA molecule that produces sustained hepatocyte-specific inhibition of *PCSK9* mRNA.[38] The LDL-C lowering potential of inclisiran has previously been demonstrated in the dose-finding Phase II ORION-1 trial,[39] and data from the recently completed open-label extension ORION-3 study demonstrated consistent lowering of LDL-C >50% with no loss of effect over 3 years of follow-up with subcutaneous injections twice yearly.[40]

In summary, novel platforms to improve supervised adherence such as siRNA, are currently being developed. While only a few years ago the concept of implementing targeted gene silencing was confined to the realm of science fiction, this is now being progressed to the point where there could be practical applications for real world medicine in the next few years.

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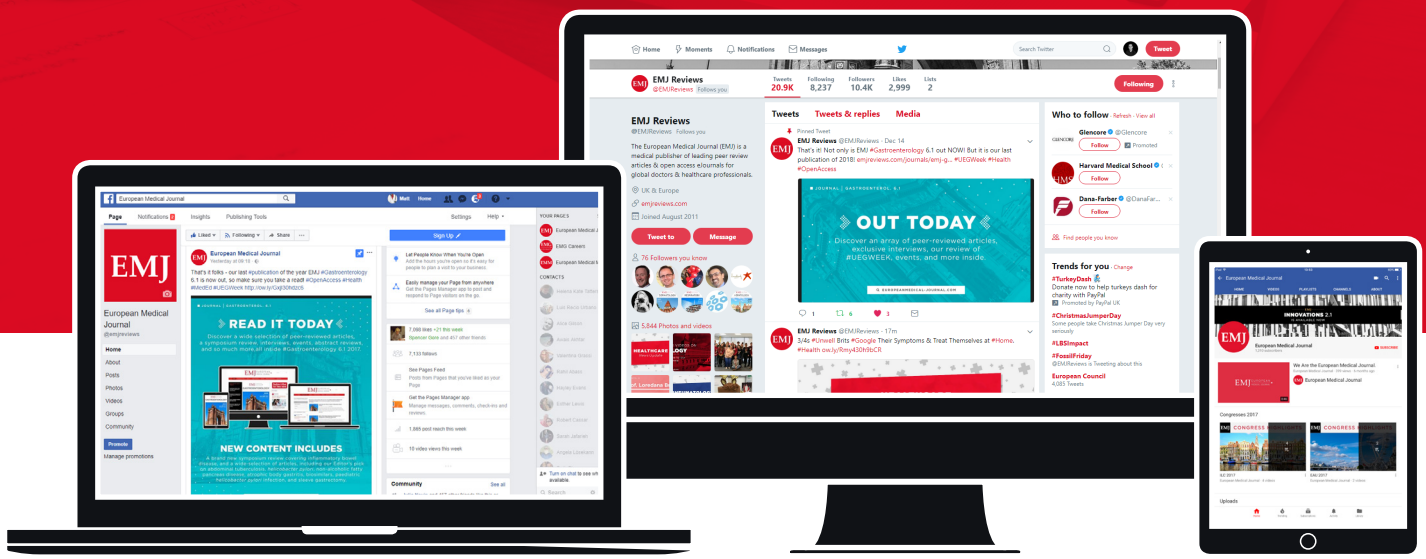

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Icosapent Ethyl for the Prevention of Cardiovascular Events

These oral and poster presentations took place between 31st August and 4th September 2019, as part of the European Society of Cardiology (ESC) Congress in Paris, France

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Disclosure: Prof Nordestgaard reports consulting/royalties/owner/stockholder of a healthcare company and consultancies or talks sponsored by AstraZeneca, Sanofi, Regeneron, Akcea, Amgen, Kowa, Denka Seiken, Amarin, Novartis, Novo Nordisk, and Silence Therapeutics. Dr Bhatt has been on the Advisory Board for Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; has been on the Board of Directors for Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; has been the Chair for American Heart Association Quality Oversight Committee; has been on the Data Monitoring Committees for the Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; has received honoraria from the American College of Cardiology (ACC)(Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); has received research funding from Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; received royalties from Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); has been a site co-investigator for Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; has been a trustee for American College of Cardiology; had unfunded research involving FlowCo, Merck, Novo

Nordisk, PLx Pharma, Takeda; other relationships include: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair). Dr Gitt received honoraria from Merck & Co., Inc. for participation in DYSIS steering committee meetings. Dr Konishi reports no conflicts of interest.

Acknowledgements: Prof Nordestgaard, Dr Bhatt, and Dr Gitt all reviewed and edited the manuscript prior to publication. Dr Konishi did not review or edit the manuscript prior to publication. Writing assistance was provided by Jenny Lloyd, Compass Medical Communications, Ltd., UK.

Support: The publication of this article was funded by Amarin Pharma, Inc. The views and opinions expressed are those of the authors and not necessarily those of Amarin Pharma, Inc.

Citation: EMJ Cardiol. 2019;7[1]:56-65.

Meeting Summary

Prof Nordestgaard said that genetic studies have shown that elevated triglyceride-rich lipoproteins can lead to atherosclerosis and inflammation, which can lead to myocardial infarction (MI). Genetic studies have also shown that lower triglyceride levels are associated with lower cardiovascular risk. Dr Bhatt then said that although low-dose omega-3 fatty acids (1 g/day) are ineffective for preventing heart disease, higher doses (1.8 g/day) have been shown to reduce coronary plaque and the risk of coronary events. He then described the recently published REDUCE-IT trial, which randomised ~8,000 statin-treated patients with elevated triglycerides (1.52–5.63 mmol/L) to icosapent ethyl 4 g/day or placebo. Those randomised to icosapent ethyl had significant reductions in triglyceride levels and cardiovascular events. American and European guidelines have now recognised that omega-3 fatty acids 4 g/day can be beneficial for the management of hypertriglyceridaemia and that icosapent ethyl, in particular, lowers the rate of cardiovascular outcomes. Dr Gitt presented data showing how many patients from DYSIS, a cross-sectional, observational study of lipid goal achievement among statin-treated patients, could benefit from icosapent ethyl. Among >60,000 patients in DYSIS, 72% were at very high cardiovascular risk, and 48% of these had triglycerides >1.52 mmol/L and could therefore potentially benefit from icosapent ethyl. Finally, Dr Konishi presented imaging data showing that eicosapentaenoic acid (EPA), of which icosapent ethyl is a purified ester, is associated with decreased plaque instability. This could help to explain how icosapent ethyl reduces cardiovascular risk.

Triglycerides, Lesson from Genetics

Professor Børge G. Nordestgaard

Based on genetic evidence, it is now known that triglyceride-rich lipoproteins lead to atherosclerosis and local inflammation, which can result in MI due to plaque rupture. Genetic studies have also shown that higher triglyceride levels are associated with a higher risk of MI and lower levels are associated with lower cardiovascular risk. Elevated low-density lipoprotein cholesterol (LDL-C), remnant cholesterol, and triglyceride levels can all increase the risk of cardiovascular disease. Chylomicrons, lipoprotein particles that consist largely of triglycerides, can also increase the risk of pancreatitis. In clinical practice, LDL-C, remnant cholesterol, and lipoprotein(a) are all important, but likely cause disease by different mechanisms. When triglycerides are degraded into toxic free fatty acids, they can cause inflammation, potentially leading to MI or acute pancreatitis. A second pathway by which triglycerides could lead to MI is via cholesterol, foam cells, and atherosclerosis.

In the Copenhagen General Population Study (N=84,177), there was a skewed distribution of nonfasting triglyceride levels.[1] Most people (73.0%) had triglyceride levels of 0–2 mmol/L,

while 27.0% had higher levels (2–10 mmol/L) that could be associated with an increased risk of cardiovascular disease. Only 0.1% had triglyceride levels >10 mmol/L, and such people are at increased risk of acute pancreatitis. In the combined Copenhagen General Population Study and the Copenhagen City Heart Study, higher nonfasting triglyceride levels were associated with higher plasma C-reactive protein (n=115,818), but there was no such correlation between LDL-C and C-reactive protein (n=115,377).[2]

Among 116,550 people from the Copenhagen General Population Study, the risks of MI and acute pancreatitis increased significantly with increasing nonfasting triglyceride levels.[3] Compared to people with triglycerides <1.00 mmol/L, those with triglycerides ≥5.00 mmol/L had a 3.4-fold higher risk of MI and an 8.7-fold higher risk of acute pancreatitis.[3] Similarly, in the Copenhagen City Heart Study and the Copenhagen General Population Study, increasing levels of nonfasting triglycerides were associated with an increased risk of MI and stroke.[1,4] These risks increased with increasing nonfasting triglyceride levels to ~5-fold for MI (Figure 1A) and ~3-fold for stroke (Figure 1B) for the highest versus lowest triglyceride levels.

People with triglyceride levels <10 mmol/L tend to have smaller lipid particles and more LDL-C; those with higher levels (10–30 mmol/L) have more very low-density lipoprotein (VLDL)/remnants; and those with very high levels (>30 mmol/L) have more chylomicrons (unpublished data). While the risk of acute pancreatitis increases with increasing triglyceride levels, the risk of MI peaks at around 30 mmol/L and then decreases at higher triglyceride levels.

In the Copenhagen General Population Study (N=106,216), remnant cholesterol (calculated as total cholesterol - LDL-C - high-density lipoprotein cholesterol [HDL-C]) increased with increasing BMI, from 0.43 mmol/L among the lowest BMI decile to 0.88 mmol/L in the highest BMI decile (p_{trend}<0.001).[5]

Using Mendelian randomisation, the impact of genetic variants on triglyceride, LDL-C, and HCL-C levels can be studied.[6] Provided enough people are studied, those with and without various genetic variants should be matched. In an old analysis from the Copenhagen City Heart Study and the Copenhagen General Population Study (N=56,657), the risk of ischaemic heart disease was increased 1.1–1.6-fold among those with elevated LDL-C, remnant cholesterol:HDL-C, or remnant cholesterol.[7] Genetically elevated levels of remnant cholesterol:HDL-C or remnant cholesterol, however, were associated with much higher risks (2.8–2.9-fold) than genetically elevated LDL-C levels (1.5-fold) (n=54,924), showing the importance of remnant cholesterol.[7]

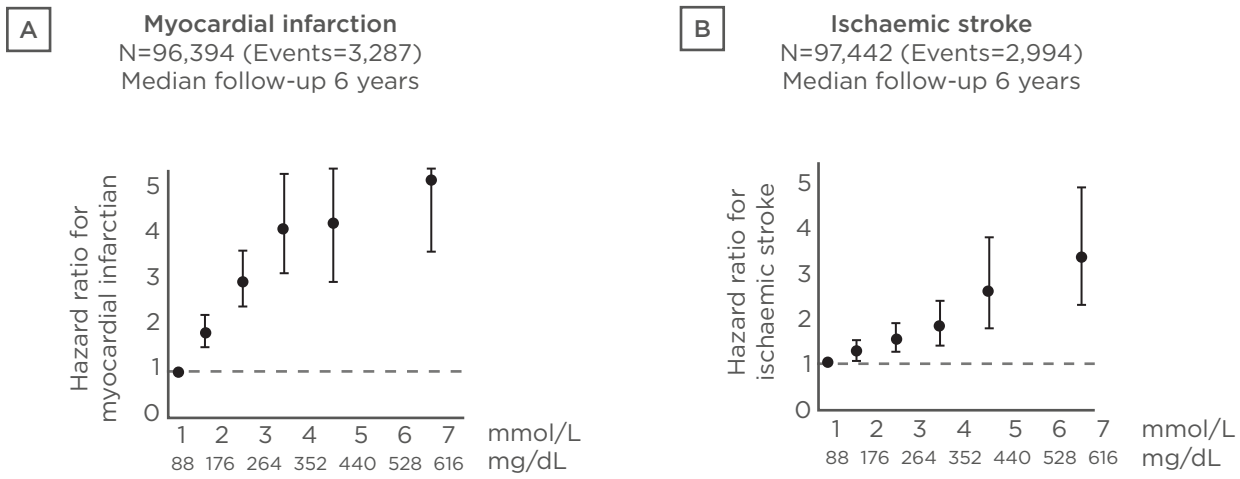

Figure 1: Increasing risk of myocardial infarction (A) and ischaemic stroke (B) with increasing nonfasting triglyceride levels.[1,4]

Other genetic studies support these data, showing that triglyceride-rich remnants can cause cardiovascular disease, independently of LDL-C and HDL-C.[8-14]

For example, two studies have examined loss-of-function mutations in the *APOC3* gene and risk of ischaemic vascular disease.[8,9] Both showed that heterozygosity for loss-of-function mutations in *APOC3* was associated with ~40% reductions in both nonfasting triglyceride levels and risk of ischaemic vascular disease.[8,9] Another study showed 27% lower triglyceride levels for *ANGPTL3* loss-of-function and, based on a meta-analysis with other studies, a 39% lower risk of coronary artery disease.[14]

When people consume an excess of high-fat foods, chylomicrons and VLDL particles are produced. Lipoprotein lipase converts these into chylomicron remnants and intermediate-density lipoprotein, causing atherosclerosis. Some proteins enhance the action of lipoprotein lipase (e.g., apolipoprotein V and GPIHBP1), while others inhibit it (e.g., apolipoprotein C3, ANGPTL3, and ANGTTL4). If these inhibitory proteins can themselves be inhibited, then lipoprotein lipase will degrade triglycerides faster and potentially enhance clearance of chylomicrons, VLDL, chylomicron remnants, and intermediate-density lipoprotein in the circulation, reducing atherosclerosis.

Prof Nordestgaard then introduced three new and ongoing trials for triglyceride-reducing therapy to reduce major atherosclerotic cardiovascular event risk after statin treatment. The REDUCE-IT trial, which will be discussed in detail by Dr Bhatt, randomised >8,000 statin-treated patients to icosapent ethyl or placebo and showed a reduction in major ischaemic events.[15] The STRENGTH trial randomised ~13,000 patients to omega-3 carboxylic acids (Epanova®) and statin or corn oil and statin.[16] The PROMINENT trial is currently recruiting ~10,000 participants, who will be randomised to the selective peroxisome proliferator alpha modulator (SPPARM-α), pemafibrate, or placebo.[17]

Prof Nordestgaard finished with the same slide that he started with, but expanded it to say that the link from triglyceride-rich lipoproteins to atherosclerosis with inflammation to MI due to plaque rupture could theoretically be attributable to various factors: coagulation, arrythmias, other inflammation, HDL-C, or small dense LDL-C; there is however no genetic evidence to support such pleiotropic effects. He reiterated that higher levels of triglyceride-rich lipoproteins increase the risk of MI, and reducing triglyceride-rich lipoprotein levels reduces the risk of MI, based on genetic data.

Does High-Dose Fish Oil Reduce Cardiovascular Events via Triglycerides?

Doctor Deepak L. Bhatt

In 2015, Prof Libby suggested that reducing triglycerides may be important for reducing cardiovascular risk.[18] However, in December 2018, the European Medicines Agency (EMA) reported that omega-3 fatty acid mixtures of EPA and docosahexaenoic acid (DHA) (1 g/day) are not considered effective in preventing heart disease.[19]

In a naturally randomised trial, Ference et al.[20] evaluated the risk of coronary heart disease among people with and without genetic variants that are associated with lower triglyceride levels (via the lipoprotein lipase pathway) and/or lower LDL-C (via upregulation of the LDL receptor). Both variants significantly reduced the risk of coronary heart disease, showing that triglycerides and LDL-C are both important. However, the implication was that for a similar reduction in coronary heart disease risk, triglyceride levels would need to be reduced ~5-fold more than LDL-C levels.

In a recent meta-analysis of 10 trials, low-medium-dose omega-3 fatty acid preparations (EPA 226–1,800 mg/day) had no significant effect on the primary cardiovascular endpoints.[21] However, in the randomised Japanese JELIS study (N=18,645), EPA (1.8 g/day) plus statin significantly reduced the incidence of coronary events versus statin alone (with no placebo) among patients with hypercholesterolaemia (2.8% versus 3.5%; p=0.011).[22] This agrees with mechanistic data from the newer randomised CHERRY study, in which medium-dose EPA (1.8 g/day) plus statin resulted in significantly more coronary plaque regression than statin alone (81% versus 61%; p=0.002)

among 193 patients with coronary heart disease after percutaneous coronary intervention (PCI).[23]

In the REDUCE-IT study, 8,179 statin-treated patients (aged ≥45 years with established cardiovascular disease or ≥50 years with diabetes and ≥1 additional risk factor) with triglycerides 1.52–5.63 mmol/L and LDL-C 1.06–2.59 mmol/L were randomised to icosapent ethyl (4 g/day) or placebo, both with continuing statin therapy.[15] The primary endpoint was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularisation, or hospitalisation for unstable angina; the key secondary endpoint was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke.[15] The median age was 64 years, 71% were male, and 58% had Type 2 diabetes mellitus.[15] The secondary prevention cohort accounted for 71% of the population, whereas the other 29% were in the primary prevention cohort.

In the REDUCE-IT study, icosapent ethyl resulted in a 19.7% reduction in triglycerides versus placebo (p<0.001).[15] There were also significant reductions in various other biomarkers and a significant increase in EPA (359%; p<0.001). Icosapent ethyl also resulted in significant reductions in the primary composite endpoint (17.2% versus 22.0%; hazard ratio [HR]: 0.75; 95% confidence interval [CI]: 0.68–0.83; p<0.001; Figure 2) and the key secondary endpoint (11.2% versus 14.8%; HR: 0.74; 95% CI: 0.65–0.83; p<0.001).[15]

There were also significant reductions in various other composite and single endpoints. In subgroup analyses, icosapent ethyl had a significant effect on the primary and key secondary endpoints among those with baseline triglyceride levels < or ≥2.26 mmol/L.[15] It also had a significant effect on the key secondary endpoint among those with baseline triglyceride levels < or ≥1.69 mmol/L.[15] Similarly, Kaplan–Meier curves of the primary and key secondary endpoints were very similar for those with achieved triglyceride levels < or ≥1.69 mmol/L.[15]

Icosapent ethyl did not only significantly reduce first events (HR: 0.75; 95% CI: 0.68–0.83), but also significantly reduced second (HR: 0.68; 95% CI: 0.60–0.78), third (HR: 0.69; 95% CI: 0.59–0.82), and fourth or more (relative risk [RR]: 0.52; 95% CI: 0.38–0.70) events.[24] Overall, there was a 30% reduction in total events in the icosapent ethyl group versus the placebo group (RR: 0.70; 95% CI: 0.62–0.78; p<0.0001).[24] For every 1,000 patients treated with icosapent ethyl for 5 years, one could expect 76 fewer coronary revascularisations, 42 fewer MI, 16 fewer hospitalisations for unstable angina, 14 fewer strokes, and 12 fewer cardiovascular deaths (overall, 159 less events).[24]

In the REDUCE-IT trial, the original triglyceride inclusion criterion was 1.69–5.63 mmol/L at the screening visit which,[25] with a 10% allowance, resulted in those with triglycerides ≥1.52 mmol/L at this visit being included.[15] However, when the baseline triglyceride level was calculated as the mean of the screening and randomisation visit values (the latter of which did not have defined limits), baseline values actually ranged from 0.91 to 15.82 mmol/L.[26] There were significant relative reductions in the primary composite endpoint with icosapent ethyl in all three baseline triglyceride tertiles (lowest: HR: 0.79; 95% CI: 0.66–0.94; p=0.0069; middle: HR: 0.80; 95% CI: 0.68–0.95; p=0.0121; highest: HR: 0.68; 95% CI: 0.57–0.80; p<0.0001), with no significant interaction by subgroup ($p_{interaction}$=0.33). Results for total events were similar (lowest: HR: 0.74; 95% CI: 0.61–0.90; p=0.0025; middle: HR: 0.77; 95% CI: 0.63–0.95; p=0.0120; highest: HR: 0.60; 95% CI: 0.50–0.873; p<0.0001; $p_{interaction}$=0.17).[26] Comparing absolute (rather than relative) risk reductions, there was no significant interaction by subgroup for the first event ($p_{interaction}$=0.12), but a larger effect at higher baseline triglyceride levels for total events ($p_{interaction}$=0.03).[26] Of note, among patients on placebo, the rate of total endpoint events increased from 75 to 87, to 107, per 1,000 patient years in the lowest to highest triglyceride tertiles, showing the detrimental impact of triglyceride level on cardiovascular risk.

A recent publication has reviewed eight key triglyceride-lowering trials (three fibrates, three omega-3 fatty acids, and two niacin).[27] Most of the studies reported significant reductions in triglyceride levels, but only one fibrate and three omega-3 fatty acid studies (including REDUCE-IT) reported significant effects on cardiovascular outcomes.

The biological effects of EPA on plaque progression include those on:

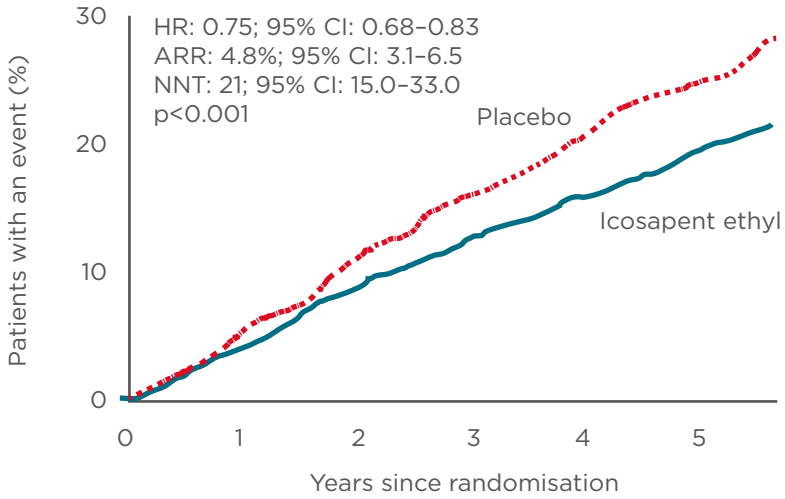

Figure 2: Reduced risk of the composite primary endpoint (cardiovascular death, myocardial infarction, stroke, coronary revascularisation, or unstable angina) with icosepent ethyl versus placebo in the REDUCE-IT trial.[15]

ARR: absolute risk reduction; CI: confidence interval; HR: hazard ratio; NNT: number needed to treat.

- Endothelial dysfunction/oxidative stress (e.g., increased endothelial function and nitric oxide bioavailability; decreased oxidised LDL, macrophages, and foam cells).
- Inflammation/plaque growth (e.g., increased EPA/arachidonic acid [AA] ratio; decreased IL-6).
- Unstable plaque (e.g., increased fibrous cap thickness and plaque stability; decreased plaque volume and arterial stiffness).[28]

It has also been associated with modest placebo-corrected reductions in blood pressure (systolic blood pressure: 1.3 mmHg; diastolic blood pressure: 0.5 mmHg).[29] Dr Bhatt noted that EPA and DHA have different effects on cellular membranes.[30] EPA tends to be associated with the hydrocarbon core, resulting in an ordered membrane, while DHA interacts with the headgroup region, resulting in a less ordered structure.[30]

He then went on to outline some ongoing studies. In the EVAPORATE study, ~60 statin-treated patients with coronary atherosclerosis and elevated triglycerides were randomised to icosapent ethyl 4 g/day or placebo, with continued statin therapy.[31] Multidetector CT angiography will be used at 9 and 18 months to assess changes in plaque volume and various other secondary endpoints. In the STRENGTH trial, ~13,000 statin-treated adults with elevated triglycerides and low HDL-C levels were randomised to omega-3 carboxylic acids 4 g/day or placebo.[16] The primary endpoint will be the time to first major cardiovascular event. In the PROMINENT study, ~10,000 statin-treated patients with Type 2 diabetes mellitus, elevated triglycerides, and low HDL-C are being randomised to pemafibrate or placebo.[17] The primary endpoint will be the time to first major cardiovascular event.

The American Heart Association (AHA) has said that the prescription omega-3 fatty acid icosapent ethyl at 4g/d has been shown to reduce atherosclerotic cardiovascular disease risk among patients with elevated triglycerides, based on the REDUCE-IT trial.[32] European guidelines recommend considering icosapent ethyl 4 g/day plus statin for those with triglycerides 1.50–5.60 mmol/L despite statin treatment.[33] Similarly, a March 2019 update from the American Diabetes Association (ADA) recommends that icosapent ethyl (but not other omega-3 fatty acid products) should be considered for patients with atherosclerotic cardiovascular disease or other cardiac risk factors who have triglycerides 1.52–5.63 mmol/L despite taking a statin.[34]

Prevalence of Hypertriglyceridaemia in Statin Treated Very High-Risk Patients Who Might Benefit from Treatment with Icosapent Ethyl for Secondary Prevention in Clinical Practice – Results of DYSIS[35]

Doctor Anselm K. Gitt

To ascertain how many patients in clinical practice might benefit from icosapent ethyl, Dr Gitt and colleagues looked at statin-treated patients in the cross-sectional, observational DYSIS study, which examined lipid goal attainment in Canada, Europe, Middle East countries, and China.

Data were collected in physicians' offices and hospital outpatient wards during 2008–2012.

DYSIS included 61,805 consecutive patients on statin treatment. Of these, 44,593 (72.2%) were at very high cardiovascular risk (defined as per 2011 European Society of Cardiology [ESC]/European Atherosclerosis Society [EAS] guidelines),[36] including patients with coronary heart disease, diabetes, chronic kidney disease, or peripheral atherosclerotic disease.

Among these very high cardiovascular risk patients, 21,312 (47.8%) had elevated triglyceride levels (>1.52 mmol/L). Patients with triglyceride levels >1.52 mmol/L were significantly more likely to be female (42.2% versus 38.6%), obese (31.0% versus 20.7%), have sedentary lifestyles (43.0% versus 37.6%), hypertensive (79.0% versus 74.9%), and diabetic (56.3% versus 45.3%) than those with triglycerides ≤1.52 mmol/L (all p<0.0001). They also had significantly higher total (4.78 versus 4.11 mmol/L) and LDL-C (2.64 versus 2.30 mmol/L) levels (both p<0.0001); and were less likely to be at an LDL-C goal of <1.81 mmol/L (19.9% versus 28.8%).

Overall, nearly half of the very high cardiovascular risk patients in DYSIS, and over a third of the total DYSIS population, treated with statins for secondary prevention had elevated triglyceride levels and may therefore benefit from additional treatment with icosapent ethyl (Figure 3). As >80% of these very high-risk patients with triglycerides >1.52 mmol/L did not reach LDL-C targets, these patients could particularly benefit from icosapent ethyl. This could result in further reductions in major ischaemic events, such as cardiovascular death.

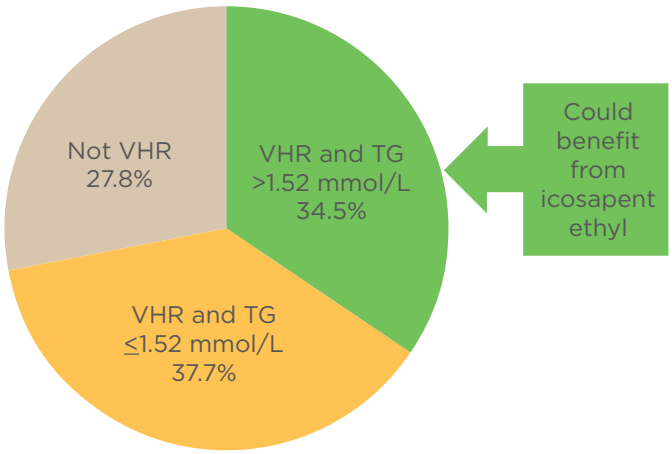

Figure 3: Pie chart showing the proportion of patients in the observational DYSIS study (which included 61,805 consecutive patients on statin treatment) who could potentially benefit from icosapent ethyl, based on their ESC/EAS-defined cardiovascular risk[36] and their triglyceride levels.

EAS: European Atherosclerosis Society; ESC: European Society of Cardiology; TG: triglycerides; VHR: very high risk.

Eicosapentaenoic Acid Therapy is Associated with Decreased Coronary Plaque Instability Assessed Using Optical Frequency Domain Imaging[37]

Doctor Takao Konishi

Dr Konishi discussed a retrospective study that used optical frequency domain imaging (OFDI) to assess the relationship between EPA therapy and coronary plaque instability.[37] They included 121 consecutive patients who underwent PCI during 2015–2018. Of these, 12 patients had received EPA and these patients were propensity score matched (1:4) to 48 of 109 who had not received EPA. The morphological characteristics of the plaque were analysed using OFDI.

Baseline characteristics (age, sex, BMI, diabetes, hypertension, chronic kidney disease, previous PCI or coronary artery bypass grafting, previous MI, prior statin use, acute coronary syndrome, and HbA1c) were balanced in the two groups.[37] Triglyceride, LDL-C, and HDL-C levels were also well matched. Those who had taken EPA had a higher mean EPA/AA ratio (1.63±0.46 versus 0.48±0.21; p<0.001).

In terms of OFDI characteristics, patients who had received EPA had a significantly lower mean lipid index (818±806 versus 1,574±891; p=0.01), lipid length (3.8±2.8 versus 6.2±2.6 mm; p=0.007), maximum lipid arc (161±106 versus 236±84 degrees; p=0.011), and macrophage grade (13.5±5.9 versus 19.3±7.4; p=0.019), but a higher minimum fibrous cap thickness (109.2±55.7 versus 81.6±36.4 µm; p=0.4) than those who had not.[37] Multiple logistic regression analyses showed that prior EPA use was independently associated with lower lipid index (p=0.043) and macrophage grade (p=0.024).

Overall, this analysis suggests that EPA therapy is associated with decreased plaque instability in patients with coronary artery disease undergoing PCI. Dr Konishi therefore suggested that patients with coronary artery disease who are at high risk of cardiovascular events should receive EPA to stabilise their coronary atherosclerotic plaques.

Dr Konishi also highlighted various previous studies that have examined the effects of EPA. Ferguson et al.[38] reported that EPA+DHA attenuated the inflammatory activation of *in vitro* human adipocytes. Niki et al.[39] randomised 95 patients on strong statin therapy to EPA or control, and found significant reductions in lipid volume and significant increases in fibrous volume in the EPA group, but not in the control group. They also found significant reductions in inflammatory cytokines in the EPA, but not in the control group.[39] Wu et al.[40] reported that EPA+DHA decreased apoptosis in one healthy subject. Lastly, Zampelas[41] reported that EPA use is associated with increased stability and decreased inflammation. Overall, these results suggest that EPA could reduce lipid core size by reducing inflammation.

Dr Konishi also discussed studies in which omega-3 fatty acids downregulate the expression of inflammation-related genes through inhibition of NF-kB signalling by blocking Iκ-β phosphorylation, through GPR 120, or the nuclear receptor PPARα/γ.[42-45] Lastly, Kanai et al.[46] reported that EPA can inhibit the ability of macrophages to secrete matrix metalloproteinases (MMP) and monocyte chemotactic protein 1 (MCP-1), and Matsumoto et al.[47] reported that EPA can attenuate upregulation of vascular cell adhesion protein 1 (VCAM-1), intercellular adhesion protein 1 (ICAM-1), and MCP-1, and the expression of MMP-2 and MMP-9 in macrophage-like cells.

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Why the Diagnosis of ATTR-Cardiomyopathy May Be a Challenge for Physicians

These scientific sessions took place on 31st August and 1st September 2019, as part of the European Society of Cardiology (ESC) Congress in Paris, France

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Disclosure: Dr García-Pavía has received speaker fees, consulting fees, and research grants from Alnylam, Pfizer, and Prothena; speaker fees from Akcea; and consulting fees from Akcea and Neuroimmune.

Acknowledgements: Writing assistance was provided by Nick Lamb, Medcopywriter, Oxfordshire, UK.

Support: The session and publication of this article were funded by Pfizer. The views and opinions expressed are those of the presenters. Content was reviewed by Pfizer for medical accuracy.

Citation: EMJ Cardiol. 2019;7[1]:66-71.

Summary

Cardiac amyloidosis is a rare but life-threatening group of disorders caused by the extracellular deposition of misfolded amyloid fibrils in cardiac tissue. Amyloid accumulation leads to cardiomyocyte toxicity, extracellular volume expansion, and ventricular pseudohypertrophy. Two types of amyloid protein are thought to be responsible for most disorders: immunoglobulin light chain, which causes light chain amyloidosis (AL); and transthyretin (TTR), which causes transthyretin amyloidosis (ATTR), of which there are two types: hereditary (hATTR) or wild-type (ATTRwt). Despite increasing clinical recognition of the disease, cardiac amyloidosis remains underdiagnosed. This article explores the epidemiology of AL and ATTR and the noninvasive techniques that help to improve diagnosis of the disorder. Cardiac amyloidosis is associated with mixed phenotype symptoms of polyneuropathy and cardiomyopathy which can lead to multiple misdiagnoses. As a result, patients can wait between 2 and 4 years for a correct diagnosis. Early diagnosis may be aided by recognising red flag symptom clusters. These include family history; neuropathy and sensory involvement; bilateral carpal tunnel syndrome; early autonomic dysfunction and gastrointestinal complaints; heart failure (HF) with preserved ejection fraction (HFpEF; without hypertension); cardiac

hypertrophy, arrhythmias, ventricular blocks, right-sided or biventricular HF, or cardiomyopathy; renal abnormalities; and vitreous opacities. Noninvasive imaging techniques have increasingly been used as an alternative to biopsy to diagnose cardiac amyloidosis with the hope of allowing physicians to provide targeted therapy for these patients. Techniques include speckle tracking echocardiography, cardiac MRI, and nuclear scintigraphy, together with biomarkers such as N-terminal pro-brain natriuretic peptide and hepatocyte growth factor (HGF). It is hoped that greater understanding of patients with ATTR may lead to increased awareness of the disorder and improve patient outcomes.

