EMJ EUROPEAN MEDICAL JOURNAL

CARDIOLOGY

ISSN 2054-3174 — Vol 3.2 • October 2015 • emjreviews.com

INSIDE
Review of
ESC 2015
London, UK

CONTENTS

CARDIOLOGY

Editorial Board

Cardiology

EMJ GORELY NEW MEDIA

European Medical Journal
EMJ Cardiology Vol 3.2
October 2015

The MedBIC,
Anglia Ruskin University,
Chelmsford, CM1 1SQ

EMJ EUROPEAN MEDICAL JOURNAL

SUBSCRIBE TO THE EMJ NEWSLETTER

www.news.emjreviews.com

Follow us:

www.emjreviews.com

EUROPEAN UNION
Investing in Your Future
European Regional
Development Fund 2007-13

Welcome

Greetings, and a very warm welcome to *European Medical Journal Cardiology*, your comprehensive guide to one of the year's most significant medical events: the European Society of Cardiology (ESC) Congress, which this year took place in the vibrant city of London.

With an extensive history of medical achievement, from the founding of Florence Nightingale's nursing school and the famous Great Ormond Street Children's Hospital, to the establishment of the world-renowned Wellcome Trust, London proved to be a fitting backdrop for this prestigious meeting. Indeed, novel scientific discovery was out in force at this year's congress, and the prevailing mood was one of unbridled innovation and creativity. There was a great deal of fascinating work on display, some of which may have a profound impact on an ever-evolving field. The academic and clinical communities continue to unlock the subtle nuances of our biological make-up, uncovering new potential pathways of treatment and ultimately providing therapies that save the lives of even more patients. Such a high quantity of information may prove a little overwhelming, and it is for this reason that we have produced a comprehensive review for both those able and those unable to attend.

Our team was in London to witness the presentations as and when they happened, and *EMJ Cardiology* presents a comprehensive summary of the main talking points. Inside our review you will find a host of content from the congress, including the most eye-catching news, as well as a hand-picked compilation of abstract reviews and interviews with our esteemed editorial board regarding the current state of the field. It is our hope that this eJournal will inspire readers of all levels of experience, and our comprehensive coverage should provide an enjoyable and educational read for cardiologists worldwide.

We would like to thank our entire readership throughout the medical community for their continued and growing support. We are proud of our accomplishments this year and are hopeful that 2016 will only serve to build on these successes. Our ultimate aim is the exchange of scientific knowledge for the betterment of medical practice and patient outcomes around the world, and any feedback from our readers is valuable in our progress. On behalf of EMJ, I would like to wish you all the best for the remainder of the year; we look forward to seeing you in 2016!

Spencer Gore

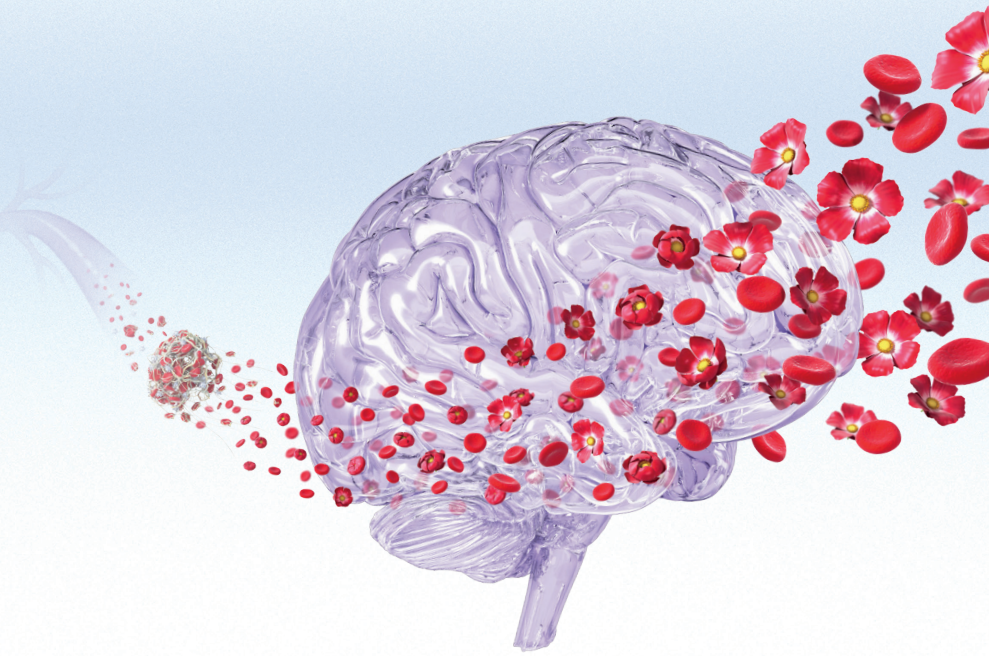
Director, European Medical Journal

European Medical Journal Cardiology is published twice a year.
For subscription details please visit www.emjreviews.com

Think Real World. Think XANTUS.

The First Published, Prospective, International, Observational Study of a NOAC in NVAF patients.[1]

Xarelto® provides confidence in clinical trials, reaffirmed in the real world.[1,2]



Xarelto®
rivaroxaban

Xarelto 15 mg / 20 mg film-coated tablets

(Refer to full SmPC before prescribing.)

▼ **This medicinal product is subject to additional monitoring.**

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

Classification for supply: Medicinal product subject to medical prescription.

Marketing Authorisation Holder: Bayer Pharma AG, D-13342 Berlin, Germany

Further information available from: xarelto.medinfo@bayer.com

Version: EU/4

NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation.

References:

1. Camm J., Amarenco P., Haas S. *et al.* XANTUS: A Real-World, Prospective, Observational Study of Patients Treated with Rivaroxaban for Stroke Prevention in Atrial Fibrillation. *Eur Heart J.* 2015:doi:10.1093/eurheartj/ehv466.
2. Patel M.R., Mahaffey K.W., Garg J. *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883–91.

 G.MKT.GM.XA.09.2015.0715

Foreword

Dr Fernando Alfonso

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

Dear Colleagues,

It is my pleasure to welcome you to this new edition of *European Medical Journal Cardiology*, which focusses on the European Society of Cardiology (ESC) Congress 2015, held in London, UK, on 29th August-2nd September.

The ESC Congress represents the world's largest scientific meeting on cardiovascular diseases (CVDs), and the scientific programme for 2015 was outstanding. The main purpose of the congress is to review the most relevant developments in the diagnosis, management, and treatment of CVDs, with the topics included in the programme covering the full spectrum of cardiovascular medicine. This year the scientific programme devoted special attention to 'Practical Sessions', focussing on case studies representing key issues faced in real-life clinical practice. Likewise, attendees learned how the ESC Clinical Practice Guidelines should be applied in challenging, day-to-day clinical scenarios. Major new ESC Clinical Practice Guidelines were released and discussed at the congress, including guidelines on: ventricular arrhythmias and sudden cardiac death, pulmonary hypertension, non-ST-elevation acute coronary syndromes, pericardial diseases, and infective endocarditis.

"This year the scientific programme devoted special attention to 'Practical Sessions', focussing on case studies representing key issues faced in real-life clinical practice. Likewise, attendees learned how the ESC Clinical Practice Guidelines should be applied in challenging, day-to-day clinical scenarios."

Prof Geneviève Derumeaux, Chairperson of the ESC's Programme Committee, invited cardiologists from all around the globe to the meeting: "We look forward to welcoming you to ESC Congress 2015 where we will bring the fight against CVD to the vibrant city of London." The theme of this year's ESC Congress was 'Environment and the Heart', which aimed to highlight the diverse interactions between CVDs and the environment, and there was also a focus on the patient experience and how patient care can be improved. This meeting also provided a unique opportunity for intense interaction with enthusiastic cardiologists from all over the world, as colleagues and, more importantly, as friends.

This edition of *EMJ Cardiology* will review selected presentations from this unique meeting for those unable to attend, as well as for those looking for a reminder of what they experienced in London.

Yours sincerely,

Fernando Alfonso

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

EMJ EUROPEAN MEDICAL JOURNAL

Available Now
EMJ Cardiology 3.1 2015

Includes a selection of the
latest articles for cardiology.

Featured articles:

Editor's Pick: State of the Art of Aortic Valve Implantation: Indications, Outcomes, and Controversies

- Pablo Salinas et al.

Cost-Effectiveness of a Novel Self-Apposing Stent in ST-Segment Elevation Myocardial Infarction (STEMI) in France

- Lieven Annemans et al.

Left Ventricular Cardiomyopathy in Mitral Valve Prolapse: Fact or Fiction?

- Christina Attenhofer Jost et al.

Functional Mitral Regurgitation: If the Myocardium Is Guilty Do We Also Need to 'Rehabilitate' the Valve?

- Martino Pepe et al.

Transcatheter Options for Treatment of Mitral Regurgitation

- Andreas Schaefer et al.

Circulating Haemoglobin Levels and the Risk of Atherosclerosis in Asian Indian Populations

- Jeetesh V. Patel et al.

The Program on the Surgical Control of the Hyperlipidemias (POSCH) and the Lipid Regulatory Hypothesis

- William E. Feeman, Jr. et al.

How I Treat: Coronary Heart Disease: The Pleiotropic Effects of Statins

- Dr Piergiusto Vitulli et al.

To subscribe to our eJournals, please click here

www.emjreviews.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

ESC ANNUAL CONGRESS 2015

EXCEL CENTRE,
LONDON, UK
29TH AUGUST-2ND SEPTEMBER 2015

Welcome to the *European Medical Journal* review of the European Society of Cardiology Congress 2015

The annual ESC congress arrived in London, UK, for the 2015 edition of this renowned event that remains the largest cardiology meeting in the world. London is a vibrant, metropolitan city immersed in history and was able to offer delegates a background of historic splendours alongside its more modern attractions; it proved to be a fitting host for such a prestigious gathering.

Over 11,300 abstracts were submitted, with more than 4,500 selected for presentation to an audience of over 32,700 healthcare professionals in attendance during the 5 days. Such a wide pool of interest underlines the ever-growing significance of revolutionary discoveries and emerging treatments across the field of cardiology, a trend that will only grow in the years ahead. The ESC President, Prof Fausto Pinto, used his address during the inaugural session to highlight the significant challenges currently facing cardiologists: "Cardiovascular disease is a major cause of death in Europe and worldwide and, despite recent decreases in mortality rates in many countries, it is still responsible for over 4 million deaths in Europe, close to half of all the deaths, at an annual cost to the region's economy estimated at about €200 billion."

Despite the scale of the task ahead, there is no doubt that cardiologists are rising to the challenges facing them, with evidence of the brilliant work currently being undertaken

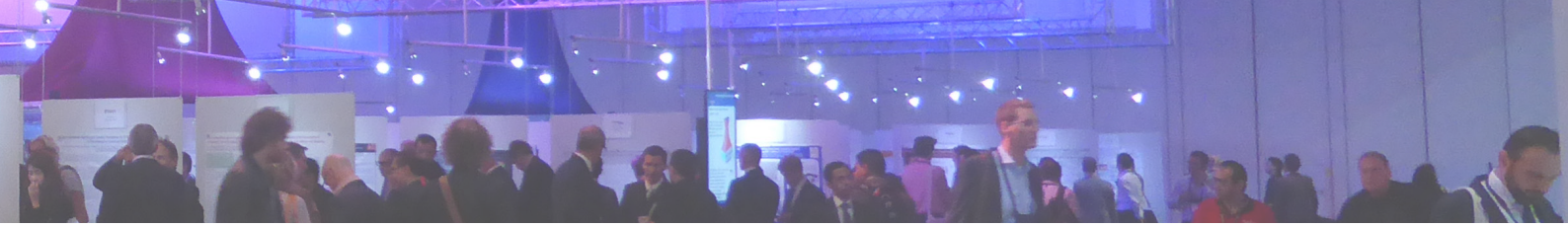
clearly displayed during the awards ceremony that honoured exceptional individuals in the field. The ESC Gold Medal was awarded to three cardiologists recognised for their exceptional contributions to medicine: Prof Keith Fox (UK), Prof Michel Haissaguerre (France), and Prof Richard L. Popp (USA). The Nursing/Allied Professional Investigator Award, which aims to recognise outstanding contributions to the understanding, prevention, and treatment of cardiovascular diseases, was given to Dr Chi-Wen Chen (Taiwan) for the study 'Health care needs in adolescents into young adults with congenital heart disease: A Delphi survey of patients, parents and healthcare providers'. The winner of the Challenging Case Report Award was Dr Enrico Ammirati (Italy) for his description of 'Cardiac tamponade and circulatory shock due to eosinophilic myocarditis unmasking a pulmonary adenocarcinoma'.

The theme of ESC Congress 2015 was 'Environment and the Heart', which aimed to highlight the many various types of relationships connecting the environment and cardiovascular diseases. Many of the presentations on display were in keeping with this concept and made for some truly fascinating insights. One standout case was a study that investigated the association between prolonged television viewing and fatal pulmonary embolism. Other notable highlights included an analysis of the effect of midday naps on blood pressure, and a report describing how the presence of depressive symptoms and extremes of blood pressure can predict the occurrence of harmful vascular events in patients with existing heart disease, diabetes, or stroke.

There were also plenty of discoveries presented at the congress that should allow for the development of new treatment options in those with serious cardiovascular conditions, such as a study suggesting that immune cell-mediated thrombotic processes could comprise a realistic target for the treatment of stent thrombosis, following the discovery that the recruitment of leukocytes is a hallmark of the condition.

There was much on offer for cardiology professionals at ESC Congress 2015, and hopefully the results on show will serve to bolster the future care of patients with cardiovascular ailments. Next year's congress will be held in Rome, Italy, and hopes are high that the developments displayed in London will be further built upon in one of Europe's most historic cities.

"Cardiovascular disease is a major cause of death in Europe and worldwide and, despite recent decreases in mortality rates in many countries, it is still responsible for over 4 million deaths in Europe, close to half of all the deaths, at an annual cost to the region's economy estimated at about €200 billion."



HIGHLIGHTS

Positive Impact of Bystander CPR in Out-of-Hospital Cardiac Arrest Survivors

CARDIOPULMONARY resuscitation (CPR) from a bystander is associated with a 30% lower risk of nursing home admission or brain damage in those who survive an out-of-hospital cardiac arrest, according to new research presented at the ESC Congress by Dr Kristian Kragholm, Department of Anesthesiology, Cardiovascular Research Centre, Aalborg University Hospital, Aalborg, Denmark.

The study reported that there were 32,883 out-of-hospital cardiac arrests in Denmark between 2001 and 2011, with a total of 2,387 adults without prior brain damage and not living in a nursing home surviving more than 30 days. The association between the occurrence of death or a composite endpoint of nursing home admission or brain damage within 1 year of the cardiac arrest and a range of patient factors was evaluated in the survivors.

"The current study shows that the benefits of bystander CPR seem to go beyond survival and also impact on the physical and mental health of survivors."

Of the 2,387 survivors, 7% died and 11% were admitted to a nursing home or diagnosed with brain damage within 1 year of the cardiac arrest. In multivariate analyses, bystander CPR was found to be the only patient factor significantly associated with a lower risk of nursing home admission or brain damage (hazard ratio: 0.67, 95% confidence interval: 0.51–0.89; p=0.005).

"The current study shows that the benefits of bystander CPR seem to go beyond survival and also impact on the physical and mental health of survivors. This novel and important finding demonstrates how vital it is that CPR is promptly initiated to increase not only chances of survival but also reduce brain damage and nursing home admission in survivors. Initiatives that improve bystander recognition of arrest and willingness to initiate CPR hold the potential to improve the chances of survival with intact function and enable survivors to carry on with their lives as before the arrest," stated Dr Kragholm in a press release dated 30th August.

Ongoing CPR Aids Better-Than-Expected Survival in Refractory Cardiac Arrest

SURVIVAL and recovery rates in cases of refractory cardiac arrest brought to hospital with ongoing cardiopulmonary resuscitation (CPR) and treated without the use of extracorporeal life systems have been shown to be higher than expected, according to

new data presented at ESC Congress by Dr Helle Søholm, a cardiologist from Copenhagen University Hospital Righospitalet, Copenhagen, Denmark. The use of CPR in cases of out-of-hospital cardiac arrest may either be terminated by pre-hospital physicians outside the hospital or continued whilst transporting patients to hospital. Currently, only 10% of the individuals who suffer an out-of-hospital cardiac arrest survive.

"Our results indicate that maybe resuscitation attempts should be extended as the prognosis for patients with refractory cardiac arrest is not as poor as we previously thought."

The Danish study included 3,992 individuals who all experienced an out-of-hospital cardiac arrest in a large urban area between 2002 and 2011, and who were treated by physician-based emergency medical services. Of these 3,992 cases, 1,285 (32%) were successfully resuscitated outside of hospital and 108 (3%) had refractory cardiac arrest and were brought to the hospital with ongoing CPR and treated conservatively without the support of extracorporeal life systems. Approximately 50% of the patients brought to the hospital with ongoing CPR were successfully resuscitated and admitted to a hospital ward.

The rate of survival in patients with refractory cardiac arrest who received ongoing CPR was 20%, compared with 42% in those who were resuscitated before arrival at the hospital ($p<0.001$). Of the survivors with high functional status (86% of those who received ongoing CPR and 84% of those successfully resuscitated prior to arrival at hospital) and subsequently discharged from hospital, approximately 90% displayed sufficient function for carrying out independent daily activities.

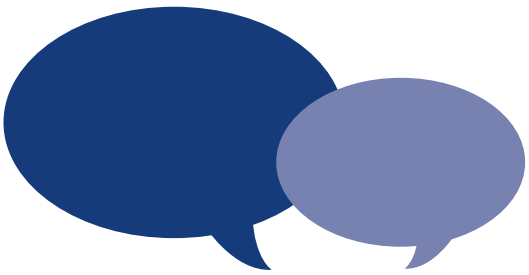
"Our results indicate that maybe resuscitation attempts should be extended as the prognosis for patients with refractory cardiac arrest is not as poor as we previously thought," stated Dr Søholm in a press release dated 29th August. The researchers therefore suggest that, due to the survival and recovery rates they observed, patients with refractory cardiac arrest should be brought to the hospital with ongoing CPR.

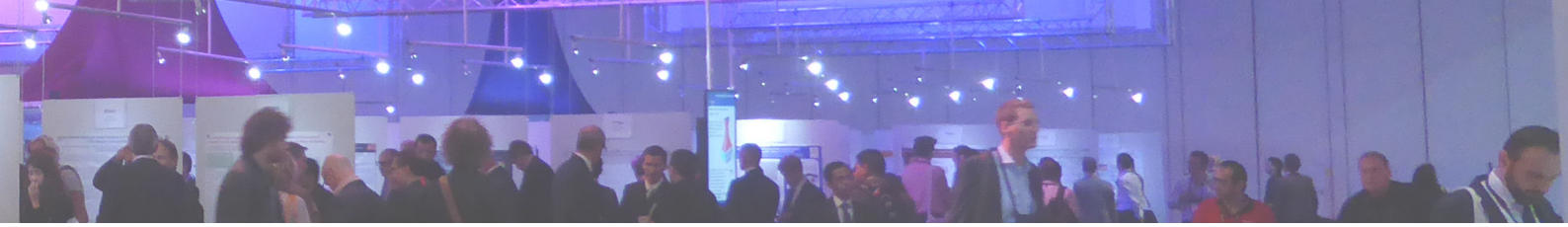
Treating Left Atrial Appendage May Diminish Long-Standing Persistent AF

ADDITIONAL electrical isolation of an area called the left atrial appendage (LAA) may improve freedom from atrial fibrillation (AF) without increasing complications in patients with long-standing AF, according to results from the BELIEF study presented at ESC Congress.

Participants

32,000+





"Empirical left atrial appendage isolation, along with the standard approach of pulmonary vein isolation (PVI) and ablation of extra-pulmonary triggers, is superior to the standard approach alone in enhancing the long-term success rate of catheter ablation," said Dr Luigi Di Biase, Director of Arrhythmia Services and Associate Professor, Montefiore-Albert Einstein Center for Heart & Vascular Care, New York City, New York, USA, and Senior Researcher, Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, Texas, USA in a press release dated 30th August.

The trial included 173 patients with 'long-standing persistent' AF, defined as AF extending beyond 1 year. Patients were randomly assigned to undergo standard treatment only (PVI and ablation of extra-pulmonary triggers, n=88) or standard treatment plus addition of LAA ablation (n=85). For the primary endpoint of recurrence of AF at 1 year, 28% of standard treatment patients were recurrence-free compared with 56% of patients who had the additional LAA ablation (hazard ratio [HR] 1.92; p=0.001). For patients who were not recurrence-free in either group, LAA isolation was conducted in a second operation.

At 24 months, after an average of 1.3 procedures, the cumulative success rate was 76% in the LAA ablation group and 56% in the standard treatment group (HR 2.24; p=0.003). There was no difference in complication rates between groups at follow-up, including transient ischaemic attacks or strokes, although the mean radiofrequency time was longer in the LAA group (93 versus 77 minutes; p<0.001). In multivariate analysis, no LAA ablation was associated with significantly higher recurrence of AF (HR 2.2; p=0.004).

ICD Monitoring Identifies Gene Associated with Sudden Cardiac Death

MONITORING of data from the use of implantable cardioverter-defibrillators (ICDs) has identified a gene polymorphism predictive of ventricular tachyarrhythmias and sudden cardiac death (SCD) in the general population, according to a study presented at ESC Congress. SCD is one of the leading causes of death in the Western world and the use of ICDs is indicated for patients who have either survived a life threatening cardiac arrhythmia or are at high risk of SCD.

"We believe this is the first time a gene variant has been identified by monitoring ventricular tachyarrhythmia in patients with ICDs and then confirmed in a wider population."

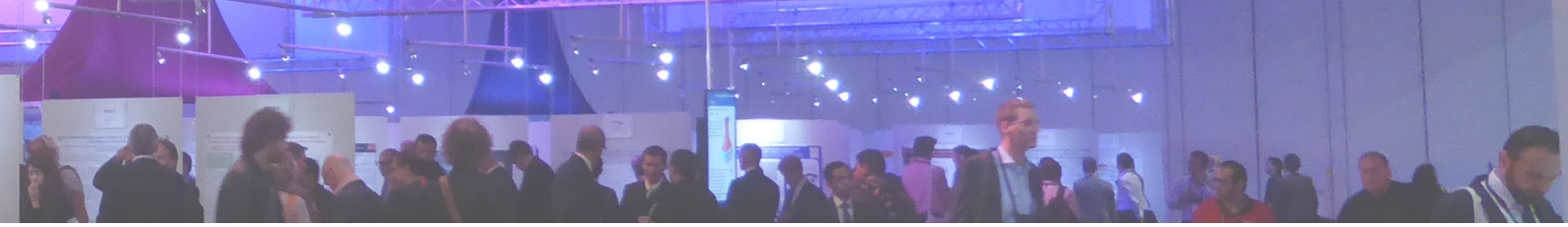
The new research, which utilised data from participants in the DISCOVERY trial and the Oregon Sudden Unexpected Death Study (Oregon-SUDS), revealed that a specific single-nucleotide polymorphism (SNP) in the *GNAS* gene is predictive of ventricular tachyarrhythmias and SCD.

The study authors collected cardiac arrhythmia data from 1,145 ICD patients included in the DISCOVERY trial to identify, after adjustment for non-genetic covariates, genes associated with increased risk of potentially life-threatening ventricular tachyarrhythmias. They identified and genotyped seven SNPs in three genes encoding G-protein subunits. The association between these polymorphisms and the occurrence of SCD were then evaluated in 1,335 patients included in the Oregon-SUDS trial. The researchers found that one SNP in the *GNAS* gene, *GNAS* c.393C>T, was significantly associated with SCD in both additive (odds ratio [OR]: 1.2, 95% confidence interval [CI]: 1.0–1.4; p=0.039) and recessive (OR: 1.5, 95% CI: 1.1–2.1; p=0.01) genetic models.

"We believe this is the first time a gene variant has been identified by monitoring ventricular tachyarrhythmia in patients with ICDs and then confirmed in a wider population. The findings may help to identify patients at increased risk of SCD," said principal investigator Prof Heiner Wieneke, Chief Physician, Department of Cardiology, Contilia Heart and Vessel Centre, St. Marien-Hospital Mülheim an der Ruhr, Mülheim an der Ruhr, Germany, in a press release dated 31st August.

Leadless Cardiac Pacemaker Results Show Promise

A LEADLESS cardiac pacemaker that received a CE mark in 2013 has demonstrated "good safety and reliable function" throughout the initial 6 months of follow-up in the prospective, non-randomised, pre-marketing LEADLESS II trial, according to results presented at ESC Congress.



The LEADLESS II trial included 526 patients with a mean age of 75.8 years and from 56 sites across three countries. All patients had indications for permanent, single-chamber, ventricular pacing and were implanted non-surgically with an active-fixation, rate-adaptive pacemaker using a steerable delivery catheter. The primary effectiveness endpoint was defined as clinically acceptable pacing capture thresholds (≤2.0 V at 0.4 ms) and sensing (R wave ≥5.0 mV or ≥ implant value) at 6 months, with the primary safety endpoint being freedom from serious adverse device effects (SADEs) over the same period.

The primary effectiveness and safety endpoints were met in 90.0% and 93.3% of cases, respectively, among the 300 patients included in the intention-to-treat primary analysis, with effectiveness met in 93.4% of successfully implanted patients. The rate of SADEs over the 6-month period was 6.7%, including cardiac perforation (1.3%), device dislodgement with successful percutaneous retrieval (1.7%), and capture threshold elevation requiring percutaneous retrieval and placement of a new leadless pacemaker (1.3%). There were no device-related infections or chronic electrical failure.

The new findings suggest that the device is effective and well-tolerated, and may serve as a viable alternative to conventional transvenous pacemakers in patients with indications for permanent pacing. "Leadless cardiac pacemakers have the potential to overcome many of the complications of conventional transvenous pacemakers," said Dr Vivek Reddy, Icahn School of Medicine at Mount Sinai, New York City, New York, USA, in a press release dated 30th August. "Transvenous leads are considered the Achilles' heel of conventional pacemakers because they are particularly susceptible to complications."

Leukocyte Recruitment is Key Feature of Stent Thrombosis

IMMUNE cell-mediated thrombotic processes could constitute an achievable target for novel therapies in the prevention of stent thrombosis (ST), according to data from the PRESTIGE study presented at ESC Congress.

"Our results suggest that immune cell-mediated thrombotic processes may be a realistic target for novel therapies to prevent ST."

Spotlight sessions 26

The PREvention of late Stent Thrombosis by an Interdisciplinary Global European effort (PRESTIGE) consortium was established to investigate the mechanisms triggering ST across Europe. The substudy group comprised patients with ST and undergoing thrombus aspiration at nine centres in Europe during 2010–2014. Overall, 253 thrombus specimens were analysed. Of these, 79 (31.2%) were from patients presenting with early ST and 174 (68.8%) from late ST, while 79 (31.2%) were from bare metal stents, 166 (65.6%) from drug-eluting stents, and 8 (3.2%) from unknown stents.

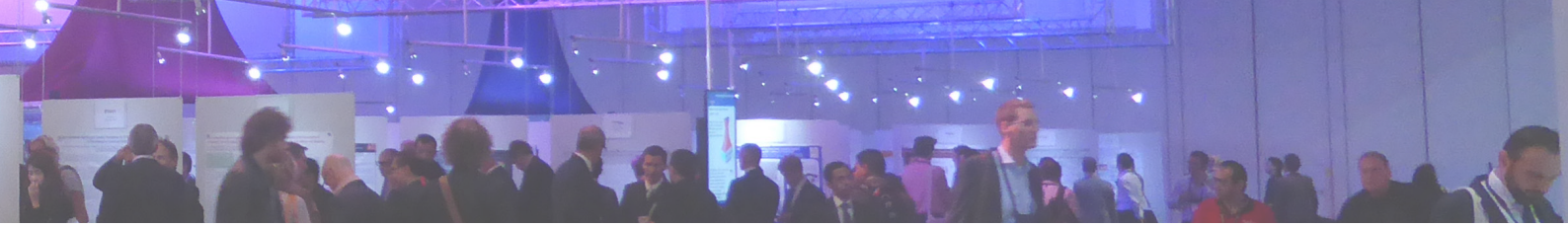
The investigators discovered that the thrombus specimens had heterogeneous morphology, with fibrin/fibrinogen fragments and platelet-rich thrombus being most common. Leukocyte infiltrations were hallmarks of both early and late ST, with neutrophils constituting the most abundant subset.

Neutrophil extracellular traps (NETs), which are prothrombotic extracellular DNA released by neutrophils, were found in 23% of samples. Eosinophils were present in all stent types, with higher numbers in patients with late ST in sirolimus-eluting and everolimus-eluting stents. "The presence of NETs supports their pathophysiological relevance in ST, while eosinophil recruitment suggests an allergic component to the process of ST," said principal investigator Prof Steffen Massberg, director of the Department of Cardiology, Ludwig-Maximilians University (LMU), Munich, Germany, in a press release dated 30th August.

He concluded: "Our results suggest that immune cell-mediated thrombotic processes may be a realistic target for novel therapies to prevent ST. Inhibition of triggers, such as extracellular nucleic acids activating the contact phase, may not only result in efficient anticoagulation in the setting of ST but might also yield less therapy-associated bleeding. Future studies should evaluate whether inhibition of immune cell-driven thrombotic pathways are effective and safe in clinical practice."

Depression and Extremes of Blood Pressure Increase Risk of Vascular Events in Heart Disease Patients

EXTREMES of blood pressure and depressive symptoms are predictive of a high risk of harmful vascular events in patients with existing heart disease, diabetes, or stroke, according to research presented at ESC Congress by Dr Bhautesh Jani, Clinical Academic Fellow, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK.



"Our findings suggest that focussing resources on monitoring blood pressure and providing treatment in patients with associated depressive symptoms could improve health outcomes by reducing the risk of further strokes or heart attacks, having heart failure, or dying from heart disease."

Over a follow-up period of 4 years, the study from Scotland investigated the occurrence of further stroke, heart attack, heart failure, or death due to heart disease in 35,537 community-dwelling patients with existing heart disease, diabetes, or stroke. A total of 3,939 patients (11%) experienced at least one major harmful event during the follow-up period, with depressive symptoms displaying a significant interaction with systolic blood pressure (SBP) in predicting an event (p=0.03). Compared with those with normal blood pressure and no depressive symptoms (and after adjustment for a range of other factors known to influence the risk of vascular events), patients categorised as having high blood pressure and depressive symptoms had an 83% higher risk of a major harmful event at 4 years (hazard ratio [HR]: 1.83, 95% confidence interval [CI]: 1.46–2.30; p<0.001) and those categorised with low blood pressure and depressive symptoms had a 36% higher risk (HR: 1.36, 95% CI: 1.15–1.62; p<0.001).

"Our findings suggest that focussing resources on monitoring blood pressure and providing treatment in patients with associated depressive symptoms could improve health outcomes by reducing the risk of further strokes or heart attacks, having heart failure, or dying from heart disease. They also indicate that patients with high or low blood pressure might benefit from screening and treatment for depression. To date there are no studies showing that treatment of depression changes or improves cardiovascular outcomes and more research is needed in this area. Studies are also needed to further understand how blood pressure and depression interact," concluded Dr Jani in a press release dated 29th August.

Colder Weather Linked to Greater Risk of STEMI

COLD weather is associated with an increased risk of serious heart attack, according to research presented at ESC Congress by Dr Shuangbo Liu, Adult Coronary Resident at the University of Manitoba, Winnipeg, Manitoba, Canada. The 6-year study found that each 10°C drop in temperature was associated with a 7% increased risk of ST-elevation myocardial infarction (STEMI).

"Our study highlights the potential influence of the environment on occurrence of STEMI."

Winnipeg is famous for its freezing winters and hot and dry summers, making it ideal for studying the effect of temperature and the environment on cardiac events. The researchers from the University of Manitoba, led by supervisor Dr James Tam, conducted a retrospective review of all STEMIs in Winnipeg over the last 6 years.

Throughout the 6-year period, there were 1,817 STEMIs. The daily temperature high was the strongest predictor of STEMI. On days with a daily high <0°C, STEMI events rates were 0.94/day, compared with 0.78/day when the daily high was >0°C. Despite yearly fluctuation, the average STEMI rate across the study period had a statistically significant linear trend across temperature ($p<0.001$). Daily high in the preceding 1 or 2 days was also predictive ($p<0.001$).

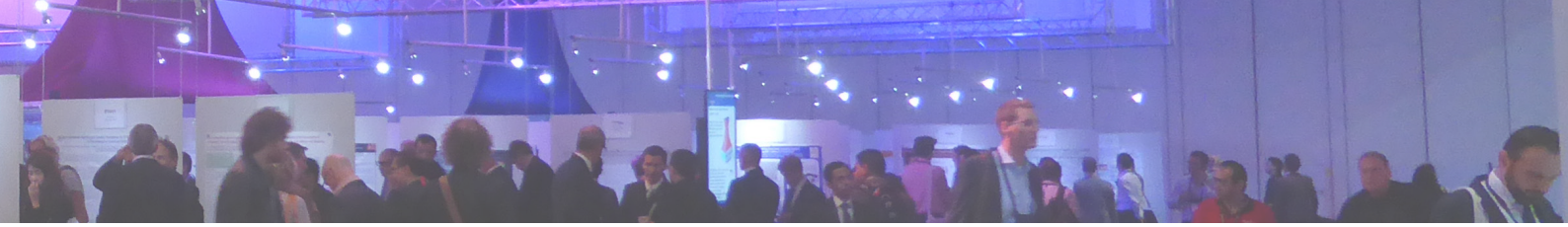
Warmer temperature ranges were not associated with higher STEMI rates. However, with every drop of 10°C in the daily high, the risk of STEMI increased by 7%. Snowfall did not demonstrate an independent association after adjusting for temperature.

In an ESC press release dated 30th August, Dr Liu reported: "Our study highlights the potential influence of the environment on occurrence of STEMI. Daily temperature can predict STEMI risk 1 or 2 days before it happens. These findings create an opportunity for future research studies to examine whether there are treatment strategies that can temper the effects of climate on the risk of heart attacks."

Environmental Factors Influence Heart Attack Outcomes

POST-HEART ATTACK outcomes can be influenced by pollution and the weather, according to new research presented at ESC Congress. The study from Poland examined the relationship between a number of environmental factors and the severity of clinical status and short-term prognosis in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS), including NSTE myocardial infarction (NSTEMI) and unstable angina.

"Weather changes like rain or heat affect our daily activity and even our productivity at work," said Ms Aneta Cislak, Research Fellow, Silesian Centre for Heart Diseases, Medical University of Silesia, Zabrze, Poland, in a press release dated 29th August. "Since this influence is so noticeable we were interested to see if weather has any connection with cardiovascular (CV) diseases including acute coronary



syndromes. Moreover, air pollution affects our health, especially in highly industrialised areas. We performed our research in Silesia, the most urbanised and industrialised region in Poland."

"Our study suggests that environmental factors may affect the severity of clinical status and short-term prognosis in patients with NSTE ACS."

A total of 2,388 patients admitted to hospital for NSTE ACS between 2006 and 2012 were enrolled in the study, and data on a number of environmental influences were obtained on the day of admission. These factors included the atmospheric pressure, air temperature, wind speed, humidity, and total solar radiation intensity; the concentrations of the most common air pollutants were also recorded. These data were then correlated with the clinical status of the patients. The researchers found that those with a high risk of myocardial infarction and bleeding, and low left ventricular ejection fraction were admitted for NSTE ACS on warmer, sunnier, drier, and windier days with higher carbon monoxide and nitric oxides.

"It should be remembered that not only do humans influence the environment, but the environment also influences humans. Our study suggests that environmental factors may affect the severity of clinical status and short-term prognosis in patients with NSTE ACS. We are now investigating the impact of meteorology and air pollution on 600,000 patients in the Silesian CV Database who were hospitalised with CV diseases in the last 10 years in Silesia," concluded Ms Cislak.

Coffee Drinking Linked to Increased Cardiovascular Risk in Young Adults with Mild Hypertension

COFFEE drinking is associated with increased risk of cardiovascular (CV) events in young adults (18–45) with mild hypertension, according to research presented at ESC Congress by Dr Lucio Mos, a cardiologist at Hospital of San Daniele del Friuli, Udine, Italy. The 12-year study discovered that heavy coffee drinkers had a 4-fold increased risk while moderate drinkers tripled their risk. Future prediabetes attenuated the associations indicating that the effect of coffee on CV events could be mediated by its long-term effect on blood pressure and glucose metabolism.

The study recruited 1,201 non-diabetic patients aged 18–45 years from the prospective HARVEST study who had untreated Stage 1 hypertension. Coffee consumption was categorised by the number of caffeine-containing cups per day: non-drinkers (0 [26.3% of participants]), moderate (1–3 [62.7%]), and heavy drinkers (4 or more [10.0%]).

"These patients should be aware that coffee consumption may increase their risk of developing more severe hypertension and diabetes in later life and should keep consumption to a minimum."

There was a linear relationship between coffee use and risk of hypertension needing treatment, which reached statistical significance for heavy drinkers. In addition, the study showed a 100% (30–210%) increased risk of prediabetes in the heavy coffee drinkers.

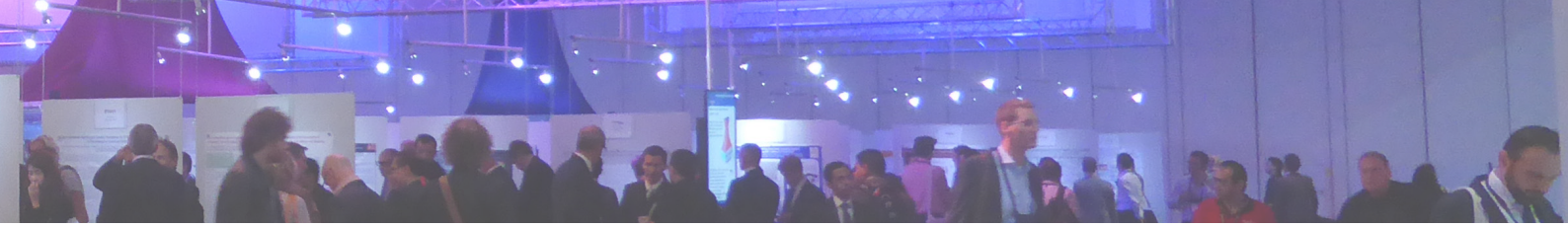
However, the risk of prediabetes related to coffee consumption varied according to the CYP1A2 genotype, which determines whether individuals are fast or slow caffeine metabolisers. The risk of prediabetes was significantly increased only in slow caffeine metabolisers, with a hazard ratio of 2.78 (95% confidence interval 1.32–5.88, p=0.0076) for heavy coffee drinkers.

Throughout the 12.5 year follow-up there were 60 CV events, 80% of which were heart attacks. In multivariate analyses including other lifestyle factors such as age and sex, moderate and heavy coffee drinkers were independent predictors of CV events, with hazard ratios of 4.3 (1.3–13.9) for heavy coffee drinkers and 2.9 (1.04–8.2) for moderate drinkers.

In a press release dated 29th August, Dr Mos concluded: "Our study shows that coffee use is linearly associated with increased risk of CV events in young adults with mild hypertension. This relationship seems to be at least partially mediated by the long-term effect of coffee on blood pressure and glucose metabolism. These patients should be aware that coffee consumption may increase their risk of developing more severe hypertension and diabetes in later life and should keep consumption to a minimum."

Too Much Television May Be Fatal

PROLONGED television viewing is associated with a greater risk of fatal pulmonary embolism (PE) according to the results of a Japanese study presented at ESC Congress 2015. Lengthy periods of time spent sitting have previously been associated with increased risk of PE, such as in the 'economy class syndrome' (ECS) associated with long-haul flights, but this was the first study to investigate



the association between television viewing habits and risk of fatal PE.

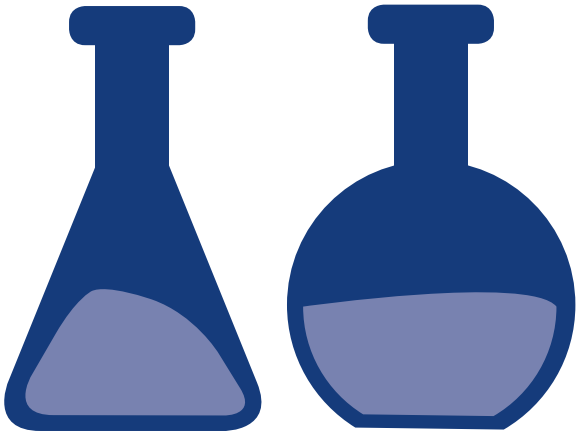
The study included 86,024 participants aged 40–79 years who were followed-up for a median of 18.4 years and who were categorised into one of three groups based of their television viewing habits: <2.5 hours/day, 2.5–4.9 hours/day, or ≥5 hours/day. The risk of death from PE was calculated for each of the three groups after adjusting for baseline age, gender, history of hypertension, history of diabetes, smoking status, drinking status, body mass index, sport and walking habits, and menopausal status. The risk of fatal PE in those who spent ≥5 hours/day watching television was shown to be twice that in those who watched <2.5 hours/day (hazard ratio [HR]: 2.38). The increase in risk relative to individuals who watch <2.5 hours/day was even more prominent in participants <60 years of age: the risk trebled in those who watched 2.5–4.9 hours/day (HR: 3.14) and increased 6-fold in those who watched ≥5 hours/day (HR: 6.49).

