TREATMENT STRATEGIES
CARDIOLOGY

Volume 5 Issue 1

- Arrhythmia Management
- Bifurcation
- Cardiogenic Shock
- Echocardiography
- Heart Failure
- Lead Extraction
- Paediatric Cardiology
- Platelet Reactivity Testing
- Rehabilitation
- Thrombosis

Papers include:

Ablation of Ventricular Tachycardias in Structural Heart Disease
Pasquale Vergara, Teresa Olóriz Sanjuán, Carla Roque and Paolo Della Bella

Circulatory Support in Cardiogenic Shock: Complicating Acute Coronary Syndromes
Matthew Lumley and Divaka Perer

Optimal Antiplatelet Treatment Strategy Based on Platelet Reactivity Testing after Coronary Stent Implantation: A Single-centre Experience
Gerhard Bauriedel, Isabell Henke and Gerhard Oltmanns

Remote Diagnosis and Management of Paediatric Heart Murmurs at John Radcliffe Hospital, Department of Paediatric Cardiology
Satish Adwani

Includes a Review of the ESC Congress 2013, Amsterdam

Ischaemic stroke: the most common thromboembolic complication in patients with AF[1]

Ischaemic stroke devastates

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This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities; concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa or when UFH is given at doses necessary to maintain an open central venous or arterial catheter; hepatic impairment or liver disease expected to have any impact on survival; concomitant systemic ketoconazole, cyclosporine, itraconazole, tacrolimus, dronedarone; prosthetic heart valves requiring anticoagulant treatment. **Warnings and Precautions:** Not recommended if liver enzymes > 2 ULN. Haemorrhagic risk: Close clinical surveillance (signs of bleeding or anaemia) is recommended throughout the treatment period, especially when haemorrhagic risk is increased or risk factors combined. Factors which may increase haemorrhagic risk: age ≥ 75 years; moderate renal impairment (CrCL 30 – 50 mL/min); P-glycoprotein inhibitor co-medication; body weight < 50 kg; acetylsalicylic acid (aspirin); NSAID; clopidogrel; selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs); other drugs which may impair haemostasis; diseases/procedures associated with a risk of bleeding such as coagulation disorders, thrombocytopenia or functional platelet defects, recent biopsy, major trauma, bacterial endocarditis, oesophagitis, gastritis or gastroesophageal reflux. Concomitant use of ticagrelor. The measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. Patients who develop acute renal failure must discontinue Pradaxa. If severe bleeding occurs, discontinue treatment and investigate the source of the bleeding. Avoid or use with caution medicinal products which may increase the risk of haemorrhage. The use of fibrinolytic medicinal products for the treatment of acute ischaemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the ULN according to the local reference range. Avoid concomitant administration with P-gp inducers. Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate; prescribers should consult the Summary of Product Characteristics for further information. 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Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price**: *110 mg* 60 capsules £65.90 *150 mg* 60 capsules £65.90 **Legal category** POM **MA numbers:** *110 mg* EU/1/08/442/007 (60 capsules) *150 mg* EU/1/08/442/011 (60 capsules) **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, Binger Str. 173, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** July 2013.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

Reference

1. Dweck M, Shah A, *et al.* Anticoagulation in atrial fibrillation: the present and the future. *J R Soc Med Cardiovasc Dis* 2012; 1(13):1-7.

Date of preparation: October 2013 **Job code:** UK/DBG-131349

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TREATMENT STRATEGIES CARDIOLOGY

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Welcome...

I am delighted to welcome you to the latest edition of *Treatment Strategies – Cardiology*, one of our flagship publications. We are excited to bring your our review of the European Society of Cardiology (ESC) Congress 2013, held in Amsterdam. The ESC Congress is the largest medical meeting in Europe, with close to 30,000 professionals in attendance. Our review brings you the most up-to-date research findings, breaking news and most innovative products showcased at the event.

This publication will also feature a wealth of papers written by leading cardiologists on a number of key areas within the field, including cardiogenic shock, echo-ventricular function and heart failure. These specially commissioned papers aim to provide a comprehensive review of the latest updates and advances within cardiology, and we hope that you enjoy their content.

2013 has been a year of change at The Cambridge Research Centre, and we are excited to bring you news of new projects and developments. These include our updated video pages, which now feature CEO interviews as well as roundtable and symposia recordings, as well as our monthly newsletters, which feature a different focus each month. We are also establishing ourselves in the world of social media, and can be found on Twitter, LinkedIn and on YouTube.

We hope that you enjoy this edition of *Treatment Strategies – Cardiology*, and please do feel free to share your thoughts and comments with us. You may also be interested in our *Treatment Strategies – Interventional Cardiology* publication, which features a review of EuroPCR 2013 as well as a wealth of papers on this therapy area. Additionally, previous editions of all of our eBooks can be found on our website.

We look forward to seeing you in Barcelona for ESC 2014.

Hannah Corby, Chief Sub-editor

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.

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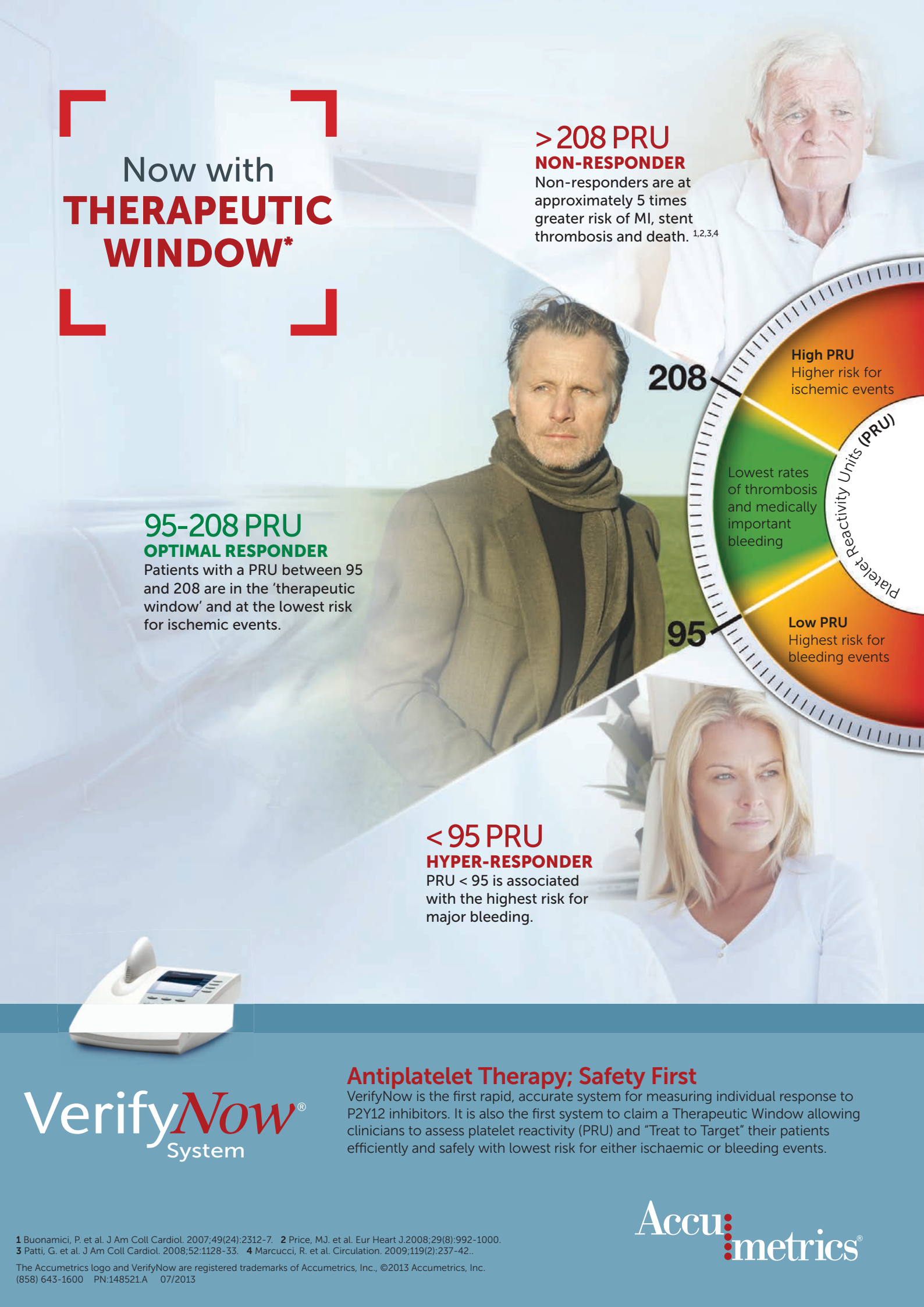