Epidemiological Data[1-3]

ATTRwt cardiomyopathy is an underdiagnosed but treatable cause of HF; however, the incidence of the clinically relevant disease remains unknown. A study in Umeå, Sweden,[1] investigated the prevalence of ATTRwt cardiac amyloidosis in >2,200 patients with HF or cardiomyopathy. In the study of 174 patients with HF and interventricular septum >14 mm, approximately 20.0% had ATTRwt amyloidosis, as measured by ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. None of the patients' blood or urine samples suggested AL, and in the total HF population the prevalence of ATTRwt amyloidosis was 1.1%, giving a prevalence of approximately 1:6,000.[1]

García-Pavía et al.[2] examined demographic and clinical characteristics of patients with ATTRwt using data from the Transthyretin Amyloidosis Outcomes Survey (THAOS).[2] THAOS is an ongoing international, longitudinal, observational registry that collects data on the natural history of ATTR, and is open to all patients with hATTR or ATTRwt and asymptomatic TTR-variant carriers.[3]

In the analysis, 758 ATTRwt patients were enrolled in THAOS, most of whom were male (94.6% versus 5.4%), and many patients experienced a significant delay in diagnosis. The mean age at enrolment was 76 years, with a mean age at symptom onset of 68 years, and a mean delay in diagnosis of 3.88 years.[2]

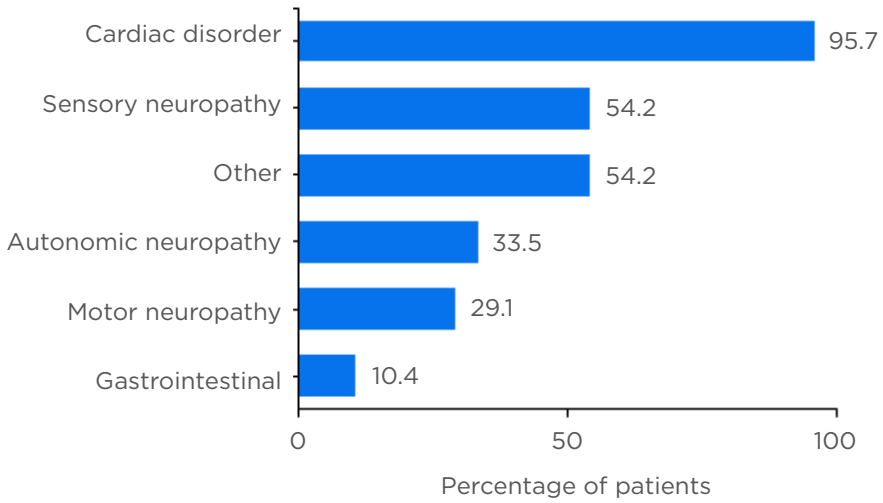


Figure 1: Symptom categories relating to transthyretin amyloidosis reported at enrolment.

Patients with symptomatic transthyretin amyloidosis wild type: n=723. Motor neuropathy includes muscle weakness and walking disability. Sensory neuropathy includes balance abnormality, neuropathic arthropathy, or pain/paraesthesia, numbness, temperature/pain insensitivity, and tingling. Autonomic neuropathy includes dizziness, dry eye, dyshidrosis, palpitations, recurrent urinary tract infections, urinary incontinence, urinary retention, vomiting, constipation, diarrhoea, early satiety, faecal incontinence, nausea, and erectile dysfunction. Other includes carpal tunnel syndrome, endocrine/metabolic disease, eye disease, genitourinary/reproductive disease, inflammatory disease, psychiatric diagnosis, and respiratory disease. Categories are not mutually exclusive.

Adapted from García-Pavía et al.[2]

Almost all patients had either a cardiac (59.8%) or mixed cardiac and neurologic (36.6%) phenotype, highlighting the need for both cardiologic and neurologic assessment of these patients. Neurologic symptoms included sensory (54%), autonomic (34%), and motor neuropathy (29%) (Figure 1). Importantly, the study confirmed that ATTRwt should not be considered an exclusively cardiac disease, but one with a heterogenous clinical spectrum.[2]

The Journey to Diagnosis of Hereditary Transthyretin Amyloidosis[4]

Multiple misdiagnoses can delay the identification of hATTR amyloidosis between 2.0 and 4.3 years.[4] The difficulty in diagnosis is believed to stem from the multisystemic nature of the disorder.[4]

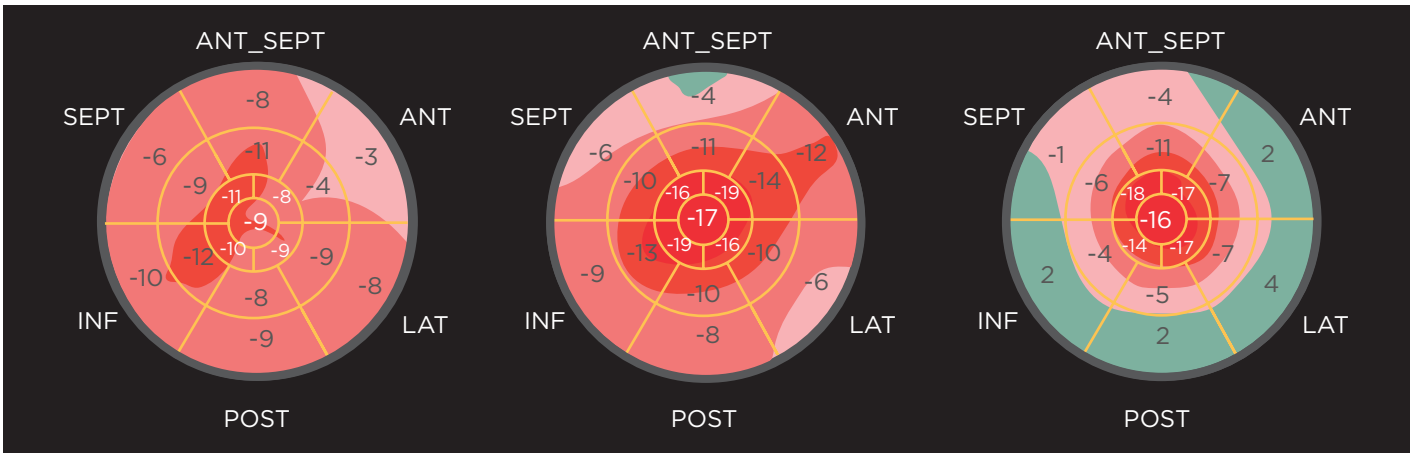
Red flag symptom clusters can be used to aid the diagnosis of hATTR amyloidosis. These include:[4]

- Family history of hATTR symptoms.
- Neuropathy and sensory involvement.
- Bilateral carpal tunnel syndrome.
- Early autonomic dysfunction and gastrointestinal complaints.
- HFpEF (without hypertension).
- Cardiac hypertrophy, arrhythmias, ventricular blocks, right sided or biventricular HF, or cardiomyopathy.
- Renal abnormalities.
- Vitreous opacities.

It is hoped that awareness of these red flag symptom clusters and diagnostic tools could lead to earlier diagnosis of hATTR amyloidosis.[4]

Imaging Biomarkers: Electrocardiogram and Scintigraphy[5-9]

Novel imaging techniques are also useful diagnostic tools showcased by Alejandro et al.[2] who used STE and classical 2D ECG to help differentiate the two subtypes of cardiac amyloidosis: AL and ATTR.[5] Left and right ventricular apical ratios (LVAR and RVAR) were compared among 78 patients with cardiac amyloidosis (47 with AL and 31 with ATTR) and 24 healthy controls. Both LVAR and RVAR were elevated in AL compared with ATTR.



Biopsy negative | Light chain amyloidsis | Transthyretin amyloidosis

Figure 2: Apical sparing ratio was higher in transthyretin than light chain amyloidosis.

Routine longitudinal strain imaging. The apical sparing ratio was calculated as the average of apical segments/ average of mid + average of basal segments.

ANT: anterior; ANT_SEPT: anteroseptal; INF: inferior; LAT: lateral; POST: posterior; SEPT: septal.

Adapted from Zhang et al.[6]

Cut-off values of LVAR >0.96 and RVAR >0.80 showed high accuracy in differentiating the two subtypes. The study authors concluded that RVAR is an easy and accessible tool for most echo laboratories to help differentiate AL and ATTR.[5]

These findings were supported by Zhang et al.[6] who used the apical sparing ratio to detect differences among 179 patients with suspected AL and ATTR cardiac amyloidosis (Figure 2). AL versus TTR was determined by mass spectrometry, if available, and TTR was assigned if biopsy, serum protein, and/or free light chain testing was negative for AL. Patients with negative endomyocardial biopsy or autopsy were included as controls. They reported that a lower ratio cut-off (0.81) than previously reported had optimal diagnostic sensitivity (72%) and specificity (64%).[6]

How does ATTR affect patient outcomes over the long term? Recent studies have shown a relatively high prevalence of ATTR in patients with aortic stenosis, the most common valvular heart disease in the Western world. A study from Israel by Zikry et al.[7] sought to examine the effects of ATTR in 86 elderly patients (mean age: 81 years) who underwent surgical aortic valve replacement or transcatheter aortic valve replacement therapy.[7]

Using nuclear cardiac imaging with ^{99m}technetium-pyrophosphate (^{99m}Tc-PYP), patients were assessed for ATTR over three timepoints: before aortic valve replacement therapy, 1 month after, and 2 years after the procedure. Patients who were positive for ATTR (14%) had a more severe clinical presentation and more advanced signs of HF than patients without ATTR. Before the intervention, the hospitalisation due to HF rate was 3.26-times higher in patients with ATTR compared to those without ATTR (p=0.01). After the intervention, diastolic function remained more severely affected in the ATTR-positive group at follow-up than in the ATTR-negative group (p=0.05). Furthermore, hospitalisation rates after intervention of HF were 2.84-times higher in patients with ATTR compared to those without (p=0.02). The findings suggested that older patients with amyloidosis have a more severe prognosis following aortic valve replacement therapy than those without amyloidosis.[7]

Diagnosis of ATTR in patients undergoing valvular intervention is of importance as it may affect their clinical outcomes and the need for pacemakers. In an accompanying presentation, Zikry et al.[8] used ^{99m}Tc-PYP scanning to examine ATTR among 86 older patients (mean age: 78 years) undergoing transcatheter aortic valve implantation (TAVI). They found that 12 (14%) patients were positive for ATTR and that conduction abnormalities were significantly more prevalent in these patients. In addition, 42% of ATTR-positive patients underwent periprocedural permanent pacemaker implantation compared to 28% implantations in the ATTR-negative group (p=0.043). There was also a significantly higher rate of new left bundle branch block development in the ATTR-positive group compared to the ATTR-negative group (39.1% versus 10.9%; p=0.03). They concluded that patients undergoing TAVI should be observed carefully for signs of conduction disorders and possible pacemaker insertion.[8]

ATTR is an underdiagnosed disease presenting with HFpEF symptomatology; therefore, Fukuzawa et al.[9] used ^{99m}Tc-DPD/MDP/HMDP bone scan scintigraphy to determine the prevalence of ATTR among 62 patients aged ≥60 years with HFpEF (left ventricular ejection fraction ≥50%). Relatively intense myocardial uptake of ^{99m}Tc-PYP was found in 7 (11%) patients, with diffuse deposition in both right and left ventricles. Patients with amyloid deposition were also older and had lower systolic blood pressure and left ventricular ejection fraction. It was suggested that the findings may allow the possibility of targeted therapy for these patients.[9]

Biological Markers and Echocardiogram Abnormalities in Cardiac Amyloidosis

Cardiac amyloidosis poses significant diagnostic and therapeutic challenges. The disorder is particularly difficult to detect early as patients can become symptomatic before any signs of cardiac amyloidosis involvement is suspected. Classical tests such as ECG pseudo-infarct and concentric hypertrophy, as well as delayed gadolinium enhancement on MRI, may lack diagnostic specificity and sensitivity if misinterpreted.

Table 1: Elevated hepatocyte growth factor and N-terminal pro-brain natriuretic peptide and clinical outcomes in amyloidosis.

Biomarker	Cut-off level	Event rate with normal level	Event rate with pabnormal level	p value for event rate in normal versus abnormal
HGF	310 pg/mL	7%	38% (19/50)	**0.0211**
NT-proBNP	332 pg/mL	0% (0/7)	35% (22/62)	**0.0562**
Troponin-T	35 ng/mL	20% (5/25)	38% (18/47)	0.1129
eGFR	45 mL/min/1.73 m^2	41% (11/27)	27% (12/45)	0.2150

eGFR: estimated glomerular filtration rate; HGF: hepatocyte growth factor; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Adapted from Zhang et al.[10]

Once cardiac amyloidosis involvement has been established, it is associated with poor survival.[10]

As multiple new therapies for AL and ATTR amyloidosis emerge, there is an increased need to identify relevant serum biomarkers that may improve prognostic and staging systems; however, there is currently a lack of international guidelines on the use of biomarkers in these patients.[10]

A potential biomarker for AL and ATTR cardiac amyloidosis is HGF. HGF is a potent angiogenic growth factor that is thought to be released during amyloid deposition in the myocardium. In their study, Zhang et al.[10] enrolled 102 patients with suspected cardiac amyloidosis, and levels of HGF, N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin-T, and estimated glomerular filtration rate were measured. Cardiac involvement was established via endomyocardial biopsy; if this was not available, transthoracic echocardiography, ECG, and cardiac MRI were used. Patients were then followed for all-cause mortality, cardiac transplant, and left ventricular assist device implantation. Of the 102 patients enrolled, 72 had known cardiac involvement. Patients were stratified using biomarker cut-off levels established from previously published models (Table 1).[10]

Results found that elevated HGF was associated with worse clinical outcomes resulting in all-cause mortality, left ventricular assist device implantation, and cardiac transplant. Kaplan–Meier analysis of survival stratified by HGF level revealed rapid divergence in survival time for HGF levels >310 pg/mL. Although NT-proNBP also predicted similar outcomes, they were not specific to cardiac amyloidosis, therefore, future studies will compare the diagnostic and prognostic specificities of HGF and NT-proNBP in patients with cardiac amyloidosis.[10]

Cardiac troponins are also chronically elevated in cardiac amyloidosis. Castiglione et al.[11] assessed the prognostic value of high-sensitivity cardiac troponin-T (hs-cTnT) and NT-proBNP in 230 patients with suspected cardiac amyloidosis. Cardiac amyloidosis was confirmed in 86 (37%) patients, 29% of whom had AL and 71% ATTR. Further results found that patients with cardiac amyloidosis had higher plasma levels of NT-proBNP (5,507 ng/L [2,348–10,326] versus 1,332 [392–3,752]; p<0.001) and hs-cTnT (65 ng/L [48–114] versus 35 [21–52]; p<0.001) than those with suspected, but not confirmed, cardiac amyloidosis. The combination of the two biomarkers improved discrimination over NT-proBNP alone (p=0.011), but not over hs-cTnT (p=0.470). An NT-proBNP level <600 ng/L or an hs-cTnT level <17 ng/L was optimal for ruling out cardiac amyloidosis (95% negative predictive value for both).[11]

How common are ECG abnormalities in patients with cardiac amyloidosis? In their retrospective,

observational study of 251 patients with cardiac amyloidosis, Martone et al.[12] found that three-quarters of the patients had ECG abnormalities (82% in ATTR versus 72% in AL; p=0.06). Rhythm disturbances were more prevalent in ATTR as evidenced by a higher burden of IV conduction delays (43% versus 21%; p<0.001) and a higher prevalence of pacemakers (24 versus 1 patient) compared with AL. After adjusting for age and sex imbalance, ATTR was independently associated with a higher prevalence of atrial fibrillation and atrioventricular conduction delays compared to AL (adjusted odds ratio: 4; 95% confidence interval: 1.4–11.2; p=0.008 and adjusted odds ratio: 6.2; 95% confidence interval: 2.6–14.9; p<0.001, respectively). By contrast, AL was associated more with low-voltage QRS.[12]

Conclusion

In summary, cardiac amyloidosis is a rare, life-threatening disease that can be challenging for physicians to diagnose due to multisystem involvement.[4] Highly specific, noninvasive cardiac tests, such as nuclear scintigraphy, have helped improve diagnosis of the disorder and offer an alternative to cardiac biopsy.[4] Plasma biomarkers, including NT-proBNP and HGF, also offer potential as diagnostic and prognostic indicators.[10] These techniques may lead to a better understanding of the disorder with the aim of improving patient outcomes.

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The Effect of De-escalated Switching Dual Antiplatelet Therapy after Acute Myocardial Infarction in Patients undergoing Percutaneous Coronary Intervention: Real-world Data from a Nationwide Cohort Study

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Disclosure: The authors have declared no conflict of interests.

Acknowledgements: This study was supported by the Health and Clinical Research Data Center at School of Public Health, Taipei Medical University, Taipei, Taiwan.

Keywords: Acute myocardial infarction (AMI), dual antiplatelet therapy (DAPT) de-escalation, $P2Y_{12}$ inhibitors.

Citation: EMJ Cardiol. 2019;7[1]:72-73. Abstract Review No. AR1.

BACKGROUND

The dual antiplatelet therapy (DAPT) de-escalation strategy is considered and used by many clinical physicians when treating acute coronary syndrome patients to reduce further risk of bleeding.[1,2] DAPT de-escalation strategies have been investigated in several clinical studies, but the data remain limited and conflicting;[3-5] therefore, current clinical practice guidelines provide no clear recommendations on de-escalation of $P2Y_{12}$ inhibitors.[6,7] The aim of the current study was to examine the effect of de-escalation of $P2Y_{12}$ inhibitor in DAPT on cardiovascular events and bleeding complications after acute myocardial infarction (AMI) in patients undergoing percutaneous coronary intervention (PCI).

METHODS

Using a nationwide database in Taiwan between July 1st 2013 and December 31st 2015, (ticagrelor was first approved by the National Health Insurance (NHI) Administration of Taiwan after July 1st 2013), the authors retrospectively evaluated patients who had received PCI during AMI hospitalisation and were initially on aspirin and ticagrelor and without adverse events at 3 months. The main outcome measurements included: 1) cardiovascular events: death and AMI readmission; 2) major bleeding events: gastrointestinal bleeding or other noncritical site bleeding that required transfusion of >2 U packed red blood cells, or intracerebral haemorrhage and other critical site bleeding leading to hospitalisation; 3) nonmajor clinically relevant bleeding: inpatient or outpatient visit for gastrointestinal and other noncritical site bleeding.

RESULTS

In total, 1,903 patients were identified as switched DAPT (to aspirin and clopidogrel) cohort and 4,059 patients as unswitched DAPT (continued on aspirin and ticagrelor) cohort. With a mean follow-up of 14 months, the incidence rates (per 100 person-year) of death and AMI readmission were 3.97 and 3.84 in the switched cohort and 1.83 and 2.23 in the unswitched cohort, respectively. An inverse probability of treatment weighted approach was used to balance baseline differences between the two groups. After adjustment for clinical variables, the switched cohort had a higher risk of death (adjusted hazard

ratio [aHR] 2.18; 95% confidence interval [CI]: 1.62–2.93; p<0.001) and AMI readmission (aHR] 1.72; 95% CI: 1.27–2.34) compared with the unswitched cohort. When compared to the risk of bleeding complications, there was no significant difference between the two groups. In patients aged ≥65 years, the risk of death and AMI readmission in the switched group were still higher than that in the unswitched group (aHR 3.30; 95% CI: 2.19–4.98, aHR 2.40; 95% CI: 1.50–3.82, respectively).

CONCLUSION

There is a possibility that unguided de-escalation of $P2Y_{12}$ inhibitor in DAPT is associated with a higher risk of death and AMI readmission in Taiwanese patients with AMI undergoing PCI. The caution surrounding unguided DAPT de-escalation is justified by the findings of this study and is reflected in real-world practice.

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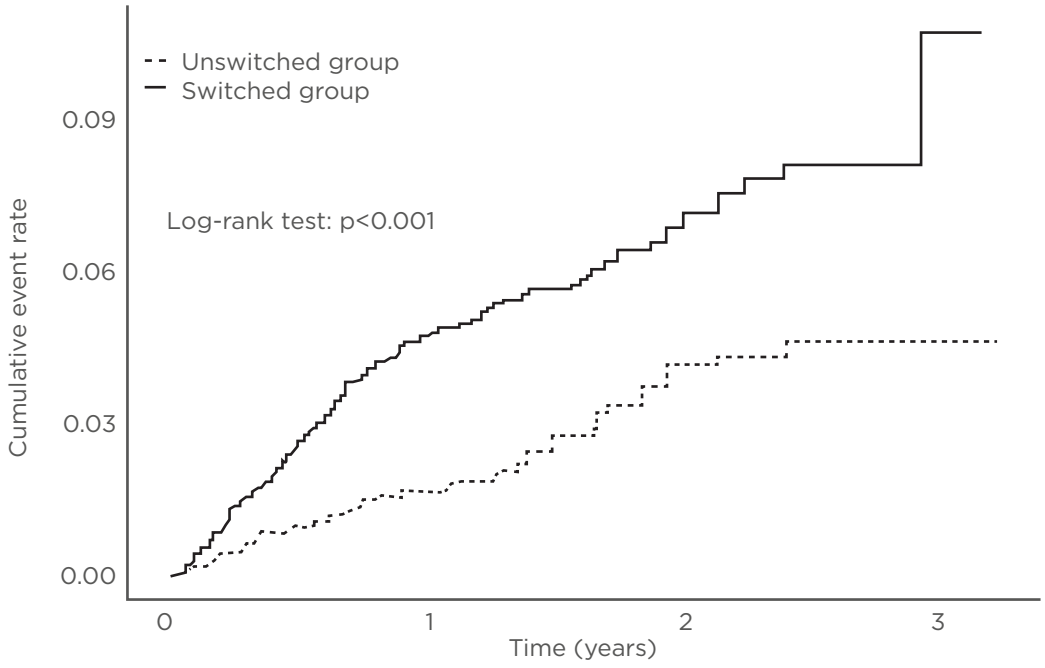

Figure 1: Survival analysis for death between unswitched and switched groups.

Th17 Signature, Autoimmunity, and Differentially Expressed Genes in Cardiomyopathy and Heart Failure

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Disclosure: Dr Myers reports grants from the National Heart, Lung, and Blood Institute, and the American Heart association during the conduct of the study. Mr Sandel and Dr Fairweather report grants from the National Heart, Lung, and Blood Institute. Dr Cunningham reports grants from the National Heart, Lung, and Blood Institute, American Heart Association, during the conduct of the study; personal fees and other from Moleculera Labs, outside the submitted work. In addition, Dr Cunningham has patents 10228376 and 9804171 with royalties paid to Moleculera labs and the Board of Regents of the University of Oklahoma and the National Institute of Health. All other authors have declared no conflicts of interest.

Keywords: Antibodies, autoimmunity, cardiomyopathy, heart failure (HF), inflammation, myocarditis, T cells, transcriptome.

Citation: EMJ Cardiol. 2019;7[1]:74-75. Abstract Review No. AR2.

BACKGROUND

Myocarditis is a common precursor to dilated cardiomyopathy (DCM) and together they are the cause of approximately half of all heart transplants, constituting a major cause of sudden death in young adults.[1] Frequently initiated by viral infection of cardiomyocytes, approximately one third of those with acute myocarditis develop a chronic autoimmune syndrome leading to DCM and heart failure (HF).[2,3] The pathogenesis and treatment of the progressive disease is not well established; therefore, uncovering the molecular basis of why patients do not recover normal ejection fraction within a year following onset of the disease is needed to develop new biomarkers and therapies. Cardiac myosin released from the damaged heart is a damage-associated molecular pattern that binds to toll-like receptor 2 (TLR2)[4,5] and TLR8,[5] promoting a Th17 pathogenesis in chronic autoimmune DCM and inducing anti-heart autoimmunity.[6] Previous studies have demonstrated elevated anti-heart and anti-human cardiac myosin IgG antibodies in myocarditis/DCM and their cross-reactivity with the beta-adrenergic receptor.[6-9] The purpose of this study was therefore to identify new biomarkers in early stages of HF in individuals who did not recover ejection fraction over a year and who were candidates for current immunotherapies.

METHODS

Patients with myocarditis and HF (N=41) within 6 months of onset were enrolled and monitored for 12 months. Serum autoantibodies and cytokines were detected by ELISA, and fluorescence-activated cell sorting analysis was performed on peripheral blood mononuclear cells. The Mann-Whitney U test was used for statistical analysis. For gene expression studies, blood from 10 DCM patients and 19 healthy controls were collected for RNA sequencing and transcriptomic analysis by Ingenuity Pathway Analysis (IPA®) and Reactome.

RESULTS

The results of the study correlate anti-human cardiac myosin autoantibodies with poor outcomes and demonstrated that they functionally act on cardiomyocytes to activate protein kinase A. Concomitantly, a Th17 immunophenotype was significantly elevated in the blood as well as in cardiac biopsies.[6] CD4+IL17+ T cells ($p=0.0008$), TGF-β (a Th17-promoting cytokine ($p<0.0001$), IL-6 ($p<0.0001$), IL-23 ($p=0.0001$), granulocyte-

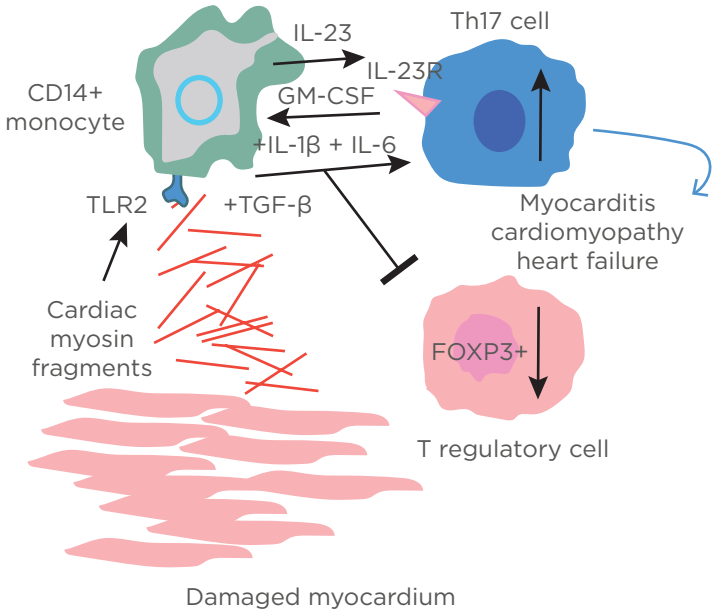

Figure 1: Diagram of the pathogenic mechanisms in the Th17 signature of myocarditis and dilated cardiomyopathy: an immunophenotype in myocarditis, dilated cardiomyopathy, and heart failure.

FOXP3+: Forkhead box P3+; GM-CSF: granulocyte-macrophage colony-stimulating factor; TGF-β: transforming growth factor beta; TLR2: toll-like receptor 2.

Adapted from Myers JM et al.[6]

macrophage colony-stimulating factor (GMCSF) (p=0.0336), and GMCSF-secreting CD4+ T cells (p=0.0006) were significantly elevated in the blood.[6] A Th17 immunophenotype was significantly associated with HF in males (p=0.029).[6] Persistent HF (New York Heart Association [NYHA] functional classification III and IV) and non-recovery of left ventricular function were associated with significantly higher percentages of IL-17A-producing T cells at baseline, 6 and 12 months after onset, and IL-17A (p=0.019) and Th17-promoting cytokines IL-6 (p=0.0001) and TGF-β (p=0.0076).[6] Regulatory T cells were significantly decreased (p=0.0006) and correlated with elevated Th17 cytokines in HF.[6] Overrepresentation analysis of differentially expressed genes (adjusted p<0.05) in blood of DCM (>1 year) patients was carried out and revealed significant (false discovery rate=1.52E-13) enrichment of neutrophil degranulation (48 genes) in IL-8, GMCSF, IL-17A, and other pathways. Neutrophil involvement is a feature of the IL-17A pathways which promote fibrosis.

CONCLUSION

In conclusion, the study illustrated a strong Th17 signature (Figure 1) in more severe HF early in the disease with anticardiac myosin autoantibodies highly elevated in non-recovery of left ventricular function. Additionally, a strong correlation with neutrophil degranulation pathways in the later disease was observed, which could become biomarkers of fibrosis progression and disease severity in patients with HF. HF identified with a Th17 signature might be treated with immunomodulatory therapies such as anti-IL-17A.

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Generating Proliferative Induced Cardiomyocyte Precursor Cells

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors would like to thank Stephanie Iris Protze (McEwen Stem Cell Institute, Toronto, Canada), Karsten Jürchott (BIH Center for Regenerative Therapies, Berlin, Germany), Ulrike Krüger (Berlin Institute of Health, Berlin, Germany), and Volkmar Falk (Deutsches Herzzentrum Berlin, Berlin, Germany) for their contributions and support throughout this project.

Keywords: Cardiac regeneration, heart disease, induced cardiomyocyte progenitor cell (iCMP).

Citation: EMJ Cardiol. 2019;7[1]:76-77. Abstract Review No. AR3.

BACKGROUND

Ischaemic injury of the adult human heart results in irreversible loss of cardiomyocytes (CM), leading to fibrosis, and eventually heart failure. Cardiac regeneration attempts involving the transplantation of somatic progenitor cells uniformly failed to provide relevant *de novo* CM and did not reverse heart failure in multiple clinical trials.[1,2] As an alternative method of CM provision, direct reprogramming of fibroblasts into induced CM (iCM) by forced expression of cardiomyogenesis-related transcription factors is currently being explored. However, reprogramming efficiency is low, and mature iCM have little or no proliferation capacity. The authors therefore developed a protocol for the genetic reprogramming of cardiac fibroblasts (CF) into iCM precursor cells (iCMP) with CM lineage commitment and evaluated their therapeutic potential in a mouse model of myocardial infarction (MI).

METHODS AND RESULTS

CF were reprogrammed into iCMP by lentiviral gene transfer of *GATA4*, *MEF2C*, *TBX5*, and *MYOCD* (GMTMy),[3] resulting in approximately 30% of cells positive for cardiac troponin T, α-actinin, and myosin heavy chain in immunostainings. The induced cells also expressed well-known cardiovascular precursor markers such as Nkx2-5, Mesp1, CXCR4, and Flk-1, and displayed robust proliferation capacity as indicated by Ki67 expression. Next, pure iCMP populations were obtained by transcriptional selection with MYH6/7-targeting molecular beacons.[4]

Thereafter, global transcriptome profiling was performed by RNA sequencing. By principal component analysis, iCMP displayed a unique gene expression profile compared to their parental CF and adult heart, indicating an intermediate state of cardiac development. Gene Ontology analyses revealed upregulation of genes associated with cardiac development, differentiation, and morphogenesis, as well

as downregulation of genes associated to cell proliferation in iCMP compared to CF. Evaluation of selected gene sets showed downregulation of nonmyocyte genes, upregulation of additional cardiac transcription factors, and upregulation of certain functional and structural genes, such as ion channel genes and contractile genes. Subsequently, iCMP were differentiated towards CM using 5-Azacytidine, TGFß, and ascorbic acid. In these differentiation assays, iCMP ceased proliferation, displayed elongated morphology, and formed prominent sarcomere-like structures. CD31-positive endothelial cells were not detected in differentiating iCMP cultures, but the presence of α-smooth muscle actin-positive smooth muscle cells was noted. iCMP-derived CM did not display spontaneous contractions within the 20-day-observation period.

To generate sufficient cell doses for intracardiac injection in a mouse model of MI, iCMP were extensively expanded in medium supporting their stable phenotype. Frozen stocks were prepared and iCMP phenotype was confirmed after thawing and recovery before *in vivo* application in male C57BL/6J mice after permanent ligation of the left anterior descending artery. Serial transthoracic echocardiographic analyses revealed that left ventricular ejection fraction was increased as early as 2 weeks after iCMP injection, compared to the no treatment and placebo control groups. This increase was stably maintained until Week 6. Similarly, cardiac output was improved 6 weeks after iCMP treatment. Additionally, an improvement in left ventricular wall thickness at diastole in mice transplanted with iCMP was observed, as well as a dramatically decreased scar size in histological sections stained with Masson's trichrome.

CONCLUSION

Taken together, iCMP generated via direct cellular reprogramming followed by transcriptional selection display a phenotype compatible with an intermediate state of cardiogenic development. They can be expanded to yield therapeutic cell doses and beneficially influence post-infarct myocardial remodelling in a rodent model. Thus, iCMP are promising candidates for novel cardiac cell therapy/regeneration strategies.

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Out-of-Hospital Cardiac Arrest - Incidence of Coronary Artery Disease, Comorbidity, and Survival

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: This study was supported by the Danish foundation Trygfonden.