"We showed that prolonged television viewing may be a risky behaviour for death from PE."

"We showed that prolonged television viewing may be a risky behaviour for death from PE," stated Mr Toru Shirakawa, a public health research fellow in the Department of Social Medicine at Osaka University, Osaka, Japan, in a press release dated 29th August. "Leg immobility during television viewing may in part explain the finding. To prevent the occurrence of PE, we recommend the same preventive behaviour used against ECS.

Late-Breaking Science submissions

232



That is, take a break, stand up, and walk around during the television viewing. Drinking water for preventing dehydration is also important."

Midday Naps Associated with Lower Blood Pressure

MIDDAY naps are associated with reduced blood pressure (BP) levels and prescription of fewer antihypertensive medications, according to results from a study presented at ESC Congress by Dr Manolis Kallistratos, a cardiologist at Asklepieion Voula General Hospital, Athens, Greece.

The study aimed to assess the effect of midday napping on BP levels in hypertensive patients. The study

included 386 middle-aged patients with arterial hypertension.

Having accounted for other factors that could influence BP, the researchers found that midday sleepers had 5% lower average 24 hour ambulatory systolic BP (6 mmHg) compared with patients who did not sleep at midday. The nappers' average systolic BP readings were 4% lower whilst awake (5 mmHg) and 6% lower while they slept at night (7 mmHg) than non-midday nappers.

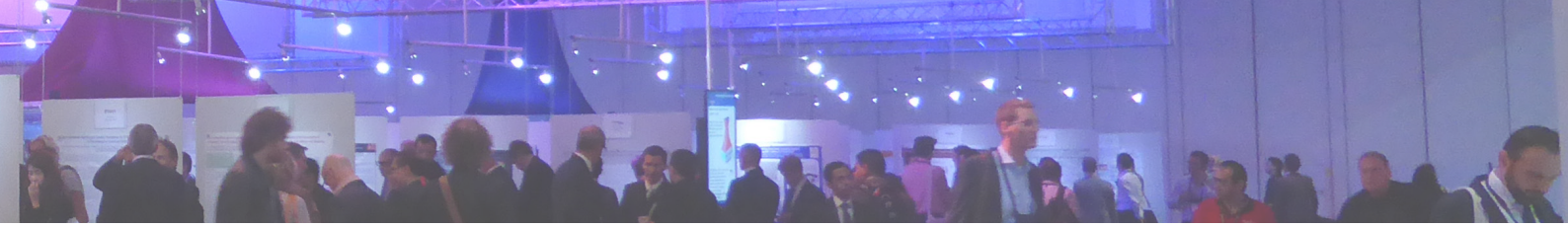
"Although the mean BP decrease seems low, it has to be mentioned that reductions as small as 2 mmHg in systolic BP can reduce the risk of cardiovascular events by up to 10%," said Dr Kallistratos in a press release published on 29th August. The researchers also found that pulse wave velocity levels in midday sleepers were 11% lower and left atrium diameter was 5% smaller.

Abstracts accepted

4,533

The length of midday sleep was linked to the burden of arterial hypertension. Patients who slept for 60 minutes at midday had 4 mmHg lower average 24-hour systolic BP readings and a 2% higher dipping status compared with patients who did not sleep at midday. Dippers had an average of 17 minutes' additional sleep than non-dippers.

Dr Kallistratos concluded: "We found that midday sleep is associated with lower 24-hour BP, an enhanced fall of BP in night, and less damage to the arteries and the heart. The longer the midday sleep, the lower the systolic BP levels and probably fewer drugs needed to lower BP."



Young Adults Living in Polluted Cities May Be at Increased Risk of Cardiovascular Disease

POLLUTED cities may increase young adults' risk of future cardiovascular disease (CVD), according to new research describing significantly elevated levels of inflammatory markers in the blood of young citizens.

The Polish study, which was presented at ESC Congress in London by Dr Krzysztof Bryniarski from the Jagiellonian University Medical College, Krakow, Poland, compared the levels of a range of inflammatory markers, including C-reactive protein (CRP), high-sensitivity CRP (hsCRP), homocysteine, and fibrinogen, in the blood of 826 randomly selected young adults living in the cities of Lublin (n=382) or Krakow (n=444). The mean age of the study participants was 18 years (range 16–22) and all had lived in their home city since birth; all were from similar types of schools and social backgrounds.

"This is the first study to establish a link between residence in a city with a very high air pollution and cardiovascular risk in young adults, in whom cardiovascular risk is typically not yet considered and who have not had contact with health services before."

The average 10-year air pollution levels in Krakow were nearly double those observed in Lublin and the levels of CRP, hsCRP, homocysteine, and fibrinogen were all significantly higher in the blood of Krakow residents compared with those from Lublin ($p<0.0001$). The highest levels of these markers were found in overweight participants (body mass index [BMI]: 25–37 kg/m^2) living in Krakow. No significant differences in blood pressure, smoking, physical activity levels, BMI, age, or other confounding factors were observed when comparing the characteristics of participants from the two cities.

"We have shown that living in a highly polluted city can have an impact on cardiovascular risk markers even at an early age. This may occur through chronic low grade inflammation. This is the first study to establish a link between residence in a city with a very high air pollution and cardiovascular risk in young adults, in whom cardiovascular risk is typically not yet considered and who have not had contact with health services before," concluded Dr Bryniarski.

CPR For At Least 35 Minutes Benefits Out-of-Hospital Cardiac Arrest

EMERGENCY medical services (EMS) should provide out-of-hospital cardiac arrests with cardiopulmonary resuscitation (CPR) for at least 35 minutes (if resuscitation is not achieved before this point) but no longer than 53 minutes, according to new research reported at ESC Congress by Dr Yoshikazu Goto, Associate Professor and Director of the Department of Emergency and Critical Care Medicine, Kanazawa University Hospital, Kanazawa, Japan.

One of the greatest predicaments facing EMS personnel and clinicians is deciding when to stop resuscitation efforts in cardiac arrest patients whilst not 'giving up'

on patients prematurely; there are concerns that lengthy resuscitation efforts could be futile and may impede provision of vital treatment to other emergency cases. The aim of the study was to ascertain for how long CPR should be provided so that both maximum survival and favourable neurological outcomes are achieved.

"We hope our findings give EMS personnel and clinicians the confidence that if they stop CPR after 35 minutes they have done everything they can do for a patient."

The Japanese study included 17,238 out-of-hospital cardiac arrests who received CPR by EMS personnel in 2011 and 2012. It was found that, whilst the probability of survival declined with each minute of CPR provided, 99.1% of all survivors and 99.2% of all survivors with favourable neurological outcomes achieved return of spontaneous circulation within 35 minutes of EMS-initiated CPR. However, CPR showed little benefit beyond this time point and no patient who received CPR for ≥53 minutes survived 1 month after the cardiac arrest.

"We hope our findings give EMS personnel and clinicians the confidence that if they stop CPR after 35 minutes they have done everything they can do for a patient. This should help them know when it is appropriate to move on to the next medical emergency," Dr Goto commented.

STEMI Risk Increased By Air Pollution Levels Within European limits

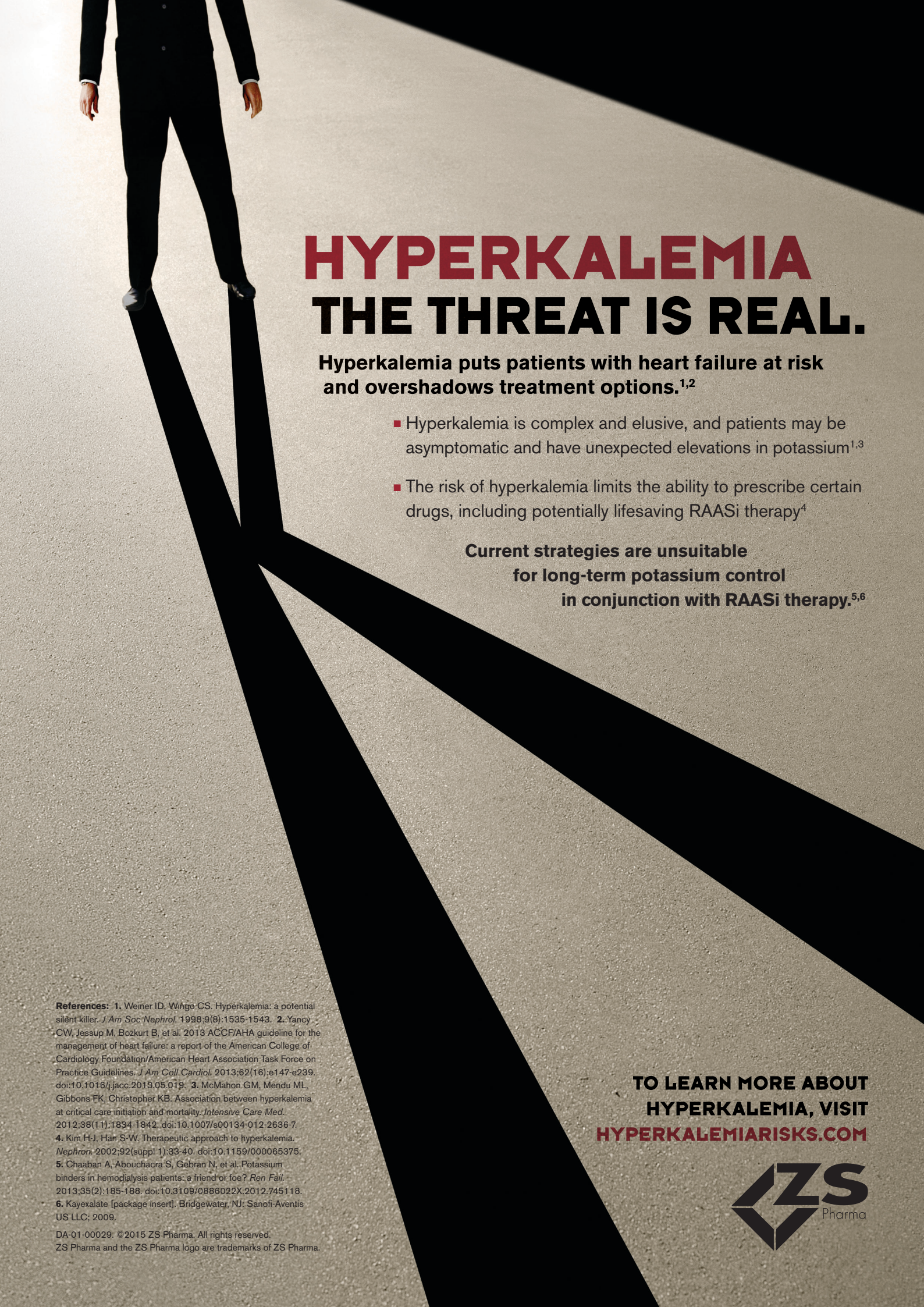
AMBIENT air pollution levels within the recommended range of the European air quality standard are associated with an increased risk of ST-segment elevation myocardial infarction (STEMI), according to new research presented at ESC Congress by Dr Jean-Francois Argacha, University Hospital Brussels, Brussels, Belgium.

Ambient air pollution is a mixture of particulate matter (PM) and gaseous pollutants, such as NO_2 and O_3. Fine particle pollution ($PM_{2.5}$) has the ability to reach the lower respiratory tract and carry high levels of toxic compounds into the body. The Belgian study analysed data describing the levels of air pollution from 2009–2013 in order to provide a real-time evaluation of air pollution exposure, adjusted for population density, in each region of the country. These data were then cross-referenced with data reporting the incidence of STEMI within the same timeframe in order to establish if there may be any relationship.

"The association between STEMI and air pollution was observed within 1 day of exposure."

There were 11,428 hospitalisations for STEMI during the study period. The researchers found that each 10 μg/m^3 increase in ambient $PM_{2.5}$ concentration was associated with a 2.8% increase in risk of STEMI, while each 10 μg/m^3 rise in NO_2 was associated with a 5.1% greater risk.

"The association between STEMI and air pollution was observed within 1 day of exposure," said Dr Argacha. "This was despite the fact that concentrations of air pollutants were within the European air quality standard. It's possible that only men were affected because of the under-representation of women in our study population (less than 25%). Nevertheless, previous studies have demonstrated that blood pressure, arterial stiffness, and heart rate variability abnormalities secondary to air pollution exposure are more pronounced in men. Sex differences in obesity and blood inflammation may worsen air pollutant effects, but this hypothesis requires further investigation."



HYPERKALEMIA
THE THREAT IS REAL.

Hyperkalemia puts patients with heart failure at risk and overshadows treatment options.[1,2]

- Hyperkalemia is complex and elusive, and patients may be asymptomatic and have unexpected elevations in potassium[1,3]
- The risk of hyperkalemia limits the ability to prescribe certain drugs, including potentially lifesaving RAASi therapy[4]

Current strategies are unsuitable for long-term potassium control in conjunction with RAASi therapy.[5,6]

References: **1.** Weiner ID, Wingo CS. Hyperkalemia: a potential silent killer. *J Am Soc Nephrol.* 1998;9(8):1535-1543. **2.** Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62(16):e147-e239. doi:10.1016/j.jacc.2013.05.019. **3.** McMahon GM, Mendu ML, Gibbons FK, Christopher KB. Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Med.* 2012;38(11):1834-1842. doi:10.1007/s00134-012-2636-7. **4.** Kim H-J, Han S-W. Therapeutic approach to hyperkalemia. *Nephron.* 2002;92(suppl 1):33-40. doi:10.1159/000065375. **5.** Chaaban A, Abouchacra S, Gebran N, et al. Potassium binders in hemodialysis patients: a friend or foe? *Ren Fail.* 2013;35(2):185-188. doi:10.3109/0886022X.2012.745118. **6.** Kayexalate [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2009.

TO LEARN MORE ABOUT HYPERKALEMIA, VISIT HYPERKALEMIARISKS.COM

ZS Pharma

Carl J. Pepine

Professor of Medicine, Division of Cardiovascular Medicine, University of Florida, Gainesville, Florida, USA.

Q: What were the principle factors that influenced your original decision to become a cardiologist?

A: I have always enjoyed science in general, in particular anatomy and physiology. When I became a physician, I was especially awed by cardiovascular (CV) physiology as well as CV pharmacology. I also admired a number of people who were in academic medicine and they were cardiologists. These factors had a major influence on my career choice.

Q: How far has our understanding of the pathophysiology of ischaemic heart disease (IHD) developed since your career began?

A: Although IHD continues to be a major worldwide threat to health and wellbeing, we have made major advances since my career started. Tremendous progress in our understanding of IHD has contributed to an important decline in CV mortality among men and more recently women in the USA and Western Europe. But these reductions are not uniform across all regions of the USA and Europe, and are far from optimal. Nevertheless, a major component of this benefit relates to secondary prevention and better understanding of an acute plaque disruption with thrombotic occlusion. This knowledge led to a reduction in mortality from acute myocardial infarction (MI). The reduction in mortality is driven by prompt restoration of coronary blood flow, mostly using percutaneous coronary intervention (PCI) plus antiplatelet agents. But population ageing in addition to epidemics of inactivity, obesity, and diabetes now yield increasing numbers of people with chronic manifestations such as stable angina. We are also seeing more plaque erosion versus plaque rupture and non-obstructive coronary artery disease (CAD).

In light of the above, considerable evidence has revised older concepts of a categorical definition of CAD as presence or absence of flow-limiting stenosis. Revised concepts now recognise CAD as a continuous spectrum of disease that is not simply limited to obstructive coronary plaque. Within this spectrum, patients may present with various syndromes ranging from totally asymptomatic to highly symptomatic with or without signs of ischaemia (i.e. insufficient myocardial blood flow). The latter may be due to multiple mechanisms, including epicardial coronary artery and/or microvascular dysfunction, spasm, and enhanced coagulation, operating alone or more often in combination.

Q: What are the most up-to-date treatments currently available for IHD? What more could be done to improve the care of patients with this condition before and after treatment?

A: Management changes include improved recognition and understanding of the demographics and consequences of various IHD syndromes. The estimated prevalence of stable angina in Western countries is ~5% and is increasing. It is therefore negatively impacting quality of life and ability to work with considerable economic consequences.

A keystone in management since the mid-1980s has been statins, which have improved outcomes in patients with acute and chronic IHD, as well as in those at high risk for IHD/CAD.

"In past years, management of patients with suspected or known stable CAD focussed on coronary angiography to identify obstructive lesions and provide direction for revascularisation."

In past years, management of patients with suspected or known stable CAD focussed on coronary angiography to identify obstructive lesions and provide direction for revascularisation. In the absence of obstructive lesions, patients were told that their symptoms were not cardiac in origin and were dismissed from specialty care. A milestone in the management of women, and probably men, with signs/symptoms of IHD without obstructive CAD was the recognition of the role of coronary microvascular dysfunction as at least one mechanism for IHD. The elderly are another cohort in whom an increase in angina is prevalent. However, the absence of robust data from this cohort, mostly composed of women, defaults such patients to management pathways designed using data collected from younger male cohorts.

Q: What are your main duties as a principle investigator for the UF Center for the NHLBI-funded Women's Ischemia Syndrome Evaluation (WISE) and the UF Regional Center for the Cardiovascular Cell Therapy Research Network (CCTRN)? What have been your most notable findings in these roles?

A: There is a substantial female excess of patients with IHD, emphasising that women differ from men concerning IHD. These differences were not recognised previously and remain very poorly understood. The central theme of the WISE is to improve our understanding of IHD among women. The problem of IHD without obstructive CAD has been a focus and, in addition to directing all of the work done at our UF Center, I have been leading investigations in this area. Our most notable finding has been the identification of coronary microvascular dysfunction in about half of the women studied without obstructive CAD. Additionally, our long-term follow-up studies have identified coronary microvascular dysfunction as an independent predictor of major adverse outcomes.

Relative to the CCTRN, we have been investigating the use of various autologous and allogeneic cell-based therapies for IHD and PAD. Thus far, we have confirmed that large-scale, randomised controlled studies can be safely conducted with very complex protocols that include local cell harvest, processing, and delivery. Overall, autologous bone marrow-derived mononuclear cells have produced only a very minimal effect on left ventricular dysfunction. We have found that this is related in part to depressed function of this bone marrow fraction. Thus our current projects are using specific cardiac stem cells that are expanded *ex vivo* and also allogeneic cells expanded from healthy donors.

Q: How important are clinical trials for advancing our knowledge of the field? Are there any reforms you would like to see in the way they are carried out?

A: Information from clinical trials is the cornerstone to advancing the practice of CV medicine, since the results form the basis for evidence-based medical knowledge. The very large-scale trials, required to detect small incremental benefit from a novel therapy when added to standard of care, have become very costly in terms of money and resources. Thus, streamlined trials using electronic health records data collected for standard of care, and without the intensive site monitoring that evolved over past decades for regulatory purposes, are being endorsed by several American funding agencies. These trials will take a number of years to become fully established in CV medicine. For example, a 20,000-patient trial (ADAPTABLE) is examining the optimal dose of aspirin (81 mg/d vs 325 mg/d) for secondary prevention over 30 months follow-up. The success of these pragmatic trials will set the direction for future CV clinical research.

Q: To what extent has the field of cardiology grown since you began your medical career? What are the most significant developments that you have witnessed during your career?

A: The field of cardiology has grown tremendously since I started my career. We now take for granted that our field covers subspecialists with unique skills in diagnostic and therapeutic application relating to coronary circulation, clinical electrophysiology, structural heart disease, advanced heart failure and transplantation, all types of CV imaging, systemic and pulmonary hypertension, peripheral arterial disease, cardio-oncology, inflammatory heart disease, etc. We

have a wide variety of non-physician providers (specialist nurses, advanced nurse practitioners, physician assistants, exercise physiologists, clinical pharmacists, etc.) to assist in the management of these patients. Therefore, I believe that most patients with CV disease in the USA and Western Europe are reasonably well managed despite the recognised shortage of physicians.

We have also learnt that coronary bypass surgery decreases mortality and MI rates in selected high-risk subgroups (e.g. severe ischaemia with left main stenosis or multi-vessel obstruction associated with diabetes). But revascularisation, by either bypass surgery or PCI, does not impact mortality or MI rates in the general stable CAD population, so it has moved to palliation for limiting symptoms persisting with 'optimal medical therapy'.

Q: In your opinion, does the general public require better education about how to prevent the onset of heart disease? What more can be done to reach this goal?

A: Clearly, yes! We must begin educating preschool-aged children about health and disease, and then in primary school about how to best maintain their health. Everyone should learn to take responsibility for their own heath maintenance.

Q: As a prominent member of many worldwide cardiological societies, do you believe that there needs to be further collaboration between cardiologists worldwide to deliver improved patient care? If so, how can this be achieved?

A: I believe that, worldwide, we need much improved collaborations between cardiologists in order to deliver better patient care. Unfortunately, I do not know how this goal can be approached at this time.

Q: What are your own research aims for the future? Are you interested in advancing your career into other areas of cardiology?

A: Management of patients with stable IHD without obstructive stenoses represents a challenge, for which there is virtually no reliable evidence-base. This represents a great opportunity for new therapeutic interventions so I will continue my work on heart disease in women. I will also continue my work in identifying new treatments targeting the pathological basis for microvascular injury/dysfunction, including ischaemia–reperfusion injury, heart failure with preserved ejection fraction, and matrix remodelling. Finally, I plan to continue my work in cell-based therapies, as there remains a substantial opportunity for advances.

Ronald J. Krone

Professor of Medicine, Cardiovascular Division,
Washington University School of Medicine, St. Louis, Missouri, USA.

Q: Please provide a brief overview of your career to date. What drew you to the study of cardiology and to your current position at the Washington University School of Medicine?

A: When I was in medical school I was fascinated by physiology, especially cardiopulmonary physiology. I enjoyed understanding the physiology of the heart and the immediacy of the problems. Of course, cardiology was quite different in those days (1970). Catheterisation was primarily directed at valve disease and physical diagnosis was key. I enjoyed the cardiac catheterisation laboratory, with cut downs on the brachial artery as our main access. I was always interested in research and worked with Dr Donald Ferguson, a surgeon, to create Blalock shunts, primarily in puppies. The aim was to develop a treatment for pulmonary hypertension and although we were not successful in preventing it, a co-worker did capture an electron micrograph showing a media smooth muscle cell 'crawling' into the lumen past the intima, presumably on its way to creating an intimal lesion which proved so difficult to treat.

I was offered a job as director of a new cardiac catheterisation laboratory at the Jewish Hospital of St. Louis, with a full appointment at Washington

University, and I have been there ever since. When I took the job, coronary angiography was in its infancy and only 15 had ever been done at the University of Chicago (with two deaths). To prepare for this career change, I attended a private hospital in East Chicago where a very active laboratory under the direction of Dr Charles Frahm was demonstrating excellent results; I took his techniques to St. Louis and developed an excellent programme. A few visits with Dr Jeff Hartzler in 1982 were instrumental in starting our PTCA program. The Jewish Hospital merged with Barnes Hospital (one block away) and formed Barnes-Jewish Hospital. It was at that time that I transitioned to primarily diagnostic invasive cardiology. I recently retired from the catheter laboratory after 43 years and am currently focussing on cardio-oncology.

Q: Please tell us a little about your current research. What are your aims and what do you hope to achieve in the next year?

A: I am active in the area of cardio-oncology (or onco-cardiology) and am currently in the final stages of a project evaluating the effect of dexrazoxane on the efficacy and safety of doxorubicin, and evaluating newer parameters of cardiac function to determine if they can predict left ventricle (LV) dysfunction at an earlier stage. We are looking at LV strain and diastolic function, as well as heart rate variability and load-independent diastolic function.

Q: Has the field of cardiology changed a great deal since your career began? What impact has this had on your role within it?

A: Everything has changed and continues to change. Changes include the development of coronary angiography, with the development of both safe methods and safe contrast, as well as the sea-change wrought by the introduction of angioplasty and stenting, cardiac transplant, the ablative techniques of electrophysiology and, of course, echocardiography with its incredible diagnostic power. Cardiologists previously had to make difficult life-saving decisions with little data, but now with imaging the diagnosis is usually clear before intervening. However, there are still situations in which the now-rudimentary interventions are carried out, and thus the high-risk scenario returns.

Q: In your opinion, what is the most personally challenging aspect of your work?

A: I am now involved in cardio-oncology and here the goal is to protect the heart to allow as much chemotherapy as is required to proceed and attack the tumour. I enjoy working with the patients, the oncologists, and participating in the unbelievable changes in cancer therapy.

Q: What is the current state of heart disease in North America, and how does its prevalence compare with that of Europe?

A: I spent a few months at the University of Paris at the Pitié-Salpêtrière Hospital in 1995 with Dr Gérard Drobinski, Dr Gilles Montalescot, and Dr Isaac Isancot. I also met Dr Yves Louvard when he was developing his radial artery techniques. I found cardiology in France innovative. They were very creative, provided excellent care, and did not have to deal with the roadblocks that we have in the USA (high price of drugs, etc.). It was a good time to visit. They had all the tools (many different stents and other devices) and we had all the hype. They had just changed the post-stent protocol to focus on platelets (acetylsalicylic acid and ticlopidine), as opposed to the cumbersome anti-thrombotic approach in the USA, which made widespread stenting practical. I think European cardiology is excellent and certainly of equal quality to that of the USA. In addition, the concentration of procedures to a few institutions ensures, as much as possible, that only experienced operators complete procedures, whereas experience is more diffused in the USA.

Q: How does the treatment of heart conditions in the USA compare with Europe in terms of the quality of care and the resources available?

A: I am very impressed with the quality of the care and resources available in Europe and I feel that they are on a par.

Q: What dietary and lifestyle factors are the greatest contributors towards cardiovascular health problems in the general public, and what can individuals do to minimise these risks? What more

could governments and healthcare providers do to try and reduce the prevalence of heart problems in the public?

A: That is a difficult question. Food producers make the things that people buy but they make no effort to improve health. I think it is only government input, especially with regard to school lunches etc., which may have an impact. Legislating salt content and the size of sugary drinks was a dismal failure in New York. People have to want to be healthy and it has to carry through the entire society.

Q: How important are events like the annual ESC congress for cardiologists and what do you feel their focus should be?

A: I think the congresses have done a great service to the field of cardiology, especially with late-breaking trials which expose the negative results as well as the positive. Didactic lectures, bringing the generalist up to date with new advances in the sub-subspecialties, are also a very important part of large general meetings.

Q: Will you be attending this year's ESC congress? What do you anticipate will be the key talking points and most influential presentations during the meeting?

A: Unfortunately, I will not be able to attend. There are so many new exciting areas in cardiology in each of the sub-specialties and one of the strong points of the ESC Congress is the bringing together of the world's experts and innovative minds and the presentation of cutting-edge information. At this time every aspect of cardiology is moving forward, with exciting advances that are validating recent theories. I expect that the latest ideas in all these areas will be presented and that the energy at the meeting will be exhilarating as it has been in the past.

"I think European cardiology is excellent and certainly of equal quality to that of the USA."

Gaetano Santulli

Columbia University Medical Center, R. Berrie Medical Science Pavilion, College of Physicians & Surgeons, New York City, New York, USA.

Q: Who or what inspired you to specialise in cardiology during your medical training?

A: I remember that at medical school I was fascinated, above all, by neurology and cardiology. For this reason predominantly, I asked my mentors (Dr Guido Iaccarino and Dr Bruno Trimarco), both cardiologists, for an experimental thesis on Stroke, which was later published in the *Journal of Hypertension*.[1] In the end, I decided to focus on the cardiovascular (CV) field and I do not regret my choice.

Q: You are highly active in fundamental research – how challenging is it to balance this with clinical work?

A: I truly consider the position of physician-scientist a privilege in two ways. Being a scientist helps a lot when making any clinical decision, and having shaped my mind as a clinician is crucial when designing experimental procedures; I am always pointing out the so-called "translational aspects" of research.

Q: What do you feel have been your most significant medical accomplishments to date?

A: From a clinical point of view, every single dialogue with a patient represents an unforgettable and fulfilling accomplishment in both my career and life. As a scientist, the most notable moments are linked to unexpected results when performing experiments: finding a mechanistic explanation to these findings is the ultimate beauty of science. Favourable decision letters for submitted papers or award letters for grant proposals also do no harm!

Q: One aspect of your research concerns the role of microRNAs in CV physiology and pathophysiology. MicroRNA networks are a relatively new area of research – could you speculate how long it may be until potential therapies targeting these pathways are investigated in randomised trials?

A: We are getting close, very close. Research in microRNA could actually represent a potential shortcut to achieving the 'precision medicine' mentioned by President Obama in his last State of the Union address before both chambers of the US Congress. I was recently invited to serve as editor for a comprehensive book – From Molecular Biology to Clinical Practice[2] – which summarises the 'state-of-the-art' in microRNA research. The book explores the scientific updates in the fields with a special focus on their importance in clinical practice. It is divided into three volumes exploring basic science, cancer, and medical evidence, respectively, and features forewords by Drs Carlo Croce and Gianluigi Condorelli, renowned experts in the field.

Q: Your research also concerns the role of calcium signalling in CV physiology – could you briefly summarise the range of CV indications in which calcium dysregulation is suspected of playing a role?

A: Calcium is undoubtedly an essential signalling molecule and is involved in a plethora of fundamental functions, including cell life and death. Between these two events, calcium finely regulates countless events such as muscle contraction, gene transcription, secretion, and generation of fuels in various metabolic pathways, to name but a few. All these aspects were recently reviewed in a detailed chapter on the topic.[3]

"From a clinical point of view, every single dialogue with a patient represents an unforgettable and fulfilling accomplishment in both my career and life."

Q: Are there any other areas of cardiology that you would like to research in the future?

A: Heart failure, arrhythmias, metabolic disease. Actually, I have recently demonstrated that a common molecular mechanism underlies the aforementioned disorders, basically relying on the calcium fluxes between endoplasmic reticulum and mitochondria. Specifically, mitochondrial calcium plays a fundamental role in post-ischaemic heart failure,[4] in atrial fibrillation,[5] and also in diabetes mellitus.[6] I am also studying the molecular bases of hypertension and angiogenesis, exploiting the expertise acquired during my MD and PhD training.

Q: How important are international congresses to cardiologists? Are there any specific congresses that you look forward to each year?

A: International congresses are very important to cardiologists. They represent a unique opportunity to discover what is 'state-of-the-art' in the field, to critically evaluate the new strategies presented to fight CV disease, and, obviously, to meet people. My favourite congresses are the annual meetings of the European Society of Cardiology (ESC), the American Diabetes Association (ADA), and the American College of Cardiology (ACC).

Q: In your opinion, what is the greatest challenge facing cardiologists today?

A: There are many challenges, of course. I would focus on just one fundamental challenge for interventional cardiologists: restenosis/thrombosis post-angioplasty. To provide a bit of background, as percutaneous coronary intervention (PCI), a leading option for revascularisation in a series of CV disorders, became widely adopted in the 1980s, restenosis after the intervention was reported in up to 60% of patients (!) The introduction of stents – first bare metal stents and then drug eluting stents (DES) – revolutionised the field, significantly reducing rates of restenosis. However, concerns have been raised over the long-term safety of DES, with particular reference to stent thrombosis, essentially due to impaired re-endothelialisation caused by the non-selective anti-proliferative properties of the eluted drugs. Indeed, these drugs inhibit not only the proliferation and migration of the 'bad' cells

responsible for restenosis (smooth muscle cells), but also the growth and mobility of the 'good' endothelial cells, indispensable for the healing of the vessel following PCI. Thus, the lack of proper endothelial coverage eventually increases the risk of thrombosis. I have recently performed some pre-clinical experiments attempting to exploit the cell-specific expression of microRNA in this sense.[7]

Q: What advice would you give to young medical students thinking about specialising in cardiology?

A: 1) Study; 2) Focus; 3) LISTEN to the patients.

REFERENCES

1. Lanni F et al. The PlA(1/A2) polymorphism of glycoprotein IIIa and cerebrovascular events in hypertension: increased risk of ischemic stroke in high-risk patients. J Hypertens. 2007;25(3):551-6.

2. Santulli G (ed.), MicroRNA: Medical Evidence: From Molecular Biology to Clinical Practice (2016) 1st edition, Cham: Springer International Publishing.

3. Santulli G, Marks AR. Essential roles of intracellular calcium release channels in muscle, brain, metabolism, and aging. Curr Mol Pharmacol. 2015. [Epub ahead of print].

4. Santulli G et al. Mitochondrial calcium overload is a key determinant in heart failure. Proc Natl Acad Sci U S A. 2015;112(36):11389-94.

5. Xie W et al. Mitochondrial oxidative stress promotes atrial fibrillation. Nature Sci Rep. 2015;5:11427.

6. Santulli G et al. Calcium release channel RyR2 regulates insulin release and glucose homeostasis. J Clin Invest. 2015;125(5):1968-78.

7. Santulli G et al. A selective microRNA-based strategy inhibits restenosis while preserving endothelial function. J Clin Invest. 2014;124(9):4102-14.

Jawahar L. Mehta

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

Q: What made you decide to specialise in cardiology during your medical training?

A: In medical school I had a cardiology professor who was an excellent clinician and he impressed me the most; he became my role model.

Q: Have you seen any changes in the types and prevalences of heart conditions you see in daily practice since you began your clinical work?

A: Oh yes, we hardly see any rheumatic or tuberculosis heart diseases, which were common when I was a budding physician in India. In the USA, we are seeing more and more heart failure – a difference from a decade or two back when ischaemic heart disease (IHD) was the most common disease seen by cardiologists. Furthermore, we no longer see many hypertensive emergencies, which were common in the 1970s.

"The development of aspirin, beta blockers, and statins has been a major boon to our patients."

Q: What changes/improvements in the treatment of patients have been particularly noticeable during your career?

A: There have been major advances in pharmacotherapy, surgery, and catheter-based strategies. The development of aspirin, beta blockers, and statins has been a major boon to our patients.

Q: The mainstream media often report on the social challenges posed by the increasing prevalence of cardiovascular disease (CVD) – is it the same story in all demographic groups? Are there any groups that are reversing the trend, or any that are of special concern?

A: South Asians seem to have some predisposition for developing coronary artery disease at an early stage and do poorly when they develop the disease. There may well be social factors responsible for this phenomenon, such as the feeling of isolation and emotional stress. In addition, this group does not indulge in regular exercise as much as is needed to metabolise the large amounts of calories that they tend to

consume. As such, South Asians (and many other groups) have a high incidence of metabolic syndrome (MetS) and clinical diabetes. Furthermore, with the growth of the Hispanic population in the USA, we may start seeing more of these patients. Despite a high incidence of MetS among Hispanics, we do not see many patients with IHD.

Q: What more could governments and healthcare providers do to try and reduce the prevalence of CVD in citizens?

A: More advertising on the hazards of smoking and over-consumption of calories. Government and healthcare providers should encourage regular exercise; it is disheartening to see so many healthcare providers being overweight.

Q: Much of your research concerns the receptor LOX-1 and its potential role in CVD – can you very briefly summarise what is known about this molecule and whether it may be a valid target for therapeutic approaches?

A: This receptor for oxidised low-density lipoprotein (ox-LDL) facilitates the binding and internalisation of ox-LDL in endothelial cells, macrophages, and smooth muscle cells – a key step in the development of atherosclerosis. We have also observed enhanced LOX-1 expression in myocardial ischaemia, hypertension, and peripheral vascular disease. LOX-1-directed therapy may be useful in the treatment of patients with these disease states. A number of companies are currently developing small molecules and biologics to counter the effect of LOX-1 activation.

Q: Are there any other areas of cardiology that you would like to research in the future?

A: Oh yes, I am getting interested in the role of long non-coding RNAs and diagnostic tools or therapeutic modalities. I am also interested in developing growth factor(s)-based therapy for IHD.

Q: How important are congresses such as ESC to cardiologists?

A: These congresses are very important in order to keep physicians updated with advances in therapy for CVDs.

Q: In your opinion, what is the greatest challenge facing cardiologists today?

A: Some cardiologists do not like cost-containment drives, particularly in the USA but also in other countries as well, although this is necessary.

Q: What advice would you give to young medical students thinking about specialising in cardiology?

A: Do what your heart desires. Do your best and do not focus on money; money will come if you do what is right for the patients. Lastly, keep your eyes and ears open, and 'think outside the box'.

Attila Roka

Clinical Cardiac Electrophysiologist, Internal Medicine Clinic, Meridian, Mississippi, USA.

Q: Please provide us with a brief overview of your career to date. What were the steps that led you to becoming a clinical cardiac electrophysiologist?

A: I graduated from the Medical School of Semmelweis University in Hungary with an MD-PhD, then pursued graduate medical education in Hungary and in the USA. After completing a clinical cardiac electrophysiology (CEP) fellowship at the Massachusetts General Hospital in Boston, I joined a private physician group in Meridian, Mississippi as an electrophysiologist. I have been interested in the electrophysiological phenomena of the heart since the beginning of my training. I first pursued research in basic science, investigating the characteristics of atrioventricular conduction in atrial fibrillation (AF). Later, my interest became more clinical, with topics such as device-based arrhythmia and cardiac resynchronisation therapy (CRT). Clinical CEP is an exciting young field of cardiology, investigating and treating important public health issues such as sudden cardiac death (SCD) and AF. There are plenty of opportunities for an electrophysiologist to perform manually and intellectually challenging procedures, participate in research, and try novel

therapies for the benefit of patients – all of which were important to me when I decided to pursue a career in this exciting field of medicine.

Q: Could you provide a brief description of the field of CEP and your role as a specialist?

A: CEP is the field of medicine investigating the electrical properties of the heart, diagnosing and treating its abnormalities. Proper cardiac pump function is dependent on carefully timed electrical impulse generation and propagation in specialised tissues. Abnormalities may manifest on a wide spectrum. Certain very symptomatic conditions, such as paroxysmal supraventricular tachycardia, can be cured with a single procedure. Others, such as syncope, may have an extracardiac cause and sometimes require lengthy workup. AF, the most common sustained arrhythmia in clinical practice, is dangerous because of its dreaded thromboembolic complications. Although a cure is not yet possible in the majority of patients, various pharmacological, ablative, and device-based treatment options provide symptomatic relief and decrease the risk of long-term complications. Implantable devices are available to treat patients with symptomatic bradycardia, or those at high risk of SCD from malignant ventricular arrhythmia. CRT is utilised in patients where cardiomyopathy is associated with electrical dyssynchrony: a non-arrhythmia indication for a pacemaker or defibrillator. The role of a clinical cardiac electrophysiologist is to evaluate, diagnose, and treat the referred patient. The safety and efficacy of antiarrhythmic medications (besides beta-blockers) is still less than desirable; most treatment options are non-pharmacological: ablations or implantable devices. In daily practice, it is rare that the electrophysiological issue is primary and can be cured by a single intervention. Most commonly, the findings are manifestations of other cardiac or extracardiac pathology and require collaboration with a referring physician to achieve optimal outcome.

Q: What new treatments have been introduced recently as a result of our growing knowledge of CEP?

A: There is a significant ongoing effort to improve the safety and efficacy of treatments for AF. This arrhythmia has a high prevalence in the elderly population, most commonly in patients with comorbidities, leading to further morbidity. Despite extensive research in this field, the pathophysiology of AF is still not fully elucidated, which limits targeted development of newer pharmacological agents. In recent years, the utilisation of non-pharmacological methods to treat AF has increased significantly. The most common procedure, electrical isolation of the pulmonary veins, is still a technically challenging and expensive procedure, with a low but existing risk of life-threatening complications such as tamponade, embolic stroke, atrio-oesophageal fistula, and pulmonary vein stenosis. Extensive monitoring is used during the procedure to decrease the risk of these complications. Still, the long-term efficacy of the procedure is less than desirable and often repeat procedures are needed. There is also an ongoing effort to decrease the long-term thromboembolic complication risk in AF: left atrial appendage occluder devices are now available, which can allow discontinuation of long-term anticoagulation in certain patients. Pacemakers and defibrillators are connected to the heart with leads – insulated, complex wires - transmitting electrical signals to the device. Complications from implanted devices – dislodgement, fracture, venous occlusion, and infective endocarditis - are mostly related to leads. Miniaturisation has allowed the development of a very small pacemaker generator, which can be directly implanted into the right ventricle with no leads, meaning the long-term complication rate can be lower. A novel defibrillator system utilises a subcutaneous electrode with no intravascular hardware, meaning most of the complications can be avoided.

"Defibrillators by themselves do not alter the course of the underlying cardiac pathology; this is why treatment with proven medications is important."

Q: In a recent paper that you co-authored, you found that recovery of left ventricular ejection fraction (LVEF) following CRT was associated with significantly reduced need for appropriate implantable cardioverter defibrillator (ICD) therapy, with patients displaying an improvement in LVEF ≥45% at lowest risk. Could you briefly summarise the implications of these findings?