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OPTIMAL RESPONDER
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1 Buonamici, P. et al. J Am Coll Cardiol. 2007;49(24):2312-7. **2** Price, MJ. et al. Eur Heart J.2008;29(8):992-1000.
3 Patti, G. et al. J Am Coll Cardiol. 2008;52:1128-33. **4** Marcucci, R. et al. Circulation. 2009;119(2):237-42..

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CONTENTS...

8th World Research Congress of the European Association for Palliative Care

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EDITORIAL ADVISORY PANEL

Foreword

Hans Erik Bøtker
Professor of Cardiovascular Medicine and Interventional Cardiology, Consultant Interventional Cardiologist, Department of Cardiology, Aarhus University Hospital Skejby

Welcome to the latest issue of *Treatment Strategies – Cardiology*. Cardiology is an important and dynamic area of medicine, in which new discoveries and developments are constantly being made. We hope that you enjoy the papers which have been selected, and that the publication offers an in-depth overview of the most important and interesting topics within the field today.

Three important articles about the potential clinical impact of remote ischemic conditioning (RIC) have been published this summer. Local ischemic pre-conditioning induced by brief periods of local ischemia of the target organ before a sustained ischemic insult preceded the concept of RIC. This intervention affords potent protection against ischemia-reperfusion injury during cardiac surgery. However, the technique carries inherent translational limitation, as it requires invasive interruption of blood flow to the target organ. RIC is induced by brief non-lethal episodes of ischemia and reperfusion to an organ or tissue remote from the heart. The discovery that RIC can be performed non-invasively using a blood pressure cuff on the upper arm to induce brief episodes of limb ischemia and reperfusion has facilitated the translation of RIC into the clinical arena.

The cardioprotective effects of RIC are at least partially mediated through the release of endogenous substances into the bloodstream. Their release is dependent on intact neural pathways and nitric oxide-sensitive nerve stimulation. Although not identified, the circulating cardioprotective factor(s) are known as blood-borne, hydrophobic and small (molecular-mass<15 kDa) compounds, which modify mitogen-activated protein kinases and finally converge at mitochondrial level to prevent mitochondrial permeability transition pores (mPTP) from opening in early reperfusion. They also activate innate organ protective mechanisms in more general terms because inflammatory responses and platelet activation are attenuated.

Until now, only smaller proof-of-concept trials have indicated that RIC may have beneficial effect. In patients undergoing elective coronary angioplasty or coronary artery by-pass surgery, RIC reduces post-procedural troponin release reflecting reduction of ischemia-reperfusion injury. In patients undergoing primary angioplasty for acute ST-elevation myocardial infarction, RIC increases myocardial salvage reflecting attenuated reperfusion injury when blood flow is restored.

In the June 2013 issue of *Circulation Cardiovascular Intervention*, Davies and co-workers from Cambridge, UK now report that reduced postprocedural troponin release by RIC before the elective coronary angioplasty can be translated into a reduction of major adverse cardiac and cerebral event (MACCE) rate up to 6 years after the coronary intervention in 192 patients. In the 17th August issue of the *Lancet*, Thielmann and coworkers from Essen, Germany add to this finding by demonstrating not only the reduction of MACCE but also a decrease in all-cause mortality of 73% in 329 patients 1 year after coronary by-pass surgery. Most recently, Sloth and coworkers from Aarhus, Denmark added further support in the September issue of *European Heart Journal* by demonstrating that the increase in myocardial salvage by RIC performed in the ambulance during transportation to primary angioplasty could also be translated into a 34% reduction of MACCE and 46% reduction of all-cause mortality among 333 patients followed up to 4 years after ST-elevation myocardial infarction.

Each of the studies has limitations. Indeed, they are not optimally powered single centre studies, and they need confirmation in larger multicentre trials. Taken together, however, the consistent and promising results of the studies indicate that this new and cheap intervention will not be lost in translation.

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ESC Congress 2013 Review

31 August - 4 September, Amsterdam

Annual Congress of the European Society of Cardiology (ESC)

INSIDE...

The Meeting

The Exhibition

Sara Taheri, *Treatment Strategies*, brings you the latest news and research, as well as the most up-to-date and innovative products on the market that were showcased at ESC 2013. The review will also detail the major award winners from the event, as well as the most important satellite symposia and other exciting sessions.

From Saturday 31st August to Wednesday 4th September 2013, Amsterdam's RAI Congress Centre was the stage for the largest medical conference in Europe. Over these five days, close to 30,000 participants, speakers and representatives from all over the world congregated in Amsterdam for this event, organised by the European Society of Cardiology (ESC). It is one of the leading events in cardiology and is officially the largest medical congress in Europe.

"The ESC Congress is really an international event. Joint sessions have been expanded to include more cardiology societies across the globe such as Japan, China, Argentina and India, to discuss the latest science and clinical practice in their region," highlighted ESC President, Prof. Panos Vardas.

RAI Convention Centre, Amsterdam was the host to this year's exciting congress.

Attendees came to find out about the science, management and prevention of cardiovascular disease and hear first-hand about the latest research.

This year's congress built on the success of previous events and offered delegates a wealth of attractions. The chosen theme of this year's congress was "The Heart Interacting with Systemic Organs", which highlighted the interactions between the heart and other organs. Experts from different fields focused on how different disorders combine and how a whole systems approach can improve patient care. Critical discussion took place on new research and techniques and collaboration with other organ experts to foster innovation in clinical and translational science.

"In the past we have viewed diseases in isolation, but many cardiac disorders also have a systemic component," says Prof. Keith Fox, Chairperson of the ESC Congress Programme Committee. "The heart interacts with the lungs, brain, kidneys, gastrointestinal system and

reproductive system."

Research from investigators around the world was presented in the form of special lectures and interactive education sessions. Leading scientists gave more than 4,000 presentations, plenary lectures and seminars on the latest research and clinical trials. This year, results from a record number of late-breaking trials were released at the congress and 10,500 abstracts were submitted from ninety countries, covering more than 145 cardiovascular issues. Altogether, there were 21 Clinical Hot Line presentations, 18 Clinical Trial Updates, 12 Basic and Translational Science Hot Lines and 16 registry studies.

"A record number of Hot Lines and scientific sessions with new formats allowed for more exchanges between peers presenting results of clinical trials, new Clinical Practice Guidelines and new devices and treatments," said Prof. Keith Fox, Chair of the ESC Scientific Programme Committee.

Some of the important studies presented, according to Prof. Fox were:

HOKUSAI-VTE: This Hot Line Sessions started off positively with the study demonstrating that Factor Xa (FXa) inhibitor edoxaban (Lixiana) was non-inferior for the primary efficacy outcome of recurrent VTE. In addition, it was found to be superior for the primary safety outcome of major or clinically relevant non-major bleeding, when compared with low-molecular weight heparin (LMWH) plus warfarin.

REALIGN: Results from this study reaffirm current guidelines, and expand the body of evidence that simple electrocardiographic determination of QRS duration remains the most important predictor of the clinical benefits of CRT, rather than measures of mechanical dyssynchrony by echocardiography (excluding patients with a narrow QRS for CRT).