Keywords: Acute coronary syndrome (ACS), cardiac arrest (CA), coronary artery disease, heart failure, outcome, percutaneous coronary intervention (PCI).

Citation: EMJ Cardiol. 2019;7[1]:77-78. Abstract Review No. AR4.

BACKGROUND

Data from the 2012 European Cardiovascular Disease Statistics show that 20% of all deaths are caused by coronary artery disease (CAD), with cardiac arrest (CA) as the most common scenario.[1] Historic angiography data have shown that CAD was present in approximately 70% of unselected out-of-hospital CA (OHCA) patients.[2] As registry and retrospective data are prone to bias, it remains unknown whether an early invasive strategy translates into improved outcome; therefore, the authors present their experience from a large urban region of Denmark.

METHODS

The purpose of the study was to describe a consecutive OHCA-cohort with regards to incidence of CAD, comorbidity, and survival rate. The authors consecutively included patients from an unselected cohort with OHCA in the capital region of Denmark (N=1,003) from 2007 to 2011. After successful resuscitation, patients were admitted for post-resuscitation care at 1 of 8 hospitals, including coronary angiography and percutaneous coronary interventions (PCI), when indicated.

RESULTS

Patients were found to be 65±15 years of age, 71% were male, 52% had shockable primary rhythm, and the median time to return of spontaneous circulation was 22 minutes (Q1–Q3: 13–37 minutes). Furthermore, the majority was unconscious at hospital admission (89%), and no previous comorbidity was noted in 38% of the patients. The majority of the cohort had OHCA due to a cardiac cause (n=806; 80%). According to angiography evaluation, 75% of the cohort had CAD, and acute coronary syndrome (ACS) was diagnosed in 39% of the total cohort (n=389). In 48% of patients with cardiac cause with ST-segment elevation, myocardial infarction was more frequent (n=236; 60% of ACS).

The authors found 30-day mortality rates in 59% of the total cohort and 46% in patients with ACS ($p_{logrank}$<0.001). A favourable neurological outcome (Cerebral Performance Category of 1 or 2) was noted in 84% of all patients discharged alive (n=347), and in 85% of patients with ACS (n=178).

In the total cohort, ACS was independently associated with a lower 30-day mortality rate (hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.51–0.75; p<0.001) after adjustment for age, pre-hospital OHCA circumstances (bystander cardiopulmonary resuscitation, public arrest, and witnessed arrest), time to return of spontaneous circulation, primary admission to a tertiary heart centre, and degree of comorbidity. In OHCA-patients with ACS only, successful PCI was independently associated with a lower 30-day mortality after adjustment for the mentioned prognostic factors ($HR_{all\ ACS}$:0.46; 95% CI: 0.31–0.67; p<0.001, HR_{STEMI}:0.43; 95% CI: 0.27–0.69; p<0.001, HR_{NSTEMI}:0.12; 95% CI: 0.03–0.51; p=0.004).

CONCLUSION

This data showed that in an unselected clinical cohort of OHCA survivors, CAD was common, and less than half of the patients were diagnosed with ACS. Furthermore, ACS was associated with a better prognosis even after adjustment for prognostic factors. Likewise, successful PCI was an independent prognostic factor; however, this may be attributable to selection bias and a direct support of early invasive strategy in all OHCA-survivors, which was not supported by clinical data. Due to the high grade of CAD, all OHCA-survivors without an obvious non-cardiac cause should have an angiography performed prior to hospital discharge.

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Analysing the Regulation of a Catecholamine-Dependent Altered cAMP Signalling in a Patient-Specific Induced Pluripotent Stem Cell Takotsubo-Model

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Disclosure: Dr Hasenfuss reports personal fees from AstraZeneca, Berlin Chemie, Corvia, Impulse Dynamics, Novartis, Servier, Springer, and Vifor outside the submitted work. All other authors have declared no conflicts of interest.

Acknowledgements: This work was supported by the German Center for Cardiovascular Research (DZHK) [FKZ 81X2300170 (to VON and KSB), and 81X2300165 (to KSB)], the BMBF grant e: Bio-Modul II-Verbundprojekt: CaRNAtion (031l0075C to GH and KSB), and the German Heart Foundation/German Foundation of Heart Research (to KSB).

Keywords: Beta-adrenergic signalling, 3',5'-cyclic adenosine monophosphate (cAMP), catecholamines, förster resonance energy transfer (FRET), induced pluripotent stem (iPSC)-cardiomyocytes, phosphodiesterase (PDE), Takotsubo.

Citation: EMJ Cardiol. 2019;7[1]:79-80. Abstract Reviews No. AR5.

BACKGROUND

Takotsubo syndrome (TTS) is characterised by acute left ventricular dysfunction in the absence of obstructive coronary lesions.[1] TTS is a life-threatening disease with a mortality rate of up to 8% in the acute phase. Furthermore, 21.8% of patients show in-house complications, such as cardiogenic shock or ventricular tachycardia.[2] Although enhanced β-adrenergic signalling and higher sensitivity to catecholamine-induced stress toxicity were identified as mechanisms associated with the TTS phenotype in the authors' former study, the pathogenesis of TTS is still not completely understood.[3] The aim of the study was to prove the hypothesis of a phosphodiesterase (PDE)-dependent regulation of 3',5'-cyclic adenosine monophosphate (cAMP) signalling in TTS under catecholamine stress.

METHODS AND RESULTS

Functional TTS-induced pluripotent stem cell-derived cardiomyocytes (TTS-iPSC-CM) were generated from six patients and the cells were treated with catecholamines to mimic a TTS-phenotype. Using a cytosolic Förster resonance energy transfer (FRET) based cAMP sensor, it was observed that β-adrenergic receptor (β-AR) stimulations led to stronger FRET responses in the cytosol of TTS-CM compared to controls. In addition to β-AR, PDE are key molecules involved in cAMP signalling in CM. At basal level, TTS-CM show a significantly higher PDE3A and a reduced PDE4D protein expression in the TTS-CM compared to control. In addition, FRET experiments show that after β-AR stimulation, the strong effects of the PDE4 family in the cytosol of control cells were significantly decreased in TTS-CM. This is in line with previously described reduction of the overall cytosolic PDE4 activity in severely hypertrophied and failing rat and mouse.[4] By analysing PDE-dependent cAMP downstream effects as PKA-dependent phosphorylation, an additional increase of phospholamban (PLN) phosphorylation (PLN-S16) was observed, especially in the control group, when treating iPSC-CM with a combination of isoprenaline and PDE4 inhibitor. In contrast, in TTS-iPSC-CM the contribution of the PDE-families PDE2, 3, or 4 to phosphorylation of PLN-S16 was increased in comparison to isoprenaline alone. This suggests that different PDE in TTS and control are involved in functional segregation of the sarcoplasmic/endoplasmic reticulum calcium ATPase 2a (SERCA2a) microdomain from the cytosol in terms of cAMP downstream effects. To directly address the hypothesis that local cAMP dynamics

might be altered in TTS, a SERCA microdomain targeted FRET based cAMP sensor was used. In contrast to the cytosolic cAMP regulation, the contribution of PDE2 and PDE3 to local cAMP degradation was increased in both TTS and control. Nevertheless, the strong PDE4 inhibitor effects in control cells are still reduced in TTS in the SERCA domain.

CONCLUSION

The data, for the first time, shows alterations of local cAMP signalling in healthy and diseased TTS-iPSC-CM. The PDE-specific contribution to cAMP degradation in the cytosol of TTS iPSC-CM is lost in the SERCA domain. Additionally, the results uncover a PDE-dependent altered β-adrenergic signalling as a potential disease cause. Furthermore, the data highlight that TTS-iPSC-CM can be used to provide a versatile tool for evaluating new treatment options for TTS as therapeutic targets.

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Single-Centre Experience with Different Regimes of Antiplatelet Therapy and Oral Anticoagulation in Transcatheter Aortic Valve Replacement

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Disclosure: Dr Veulemans, Dr Zeus, and Dr Polzin have received consulting fees, travel expenses, or study honoraries from Medtronic and Edwards Lifesciences.

Keywords: Antiplatelet therapy, outcome, transcatheter aortic valve replacement (TAVR).

Citation: EMJ Cardiol. 2019;7[1]:80-81. Abstract Review No. AR6.

BACKGROUND

Antithrombotic therapy in transcatheter aortic valve replacement (TAVR) is highly controversial. Dual antiplatelet therapy (DAPT) for 3–6 months with aspirin and clopidogrel is the current recommendation. In patients with an indication for oral anticoagulation (OAC), several regimes were described, ranging from OAC monotherapy, to dual, and even triple therapy. Besides vitamin K antagonists, non-vitamin K OAC (NOAC) are frequently used in TAVR patients with an indication for permanent OAC.

PURPOSE

The authors aimed to evaluate different antithrombotic regimes and their impact on the outcome.

METHODS

A single-centre retrospective analysis was performed in 1,160 patients treated by transfemoral TAVR approach (TF-TAVR).[1] Primary endpoints were 30-day mortality, stroke, and bleeding according to VARC-2 criteria. The secondary endpoint was all-cause mortality at 1 year.

RESULTS

In 1,160 patients with TF-TAVR, a broad range of regimes occurred in clinical practice. The majority of patients were on DAPT (637 patients; 55%), followed by vitamin K antagonists + clopidogrel (186 patients; 16%). Other patients received OAC mono (98 patients; 9%), triple therapy (93 patients; 8%), NOAC mono (31 patients; 3%), single antiplatelet therapy (SAPT [40 patients; 4%]) or NOAC + clopidogrel (31 patients; 3%).

All-cause mortality 30 days after TF-TAVR differed between the regimens (SAPT/OAC+SAPT/N-OAC+DAPT: 0.0% versus DAPT: 3.6% versus OAC: 10.2% versus NOAC: 1.3% versus NOAC+SAPT: 0.3%; pANOVA <0.0001). Severe bleeding events were comparable (SAPT: 5.0% versus DAPT: 2.4% versus OAC: 7.1% versus NOAC: 1.3% versus OAC+SAPT: 3.2% versus NOAC+SAPT: 0.0% versus N-OAC+SDPT: 4.3%; pANOVA=0.15). Stroke rates were comparable in all subcohorts as well (SAPT: 5.0% versus DAPT: 3.0% versus OAC: 7.1% versus NOAC: 2.7% versus OAC+SAPT: 1.6% versus NOAC+SAPT: 0.0% versus N-OAC+DAPT: 1.1%; pANOVA=0.13). Only two haemorrhagic strokes (5.6%) appeared under DAPT and OAC mono respectively, whereas all others were of thromboembolic origin (94.4%). Surprisingly, all-cause mortality at 1 year after TF-TAVR was higher in OAC patients compared to all other used regimes (log rank overall: p=0.0012).

CONCLUSION

Data from this retrospective analysis indicate that a variety of different antithrombotic regimes occur even in a single centre analysis. All-cause mortality was enhanced in patients with OAC. Therefore, clinical trials need to investigate if this can only be explained by additional atrial fibrillation.

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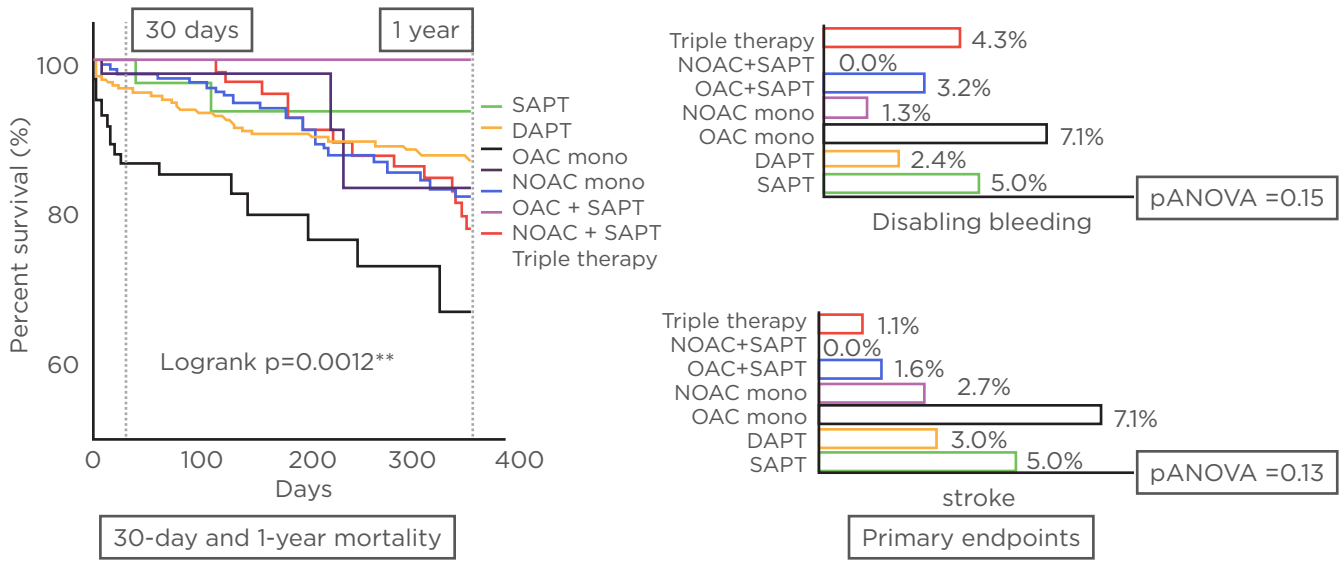

Figure 1: Primary and secondary endpoints.

DAPT: dual antiplatelet therapy; OAC: oral anticoagulation; NOAC: nonvitamin K oral anticoagulation; SAPT: single antiplatelet therapy.

Summary of Artificial Intelligence in Echocardiography for Standard Clinical Metrics

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Disclosure: Mr Hewitt and Dr Gladding are shareholders and directors of HeartLab Limited, Auckland, New Zealand.

Support: This work was supported by the Health Research Council, Auckland, New Zealand.

Keywords: Artificial intelligence (AI), deep learning, echocardiography.

Citation: EMJ Cardiol. 2019;7[1]:82-83. Abstract Review No. AR7.

BACKGROUND

This study sought to validate the use of artificial intelligence (AI) for analysis of an echocardiogram, in a clinical scenario.

A three-stage, deep learning pipeline developed in a previous body of work[1] ran on data from a different institution was utilised. Echocardiography studies were exported in Digital Imaging and Communications in Medicine (DICOM) format and stored in a folder with a separate DICOM file for each cine image. The first stage of the pipeline was to input a folder of DICOM files and classify 10 frames from each cine into one of 23 different classes representing different echocardiography views. The classification was performed using a VGG-16 convolutional neural network. The ten classifications were averaged to arrive at an end view classification for the cine. Five views of interest were passed to the second stage for further analysis: the apical two, three, and four-chamber view, and the parasternal short and long-axis. Every frame within the cine images of interest was semantically segmented using separately trained U-Net networks. In the third stage of the pipeline, the segmented views were further analysed to calculate left ventricular end systole volume (LVESV), left ventricular end diastole volume (LVEDV), left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), and left atrial volume index (LAVOLI).

METHODS

Participants were retrospectively enrolled (N=60) from a previous heart failure (HF) study in which 5-minute protocol echocardiography, 5-minute advanced ECG, metabolomic testing, and next-generation sequencing data were collected. Of these participants, 41 were HF patients and 19 acted as controls. Mean LVEF was 39±10% for HF participants and 57±5% for controls. All participants' echocardiograms were exported in DICOM format and analysed using the deep learning pipeline. A cardiology registrar independently measured the same five metrics as the deep learning pipeline.

RESULTS

Compute time per study was between 4 and 7 minutes using a single graphics processing unit. Eleven (18%) non-physiological LVESV measurements (and the corresponding LVEF measurements) were excluded. AI-generated measurements had strong, significant correlations with manual measures of LVESV (r=0.8), LVEDV (r=0.77), LVEF (r=0.71), LAVOLI (r=0.71), and LVMI (r=0.6) ($p<0.005$) (Figure 1A). Receiver operating characteristic (ROC) curve analysis showed a similar discrimination for HF between AI and manual LVEF (HF defined as LVEF <35%), and other HF biomarkers (AUC for AI: 0.88, AUC for manual: 0.93, 95% confidence interval: 0.03–0.15, p=0.19) (Figure 1B).

DISCUSSION

The results demonstrate that AI methods of echocardiography analysis are approaching the accuracy required for clinical utility.

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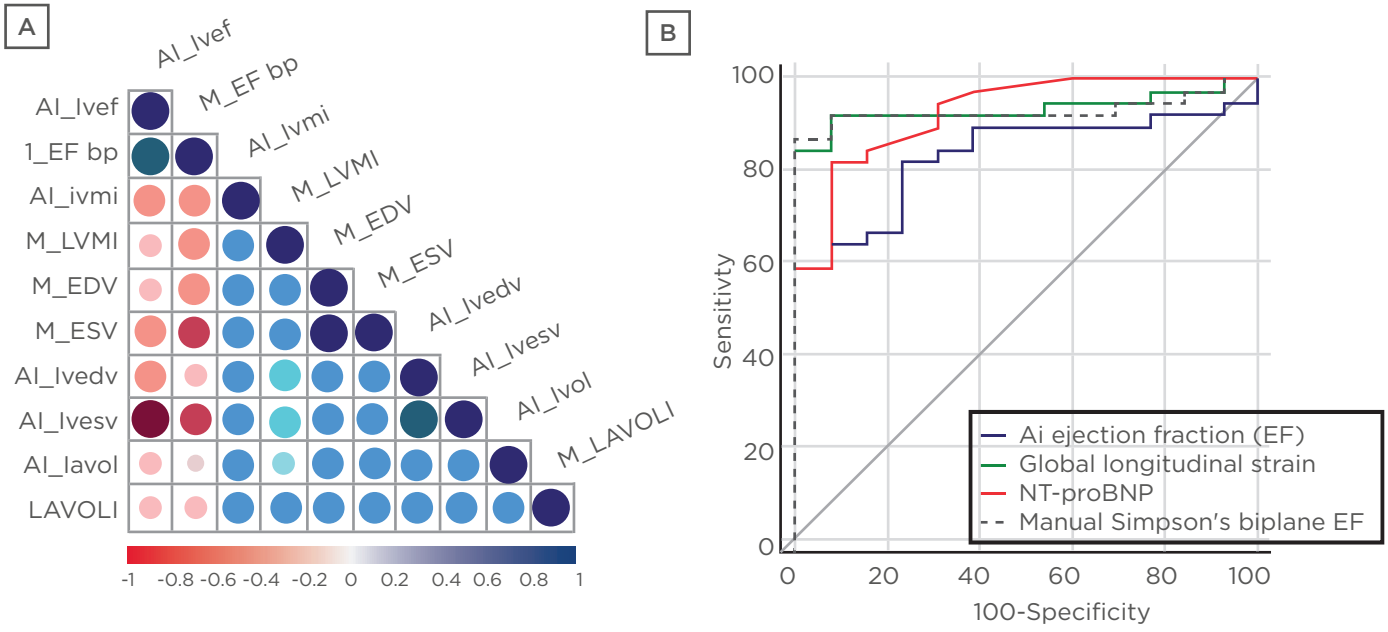

Figure 1: A) Correlation matrix comparing AI and Manual measurements. B) ROC Curve comparing diagnostic tools for HF. LVEF-based diagnostics define HF as <35% LVEF.

AI: artificial intelligence; bp: blood pressure; HF: heart failure; LAVOLI: left atrial volume index; LVEF: left ventricle ejection fraction; LVEDF: left ventricular and diastole volume; LVESF: left ventricular and systole volume; LVMI: left ventricular mass index; ROC: receiver operating characteristic.

Cardiac Rehabilitation in Heart Failure: Looking Further Ahead

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Disclosure: The authors have declared no conflicts of interest.

Received: 11.06.19

Accepted: 12.09.19

Keywords: Cardiac rehabilitation (CR), cardiac rehabilitation programmes, coronary heart disease, heart failure (HF).

Citation: EMJ Cardiol. 2019;7[1]:84-87.

ABSTRACT

Heart failure (HF) is associated with significant morbidity and mortality. Despite major advances in the treatment of HF, there are still important unmet needs among this patient population. Cardiac rehabilitation has a central role in cardiovascular prevention and for overall disease management, and can have an important impact among HF patients. The authors present a brief overview on the current role of cardiac rehabilitation among HF patients in a contemporary setting and discuss some areas of future research in the context of this intervention.

INTRODUCTION

Cardiac rehabilitation (CR) programmes play a pivotal role in the cardiovascular continuum, being of paramount importance in the management of several pathological processes.[1-3] Exercise, one of the pillars of this intervention, can have profound interactions with the cardiovascular system.[2,4] Additionally, contemporary CR programmes have evolved into comprehensive frameworks designed to provide an integrative approach to the individual patient, encompassing not only exercise training, but several other interventions on a multidisciplinary setting.[1,5] Over the last few decades, a wealth of data have shown the beneficial effects of CR, on both outcomes, such as mortality, and different measures of functional capacity and quality of life, especially in individuals with coronary heart disease,[2,3,6,7] attesting to its relevance.

MAIN BODY

Heart failure (HF) presents a major and growing challenge, having an important prevalence among several world regions and being associated with substantial morbidity, mortality, and healthcare costs.[8,9] Whilst there have been significant improvements in the management of this syndrome, in regards to pharmacological and device-based treatments there are still important unmet needs in this patient population.[8,10]

Importantly, and especially for HF with a preserved ejection fraction, this syndrome can also be associated with several changes affecting the musculoskeletal, respiratory, and peripheral vascular systems; therefore, exercise training could be particularly pertinent.[2,10,11] In addition, the ample scope of CR also makes this intervention attractive given the overall clustering of cardiovascular risk that can be present in these individuals.[1,2,5,8] As such, there has been considerable interest in the role of CR programmes among HF patients.[8,12,13]

In this regard, several studies have been designed to assess the potential impact of CR programmes.[14-16] Importantly, data on this matter should be reviewed while taking into consideration both study designs and the protean nature of this entity (as expressed by patient and programme characteristics). The HF-ACTION trial, including 2,331 patients with HF and a reduced ejection fraction, showed that an exercise training programme, although safe, was not associated with a significant reduction in all-cause mortality or hospitalisations.[17] However, when adjusting for highly prognostic covariates, including cardiopulmonary exercise test duration, left ventricular ejection fraction, history of atrial fibrillation/flutter, Beck Depression Inventory II score, and HF aetiology, there were significant reductions on all-cause mortality or hospitalisations.[17] Remarkably, and as previously discussed, these data should take possible limitations relating to the patient population studied, the design of the programme, background therapy, and the blinding status into consideration.[17,18] Indeed, the type of exercise training modality should be highlighted, as this can lead to discrepant results in terms of different CR programmes.[19] In this regard, though high-intensity interval training has shown promising results,[19,20] a recent multicentre study (the SMARTEX Heart Failure Study) compared the effects of a supervised programme of high-intensity interval training or moderate continuous training among patients with HF and a reduced ejection fraction, and this study did not show significant differences in terms of aerobic capacity or left ventricular remodelling.[21] However, before generalisation of results, it should be mentioned that the differences in training intensity between groups partly overlapped (being less than intended).[21] Additionally, in HF with a preserved ejection fraction, a pilot study appeared promising for high-intensity interval training in terms of both peak oxygen consumption and diastolic function parameters.[22] Interestingly, and showcasing the multisystemic nature of the HF syndrome, other modalities of exercise training such as those relating to the inspiratory muscles seem of potential relevance.[23] Given the present data, further research appears justified in order to ascertain the optimal strategy for HF patients with a reduced, as well as preserved, ejection fraction.[13,22,24]

Another issue worth mentioning relates to the timing of the CR intervention.[12,25] A recent Cochrane review showed that in the context of HF, CR can be of importance in the reduction of hospitalisations, as well as providing improvements in quality of life.[14] In the present meta-analysis, the authors reported no reduction in mortality, but an improvement could be present in long-term interventions.[14] This notion was previously described in the seminal study by Belardinelli et al.,[25] in which a 10-year CR programme among HF patients (with an ejection fraction <40% at baseline) was associated with significant improvements in terms of functional capacity, left ventricular ejection fraction, and cardiac mortality. The most recent Cochrane meta-analysis also reported improvements on quality of life measures,[14] a finding which has also been recently reported in an article by Taylor et al.[15] in the context of the ExTraMATCH II collaboration. Additionally, the latter analysis, which addressed individual patient data from 13 trials, encompassing a total of 3,990 patients, also reported significant improvements in exercise capacity.[15] Though these results should be interpreted in light of possible biases, as elegantly discussed by the authors and featured in the comparison of the results for the effect on mortality and hospitalisations with the Cochrane review, they reinforce the prominent role of CR among HF patients.[12,14,16,26,27] Notably, it should be stressed that despite the present data, CR uptake remains a challenge,[1,28] especially among older individuals, female patients, and those with more comorbidities.[28] As such, strategies to improve patient participation, specifically in these subgroups, are an area of growing clinical importance.[1,28]

New data aiming to ascertain the role of CR programmes among less-studied groups of patients are also emerging. Although data is limited, a recent position paper by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), described that in patients with left ventricular assist devices, CR appears a promising therapy.[29,30] Future research should allow further refinements on the impact of this intervention among left ventricular assist devices recipients.[30,31] Another rapidly expanding area of investigation concerns the possible role of exercise and CR programmes in the mitigation of cardiotoxicity associated with cancer treatments.[32] Again, preliminary data showed this strategy to be feasible,[33-35] with a recent study showing that a supervised exercise programme was able to attenuate functional decline during anthracycline chemotherapy among women with early stage breast cancer.[33] Larger studies are needed to address the potential impact of this approach, namely in terms of overall mortality and morbidity, as well as the optimal timing and programme duration.[35]

CONCLUSION

Given the present data and the growing complexity associated with HF, the role of CR remains of ample significance, as highlighted in the Class I recommendation for these programmes by the ESC.[1] As contemporary patient care evolves into an era of evermore personalised medicine, the broad scope of this time-tested intervention remains central in order to provide a holistic approach to this challenging patient population.

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Lipoprotein(a) and Calcific Aortic Valve Stenosis

EDITOR'S PICK

Our Editor's pick for this year's edition of *EMJ Cardiology* is the review paper by Kosmas et al. which presents the role of the complex polymorphic lipoprotein(a) and its implication in calcific aortic valve stenosis. Studies have previously associated enhanced levels of lipoprotein(a) with increased risk of cardiovascular disease. This paper is a comprehensive review of the current data indicating the causative role of lipoprotein(a) in aortic valve calcification and aortic valve stenosis, and outlines the need for better understanding of the complex molecular processes to ultimately reduce calcific aortic valve stenosis morbidity and mortality.

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Disclosure: Dr Kosmas and Dr Guzman have received speaking honoraria from Amgen as members of the Dyslipidemia Speaker Bureau.

Received: 09.06.2019

Accepted: 29.07.2019

Keywords: Aortic valve calcification (AVC), aortic valve stenosis (AVS), calcific aortic valve stenosis (CAVS), Lipoprotein(a) [(Lp(a)].

Citation: EMJ Cardiol. 2019;7[1]:89-97.

Abstract

Calcific aortic valve stenosis is the most common valve disease in the elderly population and is associated with significant morbidity and mortality. This condition is characterised by gradual fibrosis, thickening, and calcification of the affected leaflets, leading to decreased leaflet mobility and increased obstruction of the blood flow from the left ventricle. Lipoprotein(a) [Lp(a)] is a complex polymorphic lipoprotein with proatherogenic, proinflammatory, and prothrombotic properties. Several epidemiologic and clinical studies have described elevated Lp(a) levels as an independent causative risk factor for cardiovascular disease, including coronary artery disease, stroke, peripheral artery disease, heart failure, and venous thromboembolism. On the other hand, several studies have also described Lp(a) as a strong genetic causative risk factor for aortic valve calcification and aortic valve stenosis. In this review, the authors present and discuss the scientific and clinical evidence pertaining to the role of Lp(a) in calcific aortic valve stenosis.

INTRODUCTION

Lipoprotein(a) [Lp(a)] is a complex polymorphic lipoprotein synthesised by the liver. Lp(a) presents a similar structure with the low-density lipoprotein (LDL) molecule, only differing in the presence of the glycoprotein apolipoprotein(a) [(Apo(a)], which is covalently bound via a disulfide bond to the apolipoprotein B-100 (ApoB-100) of the LDL molecule.[1] More specifically, Lp(a) comprises one molecule of an ApoB-100-containing LDL particle and one molecule of a large, highly polymorphic glycoprotein called Apo(a). A distinctive feature of Apo(a) is the presence of triple loop structures, which are called kringles. Kringle domains are stabilised by three internal disulfide bonds and are also found in certain coagulation factors, such as plasminogen, tissue plasminogen activators, prothrombin, and urokinase. However, in contrast to plasminogen, the linker sequences that join individual kringles are glycosylated in Apo(a). The two main components of Lp(a) are covalently linked together via a disulfide bond between the ApoB-100 of the LDL moiety and one of the kringle domains in Apo(a).[2]

Plasma levels of Lp(a) are under strict genetic control mainly by the *LPA* gene, largely unaffected by food intake, type of diet, presence of inflammation, or environmental factors.[1,3] While the physiological role of the Lp(a) has not yet been well elucidated, this lipoprotein has been associated with several physiological processes, such as wound healing and tissue repair, as well as inhibition of cancer growth and spread.[4] There is extensive evidence demonstrating that Lp(a) presents proatherogenic, proinflammatory, and prothrombotic properties, because it promotes the oxidation of LDL, enhances secretion and expression of proinflammatory cytokines, promotes platelet aggregation, and impairs plasminogen activation.[5-8] Lp(a) is currently considered as an independent genetic, causative risk factor for cardiovascular disease (CVD), including coronary artery disease (CAD),[9-11] stroke,[10,11] peripheral artery disease,[11] heart failure,[12] and venous thromboembolism.[13] In addition, several studies have also described Lp(a) as a strong causative risk factor for aortic valve calcification (AVC) and aortic valve stenosis (AVS).[14-16]

Calcific AVS (CAVS) is the most common valve disease in the elderly population, affecting >1 million patients in the USA, and is associated with significant morbidity and mortality.[17] In Norway, the prevalence of AVS is also consistently increasing with age, average values being 0.2% in the 50–59 year old cohort, 1.3% in the 60–69 year old cohort, 3.9% in the 70–79 year old cohort, and 9.8% in the 80–89 year old cohort.[18] In Sweden, the age-adjusted incidence of AVS declined from 15.0 to 11.4 in men and 9.8 to 7.1 in women per 100,000 from 1989–1991 and 2007–2009, and the median age at diagnosis increased by 4 years for both men and women.[19] In a large systematic review and meta-analysis of population-based studies from 19 European countries and North America, the pooled prevalence of all AVS in the elderly (>75 years) was 12.4% and the prevalence of severe AVS was 3.4%.[20] CAVS is characterised by gradual fibrosis, thickening, and calcification of the affected leaflets, thus leading to decreased leaflet mobility and increased obstruction of the blood flow from the left ventricle.[17,21]

The pathogenesis of AVS shares many similarities to that of atherosclerosis. Several longitudinal studies have demonstrated that hypercholesterolaemia has a significant impact on the development of degenerative AVS. Notwithstanding, in several clinical studies, intensive statin therapy has failed to halt the progression of CAVS or induce its regression.[22-24] Here, it should be noted that statins have been shown to increase Lp(a) levels by roughly 10–20%,[6,25,26] which could be one explanation as to why statins were proven ineffective in halting the progression of CAVS. In contrast, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to reduce Lp(a) levels by 24.5–29.5%.[27] Related to this, it was recently shown that high levels of PCSK9 predicted development of AVS requiring surgery, although this association seemed to be driven by concurrent atherosclerotic disease.[28]

On the other hand, AVS has also been associated with several other atherogenic risk factors, such as diabetes, hypertension, smoking, male sex, as well as age, apparently due to progressive fibro-calcific remodeling.[29] In addition, there are data indicating that chronic *Chlamydia pneumoniae* infection may act as a 'trigger' and aggravate AVS via the formation of circulating immune complexes. Importantly,

a strong synergism was also observed between Lp(a) and *C. pneumoniae* IgG antibodies in circulating immune complexes.[30] In this review, the authors aim to present and discuss the scientific and clinical evidence pertaining to the role of Lp(a) in CAVS.

STUDY EVIDENCE PERTAINING TO THE ROLE OF LIPOPROTEIN(a) IN AORTIC VALVE CALCIFICATION AND STENOSIS

There is extensive evidence from genetic and clinical studies demonstrating the causative association of elevated Lp(a) with CAVS.