A: Patients with reduced LVEF are at high risk for SCD from malignant ventricular tachyarrhythmia (VTA). ICDs can effectively reduce this risk by providing timely therapy if such an event occurs. Defibrillators by themselves do not alter the course of the underlying cardiac pathology; this is why treatment with proven medications is important. A group of patients, where cardiomyopathy is associated with electrical dyssynchrony, benefits from CRT – essentially a device capable of pacing both ventricles. In most cases, this is achieved with the implantation of a biventricular defibrillator (CRT-D). Alternatively, a biventricular pacemaker (CRT-P) can be used – a cheaper, less complex device, able to provide cardiac resynchronisation, but not the protection from VTA. CRT-D is often chosen as an initial implant due to the presumed high risk of VTA, as the LVEF is low. Some patients respond so well to CRT that in addition to their symptoms, the LVEF also improves. We analysed whether this transcribes into decreased incidences of ICD therapies: if we can identify patient groups where the VTA risk is minimal after reverse remodelling occurs, they may get the same benefit from CRT-P, when the battery of the first device depletes and they need a replacement of their CRT-D. We found that patients whose LVEF improved to ≥45% and those who had no VTA before the first implant are at lowest risk. These findings may provide the basis for a prospective trial, aiming to clarify the issues of safety, efficiency, and cost-efficacy of long-term CRT.

Q: How have treatment options for patients with arrhythmia improved over the years?

A: There has been a significant improvement in the understanding of long-term risks and benefits of antiarrhythmic medications. As the safety and efficiency of these agents are less than desirable and no groundbreaking new agents are on the horizon, ongoing efforts lead to the development of non-pharmacological treatment options. Implantable pacemakers are the only effective devices capable of treating symptomatic bradycardia. ICDs were developed to decrease the risk of SCD caused by VTA. Cardiac resynchronisation therapy improved morbidity and mortality of patients with cardiomyopathy and intraventricular dyssynchrony. All of these devices are expensive and can lead to severe complications; there are ongoing studies to identify the patient groups where they can provide the most benefit. Implant techniques have improved significantly: currently almost all procedures are transvenous, with minimal perioperative complication rates. The introduction of ablative treatment options in CEP was the culmination of efforts in basic electrophysiology research, computer science, and engineering in the 1990s, when it became possible to identify intracardiac electrical phenomena in real-time and to target lesion delivery with such accuracy that it allowed safe and efficient ablation. Most recently, the number of ablations increased markedly as it emerged as an option to treat AF, a highly prevalent condition.

Q: What have been the most significant changes in clinical routine that you have witnessed during your career in cardiology so far?

A: The technological advances are continuous in the field of CEP and affect our daily practice. A few years ago, pulmonary vein isolation took several hours. Today, with advances in mapping systems, image integration, and catheters, this procedure can be performed in half the time and with better safety and efficacy. Pacemaker and defibrillator leads continue to improve: a few years ago, a biventricular device implant could be hindered by high pacing threshold or phrenic nerve stimulation – usually not an issue with the new multipolar leads (although suboptimal coronary sinus anatomy can still be a major challenge). Utilisation of novel anticoagulant agents has made some cardioversions simpler and even helped to avoid hospitalisations. As the importance of remote monitoring in the management of heart failure became apparent, we started to work more closely with heart failure specialists, many of whose patients have an implanted device that provides

valuable data on their disease: arrhythmia burden, activity, thoracic congestion.

Q: Have you noticed any changes in the prevalence and type of heart conditions in American citizens in recent years? If so, could you speculate what may be the cause(s) of this?

A: There is an ongoing, slow decline in the age-adjusted prevalence of ischaemic heart disease, thanks to the efforts made in primary and secondary prevention: smoking cessation, lifestyle education, screening and treatment of hypertension, hyperlipidaemia, and diabetes. As ischaemic heart disease is the major cause of heart failure and SCD, this will favourably affect their age-adjusted prevalence too. Overall, the net effect will be mitigated by the ageing of the general population. The strongest risk factor for AF is age, so this highly prevalent and difficult-to-treat arrhythmia is still going to pose a challenge.

Q: How would you describe the current state of healthcare in the USA? Could the introduction of 'ObamaCare' change the way in which patients with cardiological conditions are treated?

A: Healthcare in the USA is very expensive – most patients without insurance cannot afford high-quality care. There is no universal coverage; the insurance market is divided between several private insurers and the premiums are costly. Before ObamaCare, companies were able to decline coverage or raise premiums significantly due to pre-existing conditions such as hypertension, as these patients consume more healthcare resources. Government programmes were only available for selected populations: elderly, poor, veterans, etc. Efficient cardiovascular (CV) therapies – prevention, management of chronic conditions, acute care – are long-term interventions or expensive procedures. Translation of these benefits into overall health improvement for the general population was limited by these factors. ObamaCare (the Affordable Care Act) introduced several important changes that should help to improve delivery of CV care in the USA. Most importantly, companies cannot deny coverage or charge more based on health status. Overall coverage was extended via subsidised insurance and by expanding existing government plans. The rate of people without medical insurance dropped from 15.7% to 9.2% since the Affordable Care Act was signed into law (CDC and Census data). Some issues, such as over-utilisation of certain healthcare resources and quality control of delivered care, still remain. The current payment models (fee-for-service for most providers) favour procedures over preventive care. Attempts to introduce and expand managed care, aimed at reducing the cost of providing healthcare and improving the quality, are underway. The overall need for CV care in the USA will continue to increase in the near future due to the high prevalence of these conditions in the ageing population. Efforts to provide universal coverage, cost containment, and just utilisation of resources should remain the focus for improving CV care on a national level.

Q: How important is the annual ESC Congress to cardiologists such as yourself? How does this event compare with medical congresses in the USA?

A: The congress is an excellent opportunity to network with international colleagues and to get up to date with current research in CV medicine. Presenting a study provides important feedback on research and may lead to new insights or start new collaborations. Although the large cardiology congresses are international and attract an audience from all over the world, the location of the ESC Congress is more accessible for participants from several European countries, who would otherwise not be able to attend such a meeting.

Q: What advice would you give to young medical professionals who are thinking of specialising in CEP?

A: CEP is ever-growing and changing. It is an exciting field for someone who is interested in cardiology, enjoys teamwork, and would like to provide definitive care for some of the most challenging cardiac conditions.

"Efforts to provide universal coverage, cost containment, and just utilisation of resources should remain the focus..."

Martino Pepe

Interventional Cardiologist, Unità Operativa Cardiologia Universitaria, Azienda Ospedaliero-Universitaria Policlinico di Bari, Bari, Italy.

Q: Who or what first inspired you to pursue a career in cardiology?

A: I was fascinated by the first percutaneous coronary intervention I saw when I was a medical student.

Q: What has been the greatest advancement that you have witnessed in the field since you first began your clinical work?

A: Definitely the switch in the treatment of myocardial infarction from medical therapy to the invasive-percutaneous treatment.

Q: How has our understanding of the causes and mechanisms of coronary artery disease (CAD) improved over the years? How has this knowledge translated into effective treatments for the condition?

A: Deeper knowledge of atherosclerotic plaque composition and its pathophysiology has led to a more complete form of pharmacological therapy with a growing interest in high-dose statins and antiplatelet association therapy.

Q: We frequently hear that we should prepare for a large increase in the prevalence of mental health conditions such as dementia and Alzheimer's disease as the population of Europe becomes older. Should we have similar expectations for HF and CAD, and what will this mean for clinical cardiology departments?

A: The hypothesis is undoubtedly correct: the world population ageing phenomenon, particularly evident in western countries, will lead to a relevant increase of HF and CAD prevalence. Although this is obviously the result of the improvement of our medical assistance, particularly in the field of cardiology, which we are proud of, it will generate a work overload for our cardiology departments that will be very difficult to face if bigger investments are lacking.

Q: Could healthcare providers and national governments do more to educate the population on how to best prevent cardiovascular (CV) disease?

A: For sure they can; all modifiable CV risk factors need to be addressed with more effective and extensive communication campaigns, with particular attention paid to the rising and so far underestimated problem of obesity.

Q: In your opinion, how does cardiological treatment in Italy compare with that of other European countries? Are there any lessons that other nations could learn from the Italian experience?

A: It is my opinion that we have a high level of healthcare for cardiology treatments and procedures in Italy; nevertheless I am not able to make comparisons with other European systems that I do not know in depth.

Q: Are there any areas of cardiology that you would like to research in the future?

A: One of my fields of interest, besides interventional cardiology, is stem cell and gene therapy. I have already been involved in this type of research in the past and I think it could represent an additional future weapon in myocardial dysfunction treatment.

Q: What would you say is the biggest challenge facing cardiologists today?

A: The biggest challenge is, in my opinion, for cardiologists to keep objectivity of judgement in their relationship with cardiac surgeons; interventional cardiology frontiers move further every day in fields that only a few years ago belonged to cardiac surgery. A correct definition of an unbiased and tailored treatment for every single patient is the real challenge and the 'heart team' could be the means by which it may be obtained.

EMJ EUROPEAN MEDICAL JOURNAL

SUBSCRIBE

FREE TO OUR YOUTUBE CHANNEL

www.youtube.com/EMJreviews

CONGRESS HIGHLIGHTS

DISCUSSIONS

INTERVIEWS

WEBCASTS




Follow us:

www.emjreviews.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

TREATMENT OF HYPERTENSION IN NEW FRONTIERS

This symposium took place on 30th August 2015 as a part of the European Society of Cardiology (ESC) Congress in London, UK

Co-Chairs

Bryan Williams,[1] Gordon Thomas McInnes[2]

Speakers

Bryan Williams,[1] Gordon Thomas McInnes,[2] Jesús Isea-Pérez,[3] Jorge Sison[4]

1. University College London (UCL), London, UK

2. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

3. Fundación Venezolana de Cardiología Preventiva, Caracas, Venezuela

4. Medical Centre Manila, Manila, Philippines

Disclosure: Bryan Williams received speaker fees from Boehringer Ingelheim, Daiichi, Novartis, Pfizer, and Sankyo. Gordon Thomas McInnes received research grants, consultation fees, and speaker honoraria from Bayer, Boehringer Ingelheim, Novartis, Pfizer, and Takeda. Jesús Isea-Pérez participated in meetings, received speaker and advisory board honoraria, and received research/educational grants from AstraZeneca, Bayer, Novartis, Pfizer, and Sanofi-Aventis. Jorge Sison received speaker honoraria from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline (GSK), Novartis, and Pfizer, and received professional fees as principal investigator from GSK and Merck.

Acknowledgements: Writing assistance was provided by Dr Ana Rodríguez de Ledesma (ApotheCom).

Support: The symposium was jointly organised and funded by Novartis Pharmaceuticals. All authors received honoraria for preparation and delivery of their presentations. The publication of this article was funded by Novartis Pharmaceuticals. The paper is an interpretation of the views of the speakers, but is not written by them. The views and opinions expressed are those of the authors and not necessarily of Novartis Pharmaceuticals.

Citation: EMJ Cardiol. 2015;3[2]:44-52.

MEETING SUMMARY

This symposium provided an excellent forum in which to discuss the global burden of hypertension (HTN), its challenges, and approaches to best management in new frontiers. The symposium speakers also reviewed recent data for clinical practice, especially those relevant for patients at high risk of HTN. The presentations were delivered within a highly interactive setting to facilitate audience questions and discussion.

The symposium was opened by Prof Bryan Williams, who gave a description of the global burden of HTN, emphasising the need for effective, simplified treatment strategies and algorithms to effectively control blood pressure (BP). Prof Gordon Thomas McInnes then gave an overview of the challenges faced when treating HTN in the developing world and the best management practices of HTN adopted across different countries. HTN control in Latin America (LA) and the Caribbean region, and its opportunities and challenges was the subject of the next presentation given by Dr Jesús Isea-Pérez. Lastly, Dr Jorge Sison discussed HTN control in Asia and the Middle East, presenting real-world data in addition to a review of the latest clinical data on optimal management of HTN, and focussing on the use of single-pill combination (SPC) therapies. This engaging and interactive symposium was facilitated by multiple-choice questions posed by speakers, allowing audience participation via an electronic voting system. The meeting closed with a lively panel discussion and concluding remarks from Prof Bryan Williams.

This truly international symposium brought together more than 550 delegates from across Europe and North America, Africa and the Middle East, Asia and Pacific regions, and Central and South America, with attendees representing a wide range of clinical and professional settings.

Welcome and Introduction

Professor Bryan Williams

HTN is a leading risk factor of global mortality and one of the biggest contributors to the global burden of disease (GBD).[1,2] Each year, HTN is estimated to contribute to approximately 7.5 million deaths, representing around 13% of the total annual deaths worldwide.[1]

Despite the availability of effective antihypertensive agents, HTN remains difficult to control in the majority of patients.[3] Awareness of the condition is an important determinant for seeking treatment. In a cross-sectional, multinational study (Prospective Urban Rural Epidemiology [PURE]) involving 153,996 hypertensive patients across countries of all income ranges, almost half of the patients (46.4%) were unaware of their condition and remained untreated. Of those aware of the disease, BP is effectively controlled in only 35% of cases.[3]

Although much progress has been made in the control of BP, the global burden of HTN-related cardiovascular disease (CVD) remains substantial. In 2013, the GBD showed that, while the prevalence of disabilities due to ischaemic heart disease is declining, the number of years of life with disability due to HTN-related conditions has been increasing since 1990.[4] However, thanks to important advances in medical treatments, the number of CVD-free years of life associated with HTN has expanded substantially across age groups.[5] According to recent estimates, for every year gained on treatment, lifetime is extended by at least 1 month overall.[5] The improved survival of many patients with long-term HTN is resulting in a shift of the GBD, with HTN-related conditions, including angina and myocardial infarction, increasingly manifesting at an older age.[5] As the methods of detection and the control of other risk factors such as smoking and high levels of cholesterol improve, it is predicted that high BP will become better detected and managed.

The significance of HTN as a CVD risk factor is now increasingly recognised. Even in patients with controlled HTN (<140/90 mmHg), a 50% risk of a cardiovascular event is seen.[2] HTN currently contributes to 92 million years of disability, making it a leading cause of years lost to disability across the globe, and HTN is predicted to become the leading preventable cause of heart failure associated with ageing. To enable adequate BP control, effective, simplified treatment strategies and treatment algorithms need to be adopted within the current guidelines.[2]

This symposium aimed to explore: (1) the challenges of managing HTN in new frontiers, in particular in Asia, the Middle East, and LA, how these challenges may differ from those in other parts of the world, and the reasons for these differences; (2) current practice for HTN control in non-European and non-North American countries; (3) the key regional HTN guidelines, especially those of relevance to patients at high risk of CVD; (4) the clinical perspectives for real-world management of HTN, particularly in high-risk patients, and recent real-world data for the treatment of HTN in high-risk patients in the aforementioned regions.

Hypertension Management Across Borders

Professor Gordon Thomas Mcinnes

Worldwide, life expectancy has been increasing continuously and substantially over the past 40 years. Despite global and regional health crises, the gap in life expectancy between rich and poor countries has been reduced. A clear example of this can be seen in China, where a 15 year increase in life expectancy between 1970 and 2010 has been reported compared with a 9-year increase in life expectancy in the UK for the same period.[6,7]

HTN is an important public health challenge worldwide.[8] Coronary heart disease (CHD), and CVD in general, are leading causes of death globally, and in developing countries the mortality attributed to CHD is rising.[9] Much of the increase in CVD mortality can be attributed to suboptimal BP, which is considered to be the main 'correctable risk factor' for CVD and mortality.[7]

HTN is currently predicted to affect 639 million adults in developing countries, a prevalence that is expected to rise by 80% by 2025, with 1.56 billion people estimated to be affected globally (Figure 1).[8]

Between 2000 and 2025, the greatest increases in the prevalence of HTN are expected to be seen in the Middle East and North Africa (+107%), Africa (+89%), and South Asia (+81%), followed by LA (+76%), East Asia and Pacific regions (+69%), North America and Western Europe (+29%), and Eastern Europe and Central Asia (+11%). In 2010, the prevalence of HTN reached 33.5% in China, giving an estimated 330 million hypertensive patients in

this country where the rates of awareness (50%), treatment (40%), and control (10%) are low.[10]

Change to a more Western lifestyle, modernisation, and urbanisation are contributors to the shift in the burden of HTN observed across the developing world.[6,11] Regardless of age, HTN is highly associated with the risk of stroke and death due to ischaemic heart disease.[12] Of note is the logarithmic relationship between BP and mortality, which emphasises the importance of rigorous BP control.

However, BP control (<140/90 mmHg) remains low in patients with HTN across regions worldwide.[13-19] The recommendations of the most recent British and European guidelines advocate the use of dual or triple treatments in SPC therapies, with a renin–angiotensin system (RAS) blocker in combination with a calcium channel blocker (CCB) and/or a diuretic.[20,21] Compared with antihypertensive monotherapies, the use of SPC therapies for the treatment of HTN can offer increased efficacy, tolerability, and compliance. In addition, the use of SPC therapies leads to improved reductions in BP due to their multiple mechanisms acting on complementary BP-control pathways and providing neutralisation of counter-regulatory mechanisms.[22,23] The lower-dose components in SPCs and the attenuated compound-specific adverse effects result in improved tolerability.[22,23] Added to this, the use of SPC antihypertensive agents is also associated with improved treatment adherence due to their convenience and reduced pill burden.[22,23]

The variation in the burden of HTN seen across different countries can be attributed to several possible causes, including the healthcare systems, availability of resources, drugs, and technology, as well as the prevalence of high-risk conditions for HTN, such as diabetes mellitus, and drug tolerability (Table 1).[24]

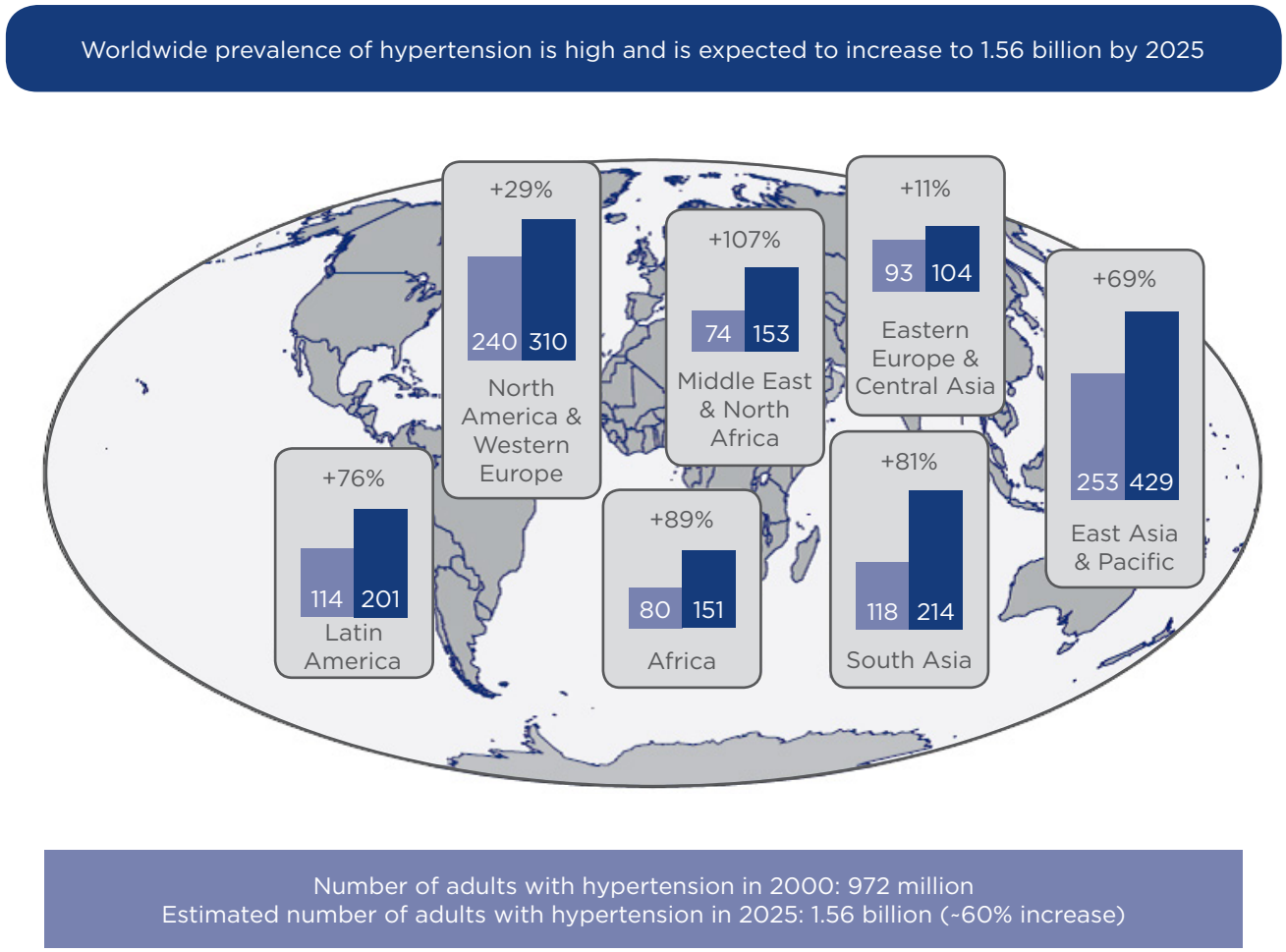


Figure 1: Worldwide prevalence of hypertension.[8]
Number or people aged ≥20 years with hypertension (in millions) for the years 2000 (light blue bar) and 2025 (dark blue bar).

Table 1: Determinants of the burden of hypertension across countries.

Healthcare system
Availability of resources, drugs, and technology
High-risk populations (e.g. patients with diabetes mellitus)
Drug tolerability
• Diuretics: dehydration (when taken during hot weather)
• Diuretics alone or in combination with β-blockers: new onset of diabetes
• Calcium channel blockers in hot weather: ankle oedema
• Angiotensin-converting enzyme inhibitors*: ethnicity-dependent variations in efficacy and adverse events

*Taiwanese hypertension guidelines strongly recommend the use of angiotensin-receptor blockers over angiotensin-converting enzyme inhibitors due to their exceptional tolerability and lowest discontinuation rate among all five classes of antihypertensive drugs tested.[24]

Hypertension Control in Latin America: Opportunities and Challenges

Doctor Jesús Isea-Pérez

The region of LA includes 41 countries that vary in terms of area, population density, and economic size. The region has 588 million inhabitants, representing 8.5% of the world's population, 81% of whom live in urban areas.[25] According to 2010 statistics, LA also has low population growth compared with the rest of the world. This is due in part to low fertility rates (2.3%) and high prevalence of contraceptive use (67%),[25] with life expectancy being 70.3 years in males and 76.6 years in females.[25] Despite important advances in recent decades, extreme variations in access to adequate medical care and education persist across LA and Caribbean (LAC) countries.[25,26] In 2010, 10% of the population in LA were living in conditions of multidimensional poverty,[26] with indigenous people having among the highest rates of morbidity and mortality.

As a consequence of the disparity in access to adequate medical care and socio-economic differences, HTN remains a major concern in LA. Among the non-communicable diseases, CVD takes the highest toll, contributing to 31% of all deaths according to 2010 estimates, and a 60% increase in this rate is predicted over the next 20 years.[25] In 2000, mortality from cerebrovascular disease (CEVD) was 2 to 4-fold higher in LA than in North America. Although both CVD and CEVD have shown a downward trend in LA during the last four decades, wide variations are reported between countries. Poverty and income inequality are driving factors of mortality in the region: 30% of premature deaths from CVD are in the poorest quintile of the population, whereas only 13% are in the wealthiest quintile.[25,27]

Available data on the distribution of cardiovascular risk factors in the LAC region are limited, and the few studies available show significant discrepancies in the prevalence estimates of HTN across the region.[28] According to estimates made in 2010 by the World Health Organization (WHO), the highest prevalence occurs in the Caribbean islands (43–56%) and the lowest occurs in Mexico and Peru (26–41%) for both men and women.[1] In 2013, the Latin American Consortium of Studies in Obesity (LASO) analysed data measuring similar indicators in thousands of individuals across eight countries in the region.[28] The study concluded that major CVD risk factors are highly prevalent in LAC, in particular low high-density lipoprotein (HDL) cholesterol and hypertriglyceridaemia (Table 2).[28] In addition, irrespective of their origin from urban or rural areas, 20–23% of the adult population in LAC have HTN.[29] Marked differences could be seen in the prevalence of HTN between LAC and the USA. While obesity, high total cholesterol, high low-density lipoprotein cholesterol, and hypertriglyceridaemia were more prevalent in the USA, low HDL-cholesterol was more prevalent in LAC.[28]

Table 2: Prevalence of risk factors in Latin America.[28]

Risk factors	Women (%)	Women (95% CI)	Men (%)	Men (95% CI)	All (%)	All (95% CI)
Smoking	19.5	11.2–31.9	32.2*	25.5–39.8	25.8	18.1–35.3
Hypertension	19.4	13.1–27.6	21.1	11.9–34.7	20.2	12.5–31.0
Diabetes mellitus	4.8	3.4–6.8	5.1	3.5–7.5	5.0	3.4–7.9
High total cholesterol	9.6	7.3–12.7	8.2	6.4–10.3	8.9	6.9–11.4
High LDL cholesterol	9.3	6.0–14.2	7.6	5.1–11.0	8.5	5.8–12.2
Low HDL cholesterol	76.9	68.2–83.9	32.8*	18.7–51.0	53.3	47.0–63.4
Hypertriglyceridaemia	23.3	17.6–30.2	29.9*	20.1–41.9	26.5	18.1–35.3

*p<0.05 for prevalence relationships between men and women, adjusted for age and study.
CI: confidence interval; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

The Latin American Consortium of Studies in Obesity (LASO) study is one of several studies that have shown a prevalence of HTN in the LA region within the range registered in developed countries (20–40%).[28,30-32] Hypertensive Latin Americans are, however, 2.7-times more likely to experience myocardial infarction than their normotensive counterparts, a ratio that reaches 3.7-times in Mexico and Venezuela.[28,30-32] In LA, the percentage of strokes attributed to HTN is among the highest in the world (up to 60–80%), with HTN being responsible for a significant number of heart failure cases (22%).[28,30-32] The impact of HTN on chronic renal disease is still unknown. As observed in other parts of the world, HTN is the highest contributor of death in LA, followed by smoking, obesity, hyperglycaemia, and hypercholesterolaemia.[33]

The prevalence of awareness and control of HTN in LAC varies between countries.[34] Surveillance of HTN prevalence studies in LAC published between 2001 and 2010 revealed that the level of awareness ranged from 53% (Peru) to 76% (Mexico) and control rates ranged from 12% (Peru) to 41% (Mexico).[34] In Venezuela, up to 41% of affected individuals do not receive pharmacological treatment. Of those receiving some medication (49%), less than 21% are appropriately controlled.[35] As observed in other LAC countries, angiotensin converting enzyme (ACE) inhibitors and β-blockers are the most frequently used antihypertensive drugs in Venezuela (33% and 25%, respectively), followed by CCBs (15%), diuretics (15%), and angiotensin-receptor blockers (ARBs; 11%).[36]

Several reasons are thought to account for low BP control rates in the LAC region, but a very important one is a lack of adherence to treatment, which can change with patient perception of disease severity (the range of which is reported to be from mild to moderate to severe, depending on the impact of HTN on patient quality of life). An analysis of almost 2,000 hypertensive patients under clinical management revealed that treatment adherence ranged from 50%, when the perception of the severity of HTN was considered mild, to 100% when it was considered severe.[36] This observation highlights the importance of education and awareness of HTN in clinical practice to improve adherence.

The Pan American Health Organization (PAHO) has played a critical role in the prevention and control of HTN in the LAC region.[37] Since 2000, PAHO has worked towards the implementation of standardised surveillance and management systems across the region and emphasised the need for healthcare strategies for effective prevention of HTN to work in close association with those for the prevention of other CVD risk factors.[37] PAHO is using innovative models of care that aim to: (1) involve both patients and communities as essential contributors to defining and monitoring plans of care; (2) use practical

algorithms for diagnosis, treatment, and follow-up; (3) assess CVD risk as a base for planning control of CVD and related risk factors; and (4) simplify treatment and facilitate the availability of medications at low cost.[37]

The following recommendations could be considered in order to improve HTN control in LAC:

- Elaborate and integrate efforts towards the enforcement of a base plan for HTN control
- Establish a wide-coverage campaign for public education
- Establish and reinforce the application of a standard of HTN prevention, diagnosis, and treatment across the region (in the form of standardised guidelines)
- Allow access to drugs free of charge by private insurers and in government-run medical centres
- Establish medical education plans for doctors and patient awareness
- Improve regular surveillance of epidemiological data on HTN, including the development of a single database across the region

Reaching Blood Pressure Control in Asia and the Middle East – Real-World Data

Doctor Jorge Sison

As has been described, the increase in prevalence of HTN has proceeded at an alarming rate, particularly in some countries of the Middle East and South Asia regions where control of BP remains very low.[8,13–19,38,39] This, in addition to the complexity of HTN and its variable pathological background, makes treatment difficult.[40]

To adequately control HTN, the majority of hypertensive patients require the use of two or more antihypertensive agents.[41] Despite this, the use of dual SPC therapies remains low in the Middle East and Asia. An illustration of this can be seen in the Philippines, where, between 2007 and 2013, the use of monotherapy has remained high (75–86%) compared with dual (11–21%) or triple (0.4–21%) SPC.[39]

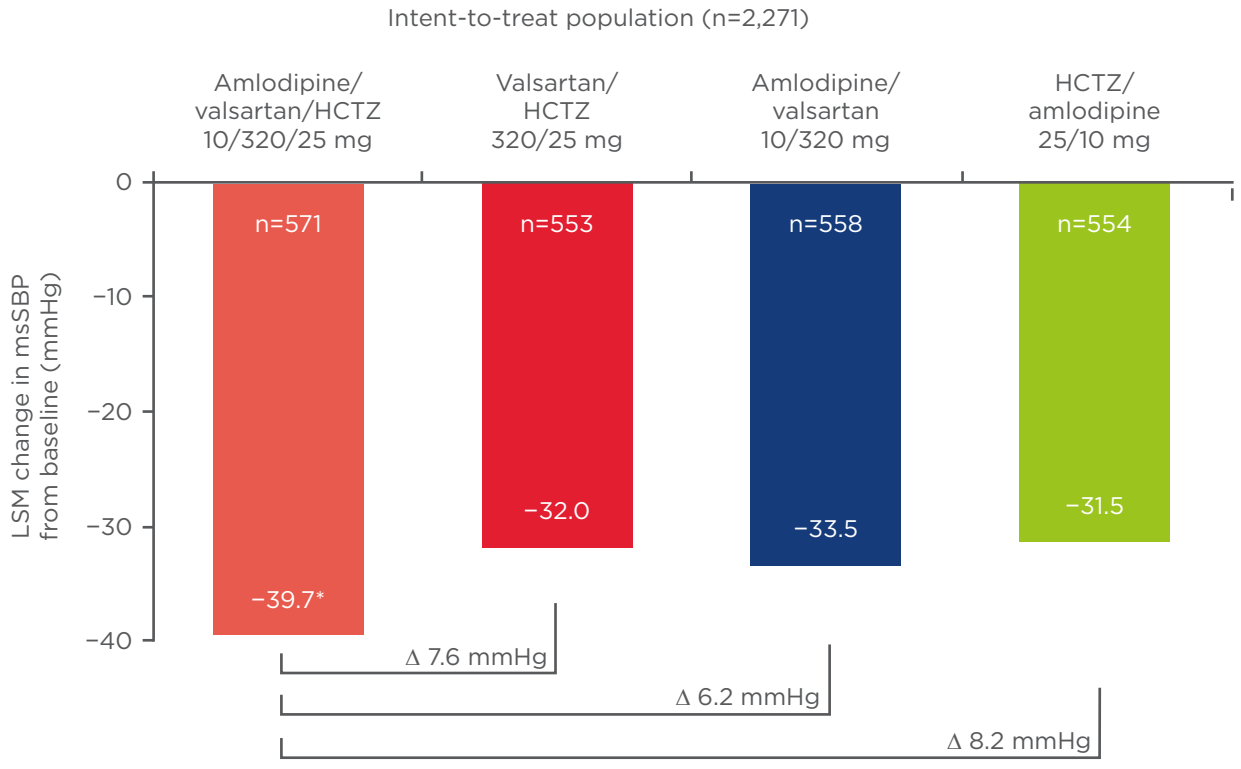


Figure 2: Triple combination therapy with AML/VAL/HCTZ reduces systolic BP significantly more than respective dual therapies.[45]

Randomised, double-blind, multinational, parallel-group, active-controlled study incorporating a single-blind run-in period (maximum 4 weeks) followed by 8-week double-blind treatment period.

*p<0.0001 versus all other combinations.

AML: amlodipine; VAL: valsartan; HCTZ: hydrochlorothiazide; SBP: systolic blood pressure; BP: blood pressure; LSM: least squares mean; msSBP: mean sitting systolic blood pressure.

Clinical studies have demonstrated that a combination of multiple antihypertensive agents is more effective than up-titrating the dose of a single agent, resulting in improvements in antihypertensive efficacy and a reduction in major adverse cardiovascular effects.[42,43] The additional BP reduction as a result of combining drugs of two different classes is estimated to be approximately five-times greater than doubling the dose of one drug.[42,43] US and European guidelines highlight the benefits of combining multiple drugs with a different mechanism of action to improve adherence and BP control. The 2013 European Society of Hypertension (ESH)/ESC guidelines recommend the use of a diuretic (thiazide) plus a CCB or RAS blocker (ACE inhibitors or ARBs), or a CCB plus RAS blocker.[21] When three drugs are required, the preferred combination is a CCB plus RAS blocker and thiazide.[21,44] Dual combination of ACE inhibitors and ARBs is not recommended.[21]

Randomised clinical trials have demonstrated that combination therapies are well tolerated and associated with high antihypertensive effects.[45-47] In patients previously uncontrolled with monotherapy, antihypertensive effects were observed at Week 16 in a dose-dependent manner after a direct switch to amlodipine/valsartan (AML/VAL) in the majority of the patients.[48] Overall, a triple therapy with AML/VAL/hydrochlorothiazide (AML/VAL/HCTZ) results in significantly greater BP reductions than dual therapies (Figure 2),[45] with systolic antihypertensive effects achieved in proportion to HTN severity.

In the real world, the efficacy and tolerability of SPC therapies have also been established by the EXCITE study.[39] The study cohort was a multi-ethnic population of more than 9,700 hypertensive patients treated for 26 weeks in routine clinical practice across the Middle East and Asia. Statistically significant and clinically meaningful BP reductions from baseline across all treatment dosages and severities of HTN were observed after 26 weeks. Oedema and peripheral oedema were the most frequently reported adverse events in the dual and triple groups. The results of the EXCITE study provide evidence that dual SPC therapy with AML/VAL and triple SPC therapy with AML/VAL/HCTZ provide clinically meaningful BP reductions and are well tolerated in a large multi-ethnic hypertensive population.[39]

Further analysis has demonstrated that the effectiveness and tolerability of dual or triple SPC regimens are maintained in patients with the highest risk of CVD events (elderly, obese, and patients with diabetes or isolated systolic HTN).[49]

Summary

The presentations and discussions in this symposium leave no doubt that HTN is a major public health challenge worldwide. The importance of HTN as a risk factor for CVD is increasingly being recognised, and HTN is predicted to become the leading preventable cause of heart failure associated with ageing. Even in patients with controlled HTN (<140/90 mmHg), there is a 50% risk of a cardiovascular event.[2] For changes in the burden of disease resulting from HTN in the developing world to be realised, simplified treatment strategies and the adoption of standardised algorithms to effectively control BP are needed. In addition, accessibility to reliable and affordable drugs, coupled with educational and awareness programmes, can help to deliver care alongside the establishment of common targets and patient monitoring. Multi-drug therapy with SPC can be used effectively and safely to improve treatment adherence in the majority of hypertensive patients, including those at high risk of CVD.

REFERENCES

1. WHO. Global atlas on cardiovascular disease prevention and control. Available at: http://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/. Last accessed: 7 September 2015.

2. [No authors listed]. Hypertension: an urgent need for global control and prevention. Lancet. 2014;383(9932):1861.

3. Chow CK et al; PURE (Prospective Urban Rural Epidemiology) Study investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013;310(9):959-68.

4. Kassebaum NJ et al. Global, regional, and national levels and causes of maternal mortality during 1990–2013: a

systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2014;384(9947):980-1004.

5. Rapsomaniki E et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet. 2014;383(9932):1899-911.

6. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71.

7. Wang H et al. Age-specific and sex-specific mortality in 187 countries, 1970-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2071-94.

8. Kearney PM et al. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217-23.

9. Critchley J et al. Explaining the increase in coronary heart disease mortality in Beijing between 1984 and 1999. Circulation. 2004;110(10):1236-44.

10. Li YC et al. [Prevalence of hypertension among Chinese adults in 2010]. Zhonghua Yu Fang Yi Xue Za Zhi. 2012;46(5):409-13.

11. Angeli F et al. Hypertension around the world: new insights from developing countries. J Hypertens. 2013;31(7):1358-61.

12. Lewington S et al; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.

13. Pereira M et al. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. J Hypertens. 2009;27(5):963-75.

14. Wolf-Maier K et al. Hypertension treatment and control in five European countries, Canada, and the United States. Hypertension. 2004;43(1):10-17.

15. Erem C et al. Prevalence of prehypertension and hypertension and associated risk factors among Turkish adults: Trabzon Hypertension Study. J Public Health (Oxf). 2009;31(1):47-58.

16. Su T-C et al. Evidence for improved control of hypertension in Taiwan: 1993-2002. J Hypertens. 2008;26(3):600-6.

17. Rampal L et al. Prevalence, awareness, treatment and control of hypertension in Malaysia: a national study of 16,440 subjects. Public Health. 2008;122(1):11-18.

18. Aekplakorn W et al. Prevalence and management of prehypertension and hypertension by geographic regions of Thailand: the Third National Health Examination Survey, 2004. J Hypertens. 2008;26(2):191-8.

19. Ibrahim MM, Damasceno A. Hypertension in developing countries. Lancet. 2012;380(9841):611-19.

20. NICE. Hypertension: Guidance and guidelines. Available at: https://www.nice.org.uk/guidance/cg127. Last Accessed: 8 September 2015.

21. Mancia G et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.

22. Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. Drugs. 2002;62(3):443-62.

23. Quan A et al. A review of the efficacy of fixed-dose combinations olmesartan medoxomil/hydrochlorothiazide and amlodipine besylate/benazepril in factorial design studies. Am J Cardiovasc Drugs. 2006;6(2):103-13.

24. Chiang CE et al. 2015 guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the management of hypertension. J Chin Med Assoc. 2015;78(1):1-47.

25. Barreto SM et al. Epidemiology in Latin America and the Caribbean: current situation and challenges. Int J Epidemiol. 2012;41(2):557-71.

26. Perel P et al. Noncommunicable diseases and injuries in Latin America and the Caribbean: time for action. PLoS Med. 2006;3(9):e344.

27. PAHO. Premature mortality due to cerebrovascular disease in the Americas, circa 2006. Available at: http://www.paho.org/bulletins/index.php?option=com_content&view=article&id=527:chronic-diseases-inequalities&Itemid=0&lang=en. Last Accessed: 5 October 2015.

28. Miranda JJ et al; The Latin American Consortium of Studies in Obesity (LASO). Major cardiovascular risk factors in Latin America: a comparison with the United States. PLoS One. 2013;8(1):e54056.

29. Hernández-Hernández R et al. Hypertension and cardiovascular health in Venezuela and Latin American countries. J Hum Hypertens. 2000;14 Suppl 1:S2-S5.

30. Rivera-Andrade A, Luna MA. Trends and heterogeneity of cardiovascular disease and risk factors across Latin American and Caribbean countries. Prog Cardiovasc Dis. 2014;57(3):276-85.

31. Lanas F et al; INTERHEART Investigators in Latin America. Risk factors for acute myocardial infarction in Latin America: the INTERHEART Latin American study. Circulation. 2007;115(9):1067-74.

32. Rubinstein A et al. High blood pressure in Latin America: a call to action. Ther Adv Cardiovasc Dis. 2009;3(4):259-85.

33. Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. N Engl J Med. 2013;369(10):954-64.

34. Burroughs Peña MS et al. Usefulness for surveillance of hypertension prevalence studies in Latin America and the Caribbean: the past 10 years. Rev Panam Salud Pública. 2012;32(1):15-21.

35. Silva H et al; CARMELA Study Investigators. Cardiovascular risk awareness, treatment, and control in urban Latin America: Am J Ther. 2010;17(2):159-66.

36. Ferrer, J. Systemic Hypertension: Impact of Its Perception on Treatment Goal Attainment. Presented at the Annual Scientific Meeting of the Venezuelan Society of Cardiology. 2004.

37. Ordunez P et al. Hypertension Prevention and Control in Latin America and the Caribbean. J Clin Hypertens (Greenwich). 2015;17(7):499–502.

38. Wang Z et al. [The current situation of blood pressure control and the influencing factors on hypertensive patients in residential communities of China]. Zhonghua Liu Xing Bing Xue Za Zhi. 2012;33(9):903–6.

39. Sison J et al. Real-world clinical experience of amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide in hypertension: the EXCITE study. Curr Med Res Opin. 2014;30(10):1937–45.