DECAAF: Results showed that in patients with atrial fibrillation, delayed enhancement magnetic resonance imaging (DE-MRI) performed before ablative treatment can stage the degree of damaged heart tissue (atrial fibrosis) and help predict whether treatment will be successful or not.

PRAMI: Results showed that heart attack patients with ST elevation who undergo a preventive procedure to unblock additional coronary arteries have significantly better outcomes than those whose treatment is confined to the culprit blockage only.

ACCOAST: In this Phase III trial, designed to test the benefits of prasugrel preloading in NSTEMI patients, there was no difference in the primary efficacy end point, but prasugrel preloading increased both surgical and non-surgical TIMI major bleeding episodes through day 7. The trial was halted early in November 2012 due to excessive bleeding and lack of ischemic benefit. This result follows the failure of the TRILOGY-ACS study in which prasugrel demonstrated non-inferiority to clopidogrel in medically managed UA and NSTEMI patients.

"These studies will influence clinical practice and will allow us to better understand of how to manage these important conditions and how to devise even newer therapies," explained Prof. Fox.

The 2013 ESC Guidelines were presented for the first time to a general cardiology audience, with new titles in arterial hypertension, cardiac pacing, diabetes, and stable coronary artery disease.

Other hot topics in cardiology were also covered in the Hot Line sessions including new oral anticoagulants, devices and interventions, the two diabetes trials focused on gliptins, heart failure and ACS to mention a few.

The congress also provided an invaluable platform for networking amongst peers and to exchange knowledge.

Around 650 journalists joined the cardiologists, cardiovascular surgeons, nurses, primary care physicians, scientists, technicians, medical students, healthcare industry leaders and regulators at the congress this year.

"Once again, they helped us reach out to the public with key prevention messages. Eighty percent of CVD could be avoided if people adopted healthier lifestyles and there is a long way to go between knowing what should be done and doing," said Kurt Huber, Chair of the ESC Press Committee.

In order to put prevention messages into practice, a dedicated cycling track was created to enable cardiologists, journalists and other attendees to cycle from the heart of Amsterdam to the congress centre each day. 5,000 bicycles were made available by the city for this new endeavor.

ESC's Young Cardiologists

The Cardiologists of Tomorrow (CoT) initiative was launched at the ESC Congress in Stockholm three years ago, and has made great progress.

'The platform was formed to help young cardiologists get in touch with their peers and to get involved in the society to build the future of cardiology' says Dr. Ewa Jankowska, a CoT nucleus member from Poland. 'It helps to promote excellence in education and actively involves young cardiologists within the ESC, thereby preparing the next generation of leaders.'

This year's CoT Track was held on Monday 2nd September and featured an interactive programme designed by and for young cardiologists.

'Our aim was to provide sessions tailored to the educational needs of cardiologists in training,' says Dr. Janine Pöss, a CoT nucleus member. 'We wanted to help them network and get integrated into the ESC family.

The programme began with a symposium presented by world famous cardiologists such as Eugene Braunwald, Salim Yusuf and Frans Van de Werf. Entitled 'Milestones in Cardiovascular Medicine', the session discussed the developments which have shaped cardiology today and how they will change practice in the future where discussed.

This was followed by a session where experts talked the audience through the process of weighing up the risks and benefits of different treatment approaches entitled 'Clinical Challenges in Cardiology'. The pitfalls of statistical analysis in clinical trials were covered in the following sessions.

In the 'Discussing the Most Challenging Clinical Cases' session, the four top scoring case reports submitted were presented with prizes. Speakers competed for the top prize of €2000, with three runners-up receiving €1000 each. Over 400 cardiologists entered and provided cases on the themes of 'The Heart Interacting with Organs' and 'Catheters and Devices'. The next 42 high scoring cases were presented throughout the meeting.

'These sessions offered young cardiologists really valuable experience of speaking at an international meeting, and provided a teaching experience that's often much more memorable than formal lectures,' says Dr. Pöss.

Dr. Pöss explained that the Cardiologists of Tomorrow activities are coordinated by a nucleus of seven young cardiologists from Spain, Germany, Portugal, Poland, Hungary, Czech Republic and France. These nucleus members have contributed to discussions for definition in the new ESC Core Curriculum for General Cardiology. The Third Edition of the ESC Core Curriculum, published in 2013 is now available.

The nucleus also plans to develop an ESC network of young cardiologists through the National Cardiac societies and national young cardiologists groups. More than 25 member countries have identified their younger members to help implement scientific activities on the national level.

Amsterdam, The Ideal Location

This year, the ESC congress returned to Amsterdam, the capital city of the Netherlands. Returning in 2013 for the fifth time in the congresses history, the last ESC congress was held here 13 years ago in 2000, and previously in 1995, 1991 and 1976.

Amsterdam was an ideal location for the world's largest meeting in cardiology. With the huge airport of Schiphol close to the RAI Congress Centre, this venue was well placed to accommodate the 30,000 attendees. The congress centre is within easy reach of the city centre and its many cultural and social attractions, including the central Dam square, with its Royal Palace.

Hans Bakker, President and CEO of Amsterdam RAI said, "We are very honoured and proud that the ESC Congress is coming back to Amsterdam. The whole destination team is completely aware of the impact of Europe's largest medical meeting and is highly committed to making ESC 2013 a resounding success. Strong co-operation between Amsterdam's local government and its business and service sectors in the selection process demonstrated a clear ambition to become the European 'City of Meetings'".

Winners of this Year's ESC Awards Ceremony

On Monday 2nd September in the Award Ceremony, the ESC President Elect Fausto Pinto presented the winners of the Young Investigators Awards, Challenging Case Reports, Moderated Posters and Nursing and Allied Health Professionals Investigator Awards

The Young Investigator Awards

Dr. Sarah Costantino
Basic Science: Hyperglycemia-induced myocardial oxidative stress and inflammation persist despite optimal glycemic control: role of mitochondrial adaptor p66shc

Dr. Holy Erik Walter
Thrombosis : Carbamylated LDL induces a pro-thrombotic state via the LOX-1 receptor and arterial thrombus formation: A novel mechanism of cardiovascular events in end-stage renal disease

Dr. Maarten Leening
Population Sciences: The healthy volunteer effect and coronary risk prediction in the general population: The Rotterdam study

Dr. Marios Margaritis
Coronary Pathophysiology and Microcirculation: A novel cross-talk between perivascular adipose tissue and the arterial wall controls redox state in human atherosclerosis

Dr. Rizas Konstantinos
Clinical Science: Low frequency waves of repolarization as a novel predictor of mortality after myocardial infarction

Nursing/Allied Professional Investigator Award

Dr. Lowrie Richard
Pharmacist-led Statin Outreach Support (SOS): Cluster randomised controlled trial in primary care

Challenging Case Report Awards

Dr Ammirati Enrico
The case report of a 31-year-old man with giant cell myocarditis successfully treated with combined immunosuppression and veno-arterial extracorporeal membrane oxygenation for 21 days

Moderated Posters

Mr. Spescha Remo Daniel
Post-ischemic *in vivo* p66shc silencing as a therapeutical strategy for ischemia/reperfusion brain injury

Dr. Perazzolo Marra Martina
The prognostic value of myocardial fibrosis in nonischemic dilated cardiomyopathy: A study by endomyocardial biopsy and cardiac magnetic resonance

Dr. Khalid Usman
Psoriasis is associated with increased risk of new-onset heart failure: A nationwide cohort study

Prof. La Gerche Andre
Right ventricular work increase during strenuous exercise is greater than for the left ventricle: Results from a real-time exercise cardiac magnetic resonance study

Dr. Paikin Jeremy
Randomized trial to examine the effect of ASA dose or ASA dosing frequency on ASA resistance after coronary artery bypass graft surgery

Dr. Menezes Alves Da Costa Leandro
Release of biomarkers compared with cardiac magnetic resonance for the diagnosis of procedure-related myocardial injury. A prospective trial using the third definition of myocardial infarction

Dr. Leening Maarten
Are osteoarthritis patients at high risk of cardiovascular disease? Results from a large prospective population-based cohort study

Dr. Lourenco Patricia
The nutritional marker pre-albumin is strongly associated with adverse outcome in heart failure

Miss Igland Jannicke
Educational differences in 28-day and 1-year survival after hospitalization for incident acute myocardial infarction - A CVDNOR project

Dr. Segreti Luca
Transvenous removal of pacing and ICD leads: 15 years experience from a referral center

Dr. Alraies Chadi
Predictors of qrs voltage recovery post-pericardiectomy in patients with constrictive pericarditis

Dr. Porta Sanchez Andreu
Thirty year experience of constrictive pericarditis: One-hundred and forty cases with a long-term follow-up

Miss Verloop Willemien
What are predictors for blood pressure lowering effect after renal denervation?