Studies Establishing the Association of Aortic Valve Calcification and Stenosis with Increased Lipoprotein(a) Levels

The first report to demonstrate an association between Lp(a) and AVS was published in 1995. The study showed that AVS was present in 36.1% of subjects with Lp(a) levels ≥30.0 mg/dL, but only in 12.7% of subjects with Lp(a) levels <30.0 mg/dL (p<0.001).[31]

In another study, which evaluated the role of novel coronary risk factors in the development of AVC, it was clearly demonstrated that patients with AVC had significantly higher serum Lp(a) levels, as compared with subjects with essentially normal aortic valve morphology (27.4 mg/dL versus 19.9 mg/dL, respectively; p=0.033). Moreover, multivariate analysis identified Lp(a) as an independent predictor of AVC.[32]

Study Evaluating the Impact of Increased Lipoprotein(a) Levels on Aortic Valve Calcification in Patients with Familial Hypercholesterolaemia

Patients with familial hypercholesterolaemia (FH) have been shown to have a higher prevalence and extent of AVC than patients with non-familial hypercholesterolaemia.[33] Exposure to classical risk factors alone cannot adequately explain the onset and progression of AVC in statin-treated FH patients.[34] On the other hand, patients with FH have been shown to have 3-fold higher plasma Lp(a) levels than controls, apparently due to variation at the LDL receptor gene locus.[35] Thus, in a study, which included 129 asymptomatic statin-treated patients with FH, and was designed to investigate whether Lp(a) concentration is associated with AVC in this cohort of patients, Vongpromek et al.[34] showed that for a 10 mg/dL increase in Lp(a) concentration in those patients, there was an 11% associated increased risk of developing AVC. Multivariate analysis again identified Lp(a) as a significant independent predictor of AVC. Of note, however, Lp(a) levels were not associated with the presence or severity of coronary artery calcification.[34]

Genetic Studies

Genome-wide association studies (GWAS) are designed to test the association between markers, called single-nucleotide polymorphisms (SNP), across the genome and disease, usually involving ≥300,000 markers that are reasonably polymorphic and are spread across the genome fairly evenly.[36] In other words, GWAS compare common genetic variants in large numbers of affected cases to those in unaffected controls to determine whether an association with disease exists.[37] GWAS have been proven to be extremely useful in determining the association between elevated Lp(a) levels and CAVS.

In a GWAS, a SNP, rs10455872, in the *LPA* locus, encoding for Apo(a), was found to be significantly correlated with AVC (odds ratio [OR] per allele: 2.05). Importantly, the association between rs10455872 and Lp(a) levels was confirmed and it was clearly shown that Lp(a) levels mediate the effect of this SNP on AVC. Furthermore, in prospective analyses, *LPA* genotype was associated with incident AVS (hazard ratio [HR] per allele: 1.68) and aortic valve replacement (AVR) (HR: 1.54).[14]

In another study, which combined data from two prospective general population studies (the Copenhagen City Heart Study and the Copenhagen General Population Study), evaluating a total of 77,680 Danish individuals for as long as 20 years, elevated Lp(a) levels and corresponding LPA genotypes (rs10455872, rs3798220, kringle IV Type 2 [KIV-2] repeat polymorphism) were associated with an increased risk of AVS in the general population. More specifically, Lp(a) levels of 5–19 mg/dL, 20–64 mg/dL, 65–90 mg/dL, and >90 mg/dL were associated with multivariable adjusted HR for AVS of 1.2, 1.6, 2.0, and 2.9, respectively, as

compared to levels of Lp(a) <5 mg/dL.[15] Notably, the risk of AVS appears to increase continually as Lp(a) levels increase. In a large retrospective analysis, which assessed the correlation between Lp(a) levels and the incidence of AVS among patients with extremely high Lp(a) levels (>150 mg/dL), the prevalence of AVS was 3.74 times higher in the patients with Lp(a) levels >150.0 mg/dL, compared with those with Lp(a) levels <30.0 mg/dL.[38]

Furthermore, in a similar study, which used a multidirectional Mendelian randomisation approach and included 100,578 individuals from the general Danish population, elevated levels of Lp(a) were once again causally associated with increased risk of AVS. More specifically, a one-standard deviation (SD) increase in Lp(a) levels was associated observationally with a multifactorially adjusted HR of 1.23, whereas the corresponding causal risk ratios based on LPA SNP and on LPA KIV-2 genotype were 1.38 and 1.21, respectively. Of note, in this study, elevated Lp(a) levels were not causally associated with increased low-grade inflammation, as measured through levels of C-reactive protein (CRP).[39]

In another prospective Mendelian randomisation study, in which serum Lp(a) levels were measured in 17,553 participants of the European Prospective Investigation into Cancer (EPIC)-Norfolk study, elevated Lp(a) levels were associated with increased risk of AVS. More specifically, after adjusting for age, sex, and smoking history, participants in the top Lp(a) tertile had a 57% higher risk of AVS, as compared with those in the bottom Lp(a) tertile. Furthermore, heterozygotes and homozygotes for the rs10455872 genetic variant in the *LPA* locus were at increased risk for AVS with HR of 1.78 and 4.83, respectively, as compared to the individuals that did not carry the abnormal variant.[40] These results were corroborated by a more recent, large case-control study, which replicated the association between *LPA* variants with AVS and showed a per risk allele OR of 1.34 for rs10455872 and 1.31 for rs3798220. Compared with individuals with no risk alleles, the homozygous OR for AVS was 2.05 for rs10455872 and 3.74 for rs3798220, while compound heterozygotes had a 2.00 OR for AVS.[41]

Studies Evaluating the Impact of Lipoprotein(a) and its Oxidised Phospholipid Content on Aortic Valve Calcification and Stenosis

In a study evaluating the impact of Lp(a) and oxidised phospholipids (OxPL) on ApoB-100 (OxPL-apoB), reflecting the biological activity of Lp(a), on AVS progression in 220 patients with mild-to-moderate AVS, elevated levels of Lp(a) and OxPL-apoB were associated with faster AVS progression and need for AVR. Based on the results of this study, the authors concluded that Lp(a) may mediate AVS progression through its associated OxPL.[16] Of note, however, among patients with age ≤57 years, progression of AVS was 2-fold faster in those in the top Lp(a) tertile, as compared with those in the middle and bottom tertiles, whereas, in patients aged >57 years, the rate of AVS progression did not differ according to levels of Lp(a).[16] This finding was corroborated in another more recent trial, in which for patients aged ≥70 years the development of AVS was not influenced by Lp(a) levels.[42]

In a secondary analysis of a randomised clinical trial, which included participants with mild-to-moderate CAVS with no indication for statin therapy from the ASTRONOMER (Effects of Rosuvastatin on Aortic Stenosis Progression) trial, the association of Lp(a) levels and its OxPL content with faster CAVS progression was actually linear. The results of this study reinforce the concept that measurement of Lp(a) levels should be performed in patients with mild-to-moderate CAVS to improve risk stratification and management.[43]

Studies Evaluating the Impact of Increased Lipoprotein(a) Levels on Aortic Valve Calcification and Stenosis in Patients with Bicuspid Aortic Valve

There is evidence suggesting that increased levels of Lp(a) are associated with the presence and severity of AVC in patients with bicuspid aortic valve (BAV). In an observational study, which looked at a small series of asymptomatic individuals with BAV, all the BAV subjects without AVC had normal Lp(a) levels, whereas 75% (3 out of 4) of cases with AVC had elevated Lp(a) levels. Although the author recognised that this was only a small series of BAV cases, notwithstanding,

it was suggested that the concept that the plasma Lp(a) concentration may play a major role in the calcification process of the BAV would be worth exploring in larger samples.[44] Later on, this concept was corroborated in another larger study, which investigated the association of Lp(a) and *LPA* KIV-2 repeat number with the presence of calcification and stenosis in patients with BAV. In that study, among BAV patients there was a clear positive association between Lp(a) levels and the degree of AVC. In contrast, lower *LPA* KIV-2 repeat numbers were observed in subjects with more severe AVC. Based on the results of this study, the authors suggested that Lp(a) may serve as a risk marker for the identification of BAV patients most likely to develop AVC and AVS.[45] However, the potential effect of lowering Lp(a) on the development and progression of AVC in patients with BAV would need to be further investigated in larger randomised controlled trials.

Studies Addressing the Question Whether the Association of Elevated Lipoprotein(a) Levels with Aortic Valve Calcification and Stenosis is Dependent upon the Concomitant Presence of Coronary Artery Disease

As previously discussed, Lp(a) is considered an independent genetic, causative risk factor for CAD. Thus, the question may be raised whether the association of elevated Lp(a) with CAVS is dependent upon, or mediated by, the concomitant presence of CAD. In a nested, case-referent study, high Lp(a) levels and a high Apo B/A1 ratio were associated with surgery for AVS in patients with concomitant CAD, but not in those with isolated AVS (without concomitant CAD).[46] However, in a more recent large genetic association study, genetically elevated Lp(a) levels were associated with CAVS independently of the presence of CAD, and individuals with high Lp(a) levels had a significantly increased risk for CAVS even in the absence of CAD. Based on the results of this study, the authors suggested that the measurement of Lp(a) levels in patients with CAVS might be proven clinically useful.[47]

POTENTIAL MECHANISMS THROUGH WHICH ELEVATED LIPOPROTEIN(a) MAY LEAD TO CALCIFIC AORTIC VALVE STENOSIS

As previously discussed, CAVS is the most common valve disease in the elderly population and its pathogenesis shares many similarities to that of atherosclerosis. Researchers have described an 'early lesion' that shared common histologic features with the early lesion of atherosclerotic plaques, suggesting that CAVS could be an atherosclerotic disease.[21] Studies indicate that inflammation, lipid deposition, and fibrosis, which are all important contributors to atherogenesis, also play an important role in the pathogenesis and progression of CAVS.[48,49] Lp(a) is a major carrier of proinflammatory OxPL.[5] OxPL co-localise with Lp(a) in arterial and aortic valve lesions and thus may be directly involved in the pathogenesis of CVD and CAVS by promoting endothelial dysfunction, lipid deposition, inflammation, and osteogenic differentiation, leading to calcification. Thus, OxPL may potentially provide a mechanistic link between CVD and CAVS.[50] In view of the similarities shared in the pathogenesis of atherosclerosis and CAVS, it can become easily understandable that molecules promoting inflammation and atherosclerosis, such as Lp(a), may also have a direct impact on CAVS.

Even though the precise mechanism by which Lp(a) promotes the initiation and progression of CAVS has not been clearly elucidated, there are multiple proposed mechanisms through which elevated Lp(a) levels may lead to CAVS. Similar to LDL, transfer of Lp(a) from the circulation into the arterial intima and aortic valve cusps leads to cholesterol deposition with subsequent thickening of the aortic valve cusps.[51]

On the other hand, Lp(a) has been shown to trigger apoptosis in endoplasmic reticulum-stressed macrophages via a mechanism requiring both cluster of differentiation 36 (CD36) and toll-like receptor 2 (TLR2). This macrophage apoptosis may signify a key process, likely contributing to early valvular lesion progression.[52,53]

Furthermore, as it was mentioned earlier, Lp(a) exhibits prothrombotic properties because it competes with plasminogen and therefore prevents plasmin from dissolving fibrin clots,[6-8]

thus leading to fibrin deposition on the aortic leaflets and subsequent progression of AVS.[51]

Lp(a) is involved in the wound-healing process and may accumulate at sites of injury[3] promoting cholesterol deposition. Thus, it may be well contemplated that accumulation of Lp(a) at sites of minor injury, such as the affected aortic leaflets at the very initial stages of AVS, may lead to increased cholesterol and thrombi deposition, thus promoting the progression of AVS.[51]

Finally, another molecule that has been implicated is autotaxin (ATX), a lysophospholipase D enzyme, which transforms lysophosphatidylcholine into lysophosphatidic acid (LysoPA). ATX is transported in the aortic valve via the bloodstream by Lp(a) and is also secreted by valve interstitial cells. ATX-LysoPA has been shown to promote inflammation and mineralisation of the aortic valve, thus promoting CAVS.[54] More specifically, pericellular LysoPA may associate with lysophosphatidic acid receptor 1 (LPAR1), which promotes nuclear translocation of NF-κB. The activation of NF-κB leads to an increased expression of IL-6 and bone morphogenetic protein 2 (BMP-2), which are known pro-osteogenic factors.[55]

A schematic of the potential mechanisms through which elevated Lp(a) may lead to CAVS is shown in Figure 1.

PRELIMINARY EVIDENCE PERTAINING TO THE EFFECT OF LIPOPROTEIN(a) LOWERING ON THE RISK OF AORTIC VALVE CALCIFICATION AND STENOSIS

In an elegant study, which used human aortic valve interstitial cells (HAVIC), it was clearly demonstrated, for the first time, that Lp(a) is causally involved in the induction of AVC. It was also shown that the *LPA* gene is locally expressed in the stenotic aortic valve. Lp(a) was found to induce osteogenic differentiation of HAVIC via induction of the gene encoding for the tissue-nonspecific alkaline phosphatase, as well as certain pro-osteogenic mediators.

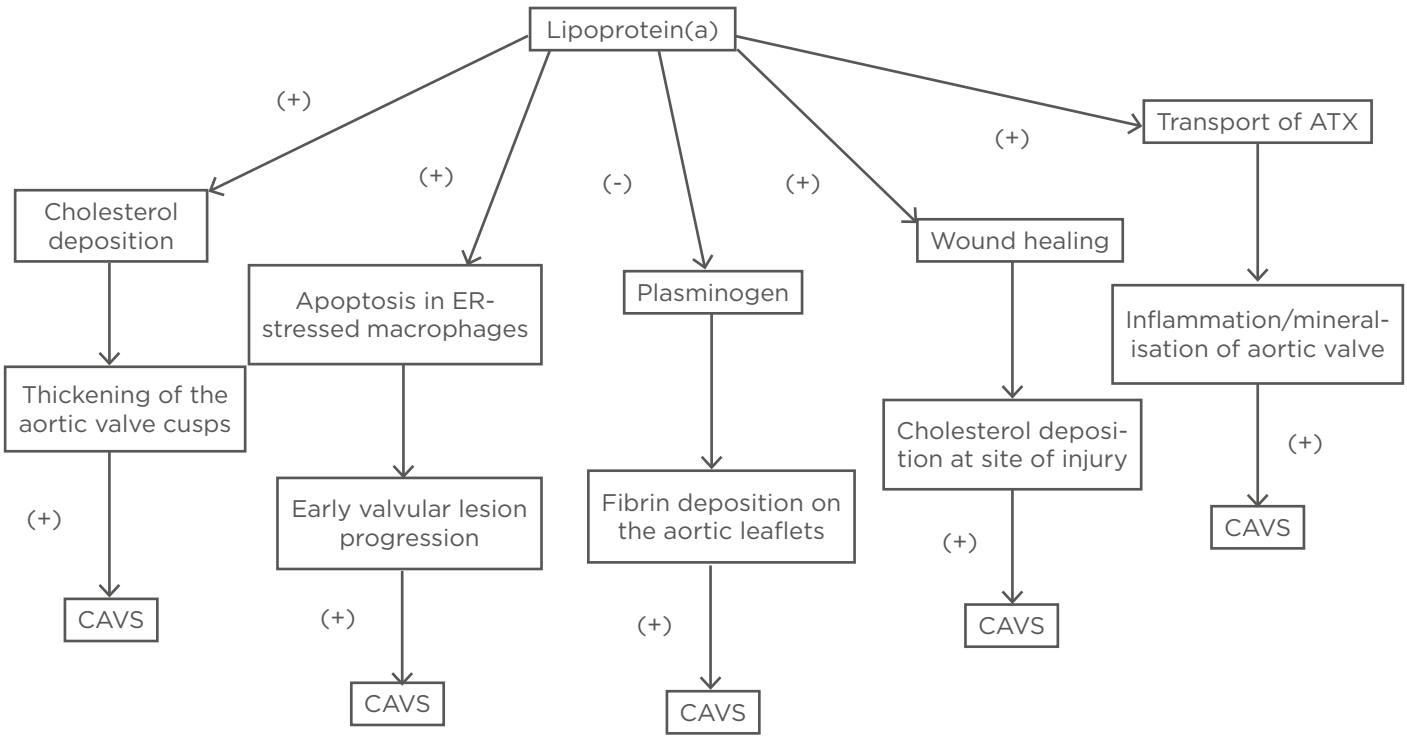

Figure 1: Potential mechanisms through which elevated lipoprotein(a) may lead to calcific aortic valve stenosis.

ATX: autotaxin; CAVS: calcific aortic valve stenosis; ER: endoplasmic reticulum.

Moreover, it was shown that the Lp(a)-induced osteogenic differentiation of HAVIC was associated with an increase in the phosphorylation of several kinases implicated in cellular remodelling and apoptosis, such as mitogen-activated protein kinase-38 (MAPK38) and glycogen synthase kinase-3 beta (GSK3β). Inhibition of MAPK38 or GSK3β led to a significant reduction of Lp(a)-induced HAVIC calcification. Thus, interfering with the Lp(a) pathway could provide a novel therapeutic approach for the prevention or even reversal of CAVS.[56]

In another multimodality imaging study, Lp(a) and OxPL promoted valve calcification in patients with AVS. In this study, Lp(a) and OxPL-apoB levels were measured in 145 patients with AVS. Initially, on baseline ^{18}F-sodium fluoride PET (^{18}F-NaF PET), patients in the top Lp(a) tertile (>35.0 mg/dL) had increased valve calcification activity compared with those in the lower tertiles. Moreover, during follow-up, patients in the top Lp(a) tertile demonstrated increased progression of valvular CT-obtained calcium score, faster haemodynamic progression on echocardiography, and an increased incidence of AVR and death compared with those in the lower tertiles. Similar results were observed with OxPL-apoB. *In vitro*, Lp(a) induced osteogenic differentiation of HAVIC through its OxPL content. The Lp(a)-induced osteogenic differentiation of HAVIC was considerably attenuated with the E06 monoclonal antibody against OxPL. Again, these findings clearly demonstrate that elevated Lp(a) and OxPL-apoB levels promote AVC, and lowering Lp(a) or inactivating OxPL may potentially lead to slowing of AVC. Thus, these findings suggest that therapeutic approaches reducing elevated Lp(a) and OxPL levels in patients with AVS could slow disease progression and delay the need for AVR.[57]

Although to date no clinical trials have been conducted to assess the impact of Lp(a) lowering on the incidence of AVS, an analysis using data from a large prospective European cohort has shown that lowering Lp(a) to <50.0 mg/dL in the general population would be theoretically expected to reduce the overall incidence of AVS by 13.9%.[58]

CONCLUSION

The above review of the scientific, epidemiological and clinical data clearly demonstrates that Lp(a) plays an independent causative role in CAVS. However, additional evidence is needed to help us better understand the precise molecular mechanisms by which elevated Lp(a) causes CAVS and promotes its progression. Furthermore, it remains to be seen if pharmaceutical interventions that decrease Lp(a) levels would also be clinically effective in reducing the risk of CAVS and its associated morbidity and mortality.

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Management of Atrial Fibrillation in Europe: Current Care Pathways and the Clinical Impact of Antiarrhythmic Drugs and Catheter Ablation

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Disclosure: Maria Velleca, Graca Costa, Laura Goldstein, Moe Bishara, Lee Ming Boo, and Qun Sha are employees of Johnson & Johnson.

Acknowledgements: Medical writing services were provided by Dr Susan Bartko-Winters from SBW Medical Writing Inc, which was funded by Johnson and Johnson.

Support: This review study and the publication of this article were sponsored by Johnson & Johnson.

Received: 26.08.2019

Accepted: 27.09.2019

Keywords: Antiarrhythmic drug (AAD), atrial fibrillation (AF), catheter ablation, clinical, economic, Europe, patient, treatment.

Citation: EMJ Cardiol. 2019;7[1]:98-109.

Abstract

Atrial fibrillation (AF), the most common form of arrhythmia, increases the risk of heart failure, stroke, and death. Management of AF focusses on effectively and safely controlling irregular heart rhythm, improving symptoms, and reducing complications. Early treatment of AF is important as it may improve patient life expectancy and quality of life (QoL). Current European guidelines recommend an integrated approach to AF management that involves shared decision making between patients and multidisciplinary teams of healthcare professionals to improve access to care and patient compliance. Treatment options include the use of anticoagulants, cardioversion, rate control therapies, and rhythm control therapies. Over the long term, rhythm control strategies that include antiarrhythmic drugs (AAD) and catheter ablation are the most common methods for controlling AF. The objective of this review is to highlight current European AF care pathway management recommendations and to examine the clinical, economic, and patient impact of different treatment options, including AAD and catheter ablation. While AAD have been shown to improve QoL and are affordable in the short term, treatment is moderately effective, associated with significant side effects, and can be costly long term. Catheter ablation is a highly effective therapy choice that improves patient wellbeing and is associated with a low rate of ablation-related complications. Compared to drug therapy, catheter ablation provides a significant reduction in AF burden, reduces rates of recurrence, provides a greater improvement in QoL, and facilitates long-term cost savings.

OVERVIEW OF ATRIAL FIBRILLATION MANAGEMENT

Atrial fibrillation (AF) is an irregular heart rhythm that can cause palpitations and fatigue. Based on the duration of episodes, AF can be categorised into several types: paroxysmal (occasional AF that stops ≤7 days), early persistent (AF that lasts 7 days to 3 months), persistent (continuous AF for >7 days), long-standing persistent (episodes occur for >12 months), or permanent (episodes continue and attempts to restore sinus rhythm are ceased).[1,2] AF is a progressive disease: 15–20% of patients with paroxysmal AF progress to persistent over 1 year.[3-5] Risk factors for AF include: lifestyle factors (e.g., obesity and smoking),[2,6] other comorbid conditions (e.g., obstructive sleep apnoea, high blood pressure, and heart failure),[6-8] and nonmodifiable factors (e.g., older age, family history or other genetic factors, and male sex).[2,7] The symptoms of AF disrupt daily life and range from mild to debilitating.[9]

Atrial fibrillation increases the risk of heart failure (5-fold risk), stroke (2.4-fold risk), and mortality (2-fold risk);[10] however, the seriousness of AF is critically misunderstood and 45% of AF patients are unaware that AF is a life-threatening condition.[11] Patients who do not experience symptoms of AF may be at greater risk of complications and disease severity due to lack of treatment. Educational and screening programmes that increase knowledge and diagnosis of AF are important tools that can reduce the risk of stroke and death in patients with AF.[12,13] Early treatment of AF is important as it may improve patient life expectancy and QoL.[2]

The 2016 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on the management of AF and the 2017 Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS)/Asia Pacific Heart Rhythm Society (APHRS)/Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE) expert consensus statement on catheter and surgical ablation of AF recommend an integrated management strategy and individualised treatment approach based on patient preferences with the aim of improving patient wellbeing, reducing hospitalisations, and reducing mortality.[1,2] The use of anticoagulants, cardioversion, rate control, and rhythm control therapies (e.g., antiarrhythmic drugs [AAD] and catheter ablation) are recommended to manage AF.[2] The objective of this review is to highlight these current European AF care pathway management recommendations and to examine the clinical, economic, and patient impact of different treatment options, including AAD and catheter ablation.

CURRENT CARE PATHWAYS FOR THE MANAGEMENT OF ATRIAL FIBRILLATION IN EUROPE

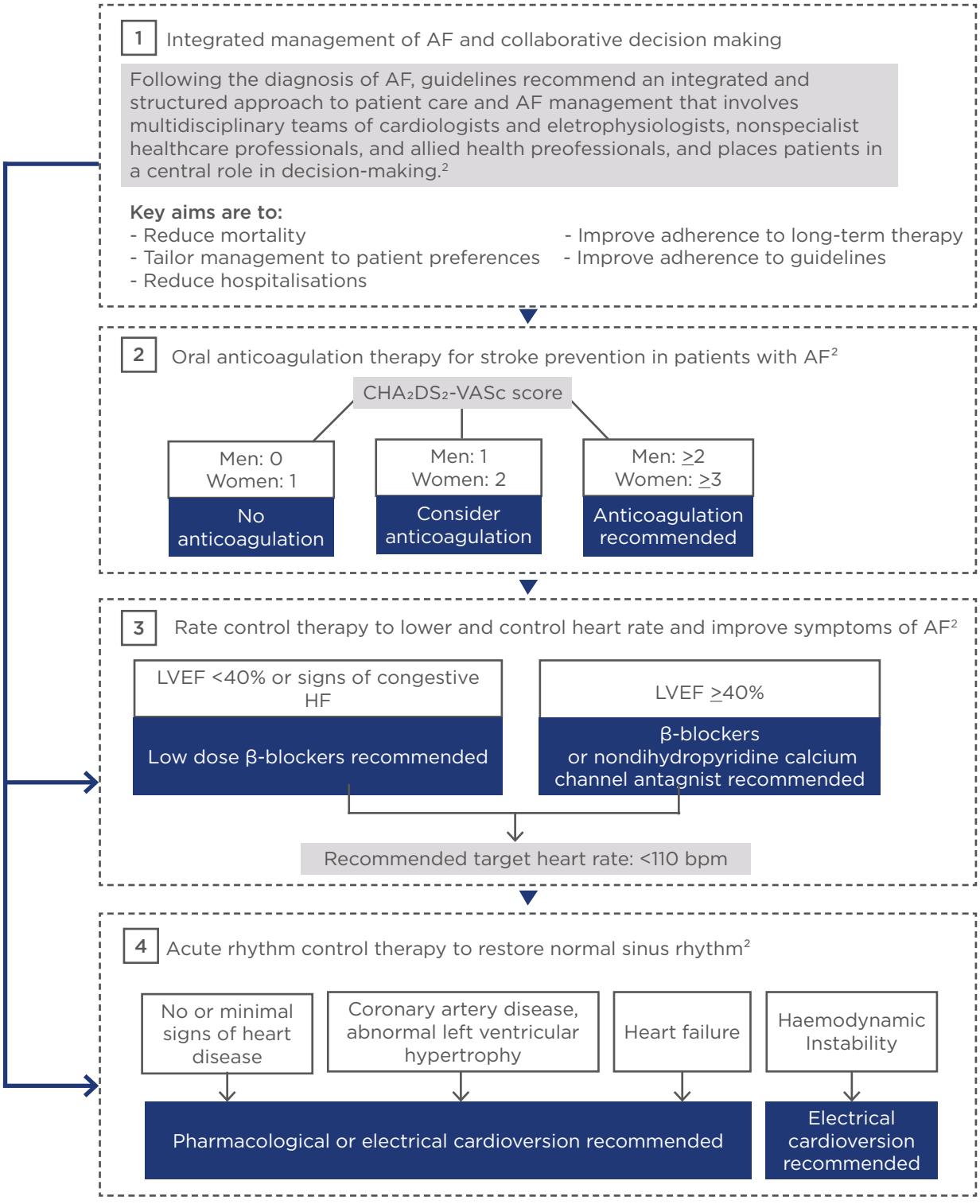
The 2016 ESC/EACTS guidelines[2] and the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement[1] provide guidance on the delivery of appropriate care for patients with AF, including: management of underlying cardiovascular (CV) risk factors and reducing stroke risk to improve life expectancy; electrical or pharmaceutical cardioversion when a patient is experiencing an AF episode; rate control therapies to control heart rate; rhythm control therapies, including AAD and catheter ablation to maintain normal sinus rhythm; and to improve QoL. An overview of these current care pathway management recommendations is provided in Figure 1.

Studies indicate that screening to identify unknown AF can identify 1.4% of the population ≥65 years of age with previously undiagnosed AF.[14] The 2016 ESC/EACTS guidelines provide recommendations for screening for AF in at-risk populations, especially the elderly and stroke survivors.[2] Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age. Recommendations for screening for AF in patients with transient ischaemic attack or ischaemic stroke incudes short-term ECG recording followed by continuous ECG monitoring for ≥72 hours. Patient-operated ECG devices, and continuous ECG monitoring using skin patch recordings have been validated for detection of paroxysmal AF, while newer technology advances (e.g., smartphones, smart watches) are currently under investigation for their potential role in detecting silent, asymptomatic AF.[2]

Figure 1: Current care pathways for the management of atrial fibrillation in Europe.

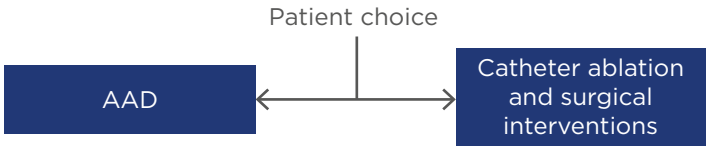
AAD: antiarrhythmic drug; AF: atrial fibrillation; AVR: aortic valve replacement; bpm: beats per minute; CABG: coronary artery bypass graft; CHA2DS2-VASc: Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); HF: heart failure; LVEF: left ventricular ejection fraction.

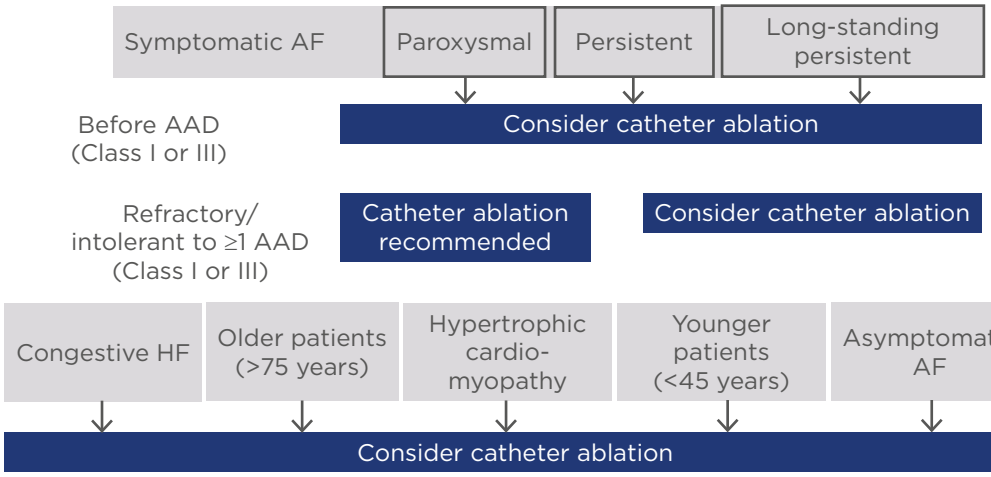
Adapted from 2017 HRS/EHRA Consensus Statement[1] and 2016 ESC Guidelines.[2]

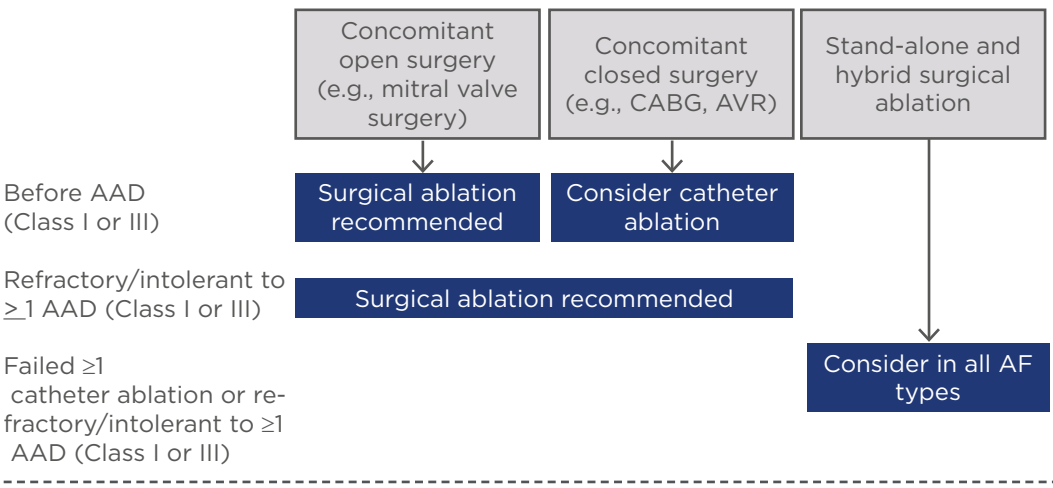


5 Rhythm control therapy to maintain normal sinus rhythm and improve symptoms of AF[1,2]

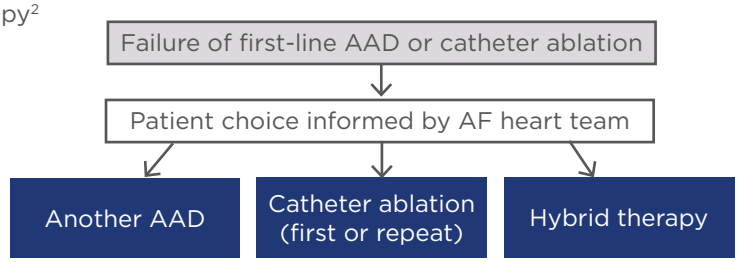
Guidelines recommend that treatment with AAD, catheter ablation, and/or surgical ablation be dependent on patient choice[1,2]
The choice of AAD needs to consider the presence of comorbidities, cardiovascular risk, potential for proarrhythmia, toxic effects, symptom burden, and patient preference.[2]







6 Selection of 2nd rhythm control therapy after failure of 1st rhythm control therapy[2]



Initial Atrial Fibrillation Patient Care Pathway Management

Following the diagnosis of AF, guidelines recommend an integrated and structured approach to patient care and AF management that involves patients and multidisciplinary teams of cardiologists and electrophysiologists, nonspecialist healthcare professionals (e.g., primary care physician, registered nurse), and allied healthcare professionals (e.g., dietician, medical technologist), and places the patient in a central role in decision-making.[2] The key aims of integrated management of AF disease and collaborative decision making are to tailor management to patient preferences, reduce hospitalisations, improve adherence to long-term therapy, and to reduce mortality.