40. Waeber B, Feihl F. [Arterial hypertension. Factors favoring long-term compliance with therapy]. Rev Med Suisse. 2007;3(93):22–4.

41. Düsing R. Optimizing blood pressure control through the use of fixed combinations. Vasc Health Risk Manag. 2010;6:321–5.

42. Sood N et al. Combination therapy for the management of hypertension: A review of the evidence. Am J Health Syst Pharm. 2010;67(11):885–94.

43. Wald DS et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122(3):290–300.

44. Mancia G et al; European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009;27(11):2121–2158.

45. Calhoun DA et al. Amlodipine/valsartan/hydrochlorothiazide triple combination therapy in moderate/severe hypertension: secondary analyses evaluating efficacy and safety. Adv Ther. 2009;26(11):1012–23.

46. Poldermans D et al. Tolerability and blood pressure-lowering efficacy of the combination of amlodipine plus valsartan compared with lisinopril plus hydrochlorothiazide in adult patients with stage 2 hypertension. Clin Ther. 2007;29(2):279–89.

47. Smith TR et al. Amlodipine and valsartan combined and as monotherapy in stage 2, elderly, and black hypertensive patients: subgroup analyses of 2 randomized, placebo-controlled studies. J Clin Hypertens (Greenwich). 2007;9(5):355–64.

48. Allemann Y et al. Efficacy of the combination of amlodipine and valsartan in patients with hypertension uncontrolled with previous monotherapy: the Exforge in Failure after Single Therapy (EX-FAST) study. J Clin Hypertens (Greenwich). 2008;10(3):185–94.

49. Assaad-Khalil SH et al. Real-world effectiveness of amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide in high-risk patients and other subgroups. Vasc Health Risk Manag. January 2015:71–8.

NEW PARADIGMS IN HEART FAILURE: RAAS INHIBITION AND THE MANAGEMENT OF HYPERKALAEMIA

This symposium took place on 29th August 2015 as a part of the European Society of Cardiology Congress in London, UK

Chair

John McMurray[1]

Speakers

Faiez Zannad,[2] Ileana L. Piña,[3] John McMurray[1]

1. University of Glasgow, Glasgow, UK

2. Henri Poincaré University of Nancy, Nancy, France

3. Montefiore-Einstein Medical Centre, Bronx, New York, USA

Disclosure: John McMurray has no relevant disclosures to declare. Faiez Zannad has acted on steering committees for Bayer, Boston Scientific, Novartis, Pfizer, ResMed, and Takeda; acted as a consultant and advisory board member for Air Liquide, Amgen, CVRx, Relypsa, Servier, St Jude, Stealth Peptide, ZS Pharma, and Quantum Genomics; and received a research grant from Roche Diagnostics. Ileana Piña has acted as a consultant and advisory board member for ZS Pharma.

Acknowledgements: Writing assistance was provided by Dr Lucy Smithers of ApotheCom and funded by ZS Pharma Inc.

Support: The symposium was organised by Medavera, Inc. and supported by an educational grant from ZS Pharma Inc. Authors received honoraria for preparation and delivery of their presentations. The paper is an interpretation of the views of the speakers, but is not written by them. The views and opinions expressed are those of the authors and not necessarily of Medavera, Inc. or ZS Pharma Inc.

Citation: EMJ Cardiol. 2015;3[2]:53-61.

MEETING SUMMARY

This educational symposium discussed advances in blocking the renin–angiotensin–aldosterone system (RAAS) for patients with chronic systolic heart failure (HF), and the issues of managing hyperkalaemia in these patients.

Prof John McMurray introduced the session, outlining the current treatment paradigm and the challenges presented by the associated risks of hyperkalaemia. Prof Faiez Zannad discussed the under-utilisation of life-saving RAAS inhibitor (RAASi) drugs in clinical practice and the benefits to be gained for patients by optimising their use. Prof Ileana Piña reviewed current advances in pharmacological treatments for chronic HF that aim to reduce the risks of renal dysfunction and hyperkalaemia. Finally, Prof John McMurray discussed the potential of new treatment paradigms for improved outcomes in patients with chronic HF.

Symposium Background and Learning Objectives

Treatment with agents that block the RAAS (RAASi) is considered the standard of care (SOC) for patients with systolic HF (HF with reduced ejection fraction [HF-REF]).[1] However, their use is associated with an increased risk of hyperkalaemia.

Hyperkalaemia is defined by an abnormally high concentration of potassium ions in the blood (>5.0 mmol/L according to US guidelines).[2] It can become a chronic, persistent condition that is an ongoing concern for patients with HF, as serum potassium levels >5 mmol/L have been associated with an increased risk of mortality in patients with cardiovascular and renal diseases.[3]

Current practice is to discontinue or reduce the use of RAASi in patients who develop hyperkalaemia. However, lack of knowledge regarding when to titrate, or the failure to titrate, these drugs leads to variation in their use in practice as clinicians attempt to avoid harm. Registries have consistently reported a large gap between real-life practice and recommended practice in international guidelines in the use of these life-saving, evidence-based therapies.[4,5]

With new options for the treatment of hyperkalaemia becoming available, it may be feasible to follow guidelines for directed medical therapy and optimise the use of RAASi, allowing patients to benefit from these life-saving treatments, before considering other therapeutic options.[6]

The learning objectives of the symposium were: 1) To explain why RAASi doses should be optimised and maintained; 2) To review the reasons why target doses are not reached for RAASi; 3) To compare and contrast new pharmacological options for RAAS inhibition and hyperkalaemia management; and 4) To describe the barriers and challenges to RAASi use in HF, in order to identify new paradigms for consideration in achieving better outcomes for HF patients.

Why Aren't We Titrating Optimal RAAS Inhibitor Life-Saving Therapy?

Professor Faiez Zannad

RAASi have a proven benefit in reducing deaths in HF patients, and international guidelines, such as those published by the European Society of Cardiology (ESC), recommend their use in patients with systolic HF.[1] Our analysis of the ESC Heart Failure Long-term Registry shows that not all patients who are eligible for these drugs are being treated with them. In this registry, <10% of eligible ambulatory patients with chronic HF are not treated with either angiotensin-converting enzyme inhibitors (ACEi) or aldosterone receptor blockers (ARBs) and beta-blockers, while around 30% of patients eligible for mineralocorticoid receptor antagonists (MRAs) are not being treated either.[4] While the majority of eligible patients in this registry were receiving RAASi, many were not receiving them at their target dose (70.7% of those on ACEi, 75.9% of those on ARBs, 82.5% of those on beta-blockers, and 69.5% of those on MRAs).[4] Previous reports in the literature from the US show higher rates of underuse, such as 80% of eligible patients receiving an ACEi or ARB, 86% receiving a beta-blocker, but only 36% receiving an MRA in the IMPROVE HF registry of outpatient cardiology practices.[7]

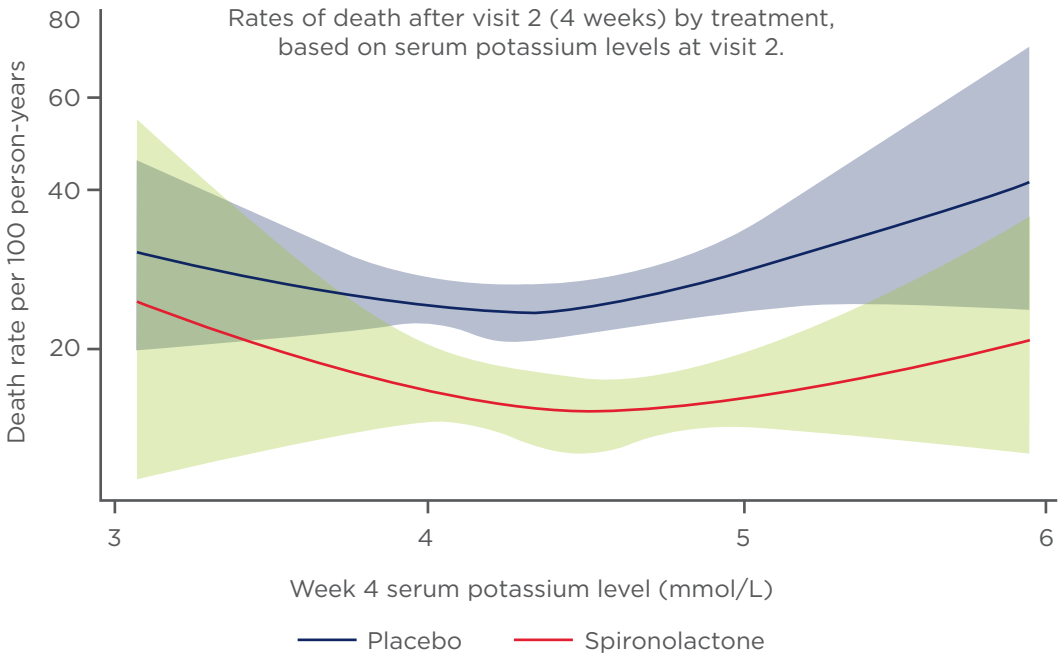


Figure 1: Mortality in the RALES study population in relation to serum potassium levels.
p<0.0001 for comparison between spironolactone and placebo. Shaded areas represent 95% confidence intervals.

The main reasons for underuse of these treatments are chronic kidney disease (CKD) and hyperkalaemia.[4,8] Hyperkalaemia is a serious threat to HF patients and is associated with increased mortality.[3] Our findings from the ESC registry study and the IMPROVE HF registry suggest that concern over these serious risks leads clinicians to discontinue RAASi or use them at doses below the guidelines' recommended target: approximately 60% of patients on ACEi or ARBs and approximately 70% of patients on beta-blockers were below the target dose at baseline and 2 years later. This is of concern as it has been shown that patients who do not receive RAASi at discharge from hospitalisation for HF have double the 30-day risk of death or readmission.[9]

Even in patients with severe renal disease, treatment with RAASi can reduce mortality.[10] The range of potassium levels in clinical trials may be underestimated, since patients with multiple comorbidities or moderate-to-severe renal impairment have typically been excluded.[11-14] In clinical practice, cardiologists treating patients with HF may have to deal with higher rates of hyperkalaemia, depending on the patient population and severity of CKD.[3,15-19] An understanding of the mechanism of action of RAASi shows that elevations in potassium levels are a common feature of all RAASi, and increases in mortality rates were seen at levels >5.0 mmol/L in the original studies (Figure 1).[20] Patients with risk factors for hyperkalaemia, including older age, diabetes, and CKD, are also those who receive the greatest absolute benefit from RAASi therapy.[3,13]

These data demonstrate that increased survival can be achieved in patients with HF who are at risk of hyperkalaemia due to the development of new hyperkalaemia therapies, through the use of algorithm-based, life-saving RAASi treatment, and by monitoring of potassium and creatinine levels.[13,21] If hyperkalaemia occurs, clinical outcomes can be optimised by the prompt recognition and management of hyperkalaemia, and the new potassium binders can potentially treat hyperkalaemia without the need to reduce or discontinue RAASi, allowing patients to continue benefitting from reduced mortality and hospitalisation.[6]

New Pharmacological Options for Heart Failure

Professor Ileana L. Piña

The treatment of HF today is complex, with challenging patients who present in clinics with more comorbidities and more advanced disease. The goals of treatment remain unchanged and aim to alleviate symptoms, reduce excess extracellular fluid volume, improve haemodynamics, maintain renal function and perfusion to vital organs, prevent hospital admissions, avoid disease progression, and reduce deaths. Optimising chronic therapy for HF patients is a key part of these goals.

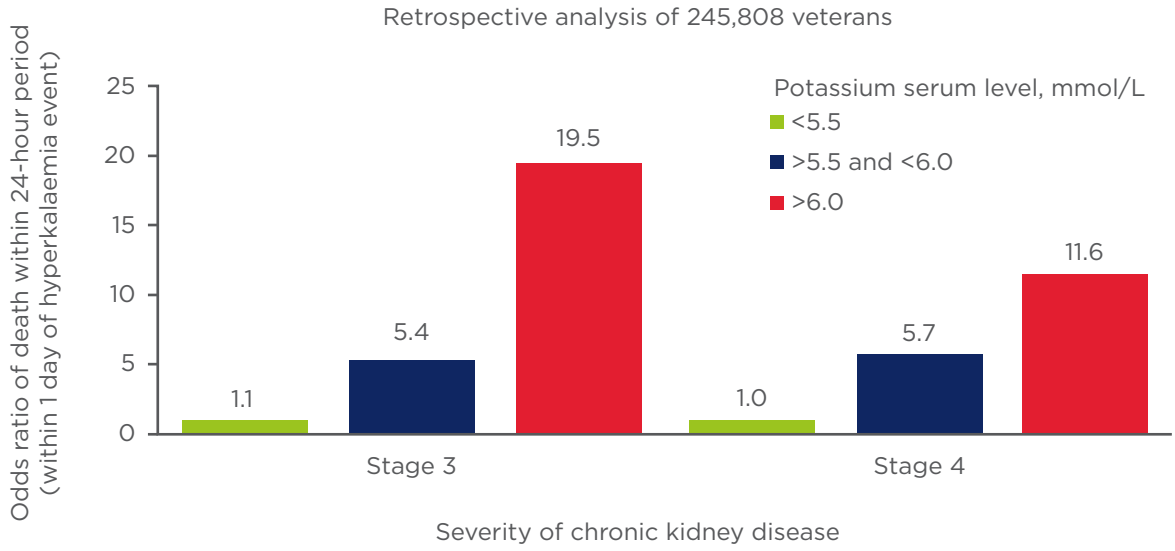


Figure 2: Risk of mortality in relation to serum potassium levels in a retrospective cohort of patients with heart failure and chronic kidney disease.[3]

Current treatment options for patients with systolic HF are limited by issues of hypotension, reductions in renal function, and hyperkalaemia. Exciting advances in pharmacological treatments for HF may overcome these limitations by addressing new targets. Currently, treatments for HF target the sympathetic nervous system, the RAAS, sodium and water retention, and loss of contractility. The question is whether the new drugs in development (vasodilators, synthetic natriuretic peptides, sinus node inhibitors, neutral endopeptidase inhibitors [used with ARBs or an angiotensin receptor neprilysin inhibitor such as valsartan/sacubitril (LCZ696)], actin–myosin binders, and potassium binders) will be subject to the same limitations or not.

Serelaxin is a new vasodilator drug that has shown efficacy for the primary endpoint of dyspnoea relief in acute HF in the RELAX-AHF trial.[22,23] Notably, the risk of cardiovascular death was significantly reduced at 6 months with SOC plus serelaxin versus SOC plus placebo (hazard ratio [HR]: 0.63, 95% confidence interval [CI]: 0.41–0.96; p=0.028), and this is now being investigated further in the ongoing RELAX-AHF-2 prospective mortality trial (NCT01870778). It is also of interest that the serelaxin group showed fewer increases in creatinine and blood urea nitrogen, indicating fewer patients at risk of reduced renal function versus the placebo group.[22,23]

Ularitide is a synthetic natriuretic peptide that causes vasodilation, diuresis, and natriuresis. It has demonstrated symptom relief and vasodilation with preserved renal function in Phase I and II trials, and is currently in a Phase III trial for safety and efficacy on clinical status and mortality outcome safety in acute HF (TRUE-AHF).[24,25] This trial aims to enrol patients within the first few hours of presenting at the hospital as there is evidence that treating patients as early as possible is beneficial.[24]

Ivabradine inhibits the sinus node by targeting the I_f pacemaker current sodium channel and hence reducing heart rate. This drug was recently approved in Europe and the USA on the basis of the SHIFT trial, which demonstrated improvements in the primary endpoint of cardiovascular mortality and hospitalisations (HR for the combined primary endpoint: 0.82, 95% CI: 0.75–0.90; p<0.001). This was driven by reductions in hospitalisations more than reductions in cardiovascular mortality.[26] Analysis of factors influencing outcomes showed that ivabradine was more effective in patients with high baseline heart rate, and in fact only about half of the patients (56%) in the trial were receiving >50% of their target dose of beta-blocker, confirming the challenge of optimising patients' chronic heart therapy.

Loss of contractility has traditionally been treated with inotropes, but their use is restricted by increased mortality. The novel selective cardiac myosin activator omecamtiv mecarbil (OM) is a promising new drug in development that does not change left ventricle contractility (dP/dt), but strengthens and prolongs it without increasing oxygen consumption in the myocardium.[27,28] In the Phase II ATOMIC-AHF trial of OM in HF, despite the study not reaching its primary endpoint of dyspnoea relief, the response appeared to be better in the cohort of patients given higher doses of the drug.[28] Further trials to assess the efficacy of this new approach in treating loss of contractility are ongoing.

An important advance in the treatment of patients with HF has been the development of potassium binders to address the need for hyperkalaemia management, in particular for hyperkalaemia resulting from RAAS inhibition. The clinical evidence base for the use of RAASi to benefit both post-myocardial infarction and chronic HF patients is strong, and hence their use is recommended by international guidelines.[2] RAASi treatment, particularly in combination with comorbidities such as CKD and/or diabetes, contributes to hyperkalaemia development in these patients. While hyperkalaemia can be controlled to some extent in clinical trials with careful patient selection and monitoring,[11,12,29] this is not representative of real-life patient populations in whom hyperkalaemia rates are notably higher.[11,30-32] These real-world rates of potassium levels ≥5.0 mmol/L, combined with the increasing prevalence of patients with combined HF, CKD, and diabetes, leads to many patients not being given RAASi because of the risk of hyperkalaemia.[33,34] It is in the best interests of clinicians and patients to manage hyperkalaemia, since it contributes to increased costs through emergency department visits and hospitalisations,[35] and increases the risk of death in HF and renal disease patients (Figure 2).[3,36]

Patients find it difficult to control potassium levels through diet alone, and since the 1950s the only pharmacological option in the USA for reducing potassium has been sodium polystyrene sulfonate

(Kayexalate®), which is neither a pleasant nor benign treatment.[37] Therefore, the availability of potassium binders is particularly welcome in order to make it possible for more patients to benefit from life-saving RAASi therapy. Zirconium cyclosilicate (ZS-9) is an insoluble, non-absorbed zirconium silicate that preferentially and selectively traps potassium ions, and is eliminated in stools (Figure 3). It has a rapid onset of action due to the selective mechanism of trapping potassium ions that starts in the upper gastrointestinal tract. ZS-9 normalises serum potassium in a median time of 2.2 hours, and consistently maintains normokalaemia across a range of patients receiving RAASi.[38,39] Another agent, patiromer sorbitex calcium, is a non-specific, organic polymer that binds potassium primarily in the colon and is then eliminated in stools. Its slow onset and low response rate of action may limit its usefulness; however, it appears to maintain normokalaemia.[40]

There are also developments in RAASi to treat HF-REF that may have less severe effects on potassium levels, in particular the non-steroidal MRA finerenone. Studies indicate that this drug's effects on potassium levels and renal function are dose-related; trials are ongoing.[41]

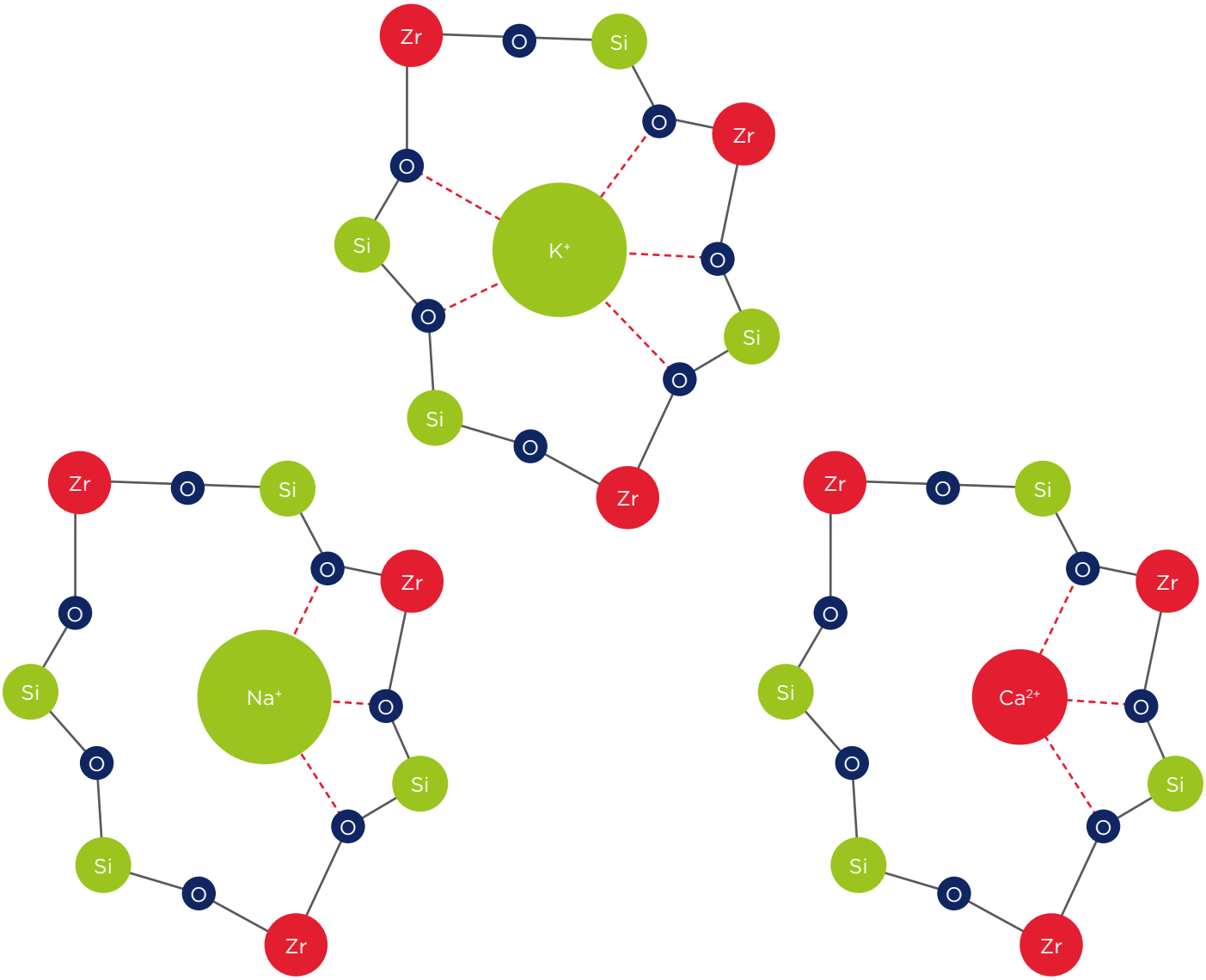


Figure 3: Mechanism of action of ZS-9 in binding potassium.
Similarly to physiological potassium channels, the pore size of ZS-9 is such that only potassium ions (K^+) interact strongly and are selectively captured.
ZS-9: Zirconium cyclosilicate.
Reproduced with permission from Stavros F et al. Characterization of structure and function of ZS-9, a K^+ selective ion trap. PLoS One. 2014;9(12):e114686.

The future prospects for the treatment of HF are exciting, with new drugs and new targets providing a wider range of options for treatment, as well as allowing better use of currently available RAASi by addressing hyperkalaemia. Lessons learned from previous trials serve to inform future studies with regards to earlier intervention and refining the choice of patient population through biomarkers. Improvement is also needed in patients' transition from acute care to chronic HF therapy in order to prevent hospital readmissions.[42]

Paradigm Shifts in the Pharmacological Management of Heart Failure

Professor John McMurray

The past 30 years have seen several paradigm shifts in the treatment of HF, which have resulted in consistent international guidelines owing to the strong evidence base for the drugs that are used today.[1,2] The core therapies for HF are beta-blockers, ACEi, ARBs, and MRAs, and there are additional roles for devices or additional drugs in selected subsets of patients. Is it possible to improve further on the current paradigm?

The recent PARADIGM-HF trial suggests that it will be possible to go beyond RAASi, not just blocking harmful neurohumoral pathways but also augmenting potentially beneficial effects. The new paradigm would aim to harness endogenous protective systems and replace existing treatments rather than adding to them. The best understood protective pathways in the heart are the natriuretic peptides, which can be augmented by inhibiting neprilysin. Neprilysin breaks down natriuretic peptides and a range of other vasoactive substances, including bradykinin, adrenomedullin, and substance P, as well as angiotensin II. Coupling neprilysin inhibition with RAASi (angiotensin receptor neprilysin inhibition [ARNi]) has the potential to reset the neurohumoral balance in patients with HF.[43,44]

The PARADIGM-HF trial compared the efficacy of ARNi versus ACEi in patients with HF-REF. Beta-blocker and MRA therapy was permitted according to guidelines. Patients were excluded if their potassium levels rose above 5.2 mmol/L during a run-in period, first on enalapril then on valsartan. The run-in was intended to identify patients susceptible to hypotension and angioedema but also excluded patients predisposed to hyperkalaemia from the trial population. The trial was stopped early due to the significant benefits demonstrated by ARNi, both for cardiovascular mortality (HR: 0.80, 95% CI: 0.71–0.89; p<0.001) and HF hospitalisations (HR: 0.79, 95% CI: 0.71–0.89; p<0.001).[43] This treatment gave incremental benefits even for patients who were treated with the full combination of beta-blocker, MRA, and ACEi.[44]

Safety data from PARADIGM-HF suggest that ARNi may be better tolerated than the ACEi comparator, enalapril. There were fewer patients in the ARNi arm with creatinine levels ≥2.5 mg/dL and slightly fewer patients with serious hyperkalaemia (potassium levels ≥6.0 mmol/dL: 5.6% on enalapril versus 4.3% on valsartan), although still a very high rate of moderate-to-severe hyperkalaemia (potassium levels ≥5.5 mmol/L: 17.3% on enalapril versus 16.1% on valsartan).[43] It has yet to be determined whether these improvements in safety and efficacy are sufficient for this new treatment to replace existing ARB or ACEi therapy.

Another potential change to the HF treatment paradigm is to inhibit the RAAS with a direct renin inhibitor in order to target the rate-limiting step of the cascade. The ATMOSPHERE trial comparing the efficacy of the direct renin inhibitor aliskiren with enalapril, both singly and in combination, on mortality and hospitalisation in patients with HF (NCT00853658), will be reporting in early 2016.[45]

Non-steroidal MRAs, which aim to have a reduced effect on renal function, may also change the treatment paradigm. The Phase IIb ARTS-HF trial of finerenone versus eplerenone was reported at the 2015 ESC Congress,[46] and a Phase III trial is planned to compare finerenone with eplerenone in patients with HF and Type 2 diabetes or CKD, who are at risk of hyperkalaemia, for efficacy in reducing mortality and hospitalisation.

As already mentioned, improvements in treatment paradigms can be anticipated with the availability of potassium binders that can treat or prevent hyperkalaemia. This could allow more patients to benefit from RAASi while reducing the risks associated with hyperkalaemia.

Further improvements to the treatment paradigm may be available owing to the development of a new RAASi. TRV(120)027 is a biased angiotensin II type 1 receptor (AT1R) ligand that selectively activates the beneficial beta-arrestin pathway, but blocks the alternative detrimental pathway from

the AT1R. It is currently being tested in a Phase II proof-of-concept trial in patients with acute HF.[47]

In summary, blocking the RAAS is the core of current treatment of HF. We have the hope of better ways of inhibiting this system through addressing new targets, such as neprilysin and renin. Hyperkalaemia and renal insufficiency remain the Achilles heel of current RAASi therapy and prevent many people from benefitting from these treatments, but this may be addressed by the new RAASi with reduced effects on potassium levels or renal function, or by using potassium binders to manage hyperkalaemia.

Panel Discussion

Prof McMurray invited Prof Piña to explain the pros and cons of the two different potassium binders discussed in the symposium. Prof Piña explained that, whereas ZS-9 was a binder with a structure that literally caged potassium ions preferentially, patiromer was an organic polymer that, when mixed with water, absorbed potassium in a non-specific manner in the colon. Potassium levels rise again after withdrawal of both binders. She noted that the best ways to use the binders were not yet determined – for example, whether they should only be used sporadically when hyperkalaemia occurred, or be prescribed concomitantly when mineralocorticoids were initiated. It would be reasonable to raise the dose of RAASi therapy in patients with controlled potassium levels. Both drugs have been followed-up for 1 year. In addition, more information was needed on their effects on other electrolytes, such as sodium, calcium, and magnesium. Prof Zannad noted that patiromer, as an organic polymer, would expand in the gastrointestinal tract, and that ZS-9, because it is an ion trap, would not expand. However, in the absence of a head-to-head trial, he could not compare the tolerability of the two therapies, although the overall safety of both appeared to be good in their respective trials.

A general practitioner from the UK confirmed the problem raised by the panel with regard to patients having their RAASi discontinued when they are hospitalised, and that non-cardiologist healthcare professionals (HCPs) were focussing too much on acute renal injury. He called for more education in hospitals regarding the balance of risk and benefit for RAASi and ways to stop hyperkalaemia. Prof Zannad agreed that the evidence from trials indicated that increases of 10–15% in creatinine were not a cause for concern, and that there was a need to educate HCPs on the importance of uptitrating a treatment once the problem has been reversed, since the benefit of RAASi on mortality is greater than the potential harm from increased creatinine. On the other hand, the risks of hyperkalaemia secondary to RAASi therapy are real and monitoring treatment is necessary. Prof Zannad emphasised that HF is a chronic disease that needs chronic, adaptive therapy with regular monitoring of patients, which has become more feasible with the advent of 'telemedicine'.

The final question was regarding advice on the rate at which RAASi could be uptitrated, following the message from the symposium that a patient's dose should ideally be optimised by the time they leave hospital, since further optimisation after discharge is unlikely. The panel agreed that this depended on the condition of the individual patient, and that the paradigm of 'start low, go slow' was good advice where time and resources allowed weekly uptitration. Prof McMurray noted that in the UK, where the median hospital stay is 8 days, most patients can be titrated to a full dose of ACEi by the time they are discharged, with HF nurses monitoring electrolyte levels after the patient goes home. Prof Piña's practice in the USA, where the mean hospital stay is 4.5 days, was to uptitrate doses daily while managing the diuretics by dose reduction, but this required experience with the drugs because creatinine levels were affected. Where shorter hospital stays are the norm, faster-acting agents would make it easier to optimise a patient's dose by the time they were discharged.

Conclusions

RAAS inhibition is a proven, life-saving therapy for patients with HF, and RAASi are recommended by international guidelines. However, there is still underuse of these treatments and many patients are not receiving optimal doses of RAASi recommended for clinical benefit. Hyperkalaemia is a key barrier to the optimal use of RAASi. New, safe, and efficacious therapies to address hyperkalaemia are being made available, which may allow patients with HF and a risk of hyperkalaemia to benefit from increased survival due to RAASi therapy. New RAASi with fewer undesirable effects could become available, with the potential to improve the paradigm for the treatment of HF.

REFERENCES

1. McMurray JJ et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-847.

2. Yancy CW et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-e239.

3. Einhorn LM et al. The frequency of hyperkalemia and its significance in chronic kidney disease. Arch Intern Med. 2009;169(12):1156-62.

4. Maggioni AP et al; Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2013;15(10):1173-84.

5. Gheorghiade M et al. Medication dosing in outpatients with heart failure after implementation of a practice-based performance improvement intervention: findings from IMPROVE HF. Congest Heart Fail. 2012;18(1):9-17.

6. Packham DK, Kosiborod M. Potential New Agents for the Management of Hyperkalemia. Am J Cardiovasc Drugs. 2015. [Epub ahead of print].

7. Fonarow GC et al. Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. Circ Heart Fail. 2008;1(2):98-106.

8. Shirazian S et al. Underprescription of renin-angiotensin system blockers in moderate to severe chronic kidney disease. Am J Med Sci. 2015;349(6):510-5.

9. Di Tano G et al. The 30-day metric in acute heart failure revisited: data from IN-HF Outcome, an Italian nationwide cardiology registry. Eur J Heart Fail. 2015;doi:10.1002/ejhf.290. [Epub ahead of print].

10. Edner M et al. Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. Eur Heart J. 2015;36:2318-26.

11. Pitt B et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17.

12. Zannad F et al; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364(1):11-21.

13. Rossignol P et al; Writing group of 10th Global Cardio Vascular Clinical Trialist forum held on December 6th-7th 2013 in Paris, France. Time to retrieve the best benefits from renin angiotensin aldosterone system (RAAS) inhibition in heart failure patients with reduced ejection fraction: lessons from randomized controlled trials and registries. Int J Cardiol. 2014;177(3):731-3.

14. Rossignol P et al. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). Circ Heart Fail. 2014;7(1):51-8.

15. Jarman PR et al. Hyperkalaemia in diabetes: prevalence and associations. Postgrad Med J. 1995;71(839):551-2.

16. Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? Arch Intern Med. 1998;158(1):26-32.

17. Sarafidis PA et al. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. Clin J Am Soc Nephrol. 2012;7(8):1234-41.

18. Stevens MS, Dunlay RW. Hyperkalemia in hospitalized patients. Int Urol Nephrol. 2000;32(2):177-80.

19. Uijtendaal EV et al. Frequency of laboratory measurement and hyperkalaemia in hospitalised patients using serum potassium concentration increasing drugs. Eur J Clin Pharmacol. 2011;67(9):933-40.

20. Vardeny O et al; Randomized Aldactone Evaluation Study (RALES) Investigators. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. Circ Heart Fail. 2014;7(4):573-9.

21. Raebel MA et al. Laboratory monitoring of potassium and creatinine in ambulatory patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Pharmacoepidemiol Drug Saf. 2007;16(1):55-64.

22. Metra M et al. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. J Am Coll Cardiol. 2013;61(2):196-206.

23. Teerlink JR et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013;381(9860):29-39.

24. Anker SD et al. Ularitide for the treatment of acute decompensated heart failure: from preclinical to clinical studies. Eur Heart J. 2015;36(12):715-23.

25. Cardiorentis. Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated Heart Failure (TRUE-AHF). NCT01661634. https://www.clinicaltrials.gov/ct2/show/NCT01661634?term=NCT01661634&rank=1.

26. Swedberg K et al; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875-85.

27. Malik FI et al. Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. Science. 2011;331(6023):1439-43.

28. Teerlink JR. A Phase 2 Study of Intravenous Omecamtiv Mecarbil, a Novel Cardiac Myosin Activator, in Patients with Acute Heart Failure. Available at: www.clinicaltrialresults.org. Last accessed: 8 October 2015.

29. Pitt B et al; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348(14):1309-21.

30. Desai AS. Hyperkalemia in patients with heart failure: incidence, prevalence, and management. Curr Heart Fail Rep. 2009;6(4):272-80.

31. Bozkurt B et al. Complications of inappropriate use of spironolactone in heart failure: when an old medicine spirals out of new guidelines. J Am Coll Cardiol. 2003;41(2):211-4.

32. Shah KB et al. The adequacy of laboratory monitoring in patients treated with spironolactone for congestive heart failure. J Am Coll Cardiol. 2005;46(5):845-9.

33. Albert NM et al. Use of aldosterone antagonists in heart failure. JAMA. 2009;302(15):1658-65.

34. Go AS et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.

35. Healthcare Cost and Utilization Project. US Agency for Healthcare Research and Quality 2015. Available at: http://hcupnet.ahrq.gov/HCUPnet.jsp. Last accessed: 8 October 2015.

36. Pitt B et al. Effect of Cardiovascular Comorbidities on the Mortality Risk Associated with Serum Potassium. Poster 2443. AHA 2014 Scientific Sessions, 19 Nov 2014.

37. US Food and Drug Administration. Sanofi-aventis U.S.LLC. KAYEXALATE® Product Information. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm186845.htm. Last accessed: 8 October 2015.

38. Packham DK et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med. 2015;372(3):222-31.

39. Anker SD et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. Eur J Heart Fail. 2015;doi:10.1002/ejhf.300. [Epub ahead of print].

40. Weir MR et al. New agents for hyperkalemia. N Engl J Med. 2015;372(16):1570-1.

41. Pitt B et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. Eur Heart J. 2013;34(31):2453-63.

42. Patel SR, Pina IL. From acute decompensated to chronic heart failure. Am J Cardiol. 2014;114(12):1923-9.

43. McMurray JJ et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.

44. McMurray JJ. Neprilysin inhibition to treat heart failure: a tale of science, serendipity, and second chances. Eur J Heart Fail. 2015;17(3):242-7.

45. Novartis Pharmaceuticals. Efficacy and Safety of Aliskiren and Aliskiren/Enalapril Combination on Morbi-mortality in Patients With Chronic Heart Failure (ATMOSPHERE). NCT00853658. https://www.clinicaltrials.gov/ct2/show/NCT00853658?term=aliskiren+enalapril&rank=2.

46. Pitt B et al. Rationale and design of MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF): a randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. Eur J Heart Fail. 2015;17(2):224-32.

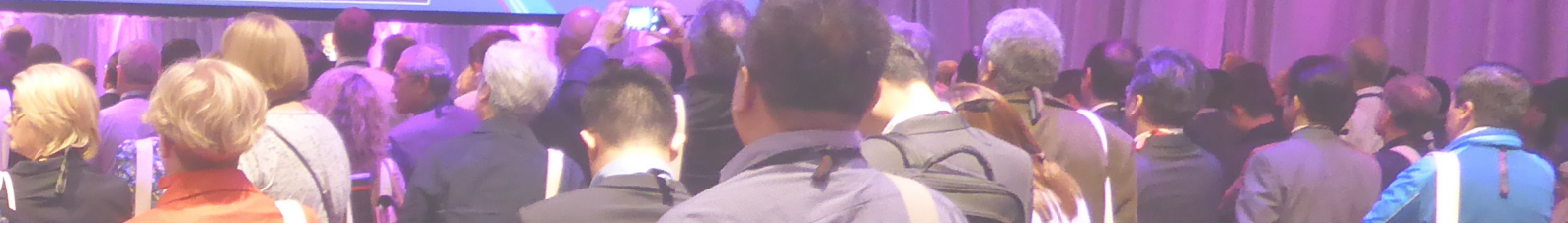
47. Felker GM et al. Heart failure therapeutics on the basis of a biased ligand of the angiotensin-2 type 1 receptor. Rationale and design of the BLAST-AHF study (Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure). JACC Heart Fail. 2015;3(3):193-201.

AWARD WINNERS AT ESC 2015

...these epigenetic changes may represent a novel target for therapeutic attempts to prevent or delay cardiac dysfunction in diabetic patients.

The outstanding research efforts of young investigators were acknowledged at ESC Congress 2015 via the presentation of Young Investigator Awards covering six overarching themes: Basic Science, Clinical Science, Thrombosis, Population Sciences, Coronary Pathophysiology and Microcirculation, and Ageing and Senescence – the latter of which was a new theme introduced at this year's event and which included Nobel laureate Prof Elizabeth Blackburn as one of its judges. Each of the winners were selected from a shortlist of finalists comprising the four highest-graded abstracts submitted to the congress under each of the six themes by researchers under 36 years of age. Each group of four shortlisted abstracts was presented at a dedicated award session open to congress delegates and adjudicated by a panel of international experts who scored each presentation in terms of originality, scientific content, presentation, and answers to questions. All prizes were presented at the main awards ceremony of the congress, with each of the six winners receiving a prize of €2,000 and each of the other finalists receiving a prize of €1,000.

The prize awarded under the theme of Basic Science went to Sarah Costantino for a study describing the role of two microRNAs (miR-218 and miR-34a) in orchestrating epigenetic remodelling of DNA/histone complexes in a mouse model of diabetic cardiomyopathy. The study found that mitochondrial oxidative stress was significantly increased in the diabetic heart, with the restoration of normoglycaemia via 3-week intensive glycaemic control (IGC) unable to abrogate this phenomenon and unable to rescue diabetes-related left ventricle (LV) dysfunction. miRNome analysis revealed that miR-218 and miR-34a were profoundly dysregulated in the heart of diabetic mice and caused persistent downregulation of methyltransferase DNMT3b and deacetylase SIRT1, respectively, with IGC failing to restore their expression or prevent disturbance of the DNMT3b/SIRT1 axis. The disruption of DNMT3b SIRT1 was shown to trigger DNA demethylation and histone 3 acetylation, which led to enhanced transcription of the pro-oxidant mitochondrial adaptor p66Shc. The use of p66Shc siRNA *in vivo* was able to blunt production of reactive oxygen species while restoring LV function in diabetic mice with IGC, which suggests that these epigenetic changes may represent a novel target for therapeutic attempts to prevent or delay cardiac dysfunction in diabetic patients.



...future studies of risk factors for SAH should be adjusted according to the number of cigarettes smoked per day by each sex, rather than applying the categories of 'current', 'previous', and 'non-smoker'.

Joni Valdemar Lindbohm received the Population Sciences prize for a study investigating the relationship between incident subarachnoid haemorrhage (SAH) and cigarette smoking. Analysing cohorts of 31,180 men and 33,504 women, both with a mean age of 45 years and representing a total of 1.38 million person-years, the study found that smoking more than one pack of cigarettes per day (21–30 cigarettes) increased the risk of SAH in women (hazard ratio [HR]: 8.2, 95% confidence interval [CI]: 3.8–17.8) more than it did in men (HR: 3.6, 95% CI: 2.0–6.3); the difference between the HRs for the two sexes was significant in all cigarette-per-day categories (likelihood ratio test [LRT]: p=0.007). When a high number of pack-years (>31) was compared with a low number of pack-years (0.1–5), the risk of SAH was increased in women (HR: 3.8, 95% CI: 1.3–11.2) but the increase in risk in men was only borderline significant (HR: 1.9, 95% CI: 0.94–4.0) and the difference between HRs for the two sexes was not significant (LRT: p=0.18). Based on these observations, the authors suggest that future studies of risk factors for SAH should be adjusted according to the number of cigarettes smoked per day by each sex, rather than applying the categories of 'current', 'previous', and 'non-smoker'.