Dr. Bromage Dan
Impact of inter-hospital transfer for primary percutaneous coronary intervention on survival (10,108 STEMI patients from the London Heart Attack Group)

Dr. Ujiie Yuichi
Analysis of failures of retrograde percutaneous coronary intervention of chronic total occlusion: From the Japanese Multicenter registry by Retrograde Summit

Four New Practice Guidelines

In order to improve clinical practice, the Committee for Practice Guidelines charged groups of European experts with the task of creating recommendations and guidelines for clinical practice. These recommendations and guidelines aimed to clarify areas of consensus and disagreement, in order to enable the delivery of the best possible guidance to practicing physicians.

The aim and purpose of the ESC guidelines is to help physicians weigh out the benefits and risks of a particular diagnostic or therapeutic procedure by presenting the user with all the pertinent information on a particular clinical issue. The guidelines should also help in everyday clinical medical decision-making.

There was plenteous Guideline activity this year and, as with every congress, the guidelines were the foundation of scientific interaction with participants. The Clinical Practice guidelines brought expertise and experience from historical and modern sources. The new Clinical Practice Guidelines presented were; Stable Coronary Artery Disease; Diabetes, Pre-diabetes and Cardiovascular Diseases; Cardiac Pacing and CRT; Arterial Hypertension.

The newest version of the Stable Coronary Artery Disease guidelines gives more prominence to new imaging techniques. These techniques include cardiovascular magnetic resonance (CMR) and coronary computed tomography (Ct) angiography in the diagnosis of CAD in patients with stable chest pain. The guidelines are there to clearly define which patients should receive coronary Ct angiography, in order to avoid the overuse of this technique. In addition, as the control of heart rate is the new treatment goal for medical therapy, the diagnostic algorithm is based on the pre-test probability of chest pain of recent onset is another new aspect that was explored.

The European Association of Cardiology, together with the European Association for the study of Diabetes, produced the 2013 Guidelines for Diabetes, Pre-diabetes and Cardiovascular Diseases. This year's guidelines introduced glycated haemoglobin (HbA1c) for the diagnosis of diabetes. The assessment of cardiovascular risk was also simplified, and risk engines are no longer advocated. Drugs are assessed, with BP targets, diet and weight loss re-evaluated. These new guidelines encourage multidisciplinary teams and nurse-led programmes to support lifestyle change and self-management. Since these patients fall between two fields of expertise, the need and importance of guidelines from both diabetologists and cardiologists was emphasised.

A practical 'how to approach' for Cardiac Pacing and CRT Guidelines was targeted at physicians, including GPs and geriatricians, cardiologists and electrophysiologists. A new classification system for bradyarrhythmias according to mechanisms rather than aetiology has been devised. The development of a logical decision tree displaying the different pacing modes based on the different clinical situations was another big innovation this year. As a result these guidelines support clinicians and lead them through a series of three or four questions.

Another multiparty party guideline, the Arterial Hypertension guidelines are produced jointly by the European Society of Cardiology and the European Society of Hypertension. These new joint guidelines redefine the approach to diagnosing and treating hypertension. Amongst the recommendations are revised definitions of hypertension, which will significantly affect diagnosis, and updated recommendations on how hypertension is treated, with a new emphasis on drug selection. There is a call for doctors to be more pro-active in initiating treatment and for patients to be more aware of the endemic problem of high blood pressure.

In the 'Meet the Task Force' sessions at this year's congress attendees had the opportunity to interact face-to-face with the experts responsible for producing these guidelines. They were able to ask questions and share their thoughts with the group of experts from the Committee for Practice Guidelines.

This year the guidelines received technical developments as the ESC launched the new Guidelines app for mobile devices. The ESC Clinical Practice Guidelines free application for Apple and android devices was introduced during 2013 Congress. The 2011 and 2012 Pocket Guidelines titles were available along with their associated interactive tools with the 2013 titles to follow shortly.

The ESC cardiology quiz, based on a review of the Guidelines, provided an enjoyable way to learn. The ESC pocket guidelines were available free for download at the ESC stand during the congress.

EECP® Therapy Presented at the Congress

Vasomedical is a medical technology company specialising in the design, manufacture and sale of medical devices for non-invasive cardiology including EECP® (Enhanced External Counterpulsation) Therapy systems.

Vasomedical's EECP® is an FDA cleared, Medicare approved, non-invasive medical therapy for the treatment of stable and unstable angina, congestive heart failure, acute myocardial infarction, and cardiogenic shock.

EECP therapy improves cardiac output, increases circulation, recruits and develops new collaterals haemodynamically. It also increases shear stress on the endothelium, improving endothelial function, reduces circulating inflammatory markers and arterial stiffness, while also inhibiting smooth muscle cell proliferation and migration.

EECP® Therapy was given a IIa Class of Recommendation in the ESC Guidelines, which were released during ESC 2013 Congress. The IIa classification signifies that the weight of evidence and level of opinion are in favour of a treatment and, in this case, that physicians should consider EECP therapy as a treatment option for patients suffering from refractory angina.

"It is a breakthrough that EECP® Therapy was included in the ESC Guidelines for the first time, and at the same time that it was given a level IIa recommendation, which means it 'should be considered' as a treatment option as opposed to 'may be considered' recommendation for a IIb rating," said Dr. Jun Ma, President and Chief Executive Officer of Vasomedical, Inc. "We are pleased that the European Society of Cardiology has recognised the value and efficacy of this treatment, as has been demonstrated by many studies. On behalf of all heart patients, we thank the many physicians in the U.S. and Europe who have done great research on EECP® Therapy and presented data to ESC for consideration."

"Throughout the past decade, EECP® Therapy has been offered to hundreds of thousands of patients in numerous centres and hospitals in the Unites States and abroad. During this time, we have gathered a wealth of data from many different studies, including randomised controlled trials published in peer-reviewed journals, and have received countless testimonials regarding an improvement to patients' quality of life," continued Dr. Ma. "We believe that this treatment option should be made available to a wider patient base. Our responsibility is not only to support and improve this technology, but also to champion the patient who is not receiving this therapy and its benefits. Furthermore, we have a social obligation to support healthcare cost reduction through expanding role of EECP therapy, which has been demonstrated in clinical literature to reduce re-hospitalisations and emergency room visits. We believe this high recommendation by ESC should help promote a broader acceptance of the EECP therapy around the world."

At the ESC Congress Vasomedical presented its core technology, EECP® Therapy, as well as its BIOX ECG Holter, ambulatory blood pressure monitors and patient management products.

In addition, the company presented two abstracts on Vasomedical's EECP® Therapy. On Sunday, 31st August, Dr. Eline Wu, from the Karolinska Institute in Stockholm, Sweden presented a session titled "Enhanced External Counterpulsation for Refractory Angina", discussing chronic care for patients with no cure.

"Dr. Wu has been involved in EECP therapy research at this prestigious institution for many years," stated Larry Liebman, Vice President of Sales and Marketing at Vasomedical. "Her knowledge and experience on the subject will make a great contribution to our effort to increase awareness about EECP Therapy among this group of health professionals."