Because the presence of CV risk factors often exacerbates AF,[2] and AF is associated with an increased risk of stroke compared to patients in sinus rhythm,[10] the initial therapeutic goal for AF is to treat any underlying CV conditions and reduce the risk of stroke.[2] The following CV risk factors and key disease-related complications are commonly assessed: stroke, heart failure, hypertension, valvular heart disease, diabetes, obesity, obstructive sleep apnoea, and chronic kidney disease.[2] To achieve CV risk reduction, lifestyle changes and the treatment of underlying CV condition are recommended.[2] Stroke prevention with oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban) is recommended in patients at risk of stroke.[2] These AF patient care pathway management strategies aim to approve patient QoL, autonomy, social functioning, and life expectancy.[2]

The CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65–74, and sex [female]) score and the HAS-BLED (hypertension, abnormal renal/liver function [1 point each], stroke, bleeding history or predisposition, labile INR, elderly [>65 years], drugs/alcohol concomitantly [1 point each]) score are used for evaluating stroke and bleeding risk, respectively, in patients with AF.[2] In patients with stroke risk factors (CHA_2DS_2-VASc score of ≥1 for men and ≥2 for women), oral anticoagulation is recommended.[2] Guidelines recommend the reduction of modifiable risk factors (e.g., treating hypertension, reducing antiplatelet and nonsteroidal anti-inflammatory drugs) in patients with AF on oral anticoagulation.[2] The guidelines also make recommendations for occlusion or exclusion of the left atrial appendage for the prevention of stroke. Anticoagulation should be continued in at-risk patients with AF for stroke prevention and left atrial appendage occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulation treatment. Further research is needed to inform the best use of left atrial appendage occlusion devices (e.g., Watchman™), especially in patients who are unsuitable for oral anticoagulation or in patients who suffer a stroke on oral anticoagulation.

Rate and Rhythm Control Strategies in Atrial Fibrillation Patient Care Pathway Management

Atrial fibrillation care pathway management includes rhythm control therapy to restore sinus rhythm during an episode of AF and rate and rhythm control therapies in the long term. Rhythm control therapies include electrical and pharmacological cardioversion with the type of cardioversion chosen dependent on haemodynamic stability, presence and type of structural heart disease, and patient choice.[2] Long-term rhythm control therapies include pharmacological (i.e., AAD), interventional (i.e., catheter ablation), or surgical (i.e., surgical ablation) options. Rhythm control strategies that include AAD and catheter ablation are the most common long-term methods for controlling AF, effectively preventing recurrence in as many as 94% of patients over the course of 1 year.[2,15-20] The choice of an alternative rhythm control therapy requires patient involvement, consideration of patient preferences, and informed decision-making with a multidisciplinary team of healthcare professionals, should the first rhythm control strategy fail.[2] Patients who experience recurrence of symptomatic AF while on AAD or after catheter ablation may choose to receive treatment with a different AAD, undergo catheter ablation again, receive hybrid therapy (i.e., combining AAD with ablation), or start rate control therapies to control AF rate or symptoms.[2]

Several therapies previously used to treat AF are no longer recommended or are only

recommended for use in select patient populations.[2] Implantable cardioverter defibrillators are not indicated for rhythm control of AF and pacemakers are only recommended for use in patients with sick sinus syndrome and/or bradycardia.

IMPACT OF ANTIARRHYTHMIC DRUG THERAPY IN THE MANAGEMENT OF ATRIAL FIBRILLATION

Overview of Antiarrhythmic Drug Therapy

AAD therapy is an integral part of maintaining sinus rhythm after cardioversion; AAD act to suppress the firing of or depress the transmission of abnormal electrical signals.[2] Several Class I (sodium channel blockers) and Class III (potassium channel blockers) AAD are available for rhythm control, including, Class 1A: disopyramide and quinidine; Class IC: flecainide and propafenone; and Class III: amiodarone, dronedarone, dofetilide, and sotalol. In the 2016 ESC/EACTS guidelines, flecainide, propafenone, dronedarone, and sotalol are recommended (Class 1A recommendation) for preventing symptomatic AF in patients with normal left ventricular function and without pathological left ventricular hypertrophy.[2]

Choice of AAD is primarily guided by safety considerations, including absolute or relative contraindications, risk factors for adverse events (AE) such as onset of new arrhythmia or exacerbation of existing arrhythmia and effects outside the heart, factors that influence drug disposition (e.g., patient age and renal or hepatic function), and patient preference.[2] Guidelines recommend placing patients in the central role in the decision-making process to improve patient compliance and reduce the clinical consequences of AF.[2]

Clinical Impact of Antiarrhythmic Drug Therapy

AAD is relatively safe and moderately effective at maintaining normal sinus rhythm. Rates for maintaining normal sinus rhythm with AAD at 1 year range from 33–56%;[21] however, 48% of patients with AF are not well managed on AAD.[22] The toxicity profile of AAD is varied and frequently includes drug-induced arrhythmia in 2–4% of patients and AE leading to treatment discontinuation in 12–19% of patients.[2,21,23] Diarrhoea, nausea and vomiting, headache, and dry mouth are commonly experienced AE associated with AAD. Treatment withdrawal rates as a result of AE vary according to medication class (Class IA: 19%, Class IC: 12%, and Class III: 13%).[21] Reported event rates for stroke, heart failure, and mortality are low; however, the potential benefits of AAD in reducing these events are yet to be established.[2,21,24]

The Impact of Antiarrhythmic Drug Therapy on Patients

AAD therapy is effective at reducing AF recurrences,[21] controlling symptoms of AF, and improving patient QoL.[25] In the A4 study, paroxysmal AF patients (N=112) treated with AAD showed a 13% reduction in symptom frequency ($p=0.002$) and a 38% reduction in symptom severity ($p<0.0001$) as measured by the AF Symptom Frequency and Severity Checklist.[25-28] Improvements in QoL were experienced at 1 year after AAD initiation as demonstrated by an increase in SF-36, including a 14% increase in the physical component ($p=0.001$) and 18% increase in the mental component ($p=0.0001$) subscales.

Economic Impact of Antiarrhythmic Drug Therapy in Atrial Fibrillation

Several studies have shown that AAD are cost effective. Treatment costs for AAD are offset by reductions in rates for AE, stroke, and mortality.[29-31] Although the initial cost of AAD treatment is relatively low, the length of treatment is indefinite and the cumulative cost of AAD increases annually. For example, one French cost analysis study found that the cumulative cost of AAD in paroxysmal AF patients treated with two AAD increased 28% annually, over 9 years.[32] Table 1 illustrates the potential treatment costs for managing patients with AF using AAD in France, Germany, Italy, Spain, and the UK, based on current efficacy and event rates for AAD and unit costs reported in the literature. The cost of AAD therapy is influenced by its toxicity level and effectiveness in restoring sinus rhythm and reducing the risk of AF-related consequences, such as stroke and heart failure.[31,33-43]

Table 1: Potential treatment costs for managing patients with atrial fibrillation with antiarrhythmic drug therapy and catheter ablation in Europe.

	Symptomatic AF episodes		Long-term AF consequences	
	Cardioversion		Stroke	Heart failure
AAD				
France[33]*	-		€298,969†	€249,358
Germany[34]	€723,690		€96,202	€206,058‡
Italy[31, 35]	€309,946		€149,695	€113,335
Spain[36,37]	€71,343§		€142,087–183,840††	-
UK[35, 38]	£410,528		£408,067‡‡	-
	Symptomatic AF episodes		**Long-term AF consequences**	
	Cardioversion	Repeat ablation	Stroke	Heart failure
Ablation				
France[33]*	-	-	€199,312†	€332,447
Germany[34, 39]	€75,516	€1,465,861	€64,135	€274,744‡
Italy[31,35,40]	€32,342	€13,422§§	€99,797	€151,131
Spain[36, 37]	€7,444§	-	€94,725–122,560††	-
UK[35, 38,39,41]	£42,838	£899,801–£2,020,708	£272,045‡‡	-

Costs are estimates for 1,000 patients, based on efficacy and event rates for AAD and ablation reported earlier, and unit costs reported in the literature. Unit costs were inflated to 2019 Euros.[42]

*based on mean per patient per event costs in AF patients; †cost reported is a mean per patient per event of stroke, transient ischaemic attack, and systemic embolism; ‡assumes costs for hospital admissions for pacer implantation represents heart failure hospitalisation; §electrical cardioversion only; ††includes fatal ischaemic stroke, and mild, moderate, and severe ischaemic stroke events; ‡‡includes intracranial haemorrhage, haemorrhagic stroke, and ischaemic stroke; §§based on mean per patient per year cost in AF patients.

AAD: antiarrhythmic drug; AF; atrial fibrillation.

IMPACT OF CATHETER ABLATION IN THE MANAGEMENT OF ATRIAL FIBRILLATION

Overview of Catheter Ablation

Catheter ablation is used to create small scars on targeted parts of heart tissue that block the abnormal electrical signals causing the arrhythmia in AF.[1,2] Ablation strategies commonly include isolation of the pulmonary veins and creation of specific lines of lesions within the left atrium.[1] Key considerations for treating patients with catheter ablation include: type of AF, presence of structural heart disease and other comorbidities, risk of complications, patient preference, degree of symptoms, candidacy for alternative therapies (e.g., rate control, AAD), patient age, and frailty.[1]

Clinical Impact of Catheter Ablation

Prior to 2012, long-term rates of freedom from atrial arrhythmia were reported to be 54.1% in paroxysmal AF patients and 41.8% in nonparoxysmal AF patients.[44] More recently, higher rates of freedom from atrial arrhythmias have been reported in clinical studies at 1 year after a single procedure with advanced catheter ablation technology in paroxysmal (84–94%)[15-20] and persistent (59–83%)[15,18,45-48] AF patients. Studies similarly show that a single catheter ablation procedure effectively maintains sinus rhythm in eligible patients with AF and heart failure (38–75%)[49-51] and in elderly patients ≥75 years of age (78%).[52]

Catheter ablation is associated with a low risk of AE. Up to 10% of patients may experience a complication.[2] Potentially life-threatening

but manageable complications may occur in 2–3% of patients (i.e., periprocedural death, oesophageal perforation or fistula, periprocedural stroke [including transient ischaemic attack or air embolism], or cardiac tamponade).[2] Complications of an unknown significance (i.e., asymptomatic cerebral embolism and radiation exposure) range from 5–20%.[2]

The relative safety of catheter ablation was reconfirmed in the largest randomised control trial examining catheter ablation in AF, the CABANA trial. In this trial, complications were rare; the most serious AE reported was cardiac tamponade (occurred in 0.8% of the study population) and there was no incidence of atrial oesophageal fistula in >1,000 symptomatic AF patients.[53] Catheter ablation also normalises the incidence of AF-related consequences during long-term follow-up.[54] Using data from a large study derived from a prospective registry, compared to matched controls without AF, AF patients who underwent ablation had similar rates of death (p<0.0001), stroke (p<0.0001), Alzheimer's dementia (p<0.0001), senile dementia (p<0.0001), and vascular dementia (p=0.001) at 1 year and 3 years.

The Impact of Catheter Ablation on Patients

Catheter ablation is highly effective at controlling AF symptoms and significantly improves patient QoL. In the CABANA trial (N=2,204 symptomatic AF patients), improvements in symptoms and QoL after catheter ablation of AF were demonstrated at 12 months and maintained at 60 months, as demonstrated by reductions in the Mayo Atrial Fibrillation-Specific Symptom Inventory (MAFSI) scores and improvements in Atrial Fibrillation Effect on Quality of Life (AFEQT) and SF-36 physical and mental component summary scores.[26]

Economic Impact of Catheter Ablation

Several studies have shown that catheter ablation of AF is cost-effective when benefits are maintained over the medium to long-term, with improved QoL and reduced cost of follow-up treatment identified as key drivers influencing cost.[31,41,55-59] European data on medical visits before and after catheter ablation are limited; however, evidence outside of Europe shows that catheter ablation reduces the need for unplanned medical visits compared to before ablation, with reductions of <80% at 2 years.[60] Table 1 illustrates the potential treatment costs for managing patients with AF with catheter ablation in France, Germany, Italy, Spain, and the UK, based on current efficacy and event rates for catheter ablation and unit costs reported in the literature. Improved efficacy and reductions in unplanned medical visits after catheter ablation can lead to reduced costs for managing AF.[31,33-41]

IMPACT OF CATHETER ABLATION COMPARED TO DRUG THERAPY IN MANAGING ATRIAL FIBRILLATION

Clinical Impact of Catheter Ablation Compared to Drug Therapy

The clinical efficacy of catheter ablation compared to drug therapy has been assessed in several global trials, including the CABANA,[53,61] CASTLE-AF,[62] and ATTEST[63] trials. These trials show catheter ablation is more effective in preventing recurrence, complications, and progression of AF than drug therapy, with a similar rate of AE. In the CABANA trial, a significant 48% improvement in freedom from atrial arrhythmia over 4-year follow-up period was demonstrated with catheter ablation, compared to drug therapy (hazard ratio [HR]: 0.52; 95% confidence interval [CI]: 0.45–0.60; p<0.001).[48] Catheter ablation was associated with reduced incidence of AF complications including death, stroke, and cardiac arrest versus no treatment.[53,61] The composite endpoint for death or CV hospitalisation was statistically different between the catheter ablation group versus the drug therapy group (51.7% versus 58.1%, HR: 0.83; 95% CI: 0.74–0.93; p=0.001). In the CASTLE-AF trial (N=363), which included patients with AF and heart failure, >60% of patients who underwent catheter ablation maintained sinus rhythm compared to ~25% of those on drug therapy at 1-year follow-up (p<0.001).[62] Catheter ablation was associated with a significant improvement of ≤47% in survival, free from death, or heart failure hospitalisation compared to drug therapy over 5 years' follow-up.[62] In ATTEST (N=255), patients with paroxysmal AF who underwent catheter ablation were 10-fold less likely to progress to persistent AF, compared to the cohort using AAD (HR: 0.11; 95% CI: 0.02–0.48; p=0.0034).[63] Studies

report a similar frequency of AE when treating patients with catheter ablation or drug therapy; however, the types of events are often specific to the treatment strategy.[53,62,64]

Patient Impact of Catheter Ablation Compared to Drug Therapy

A significantly greater improvement in patient QoL with catheter ablation of AF compared to drug therapy has been demonstrated in two randomised controlled trials: the CABANA,[26] and the CAPTAF[64] trials. In CAPTAF, SF-36 QoL summary scores measuring general health, physical health, and mental health were significantly higher among those patients treated with ablation versus drug therapy at 1 year (between-group differences: physical health: 8.9 points, p=0.003; mental health: 6.1 points, p=0.02; physical health: 5.3 points, p=0.02).[64] In CABANA, MAFSI frequency and severity scores, and AFEQT summary scores, were more favourable in the catheter ablation group than the drug therapy group at 1 year and maintained over 5 years (Figure 2).[26]

Economic Impact of Catheter Ablation Compared to Drug Therapy

Studies indicate that catheter ablation is cost-effective compared to AAD for the management of AF.[65] In a recent UK database analysis comparing 1-year resource utilisation after catheter ablation to that with AAD, catheter ablation was associated with significantly less resource utilisation than AAD over 1 year (including a 3-month blanking period), a 51% relative reduction in CV-related outpatient visits (p<0.001), and 38% lower inpatient admissions for heart failure (p=0.0318).[65] Although economic studies comparing ablation to AAD are limited across European counties, several economic analyses show that ablation is cost-effective compared to AAD due to its greater clinical effectiveness.[31,41,55-59] A French cost analysis examining the cumulative costs of paroxysmal AF treatment over 10 years showed that costs become favourable for catheter ablation at 5 years after the initial ablation procedure when compared to AAD, despite the larger initial investment.[32]

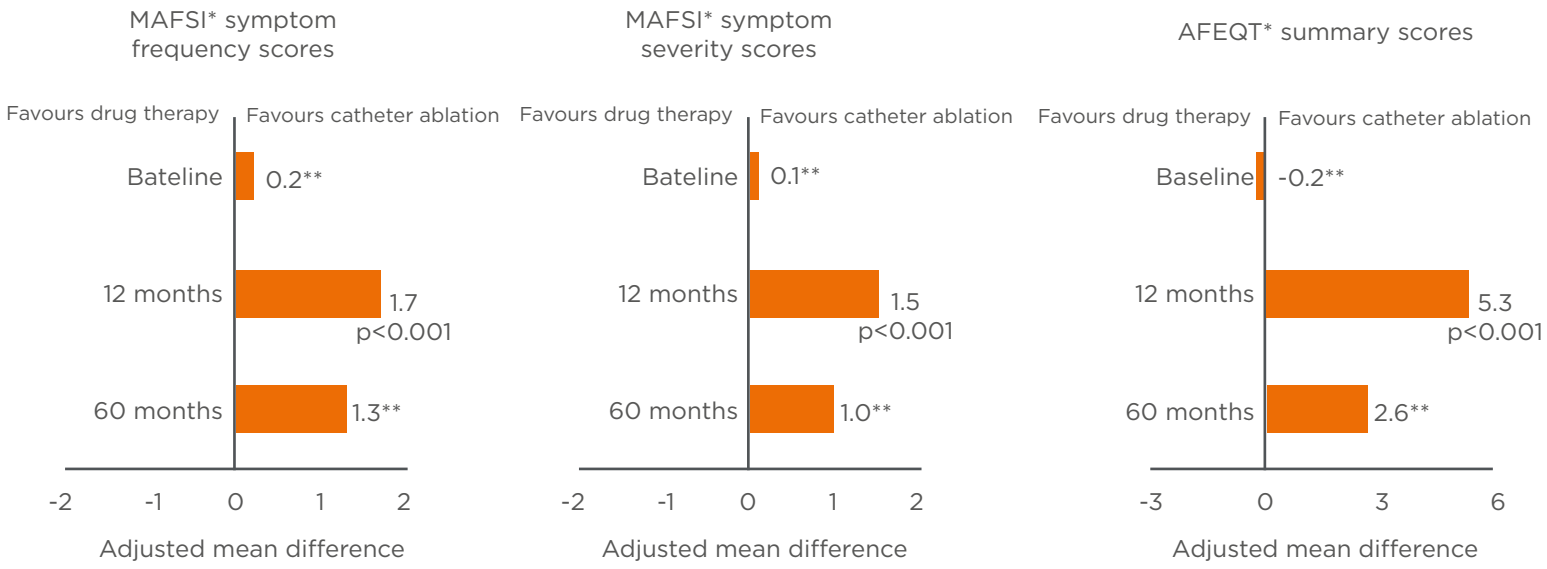


Figure 2: Significantly greater improvement from baseline in quality of life with catheter ablation than with drug therapy at 1 year and maintained over 5 years among atrial fibrillation patients in CABANA.

*As measured by the MAFSI and AFEQT questionnaire. **Statistical significance not reported.

AFEQT: Atrial Fibrillation Effect on Quality of Life; MAFSI: Mayo Atrial Fibrillation-Specific Symptom Inventory.

Adapted from Mark et al.[26]

FUTURE DIRECTIONS

The 2016 ESC/EACTS guidelines and the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement highlight key areas for future research, which will help establish the optimal strategies to be used in future recommendations and patient care pathway strategies for the management of AF.[1,2] Although CABANA and CASTLE-AF examined long-term outcomes of catheter ablation ≤5 years, further research is needed to examine long-term outcomes beyond 5 years. Further research is needed to understand key elements of integrated healthcare management teams, oral anticoagulation therapy, rhythm control outcomes, progress in rhythm control therapy, and recurrence of AF after catheter ablation. For example, with regards to an integrated healthcare management team, further research is required to understand whether a multifunctional team approach, including general cardiologists, electrophysiologists, surgeons, and other specialists, leads to better outcomes for AF patients than care delivery through isolated pillars of care, and to understand the optimal role for each member of the care delivery team. For oral anticoagulation therapy, it is unclear if a patient who has subclinical or no AF after successful catheter ablation needs oral anticoagulation, and whether there are patients who can safely discontinue oral anticoagulation therapy. Research is also foreseen to understand progress in rhythm control therapy and to determine the clinical and economical value of technological innovation for both drug therapy and ablation. Finally, there is limited data on the optimal treatment strategy in patients who experience recurrence of AF after catheter ablation and whether patients should receive a repeat catheter ablation, surgical ablation, AAD, or hybrid therapy (i.e., combining AAD with ablation).

CONCLUSION

This review promotes greater awareness and understanding of the current care pathways for the management of AF in Europe and highlights the current evidence for the clinical and economic impact of AAD and catheter ablation. Overall disease management of AF focusses on controlling the irregular heart rhythm, improving symptoms, and reducing key complications based on shared decision-making between healthcare professionals and patients. Treatment guidelines recommend rhythm control therapies to maintain normal sinus rhythm in patients with AF. Studies demonstrate that AAD therapy is moderately effective and is associated with treatment withdrawals, but it has been shown to improve QoL and is affordable over the short term. Catheter ablation is more effective at reducing symptom burden than drug therapy, is associated with lower rate of recurrence, provides a significantly greater improvement in QoL, and is less costly over the long term.

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A Review of the Burden of Atrial Fibrillation: Understanding the Impact of the New Millennium Epidemic across Europe

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Disclosure: Maria Velleca, Graca Costa, Laura Goldstein, Moe Bishara, and Lee Ming Boo are employees of Johnson & Johnson.

Acknowledgements: Medical writing services were provided by Susan Bartko-Winters from SBW Medical Writing Inc., which was funded by Johnson & Johnson.

Support: This review study was sponsored by Johnson & Johnson.

Received: 26.08.2019

Accepted: 27.09.2019

Keywords: Atrial fibrillation (AF), burden, caregiver, clinical, cost, economic, Europe, quality of life (QoL), stroke.

Citation: EMJ Cardiol. 2019;7[1]:110-118x.

Abstract

Atrial fibrillation (AF), the most common form of arrhythmia, is fast becoming one of the world's most significant health issues. It is well established that AF increases the risk of mortality, and is associated with significant morbidity, including an increased risk of stroke. AF also worsens quality of life for patients, which can also be a burden for caregivers. As a result of Europe's ageing population, the prevalence of AF is expected to rise substantially in the future. With more patients expected to be affected by AF, rates for AF-related strokes, hospitalisations, and doctor visits are also expected to rise, ultimately raising healthcare system costs across Europe. It is estimated that up to 2.6% of total annual healthcare expenditure is associated with AF in European countries. The high cost of AF is largely attributable to hospitalisations and complications such as stroke, i.e., in 2015, stroke was estimated to cost €45 billion a year in the European Union (EU). The purpose of this review is to highlight the current scale and growing burden of this new millennium epidemic in Europe. This review aims to foster a greater awareness and understanding of the magnitude of the clinical, patient, and economic burden of AF. An understanding of the burden of AF is imperative for directing care pathway management and healthcare policies that can help alleviate the burden of AF experienced by patients, caregivers, and healthcare systems in Europe.

INTRODUCTION

Atrial fibrillation (AF), the most common form of arrhythmia, is characterised by an irregular and often fast heart rhythm resulting in uncoordinated contraction of the atria. Patients with AF have an increased risk of life-threatening complications and other diseases, and AF also increases the risk for heart failure 5.0-fold, stroke 2.4-fold, and mortality 2.0-fold.[1] Furthermore, AF worsens quality of life (QoL) for patients and caregivers,[2-7] increasingly places a critical financial burden on healthcare systems, and is rapidly becoming one of the world's most significant health issues.

Currently, >11 million patients are estimated to have AF in Europe,[8] and the total healthcare costs of AF account for ≤2.6% of total healthcare expenditure in Europe.[9-12] Due to Europe's growing population, the prevalence of AF is expected to rise substantially with more patients expected to be affected by AF in the future. Rates for AF-related strokes, hospitalisations, and doctor visits are also expected to increase, ultimately raising the cost of healthcare systems across Europe. On account of the profound impact AF is expected to have in Europe, the magnitude of the clinical and economic burden of AF must be further investigated to help direct care pathway management and healthcare policies that can be used to alleviate this burden among patients, caregivers, and healthcare systems. The objective of this review is to raise awareness and understanding of the burden of AF in Europe, with a focus on France, Germany, Italy, and the UK.

EPIDEMIOLOGY OF ATRIAL FIBRILLATION

AF is categorised into several types. Patients are categorised on their most frequent pattern of AF and may have episodes of AF that fall into one or more of the following categories: paroxysmal (occasional AF that stops ≤7 days), early persistent (AF that lasts 7 days to 3 months), persistent (continuous AF for >7 days), long-standing persistent (episodes occur for >12 months), or permanent (episodes continue and attempts to restore sinus rhythm are ceased).[13,14] In Europe, 75% of patients with AF have paroxysmal or persistent AF.[15]

Demographics, Causes, and Risk Factors of Atrial Fibrillation

AF is a common age-related arrhythmia, affecting 1 in 4 adults ≥40 years of age during their lifetime;[16] furthermore, nearly 8 in 10 adults with AF are ≥65 years of age[8] and the condition occurs more frequently in males than females.[8] Specifically, among adults of European descent ≥40 years of age, men are 13% more likely to develop AF than women during their lifetime.[16] As many as 1 in 4 patients are diagnosed with AF after suffering a stroke.[14]

AF develops from structural changes to the heart due to lifestyle, other chronic conditions, and nonmodifiable factors. Abnormalities or damage to the heart's structure are the most common cause of AF, and this can be the result of high blood pressure, heart attacks, coronary artery disease, abnormal heart valves, congenital heart defects, previous heart surgery, sick sinus syndrome, an overactive thyroid or other metabolic imbalance, sleep apnoea, lung diseases, or stress due to pneumonia, surgery, or other illnesses.[13,14,16] Other factors can also cause AF, including exposure to stimulants, such as medications, caffeine, tobacco, or alcohol; lifestyle factors, including obesity[17,18] and alcohol consumption;[14,17] risks of cardiovascular disease, including smoking, stress, caffeine, and other stimulants;[14] and activity level.[13,14,17] Additional conditions e.g., high blood pressure,[17] heart failure,[16,19] history of heart attack,[16] coronary artery and other heart disease,[16,18] previous surgery,[20] sleep-disordered breathing (e.g., obstructive sleep apnoea),[17] and diabetes[17,21] also increase the risk of developing AF. Furthermore, nonmodifiable factors including older age,[14,22] congenital heart defects,[23] family history or other genetic factors,[16,24] and male sex[14,22] also add to the risk of developing AF.

The Current Scale and Growing Future Prevalence and Incidence of Atrial Fibrillation in Europe

AF is the most common type of cardiac arrhythmia worldwide, affecting >5.5 million people in the USA,[25] >16 million people across Asia Pacific,[26] and >11 million people in Europe (Figure 1A).[8,27] Over 1 million people are afflicted by AF in each of France, Germany, Italy, and the UK.[8] The number of new people diagnosed each

year with AF in Europe is >886,000, but incidence rates vary by region, from nearly 78,000 in France to >116,000 in Germany (Figure 1A).[8] AF is almost as common as stroke and cancer within Europe, including in France, Germany, Italy, and the UK.[8]

European countries have ageing populations that are growing rapidly,[28] and estimates suggest that over the next 11 years, there will be a 70% increase in the number of people affected by AF in Europe (the prevalence and incidence estimates of AF in Europe combine rates for AF and atrial flutter).[19] By 2050, Europe is projected to have the greatest increase in AF compared to other regions globally (Figure 1B).[29]

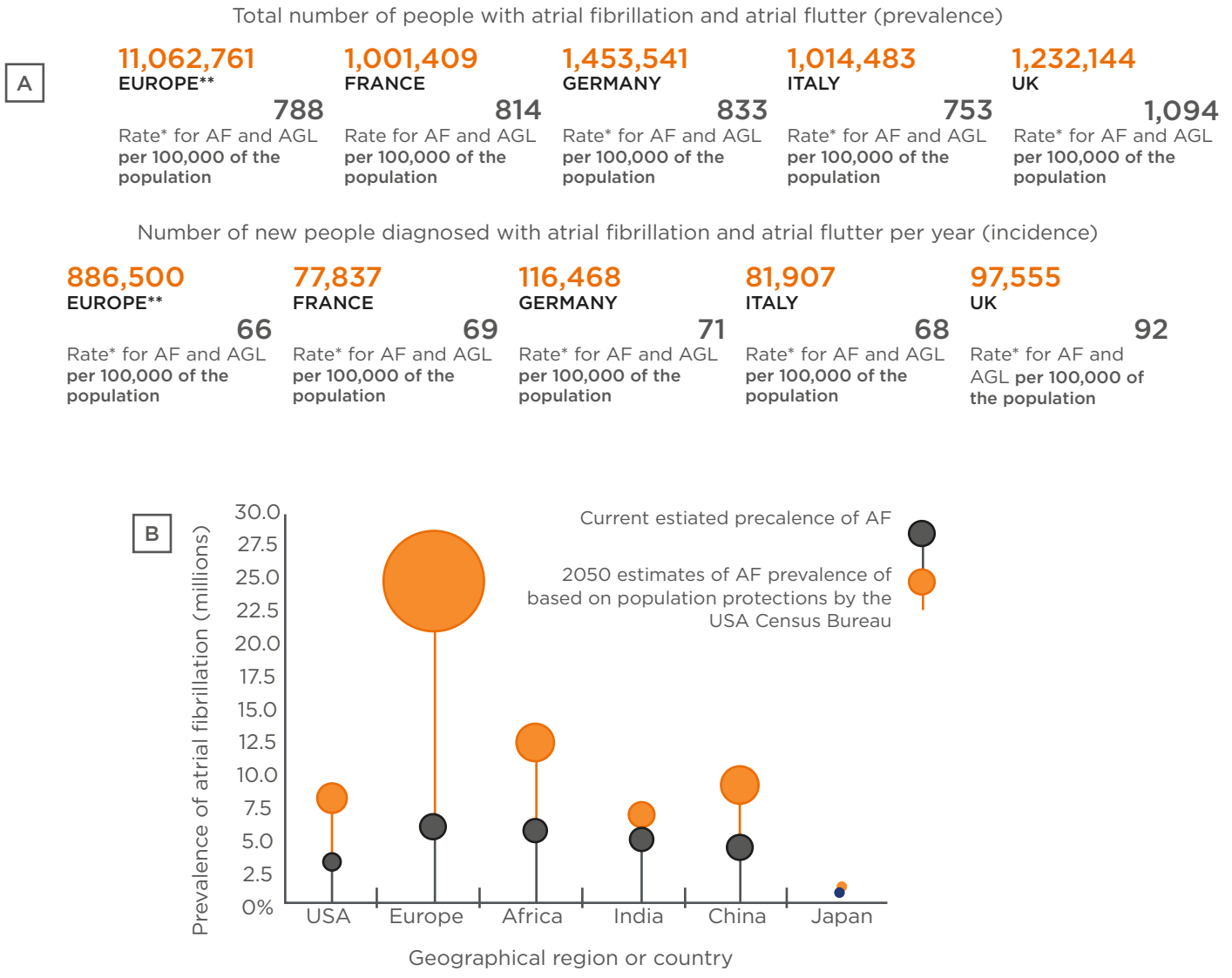

Figure 1: Prevalence and incidence of atrial fibrillation and 2050 estimated prevalence of atrial fibrillation in Europe compared to other geographical regions or countries.

A: Prevalence and incidence of atrial fibrillation (AF) and atrial flutter in Europe.

*Age-standardised values.

**Obtained for Europe, part of the Four World Regions category in the online Global Burden of Disease tool.

Adapted from Global Burden of Disease Collaborative Network (2016).[27]

B: Current estimated prevalence of AF and 2050 estimated prevalence of AF.

Adapted from Rahman et al. (2014).[29]

AF: atrial fibrillation; AFL: atrial flutter.