The Clinical Science prize was collected by Chloe Park for her study evaluating the association between LV dysfunction and cognitive impairment. A total of 1,207 community-based individuals (69±6 years) who underwent echocardiography and assessment of cognitive function using the Community Screening Instrument for Dementia (CSID) score were included in the study. After adjusting for age, sex, and ethnicity, all measures of LV function, except ejection fraction, were found to be associated with hippocampal volume. Cognitive function was significantly associated with NT-proBNP levels as well as diastolic but not systolic function. After excluding those with stroke and further adjusting for the presence of diabetes and hypertension, significant associations between hippocampal volume and NT-proBNP and peak shortening velocity in systole, but not diastolic function, were observed. Associations between CSID score and NT-proBNP and left atrial diameter (indexed to height) also remained significant after adjustment. Therefore, measures of LV global, diastolic, and systolic function were all associated with functional and structural measures of cognitive impairment in this community-based sample of older people, with none of these associations explained by concomitant risk factors.

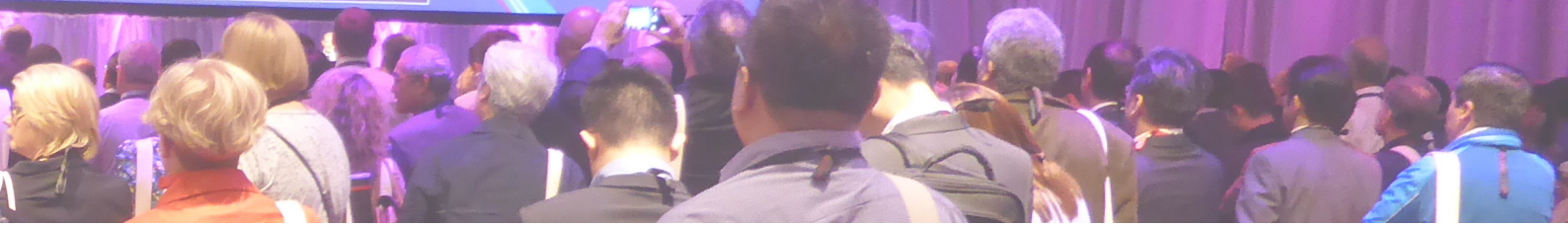
After adjusting for age, sex, and ethnicity, all measures of LV function, except ejection fraction, were found to be associated with hippocampal volume.

BEST ABSTRACT AWARD WINNERS

The study demonstrated that the accuracy of the CHA2DS2-VASc score for predicting stroke in HF patients displayed comparable accuracy to when used in AF patients.

The prize within the Thrombosis theme was awarded to Line Melgaard for her study investigating the use of a risk stratification scheme (CHA2DS2-VASc) commonly used in atrial fibrillation (AF) to assess the risk of stroke in heart failure (HF) patients in sinus rhythm. The study demonstrated that the accuracy of the CHA2DS2-VASc score for predicting stroke in HF patients displayed comparable accuracy to when used in AF patients. However, the performance of this scoring system in this high-mortality HF population was shown to be dependent on the choice of control group. The discriminatory properties of the CHA2DS2-VASc score for predicting stroke within 1 and 5 years using two definitions of controls: 'stroke free and alive' (Control Group 1) and 'stroke free or dead' (Control Group 2) were evaluated in a cohort of 33,785 Danish incident HF patients in sinus rhythm during 2000–2012 who were followed up for a mean of 2.4 years. The rate of stroke increased with increasing CHA2DS2-VASc score, with the ability of the CHA2DS2-VASc score to predict stroke at 1 and 5 years of follow-up, respectively, being: C-statistic=0.67 and 0.68 for Control Group 1, and C-statistic=0.64 and 0.60 for Control Group 2. A cut-off value of CHA2DS2-VASc=0 for identifying low-risk patients gave negative predictive values (NPVs) that varied according to control group (1 and 5 years of follow-up: NPV=91.7% and 77.9%, respectively, for Control Group 1; and NPV=98.6% and 96.5%, respectively, for Control Group 2); similar results were found with a cut-off value of CHA2DS2-VASc=1.

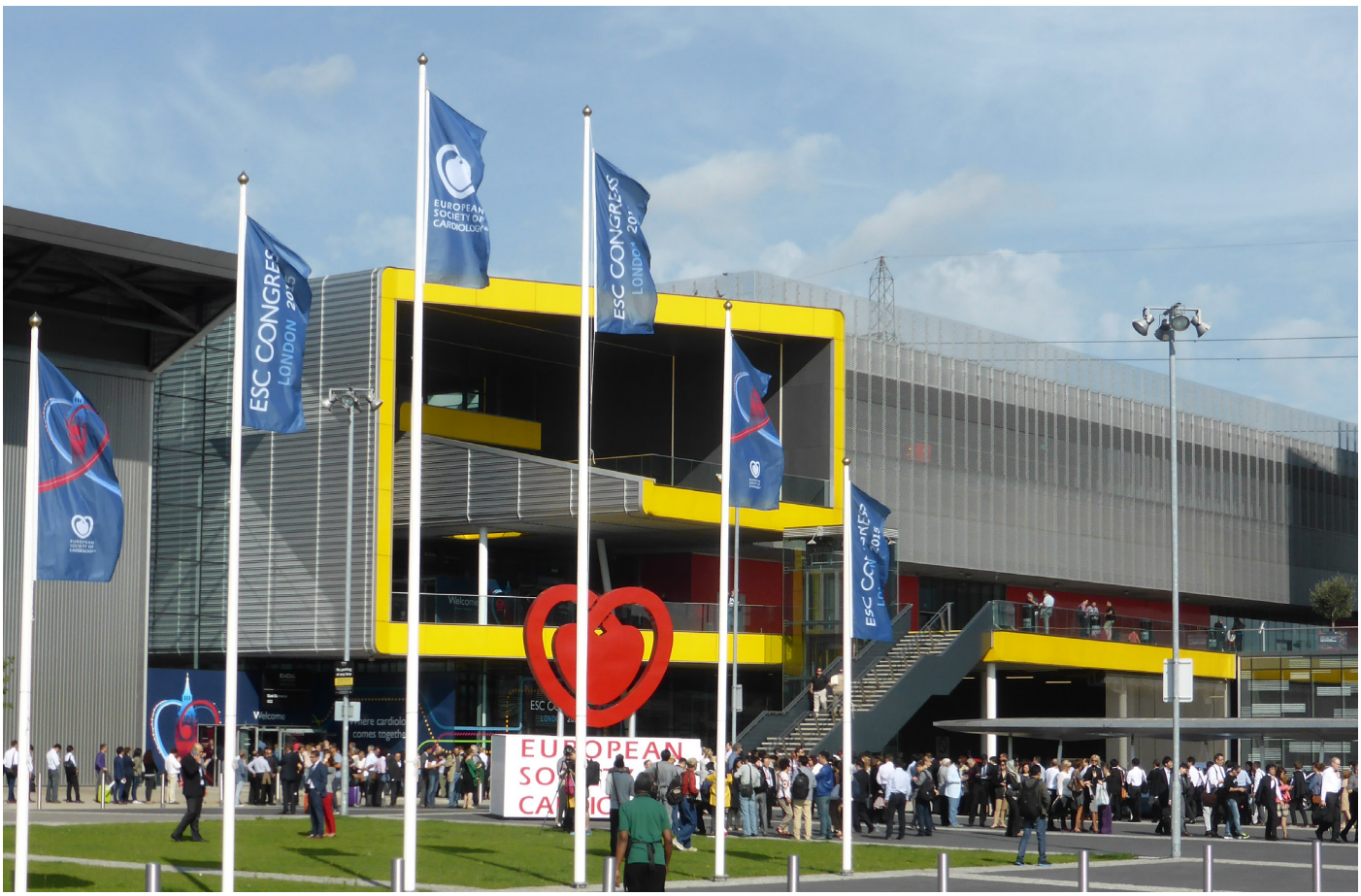
Duygu Kocyigit won the prize for abstracts submitted under the theme of Coronary Pathophysiology and Microcirculation in recognition of a study demonstrating enhanced expression of Toll-like receptor (TLR) 2 and TLR4 on platelets from patients with acute coronary syndrome (ACS). These findings suggest that platelet TLR expression may represent a potential novel prophylactic and therapeutic target in this patient group. Flow cytometry was used to evaluate platelet TLR2 and TLR4 expression in peripheral venous blood samples obtained prior to coronary angiography, and showed that TLR2 expression was significantly higher in patients diagnosed with ACS (both non-ST-segment elevation and ST-segment elevation



ACS) compared with age and gender-matched controls with normal coronary arteries (30% [11–90] versus 3% [1–5]; p<0.001) and compared with those with coronary artery disease (30% [11–90] versus 11% [5–14]; p<0.001). Platelet TLR4 expression was also more prominent in ACS patients compared with controls with normal coronary arteries (41% [20–94] versus 3% [1–4]; p<0.001) and those with stable coronary artery disease (41% [20–94] versus 12% [4–24]; p=0.003).

The inaugural prize in the Ageing and Senescence theme was awarded to Marios Margaritis, who reported findings demonstrating for the first time that a short telomere length (TL) is predictive of clinical outcome after revascularisation procedures, independent of chronological age, and that oxidative stress reduces TL, thus providing new insights into the role of biological senescence in cardiovascular ageing. The study followed two cohorts (500 patients undergoing percutaneous coronary intervention [PCI] following ST-segment-elevation myocardial infarction, and 648 patients undergoing coronary artery bypass graft [CABG]) and found that TL predicted all-cause mortality, CVD mortality, and non-fatal ACS following PCI, all independent of chronological age. Short TL predicted postoperative AF in CABG patients, high plasma malondialdehyde was associated with short blood TL, and high NADPH oxidase activity was associated with short TL in saphenous vein segments (SVs). Using Mendelian randomisation, the additive effect of the SNPs rs4673G and rs1049255C (which were associated with increased NADPH oxidase activity in SVs) also led to shortened TL in both cohorts, thus suggesting a causal relationship between oxidative stress and TL.

...telomere length predicted all-cause mortality, CVD mortality, and non-fatal ACS following PCI, all independent of chronological age.



MANAGEMENT OF VERY HIGH-RISK NON-ST-ELEVATION ACUTE CORONARY SYNDROME

***Laurent Bonello,[1,2] Marc Laine,[1] Thomas Cuisset,[3,4] Franck Thuny[1,2]**

1. Mediterranean Association for Research and Studies in Cardiology (MARS – Cardio), Service de Cardiologie, Centre Hospitalier Universitaire Marseille, Hôpital Nord, Assistance-Publique Hôpitaux de Marseille, Marseille, France
2. Vascular Research Center of Marseille, INSERM UMR-S 1076, Aix-Marseille Université, Marseille, France
3. Département de Cardiologie, Hôpital Timone, Centre Hospitalier Universitaire Marseille, Assistance-Publique Hôpitaux de Marseille, Marseille, France
4. INSERM, UMR1062, Nutrition, Obesity and Risk of Thrombosis, Marseille, France
**Correspondence to laurentbonello@yahoo.fr*

Very high-risk non-ST-elevation acute coronary syndrome (NSTE ACS) represents a cumbersome group of patients. It is defined as an NSTE ACS associated with ongoing ischaemia or a life-threatening condition that includes: acute heart failure, recurrent dynamic ST-T changes, haemodynamic instability, cardiogenic shock, life-threatening ventricular arrhythmia, mechanical complication of myocardial infarction, and recurrent or ongoing chest pain refractory to medical therapy.[1] This subgroup of patients is excluded from most of the randomised clinical trials for ACS. The guidelines advocate a three-step management protocol: treat the life-threatening condition, confirm the diagnosis, and cure the unstable coronary artery disease (Figure 1). These steps are usually taken together in order to save time. During the stabilisation of a patient, transthoracic echocardiography is performed to rule out differential diagnoses such as pulmonary embolism and aortic dissection. Very high-risk NSTE ACS patients should undergo emergent angiography. In fact, these patients should be managed in the same way as ST-elevation myocardial infarction (STEMI) patients. Guidelines advocate a time of <2 hours from first medical contact to angiography.[1]

Anticoagulant therapy should be initiated with heparin, either unfractionated or low-molecular-weight heparin, or bivalirudin as the first-line agent. Dual antiplatelet therapy with a combination of aspirin and a P2Y12-ADP receptor antagonist is also warranted.[1] There are two key points that should be addressed regarding the use of P2Y12-ADP receptor antagonists: which one to choose and when to give the loading dose (LD).

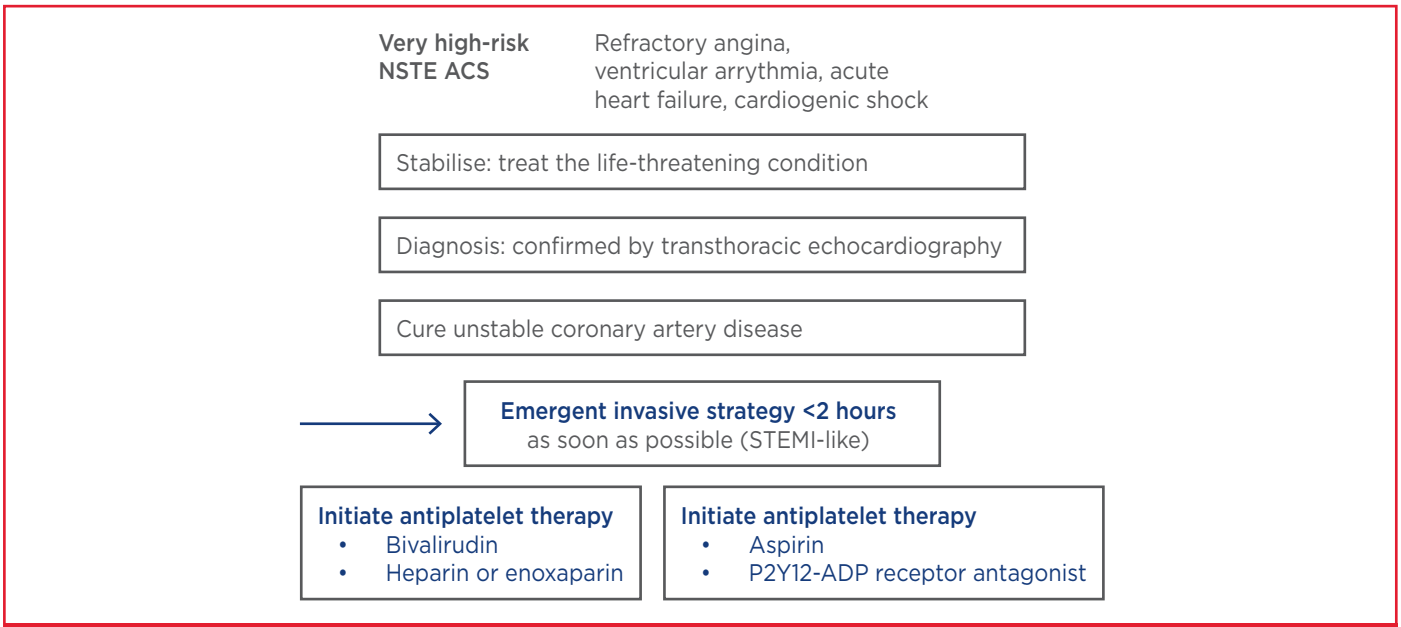


Figure 1: Management of very high-risk non-ST-elevation acute coronary syndrome (NSTE ACS).
STEMI: ST-elevation myocardial infarction.

Prasugrel and ticagrelor are faster-acting and more potent agents compared with clopidogrel, and provide an ischaemic benefit in patients undergoing percutaneous coronary intervention (PCI) for an ACS.[1-3] On the other hand, they are associated with an excess of major bleedings in non-coronary artery bypass grafts. They are therefore first-line agents, except for patients under chronic anticoagulant therapy or at high risk of bleeding.[1]

Pretreatment with a P2Y12-ADP receptor antagonist has become controversial. A meta-analysis observed no benefit from pretreatment in NSTE ACS, but a potential bleeding harm.[4] Montalescot et al.[5] designed the ACCOAST trial to address this issue. In this study, high-risk NSTE ACS patients were randomised to either prasugrel 30 mg LD given as soon as possible or to prasugrel LD given at the time of PCI. This trial was negative, showing no benefit of prasugrel pretreatment in terms of ischaemic events in these high-risk patients. In addition, there was a significant increase in major bleedings in the pretreatment group. The results were similar in all subgroups, including those who received PCI.[5]

Capodanno and Angiolillo[6] observed that, over time, there has been a steady reduction in the time to PCI in trials of NSTE ACS. Reducing the waiting time before PCI may interfere with the benefit of pretreatment. The time from diagnosis to angiography in the ACCOAST trial was 4 hours. Prasugrel and ticagrelor achieved significant platelet inhibition within 1 hour following intake, thus further reducing the potential benefit of pretreatment compared with the clopidogrel era when the time to inhibition of platelet reactivity was 6 hours.[7] The recently released guidelines for NSTE ACS state that a strategy of pretreatment could be used with ticagrelor or clopidogrel, but not with prasugrel. In fact, based on the meta-analysis and the ACCOAST trial, it is highly probable that pretreatment is of no benefit in patients undergoing very early angiography, whereas pretreatment could benefit patients that receive delayed management.[5,8]

Glycoprotein 2b/3a inhibitors have a limited use. Due to the possibility of bleeding harm and the fact that their ischaemic benefit is limited to high-risk patients, these drugs are limited to bail-out situations such as giant thrombus.[1] Cangrelor is a newly approved, intravenous P2Y12-ADP receptor antagonist with a quick onset and offset of action. It was shown to prevent ischaemic events, including stent thromboses, compared with clopidogrel LD in the CHAMPION PHOENIX trial,[9] without increasing bleedings.[1] However, the relative role of cangrelor in the era of more potent P2Y12-ADP receptor antagonists has not been investigated.

In very high-risk NSTE ACS patients, proceeding to PCI after angiography is determined by whether the patient is stabilised and whether the culprit lesion is occluded and amenable to PCI. Most patients will undergo PCI as in STEMI because they require quick reperfusion.

Overall, the management of very high-risk NSTE ACS is based on experts' opinion because these patients are excluded from most randomised controlled trials. These patients should be stabilised, diagnosis should be confirmed, and they should undergo early angiography and be managed similarly to a STEMI patient. Pretreatment of these patients with P2Y12-ADP receptor antagonists may be of limited potential benefit. Revascularisation is urgent and preferentially performed with PCI because of the unstable clinical status.

REFERENCES

1. Roffi M et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2015;pii:ehv320. [Epub ahead of print].

2. Wiviott SD et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20): 2001-15.

3. Wallentin L et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11): 1045-57.

4. Bellemain-Appaix A et al. Reappraisal of thienopyridine pretreatment in patients with non-ST elevation acute coronary syndrome: a systematic review and meta-analysis. BMJ. 2014;349:g6269.

5. Montalescot G et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med. 2013;369(11):999-1010.

6. Capodanno D, Angiolillo DJ. Pretreatment with antiplatelet drugs in invasively managed patients with coronary artery disease in the contemporary era: review of the evidence and practice guidelines. Circ Cardiovasc Interv. 2015;8(3):e002301.

7. Bonello L et al. Onset of optimal P2Y12-ADP receptor blockade after ticagrelor and prasugrel intake in Non-ST elevation acute coronary syndrome. Thromb Haemost. 2015;114(4). [Epub ahead of print].

8. Mehta SR et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358(9281):527-33.

9. Bhatt DL et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med. 2013;368(14): 1303-13.

IMAGING INFLAMMATORY ATHEROSCLEROTIC PLAQUE

***Marc Dweck,[1,2] Zahi Fayad[2]**

1. Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

2. Icahn School of Medicine at Mount Sinai, New York City, New York, USA

**Correspondence to marc.dweck@ed.ac.uk*

Inflammation plays a key role in every stage of atherosclerosis. This includes atherosclerotic plaque rupture and the precipitation of acute myocardial infarction (MI), with macrophages secreting matrix metalloproteinases that weaken the cap, predisposing it to rupture. Vascular inflammation is therefore a key imaging target and one that can be assessed in multiple different vascular beds, given that increased inflammation is rarely confined to a single plaque, but is often observed in a pan-coronary and indeed pan-vascular distribution. Two non-invasive techniques in particular have been utilised in assessing aortic and carotid plaque inflammation: magnetic resonance imaging (MRI) with ultra-small particles of iron oxide (USPIOs) and 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET). In addition, 18F-fluoride PET has recently emerged as a surrogate marker of plaque inflammation in the coronary arteries (Figure 1). Each is discussed briefly here.

After injection, USPIOs are believed to be engulfed by circulating monocytes. These particles result in dropout of the MRI signal, allowing macrophages to be tracked to sites of inflammatory recruitment within the body. This technique has been employed to study macrophage recruitment into vascular tissue, most notably in abdominal aortic aneurysms[1] and sites of carotid atheroma. Indeed, Trivedi and colleagues[2] used this macrophage labelling approach to identify carotid plaque inflammation in patients undergoing carotid endarterectomy, confirming USPIO accumulation within 24 or 30 plaques, and an association between areas of signal dropout and histological evidence of macrophage accumulation.

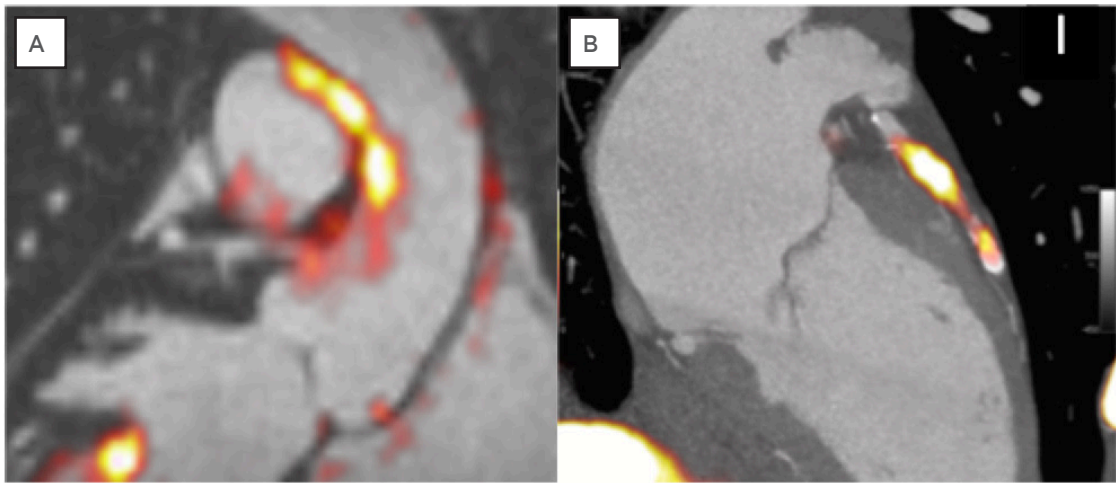


Figure 1: Imaging atherosclerotic inflammation.
Panel A: Fused 18F-fluorodeoxyglucose PET/MRI imaging of the ascending aorta. Increased uptake is observed in the arch of the aorta. Panel B: 18F-fluoride PET/CT image demonstrating a focal region of increased uptake in the left anterior descending artery.

Subsequently, Tang and colleagues[3] showed that the intensity of the USPIO signal could be reduced by intensive statin therapy for 3 months, indicating that this approach could be used to assess the anti-inflammatory properties of atherosclerotic therapies.

18F-FDG is a PET tracer and glucose analogue that has become widely used in assessing vascular inflammation, on the basis that macrophages use more glucose than surrounding cells. Indeed, in a study of 17 patients undergoing carotid endarterectomy, an excellent correlation between the 18F-FDG signal and macrophage burden on histology ($r=0.85$, $p<0.001$) was observed.[4] Moreover, clinical studies have demonstrated increased 18F-FDG uptake in carotid culprit plaque following stroke or transient ischaemic attack,[5] excellent inter-scan reproducibility,[6] and reduced plaque 18F-FDG activity through treating patients with statins.[7] On the basis of these favourable characteristics, this approach has been applied to investigate the efficacy of novel atherosclerotic agents and to demonstrate their ability to impact vascular inflammation. Most notably, 18F-FDG has been used in a subgroup of patients participating in the recent randomised controlled trial of dalcetrapib therapy, demonstrating no impact of this agent on the 18F-FDG signal and mirroring the clinical results of the larger study as a whole.[8]

Translation of these two techniques into the coronary vasculature has to date proved largely disappointing. Despite early promise, 18F-FDG is frequently limited by myocardial uptake of the tracer, which frequently obscures activity in the closely adjacent coronary vasculature.[9,10] The spatial resolution of USPIO imaging is not currently sufficient to allow imaging of coronary atherosclerotic plaque. However, a novel PET tracer, 18F-fluoride has recently emerged, which appears to localise to individual inflamed coronary plaques. 18F-fluoride binds preferentially to regions of newly developing micro-calcification, providing different information to the macroscopic calcium detected by computed tomography.[11] Given that calcification is believed to occur as a healing response to inflammation, detection of the early stages of this process identifies inflamed plaques that remain in need of healing. Indeed, histological and virtual histology intravascular ultrasound studies have demonstrated that increased 18F-fluoride activity is observed in atherosclerotic plaques, with evidence of increased macrophage burden, positive remodelling, large necrotic cores, and high levels of cell death.[9] Moreover, in clinical studies, increased 18F-fluoride activity identified stable patients with increased cardiovascular risk scores[12] and localised to the culprit plaque in 37 out of 40 patients who had sustained a recent MI.[9] The ability of this tracer to predict MI prospectively is currently being evaluated in the PREFFIR trial (NCT02278211).

In summary, non-invasive methods for measuring vascular inflammation are developing rapidly and hold great promise in measuring atherosclerotic disease activity. These can be used as surrogate endpoints for trials of novel atherosclerotic medication, and also hold promise in improving risk prediction models of MI.

REFERENCES

1. Richards JM et al. Abdominal aortic aneurysm growth predicted by uptake of ultrasmall superparamagnetic particles of iron oxide: a pilot study. Circ Cardiovasc Imaging. 2011;4(3):274-81.

2. Trivedi RA et al. Identifying inflamed carotid plaques using in vivo USPIO-enhanced MR imaging to label plaque macrophages. Arterioscler Thromb Vasc Biol. 2006;26(7):1601-6.

3. Tang TY et al. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study. Evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. J Am Coll Cardiol. 2009;53(22):2039-50.

4. Tawakol A et al. In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. J Am Coll Cardiol. 2006;48(9):1818-24.

5. Rudd JH et al. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. Circulation. 2002;105(23):2708-11.

6. Rudd JH et al. (18)Fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible: implications for atherosclerosis therapy trials. J Am Coll Cardiol. 2007;50(9):892-6.

7. Tahara N et al. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. J Am Coll Cardiol. 2006;48(9):1825-31.

8. Fayad ZA et al. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. Lancet. 2011;378(9802):1547-59.

9. Joshi NV et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. Lancet. 2014;383(9918):705-13.

10. Rogers IS et al. Feasibility of FDG imaging of the coronary

arteries: comparison between acute coronary syndrome and stable angina. JACC Cardiovascular imaging. 2010;3(4):388-97.

11. Irkle A et al. Identifying active vascular microcalcification by (18)F-sodium fluoride positron emission tomography. Nat Commun. 2015;6:7495.

12. Dweck MR et al. Coronary arterial 18F-sodium fluoride uptake: a novel marker of plaque biology. J Am Coll Cardiol. 2012;59(17):1539-48.

ACUTE CORONARY SYNDROMES IN YOUNG (<45 YEARS) PATIENTS. ONE-YEAR COHORT FROM POLISH NATIONAL PCI REGISTRY

***Robert J. Gil,[1] Tomasz Pawłowski,[1] Zbigniew Siudak,[2] Andrzej Ochala,[3] Jacek Legutko,[2] Dariusz Dudek[2]**

1. Department of Invasive Cardiology, CSK MSW, Warsaw, Poland
2. Department of Cardiology and Cardiovascular Interventions, Collegium Medicum, Kraków, Poland
3. Department of Cardiology, Katowice, Poland
**Correspondence to scorpirg@gmail.com*

The Scientific Committee of the ESC Congress 2015 chose the abstract "Acute coronary syndromes in young (<45 years) patients. One-year cohort from Polish National PCI Registry" for the poster presentation. It was presented on the first day of the congress, during the poster session entitled "Infarction acute phase STEMI III".

The basis of our research was the everyday observation that an increasing number of young patients are being treated for acute coronary syndrome (ACS). So far, myocardial infarction and unstable angina are recognised to be rare in young people in the third or fourth decade of life.

All catheterisation laboratories in Poland are obliged to follow the internet-based database known as the Polish National Percutaneous Coronary Intervention (PCI) Registry. This database reports demographics, risk factors, and the angiographic and treatment data of every patient treated in Poland. The records are entered by physicians and technicians after both elective and urgent procedures. Each record also covers in-hospital major adverse cardiac events. The treatment strategy (by intention to treat) is indicated by the invasive cardiologist for every single patient (PCI, coronary artery bypass graft [CABG], medical therapy).

In 2014, Polish invasive cardiologists performed 112,188 coronary angiographies in ACSs, followed by 69,033 coronary angioplasties. From the registry database, all patients <45 years old were selected. In total we identified 3,806 (3.4%) patients <45 years old who underwent coronary angiography. Primary coronary angioplasty was performed on 2,140 (3.09%) of the patients. The mean age of the studied population was 39.8±5.3 years. The most frequent risk factors were hypertension (42.7%) and smoking (36.2%). Diabetes was diagnosed in 7.1% of patients from the young cohort, while 23.3% had a history of previous cardiovascular events (stroke, infarction, PCI, CABG). ST elevation myocardial infarction (STEMI) was diagnosed in 36.2%, followed by non-STEMI (23.2%), and unstable angina in 40.5%. Angiographic presentation was varied and there was single vessel disease in 40% and multivessel disease without left main stenosis in 20%, while multivessel disease with left main stenosis was present in 2.5% of cases. Isolated left main stenosis was diagnosed in 0.5% of patients. No lesions or minor lesions were present in 37% of the studied population. Preferred treatment was coronary angioplasty – performed in 57.3% of cases, although cardiac surgery was scheduled for 3.7%. The remaining population was treated by optimal medical therapy. The rate of death in the cath lab was 0.3%. During hospital follow-up, percentage of death was 0.4% as well as stroke, and major bleeding was observed in 0.01% of patients.

We found that ACS was not confirmed with coronary angiography in a relatively large proportion of the young patients with preliminary ACS diagnosis. From this, our research also showed that in some patients, despite young age, multivessel disease is present. Analysing the risk factors of the studied cohort, we must recognise that primary prevention is important for the growing population of younger patients.

SAFETY AND EFFICACY OF DAPTOMYCIN IN THE TREATMENT OF PATIENTS WITH INFECTIVE ENDOCARDITIS: REAL-WORLD EXPERIENCE FROM A EUROPEAN REGISTRY

***Achyut Guleri,[1] Riccardo Utili,[2] Pascal Dohmen,[3] Nicola Petrosillo,[4] Cornelia Piper,[5] Rashidkhan Pathan,[6] Kamal Hamed[7]**

1. Lancashire Cardiac Centre, Blackpool Teaching Hospitals, Blackpool, UK
2. A.O.R.N. Monaldi - U.O.C. Medicina Infettivologica e dei Trapianti, Naples, Italy
3. Charité-Universitätsmedizin Berlin, Berlin, Germany
4. I.N.M.I. "L. Spallanzani" - U.O.C. Infezioni Sistemiche e dell'Immunodepresso (II Divisione), Rome, Italy
5. Herz und Diabeteszentrum NRW, Bad Oeynhausen, Germany
6. Novartis Healthcare Pvt. Ltd., Hyderabad, India
7. Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA
**Correspondence to Dr.Guleri@bfwhospitals.nhs.uk*

This poster discussed the real-world effectiveness and tolerability of daptomycin in patients with infective endocarditis (IE) caused by Gram-positive bacteria.[1] Given the increasing resistance to antibiotics, clinical management of IE remains a challenge. Daptomycin is approved at a dose of 6 mg/kg/day for the treatment of *Staphylococcus aureus* right-sided IE (RIE) and/or bacteraemia associated with RIE.[2,3] A higher dose of daptomycin (>6 mg/kg) is recommended in patients with difficult-to-treat infections.[1] More recently, the European Society of Cardiology's guidelines for the management of IE recommend daptomycin ≥10 mg/kg/day combined with a second antibiotic for the treatment of staphylococcal IE.[4] The poster highlighted real-world clinical experience from the European CUBICIN® Outcomes Registry and Experience (EU-CORE℠) of daptomycin in patients with left-sided IE (LIE) and both left and right-sided IE (LRIE), in addition to patients with the approved RIE indication, across 18 countries in Europe (12), Latin America (5), and Asia (1).

Patients with IE who had received at least one dose of daptomycin between January 2006 and April 2012 and had not been part of a controlled clinical trial were included in the registry. Data were collected using standardised case report forms and patients were followed for up to 2 years. The clinical outcome was assessed as success (cured or improved), failure, or non-evaluable. Adverse events (AEs) and serious AEs (SAEs) up to 30 days post-treatment, regardless of their relationship to daptomycin, were recorded.

A total of 6,075 patients were enrolled in the registry, of whom 610 were reported with IE as primary infection: 414 (68%) patients had LIE, 149 (24%) had RIE, and 47 (8%) had LRIE. The most common primary infecting pathogen was *S. aureus* (LIE 37%, RIE 48%, and LRIE 38%). Methicillin-resistant *S. aureus* (MRSA) was identified in 39 (14%) patients with LIE, 11 (10%) patients with RIE, and 3 (10%) patients with LRIE. The median duration of daptomycin therapy was 21 (range: 1–132) days for LIE, 23 (range: 1–110) days for RIE, and 15 (range: 5–118) days for LRIE. Overall clinical success was achieved in 80% of patients (LIE 77%, RIE 89%, and LRIE 83%). Daptomycin at doses ≥8 mg/kg showed higher success rates (LIE 92%, RIE 94%, and LRIE 88%) compared with doses <8 mg/kg (LIE 74%, RIE 88%, and LRIE 85%). Clinical success rates in patients with *S. aureus* infection were 78% (72% for MRSA), 87% (91% for MRSA), and 91% (67% for MRSA) for LIE, RIE, and LRIE, respectively. Patients who were followed for up to 2 years showed a sustained overall clinical success rate of 87% (LIE 88%, RIE 94%, and LRIE 78%). AEs possibly related to daptomycin were reported in 18 (3.0%) patients. Elevation of creatine phosphokinase levels possibly related to daptomycin was observed in 11 patients (LIE 8, RIE 2, and LRIE 1). SAEs possibly related to daptomycin were reported only in patients with LIE (n=6, 1.4%). Study drug discontinuations due to AEs were reported in 7.2%, 3.4%, and 4.3% of LIE, RIE, and LRIE patients, respectively.

In conclusion, these results showed that patients with IE were treated successfully with daptomycin in the real-world setting. Daptomycin was found to be effective and well-tolerated in patients with LIE and LRIE, in addition to patients with RIE (approved indication). A sustained and relapse-free outcome was also observed in a high proportion of IE patients followed for up to 2 years.

Several interesting queries from the audience during the poster session included obtaining patient consent when using a higher-than-licensed dose, first-line use of daptomycin in IE patients referred to a tertiary cardiac centre with limited blood culture isolate information, prosthetic valve IE, and combination antibiotic therapy. Dr Guleri clarified all of the queries regarding daptomycin use in IE patients.

REFERENCES

1. Smith JR et al. High-dose daptomycin therapy for staphylococcal endocarditis and when to apply it. Curr Infect Dis Rep. 2014;16(10):429.

2. Fowler VG Jr et al; S. aureus Endocarditis and Bacteremia Study Group. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med. 2006;355(7):653-65.

3. US Food and Drug Administration. Development & Approval Process (Drugs). Available at: http://www.fda.gov/drugs/developmentapprovalprocess. Last accessed: 14 September 2015.

4. Habib G et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;pii:ehv319. [Epub ahead of print].

ACUTE CARDIAC CARE IN THE EMERGENCY DEPARTMENT

***Frederik H. Verbrugge**

Department of Cardiology,
Ziekenhuis Oost-Limburg, Genk, Belgium
**Correspondence to frederik.verbrugge@zol.be*

The large part of this Rapid Fire Abstract Session focussed on acute coronary syndrome (ACS) in patients presenting at the emergency department. Dr Gimenez (Basel, Switzerland) kicked off the session by comparing strategies to safely rule out myocardial infarction (MI) based on biomarker measurements. In a retrospective analysis of >1,000 patients from the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) study (NCT00470587), she found that the negative predictive value for MI was similar with a rule out strategy using high sensitivity troponin T (hs-TnT) levels <5 ng/L versus the traditional 99th percentile upper limit of normal (<14 ng/L) together with a dynamic increase of <4 ng/L over a 2 hour time interval. Interestingly, although equally safe to rule out MI, the latter strategy, by incorporating dynamic information, was able to rule out significantly more patients (64% versus 24%). In a second analysis of the same study, Dr Gimenez showed that measurement of copeptin in addition to hs-TnT did not improve efficient rule-out of MI. However, it was highlighted in a subsequent presentation by Dr Morawiec (Zabrze, Poland) that copeptin might still have a role as a prognostic biomarker, being associated with all-cause mortality and major adverse cardiovascular events in a group of patients presenting with non-ST-elevation MI or unstable angina. Another biomarker study, presented by Dr Puelacher (Basel, Switzerland), provided some reassuring data that haemolysis, although as frequent as 14% by visual assessment in the lab, did not decrease the diagnostic accuracy of cardiac troponin testing, which has become vital in patients with suspected ACS. Dr Vives Borràs (Barcelona, Spain) reminded us how one could get fooled by looking only at the electrocardiogram without biomarker measurements available. He showed that patients with acute circumflex artery occlusion frequently (~40%) present without ST elevation, potentially leading to treatment delays. Interestingly, patients with concomitant right coronary artery stenosis or kidney dysfunction were more likely to present without ST elevation. Dr Nowak (Detroit, MI, USA) made the point that if high sensitivity troponin tests are used increasingly in the emergency department, clinicians will be confronted with measurable troponin levels in non-ACS patients too. Yet the meaning of elevated troponin in such patients, especially when no other cardiac disease

can be found, remains unclear. Finally, our own study reported on the efficacy of point of care testing for heart type fatty acid binding protein (H-FABP) in patients at high pretest probability for ACS. The benefit of point of care testing is that it is readily available without the need for a lab. The results of our study show that although hs-TnT generally outperforms point of care H-FABP, both biomarkers perform equally well when assessed within 3 hours of chest pain onset. This finding might be especially interesting for general practitioners confronted with a patient who has sudden onset chest pain. In addition, it was demonstrated that H-FABP was an independent predictor of all-cause mortality, even after extensive adjustments for age, gender, cardiovascular risk factors, and renal function.

ANTITHROMBOTIC THERAPY IN PATIENTS WITH ACUTE CORONARY SYNDROME AND ATRIAL FIBRILLATION. RISK ASSESSMENT: THROMBOSIS VERSUS BLEEDING

***Uwe Zeymer**

Klinikum Ludwigshafen; IHF GmbH Institut für Herzinfarktforschung, Ludwigshafen, Germany
**Correspondence to uwe.zeymer@t-online.de*

The number of patients with acute coronary syndrome (ACS) and known or new-onset atrial fibrillation (AF) is steadily increasing due to the ageing population. Recent studies report the prevalence of AF in ACS patients to be 10–15%. These patients have an increased risk of embolic (stroke, systemic embolism), thrombotic (myocardial infarction, stent thrombosis), and bleeding events. Because all three types of event can result in mortality, patients with ACS and AF display a 2 to 3-fold higher risk of mortality compared with ACS patients without AF. All ACS patients with AF display a CHA2DS2-VASc score ≥1 and therefore have an indication for oral anticoagulation as well as antiplatelet therapy, especially after stent implantation. Combination antithrombotic therapy with oral anticoagulation and antiplatelet therapy is known to be associated with increased risk of bleeding complications. The most feared bleeding complication is intracranial haemorrhage, which occurs in about 0.5% of patients treated for ACS and which is associated with a mortality of about 35%.