On Monday, 2nd September, Dr. Vyacheslav Ryabov from Tomsk, Russia presented a poster (P4019) titled "Effects of enhanced external counterpulsation on endothelial function and antithrombogenic activity of vascular endothelium in patients with angina" during Poster Session 5.

"Dr. Ryabov was one of the first physicians in the Russian Federation to introduce EECP therapy as an effective adjunctive treatment and has studied and reported his results at major cardiology conferences and symposia in Russia for the past several years," said Mr. Liebman. "Having these two abstracts on EECP therapy selected for presentation at the ESC, from the over 9,000 abstracts submitted, is an honour for these physicians and their institutions and also highlights that there is a significant interest in learning more about EECP therapy and its positive effects on treating cardiovascular disease."

Ergometer for Use in Magnetic Resonance Devices

Ergospect, developer and producer of MRI- compatible ergometers, showcased the Diagnostic Pedal Cardio at the ESC Congress. The Cambridge Research Centre spoke to Ergospect's CEO, Mr. Thomas Hugl about the device. This specially designed Diagnostic Pedal Cardio allows for the examination of different muscle groups, the myocardium and the musculoskeletal system by simulating stress situations inside the MRI bore.

This is important issue to bear in mind since some medical conditions may not be identified during rest, but these can be examined during stress or physical exercise with advanced MRI techniques.

To examine and evaluate such conditions of the myocardium, stress MRI is used with the administration of drugs like Dobutamine and Adenosine to stress the cardiovascular system.

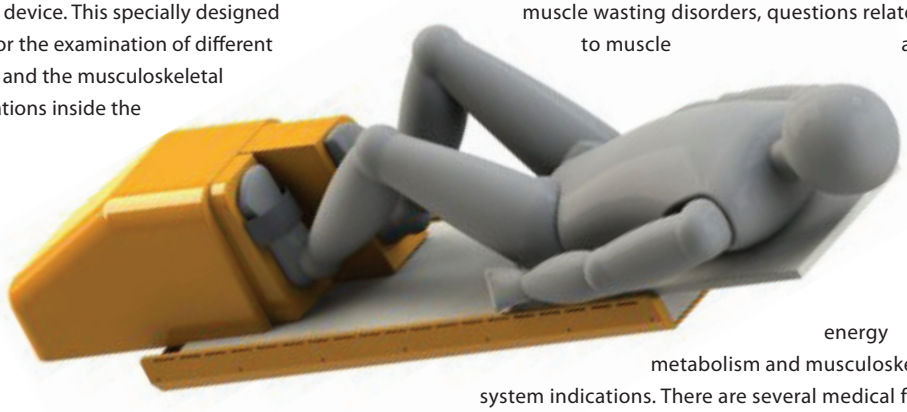
The use of such drugs is complicated and their use does not reflect physiological reality of daily situations.

Up until the development of the Pedal Cardio there were few or no suitable devices available to create the required myocardium stress conditions needed for monitoring.

Now, the newly developed Diagnostic Pedal Cardio enables a step exercise inside the MRI bore, to mirror routine daily situations or training conditions. The ergometers are compatible with all MRI-systems (up to 7 Tesla and higher) and have been especially designed to stress-test the heart in a magnetic resonance bore. Thus it is possible to investigate the performance and perfusion of the myocardium during dynamic exercise via magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS) in clinical routine examination.

The advantage of using the Pedal Cardio when creating the stress conditions is that the human body is exposed to an accurate, constant workload for a specific period of time during an MRI measurement. It is revolutionary in that during the examination the workload intensity is constantly variable in order to simulate routine stressful situations and the resulting physiological changes in the musculoskeletal system are measured simultaneously inside the MRI bore.

This Pedal Cardio also enables medical experts to collect the required information faster and with greater accuracy, which helps to identify medical problems such as occlusive diseases, stenotic lesions or occlusions, metabolic and muscle wasting disorders, questions related to muscle and energy metabolism and musculoskeletal system indications. There are several medical fields of applications for this technology. These include: angiography, cardiology, neurology, orthopaedics, sports medicine, vascular surgery or pharmaceutical compatibility examinations.



Award Winning Mobile C-arms

Ziehm Imaging, the market and innovation leader for mobile C-arms, presented its multiple award-winning range of products as well as a number of new technologies for intraoperative imaging at this year's ESC congress. Among the highlights are the new Ziehm Vision and SmartDose, a comprehensive concept for dose reduction in intraoperative imaging.

Powerful mobile C-arms and SmartDose ensure optimum imaging with the new generation of the Ziehm Vision RFD Hybrid Edition, the innovation leader Ziehm Imaging presents a mobile C- arm tailored exactly to hybrid operating room (OR) requirements. Fully motorised in four axes, intuitive joystick operation, intelligent collision protection and maximum image quality with minimal dose levels make the new C-arm the best solution for all hospitals that ask for mobile and powerful imaging in hybrid ORs.

Mobile C-arms offer a flexible, space- and cost-saving alternative to fix installed systems and are winning over more and more hospital users. With its latest system Ziehm Imaging is driving forward the development of mobile imaging: "With the new generation of the Ziehm Vision RFD Hybrid Edition we are offering, for the first time, full motorisation of a mobile C-arm in four axes: horizontal, vertical, orbital rotation and in angulation. Each position can be stored at the touch of a button and called up again at any time," says Klaus Hörndler, Managing Director of Ziehm Imaging.

The operator must deliberately touch any two contact points on the joystick (Position Control Centre) with the fingers to activate movement of the C-arm – any accidental operation of the C-arm is thus prevented. The joystick module also has a function for defining an isocenter around which the system moves concentrically. In addition to numerous orthopedic applications (e.g. spine), the isocentric functionality offers added clinical value, in particular for cardiac applications.

For more information please visit
www.ziehm.com

BIOTRONIK Announces ProMRI® Technology Extension for Full-body MR Scans

BIOTRONIK, a leading manufacturer of cardiovascular technology, announced an extension of its ProMRI® technology. BIOTRONIK has combined advanced pacemaker and ICD technology with the option for patients to undergo MR scans. This makes BIOTRONIK the only company worldwide to allow ICD and heart failure patients (CRT-D and CRT-P) to take advantage of potentially life-saving MR scans. The new extension of ProMRI® technology means that even full-body scans are now available for pacemaker patients, placing BIOTRONIK's implants firmly at the forefront of cardiac device innovation.

With BIOTRONIK's Lumax 7, the Ilesto and Iforia ICDs/CRT-Ds, and the Evia HF-T, patients can have more than 88% of all required MR scans. Patients implanted with the Evia single and dual chamber devices can now have all required scans, including liver and heart scans.

BIOTRONIK received CE mark for its full-body scan ProMRI® technology with a backwards compatibility in mid-August. These cardiac devices are also equipped with BIOTRONIK's Home Monitoring®, which rapidly detects deterioration in patients' clinical status and automatically transmits data on a daily basis. This enables physicians to adapt patient therapy at a very early stage.

At the ESC Congress 2013 Late-breaking results from the BIOTRONIK IN-TIME Study, which evaluated the influence of implant-based BIOTRONIK Home Monitoring® on the clinical management of heart failure patients, was presented by Prof. Gerhard Hindricks, MD, and discussed with Prof. Angelo Auricchio.

Christoph Böhmer, President International at BIOTRONIK explained "Our technologies, like ProMRI® enabling full-body scans and BIOTRONIK Home Monitoring®, have proven our reliability in making a real difference in patients' lives."

For more information, visit:
www.biotronik.com

State of the Art and Future Directions in Advanced Cardiac Imaging

On Saturday, 31st August, Toshiba Medical Systems presented its Lunch Satellite Symposium. This was entitled "State of the Art and Future Directions in Advanced Cardiac Imaging" and was chaired by Dr. Koen Nieman, Erasmus University Hospital, The Netherlands and Dr. Jose Zamorano, Hospital Ramony Cajal, Spain.