With the growing number of patients affected by AF in Europe, the number of AF-related stroke events and medical visits are also expected to increase within the next 11 years by an additional 280–340,000 new ischaemic strokes, 3.5–4 million hospitalisations for AF, and 100–220 million outpatient visits.[19]

CLINICAL BURDEN OF ATRIAL FIBRILLATION

Symptoms of Atrial Fibrillation

AF and its related symptoms are a major therapeutic challenge and burden to healthcare systems.[30] The symptoms of AF disrupt daily life and range from mild to debilitating.[5] The frequency and severity of symptoms varies from patient to patient, and within a patient, and symptoms can fluctuate widely over time. These factors contribute to challenges in clinical decision-making in management of treatment.[30] The most common symptoms are palpitations (65%), fatigue (50%), shortness of breath (43%), malaise (30%), dizziness (19%), anxiety (12%), chest pain (12%), and other symptoms (5%),[19,30,31] and >50% of AF patients have a reduced ability to exercise.[30]

An estimated 15–30% of AF patients experience silent AF, meaning that their AF is not associated with symptoms.[30] Asymptomatic AF patients may be at a greater risk of complications and disease severity due to lack of treatment. Patients with silent AF experience a decreased general health and QoL compared to healthy individuals, which is driven by their comorbid conditions.[32] The pattern of AF is different among symptomatic and asymptomatic patients, i.e., persistent and permanent AF are two and three times more common in asymptomatic patients than symptomatic patients, respectively.[15] The higher pattern of permanent AF among asymptomatic AF patients than in symptomatic patients is primarily due to lower treatment management, given its asymptomatic nature.[15]

Clinical Consequences of Atrial Fibrillation

AF increases a patient's risk of life-threatening events and conditions, including stroke, heart failure, and death. Compared to patients without AF, AF patients have an increased relative risk of heart failure (399%), major cardiovascular events (96%), ischaemic heart disease (61%), chronic kidney disease (64%), dementia or cognitive impairment (40%), peripheral artery disease (31%), and cardiovascular mortality (103%).[1,17,33] Stroke is a serious complication of AF that is associated with long-term disability and mortality. Based on pooled estimates from studies conducted in the last 5 years, patients with AF have a 142% increased risk of any stroke and a 133% increased risk of ischaemic stroke.[1] Stroke in AF patients is more severe and debilitating than in patients who do not have AF. Analysis of the North Dublin Population Stroke Study revealed that patients with AF have greater neurologic impairment and functional disability than patients without AF, and ≤3 months after a stroke, patients with AF are significantly more disabled than patients without AF.[34] In general, an estimated 30% of stroke patients will have a second stroke, and risk of a second stroke is nearly 9-fold higher than that in the general population.[35] Heart failure is a common complication of AF that increases the risk of mortality and lengthens hospital stay.[36,37] The risk of mortality is two times greater in heart failure patients with a new AF diagnosis, than in heart failure patients without AF.[19] Furthermore, AF is independently associated with a significantly greater risk of mortality even without the presence of other conditions; patients with AF have a 46% greater risk of mortality than patients without AF, based on pooled estimates from studies in the last 5 years.[1,17]

Impact on Quality of Life

Patients with AF have a significantly lower QoL than the general population as measured by various validated QoL instruments.[3-5,7,38] The symptoms experienced by patients with AF have been associated with a 19% impairment in functional status, based on functional capacity as measured by the Goldman Specific Activity Scale,[38] a 25% disruption to daily activities as measured using the illness intrusiveness scale,[39] and a ≤47% reduction in QoL as measured using the SF-36 QoL scale.[38,39] Patients with AF or other cardiovascular diseases such as coronary artery disease, congestive heart failure, and history of heart attack have similar reductions in QoL.[7,38] Patients with intermittent AF, paroxysmal, and early persistent AF, have worse

QoL than those with chronic AF (persistent and permanent AF).[5]

Severe consequences of AF, such as stroke, can have a devastating impact on patient QoL and the ability to perform daily activities. Stroke can cause significant impairment in physical, psychological, and social function, and can reduce a patient's ability to carry out routine activities.[40] Limitations a patient might experience after a stroke include paralysis, depression, personality changes, problems with communication, anxiety, memory loss, and cognitive impairment.[40] Furthermore, AF-related stroke is more severe and more devastating than stroke in patients who do not have AF.[34,41]

Burden of Atrial Fibrillation to Caregivers

Caring for family members with AF can be burdensome. Some form of caregiver assistance is required in 63% of elderly patients with AF,[42] and in 80% of AF patients recovering from stroke.[6] Patients with AF may require caregiver assistance for many activities associated with daily living. These include assisting with activities that the individual struggles with due to tiredness; assisting or confirming correct dosage of medication and administration of medication; monitoring for signs of bleeding; providing assistance and transportation to medical appointments, including with the primary care physician or anticoagulation clinic for regular monitoring; and/or ensuring adherence to any dietary restrictions.[43] As a result, caregivers of patients with AF experience considerable changes to their daily lives, including potential disruptions to their schedules, lack of family support, health problems, and financial burden.[2] Caregivers are at high risk of burnout when they are required to provide care for long hours and when they care for patients who are frail, sick, or disabled; for those patients who have low QoL; have experienced or are at high risk of stroke; and patients with low levels of independence.[2,6] Burden to caregivers may in turn lead to inadequate patient support, physical and emotional stress, caregiver burnout, andsuboptimal patient care outcomes.[43]

ECONOMIC BURDEN OF ATRIAL FIBRILLATION

Total Healthcare Costs

The economic burden of AF is high and places a critical financial burden on healthcare systems in Europe. The reported annual healthcare costs of AF range from €660–3,286 million (France: €1,942 million,[11] Germany: €660 million,[10,44] Italy: €3,286,[10] and the UK: £1,307[12]), accounting for 0.28–2.60% (France: 2.60%,[11] Germany: 0.28%,[10,44] Italy: 2.49,[10] and the UK: 0.90–2.4%[12]) of total healthcare spending (Figure 2A). It is important to note that the cost associated with AF and the percentage of total healthcare spending for France is based on in-patient and rehabilitation costs to hospitals for AF patients hospitalised for cardiovascular reasons only (excluded in the study were minor cardiovascular complications, community consultation, and prescription); therefore, these costs likely do not fully represent the total cost in France.[11] Moreover, estimates for Germany[10,44] and the UK[12] are based on direct costs only. The high cost of AF is largely attributable to hospitalisations and complications such as stroke.[10,12] National healthcare costs for AF in these countries are similar to those for other cardiovascular diseases (e.g., heart failure, stroke, coronary artery disease, angina, and acute coronary syndrome).[11,12,44-49] Although the costing studies were conducted across different timespans and measure different variations of cost, the high cost burden AF places on healthcare systems in Europe is unequivocal.

Direct and Indirect Costs

Direct (e.g., hospitalisations, outpatient and physician visits, prescriptions, laboratory testing, and long-term care) and indirect (e.g., work productivity losses and support provided by caregivers) costs for the management of AF are highly variable across European countries. Direct costs are high, and account for 2.6% of hospital expenditures in France[11] and 0.9–2.4% of total annual healthcare expenditures in the UK.[12] Annual direct per-patient costs are similar in France,[50] Germany,[51,52] Italy,[53] and the UK,[12] and annual indirect per-patient costs are highly variable by country, with the highest costs reported in Germany[49,51,53] (Figure 2B).

	France[11] (2012)	Germany[10,44] (2004)	Italy[10] (2006)	UK[12] (2000)
Cost associated with atrial fibrillation	€1,942M**	€660M***	€3,286	£1,307***
Percentage of total healthcare spending	2.60%**	0.28%***	2.49%**	0.90-2.40%***

A

	France[50] (2002)	Germany[51,52] (2004/2005)	Italy[53] (2006)**	UK[12] (2000)
Direct cost	€3,016*	€3,564	€3,019	£2,175
Indirect cost	€193	€2,023	€206	NR
Total	**€3,209**	**€5,586–7,688**	**€3,225**	**NR**

B

Figure 2: Healthcare costs of atrial fibrillation in France, Germany, Italy, and the UK.

A: Annual total healthcare costs of atrial fibrillation (AF). *Based on limited country data reporting. **Based on inpatient and rehabilitation costs to hospitals for AF patients hospitalised for cardiovascular reasons (study excluded minor cardiovascular complications, community consultation, and prescription; therefore, these costs do not represent the total cost in France). ***Based on direct costs.

B: Annual direct and indirect cost of AF per patient. Direct cost was calculated by excluding costs for loss of work from the total per-patient cost reported for the societal perspective in Le Heuzey et al.[21] Drug costs contained out-of-pocket costs; however, the authors noted that these costs were not statistically different from the those in the healthcare payer perspective; therefore, drug costs were assumed to be direct costs. **Based on 1-year follow-up costs after index admission.

AF: atrial fibrillation; NR: not reported.

Persistent AF can cost significantly more to treat than paroxysmal or permanent AF. In one analysis of direct and indirect costs in patients with AF in Germany and Sweden, costs were lowest for permanent AF and highest for persistent AF in Germany; however, in Sweden costs were equally high for paroxysmal and persistent AF.[50] Lower costs for permanent AF can be attributed to the fact that the presence of AF is accepted by the patient and the physician, and a decision has been made not to pursue treatment to restore or maintain sinus rhythm.[13,14]

Hospital costs represent the largest expense in AF management, and account for 44–78% of AF management costs.[10,12,44,51,53] In-patient costs account for 50–70% of annual direct costs.[9] The reported mean annual cost of in-patient care per patient in Europe is variable, with the highest costs reported in France and Germany (in-patient cost: France: €3,016,[21] Germany: €2,464–6,000,[50,51] Italy: €1,778,[53] and the UK: £1,679[12]). Healthcare resource use in AF patients is high, with ≤40% of AF patients hospitalised each year primarily due to heart failure and arrhythmia recurrence.[14] Hospitalisation costs can be two times higher for persistent AF than paroxysmal AF,[21] and other factors associated with a high hospital cost include stroke and bleeding events, high stroke risk, high bleeding risk, and presence of other conditions.[54]

The Impact of Stroke on the Costs of Atrial Fibrillation

The cost for the treatment and prevention of stroke in AF is high, contributing substantially to the total healthcare cost of AF. In Europe, the cost of AF-related stroke is 7–60% higher than the cost of stroke in patients without AF.[11,41,55-60] Higher costs associated with AF-related stroke are due to hospitalisations, inpatient rehabilitation, longer hospital stays, hospital readmissions, and greater use of nursing care.[9,55] In 2015, stroke was estimated to cost €45 billion a year in the European Union (EU).[61] Contributing to this burden were direct healthcare costs (€20 billion), informal care (€16 billion), and productivity losses

(€9 billion).[61] The annual per-patient costs for AF-related stroke for France,[11] Germany,[55] Italy,[62] and the UK[56] are presented in Figure 3. Although the studies are from different years, ranging from 2002 to 2015, and measure different variations of cost, it is clear that the annual per-patient cost of stroke across these European countries is substantial.

FUTURE DIRECTIONS

Although this review provides a comprehensive summary of the burden of AF in Europe based on the available literature, the epidemiological, clinical, and economic findings are mostly based on a limited number of studies that were published over the past 10 years. Because diagnostic and management strategies for AF have evolved and changed dramatically from the previous decade, it is conceivable that the results presented in this review may overestimate or underestimate the true economic burden of AF. More recent studies are needed to further elucidate the current burden of AF for Europe and individual European countries. The 2016 European Society of Cardiology's (ESC) guidelines for the Management of AF also highlights several gaps in the knowledge, where evidence is currently being developed or requires additional research, which will help to further establish the magnitude of the burden of AF.[14] In particular, the guidelines suggest that several specific AF groups should be studied to better characterise their risk of AF, stroke, and other AF-related comorbidities e.g., patients with one stroke risk factor, non-Caucasian patients, and female patients. Differences in the overall management e.g., different treatment for concomitant cardiovascular diseases, may help explain the variability in the reported rates of new (incident) AF cases, all (prevalent) AF cases, and AF complications. The guidelines also highlight that the major causes of AF require better characterisation by patient group, and should consider the key comorbidities associated with AF and pathophysiological distinct types of AF.[14] In addition, the guidelines suggest that models of care that integrate patient shared-decision-making to identify appropriate care pathway management may be of particular value in the management of AF. Further research is needed to identify the number of patients affected by AF, the impact on disease progression, and the management costs among different patient subgroups.

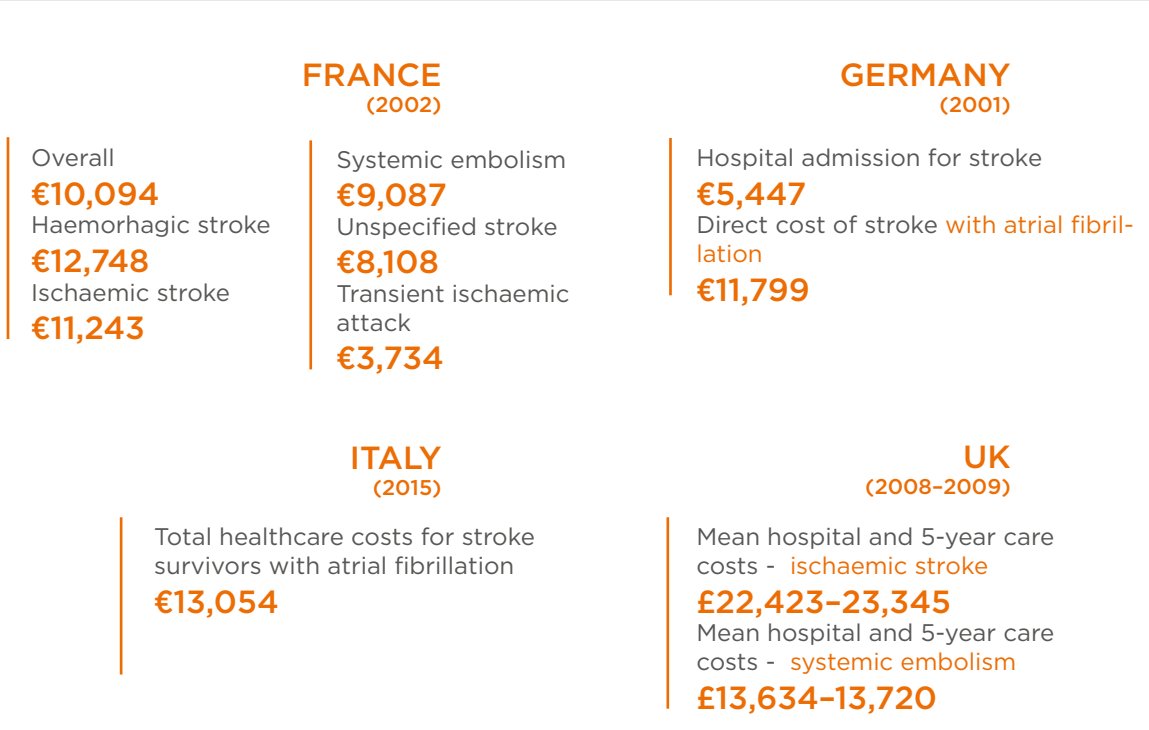

Figure 3: Annual per-patient cost of atrial fibrillation-related stroke in France,[11] Germany,[55] Italy,[62] and the UK.[56]

CONCLUSIONS

This review promotes a greater awareness and understanding of the magnitude of the clinical, patient, and economic burden of AF to caregivers and healthcare systems in Europe. AF affects an estimated 11 million people in Europe and by 2050, Europe is projected to have the greatest increase in AF (to 18 million people) compared to other regions globally. Patients with AF have an increased risk of mortality and comorbidities, such as risk of heart failure, as well as significant decreases in QoL which can be burdensome to their caregivers. The reported annual healthcare costs of AF in France, Germany, Italy, and the UK ranges from €660–3,286 million, accounting for 0.28–2.60% of total healthcare spending in these European countries. The high cost of AF is largely attributable to hospitalisations and complications such as stroke. In 2015, stroke was estimated to cost €45 billion a year in the EU. Ongoing and future epidemiological, clinical, and costing studies are necessary to understand the full scale of the clinical, patient, and cost burden of AF for Europe and individual European counties. The data gathered thus far warrants greater need and attention in understanding and tackling this new millennium epidemic.

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Tricuspid Regurgitation: No Longer the 'Forgotten' Valve

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Disclosure: Dr Swaans and Dr van der Heyden are both faculty members of the Abbott's Crossroads training facility. The other authors have declared no conflicts of interest.

Keywords: Repair, replacement, structural heart interventions, tricuspid valves (TV).

Citation: EMJ Cardiol. 2019;7[1]:119-127.

Abstract

Considered initially as a bystander, tricuspid regurgitation has shown to be an important predictor of mortality in patients with left-side valvular or myocardial disease. However, a sizeable number of patients remain untreated until the end stage when cardiac surgery presents a prohibitive risk. The emergent need in finding a treatment for patients with tricuspid regurgitation deemed for surgery options have encouraged the development of transcatheter tricuspid valve interventions. These procedures mimic classical surgery techniques and they are mainly divided in two categories: repair (annuloplasty, coaptation devices, edge-to-edge techniques) and transcatheter tricuspid valve replacement. This review aims to provide an updated overview and a clinical perspective on novel transcatheter tricuspid valve interventions, highlighting potential challenges and future directions.

INTRODUCTION

In the last two decades, the interest in tricuspid valve (TV) treatment has increased;[1,2] nevertheless, there is still a large percentage of the population with tricuspid regurgitation (TR) who do not receive a surgical treatment because of the high-risk profile. Patients with untreated TR have a poor prognosis[3] and most of them receive lifetime medical therapy until intractable right heart failure and end-organ dysfunction appear.

Valve regurgitation remains the principal pathology of the TV and it is more often secondary rather than caused by a primary valve lesion. Annular dilatation and increased tricuspid leaflet tethering in relation to high right ventricular (RV) pressure and/or volume overload cause secondary TR. Left-sided heart disease, atrial fibrillation, or pulmonary hypertension are frequently involved in the pathogenesis of TR.[4] All these evidences changed the management of TR into a more aggressive surgical approach, and the most recent guidelines recommend surgical repair of concomitant replacement during left valve surgery, even in patients with tricuspid annular dilatation or recent signs of right heart failure with non-severe TR.[5]

Despite the improvement in operative techniques, the in-hospital mortality in patients with combined surgery or isolated TR who underwent surgical replacement (12.6% and 7.1%, respectively) or repair (10.8% and 8.1%, respectively) is still high.[6] Moreover, previous TV surgery recurrence of moderate or severe TR may be as high as 60% at 5 years[7] and reoperation is necessary in approximately 20% of patients within 10% after TV surgery.[8] While redo surgery is the treatment

of choice for a degenerated bio-prosthesis or deterioration of the ring annuloplasty, it may be associated with a very high mortality rate reaching 35% at 30 days,[9] particularly in patients with comorbidities.

Patients with TR and high risk for surgery (multiple comorbidities, advanced age, RV dysfunction, previous surgery) were until recently predestined to conservative treatment. The promising results in the field of aortic and mitral valve percutaneous interventions in high-risk patients have encouraged the development of percutaneous tricuspid interventions. Nevertheless, percutaneous treatment of TR is a more complex procedure, and therefore better understanding of TR mechanism is fundamental.

Shortly, the pathophysiology of functional TR can be divided into three phases. Initially, left-side heart disease, may determine impairment of RV, with progressive dilatation, which can lead to tricuspid annulus (TA) enlargement. In the second phase, the progressive dilation of the RV and TA can result in a poor leaflet coaptation leading to significant TR. Finally, in the third phase continuous distortion of RV geometry especially on the anterior wall associated with tethering of the leaflets will get worse the degree of TR.

Unfortunately, TR has a silent evolution and patients are often referred in the latest phase, when they present with RV dysfunction and an important gap coaptation.

Until now, >18 devices have been developed or are under development for the pathologic tricuspid apparatus treatment (Figures 1 and 2). Based on type of procedure (repair or replacement) they are divided in four categories: TV annuloplasty devices (suture-based or rings), coaptation devices, edge-to-edge techniques (Figure 1), and transcatheter TV replacement (orthotopic and heterotopic-caval valve implantation) (Figure 2).

Few of these were previously successfully used in percutaneous mitral valve interventions and they were transferred to TV.[10,11] Nevertheless, the majority of the studies performed with these devices are in the initial phase (first in humans and safety and feasibility studies).

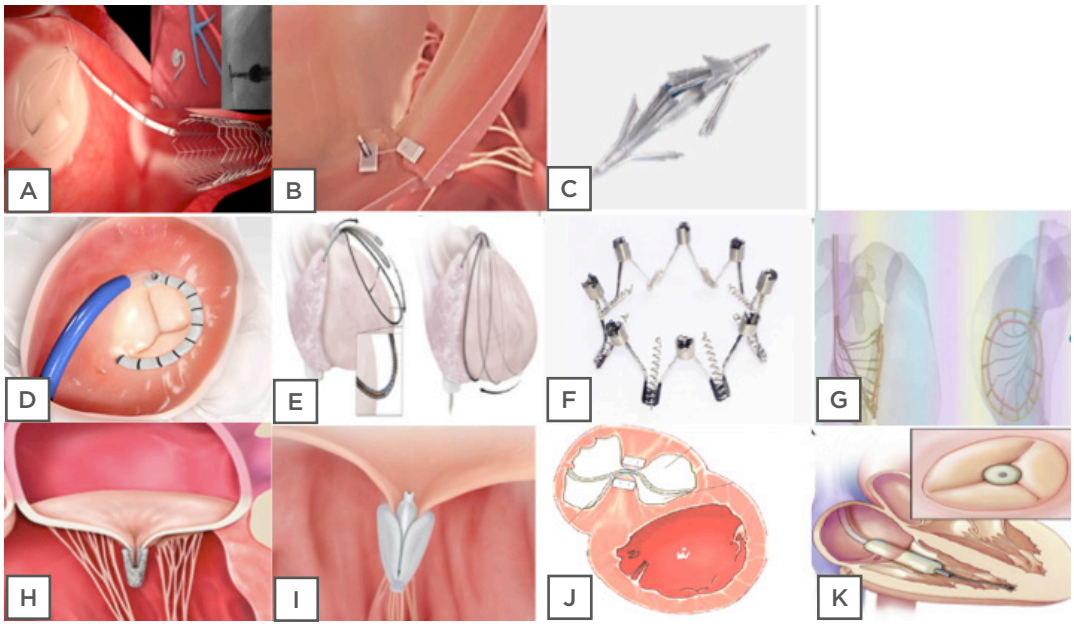

Figure 1: Tricuspid valve repair. Tricuspid annuloplasty devices: 'Suture based'; A) Tricinch; B) Trialign; C) MIA. 'Rings based'; D) Cardioband; E) Traipta; F) Milipede; G) Da Vingi. Edge-to-edge techniques devices; H) Mitraclip; I) PASCAL; J) PASTA. Coaptation devices; K) Forma.

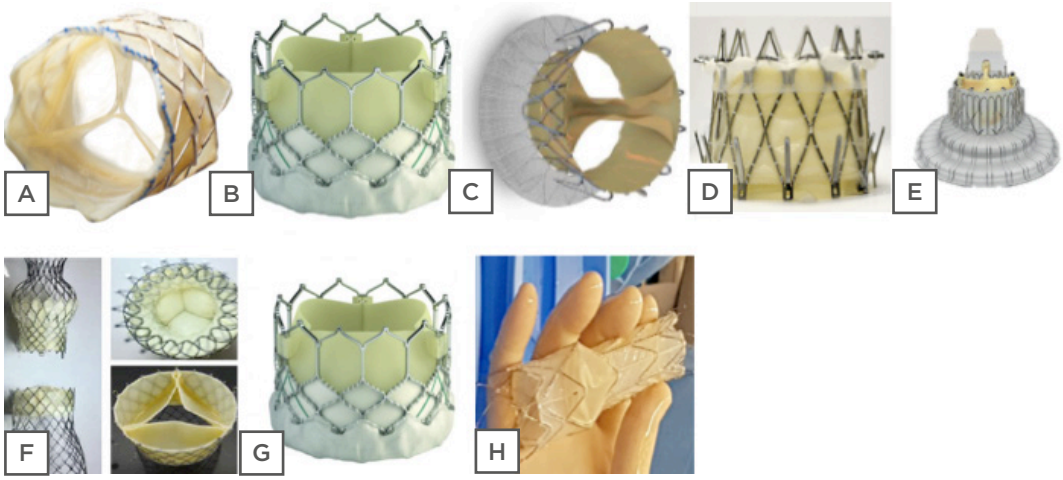

Figure 2: Devices for percutaneous tricuspid valve replacement. Orthotopic valve implantation: A) Melody; B) Sapien; C) Trisol; D) Navigate; E) Lux-Valve. Heterotopic valve implantation; F) TricValve; G) Edwards Sapien; H) Tricento.

TRICUSPID VALVE ANNULOPLASTY DEVICES

The TriCinch System Device

The 4Tech TriCinch™ Coil System (4Tech Cardio Ltd., Galway, Ireland) is a novel percutaneous device for severe functional TR designed to reduce TA dimensions. An anchor is placed in the anteroposterior annulus and connected to a stent, which is then implanted into the inferior vena cava (IVC). The applied traction force between both reduces the annulus dimension and TR. In the PREVENT trial (early feasibility study, 24 patients), the anchoring system (stainless steel corkscrew) was implanted in the anteroposterior portion of the TA. The procedural success was 75%. At the 6-month follow-up, 75% of patients had functional Class I or II.[12]

The clinical trial 'Evaluation of the Percutaneous 4Tech TriCinch Coil Tricuspid Valve Repair System'[13] will include 90 patients with significant functional TR and high risk for surgery. The main objective is to prove safety and performance of the newest Tricinch Coil System device (the stainless steel corkscrew was replaced by coil system which is implanted in the anteroposterior commissure and externalised in the pericardial space).

Trialign Device

The Trialign system (Mitralign Inc., Tewksbury, Massachusetts, USA) attempts to replicate the results of the current modified Kay annuloplasty (conversion of an incompetent TV into a competent bicuspid valve). During the procedure, two polyester pledgets are anchored at the TV annulus in the posteroanterior and posteroseptal positions and cinched together to obliterate the posterior leaflet.[14] Initially, only one pair of pledgets was implanted for each patient but later, in patients with very large annulus, multiple pledgets were used ('side by side' or 'in series'). The USA early feasibility study SCOUT I[10] included 15 patients with 93% procedural success and 30-day technical success of 80%. A significant reduction of the TA diameter and the regurgitant orifice area as well as an improvement in the patients' symptoms was observed at the 30-day follow-up. Currently, SCOUT II CE Mark study is enrolling 60 patients in different centres in Europe and the USA with favourable preliminary results.[15]

Minimally Invasive Annuloplasty Device

Minimally invasive annuloplasty (MIA™) is a transcatheter tricuspid annuloplasty device designed to reproduce, percutaneously, the open surgical bicuspidisation procedure of the TV. It is composed of a thermoplastic elastomer (MyoLast) and low mass polymeric, compliant, self-tensioning anchors (PoliCor).

The catheter-based system provides a customisable number of implants deployed to the target annulus, allowing further catheterisation, or surgery if it is needed. The device is surgically implanted through a 16 F steerable delivery system. The first of 40 patients in the STTAR study were already successfully treated.[4]

Cardioband Device

The Cardioband repair system (Edwards Lifesciences, Irvine, California, USA) was initially designed for the treatment of secondary mitral regurgitation (MR); the results showed a 95% MR reduction (MR ≤2) sustained at 1-year follow-up.[16] Moreover, the device was successfully used in patients with severe functional TR, receiving the CE Mark approval in May 2018 (the only transcatheter device for tricuspid regurgitation with CE Mark approval). The results from the TRI-REPAIR[17] study were recently presented, showing echocardiographic and clinical parameter improvements at 6 months follow-up. The device is designed as a percutaneous annuloplasty band using a transfemoral approach. Cardioband implantation starts next to the anteroseptal commissure and continues along the anterior leaflet until anteroposterior commissure. After Cardioband cinching, the device reduces the TA dimensions.

Transatrial Intrapericardial Tricuspid Annuloplasty Device

The action mechanism of Traipta (transatrial intrapericardial tricuspid annuloplasty) device is based on an extracardiac tricuspid annuloplasty. The device is positioned in the pericardial space and delivered by puncture through the right atrial appendage.[18] Pericardial access is obtained by puncturing the RA appendage from within, after transfemoral venous access. An adjustable circumferential implant, which exerts compressive force over the annulus, is delivered along the AV groove within the pericardial space. Tension on the implant is then adjusted interactively to modify TA geometry and thereby reduce TR. The RA puncture is then sealed using a nitinol closure device.

Preclinical experience in animals showed good safety of the implant with significant annular area reduction.[18] There are still issues to address such as coronary artery compression and control of the pericardial sheath before first-in-human testing can occur.

The Millipede™ System

The Millipede system (Millipede, LLC, Ann Arbor, Michigan, USA) is a repositionable and retrievable complete ring, which can be implanted surgically or via a transcatheter on the atrial side of the native TA to restore its shape and diameter. Designed initially for the mitral valve, it was used successfully in two cases for TR with significant reduction of annulus dimension (36%) and TR grade.[19]

DaVingi™ Tricuspid Regurgitation System

This is a two-step procedure using a novel annuloplasty approach based on the tissue-healing process to achieve a strong neoannulus and to allow an aggressive annular reduction. During the first procedure, a direct percutaneous annuloplasty is performed. Predictable annular physiologic constriction using an adjustment tool takes place in a second stage (90 days) after a period of tissue healing. To date, four cases have been performed in a first-in-human study.[20]

COAPTATION DEVICES

Forma™ Device

The Forma Repair System (Edwards Lifescience) is a valve spacer, which is positioned into the regurgitant orifice to create a platform for native leaflet coaptation. The device is delivered through axillary venous access and is then distally anchored to the RV apex. It is a fully retrievable device until sheath removal. Proximal fixation is obtained in a small surgically prepared pocket. The results of 1-year follow-up of SPACER-trial in 18 patients showed a reduction of TR and improvement in New York Heart Association (NYHA) functional class and 6-minute walk test. One patient presented device thrombosis at 4-month follow-up.[21]

MitraClip™ Device

More than 650 procedures have been performed worldwide, and the multicentre TriValve registry showed that this therapy is so far the most frequent technique applied for percutaneous

TR treatment.[22] Preliminary evidence suggests that MitraClip is safe, feasible, and associated with an improvement in NYHA functional class and 6-minute walking distance at short-term follow-up. In a recent study, the procedural rate success was 81%.[22] Small TR coaptation gap size and central/anteroseptal TR jet locations were identified as independent predictors of procedural success and coaptation gap >10 mm, ORE >0.6 cm^2, tenting area >2.1 cm^2, and TV vena contracta >11 mm as predictors of unfavourable TR repair.[22] In patients with severe mitral and tricuspid regurgitation, concomitant MitraClip appears to improve functional status and biventricular haemodynamics early after the intervention and mid-term follow-up.[11] Moreover, TRILUMINATE CE Mark trial[23] enrolled 85 patients over 25 centres in Europe, Canada, and the USA, and preliminary results will be available soon.

PASCAL™ Device

The Edwards PASCAL transcatheter mitral valve repair system (Edwards Lifesciences) integrates technical aspects from the Forma and the MitraClip devices by combining a 10 mm central spacer and two paddles (25 mm width) and clasps (10 mm length) that attach the device to the valve leaflets, thus overcoming possible limitations of the former devices separately. In patients with severe MR, it showed to be a feasible option in preliminary efficacy data.[24] The first successful case treating severe TR with PASCAL device was recently reported.[25]

Pledget-Assisted Suture Tricuspid Annuloplasty Device

The pledget-assisted suture tricuspid annuloplasty (PASTA) device reduces the TV orifice by opposing septal and lateral targets on the TA using percutaneously pledged sutures. The specific annular targets for PASTA device are the mid-anterior leaflet and the posterioseptal leaflet commissure. Because there is no anatomic septal annulus, the septal pledget target incorporates interventricular septal myocardium between the base of the septal leaflet and the coronary sinus. The result is a double-orifice TV. Preliminary studies in animals showed a reduction in annular area and TR; nevertheless, serious complications were common in this technical development study but were mostly related to apical access.[26]

TRANSCATHETER TRICUSPID VALVE REPLACEMENT (ORTHOTOPIC CONCEPT)

Melody and Edwards Sapien™ Tricuspid Valve for Valve-in-Valve and Valve-in-Ring

Patients with previous TV repair or replacement who require a tricuspid reintervention have a prohibitive surgical risk.[9]

Transcatheter valve implantation has been successfully implanted via the transatrial, transjugular, or transfemoral approaches. Two different transcatheter heart valves have been successfully implanted during tricuspid valve-in-valve or valve-in-ring procedures: the Edwards Sapien valve and the Melody valve (Figure 2). The biggest registry of transcatheter TV replacement included 306 patients (284 patients with valve-in-valve and 22 patients with valve-in-ring).[27] Post-procedure, 83% of the patients presented none or trivial TR. During follow-up (3 years), 31 patients (10%) underwent re-intervention on the TV and survival rate was 83%.

NAVIGATE, TRISOL, LUX-VALVE IN TRICUSPID NATIVE VALVE

NaviGate™

The NaviGate bioprosthesis is a novel self-expanding valved stent designed to treat functional TR. The preclinical evaluation showed that the NaviGate device is safe, feasible through two different approaches with a stable engagement of the native annulus, and has excellent haemodynamic and valve performance. The configuration of the stent is specifically designed in a geometry that engages the TA and TV leaflets from both inferior and superior aspects and maintains a minimal extension into both the atrium and ventricle to avoid flow dynamics alterations. Notably, 27 patients received NaviGate valve with excellent results and low rate of paravalvular leakage; nevertheless, 30-day mortality was 11%. Although the preliminary results are promising, there are some

pitfalls that still have to be addressed, such as device anchoring and sealing (large asymmetric annulus, minimal calcium), delivery system size (42 OD), and leaflet durability (risk of thrombosis).[28]

Trisol

Trisol valve is a percutaneous valve design for TR taking into consideration the RV afterload after the valve implantation. The valve apparatus is built as a single bovine pericardial piece, attached to the nitinol frame in two opposite central commissures, and functions as two separate leaflets. The leaflets move to the centre of the lumen during diastole, enabling two large lumens for the diastolic filling of the RV. During the systole the pericardium (one big leaflet) acquires the dome shape, which increases the closing RV volume with pressure relief and function preservation. Further investigations are necessary before the first-in-human studies are performed.[29]

LUX-Valve™

The LUX-Valve (Jenscare Biotechnology, Ningbo, China) is a self-expanding bovine pericardial tissue valve mounted on a nitinol stent frame with transatrial access. The device has a self-adaptive skirt to minimise paravalvular leakage and a mechanism for secure anchoring within the RV. To date, only experimental data are available.[4]

CAVAL VALVE IMPLANTATION (HETEROTOPIC CONCEPT)

In patients with limited tricuspid therapeutic options, an alternative approach to percutaneous treatment of TV is to implant transcatheter prosthesis in IVC (single valve approach) or in combination with a superior vena cava valve (dual valve approach) to prevent caval backflow of TR and mitigate systemic venous congestion. In the presence of advanced RV dysfunction, the single valve approach appears to be safer compared with the dual-valve approach because it reduces RV preload, but single valve implantation is potentially less effective regarding haemodynamic and clinical improvement because of collateral circulation. More than 40 patients benefited from Caval Valve Implantation (CAVI) prosthesis using Edwards Sapien valve or Tricvalve, of whom the majority were compassionate cases.[30] Published data,[30] in an early clinical experience, showed improvement in NYHA class and haemodynamic parameters but 1-year mortality was high (63%).