Proper risk stratification would seem warranted in order to improve the prognosis of the high-risk subgroup of patients with ACS and AF. Guidelines recommend the use of the CHA2DS-VASc score for embolic risk stratification, and use of the GRACE score for thrombotic risk stratification. There are only two overlapping factors between these two scoring systems: patient age and congestive heart failure. For the assessment of bleeding risk there are two commonly used scores: HAS-BLED, which applies to AF patients; and CRUSADE, which applies to ACS patients. Hypertension, impaired renal function, and prior stroke are overlapping factors between these two scoring systems. Therefore, the clinician is left with uncertainty as to which score to use. The overlap between the CHA2DS2-VASc and HAS-BLED scoring systems is much higher, indicating that patients with a higher embolic risk also have a higher bleeding risk. The prediction of risk in an individual patient is therefore difficult for several reasons:

- An individual patient's risk is not predictable, only the risk displayed by a cohort of patients
- The risk of adverse events (ischaemia versus bleeding) caused by the strategy or therapy chosen for the individual patient is not predictable
- A risk of 5% means that 95% will not experience an event, which underscores the problem of risk prediction for individual patients
- Risk scores may not include parameters that are important for individual patients (e.g. comorbidities, frailty, social background)

In conclusion, we need more data to be able to determine the embolic, thrombotic, and bleeding risks of individual patients, and to be able to tailor the intensity and duration of combination antithrombotic therapy accordingly.

DIABETES AND CARDIOVASCULAR DISEASE – FROM EUROASPIRE TO GLOBAL ASPIRE?

***Lars Rydén**

Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden
**Correspondence to lars.ryden@ki.se*

Research provides new knowledge on the best way to manage patients with different types of diseases. These achievements are put into management guidelines that serve as a platform for educating the medical profession. One method to determine if all day practice adheres to guidelines is to conduct practice surveys; a field in which this has been carried out on several occasions since 1994 is that of cardiovascular prevention. As illustrated in Figure 1, new editions of the guidelines are followed by implementation education and surveys (EUROASPIRE I–IV):

The surveys identify risk factors in coronary patients, determining their management through lifestyle advice and the use of drug therapy. They also present an objective assessment of the clinical implementation of current evidence-based knowledge.

New with EUROASPIRE IV is the incorporation of the Euro Heart Survey on diabetes and the heart, examining not only the prevention of diabetes in a general sense but also how people with prediabetes and diabetes were diagnosed and managed.

Trained research assistants retrospectively identified patients with verified coronary artery disease (>6 months and <3 years prior to the date of interview) by review of medical notes. Identified patients were invited to a personal interview and examination during which a number of recordings were made, among them height, weight, waist circumference, blood pressure, cholesterol, triglycerides, HbA1c, and fasting glucose. In addition, participants in whom the glucometabolic state was unknown were subjected to an oral glucose tolerance test. The outcome of the interview and testing was balanced against guideline-recommended treatment targets.

As an example, about 20% of 6,187 participants had previously undiagnosed diabetes, since they had not been tested as recommended in the guidelines. Blood pressure control (target <140/90 mmHg) and lipid control (target <1.8 mmol/L) in patients with and without newly detected or known diabetes is illustrated in Figure 2. As can be seen, a rather large proportion (red fields) are well above the recommended levels.

Figure 1: The flow of European guidelines for cardiovascular prevention, implementation efforts, and surveys to check how well these guidelines are followed by practising physicians.

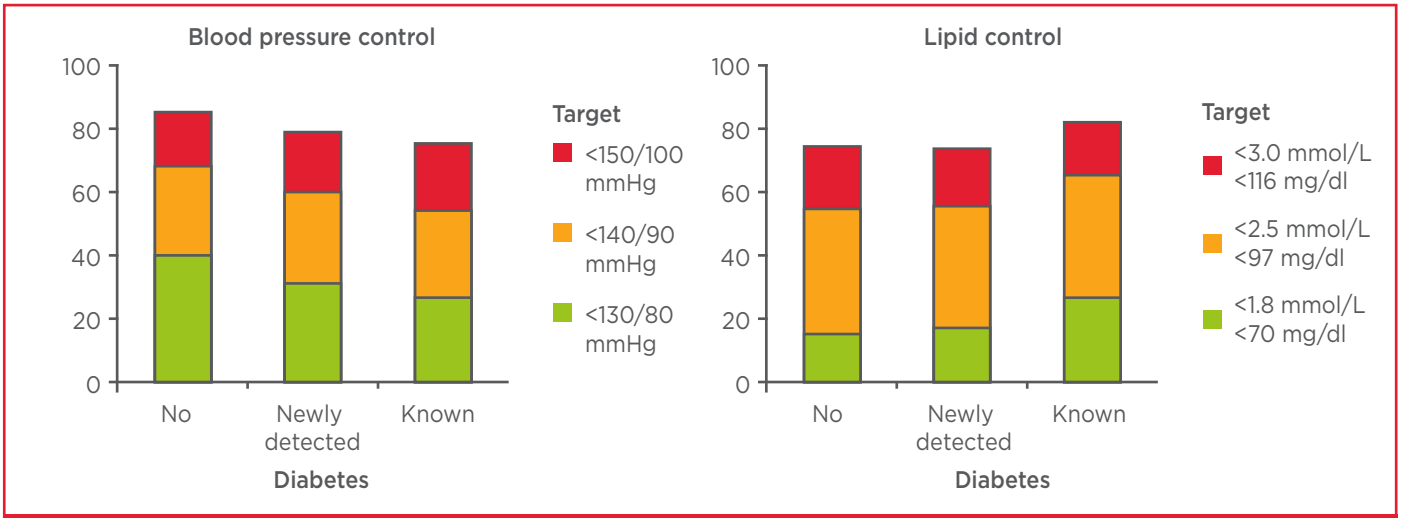


Figure 2: Proportion of investigated patients reaching different blood pressure (left panel) and LDL-cholesterol (right panel) targets.[1]

Dietary advice had been given to 65% of the patients with previously diagnosed diabetes.

A high proportion of the participants (60–70%) reported low physical activity.

The strengths of the surveys are that many countries from all over Europe are represented and the patient cohorts are large. Moreover, the investigation was conducted at a reasonable time after the index event, allowing the managing team to see the patient for a time period long enough to reach recommended treatment targets.

Potential concerns are the risk of a positive centre selection (which if anything may indicate that the results are better than in a general sample) and the accuracy of medical records.

In conclusion, these results show that:

- There is a need for continuous evaluation of guideline implementation
- The EUROASPIRE concept has the potential to improve patient management
- This protocol can be applied outside of Europe

REFERENCES

1. Gyberg V et al. Improved but still not satisfactory detection and management of patients with diabetes and coronary artery disease. A report from the EUROASPIRE IV survey. Cardiovasc Diabetol. 2015. In press.

CARDIOPROTECTION AND THYROID HORMONE

***Alessandro Pingitore,[1] Francesca Forini,[1] Claudia Kusmic,[1] Giorgio Iervasi,[1] Paolo Grigolini[2]**

1. Institute of Clinical Physiology, Consiglio Nazionale delle Ricerche (CNR), Pisa, Italy
2. Center for Nonlinear Science, University of North Texas, Denton, Texas, USA
**Correspondence to pingi@ifc.cnr.it*

Cardioprotection relates to the methods and mechanisms leading to a reduction in infarct size, which are therefore involved in the evolution of post-ischaemic heart failure. This is a growing area of research because ischaemic heart disease is currently the leading cause of morbidity and mortality worldwide. A key challenge in these studies is understanding how to unravel the complexity of cardioprotection, which includes the mechanisms leading to myocardial damage, the cascade of cellular signalling pathways activated, the cellular and extracellular regions involved, and understanding how these are all interconnected. The bulk of the biomolecular knowledge on cardioprotection has been poorly translated into clinical routine. This lack of translation has been attributed to poor design of clinical trials and, in experimental studies, the neglect of confounding factors that commonly complicate clinics. Therefore,

cardioprotection in a clinical setting needs to be considered as a complex and interconnected pathophysiological phenomenon. Additional complexity arises from the numerous genomic and non-genomic actions of thyroid hormones (THs) on the heart. The THs play a key physiological role in cardiovascular homeostasis, which is highlighted by evidence showing that changes in thyroid metabolism, in particular low triiodothyronine syndrome, occurring in acute myocardial infarction and heart failure are associated with poor prognosis[1,2] and electrical instability.[3] Treatment with TH has been demonstrated to have a cardioprotective effect through the preservation of mitochondrial function and potential induction of cell regeneration and growth. Recent experimental results have shown that TH treatment lowers the production of mitochondrial reactive oxygen species and favours mitoKATP channel opening in both *in vivo* and *in vitro* models of cardiomyocyte stress.[4] Furthermore, TH can limit ischaemia–reperfusion injury via a fine balance between pro-apoptotic and pro-survival signalling pathways, which are promoted through the TH receptor (TRα1).[5]

Taken as a whole, cardioprotection and heart/TH interactions represent the expression of complex networks of cooperating units within a biological system.[6] Cardioprotection is currently still an 'open book' in the clinical scenario where the complexity of the relationship between organs and systems has to be taken into account. In this scenario, the TH system may be a newly identified player orchestrating the different molecular, tissue, and cellular elements involved in cardioprotection.

REFERENCES

1. Pingitore A et al. Triiodothyronine levels for risk stratification of patients with chronic heart failure. Am J Med. 2005;118(2): 132-6.

2. Iervasi G et al. Association between increased mortality and mild thyroid dysfunction in cardiac patients. Arch Intern Med. 2007;167(14):1526-32.

3. Zhang Y et al. Thyroid hormone replacement therapy attenuates atrial remodeling and reduces atrial fibrillation inducibility in a rat myocardial infarction-heart failure model. J Card Fail. 2014;20(12):1012-9.

4. Forini F et al. Triiodothyronine prevents cardiac ischemia/reperfusion mitochondrial impairment and cell loss by regulating miR30a/p53 axis. Endocrinology. 2014;155(11):4581-90.

5. Pantos C et al. Acute T3 treatment protects the heart against ischemia-reperfusion injury via TRα1 receptor. Mol Cell Biochem. 2011;353(1):235-41.

6. Grigolini P. Emergence of biological complexity: Criticality, renewal and memory. Chaos Solitons Fractals. 2015. In Press.

METABOLIC SYNDROME IN INDIA: IS IT UNIQUE?

***Arvind Kumar Pancholia**

Department of Medicine, Modern College; Department of Clinical & Preventive Cardiology, Arihant Hospital & Research Center and Gokuldas Heart Center, Indore, India

**Correspondence to drpancholia@gmail.com*

Metabolic syndrome (MetS) is now being increasingly recognised as an emerging threat that is likely to overrun the desktops of public health policy planners for decades to come. The clusters that cause this syndrome and its aetiopathogenesis remain varied in different ethnic populations, regions, and countries. Factors like migration, socioeconomic status, lifestyle, and nutrition habits also play an important role. Therefore, research into MetS provides an interdisciplinary forum through which to explore the pathophysiology, recognition, and treatment of the cluster of conditions associated with the evolving entity of MetS. These include, but are not limited to: central obesity, endothelial dysfunction, insulin resistance, dyslipidaemia, glucose intolerance, Type 2 diabetes, pre-thrombosis, pro-inflammatory states, hyperinsulinaemia, hyperuricaemia, hypertension, cardiovascular disease, and polycystic ovary syndrome. The individual conditions are only part of a more generalised problem that requires more than simply correcting a single lab value. For the majority of those affected, inappropriate, poor, or defective nutritional status and lack of physical activity are the root causes of the disease process.

The emerging average Asian Indian urban migrant carries the phenotype of a higher percentage of body fat at a lower value of body mass index (BMI), high waist–hip ratio (WHR) at a relatively low waist circumference, and less lean body mass

compared with other ethnic groups. Asian Indian migrants have higher values of BMI and WHR and thicker skinfolds compared with urban subjects in India, and Asian Indian men have significantly thicker truncal skinfolds compared with Caucasians. High body fat, often at BMI values that are in the non-obese range, is another characteristic phenotypic feature of Asian Indians, as reported by several groups. This leads to abnormal lean body mass (muscle) to fat ratio; sarcopaenia with a higher body fat composition. The emerging Asian Indian phenotype is high body fat with relatively lower BMI, less lean body mass (particularly in lower limbs), high body fat/BMI ratio, high WHR (absolute value of waist circumference may not be excessive), variable subscapular/tricep ratio, and high intramyocellular lipids. Thus Asian MetS is the culmination of the adverse metabolic and clinical effects of insulin resistance. Its high and increasing prevalence, as well as its profound impact on the major diseases, require that clinicians consider its diagnosis and management on a routine basis.

DEVICE-BASED REMOTE MONITORING MAY OFFER MORTALITY BENEFIT IN IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR PATIENTS

***Guilherme Portugal**

Department of Cardiology,
Hospital de Santa Marta, Lisbon, Portugal
**Correspondence to gfportugal@gmail.com*

Patients who receive an implantable cardioverter-defibrillator (ICD) are at high risk of cardiovascular (CV) events during follow-up. Challenges in these patients include maintaining adherence to strict guideline-mandated therapies, prevention and management of acute decompensations, device programming review, and optimisation of care. Device-based remote monitoring (RM) offers the opportunity for continuous monitoring of device function in addition to clinically relevant physiological parameters, which may help guide therapy in these patients. Recent data suggest that device-based RM may also offer benefits regarding patient outcomes.

We designed a retrospective cohort study of consecutive patients who underwent ICD implantation with the aim of assessing the effect of RM on hospital readmissions and mortality. Data on hospitalisations and mortality was systematically assessed using a nationwide healthcare platform and patient records were analysed to determine the cause of hospitalisation or death.

A total of 317 patients were included in the analysis, 121 of whom were under RM from the first outpatient visit post-ICD implantation. The mean follow-up was 44 months and the implanted and non-implanted groups were balanced with regard to patient characteristics, with no significant differences in age, left ventricular ejection fraction, or New York Heart Association classification. The use of RM was associated with lower overall mortality (hazard ratio [HR]: 0.51, confidence interval [CI]: 0.28–0.90; p=0.021) and lower incidence of a composite endpoint of CV mortality or hospital admission for heart failure (HR: 0.47, CI: 0.27–0.82; p=0.008). In multivariate analysis, RM was found to be an independent predictor of long-term survival (HR: 0.45, CI: 0.24–0.87; p=0.017).

These results shed some light on the clinical benefits of RM in this complex patient population. Although further data are needed, including results from ongoing randomised clinical trials, a growing body of evidence suggests that device-based RM has a significantly positive impact on the health and survival of these patients. In fact, this technology allows physicians to receive individualised alerts and tap into information such as intrathoracic impedance (a surrogate for pulmonary oedema), which was previously unavailable. Despite some logistical obstacles, such as hardware availability and dedicated staff, that still need to be overcome in order to be able to offer this technology to all patients, device-based RM may soon become the standard of care in intracardiac device recipients.

ENVIRONMENTAL EFFECTS ON PATIENTS WITH PACEMAKER AND ICD - MOBILE TELEPHONES

***Haran Burri**

Cardiology Service, Geneva University Hospitals, Geneva, Switzerland
**Correspondence to haran.burri@hcuge.ch*

Almost all patients with cardiac implantable electronic devices (CIEDs) currently have mobile phones. As shown by reports dating back to the 1990s, there is a potential risk for electromagnetic interference (EMI) between mobile phones and CIEDs due to emissions from digital phones that may cause oversensing. This may result in pacemaker (PM) dysfunction with inhibition of pacing, noise reversion with asynchronous pacing, inappropriate atrial tracking, or mode switch, whereas in implantable cardioverter-defibrillators (ICDs), inappropriate shocks may occur. Based on these results and also on regulations for testing, all CIED manufacturers currently recommend a safety distance of at least 15 cm between mobile phones and the implanted device. However, these recommendations do not reflect current risk due to: 1) the presence of effective filters in current CIEDs; 2) different signal characteristics of 3G (Universal Mobile Telecommunications System) and 4G (Long-Term Evolution) standards compared with the 2G (Global System for Mobile Communications) standard, which makes EMI less likely (e.g. lower maximum power, higher frequency with lower tissue penetration, etc.); and 3) better provider coverage resulting in lower emission power of mobile phones under normal operating conditions. The overwhelming evidence published these last 15 years points towards a negligible risk of EMI between mobile phones and CIEDs. In fact, most manufacturers perform optional testing that would allow their PMs and ICDs to be exposed to mobile phones without any restriction, but maintain the 15 cm warning to avoid possible legal issues. Other transmission standards such as Bluetooth and Near Field Communication carry a negligible risk of EMI due to the very low power emissions.

Another consideration is a possible magnetic effect between mobile phone earpiece speakers (which have small but powerful magnets) and CIEDs. This may cause asynchronous pacing of PMs, or temporary inactivation of ICD therapy. Even though *in vitro* experiments have shown that the risk exists, there have not been any published reports of this occurring *in vivo*. Ideally, mobile phones should be tested for a possible magnetic effect at in-office device follow-up. The risk of a magnetic effect is higher with mobile phone accessories such as earphones and wireless chargers, which should not be placed in contact with the CIED.

Lifestyle recommendations to patients should be evidence-based (and the data point towards negligible risk of EMI with mobile phones), pragmatic (accepting a very small risk), and should avoid unnecessary stress to CIED patients, allowing them to live as normally as possible.

E-CIGARETTES: FRIEND OR FOE?

***Peter Hajek**

Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
**Correspondence to p.hajek@qmul.ac.uk*

This invited presentation reviewed the key points regarding the current hopes and concerns surrounding the increasing popularity of electronic cigarettes (ECs) and the relevant evidence. If a much safer nicotine-delivery product were to replace cigarettes, then a major cause of preventable death and disease would be removed and the benefits to public health would be enormous. The tobacco-control activists, however, have generally not embraced the inherent promise in the spontaneous rise of ECs due to several strong concerns. Two major questions surrounding the use of ECs are: 1) whether vaping is substantially safer than smoking; and 2) whether an increasing use of ECs may lead to an increasing use of cigarettes. The second concern, sometimes

phrased as a 'gateway' or 'renormalisation' hypothesis, sounds improbable because safer technologies have always replaced less safe ones rather than boosting their sales. However, two theoretical pathways to such an outcome can be imagined: smoking rates would increase if the number of smokers who successfully quit by using ECs was overtaken by the number of non-smokers who start using ECs and subsequently switch from vaping to smoking; and/or if smokers who would otherwise quit instead started to vape and continued to smoke at the same rate instead of quitting (and the number of such cases was larger than the number of smokers who did quit by using ECs).

Regarding the relative safety of ECs compared with smoking, the toxicants in tobacco smoke responsible for smoking-related morbidity and mortality are either absent in EC vapour or present at levels many times lower than in smoke. The main chemicals present in EC vapour and not in tobacco smoke (propylene glycol and vegetable glycerol) are not considered to pose any major risks when inhaled. Ongoing vigilance and monitoring of contaminants and flavourings are needed, but the current best estimate is that any risks that ECs may pose in the long term are likely to be <5% of the risks of smoking.

The evidence is also reassuring regarding the concern that ECs may attract non-smokers who become vapers and then subsequently switch to smoking. Non-smokers do experiment with ECs, but, as with nicotine-replacement products, they find them remarkably unappealing; progression to regular vaping, let alone daily use, is extremely rare. Where population data are available (UK, USA, and France), the increase in adolescent experimentation with ECs has been accompanied by an accelerated decline in smoking prevalence in this age group. This does not necessarily mean that experimentation with ECs reduces experimentation with cigarettes, but it clearly shows that it does not increase it. In the UK, where detailed ongoing monitoring of smoking behaviour in the population exists, EC use has become a major smoking-cessation aid. The evidence shows that ECs act as a gateway away from smoking rather than into it.

Some concerns remain. While it is undoubtedly beneficial for smokers to switch to vaping, it would be best for non-smokers if they did not start smoking or vaping, and ECs should not be sold or promoted to non-smoking minors. The fact that currently available ECs are not attractive to non-smokers does not necessarily mean that this will remain true in the future. Ongoing monitoring of the contents of ECs, in addition to monitoring of their impact on the population, is needed so that regulatory measures can be taken should any problems emerge.

The overall impact of allowing ECs to compete against cigarettes is likely to be highly positive. It is unfortunate that the forthcoming European Tobacco Products Directive will regulate ECs more strictly than cigarettes and, in doing so, favour their deadly competitor. Hopefully this will not stop smokers from switching to vaping and there will remain a realistic chance that, in countries where ECs remain available, cigarette use will continue to decline until it virtually disappears.

TISSUE FACTOR ENCRYPTION AND DECRYPTION: FACTS AND CONTROVERSIES

***Philip Hogg**

ACRF-Centenary Cancer Research Centre and NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia

**Correspondence to philip.hogg@ctc.usyd.edu.au*

Tissue factor (TF) is a membrane cofactor that binds and promotes the catalytic activity of blood coagulation factor VIIa. The TF/VIIa complex activates factor X by discrete proteolysis, which leads to the thrombin burst that is important for a stable thrombus. TF functions as a haemostatic envelope in the extravascular compartment where it promptly activates coagulation upon breach of the vessel wall. Monocytes and/or neutrophils provide TF in the intravascular compartment. While TF on cells of the vascular adventitia is constitutively active, myeloid TF exists predominantly in a noncoagulant or cryptic form,

with acute events leading to local decryption of the cofactor.

A variety of experimental observations imply that decryption of TF on the surface of myeloid cells involves both surface exposure of negatively charged phosphatidylserine and a dithiol/disulphide switch in the protein.[1] The switch involves cysteine residues at positions 186 and 209 in the membrane-proximal domain of TF. The disulphide bond between these two cysteines is broken in cryptic TF and present in active TF. The oxidoreductase protein disulphide isomerase (PDI) is essential for thrombus formation *in vivo* and has been implicated in decryption of myeloid TF triggered by either activation of a purinergic receptor or complement.[2] Unpublished results were presented showing that oxidised PDI can directly mediate formation of the Cys186–Cys209 disulphide bond in cryptic soluble TF, as well as showing evidence of a role for the TF N-terminal Cys49–Cys57 disulphide bond in controlling the redox state of the C-terminal Cys186–Cys209 disulphide bond.

Proof or otherwise for this molecular mechanism of control of myeloid TF activity *in vivo* is lacking. There is currently no method of measuring the redox state of TF cysteines 186 and 209 *in vivo*, which is what is needed to test the dithiol/disulphide switch mechanism. As TF is present in catalytic amounts within the circulation, protein chemical characterisation of the cofactor is problematic. There was discussion of possible mouse models that could be developed to test the *in vitro* observations. Single cysteine mutants of TF are poorly expressed at the cell surface in mice, although it is possible that a double Cys186/Cys209 mutant might be expressed similarly to the wild-type protein. This mutant mouse will indicate whether the reduced TF is truly cryptic.

REFERENCES

1. Chen VM, Hogg PJ. Encryption and decryption of tissue factor. J Thromb Haemost. 2013;11 Suppl 1:277-84.

2. Chiu J et al. Protein disulphide isomerase in thrombosis. Semin Thromb Haemost. In press.

PLURIPOTENT STEM CELL-BASED THERAPIES IN VASCULAR REGENERATION

***Jean-Sébastien Silvestre**

INSERM UMRS 970, Université Paris Descartes, Sorbonne Paris Cité, Paris, France
**Correspondence to jean-sebastien.silvestre@inserm.fr*

Stem cell-based therapies for vascular regeneration in patients with ischaemic diseases initially relied on a very simple concept: therapeutic stem/progenitor cells might differentiate into vascular cells, mainly of endothelial phenotype, increasing new vessel formation and tissue perfusion in the ischaemic milieu. This exciting notion challenged the scientific community to start the quest for the Holy Grail of vascular regenerative medicine; the search for the ideal source of endothelial stem/progenitor cells. This concept led to the development of salutary approaches based on the use of therapeutic autologous adult stem cells thought to contain such bona fide endothelial progenitor cells as bone marrow or peripheral blood-derived mononuclear cells.[1]

Beside the classical technical caveats including modalities of cell transfer and optimisation of cell engraftment, the negative impact of cardiovascular risk factors, as well as the low rate of incorporation of adult stem cells in the targeted vasculature, likely explain the mixed results obtained in numerous Phase I–II clinical trials incorporating patients with peripheral artery or cardiac diseases. Hence, alternative sources of stem cells have been considered to leverage their intrinsic pluripotentiality and drive them towards a vascular lineage. Both embryonic stem cells (ESC) and induced pluripotent stem cells have then been tested in various experimental models of post-ischaemic vascularisation.

However, it is unlikely that a single even highly competent and plastic pluripotent cell can at each crossroad take the unique and correct decision required to become a vascular cell, especially in an ischaemic tissue.[2] Consistent with this, various cell culture techniques have been developed to obtain specific vascular progenitor cells from ESC

or induced pluripotent stem cells. Interestingly, a purified population of multipotent cardiovascular progenitors has recently been isolated, sorted, and characterised. These cardiovascular progenitors are derived from human ESC (hESC) treated with the cardiogenic morphogen bone morphogenetic protein 2 and Wnt3a, and are depicted by the expression of octamer-binding transcription factor 4, mesoderm posterior 1 (MesP1), and stage-specific embryonic antigen 1 (SSEA-1). This progenitor population is able to generate cardiomyocytes as well as endothelial cells and smooth muscle cells, and is currently being evaluated for the treatment of severe heart failure.[3,4] In this line, hESC-derived SSEA-1+/MesP1+ cells, or their progeny obtained after treatment with VEGF-A or PDGF-BB, show an unchallenged capacity to enhance post-ischaemic revascularisation in mice with critical ischaemia, especially when compared with adult stem cells.[5] However, as for their adult counterpart, hESC-derived SSEA-1+/MesP1+ cells do not structurally integrate within the recipient vascular network, but likely release biomolecules that fine-tune endogenous repair processes. A precise characterisation of the cell-released factors purportedly accounting for their benefits still remains elusive, but there is mounting evidence to suggest that stem cells can release extracellular membrane vesicles (EVs) that may contain vascular regenerative entities. Of note, in preliminary studies, we have documented that the preservation of post-infarct cardiac function afforded by hESC-derived SSEA-1+/MesP1+ cells could be equalled by their respective EV delivery. Definite confirmation that the effects of cells can be recapitulated by the factors that they secrete could lead to cell-free therapies, and would have major clinically relevant advantages with regard to manufacturing, streamlining of the regulatory path, and final costs.

REFERENCES

1. Silvestre JS et al. Postischemic revascularization: from cellular and molecular mechanisms to clinical applications. Physiol Rev. 2013;93(4):1743-802.

2. Puceat M. Could a pluripotent stem cell give rise to a high yield of a single cell lineage: a myocardial cell? Curr Opin Genet Dev. 2013;23(4):498-9.

3. Blin G et al. A purified population of multipotent cardiovascular progenitors derived from primate pluripotent stem cells engrafts in postmyocardial infarcted nonhuman primates. J Clin Invest. 2010;120(4):1125-39.

4. Menasché P et al. Human embryonic stem cell-derived cardiac progenitors for severe heart failure treatment: first clinical case report. Eur Heart J. 2015;36(30):2011-7.

5. Richart A et al. MicroRNA-21 coordinates human multipotent cardiovascular progenitors therapeutic potential. Stem Cells. 2014;32(11):2908-22.

INTERNATIONAL, LARGE-SCALE, REAL-WORLD CLINICAL DATA CONFIRM THE SAFETY PROFILE OF RIVAROXABAN

***John Camm**

Division of Clinical Sciences, St George's Hospital, University of London, London, UK
**Correspondence to jcamm@sgul.ac.uk*

Disclosure: John Camm is a consultant to Bayer, Boehringer Ingelheim, Pfizer, BMS, and Daiichi Sankyo.
Support: The publication of this article was funded by Bayer Pharmaceuticals. The views and opinions expressed are those of the authors and not necessarily of Bayer Pharmaceuticals.
Received: 11.09.15 **Accepted:** 12.10.15
Citation: EMJ Cardiol. 2015;3(2):82-88.

ABSTRACT

Rivaroxaban is a direct factor Xa inhibitor and a non-vitamin K antagonist (VKA) novel oral anticoagulant (NOAC) approved for a number of indications. It has been approved since 2011 by both the United States Food and Drug Administration and the European Medicines Agency for use in patients with non-valvular atrial fibrillation (NVAF) to reduce the risk of stroke and systemic embolism. However, anticoagulant therapy (both VKAs and NOACs) has been associated with an increased risk of bleeding. Although the majority of bleeding events are minor from a clinical standpoint (e.g. ecchymoses), major bleeding events have also been reported. This warrants the need for robust and large-scale clinical and safety data to guide physicians in patient selection, risk stratification, and treatment choice. While NOACs have been subject to a number of randomised clinical trials, observational studies, and real-world registries, large-scale observational studies are still scarce. This article reviews the newly published data from the XANTUS and the United States Department of Defense post-marketing safety surveillance studies, two landmark real-world observational studies on rivaroxaban use and safety in NVAF patients, and puts them in perspective with regard to clinical trial data and other real-world data. Both sets of results were presented at the European Society of Cardiology Congress on 31st August, 2015. This data collection represents more than 45,000 patients from 22 countries.

Keywords: Non-valvular atrial fibrillation, bleeding, stroke, rivaroxaban, real-world data.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is estimated to affect about 10 million patients in Europe.[1] This number is expected to rise, with a lifetime risk of 22–26%. Patients with AF display a 5-fold risk of experiencing a stroke.[2-4]

Oral anticoagulation therapy to reduce the risk of stroke in patients with AF is partly represented by vitamin K antagonists (VKAs), such as warfarin, which have been available for decades and are a standard prophylactic therapy. However, warfarin use has been associated with a number of challenges in daily clinical practice, including many drug–drug and drug–food interactions, and can represent a burden for many patients due to the need for strict monitoring, dose titration, and patient education in order to remain in the therapeutic window with an international normalised ratio of 2.0–3.0.

A novel pharmacological class, novel oral anticoagulants (NOACs), has emerged in the past decade. This class includes, in historical order, dabigatran, rivaroxaban, apixaban, and edoxaban. All four of these compounds have been demonstrated to be as effective as VKAs for stroke prevention in patients with non-valvular AF (NVAF), and subsequently approved in that indication.[5-8] Rivaroxaban is a direct factor Xa inhibitor NOAC approved for a number of indications. It has been approved since 2011 by both the United States

Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the reduction of risk of stroke and systemic embolism (SE) in patients with NVAF. However, anticoagulant therapy (both VKAs and NOACs) has been associated with an increased risk of bleeding.[7,9] Although the majority of bleeding events are minor from a clinical standpoint (e.g. ecchymoses), major bleeding events have also been reported. This warrants the need for robust and large-scale efficacy and safety data to guide physicians in patient selection, risk stratification, and treatment choice. While NOACs have been subject to a number of randomised clinical trials, observational studies, and real-world registries, large-scale observational studies are still scarce.

This article reviews the newly published data from the XANTUS and the United States Department of Defense post-marketing safety surveillance (US DoD PMSS) studies, two landmark real-world observational studies on rivaroxaban use and safety in NVAF patients, and puts them in perspective with regard to both clinical trial data and other real-world data. Both sets of results were presented at the European Society of Cardiology (ESC) Congress on 31st August, 2015. This data collection represents more than 45,000 patients from 22 countries.

THE XANTUS STUDY

The XANTUS study (NCT01606995) was a large, international, real-world, prospective, single-arm, observational, post-authorisation, non-interventional study that aimed to collect clinical safety and efficacy data on rivaroxaban for stroke prevention in a cohort of patients with NVAF.[10] This study was the first large study to describe the use of rivaroxaban in routine clinical practice for NVAF in a broad patient population, and was designed in agreement with the EMA. Camm et al.[11] presented the preliminary results of this study at ESC Congress 2015. This presentation was accompanied by a peer-reviewed article published on the same date in the *European Heart Journal*.[12]

Methods

Consenting patients with NVAF and who were initiated on rivaroxaban were included in the study, irrespective of stroke risk, and followed for 1 year, with 3-monthly follow-up visits, or for at least 30 days after permanent discontinuation. Dosing regimens were determined by the treating physician. Safety findings were reported, with all adverse events (AEs) being labelled as 'AE' or as 'serious AE' (SAE); the latter were followed-up until final outcome. Some AEs, such as major bleeding (as defined by the International Society on Thrombosis and Haemostasis criteria), symptomatic thromboembolic events (TEEs; including stroke, SE, transient ischaemic attacks [TIAs], myocardial infarction [MI]), and all-cause death were centrally adjudicated.

Clinical outcomes were also reported, in the form of management of bleeding events and stroke occurrence, as well as treatment persistence, self-reported patient satisfaction, and healthcare resource use.

Results

Patient demographics

A total of 6,784 patients (mean age: 71.5 years, range: 19–99; patients >75 years: 37%) from 311 centres in Europe, Israel, and Canada were enrolled in the study between June 2012 and December 2013 and received rivaroxaban. The most common rivaroxaban dosing regimen was 20 mg once daily (OD; 78.7%), with 20.8% of patients receiving 15 mg OD and 0.5% receiving a different dose. Overall, 59% of patients were male and 54.5% of patients were VKA-naïve. With regard to renal function, 9.4% of patients had moderate or severe renal impairment (as defined by creatinine clearance [CrCl] <50 mL/min), with 1.4% displaying CrCl ≤30 mL/min. Paroxysmal AF was present in 40.6% of patients, persistent or permanent AF present in 40.7%, and 18% of patients were first diagnosed with AF. Regarding patient history: 19.0% of patients had prior stroke, TIA, or SE; 18.6% had congestive heart failure; 74.7% had hypertension; and 19.6% had diabetes.

The mean CHADS2 (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke) score[13] was 2.0 (median: 2.0), for a mean CHA2DS2-VASc score[14] (incorporating the CHADS2 score plus female gender, vascular disease, and age 65–74 years) of 3.4 (median: 3.0); 13% of patients had a CHA2DS2-VASc score of 0 or 1. Mean treatment duration in the overall cohort was 329 days (standard deviation [SD]: 115 days; median: 366 days).

Treatment persistence was high, with 79.9% of patients remaining on rivaroxaban therapy

throughout the 1-year study period, which is of clinical importance with respect to the protective effects of NOACs against the risk of stroke. A total of 598 patients (8.8%) had at least one therapy interruption (median duration: 4 days), mainly due to the need for surgery or the occurrence of bleeding or another AE.

Primary outcomes: safety

AEs were reported in 2,709 patients (39.9%), of whom 1,203 (18% of the overall cohort) experienced an SAE (Table 1). Overall, 1.9% of the patients experienced treatment-emergent major bleeding (n=128; 2.1 events per 100 patient-years). The on-treatment all-cause mortality rate was 1.7% (1.9 events per 100 patient-years), with fatal bleeding occurring in 0.2% of all cases (0.2 events per 100 patient-years). Unadjusted AE rates and comorbidities were higher in patients receiving rivaroxaban 15 mg OD. Overall, the rates of stroke and major bleeding were low and increased progressively over time in this real-world, clinical practice cohort.

Secondary outcomes

The overall rate of symptomatic TEEs (stroke, TIA, SE, MI) was 1.6% (108 patients), which comprised of 0.6% experiencing stroke, 0.1% experiencing SE, 0.5% experiencing TIA, and 0.4% experiencing MI (Table 2).

Table 1: Treatment-emergent adverse events in the XANTUS study.

Adjudicated endpoint	Rivaroxaban (n=6,784), incidence (%)
All-cause mortality	118 (1.7%)
Thromboembolic event (stroke, SE, TIA, MI)	108 (1.6%)
Major bleeding	128 (1.9%)
Mucosal bleeding	60 (0.9%)
Haemoglobin decrease ≥2 g/dL	52 (0.8%)
Transfusion of ≥2 units of packed red blood cells or whole blood	53 (0.8%)
Critical organ bleeding	43 (0.6%)
Intracranial haemorrhage	26 (0.4%)
Fatal bleeding	12 (0.2%)
Non-major bleeding events	878 (12.9%)
Major bleeding is collected as serious or non-serious adverse event and defined as overt bleeding associated with a fall in haemoglobin of ≥2g/dL or a transfusion of ≥2 units of packed red blood cells or whole blood or a critical site bleeding or a fatal outcome. Treatment emergent: period at start of study medication to 2 days after last dose. Note: only specific adverse events are shown, not all, namely thromboembolic, bleeding, and all-cause mortality.	

MI: myocardial infarction; SE: systemic embolism; TIA: transient ischaemic attack.

Table 2: Treatment-emergent secondary outcomes (symptomatic thromboembolic events) in the XANTUS study.

Adjudicated endpoint	Rivaroxaban (n=6,784), incidence (%)
Symptomatic thromboembolic events (stroke, TIA, SE, MI)	108 (1.6%)
Stroke and SE	51 (0.8%)
Stroke	43 (0.6%)
SE	8 (0.1%)
TIA	32 (0.5%)
MI	27 (0.4%)

MI: myocardial infarction; SE: systemic embolism; TIA: transient ischaemic attack.

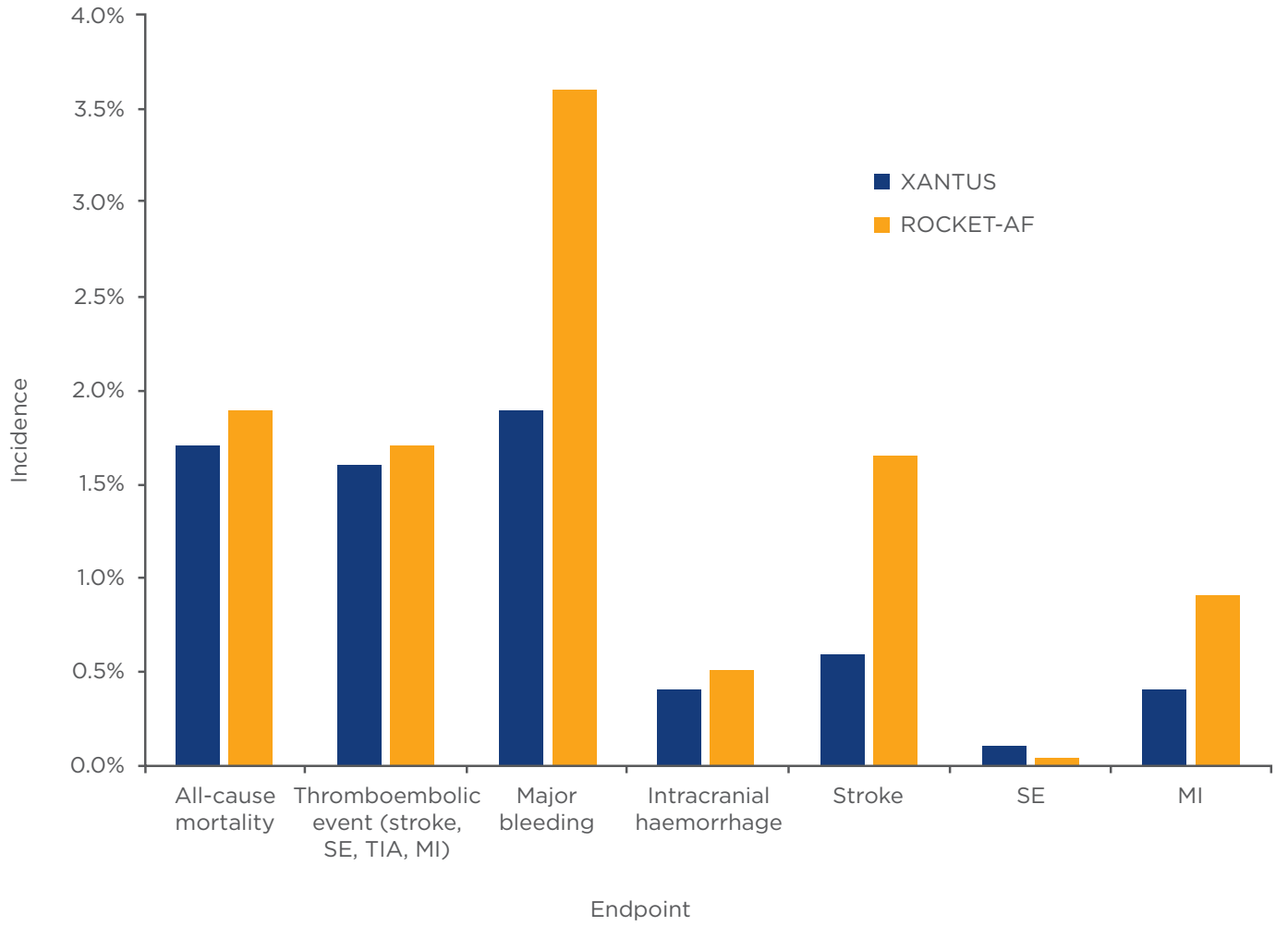


Figure 1: Safety endpoints and clinical outcomes in the XANTUS and ROCKET-AF studies.
MI: myocardial infarction; SE: systemic embolism; TIA: transient ischaemic attack.
Note: results are not intended for direct comparison.

XANTUS Results and Findings from the ROCKET-AF Registration Clinical Trial

The registration trial for rivaroxaban in NVAF was the Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study.[7,9] Patients in this trial had a mean $CHADS_2$ score of 3.5 (versus 2.0 in XANTUS) and incidence of major bleeding was 3.6 events per 100 person-years (versus 2.1 per 100 person-years in XANTUS). Therefore, the patients in XANTUS were at lower risk than those in the ROCKET-AF study.

The incidences of all-cause mortality, major bleeding, stroke, and MI were lower in the XANTUS study than in the ROCKET-AF study (Figure 1). Rates of fatal bleeding, critical organ bleeding, and intracranial haemorrhage per 100 person-years were similar between the two studies. It is to be noted that while methodological discrepancies limit the comparison of studies, this confirmation nevertheless provides some insight into the safety profile of rivaroxaban.