The programme comprised of lectures on; 2D Wall Motion Tracking in non-STEMI, Coronary subtraction on 2nd generation 320 row detector CT, CORE320 in clinical practice and Real- time Fusion of Ultrasound and CT.

Dr. Koen Nieman gave the introduction to this symposium and was followed by Dr. Sebastian Sarvari's, Oslo University Rikshospitalet , Norway, lecture on 2D Wall Motion Tracking in non-STEMI.

Coronary subtraction on 2nd generation 320 row detector CT was the second lecture of this symposium presented by Dr. Klaus Kofoed, Rigshopitalet, Denmark.

Dr. Joao A. Lima, John Hopkins University, USA presented the third lecture entitled - CORE320 in clinical practice.

Finally the Dr. Jose Zamorano summarised all of the findings and brought it all together in his presentation - Realtime Fusion of Ultrasound and CT. The session finished with closing remarks by Dr. Koen Nieman.

The conclusion reached was that hybrid imaging including coronary tomography plus 3D myocardial mechanics is feasible from 3D data obtained with both techniques separately and processed with a new software. This new technology provides a promising tool for research and clinical routine for a better understanding of myocardial mechanics and its relationship with coronary ischaemia.

For more information, please visit:
www.medical.toshiba.com

MitraClip® System Demonstrates Positive Clinical and Quality-of-Life Results

Earlier this year Abbott announced data from the EVEREST II (Endovascular Valve Edge-to-Edge REpair STudy) High Surgical Risk cohort evaluating the company's first-in-class catheter-based MitraClip® System for the treatment of mitral regurgitation (MR). The MitraClip® System was showcased at the ESC Congress.

Abbott's MitraClip® System, an investigational device in the United States, received CE Mark in 2008 and is commercially available in approximately 30 countries, with more than 8,000 patients treated to date. The device is delivered to the heart through the femoral vein, a blood vessel in the leg, and is designed to reduce MR by clipping together the leaflets of the mitral valve to allow the heart to more efficiently pump blood.

The EVEREST II High Surgical Risk cohort included data from patients enrolled in the multi-centre EVEREST II High Risk and REALISM continued access studies. Findings from 351 symptomatic U.S. patients deemed too high risk for open mitral valve surgery demonstrated:

- A 30-day mortality rate significantly lower than expected for surgery
- A low rate of adverse events, despite high surgical risk patient profiles
- An implant success rate of 96 percent
- Acute reduction in MR to 2+ or less achieved in 86 percent of patients treated with the MitraClip® device
- Clinically significant improvement in left ventricular size, significant improvements in NYHA Functional Class and SF-36 Quality-of-Life scores
- Significantly reduced rates of hospitalisation for heart failure

"These results add to the large and growing body of data that show that the first-in-class percutaneous MitraClip therapy can have positive results for high surgical risk patients suffering from the debilitating symptoms of significant mitral regurgitation," said Dr. Charles A. Simonton, Divisional Vice President, Medical Affairs, and Chief Medical Officer, Abbott Vascular. "We look forward to the 20th March FDA Advisory Committee Meeting to discuss the MitraClip® System as a treatment option for this patient group in the United States."

For more information, please visit:
www.abbott.com

ReOxy, a Treatment Device for Controlled Hypoxic Breathing Therapy

Ai Mediq S.A. is a company specialising in research, development and manufacturing of non-invasive medical devices. They were showcasing their latest product, ReOxy, this year at the ESC Congress. ReOxy is a treatment device for controlled hypoxic breathing therapy based on innovative SRT (Self-Regulated Treatment) technology.

It is a compact, mobile and easy-to-use device that does not require a specially-equipped room.

ReOxy provides Interval normobaric hypoxic therapy with controlled SpO2 measurements and related vital alarm functions.

The device stimulates long-term adaptive response at systematic, organic, tissue and cellular levels, and this method is successfully used in the treatment of cardiovascular, bronchopulmonary disease, with associated diseases and cerebrovascular and metabolic diseases.

ReOxy uses Self Regulated Treatment (SRT-technology) which relies on the principle of biological feedback, where patient bodily reaction defines impact parameters and controls them over the whole treatment period. An in-built software module automatically identifies the necessary hypoxic impact parameters, based on the results of hypoxic tests.

ReOxy indications include:

- Cardiovascular/ Cerebrovascular diseases: Arterial Hypertension, Coronary Artery Disease, Chronic Heart Failure, Transient Ischaemic Attack
- Metabolic diseases: Type 2 Diabetes Mellitus, Hypercholesterolaemia, Obesity and Metabolic Syndrome
- Bronchial Asthma and Chronic Obstructive Pulmonary Disease
- Primary and secondary prevention of cardiovascular and cerebrovascular diseases

www.reoxy.lu

The Reitan Catheter Pump

CardioBridge GmbH presented their the Reitan Catheter Pump (RCP), a percutaneous circulatory support device at the ESC congress.

The Reitan Catheter Pump is a novel rhythm independent percutaneous circulatory support device that can be used safely in high risk patients undergoing percutaneous intervention.

The unique design of CardioBridge's RCP is a foldable propeller feature surrounded by a protective cage at the tip of a 10F catheter. The RCP is introduced via a sheath in the femoral artery and resides in the proximal descending aorta. The pump reduces afterload as well as filling pressures and increases and improves flow and pressure towards the visceral organs, especially the kidneys.

Early experience may suggest protection against haemodynamic compromise during ischaemic PCI complications

The Reitan Catheter Pump is indicated in patients with a need for circulatory support throughout periods of compromised left ventricular function. The clinical experience with the RCP has shown promising haemodynamic results, which make the RCP an attractive and easy to use alternative to other percutaneous support systems including the IABP, particulary in cases when disturbed heart rhythm attenuates the effect of the IABP and more substantial circulatory support is needed.

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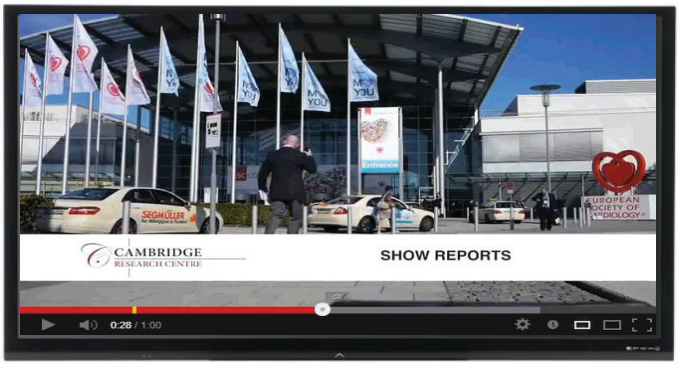

LIGHTS... CAMERA... ACTION!!!

Tune into the latest videos, interviews, symposium reviews, show reports and round-table discussions.

Be sure to look out for our 10 post-congress videos.

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ONGLYZA® Achieves Primary Safety Endpoint, in SAVOR Cardiovascular Outcomes Trial

ONGLYZA® (saxagliptin) achieves primary safety endpoint, demonstrating no increased risk for cardiovascular death, heart attack or stroke in SAVOR cardiovascular outcomes trial.

AstraZeneca and Bristol-Myers Squibb announced the full results of the SAVOR clinical trial in 16,492 adult patients with type 2 diabetes at high-risk for cardiovascular diseases during ESC 2013.

In this study, Onglyza (saxagliptin) met the primary safety objective, demonstrating no increased risk for the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction (MI) or non-fatal ischaemic stroke, when added to a patient's current standard of care, with or without other anti-diabetic therapies, as compared to placebo. Onglyza did not meet the primary efficacy endpoint of superiority to placebo for the same composite endpoint. Patients treated with Onglyza experienced improved glycaemic control and reduced development and progression of microalbuminuria over two years as assessed in exploratory analyses.