The main advantage of this procedure is that it is easy to implant through transfemoral access. The safety and efficacy of Edwards Sapien valve implantation at the IVC is currently being studied in the TRICAVAL[31] and HOVER[32] trials (Figure 2).

Tricento™ Device

The Tricento transcatheter heart valve is composed of a bicavally-anchored covered stent with lateral bicuspid valve element (to the right atrium) made of thin porcine pericardium leaflets requiring only a low closing pressure. The device, as with other heterotopic devices, aims to abolish the systolic backflow in both the inferior and superior caval veins. Because there is a great amount of variability regarding the anatomy of the caval veins and the right atrium, the stent needs to be custom made. The first-in-human data was recently published showing reduction of caval vein regurgitant volume with stable position in the follow-up (Figure 2).[33]

CLINICAL PERSPECTIVES ON TRANSCATHETER TRICUSPID INTERVENTIONS

There is no doubt of the necessity to find treatment options for severe TR. In the last decade, the number of devices destined to treat severe TR multiplied. The TV is no longer the 'forgotten valve' and today's clinicians are witnesses of a real device parade (Figure 1). Some of the devices were successfully used in mitral or aortic valve percutaneous treatment (MitraClip, Cardioband, Mitralign, PASCAL, Millipede devices, Edwards Sapien, and Melody valve). Moreover, a big proportion of devices are still in the early development stages and long-term follow-up data are not available. The only device with a CE Mark for TR is Cardioband; others such as Tricinch, Trialign, MitraClip, or Forma are still enrolling patients in CE Mark trials.

Most percutaneous annuloplasty devices reproduce well-established surgical techniques and they are divided into suture-based and rings. The acute results are encouraging, showing reductions in annulus dimension and

improvements in quality of life and symptoms (Table 1).

For those cases with massive TR with a big gap between the leaflets, the Forma device also showed improvement in quality of life parameters and symptomatology.

Edge-to-edge techniques, particularly MitraClip, have become the first-choice approach for high-risk patients with functional TR, likely because of wide availability and operator familiarity. The other two devices (PASCAL and PASTA) are still in the early stages of development.

For situations in which tricuspid repair is not possible, five valves were designed for percutaneous tricuspid replacement (two of them are also available for valve-in-valve and valve-in-ring procedures) (Figure 2). Special precautions are taken into consideration during valve implantation and different strategies were proposed to avoid A-V node conduction system damage. The Trisol valve brings a new concept regarding the RV closing volume, which permits pressure relief and function preservation of RV. Despite the complex anatomy of the TA, only a small percentage of cases presented residual TR after valve implantation (Table 1).

The three heterotopic valves available are designed to relieve the symptoms and reduce the backflow in the caval veins. Nevertheless, this therapy was used in pluripathologic patients, the majority of whom were compassionate cases and the mortality rate was >50% at 1-year follow-up because of patients' pre-existing conditions.

All these therapies showed promising results in terms of acute procedural success but follow-up data are missing in most of them. Despite the acute procedural success rate, technical details such as sheath size (Table 1), possible anatomic complications, and the pre-existing leads in RV should be taken into consideration.

There is still a paradox between the TR prevalence, surgical, and percutaneous treatment. Only a few patients with severe TR, high risk, and who are deemed for surgery are suitable for first-in-human or early feasibility studies. The majority of the enrolling studies are excluding real symptomatic patients with pulmonary hypertension, severe RV dysfunction, or severe left ventricle dysfunction.

CONCLUSION

TV is no longer the 'forgotten valve': for patients with severe TR and high surgical risk, several percutaneous options are available. Nevertheless, all these therapies are in a growing phase and not all possible candidates are suitable for these new techniques.

Table 1: Summary of transcatheter tricuspid valve devices and their general characteristics and trial results.

Device	Technique	Access/ sheath size (F)	Exclusion criteria	Number of patients included in published studies	Procedural success	Results	Study
Tricinch	Annuloplasty	TF/24	Previous cardiac surgery, severe pulmonary hypertension, severe left/ right ventric-ular dysfunction, IVC >43 mm.	24	75%	Improvement in QoL, 6MWT, and NY-HA at 6 months FU.	PREVENT[34]
Trialign	Annuloplasty	TJ/14	Severe left ventricular dysfunction, IVC >55 mm.	30	93%	Reduction of annular dimension, EROA. Improvement in NYHA, 6MWT, QoL at 30 days FU.	SCOUT I[35]
MIA system	Annuloplasty	S/16	No available data.	4	100%	Reduction of annular dimensions.	STTAR FIH study (un-published)
Cardioband	Annuloplasty	TF/24	Previous tricuspid surgery, severe pulmonary hypertension, severe left ventricular dysfunction.	30	100%	Reduction of annular dimensions, EROA. Improvement in NYHA, 6MWT at 30 days and 6 months FU.	TRI-REPAIR[17]
TRAIPTA	Annuloplasty	TF/14	No available data.	9*	100%	Reduction of annular dimensions and increasing of coaptation length.	Early feasibility studies awaited (2019)
Millipede system	Annuloplasty	S/TF/-	Previous tricuspid surgery.	2	100%	Reduction of annular dimensions.	FIH study (unpublished)
DaVingi TR system	Annuloplasty	TJ/22	No available data.	4	100%	Reduction of annular dimensions.	FIH study[20]
FORMA	Coaptation devices	Axillary vein/20-24	Previous tricuspid surgery, severe pulmonary hypertension, severe left ventricular dysfunction.	78**	89%	Reduction of annular dimensions, Improvement in NYHA, 6MWT at 12 months FU.	SPACER Trial[21]
MITRACLIP	Tricuspid edge-to-edge techniques	TF/24		117	81%	Reduction of EROA, hospitalisation and mortality.	Early feasibility studies[22]
PASCAL	Tricuspid edge-to-edge techniques	TF/22	No available data.	12	92%	Improvement in NYHA, 6MWT at 30 days FU.	Early feasibility studies awaited (unpublished)
PASTA device	Tricuspid edge-to-edge techniques	TJ/TA/8-12	No available data.	22*	90%	Reduction of annular dimensions at 30 days.	Early feasibility studies awaited (unpublished)
Edwards Sapien/ Melody	Valve replacement	TF/16-20	Annulus diameter, RV lead.	308	83%	83% of survival at 3-year FU.	TTVR registry[36]
NAVIGATE valve	Valve replacement	TA/TJ/42	Previous cardiac surgery, annulus diameter (>52 mm), RV lead.	27	100%	Low rate of PVL.	FIH study[28]
TRISOL valve	Valve replacement	TJ/30	No available data.	No available data.		RV consideration.	Advanced preclinical stage[29]
LUX-Valve	Valve replacement	TA/-	No available data.	9*	100%	Low rate of PVL	Advanced preclinical stage[4]
Edwards Sapien/ TricValve	Heterotopic device	TF/TJ/16-27	Severe pulmonary hypertension, severe right ventricular dys-unction IVC >30 mm for Edwards Sapien, IVC >35 mm for TricValve.	25	92%	Improvement in haemodynamic parameters and NYHA class.	FIH study[30]
Tricento THV	Heterotopic device	TF/24	IVC >42 mm.	1	100%	Reduction of caval vein regurgitant volume.	FIH study[33]

6MWT: 6-minute walk test; F: French; FIH: first in human; FU: follow-up; IVC: inferior vena cava; NYHA: New York Heart Association; RV: right ventricle; PVL: paravalvular leakage; S: surgical; TA: transatrial; TF: transfemoral; TJ: transjugular.

*Studies in animals **Results available in 18 patients

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Chemokines: A Potential Therapeutic Target for the Stabilisation of Vulnerable Plaque

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Disclosure: The authors have declared no conflicts of interest.

Received: 15.04.19

Accepted: 14.05.19

Keywords: Acute coronary syndrome (ACS), atherosclerosis, chemokines, inflammation, plaque vulnerability.

Citation: EMJ Cardiol. 2019;7[1]:128-138.

Abstract

The introduction of lipid lowering medications was initially thought to provide a solution to the growing burden of coronary heart disease. However, 30 years later, the rates of acute coronary syndrome remain unacceptably high. This realisation forced cardiovascular scientists to look beyond lipids and led to the now widely accepted understanding of atherosclerosis pathobiology: immune-facilitated lipid retention with focal and generalised chronic inflammation. A fundamental component of this inflammatory process is chemokines: a class of cytokines characterised by their ability to facilitate cell recruitment, although it is now known that their function extends beyond chemotaxis. Mounting evidence suggests that chemokines are essential for the destabilisation and subsequent rupture of atherosclerotic plaque. Therefore, chemokine pathways provide a novel therapeutic target for plaque stabilisation. This review addresses the role of chemokines in regulating plaque vulnerability and discusses therapeutic approaches targeted at manipulating chemokine pathways.

INTRODUCTION

In the late 20th century, lipid lowering medications appeared to be the answer for coronary heart disease. However, despite reductions in mortality, the incidence of acute coronary syndrome (ACS) still remains unacceptably high.[1] The last decade has seen a significant shift in the understanding of atherosclerosis pathobiology; the disease is now widely accepted as a product of immune-facilitated lipid retention with focal and generalised chronic inflammation.[2] Furthermore, it is known that certain features of atherosclerotic plaque determine its vulnerability, and therefore its susceptibility to rupture. With this enhanced understanding comes a new generation of therapies targeted at the inflammatory response. Nevertheless, manipulation of the immune system is not without its challenges and the optimal target for anti-inflammatory drugs remains elusive. This review aims to address the role of chemokines in regulating plaque vulnerability and discuss therapeutic approaches targeted at manipulating chemokine pathways.

CHEMOKINES

Chemokines are a class of cytokines characterised by their ability to exert chemotactic effects, although their functionality does not stop there. Chemokines are divided into four subclasses by virtue of their N-terminal cysteine residue arrangement: C, CC, CXC, and CX3C.[3] Chemokines act via a family of class A G-protein-coupled receptors, collectively termed chemokine receptors. Commonly, a single chemokine ligand is shared by a number of receptors, for example, CCL5 interacts with CCR1, CCR3, and CCR5. Multiple cell types secrete chemokines and express their cell surface receptors. In the setting of atherosclerosis, white blood cells (WBC), platelets, endothelial cells (EC), and smooth muscle cells (SMC) contribute the vast majority of chemokine ligands and receptors.[3]

VULNERABLE PLAQUE

ACS is a clinical manifestation incorporating both unstable angina and myocardial infarction, with and without ST-segment elevation. Most commonly ACS is preceded by rupture of a vulnerable coronary plaque leading to thrombosis and subsequent occlusion of blood flow.[4] There is increasing evidence that suggests plaque stability is regulated by chemokines (Table 1). Chemokines regulate plaque stability by modulating immune cell infiltration, systemic inflammation, fibrous cap thickness, necrotic core size, collagen content, and SMC accumulation (Figure 1).

IMMUNE CELL INFILTRATION

Immune cell infiltration is a hallmark pathological feature of atherosclerosis. Although monocytes/macrophages are the primary immune cell linked to atherosclerosis, plaque stability is the product of a complex interplay between several WBC including monocytes, macrophages, neutrophils, and lymphocytes.[2] Recruitment of WBC to atherosclerotic lesions is driven by a chemotactic gradient, produced largely by a dysfunctional endothelium. Once recruited, many cells become trapped in the lesion and secrete a plethora of proinflammatory cytokines. Prolonged inflammation ultimately degrades plaque structure and renders the lesion susceptible to rupture.[2]

Monocytes/Macrophages

Circulating monocytes demonstrate heterogeneity by differential expression of chemokine receptors. Plaque progression relies heavily upon the continual recruitment of monocytes and, unsurprisingly, plaque vulnerability is closely related to macrophage content. Classical monocytes, which account for up to 90% of circulating monocytes, typically employ CCR2 and CX3CR1 to migrate into plaque.[35] On the other hand, non-classical monocytes primarily use CCR5.[35] Deficiency in any one of the aforementioned chemokine receptors or their respective ligands results in a substantial decrease in monocyte recruitment to plaque. On the other hand, combined inhibition of CCL2, CX3CR1, and CCR5 completely inhibits intraplaque macrophage accumulation.[36] These three chemokine axes work together to direct monocyte recruitment to sites of atherosclerotic lesions; hence, CCL2, CCL5, and CX3CL1 are all highly expressed in vulnerable plaque.[37]

Although monocyte recruitment appears largely dependent upon activation of CCR2, CCR5, and CX3CR1, inhibition of other chemokine pathways also suppresses macrophage accumulation within plaque. This suggests that activation of the primary chemotactic pathways requires functional secondary interactions. For example, activated platelets deposit CCL5 on the surface of EC which interacts with HNP1, secreted from neutrophils, to promote monocyte adhesion. Blocking this HNP1–CCL5 heterodimer stunts myocyte recruitment.[14] A similar heterophilic interaction occurs between CCL5 and CXCL4, which, when inhibited, suppresses monocyte infiltration.[12]

The chemokines CXCL16 and CX3CL1 are unique multifunctional proteins that can be both expressed on the cell surface or cleaved to act as a soluble ligand. Membrane-bound CX3CL1 facilitates monocyte adhesion to an inflamed endothelium and the formation of platelet-monocyte complexes that are subsequently recruited to plaque.[38] The role of CXCL16 is more elusive. Deficiency of CXCL16 in mice increases plaque size, which is thought to be the result of reduced oxidised-low-density lipoprotein scavenging and apoptotic body clearance.[32]

Table 1: Role of chemokines in modulating plaque stability.

Ligand	Receptor	Effect on Stability	Function in Plaque	Reference
CCL1	CCR8	↔	SMC recruitment	5
CCL2	CCR2	↓	Monocyte recruitment ↑ MMP expression and activity Crosstalk between macrophages and SMC	6, 7, 8
CCL3	CCR5	↓	Neutrophil recruitment ↑ Neutrophil activity ↓ Neutrophil apoptosis	9
CCL4	CCR5	↓	Facilitates EM transition	10
CCL5	CCR5	↓	Monocyte, T-cell, and neutrophil recruitment CCL5-HNP1 heterodimers CCL5-CXCL4 heterodimers	11-14
CCL17	CCR4	↓	Limits T-reg expansion	15
CCL19/21	CCR7	↔	Macrophage egress from plaque M1 macrophage migration ↑ Th2 and T-reg activity ↓ Th1 response	16-19
CCL20	CCR6	↑	B-cell recruitment	20
CXCL1	CXCR2	↔	EPC mobilisation and migration Facilitates plaque regression Leukocyte recruitment	21
CXCL4	CCR1	↓	Induction of M4 macrophages Monocyte recruitment	22
CXCL5	CXCR2	↑	Limits foam cell formation	23
CXCL8	CXCR1/2	↓	Neutrophil recruitment	24
CXCL10	CXCR3	↓	↑ Th1 cell ↓ T-reg response	13,25-27

Table 1 continued.

Ligand	Receptor	Effect on Stability	Function in Plaque	Reference
CXCL12	CXCR4	↑	Cell survival in endothelial and SMC SPC mobilisation and migration ↑ VE-cadherin expression in endothelium ↑ Neutrophil activity and survival ↑ Contractile response of SMC	28-31
CXCL16	CXCR6	↔	Promotes ox-LDL scavenging and apoptotic body clearance Unfavourable effect on stability when overexpressed	32,33
CX3CL1	CX3CR1	↔	Platelet-monocyte complex formation Cell survival for monocytes and SMC Monocyte recruitment and adherence Required for EPC protective effect	6,21,22
IL-10	CXCR3	↔	↑ SMC proliferation	34

EM: endothelial-mesenchymal; EPC: endothelial progenitor cell; HNP1: human neutrophil peptide 1; IL-10: inducible protein-10; MMP: matrix metalloproteinase; ox-LDL: oxidised low-density lipoprotein; SMC: smooth muscle cell; SPC: smooth muscle progenitor cell; Th: T-helper cell; T-reg: regulatory T-cell; VE-cadherin: vascular endothelial cadherin.

Conversely, CXCL16 overexpression promotes plaque destabilisation.[33]

In humans, high levels of soluble CXCL16 is prognostically unfavourable in ACS patients.[32] This discrepancy may be the product of differing effects of membrane-bound versus soluble CXCL16.

CXCL5 does not directly recruit monocytes to the dysfunctional endothelium; nevertheless, it is involved in macrophage trapping within plaque. Inhibition of CXCL5 increases monocyte-derived foam cell accumulation in plaque. Analogously, exogenous administration of CXCL5 limits foam cell formation. This effect is as a result of CXCL5/CXCR2 signalling, which improves cholesterol efflux from macrophages by upregulating *ABCA1* expression.[23] In humans, there is a strong negative association of circulating CXCL5 levels with coronary artery disease severity.[39]

Lymphocytes

T cells are a heterogenous population with many subtypes, several of which are involved in atherosclerosis. Th1 cells are the most abundant T cell in human atherosclerotic plaque. IFN-gamma is the prototypic cytokine secreted from these cells and is known to promote plaque vulnerability by impairing collagen formation and maturation.[40] Th1 cells express high levels of CXCR3, which is required for their migration into atherosclerotic plaque.[25] Antagonism of CXCR3 or its ligand CXCL10 alters the T-cell response to an atherogenic stimulus by reducing Th1 cell infiltration and increasing regulatory T-cell (T-reg) accumulation.[26] Inhibition of the CXCL10/CXCR3 axis produces a more stable plaque phenotype and in humans, high CXCL10 expression is predictive of vulnerable plaque.[27]

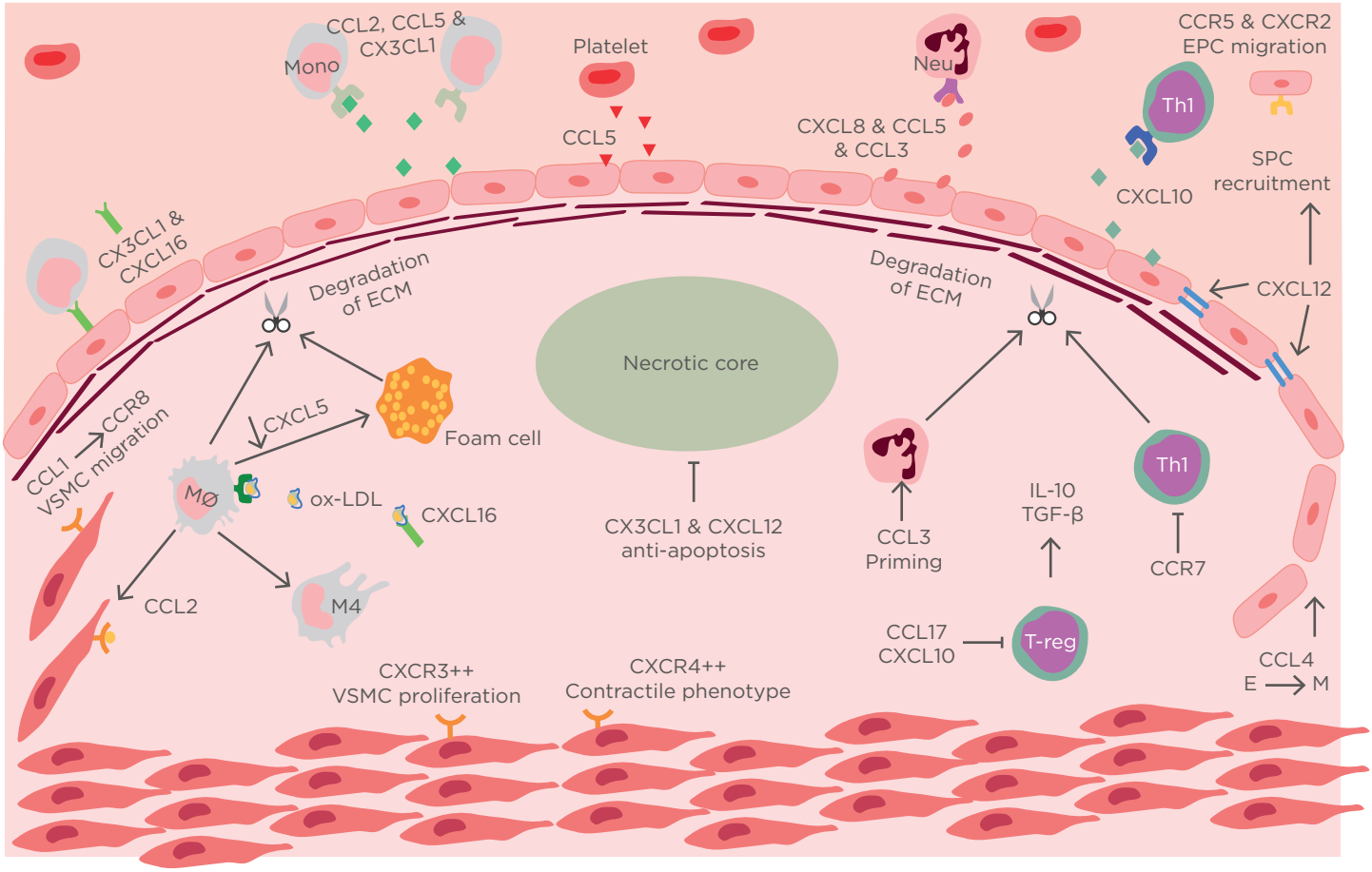

Figure 1: Chemokines in the destabilisation of atherosclerotic plaque.

Immune cells are recruited to atherosclerotic lesions by chemokines, primarily produced by the dysfunctional endothelium. Platelets also contribute to the chemotactic gradient by secreting CCL5. The secretion of MMP from intraplaque immune cells leads to the degradation of collagen. The necrotic develops as a result of impaired efferocytosis. Endothelial-mesenchymal transition occurs in advanced lesions, mediated by CCL4.

E ⟶ M: endothelial mesenchymal transition; EPC: endothelial progenitor cell; mono: monocyte; Mø: macrophage; Neu: neutrophil; ox-LDL: oxidised-low-density lipoprotein; TGF-β: transforming growth factor β; Th1: T-helper cell 1; VSMC: vascular smooth muscle cell.

Moreover, dual inhibition of CCR5 and CXCR3 suppresses the T-cell response in atherosclerosis, by reducing T-cell accumulation and INF-gamma expression by 95% and 98%, respectively.[13]

CCR7 is another chemokine receptor involved in regulating the T-cell response. CCR7 knockout exacerbates atherosclerotic disease progression.

CCR7-deficient mice display enhanced T-cell accumulation in plaque and polarisation of the T-cell response, whereby serum levels of IL-4 and TGF-β decrease and IL-12p40 and IL-17F increase. This implies that CCR7 signalling is responsible for maintaining the Th2 and T-reg response, while suppressing Th1 activity.[16] In parallel, CCR7 expression in peripheral blood mononuclear cells is significantly reduced in patients with unstable coronary disease compared to those with a stable disease phenotype. Treatment of these patients with aggressive statin therapy has been shown to enhance CCR7 expression.[17]

T-regs are important negative regulators of the T-cell response. Naturally, T-regs account for 1–5% of the total lesional T cells. CCL17, a dendritic cell-derived chemokine, is known to limit T-reg expansion. CCL17 deficiency enhances T-reg expansion, increases T-reg intraplaque accumulation, and attenuates atheroma progression. Additionally, atherosclerotic lesions in CCL17-deficient mice, display a more stable

phenotype with increased SMC content. These findings are supported by the elevated expression of CCL17 observed in human atherosclerotic tissue.[15] Similar to T-regs, B-cells appear to be atheroprotective. Global B-cell deletion exacerbates the development and progression of atherosclerosis in mice.[20] B-cells are recruited to plaque via CCL20/CCR6 and adoptive transfer of $CCR6^{+/+}$ B-cells to $ApoE^{-/-}$ mice induces plaque regression.[20]

Neutrophils

More recently, neutrophils have been identified as key players in plaque instability. Activation of neutrophils results in the release of preformed inflammatory proteins and ultimately the generation of neutrophil extracellular traps, which in turn drive plaque rupture.[4] Neutrophils naturally express CCR5, which can be increased by the presence of a high-fat diet.[9] It has been demonstrated that platelet-derived CCL5 acts via CCR5 to induce neutrophil migration into plaque.[11] CCL5 is also known to interact with CXCL4 and specific blocking of this interaction reduces neutrophil recruitment and neutrophil extracellular traps formation.[12] Furthermore, CXCL8, produced largely by monocytes and macrophages, promotes lesional neutrophil accumulation via CXCR1 and CXCR2. In human subjects with stable coronary artery disease, baseline serum CXCL8 is a robust predictor of future cardiovascular events.[24]

The chemokine receptors CXCR2 and CXCR4 function in an opposing fashion to regulate neutrophil trafficking. CXCR2 is required for neutrophil recruitment from the bone marrow. In contrast, activation of CXCR4 promotes neutrophil retention in the bone marrow.[41] Mice treated with a CXCR4 antagonist display a 4-fold increase in relative neutrophil accumulation within plaque[42] and a higher incidence of intraplaque haemorrhage.[28] Neutrophils lacking functional CXCR4 have augmented myeloperoxidase activity and enhanced cell survival, illustrating that CXCR4 deficiency not only increases neutrophil homing to plaque, but also amplifies their activity.[28] CCL3 plays a similar role in neutrophil homeostasis. Haematopoietic deficiency of CCL3 reduces both circulating and plaque neutrophil content, which is most probably attributable to higher rates of apoptosis observed in CCL3-deficient neutrophils. Additionally, the absence of CCL3 impairs neutrophil responsiveness to other chemotactic stimuli, such as CXCL1.[9]

Chemokines and the Necrotic Core

Generation of the necrotic core results from impaired efferocytosis: a combination of profound intraplaque apoptosis and reduced phagocytic capacity of macrophages. Chemokines have direct and indirect effects on the necrotic core. Indirectly, chemokines mediate immune cell infiltration and thus, the extent of intraplaque apoptosis. Directly, chemokines are involved in cell survival signalling and macrophage polarisation. Treatment of mice with CX3CL1-fc, a long acting CX3CR1 agonist, reduces necrotic core burden, at least partly due to the antiapoptotic effects of CX3CL1 signalling in macrophages and SMC.[43] CXCL12 is known to have a similar effect, whereby CXCL12/CXCR4 signalling counteracts apoptosis in endothelial and SMC.[29]

Macrophage populations differ in their response to various chemotactic stimuli and their phagocytic ability. M1 macrophages migrate in response to CCL19/CCL21 signalling via CCR7. Although M2 macrophages express similar amounts of CCR7 they do not respond to CCL19/CCL21 stimulation.[18] CCL19/CCL21 signalling has also been implicated in macrophage egress from lesions. Inhibition of both ligands suppresses plaque regression and it has been proposed that the macrophage egression properties of statins may be CCR7-dependent.[19] The platelet-derived chemokine, CXCL4, has recently been shown to induce a novel macrophage phenotype, termed M4. M4 macrophages display a pro-inflammatory phenotype, characterised by high IL-6, TNFα, and matrix metalloproteinase-7 (MMP-7) expression, in combination with reduced phagocytic capacity. High intraplaque accumulation of M4 macrophages is associated with features of vulnerability.[22] This indicates that platelet activation may promote progression of the necrotic core via the secretion of CXCL4.

CHEMOKINES AND THE FIBROUS CAP

The fibrous cap is typically a collagen-rich structure interspersed with SMC that acts as a barricade between the pro-thrombotic core of a lesion and the circulating coagulation factors.

Neointimal recruitment of SMC is facilitated by CCL1 and CCR8.[5] Continual SMC recruitment in combination with the deposition, cross-linking, and maturation of collagen leads to the formation of the fibrous cap. The thickness, and therefore stability, of the cap is largely dependent on two factors: MMP expression and SMC content. Rupture-prone regions of human atherosclerotic plaque show increased levels of MMP 1, 3, 8, 9, 11, 14, and 16, in combination with reduced SMC accumulation.[44]

There is extensive evidence describing a regulatory effect of chemokines on MMP activity. Stimulation of monocytes with either CCL2, CCL3, CCL4, or CCL5 increases the expression of MMP-9 and MMP-14.[6,7] It is thought that these effects are primarily mediated via CCR1 and CCR2, as mice deficient in these receptors have diminished MMP production.[45,46] Additionally, CCL2 is known to mediate cross-talk between macrophages and SMC, particularly in a high glucose environment. In this setting, macrophage-derived CCL2 increases MMP-1 and MMP-9 secretion from SMC.[8]

Chemokines modulate SMC accumulation and functionality in plaque. Mice deficient in CCR5 show increased SMC and IL-10 intraplaque expression, suggesting that CCR5 may be a negative regulator of SMC migration into plaque.[47] Alternatively, activation of CXCR3 enhances SMC proliferation.[34] Similarly to many of the cells involved in atherosclerosis, SMC demonstrate plasticity, which can be influenced by CXCR4. SMC-specific CXCR4-deficiency causes a phenotypic switch from contractile to synthetic: a switch associated with foam-cell formation.[30] Smooth muscle progenitor cells, when recruited to atherosclerotic lesions, promote stability. CXCL12 treatment mobilises smooth muscle progenitor cells from the bone marrow and recruits them to atherosclerotic plaque. Mice treated with CXCL12 display increased fibrous cap thickness.[31] In humans, plasma CXCL12 expression is reduced in patients with coronary heart disease, particularly in those with an unstable phenotype.[48] This reduction in CXCL12 may produce the upregulation of the CXCL12 receptor, CXCR4, seen in patients with unstable lesions.[49]

Endothelial Integrity

Plaque erosion, characterised by endothelial denudation at the plaque-blood interface, is another mechanism that promotes instability. Endothelial-mesenchymal transition, a process whereby EC polarise toward a myofibroblast-like cell and accumulate within plaque, is known to alter plaque stability. The extent of endothelial-mesenchymal transition is greatly increased in unstable and ruptured plaques.[10] Yang et al.[50] demonstrated that foam cell-derived CCL4 acts via EC-expressed CCR5 to promote endothelial-mesenchymal transition in atherosclerotic plaque: a process that could be inhibited by maraviroc, a commonly available CCR5 antagonist. Activation of CXCR4 by its ligand CXCL12 provides an antiatherogenic effect by enhancing endothelial barrier function. More specifically, CXCL12/CXCR4 signalling increases vascular endothelial cadherin expression, therefore stabilising endothelial junctions.[30]

Endothelial progenitor cells (EPC) are important for maintaining a functional endothelium. Patients with atherosclerosis have reduced EPC numbers and enhancing EPC activity has been shown to promote plaque regression.[51] EPC recruitment to plaque is driven by the activation of CCR5 and CXCR2. CCR5 overexpression in mice, dramatically increases lesional EPC recruitment, EC coverage of coronary plaque and systemic nitric oxide levels; indicating improved EC function.[21] Similarly, CXCR2 antagonism blunts EPC migration and EPC induced plaque regression. In the same study, it was found that CX3CR1 expression was required for the atheroprotective effects of EPC, despite the fact that CX3CR1-deficiency did not alter EPC migration.[52]

THERAPEUTIC CHEMOKINE MODULATION TO ENHANCE PLAQUE STABILITY

Plaque stability is largely influenced by inflammation. As such, immunotherapies provide a novel method for promoting stability of atherosclerotic lesions. Results from the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS)[53] confirmed that specifically targeting components of the inflammatory response can be effective in the secondary prevention of cardiovascular disease.

However, immunotherapies have a common pitfall: potential oversuppression of the immune system, rendering the host susceptible to infection.[53] This adverse effect is the primary barrier stalling the large-scale implementation of immunotherapies in patients with atherosclerosis. Proper immune function is a delicate balance between infection (underactivation) and inflammation (overactivation). Therefore, finding the ideal therapeutic target that does not offset this equilibrium remains key to developing effective immunotherapies.

As described above, chemokines are an essential component of the inflammatory response, ultimately responsible for the destabilisation of plaque. Consequently, chemokine-targeted therapies have gained popularity in recent years. Numerous preclinical studies have demonstrated that antichemokine therapies are effective at reducing plaque burden and instability. Despite this, there is a lack of translational data confirming these findings in patients with atherosclerotic disease.