UNITED STATES DEPARTMENT OF DEFENSE POST-MARKETING SAFETY SURVEILLANCE STUDY

Methods

This PMSS study is a 5-year, retrospective, observational study with no comparator arm that aims to evaluate major bleeding in patients taking rivaroxaban who have NVAF or are undergoing total hip and/or knee replacement procedures. It was designed in collaboration with the US DoD, which possesses an integrated electronic health record database of almost 10 million patients. For the current analysis, the database

was used to identify major bleeding-related hospitalisations among patients with NVAF and treated with rivaroxaban. Additional data on fatal events and major bleeding management (surgical interventions, intensive care unit hospitalisations, and transfusions) were collected. Data on patient demographics, comorbidities, and risk factors were also collected to allow for in-depth analysis of major bleeding patterns and clinical settings. Of note, the major bleeding events in the US DoD PMSS did not go through any adjudication process, which may be a study limitation.

This study was developed in agreement with the FDA as part of a post-marketing requirement and is still ongoing. Preliminary results at 15 months have already been published, encompassing data in NVAF patients from 1st January 2013 to 31st March 2014. These results were published in *Clinical Cardiology* in February 2015.[15] Similarly, an 18-month update was presented at the 2015 American College of Cardiology Scientific Session on 15th March 2015.[16] Peacock et al.[17] presented the 2-year preliminary data at the ESC Congress on 31st August 2015.

Results

A total of 39,052 patients receiving OD rivaroxaban therapy were identified between January 2013 and December 2014. Descriptive data were reported including patient demographics, comorbidities, concomitant medications, bleeding hospitalisations and management, bleeding characteristics, and outcomes.[16,17]

Safety: major bleeding

The incidence of at least one major bleeding event, identified with the validated Cunningham database algorithm,[18] was 2.89 events per 100 person-years (95% confidence interval: 2.71–3.08; n=970). The majority (87.2%) of major bleeding events were gastrointestinal haemorrhages (n=846). Incidences of intracranial and genitourinary haemorrhages were 8.1% (n=79) and 0.6% (n=6), respectively. Other or unspecified bleeding represented 4.0% of cases of major bleeding (n=39). Most major bleeding patients were discharged to home, and the mean length of hospitalisation was 4.0 days (SD: 3.4). Overall, 42.3% of patients with major bleeding were transferred to an intensive care unit, and 51.5% received a blood transfusion.[16,17]

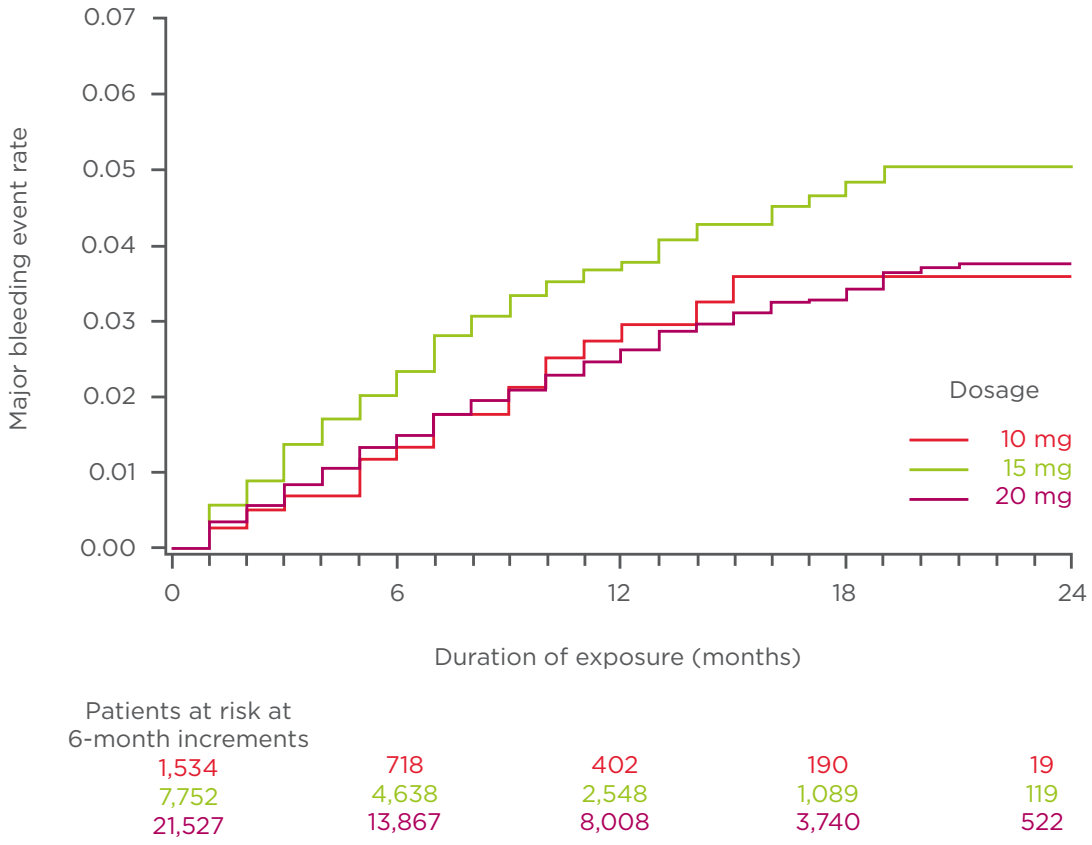


Figure 2: Cumulative incidence of major bleeding by rivaroxaban dose in the United States Department of Defense post-marketing safety surveillance study: preliminary analysis of the first 30,813 patients.

Safety: mortality rates

The researchers observed a very low incidence of fatal bleeding (0.1%, 95% CI: 0.07–0.15; n=35); the mean age at time of death was 80.3 years. Of the fatal bleedings, 74.3% were intracranial haemorrhages and 25.7% were gastrointestinal bleedings.[16,17] Tamayo et al.[16,17] also presented the results of the cumulative incidences of major bleeding according to rivaroxaban dose, which were produced through an earlier interim analysis on the first 30,813 patients (Figure 2).

United States Department of Defense Post-Marketing Safety Surveillance Study Results and Findings from the ROCKET-AF Registration Clinical Trial

Overall, patterns and rates of major bleeding in real-world clinical practice were consistent with those reported in the ROCKET-AF study, as was previously observed in the earlier reporting from the 15-month results.[7,9,15] The incidence of major bleeding seems to be low in this post-marketing setting; the upcoming 5-year results should continue to provide insights into the use of rivaroxaban in routine clinical practice.

DISCUSSION

Randomised clinical trials are the most rigorous way to evaluate a drug, and are designed to produce a new hypothesis. This hypothesis can be placed into perspective with observational prospective studies or registries, which conversely aim to produce a picture of routine clinical care, clinical settings, and patient characteristics at a given time and place.

While the initiation of randomised clinical trials is pivotal to determine the efficacy and safety of a potential new drug versus standard therapy, their impact can be challenged by a variety of factors. Patients in such trials are selected with narrow inclusion criteria, alongside multiple exclusion criteria, and are treated in selected expert centres which are likely to monitor them more closely. Quality of care, study requirements, and strict protocols can impact the benefit–risk balance, thus creating differences compared with what may be obtained in a real-world, routine clinical practice cohort.

Registries and large-scale observational studies providing a broad range of clinical settings and patient baseline characteristics are essential to complement the results from randomised clinical trials, and these designs are complementary. However, the limitations of prospective, observational data collection are mainly based on the generation of residual confounding and false/under-reported data. In addition, data comparison between centres can sometimes be challenging due to differences in baseline characteristics and socioeconomic factors across diverse regions. Nevertheless, these initiatives can provide a picture of what to expect in daily clinical practice. This further insight, when taken into account alongside clinical trial evidence, can help to refine guidelines, patient stratification rationales, and standardised treatment protocols.

CONCLUSION

In conclusion, the findings of the XANTUS and the US DoD PMSS studies reaffirm the benefit-to-risk profile of rivaroxaban, as determined in pivotal clinical trials such as the Phase III ROCKET-AF study, and may help physicians make informed decisions on treatment selection. While any direct comparison cannot be performed between clinical trials and observational studies due to strong differences in design, data collection, exposure, patient population, and inclusion/exclusion criteria, the real-world data may help physicians put the results of the ROCKET-AF study into context.

Acknowledgements

Medical writing assistance was provided by Dr Caroline Charles (Scilink Medical Writing, Biarritz, France).

REFERENCES

1. Zoni-Berisso M et al. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213-20.
2. Mant J, Edwards D. Stroke prevention in atrial fibrillation: putting the guidelines into practice. Drugs Aging. 2010;27(11):859-70.
3. Andrade J et al. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res. 2014;114(9):1453-68.

4. Sanna T et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370(26):2478-86.

5. Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51.

6. Granger CB et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92.

7. Patel MR et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-91.

8. Giugliano RP et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093-104.

9. Goodman SG et al. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). J Am Coll Cardiol. 2014;63(9):891-900.

10. Camm AJ et al. XANTUS: rationale and design of a noninterventional study of rivaroxaban for the prevention of stroke in patients with atrial fibrillation. Vasc Health Risk Manag. 2014;10:425-34.

11. Camm AJ et al. XANTUS: low rates of bleeding and stroke in a real-world prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Abstract 5072. ESC 2015, 29 August–2 September 2015.

12. Camm AJ et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J. 2015. pii: ehv466. [Epub ahead of print].

13. Gage BF et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864-70.

14. Lip GY et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.

15. Tamayo S et al. Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27 467 patients taking rivaroxaban. Clin Cardiol. 2015;38(2):63-8.

16. Tamayo S et al. Post-marketing pharmacovigilance study for the active detection and evaluation of major bleeding in rivaroxaban users with non-valvular atrial fibrillation. J Am Coll Cardiol. 2015;65(10_S).

17. Peacock F et al. Major bleeding in a post-marketing assessment of 39,052 non-valvular atrial fibrillation patients on rivaroxaban. Abstract P4066. ESC 2015, 29 August–2 September 2015.

18. Cunningham A et al. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf. 2011;20(6):560-6.

REAL-WORLD REGISTRY STUDY CONFIRMS FONDAPARINUX OVER LOW-MOLECULAR-WEIGHT HEPARIN FOR NSTEMI

***Tomas Jernberg, Karolina Szummer**

Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden
**Correspondence to tomas.jernberg@karolinska.se*

Disclosure: Tomas Jernberg and Karolina Szummer have both received honoraria for lectures from Aspen. Karolina Szummer has also received honoraria for lectures from AstraZeneca.
Support: The publication of this article was funded by Aspen. The views and opinions expressed are those of the authors and not necessarily of Aspen.
Received: 21.08.15 **Accepted:** 07.10.15
Citation: EMJ Cardiol. 2015;3[2]:89-93.

ABSTRACT

The pivotal Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial demonstrated that fondaparinux was non-inferior to enoxaparin in reducing ischaemic outcomes in patients with a non-ST segment elevation myocardial infarction (NSTEMI). However, fondaparinux was associated with a lower number of patients experiencing major bleeding events. Based on these results suggesting a better benefit-to-risk ratio over enoxaparin, the European Society of Cardiology recommended fondaparinux as the first-line anticoagulation therapy in patients with an NSTEMI in 2007. A registry study conducted in Sweden provides real-life clinical data and confirms the clinical relevance of fondaparinux use over low-molecular-weight heparin in routine clinical care. This article aims to review the place of fondaparinux in acute coronary syndrome patients, and to provide an analysis of clinical trial data along with real-life data.

Keywords: Acute coronary syndrome (ACS), myocardial infarction (MI), fondaparinux, low-molecular-weight heparin (LMWH), registry data, NSTEMI: non-ST segment elevation myocardial infarction.

INTRODUCTION

Clinical research on antithrombotic therapy in acute coronary syndrome (ACS) is focussed on reducing ischaemic outcomes, ideally without compromising on safety and with special regard to bleeding events, which are associated with increased mortality rates.[1] Anticoagulants have demonstrated their efficacy in reducing the occurrence of major ischaemic events in ACS. This includes enoxaparin, a low-molecular-weight heparin (LMWH) which reduces the risk of death or myocardial infarction (MI) by 16% (odds ratio [OR]: 0.84, 95% confidence interval [CI]: 0.76–0.92) when compared with unfractionated heparin (UFH). Nevertheless, this benefit comes at the price of an increased risk of major bleeding (OR: 1.25, 95% CI: 1.04–1.50).[2]

Fondaparinux sodium (Arixtra®, Aspen Pharma) is a synthetic, selective anti-Xa anticoagulant that was approved in Europe by the European Medicines Agency in 2007 for the treatment of unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI) in adults for whom urgent (<120 mins) invasive management (percutaneous coronary intervention [PCI]) is not indicated.[3] Fondaparinux is administered subcutaneously for a bioavailability of 100% and a half-maximal plasma level reached after 25 minutes; these pharmacokinetic properties allow for a once daily formulation without the need for laboratory monitoring.[4]

The pivotal Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial demonstrated that fondaparinux was non-inferior to enoxaparin in reducing ischaemic outcomes in patients with an NSTEMI.[5] However, fondaparinux was associated with a significantly lower number of patients experiencing major bleeding events.

Based on these results suggesting a better benefit-to-risk ratio over enoxaparin, the European Society of Cardiology (ESC) recommended fondaparinux as the first-line anticoagulation therapy in patients with an NSTEMI in 2007.[6] This article aims to review the place of fondaparinux in ACS patients, and to provide an analysis of clinical trial data along with real-life data.

THE NEED FOR REGISTRY DATA: LIMITATIONS OF RANDOMISED CONTROLLED TRIALS

The implementation of a clinical randomised controlled trial (RCT) is the best way to compare two treatment options because it eliminates the problem of confounding. However, the impact of RCTs today is often limited by selecting patients through the use of narrow inclusion criteria and multiple exclusion criteria. In addition, RCTs are conducted in selected expert centres with selected doctors, who are likely to monitor patients more closely due to the requirements of the study and the quality of care that is to be expected of a high-level care facility. These factors can have an impact on the clinical outcomes and the risk–benefit balance, which can be diverted from 'real-world' data that could be obtained in an unselected patient population.

In a recent study of MI survivors, the median age was 10 years older and the long-term risk was 2 to 3-times higher in real-world data from a national registry compared with results from recently performed RCTs. These results raise questions about the generalisability of the results from many RCTs. Our registries should therefore be used more often to evaluate new treatments and/or to confirm RCT results. The implementation of registry-based clinical RCTs is a new concept that may not only lower the costs of randomised studies but also increase the value of the results of such trials.

AVAILABLE CLINICAL DATA FOR FONDAPARINUX VERSUS LMWH IN NSTEMI

OASIS-5 Study

OASIS-5 was a randomised, double-blind, parallel-group trial that aimed to compare fondaparinux (2.5 mg per day for up to 8 days) with enoxaparin (1 mg/kg twice daily [once daily in those with renal dysfunction] for up to 8 days) in patients with NSTEMI (n=20,078).[5] The primary endpoint was occurrence of death, MI, or refractory ischaemia at Day 9. Fondaparinux was demonstrated as non-inferior to enoxaparin in reducing ischaemic outcomes. However, fondaparinux had a lower risk of in-hospital and post-hospitalisation bleeding events, including major bleeding (180 days of follow-up: 4.3% versus 5.8%; hazard ratio [HR]: 0.72, 95% CI: 0.64–0.82; p<0.001), which in turn was associated with short and long-term reductions in mortality.

In addition, fondaparinux was demonstrated to be slightly safer with respect to the occurrence of stroke compared with enoxaparin (180 days of follow-up: 1.3% versus 1.7%; HR: 0.78, 95% CI: 0.62–0.99; p=0.04). In a *post hoc* analysis of the trial results, patients with moderately reduced renal function, despite being exposed to a higher risk of bleeding,[7] were associated with a higher reduction in bleeding events in the fondaparinux group compared with the LMWH treatment group.[8] Patients undergoing PCI over the course of a hospitalisation generated similar results to those from the general OASIS-5 cohort, despite a higher risk of thrombus formation on the angioplasty device in the fondaparinux group.[9] Administration of UFH during PCI successfully prevented almost all cases of catheter thrombosis without leading to increased bleeding risk.[9]

Data from SWEDEHEART

While the well-designed OASIS-5 study demonstrated the favourable efficacy and safety profiles for fondaparinux, new clinical data and real-world data describing daily clinical practice are still relevant and help refine ACS management. In a study published in February 2015, routine clinical practice results from the robust, large, and independent Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry database confirmed the OASIS-5 findings.[10]

SWEDEHEART is a national Swedish registry launched in 2009 after the merger of several coronary artery disease (CAD) registries initiated in previous decades, thus containing data from the beginning of the 1990s. This registry aims to support the improvement of care and evidence-based development of therapy for CAD.

This registry encompasses all consecutive patients hospitalised for ACS or undergoing coronary

angiography/angioplasty or heart surgery for any indication in one of the 72 Swedish hospitals that provide care for acute cardiac diseases. As it has become an integrated part of patient care in these facilities, about 80,000 new cases are entered into the registry every year, including 20,000 with acute MI, 10,000 with UA, 25,000 with other causes for their symptoms, 40,000 undergoing coronary angiography/angioplasty, and 7,000 undergoing heart surgery.[11]

This online case report database is shared among all hospitals and comprises 106 variables, including patient demographics, admission logistics, risk factors, past medical history, medical treatment before admission, electrocardiographic changes, biochemical markers, other clinical features and investigations, medical treatment in hospital, interventions, hospital outcome, discharge diagnoses, and discharge-medications. The database also includes additional variables such as whether the patient is younger than 75 years and hospitalised for acute MI, undergoing coronary angiography/angioplasty, or operated for cardiac or thoracic aortic disease.

OBJECTIVES

The SWEDEHEART registry study was a prospective cohort study that aimed to assess the rate of ischaemic and bleeding events among a wide range of non-selected, non-trial patients with NSTEMI who were treated with either fondaparinux or LMWH.[10] This study also aimed to assess the association between the two anticoagulants and outcome, both in patients with reduced renal function and in patients undergoing PCI.

METHODS AND PATIENTS

All patients aged 18 years or older who had NSTEMI that had been registered for the first time (n=40,616; median age: 73 years; 37.2% female) and who were treated at one of the 72 Swedish hospitals providing acute cardiac care with either fondaparinux or LMWH between 1st September 2006 and 30th June 2010 were included in the study. The outcomes were severe in-hospital bleeding events and death, and 30 and 180-day major bleeding, death, stroke, and recurrent MI.

Table 1: Clinical outcomes according to treatment group.

Outcome	Fondaparinux group (n=14,791), %	LMWH group (n=26,825), %	Odds ratio (95% confidence interval)*
Bleeding			
In-hospital	1.1	1.8	0.54 (0.42–0.70)
30 days	1.4	2.1	0.56 (0.44–0.70)
180 days	1.9	2.8	0.60 (0.50–0.74)
Death			
In-hospital	2.7	4.0	0.75 (0.63–0.89)
30 days	4.2	5.8	0.83 (0.72–0.96)
180 days	8.3	11.8	0.77 (0.69–0.86)
MI			
30 days	9.0	9.5	0.94 (0.84–1.06)
180 days	14.2	15.8	0.97 (1.89–1.06)
Stroke			
30 days	0.5	0.6	1.11 (0.74–1.65)
180 days	1.7	2.0	0.98 (0.79–1.22)
Bleeding, death, MI, or stroke			
30 days	14.0	16.85	0.83 (0.75–0.90)
180 days	22.7	27.5	0.81 (0.75–0.88)

*Adjusted for admitting hospital, calendar time, and baseline characteristics.
LWMH: low-molecular-weight heparin; MI: myocardial infarction.

Logistic regression was used to determine the OR and CI for the occurrence of an event at each time point. Adjustments for year, admitting hospital, baseline characteristics, and in-hospital revascularisation were performed.

RESULTS

Patient Population

While the rates of prior bleeding events and haemorrhagic stroke were similar between both treatment groups, patients who received fondaparinux were younger (mean: 2 years younger) and fewer had prior MI (28.2% versus 32.2%), and fewer patients had been previously diagnosed with congestive heart failure (14.5% versus 18.7%) when compared with the LMWH group. Overall, 41.6% of patients underwent PCI during the initial hospital stay, with a difference between both treatment groups (fondaparinux: 46.4%; LMWH: 38.9%).

Therapy Use

Overall, 36.4% of patients (n=14,791) received fondaparinux while hospitalised versus 63.6% of patients (n=25,825) who received LMWH (mainly enoxaparin). Fondaparinux use increased from 0.7% of patients during the first calendar year to 84.8% in the final calendar year of the study. This steep increase can be linked to the ESC and the Swedish National Board of Health and Welfare recommendations for fondaparinux as the first-choice therapy in NSTEMI in the early phase of the study.[6]

Severe Bleeding Events and Death Rates

The odds of severe bleeding and death in routine clinical care were lower in the fondaparinux treatment group versus LMWH, either during the initial hospitalisation or at 30 or 180 days of follow-up (Table 1). However, the rates of MI and stroke were comparable between both treatment groups.

Overall, the real-life data from the SWEDEHEART study support the OASIS-5 study that was published in 2006, as the results match those obtained in the clinical trial setting.

Patient Subpopulations

In patients with renal dysfunction, bleeding rates were lower in the fondaparinux group versus the LMWH group during hospitalisation and at 30 and 180 days follow-up, although the results were not significant due to wide CIs in patients with severely impaired renal function. Similar results were observed among patients with impaired renal function for in-hospital and 30-day death events. As renal dysfunction was associated with a significant, 5-fold higher rate of severe bleeding, the prevention of such events might translate into fewer death events.

However, in patients with the lowest estimated glomerular filtration rate (eGFR; patients with eGFR ≤15 mL/min/1.73 m^2), these results were not statistically significant, possibly due to a low number of patients and a wide CI. It is to be noted that severe renal dysfunction (eGFR <20 mL/min/1.73 m^2) is a contraindication to fondaparinux and dose adjustment may be needed for LMWH. Patients who underwent PCI during the first hospitalisation generated comparable results to the general population. The OR suggested a benefit from fondaparinux over LMWH with regard to in-hospital bleeding events and mortality, although the results did not reach statistical significance (OR: 0.89, 95% CI: 0.57–1.38; and OR: 0.67, 95% CI: 0.33–1.05, respectively).

DISCUSSION

This registry study conducted in Sweden provides real-life clinical data and confirms the clinical relevance of fondaparinux use over LMWH (the majority of which was enoxaparin) in routine clinical care. The authors acknowledge that the study was limited by its observational design that can generate residual confounding, and the possibility of bleeding being under-reported in registries. There was also a lack of information on the dose and duration of the therapies used, which could have provided more in-depth insights into the benefits of fondaparinux regimens over LMWH.

One of the strengths of this study was the population-based design, which provided a wide range of clinical settings and patients, and the availability of variables such as baseline kidney function and history of prior cardiac intervention. Another strength was the broad coverage of the SWEDEHEART registry in Sweden, as 86% of the total ACS patients were captured. The consistency between the clinical trial findings and the registry data obtained in a broader, heterogeneous population provides a robust platform of risk–benefit balance for fondaparinux to warrant the implementation of guideline recommendations in NSTEMI management.

Acknowledgements

Medical writing assistance was provided by Dr Caroline Charles (Scilink Medical Writing, Biarritz, France).

REFERENCES

1. Eikelboom JW et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation. 2006;114(8):774-82.

2. Murphy SA et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. Eur Heart J. 2007;28(17):2077-86.

3. European Medical Agency. Annex 1: Summary of Product Characteristics. 2007. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000403/WC500027746.pdf. Last accessed: 15 August 2015.

4. Samama MM, Gerotziafas GT. Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux). Thromb Res. 2003;109(1):1-11.

5. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes; Yusuf S et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354(14):1464-76.

6. Bassand JP et al. [Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes]. Rev Port Cardiol. 2008;27(9):1063-143.

7. Santopinto JJ et al. Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: findings from the global registry of acute coronary events (GRACE). Heart. 2003;89(9):1003-8.

8. Fox KA et al. Influence of renal function on the efficacy and safety of fondaparinux relative to enoxaparin in non ST-segment elevation acute coronary syndromes. Ann Intern Med. 2007;147(5):304-10.

9. Mehta SR et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. J Am Coll Cardiol. 2007;50(18):1742-51.

10. Szummer K et al. Association between the use of fondaparinux vs low-molecular-weight heparin and clinical outcomes in patients with non-ST-segment elevation myocardial infarction. JAMA. 2015;313(7):707-16.

11. Jernberg T et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart. 2010;96(20):1617-21.

SELF-EXPANDING CORONARY STENTS: RATIONALE, CLINICAL STATUS, FUTURE PROSPECTS

***Rainer Wessely,[1] Giovanni Amoroso[2]**

1. Cologne Cardiovascular and Chest Center, Cologne, Germany
2. Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands
**Correspondence to rwessely@web.de*

Disclosure: Prof Dr R. Wessely and Dr G. Amoroso have received minimal consulting speaker fees from STENTYS.
Support: The publication of this article was funded by STENTYS. The views and opinions expressed are those of the authors and not necessarily of STENTYS.
Received: 01.12.14 **Accepted:** 15.06.15
Citation: EMJ Cardiol. 2015;3[2]:94-106.

ABSTRACT

The mechanical treatment of coronary artery stenoses by placement of balloon-expandable (Bx) coronary stents has become the most widely used invasive treatment for symptomatic coronary artery disease (CAD). However, the mechanical properties of Bx stents may be limited and are frequently not well adapted to the requirements of the biological system. Consequently, there is evidence that the mechanical shortcomings of Bx stents, such as conformability to the vascular wall, stent underexpansion or oversizing, adaptability to vessel tapering, scaffolding of bifurcated lesions, inability to address vessel remodelling, and achieving optimal drug delivery, could translate into adverse clinical events. New, enhanced technology now allows the application of a number of self-expanding (Sx) coronary stents to treat CAD. Various clinical trials have proven coronary applicability and the clinical safety and efficacy of Sx stents. It is expected that this new generation of endovascular prostheses that are specifically tailored to the needs of the coronary arteries can overcome some of the limitations that are associated with Bx stents, while maintaining their valuable, traditional features. Clinical results of Sx stents may be further improved by continuous development of these devices.

Keywords: ST segment elevation myocardial infarction (STEMI), STENTYS, self-apposing stent, self-expanding (Sx) stent, stent underexpansion, stent strut malapposition.

INTRODUCTION

A contemporary coronary stent is an extraordinary piece of engineering and the result of continuous research and application of multidisciplinary knowledge (chemistry, mechanics, physics, hydraulics, etc.). In the ideal device, vessel scaffolding is consistent over time and does not interfere with blood vessel rheology or vascular healing. In contrast, drug delivery should be limited in time but be geographically homogeneous along the treated vessel surface. Despite the tremendous and continuous efforts made to enhance the efficacy and safety of these devices, balloon-expandable (Bx) stents can still encounter failures inherent in their construction and design, both during and after implantation.

Consequently, there is emerging evidence that the mechanical shortcomings of Bx stents can translate into adverse clinical events (ACEs). An overview of the limitations of contemporary coronary stents is provided in Table 1 and further discussed below. However, the metal backbone of Bx stents also exhibits advantageous features that enable the widespread use of this technology. These features comprise a suitable radial force, relatively thin struts that facilitate healing, the possibility of a low profile due to thinner struts and refined crimping technology, and radiopacity.

Self-expanding (Sx) stents were introduced in peripheral transluminal angioplasty during the last decade of the previous millennium and are now widely used in other areas of interventional medicine. Their use is not confined to peripheral

vascular indications and also stretches to gastrointestinal and pulmonary purposes, in particular in the context of obstructive neoplastic disease. Within the endovascular sector, they are now routinely employed not only for classical percutaneous transluminal angioplasty, e.g. of the lower extremities,[1] but also in aortic repair[2] and neurovascular interventions.[3]

New, enhanced technology now allows the application of the Sx stent concept in the treatment of coronary artery disease. It is expected that this new generation of endovascular prostheses specifically tailored to the needs of the coronary arteries can overcome the limitations that are associated with Bx stents, while maintaining their valuable, traditional features. This review will focus on the mechanical and biological shortcomings of conventional Bx stents and highlight the intriguing new features that new Sx platforms offer.

LIMITATIONS OF BALLOON-EXPANDABLE STENTS

Conformability: Support of the Vascular Wall

Fundamental mechanical requirements for coronary stents include flexibility to conform to the curved configuration of coronary arteries as well as providing a sustained, uniform support of the vascular wall. Among Bx stents, substantial differences regarding these mechanical properties have been described.[4-6] While there is currently no long-term assessment of the clinical impact of stent conformability available, a recent study found no difference within the first year of implantation with regard to stent placement in angulated lesions versus straight lesions when a second-generation drug-eluting stent (DES) was implanted.[7]

The potential consequences of suboptimal conformability are: firstly, vessel curvature is altered, which leads to flow alterations that may have an unfavourable impact on the occurrence of restenosis and stent thrombosis;[8] secondly, non-conformability greatly increases the likelihood of stent strut malapposition at the vascular wall, which is commonly associated with impaired healing[9] and reduced drug delivery to the vascular wall.[10] Again, this malapposition may consequently lead to an increase in neointima formation and thus restenosis, as well as providing a conducive environment for stent thrombosis.

Vessel Tapering

Bx stents provide a fixed diameter that can be altered to a certain extent by balloon inflation. However, especially in left main[11] as well as long and bifurcated lesions,[12] vessel tapering can be substantial,[13] which cannot be adequately emulated by conventional Bx stents. It remains almost impossible to appropriately size a conventional stent, at least in longer lesions, and thus inappropriate stent sizing may lead to endothelial dysfunction and increased wall stress.[14]

Bifurcated Lesions

All of the previously mentioned mechanical properties are of integral and particular importance in bifurcation lesions, in which vessel tapering, flow disturbances, endothelial dysfunction, inappropriate stent expansion, and accelerated, delayed, or inhibited strut coverage may converge and impact on clinical outcome.

Table 1: Current limitations of balloon-expandable and self-expanding stents.

Balloon-expandable stents	Self-expanding stents
• Stent strut malapposition • Conformability • No self-adjustment to tapered lesions • No self-adjustment to vessels undergoing positive remodelling • Cell size allowing plaque protrusion/prolapse • Unequivocal strut coverage in bent lesions • Stent overexpansion • Stent underexpansion • Edge dissection • Immediate vascular injury • Side-branch access	• Limited availability of length • Stent deliverability • Price • Radial force • Precise stent deployment • Foreshortening during implantation • Unfamiliar implantation technique

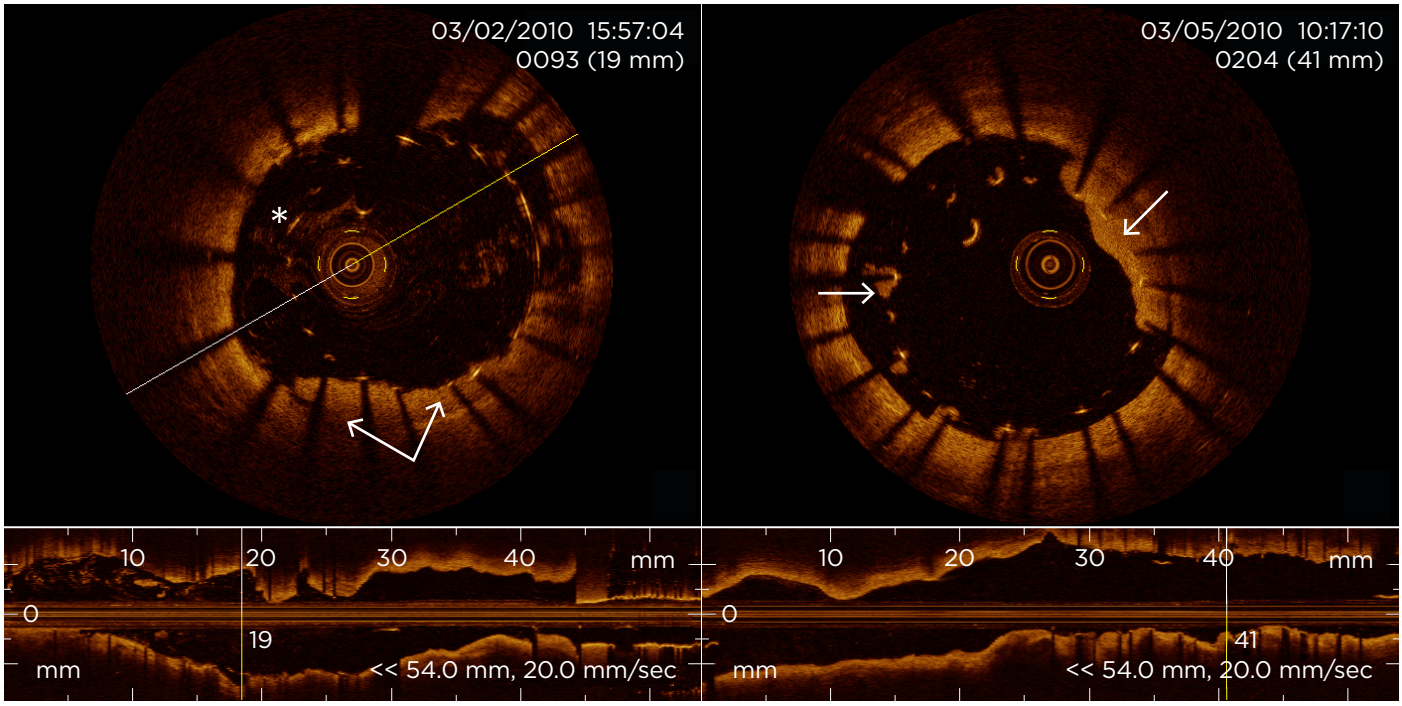


Figure 1: Optical coherence tomography (OCT) images of stent underexpansion and strut malapposition. Stent underexpansion and stent strut malapposition, as assessed by OCT, in a balloon-expandable stent immediately after stent placement and at 3 days after percutaneous coronary intervention. The left panel (Day 0) reveals stent strut malapposition (asterisk) as well as struts that are apposed to what is most likely wall-adherent thrombotic material (arrows). Three days later (right panel), there is cellular material, most likely thrombus and fibrin, covering malapposed stent struts (arrows).

Vessel Remodelling and Stent Underexpansion

Vasospasm and vascular remodelling can make the appropriate choice of stent size quite challenging. This is particularly the case in acute myocardial infarction (AMI), as well as in acutely revascularised chronic total occlusions (CTOs). In this context, a recent study showed that vessel size increases following successful revascularisation in AMI patients,[15] which subsequently increases the likelihood of stent thrombosis compared with stable coronary lesions.[16,17] This is also frequently the case for CTOs, in which the distal vessel diameter increases over time in the absence of positive remodelling and despite persistent endothelial dysfunction;[18] one of the reasons for this is the temporary or ongoing impairment of vasomotor tone after vessel reopening.

Stent Oversizing

Stent underexpansion is considered to be one of the most important predictors of stent thrombosis[19] and, therefore, interventionalists try to avoid this situation. However, by doing so, this raises the risk of oversizing the stent, which is associated with accelerated vascular injury and can precipitate processes that lead to augmented neointima formation. In an accepted animal model of coronary stenting, a DES loses its advantages over a bare metal stent (BMS) with higher balloon-to-vessel ratios in terms of reduction of neointima formation.[20]

Drug Delivery

Stent over or underexpansion as well as kissing balloon techniques may negatively impact upon the drug delivery from a coated stent.[21] Clinical evidence suggests a relationship between biomechanical stent properties and both angiographic and clinical outcome in humans.[22]

CLINICAL CONSEQUENCES OF BALLOON-EXPANDABLE STENTS

Evidently, there are important mechanical limitations of Bx stents that together may result in ACEs. These may include acute, subacute, late, or very late stent thrombosis, myocardial infarction (MI), restenosis, or neoatherosclerosis. This is

particularly applicable to the first-generation Bx stents; second-generation stents with improved design show better clinical results,[23] although the mechanical limitations remain.

Polymer Damage and Platform Damage/Loss

Most of the current DESs make use of a thin polymeric layer in which the anti-proliferative drug is embedded. The polymer can be durable or biodegradable. Irregularities or defects in the polymer coating have emerged as a potential factor in determining the outcome of DES implantation.[24] Since Bx stents are crimped onto the balloon without any protection on the outer side, drug-eluting Bx stents can undergo different degrees of polymer damage due to manual handling, navigation through the catheter, or engagement in complex lesions (tortuosity, calcification, bifurcations). For example, using electron microscope investigation, Wiemer et al.[24] reported the occurrence of polymer damage on the abluminal surface of stents for which implantation failed in between 3% (durable polymers) and 20% (bioabsorbable polymers) of cases. Polymer damage leads to non-uniform delivery of the drug, an excessive inflammatory response, and thrombogenicity, with stent failure ranging from restenosis to stent thrombosis. Strikingly, this study also showed polymer damage on the luminal stent surface, i.e. the inner surface, in contact with the balloon before delivery. Polymer-free, drug-eluting Bx stents are under development[25] but, so far, have not achieved widespread clinical use.

Although complications such as stent damage/dislocation are quite rare (<1%) thanks to the development of very low-profile and factory-crimped Bx devices, they still cause severe adverse events (AEs) (including death) and/or pose serious technical challenges in acute treatment.[26]

Stent Strut Malapposition

Malapposed stent struts that have no physical contact to cellular structures of the vascular wall do not allow direct ingrowth of neointimal tissue and are likely to accumulate acellular masses, such as fibrin clots. Fibrin is readily identified in lesions that have been histologically investigated subsequent to an acute coronary event.[27] In fact, most studies that have investigated the possible clinical causes of stent thrombosis using contemporary intravascular imaging devices have identified stent underexpansion and stent strut malapposition as a frequent finding.[28] These clinical and pathophysiological observations were confirmed in an *ex vivo* stent model.[29] In simple terms, stent strut malapposition can occur via two distinct mechanisms: stent underexpansion/undersizing and/or vascular remodelling. An example of stent underexpansion, strut malapposition, and their short-term consequences is provided in Figure 1.

Stent underexpansion is observed in 15-20% of stented lesions.[30,31] It can, however, be reliably prevented by the use of intravascular imaging techniques such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), which, unfortunately, are both costly and time-consuming. This can add value particularly in re-opened CTO vessels or bifurcations. Stent strut malapposition can also occur at later time points following stent placement. A serial IVUS study in stented patients found that malapposition can occur months or even years after stent implantation, with the possibility of subsequent healing or, in contrast, persistence of malapposition.[32] In addition, this clinical study showed stent strut malapposition in 73.9% of DESs that were involved in very late stent thrombosis.

Otake et al.[33] showed that stent strut malapposition is also dependent on symmetrical stent expansion. This group found a linear relationship between the extent of asymmetrical deployment and strut malapposition in cases where stents were deployed asymmetrically.[33] Interestingly, the authors also identified increased thrombus formation in asymmetrically deployed Bx stents that showed evidence of strut malapposition.

Stent strut malapposition may appear more frequently in DESs since these particular stents are designed to inhibit neointima formation, which is, to a certain degree, required for strut healing. This was confirmed by a recent study that applied intravascular imaging via OCT. This study was able to confirm that uncovered struts were most likely malapposed to the vascular wall following implantation of a paclitaxel-eluting stent.[34]

Strut malapposition may be linked to a specific cellular response. This is suggested by a study that compared the cellular responses in patients suffering from late stent thrombosis with or without strut malapposition.[35] In this analysis, very late stent thrombosis was associated with histopathological signs of inflammation and evidence of vessel remodelling as assessed by

IVUS. Compared with other causes of MI, eosinophilic infiltrates were more common in thrombi harvested from very late DES thrombosis and positively correlated with the extent of stent strut malapposition.

Strut malapposition is associated with both an increase in neointima formation and thus restenosis, as well as stent thrombosis.[36] Besides restenosis and thrombosis, formation of neoatherosclerosis has been associated with delayed healing, in particular in drug-eluting Bx stents.[37] A recent imaging study suggests that late coronary events are in part precipitated by the development of neoatherosclerosis in some DESs.[38] Another recent report confirms these findings.[39]

Stent Fracture

Besides stent strut malapposition, stent fracture is not a rare finding in patients who received a Bx stent and who present with stent thrombosis. The Nordic Intravascular Ultrasound Study found that 16% of DESs and 24% of BMSs were fractured in patients that presented with stent thrombosis. Stent fractures are more likely to occur in longer stented lesions, thus reflecting the important mechanical component of the pathogenesis of stent fracture.[40]

Stent Recoil

Stent recoil refers to the reduction of the internal surface/volume of stents after their placement, due to shrinkage of the stent platform. Different studies have reported stent recoil of about 3-5% for the currently available Bx stents; stent recoil is one of the predictors of restenosis after drug-eluting Bx stent implantation. The degree of stent recoil is due to both the intrinsic properties of the stent material and the specific geometrical design of the stent. A higher-than-expected rate of stent recoil has led, for example, to significant changes in the design of the ABSORB bioabsorbable scaffold.[41] Sx stents, because of their intrinsic properties, are not affected by stent recoil.[42] Furthermore, in the case of positive remodelling of the coronary vessel, Sx stents follow the growth of the coronary lumen.[15]

Longitudinal Compression

Longitudinal compression has recently emerged as a serious potential complication of Bx stent placement: this refers to *in situ* stent shortening, with stent rings coming close to each other or even overlapping, after recrossing the stent with other devices such as post-dilatation balloons, stent delivery systems, or IVUS catheters. Longitudinal compression can lead to incomplete lesion coverage, stent displacement, intraluminal strut protrusion, or device embolisation.[43] Although the clinical consequences of longitudinal compression have not been fully elucidated, we can speculate regarding multiple, potential AEs ranging from restenosis to stent thrombosis to MI. Bench studies have shown that stent design is a major predictor of longitudinal compression, which can reach up to 47% of the nominal length in case of peak-to-peak design and fewer links between stent rings.[44] Malapposition of the stent can play a significant role in longitudinal compression by giving an edge to the crossing device upon which to get entrapped. For this reason, Sx stents that provide immediate apposition and active adherence to the vessel wall are apparently devoid of this recently observed complication.