The major secondary composite endpoint of cardiovascular death, non-fatal MI, non-fatal ischaemic stroke or hospitalisation for heart failure, unstable angina or coronary revascularisation was balanced across the two arms. One component of the composite secondary endpoint, hospitalisation for heart failure, occurred more in the Onglyza group compared to placebo. Rates of pancreatitis were low and balanced between Onglyza and placebo. Overall rates of malignancy were balanced, and the observed rates of pancreatic cancer were lower in the Onglyza group than in the placebo group. More patients in the Onglyza group reported at least one hypoglycaemic event compared to placebo. Results were presented during a Hot Line session at the ESC Congress 2013, and published in The New England Journal of Medicine.

In the past, questions have been raised about the safety of many diabetes treatments, in particular regarding their impact on the risk of cardiovascular death, heart attack or stroke.

Led by the academic research organisations TIMI Study Group and Hadassah University Medical Center and conducted at more than 700 sites worldwide, SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) was a randomised, double-blind, placebo-controlled trial of 16,492 patients designed to evaluate the cardiovascular safety and efficacy of Onglyza in adults with type 2 diabetes at risk for cardiovascular death, heart attack and stroke, compared to placebo.

"Given the correlation between diabetes and cardiovascular complications, there is a need for thorough assessments of the cardiovascular risks among therapies that improve glycaemic control," said Deepak L. Bhatt, MD, MPH, Senior Investigator of the TIMI Study Group, Brigham and Women's Hospital, and a Principal Investigator for the trial. "The results from SAVOR add important evidence to the overall body of data to further define the clinical profile of saxagliptin for the treatment of type 2 diabetes."

"No other DPP-4 inhibitor and few other anti-hyperglycaemic agents have been studied as extensively as Onglyza to address the question of cardiovascular safety," said Brian Daniels, MD, Senior Vice President, Global Development and Medical Affairs, Research and Development, Bristol-Myers Squibb. "Bristol-Myers Squibb and AstraZeneca are dedicated to meeting needs of physicians and patients in diabetes care and helping to ensure a better understanding of the value of our medications."

"SAVOR is an important contribution to our knowledge of the safety of Onglyza in type 2 diabetes patients at an increased risk for cardiovascular events similar to those found in a real-world population," said Briggs Morrison, MD, executive vice president, Global Medicines Development, AstraZeneca. "In addition, the data on pancreatitis and pancreatic cancer in a study of more than 16,000 patients provide important and timely scientific information from a robust, randomised trial for the diabetes community."

Harvey the Cardiopulmonary Patient Simulator was on display at Leardal's booth at ESC Congress.

Harvey has been a proven simulation system used to teach bedside cardiac assessment skills that can be transferred to real patients. Having been used for nearly 40 years, Harvey is the longest continuous university-based simulation project in medical education.

Harvey - The Cardiopulmonary Patient Simulator

There are several benefits with using Harvey as a Cardiopulmonary Patient Simulator, which the team kindly highlighted. In the first instance, Harvey realistically simulates nearly any cardiac disease at the touch of a button by varying blood pressure, pulses, heart sounds and murmurs.

Additionally Harvey has been dramatically updated over recent years with state-of-the-art technology. Today, the current version of Harvey's software covers history, bedside findings, all laboratory data, medical, and surgical treatment. And finally, thousands of students, residents, physicians, physician assistants, nurses and nurse practitioners train annually on Harvey, at hundreds of medical centres worldwide, making this stimulator device a valuable resource for the cardiology community.

Huntleigh - The Revolutionary Dopplex ABIlity Device

The Cambridge Research Centre visited Huntleigh's Stand for a demonstration of the new Huntleigh Dopplex ABIlity device at the ESC Congress 2013. This device automatically measures the Ankle Brachial Pressure Index Measurement (ABPI) in less than 5 minutes and has revolutionised ABPI Measurement. The test can be requested when a patient has swelling, discomfort or slow to heal ulcers on their legs.

Patients can come straight from the waiting room for the test, and the device can take measurements over tights and socks, which helps to maintain comfort and dignity of the patient. The complete procedure takes less than 20 minutes from entering the treatment room and performing the test. It is a very useful assesment, which can help speed up referral to secondary care, improve healing of leg ulcers and reduce painful swollen legs.

As well as giving measurements quickly and simply it is also a portable device, enabling measurements to be more efficient. This can lead to the prioritisation of clinical services by improving clinical pathways.

Results are calculated, interpreted and displayed with Pulse Volume waveforms on the LCD panel, and can be printed via the integral printer.

In conjunction with this Huntleigh were also showcasing their world-renowned Dopplex handheld Doppler range, offering even greater performance, quality and reliability.

CellAegis autoRIC™ Device

During the ESC Congress 2013, CellAegis Devices, were highlighting the autoRIC™ Device for Remote Ischaemic Conditioning.

The autoRIC™ Device is a non-invasive device that automates the process of remote ischaemic conditioning (RIC). RIC uses short controlled sequences of repeated inflation (ischaemia) and deflation (reperfusion) of a cuff placed around the arm or leg to temporarily cut off and then restore blood flow to that limb. This induces the body to activate an innate mechanism of metabolic protection in response to the restricted blood flow enabling cells in the heart and other remote organs to withstand periods of oxygen starvation and death.

Compared with current methods that require manual operation of a standard blood pressure cuff, the autoRIC™ is the first technology to automate the process of RIC at the point of care. CellAegis Devices states that the autoRIC™ will save up to 40 minutes of a healthcare professional's time. CellAegis' autoRIC device offers a convenient and accurate method to automate RIC at the point of care. The device also provides a safer method of RIC by removing the risk of a limb being left occluded or unattended and also reducing tissue injury from heart procedures. RIC can be used to protect against ischaemia-reperfusion injury in patients before undergoing cardiac intervention or surgery (pre-conditioning). It may also be given to patients during ischaemia (peri-conditioning) or after the ischaemic event (post-conditioning).

Earlier this year, CellAegis revealed the first clinical trial program in the European Union to evaluate the use the autoRIC™ Device for Chronic Remote Ischemic Conditioning (CRIC). A quarter of patients suffering a heart attack show symptoms of heart failure at the time of admission, and CRIC has the potential to interrupt this disease process.

In the DREAM study (Daily REmote Ischemic Conditioning following Acute Myocardial Infarction), a University of Leicester-sponsored Phase II, randomised, placebo-controlled clinical study, CRIC will be evaluated for its ability to prevent negative remodeling of the heart in patients following an acute myocardial infarction.

RIC has been shown to reduce the larger injury from ischemia reperfusion to heart and other organs, including myocardial infarctions, cardiac surgery, stroke, trauma, and organ transplantation. Data from various studies have shown that RIC can reduce heart damage by up to 40-50% in an evolving heart attack, as well as improve left ventricular ejection fraction in left anterior descending coronary artery (LAD) infarction and reduce damage and late adverse events during elective PCI, as well as decrease incidences of contrast-medium-induced nephropathy. A preclinical study concluded that although a single early episode of remote per-conditioning decreases infarct size, repeated remote CRIC further reduced adverse LV remodeling and improved survival in a dose-dependent fashion.

The autoRIC™ Device is CE Marked and Health Canada approved.

CellAegis' autoRIC™ Device has potential applications across the spectrum of care: in acute care settings, including treatment of patients in the ambulance or emergency room, prior to surgery, and in the home for chronic treatment.

RIC has the potential to revolutionise the treatment of ischemic-related reperfusion injury. In cardiovascular care, the potential impact may be similar to that of stents in the cath lab three decades ago.

CellAegis received CE Mark Certification for the autoRIC™ Device in July 2012, and Health Canada granted a Medical Device Class III license for its use in February 2013.

Please visit www.cellaegisdevices.com

Actellion Presented Additional Macitenan Data In Pulmonary Arterial Hypertension

On the 31st August 2013, Actelion Ltd announced that further data on its investigational drug macitentan (Opsumit®) from the SERAPHIN study would be presented at the European Society of Cardiology (ESC) Congress 2013 and at the European Respiratory Society (ERS) Annual Congress in Barcelona, Spain (7-11 September 2013).