CCL2/CCR2

The CCL2/CCR2 axis is the most commonly targeted chemokine pathway in atherosclerosis. Generally speaking, inhibition of this pathway stunts progression and promotes a morphologically stable plaque. Local gene silencing of CCL2 reduces plaque disruption rates by approximately 80%, in mice. This improved stability was facilitated by increased fibrous cap thickness and SMC and collagen content, in combination with a large reduction in lesional macrophage accumulation.[54] Antagonism of CCR2 produces similar results. Bot et al.[55] reported that administration of 15a, an orthosteric small molecule CCR2 antagonist, greatly reduced intraplaque macrophage accumulation and necrotic core size. 15a also reduced circulating classical monocytes number, suggesting that CCR2 is required for classical monocyte recruitment from the bone marrow.[55] On the contrary, a reduction in circulating monocyte numbers may imply an impaired immune response. Another CCR2 antagonist, 7ND, has been trialled in mice and rabbits. Treatment of ApoE$^{-/-}$ mice with 7ND increased the plaque stability score, as measured by collagen, macrophage, and lipid composition of the lesion.[56] In rabbits, administration of 7ND prevented plaque disruption, which was associated with an increase in fibrous cap thickness.[57] Evidently, inhibition of the CCL2/CCR2 axis is effective at suppressing the atherogenic immune response. However, recent evidence suggests that the efficacy of such treatment is related to circadian rhythm and thus, dosing is time dependent. Winter et al.[58] demonstrated that myeloid cell recruitment from bone marrow is not constant; it occurs in peaks throughout the day. As such, the authors further reported that CCR2 neutralisation is most effective when administered just prior to the peak of myeloid cell recruitment.[58]

To the authors' knowledge, there has only been one CCR2 antagonist trialled in humans. Gilbert et al.[59] employed MLN1202, a CCR2-specific monoclonal antibody, to assess the effect of CCR2 blockade on C-reactive protein levels in individuals at increased risk of atherosclerosis. This study demonstrated that short-term CCR2 blockade was not only safe but efficacious in suppressing atherosclerosis-associated inflammation. Larger Phase III trials are required to confirm these findings and evaluate long-term safety and efficacy of CCR2 antagonism in humans with atherosclerotic disease.

CX3CR1

Many of the methods employed to disrupt chemokine pathways are not easily translatable to human clinical trials. To address this, Zhou et al.[60] developed an anti-CX3CR1 vaccination, which was trialled in ApoE$^{-/-}$ mice. Vaccinated mice showed a 35% reduction in plaque size and a 5-fold reduction in macrophage infiltration. Despite this, the M1/M2 lesional macrophage ratio or SMC content was unaltered by vaccination.[60] In direct contrast, Riopel et al.[43] reported that enhanced CX3CR1 activation is atheroprotective, whereby, administration of CX3CL1-fc to mice produced a more stable plaque. CX3CL1-fc treated mice had reduced M1 and T-cell accumulation and a smaller necrotic core. Moreover, these mice had enhanced intraplaque SMC and collagen content.[43]

CCL5/CCR5

The CCL5/CCR5 axis has also been an attractive target for modulating plaque. Met-RANTES, a CCR1 and CCR5 antagonist, displays a significant atheroprotective effect. LDLr$^{-/-}$ mice treated

with Met-RANTES show reduced macrophage and lymphocyte infiltration and reduced MMP-9 expression. Consequently, these lesions had a thicker fibrous cap and increased intraplaque collagen.[61] Similar effects were reported with the use of [^{44}AANA^{47}]-RANTES, a CCL5 antagonist. Administration of [^{44}AANA^{47}]-RANTES promoted regression of established lesions and produced a more stable plaque.[62] The CCR5 antagonist maraviroc, also appears effective at stunting plaque progression. In a mouse model of late-stage atherosclerosis, daily administration of maraviroc attenuated plaque progression and intraplaque macrophage accumulation.[63]

Other Chemokine Targets

Several other chemokine ligands and receptors have been targeted in atherosclerosis. Administration of a CXCL10-neutralising antibody has been shown to prevent vulnerable plaque development by increasing lesional SMC and collagen content, while significantly reducing the relative necrotic core size.[27] Evasin-3, a CXCL1 and CXCL2 antagonist, promotes plaque stabilisation by reducing intraplaque neutrophil infiltration and MMP-9 expression.[64] Antagonism of CXCR3 or CCL17 may also promote plaque stabilisation by increasing T-reg expansion. Inhibition of either receptor causes an increase in T-reg expansion and a reduction in plaque progression.[15,26]

A group of scavenger receptors involved in the regulation of chemokine activity have recently been described in the literature, termed atypical chemokine receptors (ACKR). ACKR differ from classical chemokine receptors as they do not couple G proteins; thus, they act to scavenge, internalise, and transport chemokines without initiating a signalling cascade.[65] There are currently four known ACKR, two of which are clearly involved in the progression of atherosclerosis. ACKR1, expressed primarily on erythrocytes and venular EC, binds >20 different inflammatory chemokines. ACKR1-deficiency in mice stunts atherogenesis and skews macrophage polarisation toward a less inflammatory phenotype.[66] ACKR1-deficiency has also been shown to suppress macrophage migration by inhibiting CCL2 expression on the surface of erythrocytes.[67] In contrast, ACKR3 appears to be atheroprotective. Genetic ablation of ACKR3 increases systemic cholesterol levels and promotes progression of atherosclerotic lesions.[68] Moreover, ACKR3 is involved in mediating EPC survival and homing as well as vascular SMC migration.[65] Pharmacological manipulation of ACKR expression may provide a novel mechanism to regulate chemokine activity and minimise global immune suppression. Therefore, future studies investigating the possibility of pharmacological ACKR modulation would be of great benefit to cardiovascular research.

CURRENT AND FUTURE DIRECTIONS

Despite abundant preclinical data, there is limited translational research investigating the effect of antichemokine medications in patients with atherosclerotic disease. This may be due to the potential increased risk of infection and/or the enormous cost associated with drug development. However, results from oncological studies suggest otherwise. Many antichemokine therapies have been trialled in cancer patients and demonstrate a sound safety and tolerability profile.[69] Adapting these medications for use in cardiovascular disease may allow cost and time-effective development of antiatherogenic, chemokine-targeted therapies. Future studies should aim to translate lab-based findings into robust clinical trials, potentially drawing from the methodology employed in the CANTOS study.[53]

CONCLUSION

Chemokines are unequivocally involved in all stages of atherosclerosis. Evidently, the role of chemokines extends well beyond the sole recruitment of immune cells and there are now abundant data implicating chemokines in the destabilisation of atherosclerotic plaque. Manipulation of chemokine pathways represents a novel therapeutic target for the stabilisation of coronary plaque; nevertheless, is not without its challenges. Careful selection of drug targets may help mitigate risk and ultimately produce an effective antichemokine therapy.

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Circulating Cardiac Biomarkers in Heart Failure: A Critical Link to Biomarker-Guided Therapy

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Disclosure: The author has declared no conflicts of interest.

Received: 08.02.19

Accepted: 03.04.19

Keywords: Biomarkers, clinical outcomes, heart failure (HF), prediction, risk stratification.

Citation: EMJ Cardiol. 2019:7[1]:139-147.

Abstract

Current clinical guidelines for the diagnosis, treatment, and prevention of heart failure (HF) are the incorporated measure of biomarkers, predominantly natriuretic peptides (NP), cardiac troponins, soluble ST2 (sST2), and galectin-3, all of which serve as surrogate diagnostic and predictive factors. Whether levels of these biomarkers, measured in a longitudinal manner in HF patients, retain their prognostic power over a course of HF therapy and support continuation of these treatments is not fully understood. The aim of this review is to summarise knowledge regarding the use of single and serial measures of cardiac, biological markers as a surrogate endpoint to predict HF-related clinical events. Cardiac biomarkers, predominantly N-terminal segment of brain natriuretic peptide (NT-proBNP) and sST2, are surrogate biomarkers for numerous clinical studies that have assumed a pivotal role in multiple biomarker strategies preceding HF-related outcomes. It has been suggested that biomarker-guided therapy with serial biomarker measures could be a powerful means to appraise composite risk score and predict HF-related outcomes based on therapeutic adjustment. In the future, large controlled clinical trials should be better designed for justification of an individualised strategy for HF therapy.

INTRODUCTION

A contemporary conceptual framework that was proposed to distinguish between different chronic heart failure (HF) patients has highlighted varying responses to therapeutic interventions, especially in patients of different ages and with several comorbidities.[1,2] Whether the measure of biomarker serum levels can be determined as a surrogate endpoint for HF-adjusted therapy and suggest clinical outcomes is uncertain, and appears to be controversial in several investigations.[3-7] Current HF therapy is associated with improved survival over time in patients with HF-reduced ejection fraction (HFrEF), but not for those with HF preserved (HFpEF) or mid-range (HFmrEF) ejection fraction.[3] Conventional approaches for HF treatment aim to affect neuroendocrine modulation using angiotensin receptor-neprilysin inhibitors/angiotensin receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEI), beta-blockers, or mineralocorticoid receptor antagonists. Although the high prescription rate of these drugs has helped HF survival in developed countries,[4-7] the 5-year survival rate for HF patients in developing

countries, regardless of disease phenotype, has failed to exceed 39–43%.[8] In fact, maladaptive cardiac remodelling, endothelial dysfunction due to microvascular inflammation, oxidative stress, acceleration of atherosclerosis, and metabolic abnormalities with continuous deterioration of target organ function (heart, vessels, lungs, kidneys, brain, and skeletal muscles) are not tightly controlled by these drugs, and are problems that remain core elements of HF pathogenesis.[9,10] In this context, biological markers that reflect the consequent manifestation of HF-evolved pathological abnormalities could be useful in identifying the risk of outcomes.[11,12] A similar approach appears to be cost-effective for both inpatients and outpatients with HF.[13,14] The aim of this review is to summarise information relating to the use of single and serial measures of cardiac biological markers as a surrogate endpoint to predict HF-related clinical events.

TECHNIQUE FOR INFORMATION SOURCING

Original articles and higher precision reviews written in English and published within the last 5 years were found in MEDLINE (Ovid), EMBASE, PubMed, ScienceDirect, and other databases such as Web of Science, using keywords: "heart failure", "biomarkers", "surrogate endpoints", "natriuretic peptides (NP)", "soluble suppressor of tumorigenicity-2", "cardiac troponins", "galectin-3". Keywords were designed to be more sensitive using thesaurus tools such as Medical Subject Headings (MeSH) in MEDLINE, and Excerpta Medica Thesaurus (EMTREE) terms in EMBASE. Major descriptors of the articles, titles, and abstract fields were also checked. All selected articles were analysed depending on their quality and relation to the aim of the review and enrolled to the list for further checking depending on whether the references were focussed on target approach.

BIOMARKERS FOR HEART FAILURE

Current clinical recommendations support the use of cardiac biomarkers to stratify, diagnose, and predict clinical outcomes in HF.[6,7] Although NP (i.e., BNP: brain natriuretic peptide; NT-proANP: N-terminal pro-atrial natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide) are widely used to predict all-cause specific endpoints in HF patients, the 2017 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) guidelines for the management of HF have incorporated several additional cardiac biomarkers (cardiac troponins, galectin-3, and soluble ST2 [sST2]).[7] In fact, the diagnostic and predictive attributes of biomarkers for damage (cardiac troponins) and biomechanical stress (NP, galectin-3, and sST2) in HF have been established. However, the predictive value of growth and differentiation biomarkers, such as growth differentiation factor-15 (GDF-15), in different phenotypes of HF is still under discussion.[15,16]

Table 1 provides a comparison of conventional and novel biomarkers. Peak concentrations for the majority are applied as risk stratification and diagnostic tools for HF, but NP were predominately recommended for HF guidance and prediction of clinical outcomes. However, the predictive values of NP were sufficiently variable depending on age, comorbidities (including Type 2 diabetes mellitus, abdominal obesity, atrial fibrillation/flutter), and medical treatment.[17-19] Novel biomarkers, such as procalcitonin, adrenomedullin/N-terminal fragment of adrenomedullin, microRNA, and other less known biomarkers (human epididymis protein 4, insulin-like growth factor-binding protein 7, soluble CD146, IL-6, endothelial cell derived micro vesicles, and endothelial and mononuclear progenitor cells) require investigation in large clinical trials and to be compared with each other, as well as conventional biomarkers.[20] Moreover, biomarkers have been distinguished in their ability to predict the onset of different HF phenotypes. Indeed, NP and high-sensitivity troponin strongly predict HFmrEF, whereas NP are better predictors of HFrEF in comparison to HFmrEF and do not differ in their association with incident HFmrEF and HFpEF.[21]

Table 1: Conventional and novel biological markers in heart failure: accompany to clinical hard endpoints.

Biomarker	Risk stratification	Diagnosis of acute and non-acute onset of HF	HF therapy guidance	Prediction of HF-related outcomes
Biomechanical stress biomarkers				
BNP	++	++	+	++
NT-pro BNP	++	++	+	++
NT-proANP	+	++	-	+
NT-proADM	-	++	-	+
sST2	-	-	-	++
Galectin-3	+	++	-	-
PCT	-	+	-	++
Damage biomarkers				
hs-TnT/I	+	++	-	-
Growth and differentiation biomarkers				
GDF-15	+	++	-	-
miRNA	++	-	-	+

BNP: brain natriuretic peptide; GDF: growth differentiation factor; HF: heart failure; hs-TnT/I: high sensitivity cardiac troponin T/Index; miRNA: microRNA; NT-proADM: N-terminal fragment of adrenomedullin; NT-proANP: N-terminal fragment of atrial natriuretic peptide; NT-proBNP: N-terminal fragment of brain natriuretic peptide; sST2: soluble suppressor of tumourgenecity-2; PCT: procalcitonin.

+: mildly corresponded; ++: moderately corresponded; +++: strongly corresponded

LONGITUDINAL TESTING AND OUTCOMES IN BIOMARKER-GUIDED STUDIES

Whether the levels of these biomarkers, measured in a longitudinal manner in HF patients, retain their predictive power over a course of HF treatment and support HF-guided therapy is not fully understood. Indeed, circulating levels of some biomarkers, such as NP, appear to correlate with body mass, kidney function, and ageing. Another aspect requiring more clarity is the identification of an optimal time window for biomarker measurement. For example, at hospital admission NP levels can better provide predictive value for in-hospital mortality, whereas at discharge, NP levels stronger predict the need for re-admission as opposed to risk of death. Additionally, measurement of NT-proBNP levels after initiation of HF therapy aims to predict a long-term favourable effect of the therapy, but a risk of clinical outcomes is an attributed trend of biomarker changes signifying need for a follow-up. Moreover, fluctuations of serial NP levels received during longitudinal serum biomarker home monitoring in post-acute, decompensated HF patients are extremely high and, as demonstrated in the HOME HF study,[22] may never be <30%. In fact, in this study, dispersions of NP data between measures surged depending on the time period after discharge from hospital, with as high as 73.6% being reported at 120 days of ambulatory period. Additionally, some drugs given to HF patients can directly influence metabolism and cardiac biomarkers unrelated to HF severity.[22,23] For instance, clinical studies in which HF patients with diabetes were enrolled have revealed that the sodium glucose co-transporter-2 inhibitors, i.e., canagliflozin and empagliflozin, reduce serum levels of NT-proBNP directly through attenuation of kidney clearance and modulation of neprilysin activity, as well as indirectly via lowered fluid retention that improves HF outcomes, including HF-related death, hospital admission due to HF, and all-causes.[24,25] Taken together, this evidence shows that serial NP measurements have

potential value as an index of emerging clinical deterioration for short-term and long-term periods in HF patients; however, this should be considered on a patient-by-patient basis.[26,27] Consequently, there is great interest in other predictive biomarkers that can attenuate the discriminative ability of NP during treatment of HF. However, there are still sufficient differences between various cardiac biomarkers for maintaining HF therapy guidance that require more large clinical trials in the future.

SUGGESTION OF HEART FAILURE-RELATED OUTCOMES WITH CARDIAC BIOMARKERS

There are controversial issues regarding correspondence between dynamics of conventional cardiac biomarkers and clinical outcomes in HF patients. Table 2 summarises data regarding serum levels of cardiac biomarkers and clinical outcomes in HF patients included in large clinical trials.

Angiotensin-Converting Enzyme Inhibitors

In the pre-beta-blocker era, clinical trials have demonstrated that ACEI treatment in chronic HFrEF and HFpEF patients decreases plasma BNP and NT-proBNP dose-dependently, and that this effect strongly corresponds with improved clinical status, left ventricular ejection fraction (LVEF), exercise capacity, and survival.[28-30] However, the levels of other HF severity biomarkers, such as epinephrine, aldosterone, and endothelin-1, are not significantly affected by ACEI.[30] On the contrary, in the randomised CONSENSUS-I controlled trial, ANP levels in an ACEI enalapril cohort had demonstrated a decreasing trend, despite there being no significant correlation between ANP levels and clinical outcomes/LVEF at the end of the study.[31,32] The Ramipril Trial Study Group revealed that ramipril was able to reduce the plasma concentration of BNP in HFrEF and improve clinical status.[33] Some small clinical studies specifically analysing acute/acutely decompensated HF have demonstrated the clinical benefit of ACEI through declining NP serum levels.[47,48] The lack of a strong relationship between longitudinal changes in the levels of NP, survival, and LVEF requires further explanation. It is likely that other biomarkers, including neuropeptides and neurohormones (angiotensin-II, endothelin-1, aldosterone), are not sufficiently modulated by ACEI.[34] However, this trial has forced the incorporation of spironolactone into ACEI-based treatment schemes for HF. In this trial, patients included in both spironolactone and placebo cohorts received several ACEI as concomitant therapy, i.e., captopril (63.4% and 62.1%, respectively), enalapril (13.5% and 16.5%, respectively), and lisinopril (15.6% and 13.1%, respectively). It should be noted that during this period, analytical procedures for NP measure had not yet been standardised, and various methods (radioimmunoassay, immunoluminometric, enzymatic, or luminescence immunoassay) with variable analytic accuracies for the determination of other biomarkers were widely used.[49] Thus, most clinical studies examining multiple biomarkers, including NP in the same HF patient cohorts using the same highly sensitive analytic methods, have turned out to be necessary. Using this approach, it was established that the decrease in BNP/NT-proBNP among in-patients with acute/actually decompensated HF was associated with a clinically beneficial outcome, whereas no change or an increase in BNP/NT-proBNP levels were related to increased hospital stay and HF-related death.[47,50]

Mineralocorticoid Receptor Antagonists

The RALES study was the first investigation specifically analysing the mineralocorticoid receptor antagonist spironolactone in patients with severe, congestive HF. In the study, spironolactone exhibited an ability to reduce circulating levels of both BNP and NT-proANP, as well as improving survival in HFrEF patients (LVEF <25%), whereas there was an increase of angiotensin-II and aldosterone I levels, and no change to endothelin-1 levels, in the spironolactone group.[34] Later, in the TOPCAT study, spironolactone did not sufficiently reduce the incidence of death from cardiovascular causes, aborted cardiac arrest, or hospital admissions in HFpEF patients, while BNP/NT-proBNP levels were significantly decreased.[35]

Table 2: Accordance between serum levels of cardiac biomarkers and clinical outcomes in heart failure patients included in large clinical trials.

Drug name	Drug class	Trial acronym	Patient population	Changing of cardiac biomarkers	Clinical outcomes
Imidapril[28]	ACEI	-	HFrEF	↓BNP/NT-proBNP	↑clinical status, exercise capacity
Enalapril[29,30]	ACEI	-	HFrEF/HFpEF	↓BNP/NT-proBNP	↑clinical status, LVEF, exercise capacity, and survival
Enalapril[31,32]	ACEI	CONSENSUS I	HFrEF	↓ANP	no related changes in ANP, left atrial size, or systolic function
Ramipril[33]	ACEI	Ramipril Trial Study Group	HFrEF/HFpEF	↓BNP	↑clinical status, ↓hospitalisation
Spironolactone[34]	MRA	RALES	HFrEF	↓NT-proANP, ↓BNP, ↑A-II, ↑Aldo	↑clinical status, ↑survival
Spironolactone[35]	MRA	TOPCAT	HFrEF/HFpEF	~BNP/NT-proBNP	↓risk of all-cause, ↓↓HF-related mortality, ↓↓risk of hospital admission
Spironolactone[36]	MRA	EPHESUS	HFrEF	↓BNP, ↓endothelin-1	Endothelin-1 predicted ↓↓HF-related death and hospital admission independently from longitudinal BNP changes
Carvedilol[37]	βAB	COPERNICUS	HFrEF	Uncertain ↓ and ↑ NP	No significant interaction between NT-proBNP and improved outcomes
Carvedilol[38]	βAB	Australia-New Zealand HF trial	HFrEF	↓BNP, ↓NT-proADM	↓↓risk of all-cause and HF-related mortality, ↓↓risk of hospital admission and sudden death
Metoprolol[39]	βAB	MERIT-HF	HFrEF	↓BNP dose-dependently	↓↓hospitalisations, ↓symptoms, ↑quality of life
Bisoprolol[40]	βAB	CIBIS-II	HFrEF	~BNP/NT-proBNP	Improved clinical outcomes
Valsartan[41-43]	ARB	Val-HeFT	HFrEF	↓↓BNP/NT-proBNP, ↓CRP, ↓endothelin	↓↓risk of all-cause and HF-related mortality, ↓↓risk of hospital admission
Sacubitril/valsartan[44-46]	ARNI	PARADIGM-HF	HFrEF	↑↑↑ANP/BNP, ↓↓NT-proBNP, ↓CRP, ↓hsTnT, ↓sST2, ~GDF-15	↓all-cause mortality, ↓↓combined endpoint of CV death or hospitalisation for HF, ↓↓HF death

A-II: angiotensin-II; ACEI: angiotensin-converting enzyme inhibitor; Aldo: aldosterone; ARB: angiotensin receptor blocker; ARNi: angiotensin receptor-neprilysin inhibitor; CRP: C-reactive protein; CV: cardiovascular; GDF: growth differentiation factor; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; hsTnT: high sensitivity cardiac troponin T; LVEF: left ventricle ejection fraction; MRA: mineralocorticoid receptor antagonist; NT-proADM: N-terminal fragment of adrenomedullin; NT-proANP: N-terminal fragment of atrial natriuretic peptide; NT-proBNP: N-terminal fragment of brain natriuretic peptide; sST2: soluble suppressor of tumourgenecity-2.

↑: mild increase; ↑↑: moderate increase; ↑↑↑: severe increase; ↓: mild decrease; ↓↓: moderate decrease; ↓↓↓: severe decrease; ~: no effect.

In the EPHESUS trial, HFrEF patients with increased circulating levels of endothelin-1 had exaggerated risk of HF-related death and hospital admission regardless of BNP alterations during treatment with eplerenone.[36] It is worth noting that this trial was provided in the HF treatment beta-blocker era, and patients, who had received either spironolactone or placebo, were treated with beta-blockers as a concomitant medication.

Beta-Blockers

The era of beta-blocker implementation in HF therapy began with several clinical trials (e.g., COPERNICUS, IMPACT-HF, MERIT-HF, CIBIS-II, COMET), in which improved survival in HFrEF was completely determined. Unfortunately, the COPERNICUS[37] study and an Australia-New Zealand heart failure trial[38] have shown that carvedilol effectively decreased all-cause and HF-related mortality rate and hospital admission regardless of BNP/NT-proBNP dynamic. In fact, long-term clinical outcomes in HFrEF patients could be improved even if NP levels were surging. Although pre-treatment plasma BNP/NT-proBNP remained to be independent predictors of all-cause and HF-related mortality and HF-dependent hospitalisation, carvedilol improved survival in HFrEF patients independently from biomarker levels.[51] The initiation of metoprolol treatment in HFrEF patients was associated with the soaring of BNP/NT-proBNP levels,[52] which was sufficiently pronounced in individuals staged III-IV New York Heart Association (NYHA) functional class.[53] Metoprolol did not demonstrate differential impact on survival in HF patients through dose-dependence, while serum levels of BNP were changed dose-dependently.[40] In the CIBIS-II trial, bisoprolol did not significantly impact BNP levels, while it did improve survival and attenuate the clinical status of HFrEF patients.[40] The results of the STARS-BNP Multicentre Study have shown that the combined use of ACEI and beta-blockers can reduce BNP levels in HFrEF patients, but this effect appeared to be dose-dependent and mean dosages of both drugs were significantly higher in the patients with best BNP control; this contrasts with the mean increase in loop diuretic furosemide dosage that was similar in both groups (best and worst BNP control, respectively).[54] In fact, the best BNP control was reported in patients with the lowest risk of HF-related death and hospital stay for HF.[55] Overall, patients with severe HFrEF and levels of BNP >1,000 pg/mL had a 40% risk of acute decompensation of HF after an initiation or increase of beta-blocker therapy.[55] Thus, uncertain evidence of contra directed BNP/NT-proBNP levels in severe HFrEF, and data that confirmed decreasing serum levels of these biomarkers in mild-to-moderate HFrEF patients, reflected a risk of potential beta-blocker side effects as opposed to a negative impact of the drugs on HF evolution in long-term perspectives.

Angiotensin-Receptor Blockers

ARB appeared to be promising drugs for improved survival in HF, offering benefits over ACEI. The first results of ARB implementation have shown positive effects on decreeing serum levels of biomechanical stress markers such as NP. In the Val-HeFT study, serial measures of BNP/NT-proBNP concentrations taken at 4-month intervals in HFrEF patients treated with ARB valsartan were performed.[41] The results of the study illustrated a superior strategy for the risk stratification of stable patients with chronic HF using the determination of NT-proBNP serum levels. However, there was a small proportion of the HF patients showing increased BNP/NT-proBNP serum levels despite contemporary treatment, including ARB valsartan, beta-blockers, spironolactone/eplerenone, loop diuretic, and non-frequently digoxin.[42,43] Investigators concluded that the trend in soaring NP levels was an independent predictor of all-cause and HF-related mortality and hospitalisation, regardless of the kind of HF therapy.[43] Interestingly, non-responders for ARB therapy in the Val-HeFT study that associated with increased levels of BNP/NT-proBNP had frequently higher levels of endothelin-1 and CRP than those who had exhibited low levels of NP.[42,56] Additionally, serial measures of NT-proBNP were done in 3,480 HFpEF patients in the I-PRESERVE study to identify whether ARB-based treatments for HF have a distinguishing impact on morbidity and mortality across serum NP levels.[44] The investigators have ascertained that the beneficial effect of ARB irbesartan on clinical outcomes, including all-cause mortality, HF-related death, sudden death, or HF hospitalisation was found alongside increased NT-proBNP levels at baseline.

Angiotensin Receptor-Neprilysin Inhibitors

A new class of angiotensin receptor-neprilysin inhibitor agent called sacubitril/valsartan in addition to a conventional treatment in the PARADIGM-HF trial led to a 4-fold increase in ANP/BNP due to mediating metabolism of neprilysin and moderate decreases in NT-proBNP.[45] Therefore, cardiac troponin, hs-CRP, and sST2 levels, which were unrelated to neprilysin activity, also decreased. These changes accompanied fewer all-cause and HF-related deaths or HF admissions in patients with NT-proBNP levels lowered to 1,000 pg/mL compared to patients with levels that remained above this value.[46] Another result of the PARADIGM-HF trial was an effect on GDF-15 dynamics. Although the levels of GDF-15 at baseline were associated with higher mortality risk, the combined endpoints of CV death and hospitalisation for HF and HF death, and changes in GDF-15, were not influenced by sacubitril/valsartan.[57] Yet, longitudinal changes in galectin-3 were not associated with the natural evolution of HF.[58] Consequently, it is not fully clear whether this biomarker could be useful for guided therapy in HF.

Biomarker-Guided Therapy as a Component of Individual Approach in Heart Failure

Early clinical trials regarding NP-guided therapy for HF have reported inconsistent results, frequently dependent on statistical power, limiting sample sizes, and repeating measures of biomarkers.[59,60] Therefore, HF patient cohorts involved in the studies have displayed large biological heterogeneity at the levels of CV risk, metabolic profile, and adverse events. The GUIDE-IT study indicated that the goal of HF treatment could be achieving a target NT-proBNP level of <1,000 pg/mL.[61] The strategy of HF therapy, which is based on serial NT-proBNP measures, did not improve HF clinical outcomes.[62,63] In contrast, the Bio-SHiFT study[64] has revealed that individual patterns of longitudinal changes in multiple biomarkers, including NT-proBNP and hs-CRP, may be useful for a prognostication of HF-related outcomes and response to treatment. Additionally, the results of the TIME-CHF trial have shown that the beneficial effect of NT-proBNP-guided treatment was found only in HFrEF patients aged <75 years, and not in those aged ≥75 years.[64] This positive impact of NT-proBNP-guided therapy was associated with reduced risk of recurrent HF-related and all-cause hospital admissions and all-cause death.[65] Thus, NP revealed a potential association with HF clinical outcomes predominantly in HFrEF patients. Attempts to improve predictive values of NP mostly affect implementation of multiple biomarker models shaping from NP, hs-CRP, sST2, galectin-3, hs-troponin T, and several novel biomarkers (miRNA, GDF-15, metabolic factors).[66] Lastly, although meta-analyses that depicted NT-proBNP-guided HF treatment had produced controversial results,[67,68] the combination of NP and sST2 appeared to be reinforced in a new investigation to clearly explain the meaningful longitudinal changes of markers in the treatment programme of HF patients aimed at improving prognosis. In fact, future clinical trials are needed to provide a direct comparison between traditional and novel biomarkers in preceding HF clinical outcomes and adjusting treatment programme to improve prognosis. It is likely that the combined biomarker measure could significantly improve prediction of clinical outcomes in HF patients as opposed to single biomarker measures, and open new perspectives for biomarker-guided targeted HF therapies.

CONCLUSION

Cardiac biomarkers, predominantly NT-proBNP and sST2, are surrogate biomarkers for numerous clinical studies that have assumed a pivotal role in multiple biomarker strategies for preceding HF-related outcomes. It has been suggested that biomarker-guided therapy with serial biomarker measures could be a powerful tool to appraise composite risk score and predict HF-related outcomes based on therapeutic adjustment. In the future, large controlled clinical trials should be better designed for a justification of individual strategy in HF therapy.

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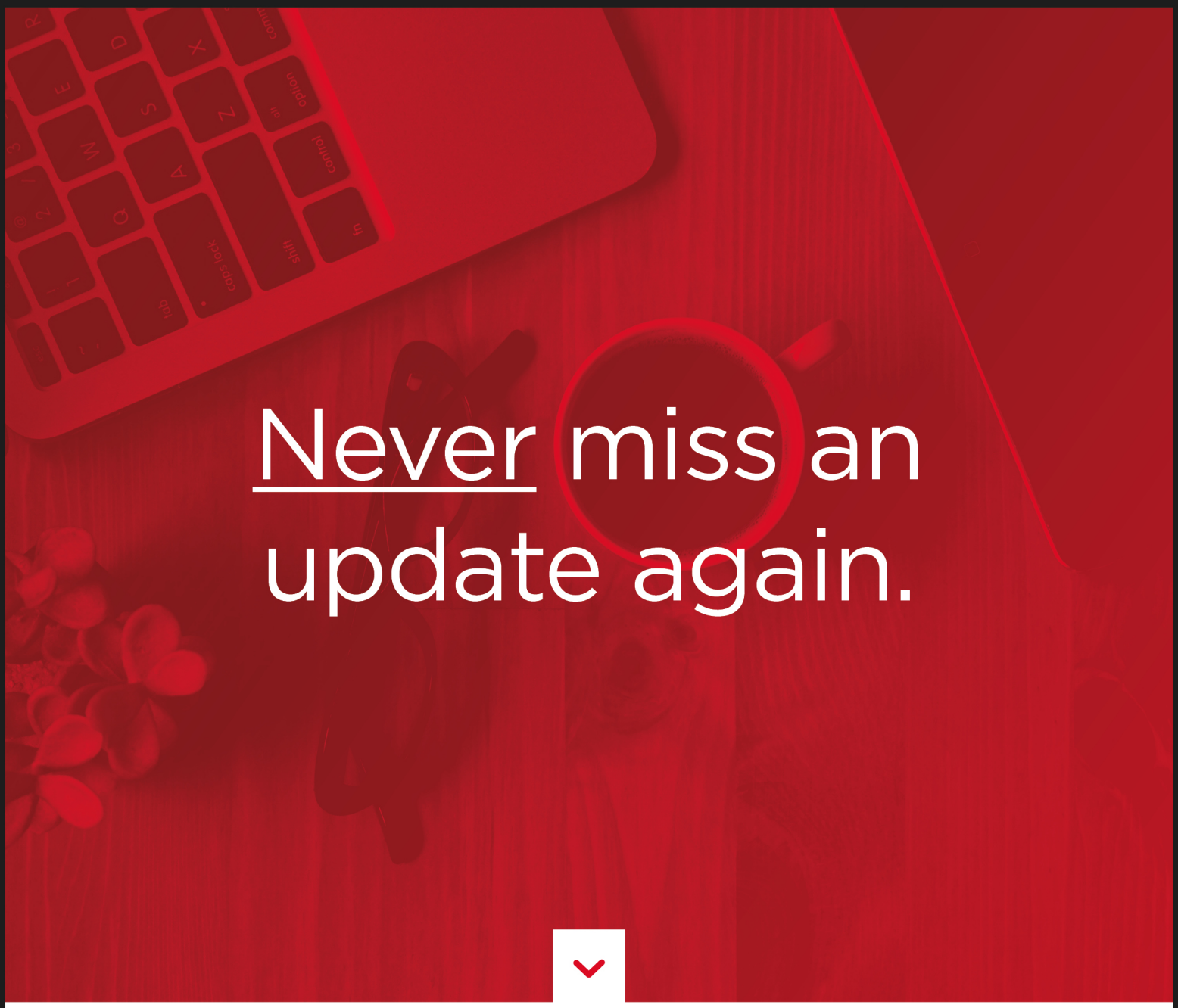

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