Late mechanical stent deficiencies cannot be readily detected in most patients unless they suffer from an adverse cardiac event. Therefore, interventionalists rely on the quality of the device and the procedure during percutaneous coronary intervention (PCI). Thus, improvements in stent design are warranted to ensure an appropriate long-term outcome for patients not impeded by mechanical stent shortcomings, which may become clinically apparent over time.

THE CONCEPT OF THE SELF-EXPANDING CORONARY STENT

Historical Development

The first Sx stent, the Wallstent, was a stainless steel stent first tested in humans in 1986. This was followed by the development of nitinol stents. A shape-memory alloy was developed at the US Naval laboratories in 1962. It was made of 55% nickel and 45% titanium. The team named their new alloy Nitinol (pronounced night-in-all). The 'Ni' and 'Ti' are the atomic symbols for nickel and titanium, and the 'nol' represents the Naval Ordinance Laboratory where it was discovered. Its unique characteristics are shape-memory and superelasticity. Shape-memory allows the nitinol material to be deformed and then, upon heating above its 'transition temperature', it will recover its original 'undeformed' shape. The Radius stent, which received FDA approval for coronary use, and the Symbiot covered stent for saphenous

vein graft interventions are examples of early-generation nitinol stents.

Characteristics and Clinical Data of the STENTYS® Self-Expanding Stent

The STENTYS® Coronary Stent (STENTYS S.A., Paris, France) is a self-apposing nitinol stent with a nominal strut width of 68 µm (0.0027"). The stent is compatible with a 6 Fr guide catheter and is delivered using a rapid-exchange delivery system over a conventional 0.014" guide wire. The device is deployed by withdrawal of a retractable sheath, and is available in three lengths (17, 22, and 27 mm) with diameters suitable for vessels ranging from 2.5-3.0 mm (small), 3.0-3.5 mm (medium), and 3.5-4.5 mm (large). The stent is available in a bare-metal version, a paclitaxel-eluting version, and in a sirolimus-eluting version (1.4 µg/mm^2 of stent), all of which are incorporated in a proprietary coating (ProTeqtor®), a durable polymer matrix of polysulfone and a soluble polyvinylpyrrolidone that acts as an excipient. It has a closed-cell design with a cell area of 0.95 mm^2, which is much smaller than that of Bx stents.

The expansive property of the STENTYS stent was substantiated in the APPOSITION I study[15] (BMS version in ST segment elevation myocardial infarction [STEMI], and as evidenced by a 19% increase in stent area following a 19% increase in lumen area of the distal reference vessel at 3 days post STEMI, as measured by IVUS). In the APPOSITION II trial,[45] the self-apposing STENTYS® BMS was compared with Bx stents and proved to be superior with respect to acute stent apposition, as assessed by OCT. At 3 days post implantation, it was shown that the STENTYS mean stent area increased further while the rate of malapposed struts decreased, suggesting that the stent conforms to changes in vessel anatomy during the first days after the index event. On a per-patient basis, none of the STENTYS stents were malapposed (defined as ≥5% malapposed struts) compared with 28% in the Bx stent group at 3 days follow-up ($p<0.001$). The APPOSITION III registry[46] of 1,000 STEMI patients showed highly satisfactory clinical results, in particular in patients that were post-dilated (major adverse cardiac event rate at 12 months: 8.4%). The APPOSITION IV[47] study compared the STENTYS® Sirolimus-Eluting Stent (SES) with the Resolute stent. The STENTYS SES was equivalent to a conventional drug-eluting Bx stent with respect to late stent strut apposition and coverage at 9 months. However, stent strut apposition and coverage at 4 months was significantly better in the STENTYS group. Satisfying results with the STENTYS stent were also demonstrated in the OPEN I and II bifurcation studies.

The recently completed SETUP trial[48] evaluated a new delivery system for the STENTYS stent. The self-apposing STENTYS® Xposition S is folded on a delivery balloon that is covered with a distal splittable 0.0032" sheath assembly. The nominal diameter of this delivery balloon is the same as the smallest diameter for which the stent is suitable. When the semi-compliant delivery balloon is inflated within the sheath using low pressures starting at 8 atm, it causes the sheath assembly to split, thus allowing the STENTYS stent to deploy in the coronary artery at the desired location. The results show that this new system facilitates exact positioning and delivery of the stent. The use of this device could be considered in anatomical subsets with a high risk of stent mis-positioning and stent mis-sizing, such as lesions with a very high thrombotic burden, lesions located in ectatic/aneurysmal vessels, or bifurcation lesions with large differences between the proximal and distal diameters, lesions of the left main coronary artery, and ostial located lesions.

Mitigating Balloon-Expandable Stent Shortcomings

Stent strut malapposition, stent under and overexpansion, non-uniform distribution of strut geometry, and cell size are important features that should be resolved in upcoming generations of stent development, in particular for complex lesions such as AMI, bifurcation, and tapered as well as angulated lesions.

Sx stents would likely bridge the gap of acute and acquired stent strut malapposition through self-alignment of the stent struts to the vascular wall, thus facilitating strut healing and optimal drug delivery to the vessel wall. Furthermore, consistent strut apposition in tapered vessels and downstream vessel remodelling, as is consistently the case in AMI lesions and revascularised CTOs for example, would be feasible. Additional features of the STENTYS Sx stent system, such as disconnectable interconnectors, allow further improvements in the scaffolding of bifurcated lesions.

PCI would, in many instances, be easier to perform because the likelihood of acute and subacute strut malapposition is significantly decreased.

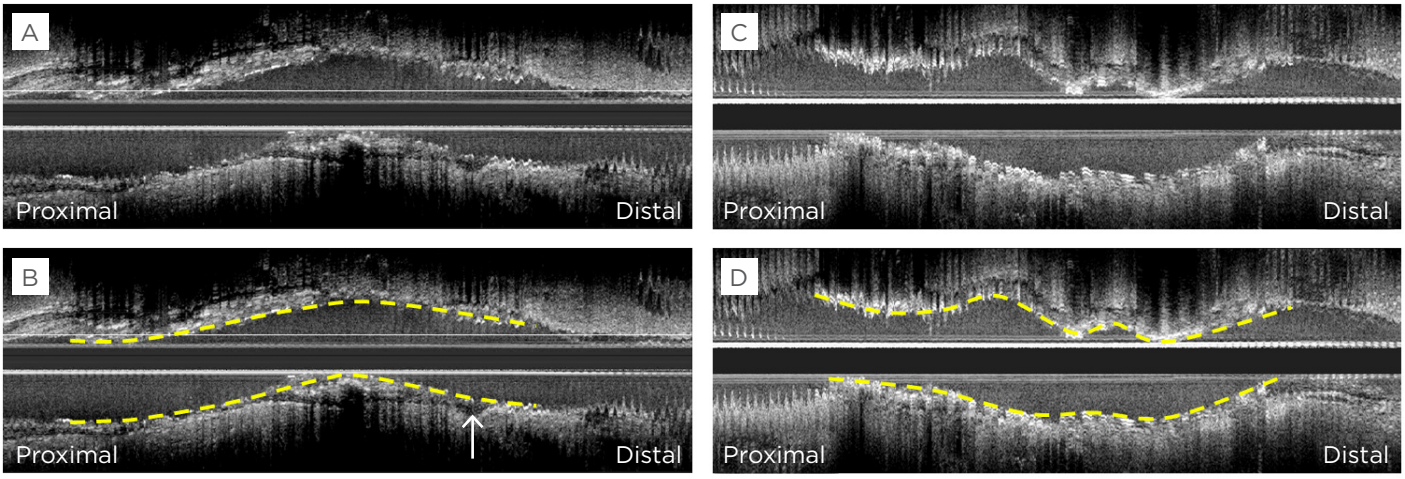


Figure 2: Stent conformability.
Stent conformability compared between balloon-expandable stents (A and B) and self-expanding stents (C and D). Non-apposed stent struts are visible only in the balloon-expandable stent images (arrow). Optimal stent conformability is provided by the self-expanding stent only. To facilitate stent strut visibility for the reader, stents are followed in B and D by a dotted yellow line. Otherwise, images A and B as well as C and D are identical.

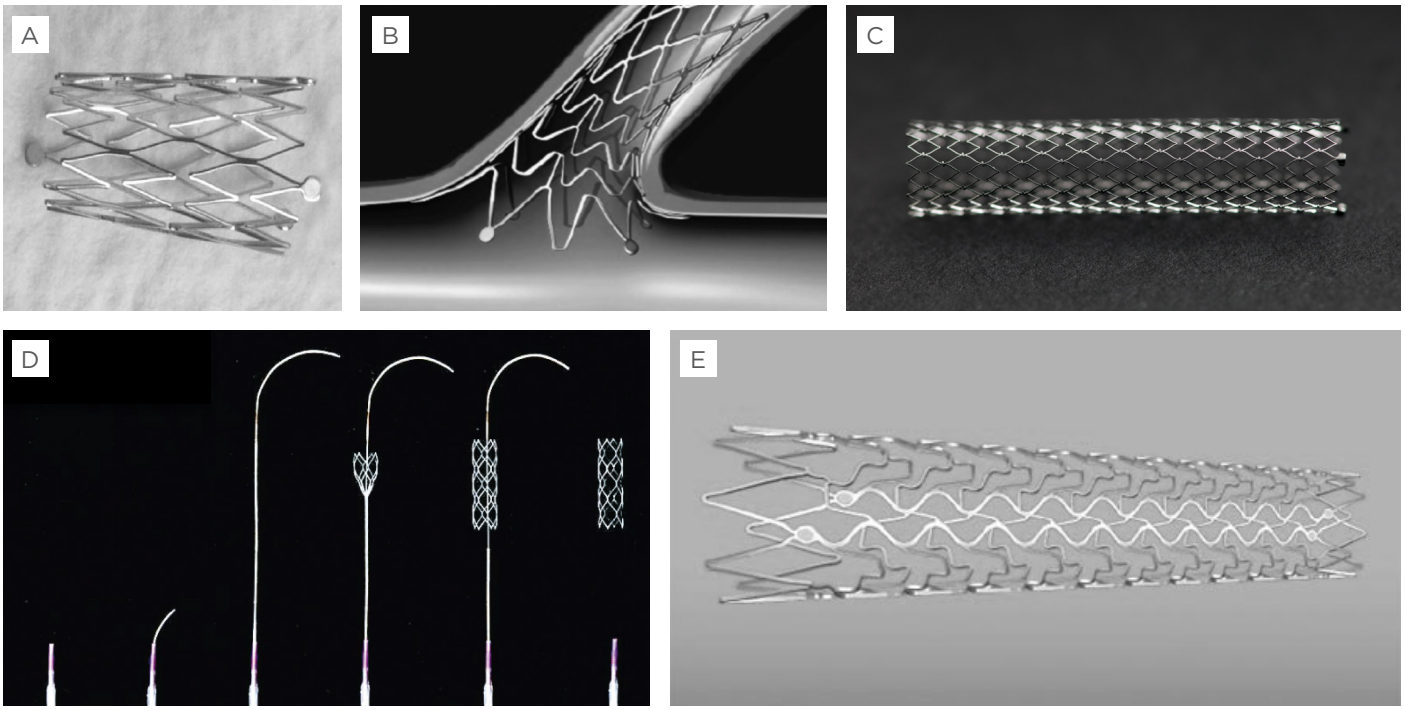


Figure 3: Overview of contemporary self-expanding stent platforms.
A) Axxess™ stent, B) Cappella stent, C) STENTYS® stent, D) CardioMind Sparrow™ stent, E) vProtect™ stent. Further information about the different stent platforms is provided in the text.

Stent conformability and self-adaptation to the natural vessel are likely to improve the properties of blood flow in revascularised lesions (Figure 2). Since divergent patterns of blood flow are negatively associated with vascular healing as well as adverse coronary events,[49] this could be of particular importance for overall long-term stent performance. In addition, it has been suggested that Sx stents may decrease the incidence of no-reflow and side-branch occlusion compared with Bx stents.[50] In this context, Sx stents can also be associated with lower edge dissections[51] that

are also known to precipitate adverse cardiac events,[52] even when they can be considered minor. The SCORES trial suggested that the lower immediate pressure of Sx stent deployment compared with high-pressure Bx stent placement may induce less biomechanical injury to the vascular wall,[53] which is possibly followed by a lower rate of restenosis and presumably improved vascular healing.[54]

Considering these features, the concept of implanting Sx stents in STEMI lesions is of particular interest. No-reflow is a major complication following stent-based revascularisation and adversely influences short and long-term outcomes.[55] No-reflow is multifactorial; however, thrombus fragmentation, mobilisation, and distal embolisation are believed to be the main factors that cause no-reflow in primary PCI for STEMI.[56] The STENTYS stent has been used for the specific treatment of STEMI lesions in several studies. This concept builds on the presumption that choice of stent size can be difficult in STEMI lesions because coronary spasm may impede visual vessel size assessment. Secondly, the high pressures that are necessary for Bx stent deployment are generally not necessary for Sx stent implantation. Therefore, the necrotic core may not be penetrated by self-apposing stent platforms, whereas mandatory balloon inflation of a conventional stent has a higher likelihood to penetrate the necrotic core and cause thrombus fragmentation after stenting.[57] Besides potential advantages in the acute situation, stent malapposition is frequently detected after primary PCI for STEMI. Indeed, there was significantly lower stent strut malapposition in the APPOSITION II study 3 days post implantation in favour of Sx versus Bx stents (0.58% versus 5.46%, $p<0.001$).[45]

Other interventional scenarios that could be potentially targeted by Sx stents are tapered lesions, left main lesions, aneurysms, coronary artery bypass grafts, large vessels, etc. However, limited reliable clinical data regarding these lesion subtypes are available.

The problems inherent with polymer damage during navigation and deployment of Bx stents are not present in the case of Sx stents because the stent is protected by its external sleeve during navigation and the device does not undergo high-pressure balloon deployment. The external sleeve of Sx stents offers the additional advantage of protecting the device from strut damage and dislocation, and, in the worst case scenario, stent loss during navigation and deployment.

SELF-EXPANDING STENT PLATFORMS

Just as for Bx stents, not all Sx stent systems are the same. They differ in terms of strut length, flexibility and ability to appose, radial and chronic outward forces, strut thickness, ease and accuracy of deployment, and foreshortening. The performance of an Sx stent is dependent on both the material it is made from and the stent design. Sx stents are generally manufactured from nitinol, an alloy of nickel and titanium in roughly equal proportions that incorporates various favourable properties for the purpose of stent design: shape-memory, fatigue resistance, biocompatibility, and superelasticity. Various nitinol Sx stent platforms are currently under clinical investigation or are commercially available in selected countries. An overview of the various Sx stent types is provided in Figure 3. Most contemporary Sx platforms are designed to treat bifurcations (Axxess™, Cappella Sideguard, Galway, Ireland), including the STENTYS Self-Apposing® stent, which has now been clinically evaluated for other additional applications such as AMI. The vProtect™ Luminal Shield (Prescient Medical, Inc., Doylestown, Pennsylvania, USA) was designed to stent intermediate lesions (vulnerable plaques). CardioMind Sparrow™ is a small Sx stent that is mounted on a 0.014" guide wire and specifically designed to treat small vessels. Not all Sx stents are made of nitinol. The Wallstent,[58] which is no longer commercially available as a coronary Sx stent, was a stainless steel woven mesh constructed of 16 wire filaments. Due to the difference in material and stent design, the Wallstent is unable to appose completely to the vessel wall compared with, for example, the good apposition of the STENTYS stent.[45]

Intravascular Imaging Reveals Stent Benefits

OCT is a sensitive method to visualise mechanical as well as biomechanical properties of coronary stents.[59] OCT is able to highlight the favourable findings of Sx stents compared with Bx stents, including conformability, strut apposition, and self-alignment to the vascular wall. These properties have been investigated in the APPOSITION II trial,[45] which confirmed that strut apposition is significantly improved with Sx stents in patients presenting with AMI compared with conventional Bx stents.

Potential Self-Expanding Stent Limitations

Sx stents in their current form reveal some limitations that are important to acknowledge. The chronic outward force is generally lower than that of balloon pressures used to deploy Bx stents,[60] which can be of some limitation specifically in calcified lesions. Deliverability of Sx stents can be cumbersome as the advancement of the delivery system and precise positioning is sometimes challenging and requires some training. Thus, success rates regarding stent delivery are somewhat lower compared with Bx stents, in particular in tortuous, calcified, and distal vessels. Recently, however, a novel balloon delivery system was developed for the self-apposing STENTYS SES, consisting of the inflation of a balloon at low pressures to split the covering delivery sheath longitudinally, which releases the stent. It then deploys and apposes to the vessel wall where the 'jailed' sheath is then retracted. This system aims for easy delivery and a highly precise longitudinal placement of the Sx stent.[48]

Table 2: Clinical trials involving self-expanding stent systems.

Stent	Study name	Pts.	Background/Primary endpoint	Remarks	Reference
Axxess™	AXXESS	43	Safety and efficacy study/6-month in-segment restenosis	Bare-metal version of Axxess™ stent 6-month F/U completed	61
	AXXESS PLUS	139	Single-arm, safety and efficacy trial/6-month LLL	Axxess™ plus DES (Biolimus A9) 6-month MACE: 11.2%; TLR: 7.5%; LLL: 0.09 mm F/U through 3 years completed	62
	DIVERGE	302	Single-arm study/MACE	*De novo* bifurcations included only, no control group MACE rate: 7.7% (0.7 death, 3.3% NQWMI, 1% QWMI, 4,3% TLR)	63
	AXXENT	33	Single-arm pilot study in left main/MACE at 6 months	12-month follow-up completed MACE at 6 months: 18.2%	64
Cappella Sideguard™	Doi H et al.	25	Safety and feasibility trial	*De novo* bifurcations only, no control group 6-month TLR rate: 12.5%	65
CardioMind Sparrow™	CARE I	21	Safety and feasibility trial	Binary restenosis rate 20% at 6 months, single-arm study 2 MACE events at 24 months F/U	N/A
	CARE II	100	Randomised/LLL	Lesions ≤20 mm length between 2.00-2.75 mm 36 CardioMind BMS (LLL 0.86 mm), 36 SES (LLL 0.29 mm), 30 BMS (LLL 0.94 mm)	N/A
STENTYS®	OPEN I	60	Safety and feasibility trial/6-month MACE	*De novo* bifurcations only including the STENTYS BMS and DES (paclitaxel), no control group 6-month MACE: BMS 27.3%, DES 3.7% LLL BMS 0.86 mm, DES 0.39 mm	66
	OPEN II	200	Safety and feasibility trial/6-month MACE	STENTYS DES (paclitaxel), no control group 6-month MACE: 10.1%, Death: 0.5%; ST: 1.0% 12-month MACE: 13%, Death: 1.4%, ST: 2.0% Kissing balloon has no effect on MACE.	67
	APPOSITION I	25	Safety and feasibility trial/6-month MACE	STEMI lesions only STENTYS BMS, no control group 6 months: binary restenosis 25%, MACE 12% (3 TLR)	15

Table 2 continued.

Stent	Study name	Pts.	Background/Primary endpoint	Remarks	Reference
STENTYS®	APPOSITION II	80	Randomised/stent strut malapposition at 3 days	STEMI lesions only treated with BMS STENTYS BMS versus Abbott Vision/ Medtronic Driver Malapposed stent struts by OCT assessment 0.58% for STENTYS vs. 5.46% for Multi-Link Vision (p<0.001). MACE at 6 months 2.3% vs. 0% (p=NS).	45
	APPOSITION III	965	Non-randomised, observational study/ 12-month MACE	STENTYS BMS 74%/DES (paclitaxel) 26% 12-month results: MACE 9.3% (after post-dilation: 8.4%), cardiac death 2% 24-month results: MACE 11.2%, cardiac death 2.3%	46
	APPOSITION IV	150	Randomised, FIM trial for STENTYS DES (sirolimus)/4 or 9-month malapposition and strut coverage	STEMI lesions only STENTYS DES (sirolimus) vs. Medtronic Resolute 4-month results: malapposed stent struts by OCT 0.07% for STENTYS vs. 1.16% for Resolute (p=0.002). Total stent coverage 33.3% STENTYS vs. 3.8% Resolute (p=0.02) 9-month results: No difference in malapposition, strut coverage, or MACE. LLL 0.04 mm STENTYS vs. 0.17 mm Resolute. Greater mean lumen diameter in STENTYS arm (p=0.01).	47
	SETUP	25	Feasibility study, FIM trial for balloon-delivery system of STENTYS SES/ technical success	1 month: 100% technical success, 0% geographical miss	48
vProtect™ Luminal Shield	SECRITT	21	Safety and feasibility trial	TCFA lesions were sealed with vProtect™ Luminal Shield stent only, no control group; no MACE at 6-months F/U	68

DES: drug-eluting stent; MACE: major adverse cardiac event; TLR: target lesion revascularisation; LLL: late lumen loss; ST: stent thrombosis; NQWMI: non-Q wave myocardial infarction; QWMI: Q wave myocardial infarction; NS: not significant; F/U: follow-up; BMS: bare-metal stent; SES: sirolimus-eluting stent; STEMI: ST segment elevation myocardial infarction; OCT: optical coherence tomography; TCFA: thin-cap fibroatheroma; N/A: not yet published.

The variety of stent lengths that are currently available is confined to a limited number; the same is true for the available diameter sizes of some Sx stents. Due to current limitations of the delivery system, very long stents are generally not available at this time. Because precise positioning remains a challenge, overlapping Sx stents can be difficult. In addition, distal positioning of a second Sx stent through an already implanted Sx stent is generally not recommended, at least in smaller vessel sizes, because there can be issues associated with stent injury and shifting of the implanted Sx stent. Post-dilation of the stent is generally recommended to ensure that the stent is well expanded over its entire length.[46]

STUDIES WITH SELF-EXPANDING STENTS

Most clinical trials that examined the outcome of patients who received Sx stents have been carried out as feasibility and safety studies that were single-arm and included only a limited number of patients. However, as is particularly the case for the STENTYS stent, larger series with appropriate control groups are now available. A detailed overview of contemporary clinical trials is provided in Table 2. Most human trials have been carried out in a selected patient or lesion subgroup, in particular in patients that presented with AMI or bifurcation lesions. Despite all the trials available

to date not being powered to address clinical outcomes, they have mostly provided proof-of-concept. In this context, it is important to acknowledge that contemporary Sx stent platforms are at least as safe and effective as Bx stents and that stent placement is feasible in the scenarios that were covered in these mostly observational trials. Therefore, initial clinical trials comparing the performance of Sx stents with Bx stents in confined clinical scenarios have shown clearly encouraging results and proof-of-concept, despite the fact that clinical outcomes have not been primarily studied.

FUTURE DIRECTIONS AND CONCLUSION

Bx stents and Sx stents came almost simultaneously to the market nearly 30 years ago. Since then, Bx stents have been significantly improved, resulting in favourable clinical results and better ease of use. On the other hand, Sx stents were slowly abandoned after the first experiences and only recently, thanks to the clinical applications of the nitinol alloy, have they experienced a strong reappraisal. For this reason, the currently available devices could take advantage of further refinement in order to close the gap or even to surpass Bx stents. Device improvement and 'cultural acceptance' by interventional cardiologists, who are now more experienced, are critical for the clinical advancement of Sx technology.

Regarding mechanical improvements, there are several challenges that should be considered by manufacturers of Sx stents. These include a smaller profile of the delivery device to facilitate navigation through complex anatomy and enabling 5 Fr compatibility. Visibility should be improved in order to expedite ostial positioning and overlapping stents. This could be accomplished by adding markers or by enhancing radiopacity. Longer devices are needed for diffuse disease. Reduced strut profile and density is needed to enable treatment of small vessels, but needs to be balanced against maintaining a sufficient radial force.

Changing from Bx stents to Sx stents involves a complete change of mindset. One has to get used to them to appreciate the strengths and weaknesses in their application. The combination of the best of both worlds, a balloon delivery system (ease of deployment) with an Sx stent (efficacy), would represent a major advancement in coronary interventions.

REFERENCES

1. Mewissen MW. Primary nitinol stenting for femoropopliteal disease. J Endovasc Ther. 2009;16(2 Suppl 2):II63-81.

2. Oberhuber A et al. Influence of different self-expanding stent-graft types on remodeling of the aortic neck after endovascular aneurysm repair. J Endovasc Ther. 2010;17(6):677-84.

3. Wakhloo AK et al. Advances in interventional neuroradiology. Stroke. 2009;40(5):e305-12.

4. Rieu R et al. Assessment of the trackability, flexibility, and conformability of coronary stents: a comparative analysis. Catheter Cardiovasc Interv. 2003;59(4):496-503.

5. Foin N et al. Maximal expansion capacity with current DES platforms: a critical factor for stent selection in the treatment of left main bifurcations? EuroIntervention. 2013;8(11):1315-25.

6. Mortier P et al. Virtual bench testing of new generation coronary stents. EuroIntervention. 2011;7(3):369-76.

7. Gomez-Lara J et al. Risk of target lesion failure in relationship to vessel angiographic geometry and stent conformability using the second generation of drug-eluting stents. Am Heart J. 2011;162(6):1069-1079.e2.

8. Nakazawa G et al. Pathological findings at bifurcation lesions: the impact of flow distribution on atherosclerosis and arterial healing after stent implantation. J Am Coll Cardiol. 2010;55(16):1679-87.

9. Gutiérrez-Chico JL et al. Vascular tissue reaction to acute malapposition in human coronary arteries: sequential assessment with optical coherence tomography. Circ Cardiovasc Interv. 2012;5(1):20-9, S1-8.

10. Hwang CW et al. Thrombosis modulates arterial drug distribution for drug-eluting stents. Circulation. 2005;111(13):1619-26.

11. Zeina AR et al. Dimensions and anatomic variations of left main coronary artery in normal population: multidetector computed tomography assessment. Coron Artery Dis. 2007;18(6):477-82.

12. Legrand V et al. Percutaneous coronary intervention of bifurcation lesions: state-of-the-art. Insights from the second meeting of the European Bifurcation Club. EuroIntervention. 2007;3(1):44-9.

13. Zubaid M et al. Normal angiographic tapering of the coronary arteries. Can J Cardiol. 2002;18(9):973-80.

14. Chen HY et al. Effects of stent sizing on endothelial and vessel wall stress: potential mechanisms for in-stent restenosis. J Appl Physiol (1985). 2009;106(5):1686-91.

15. Amoroso G et al. Assessment of the safety and performance of the STENTYS self-expanding coronary stent in acute myocardial infarction: results from the APPOSITION I study. EuroIntervention. 2011;7(4):428-36.

16. Leibundgut G et al. Stent thrombosis up to 3 years after stenting for ST-segment elevation myocardial infarction versus for stable angina--comparison of the effects of drug-eluting versus bare-metal stents. Am Heart J. 2009;158(2):271-6.

17. Gonzalo N et al. Incomplete stent apposition and delayed tissue coverage are more frequent in drug-eluting stents implanted during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction than in drug-eluting stents implanted for stable/unstable angina: insights from optical coherence tomography. JACC Cardiovasc Interv. 2009;2(5):445-52.

18. Tomasello SD et al. Retrograde approach for revascularization of

coronary chronic total occlusion. Minerva Cardioangiol. 2012;60(5):461-72.

19. van Werkum JW et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol. 2009;53(16):1399-409.

20. Carter AJ et al. Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. Cardiovasc Res. 2004;63(4): 617-24.

21. Wessely R. New drug-eluting stent concepts. Nat Rev Cardiol. 2010;7(4): 194-203.

22. König A et al. Influence of stent design and deployment technique on neointima formation and vascular remodeling. Z Kardiol. 2002;91 Suppl 3:98-102.

23. von Birgelen C et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. Lancet. 2014;383: 413-23.

24. Wiemer M et al. Scanning electron microscopic analysis of different drug eluting stents after failed implantation: from nearly undamaged to major damaged polymers. Catheter Cardiovasc Interv. 2010;75(6):905-11.

25. Wessely R et al. Inhibition of neointima formation by a novel drug-eluting stent system that allows for dose-adjustable, multiple, and on-site stent coating. Arterioscler Thromb Vasc Biol. 2005;25(4):748-53.

26. Kammler J et al. Long-term follow-up in patients with lost coronary stents during interventional procedures. Am J Cardiol. 2006;98(3):367-9.

27. Finn AV et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation. 2007;115(18):2435-41.

28. Alfonso F et al. Combined use of optical coherence tomography and intravascular ultrasound imaging in patients undergoing coronary interventions for stent thrombosis. Heart. 2012;98(16):1213-20.

29. Kolandaivelu K et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation. 2011;123(13):1400-9.

30. Kume T et al. Intravascular ultrasound assessment of postprocedural incomplete stent apposition. J Invasive Cardiol. 2012;24(1):13-6.

31. van der Hoeven BL et al. Stent malapposition after sirolimus-eluting and bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: acute and 9-month intravascular ultrasound results of the MISSION! intervention study. JACC Cardiovasc Interv. 2008;1(2):192-201.

32. Lee CW et al. Intravascular ultrasound findings in patients with very late stent thrombosis after either drug-eluting or bare-metal stent implantation. J Am Coll Cardiol. 2010;55(18):1936-42.

33. Otake H et al. Local determinants of thrombus formation following sirolimus-eluting stent implantation assessed by optical coherence tomography. JACC Cardiovasc Interv. 2009;2(5):459-66.

34. Davlouros PA et al. Neointimal coverage and stent strut apposition six months after implantation of a paclitaxel eluting stent in acute coronary syndromes: an optical coherence tomography study. Int J Cardiol. 2011;151(2):155-9.

35. Cook S et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation. 2009;120:391-9.

36. Liu X et al. A volumetric intravascular ultrasound comparison of early drug-eluting stent thrombosis versus restenosis. JACC Cardiovasc Interv. 2009;2(5): 428-34.

37. Park SJ et al. In-stent neoatherosclerosis: a final common pathway of late stent failure. J Am Coll Cardiol. 2012;59(23):2051-7.

38. Habara M et al. Morphological differences of tissue characteristics between early, late, and very late restenosis lesions after first generation drug-eluting stent implantation: an optical coherence tomography study. Eur Heart J Cardiovasc Imaging. 2013;14(3):276-84.

39. Karanasos A et al. In-stent neoatherosclerosis: a cause of late stent thrombosis in a patient with "full metal jacket" 15 years after implantation: insights from optical coherence tomography. JACC Cardiovasc Interv. 2012;5(7): 799-800.

40. Doi H et al. Classification and potential mechanisms of intravascular ultrasound patterns of stent fracture. Am J Cardiol. 2009;103(6):818-23.

41. Tanimoto S et al. Comparison of in vivo acute stent recoil between the bioabsorbable everolimus-eluting coronary stent and the everolimus-eluting cobalt chromium coronary stent: insights from the ABSORB and SPIRIT trials. Catheter Cardiovasc Interv. 2007;70(4):515-23.

42. Bosiers M et al. Does free cell area influence the outcome in carotid artery stenting? Eur J Vasc Endovasc Surg. 2007;33(2):135-41; discussion 142-3.

43. Bartorelli AL et al. Stent longitudinal distortion: strut separation (pseudo-fracture) and strut compression ("concertina" effect). EuroIntervention. 2012;8(2):290-1.

44. Prabhu S et al. Engineering assessment of the longitudinal compression behaviour of contemporary coronary stents. EuroIntervention. 2012;8(2):275-81.

45. van Geuns RJ et al. Self-expanding versus balloon-expandable stents in acute myocardial infarction: results from the APPOSITION II study: self-expanding stents in ST-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2012;5(12):1209-19.

46. Koch KT et al. One-year clinical outcomes of the STENTYS Self-Apposing® coronary stent in patients presenting with ST-segment elevation myocardial infarction: results from the APPOSITION III registry. EuroIntervention. 2015;10(11);doi:10.4244/EIJY15M02_08. [Epub ahead of print].

47. van Geuns RJ et al. STENTYS self-apposing® sirolimus-eluting stent in ST-segment elevation myocardial infarction: results from the randomized APPOSITION IV trial. EuroIntervention. 2015. [Epub ahead of print].

48. Lu H et al. First-in-man evaluation of the novel balloon delivery system STENTYS Xposition S for the self-apposing coronary artery stent: impact on longitudinal geographic miss during stenting. EuroIntervention. 2015;11(1);doi:10.4244/EIJY15M05_07. [Epub ahead of print].

49. Lüscher TF et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. Circulation. 2007;115(8):1051-8.

50. König A et al. Stent design-related coronary artery remodeling and patterns of neointima formation following self-expanding and balloon-expandable stent implantation. Catheter Cardiovasc Interv. 2002;56(4):478-86.

51. Hirayama A et al. Angiographic and clinical outcome of a new self-expanding intracoronary stent (RADIUS): results from multicenter experience in Japan. Catheter Cardiovasc Interv. 2000;49(4):401-7.

52. Choi SY et al. Intravascular ultrasound findings of early stent thrombosis after primary percutaneous intervention in acute myocardial infarction: a Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) substudy. Circ Cardiovasc Interv. 2011;4(3):239-47.

53. Shin ES et al. Comparison of acute vessel wall injury after self-expanding stent and conventional balloon-expandable stent implantation: a study with optical coherence tomography. J Invasive Cardiol. 2010;22(9):435-9.

54. Tanaka S et al. Prospective randomized trial comparing a nitinol

self-expanding coronary stent with low-pressure dilatation and a high-pressure balloon expandable bare metal stent. Heart Vessels. 2008;23(1):1-8.

55. Rezkalla SH et al. No-reflow phenomenon following percutaneous coronary intervention for acute myocardial infarction: incidence, outcome, and effect of pharmacologic therapy. J Interv Cardiol. 2010;23(5):429-36.

56. Niccoli G et al. Myocardial no-reflow in humans. J Am Coll Cardiol. 2009;54(4):281-92.

57. Brosh D et al. Effect of no-reflow during primary percutaneous coronary intervention for acute myocardial infarction on six-month mortality. Am J Cardiol. 2007;99(4):442-5.

58. Strauss BH et al. Relative risk analysis of angiographic predictors of restenosis within the coronary Wallstent. Circulation. 1991;84(4):1636-43.

59. Bezerra HG et al. Optical coherence tomography versus intravascular ultrasound to evaluate coronary artery disease and percutaneous coronary intervention. JACC Cardiovasc Interv. 2013;6(3):228-36.

60. Grenacher L et al. In vitro comparison of self-expanding versus balloon-expandable stents in a human ex vivo model. Cardiovasc Intervent Radiol. 2006;29(2):249-54.

61. Dubois CL, Wijns W. The AXXESS™ self-expanding biolimus A9™ eluting stent system for coronary bifurcation lesions. EuroIntervention. 2010;6 Suppl J:J130-4.

62. Grube E et al. Six-month clinical and angiographic results of a dedicated drug-eluting stent for the treatment of coronary bifurcation narrowings. Am J Cardiol. 2007;99(12):1691-7.

63. Verheye S et al. 9-month clinical, angiographic, and intravascular ultrasound results of a prospective evaluation of the Axxess self-expanding biolimus A9-eluting stent in coronary bifurcation lesions: the DIVERGE (Drug-Eluting Stent Intervention for Treating Side Branches Effectively) study. J Am Coll Cardiol. 2009;53(12):1031-9.

64. Hasegawa T et al. Analysis of left main coronary artery bifurcation lesions treated with biolimus-eluting DEVAX AXXESS plus nitinol self-expanding stent: intravascular ultrasound results of the AXXENT trial. Catheter Cardiovasc Interv. 2009;73(1):34-41.

65. Doi H et al. Serial intravascular ultrasound analysis of bifurcation lesions treated using the novel self-expanding sideguard side branch stent. Am J Cardiol. 2009;104(9):1216-21.

66. Verheye S et al. Six-month clinical and angiographic results of the STENTYS® Self-Apposing Stent in Bifurcation Lesions. EuroIntervention. 2011;7:580-7.

67. Naber C et al. Final results of a self-apposing paclitaxel-eluting stent fOr the PErcutaNeous treatment of de novo lesions in native bifurcated coronary arteries study. EuroIntervention 2015;11-online publish-ahead-of-print June 2015.

68. Wykrzykowska JJ et al. Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries: report of the pilot study vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT). EuroIntervention. 2012;8(8):945-54.

EMJ EUROPEAN MEDICAL JOURNAL

EUROPEAN MEDICAL JOURNAL

provides influential articles, presentations of up-to-date scientific research and clinical practice, and in-depth reviews of international medical congresses.

Please click **here** to:

- subscribe and receive the latest publications, newsletters & updates from **EMJ**
- view each edition in convenient eBook format; desktop, tablet & smartphone compatible

Follow us:

www.emjreviews.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

Buyer's Guide

- ACCRIVA DIAGNOSTICS
- ACTELION PHARMACEUTICALS LTD.
- ADVANCED COOLING THERAPY
- ADVANCED MEDICAL EDUCATION
- AEGERION PHARMACEUTICALS SARL
- AGFA HEALTHCARE
- AI MEDIQ S.A.
- AMGEN
- ASPEN EUROPE
- ASTRAZENECA
- AUM CARDIOCASCULAR, INC.
- BAYER HEALTHCARE
- BEPATIENT
- BIOCARE CO., LTD.
- BIOTRONIK
- BLUEPRINT GENETICS OY
- BOEHRINGER INGELHEIM
- BPLAB
- BRISTOL-MYERS SQUIBB
- CARDIOME AG
- CARDIOSECUR
- CAREWELL ELECTRONICS CO., LTD.
- CELLAEGIS DEVICES, INC.
- CHINA QINGDAO BRIGHT MEDICAL MANUFACTORING, CO., LTD.
- CIRCLE CARDIOVASCULAR IMAGING
- COVANCE
- CUSTO MED GMBH
- DAIICHI SANKYO EUROPE GMBH
- DAILYCARE BIOMEDICAL
- DEFIBTECH
- DOCCHECK MEDICAL SERVICES GMBH
- DOT MEDICAL LTD.
- DSM NUTRITIONAL PRODUCTS LTD.
- EDAN INSTRUMENTS, INC.
- EDWARDS LIFESCIENCES
- ELI LILLY AND COMPANY LTD.
- ESAOTE
- FERRER INTERNATIONAL S.A.
- FRESENIUS MEDICAL CARE
- FUKUDA DENSHI
- GE HEALTHCARE
- GENZYME, A SANOFI COMPANY
- GLENMARK PHARMACEUTICALS LTD.
- GSK
- HEALTH IN CODE
- HITACHI MEDICAL SYSTEMS EUROPE
- I-COR
- ITAMAR MEDICAL LTD.
- KANEKA PHARMA EUROPE N.V.

Cardiology

- LABTECH LTD.
- LEV EL DIAGNOSTICS OF HEART DISEASES
- LITTMANN / 3M HEALTH CARE
- MALTRON INTERNATIONAL LTD.
- MEDIMATIC
- MEDIS MEDICAL IMAGING SYSTEMS BV
- MEDITEK LTD.
- MEDLEY FARMACEUTICA
- MEDTRONIC
- THE MENARINI GROUP
- MICROLIFE AG
- MIDES GMBH
- MINDRAY
- MORTARA INSTRUMENT, INC.
- MSD
- MYLAN
- NEUROVIVE PHARMACEUTICAL AB
- NORAV MEDICAL
- NORTHEAST MONITORING, INC.
- NOVARTIS PHARMA AG
- PFIZER
- PHILIPS HEALTHCARE
- PORTOLA PHARMACEUTICALS, INC.
- RANDOX LABORATORIES
- RESMED
- ROCHE DIAGNOSTICS INTERNATIONAL LTD.
- SANOFI
- SANOFI REGENERON
- SCHILLER
- SCHWARZER CARDIOTEK GMBH
- SCOTTCARE CORPORATION
- SERVIER
- SHIRE INTERNATIONAL GMBH
- SIEMENS AG HEALTHCARE SECTOR
- SINGULEX
- SOMNOMEDICS GMBH
- ST. JUDE MEDICAL
- STORZ MEDICAL AG
- SUNSHINE HEART
- TAKEDA PHARMACEUTICALS INTERNATIONAL
- THROMBOSIS RESEARCH INSTITUTE
- TOMTEC IMAGING SYSTEMS GMBH
- TOSHIBA MEDICAL SYSTEMS
- UNITED THERAPEUTICS EUROPE LTD.
- VALES&HILLS BIOMEDICAL TECH LTD.
- VASOMEDICAL, INC.
- VECTRACOR, INC.
- ZEUS SCIENTIFIC
- ZOLL MEDICAL CORPORATION