At the ESC Congress 2013, this data was presented by Dr. Nazzareno Galiè from the Institute of Cardiology, University of Bologna, Bologna, Italy. This was an oral presentation entitled 'Sustained effect of macitentan, a novel oral endothelin receptor antagonist, on exercise capacity and the association of its measure with long-term outcomes in pulmonary arterial hypertension', and it was presented on September 1st at 11:00 during the session 'Advances in Drug Therapy for PAH'.

Dr. Adam Torbicki of the Department of Pulmonary Circulation and Thromboembolic Diseases, Center of Postgraduate Medical Education, ECZ-Otwock, Poland, also gave an oral presentation 'Effect of macitentan on haemodynamics in patients with pulmonary arterial hypertension: Results from the long-term, randomised, placebo-controlled SERAPHIN trial' at 11:15 on September 1st in the same session.

AMGEN®

Amgen Highlight Data on Omecamtiv Mecarbil and AMG 145

Amgen presented data at this year's ESC Congress to highlight their R&D efforts to develop novel treatments for urgent cardiovascular needs.

Amgen presented new data on omecamtiv mecarbil. This is a small molecule cardiac myosin activator that is being studied for the treatment of heart failure in collaboration with Cytokinetics.

Data presented on omecamtiv mecarbil included ATOMIC-AHF: Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure: Results from ATOMIC-AHF, Abstract 4503.

Data was also presented on AMG 145, an investigational human monoclonal antibody that inhibits PCSK9, a protein that reduces the liver's ability to remove low-density lipoprotein cholesterol (LDL-C), from the blood.

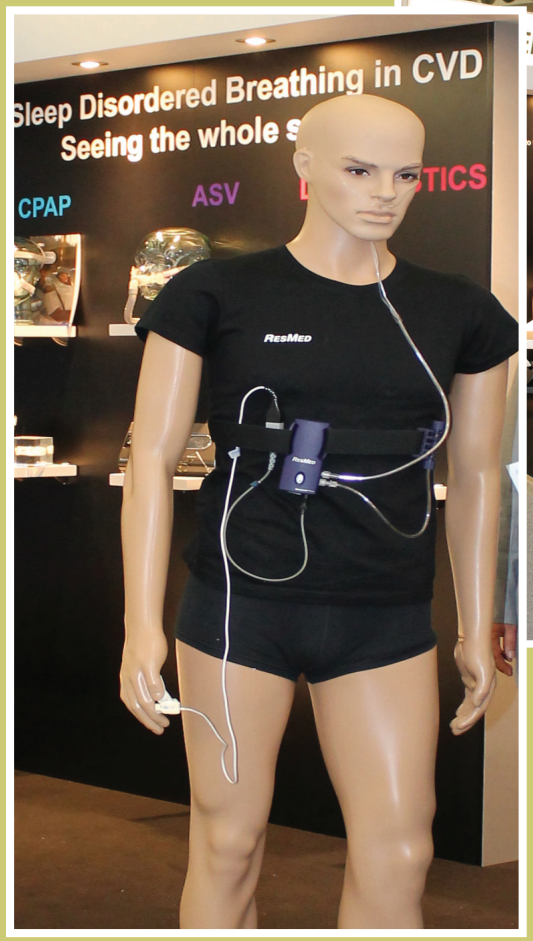
Data presented on AMG 145 included:
- Efficacy of AMG 145, a Fully Human Monoclonal Antibody to PCSK9: Data from 1252 Patients in Four Phase 2 Studies, Abstract 831.
- Safety of AMG 145, a Fully Human Monoclonal Antibody to PCSK9: Data from Four Phase 2 Studies in 1314 Patients, Abstract 683.
- Statin Therapy is a Major Determinant of PCSK9 Plasma Concentration: Data from Four Clinical Trials with AMG 145, Abstract P681.
- Intolerance to Statins and Response to PCSK9 Inhibition with AMG 145, Abstract P682.
- Safety, Tolerability, and Efficacy of Long-term Administration of AMG 145: Preliminary Results from the OSLER Study , Abstract P4182.

Amgen is establishing its presence in cardiovascular medicine and is committed to addressing difficult scientific questions, with the goal of advancing cardiac care and improving the lives of patients.

SERVE-HF; the World's Largest Study of Sleep-Disordered Breathing in Heart Failure Completes Recruitment

Results, expected in 2016, set to demonstrate the impact of effective treatment of central sleep apnoea on morbidity and mortality in a heart failure population

ResMed (RMD), is a leading developer, manufacturer and marketer of ground-breaking medical products for the screening, treatment and long-term management of sleep-disordered breathing (SDB) and other respiratory disorders. They are a pioneer and global leader in sleep and respiratory medicine. During the European Society of Cardiology Congress 2013, ResMed announced that SERVE-HF has completed enrollment. SERVE-HF is an international, randomised study of 1,325 participants which is investigating if the treatment of central sleep-disordered breathing (central sleep apnoea) improves survival and outcomes of patients with stable heart failure.



Approximately 14 million people in Europe are living with heart failure and central sleep-disordered breathing is known to be a highly prevalent comorbidity in these patients. With an estimated 30-50 percent of heart failure patients potentially at risk, the results from SERVE-HF may have important consequences for the future management of these patients.

"We owe much to the commitment and dedication of SERVE-HF investigators and to a strong collaboration between sleep specialists and cardiologists," said co-principal investigator, Prof. Martin Cowie of the Royal Brompton Hospital in London. "We now look forward to results in 2016 and to a fuller understanding of just how important the treatment of central sleep-disordered breathing is in heart failure patients."

For the first time SERVE-HF will provide conclusive evidence of the health impact of effectively treating heart failure patients who have central sleep-disordered breathing. The trial began in 2008 and has been sponsored by ResMed. Designed as an event-driven study, its completion is anticipated by mid-2015 and results are expected to be available in 2016.

Studies have demonstrated that patients with an abnormal waxing and waning breathing pattern, called central sleep apnoea with Cheyne–Stokes respiration (CSA-CSR), have a poorer quality-of-life and increased mortality. Between 30-50 percent of patients with heart failure may suffer from central sleep-disordered breathing, meaning that this condition likely applies to millions of patients across Europe living with stable heart failure. However, studies have so far indicated that treatment of CSA-CSR with PaceWave™ Adaptive Servo-Ventilation (ASV) during sleep normalises breathing, controls sleep-disordered breathing, improves cardiac function and may lead to increased survival and better quality-of-life.

For more information on ResMed, visit www.resmed.com

H-FABP
Biomarker of Ischemia

Randox, an international clinical diagnostics company, presented exciting products at ESC 2013, which included automated biochemistry assays for the biomarker of myocardial ischemia, Heart-type Fatty Acid Binding Protein (H-FABP).

H-FABP identifies a very high-risk group of patients who warrant further investigation and possible intervention. It is a biomarker of myocardial ischemia, detectable as early as 30 minutes from chest pain onset and can facilitate the earlier management of patients with suspected acute coronary syndrome (ACS), alongside Troponin. H-FABP is a low molecular-weight cytoplasmic protein that is involved in the intracellular uptake and buffering of free fatty acids in the myocardium. Its low molecular weight and cytoplasmic location enables H-FABP to be a highly sensitive early rise marker of ACS, H-FABP concentrations peak at approximately 6-8 hours and return to normal within approximately 24-30 hours. Although H-FABP has similar release kinetics to myoglobin, it is approx 15-20 times more cardiac specific, and a more effective marker of myocardial injury.

Cardiovascular disease (CVD) is responsible for over a large number of deaths each year and costs the global economy billions of dollars. One of the most common signs of CVD is chest pain, which leads to an estimated 5% of all visits to the Emergency Department and around 25% of all Emergency Department admissions. Often, the majority of patients attending hospital with chest pain do not actually have a cardiac-related condition, yet many are admitted and often receive a high level of cardiac care. Frequently, such patients are admitted as a precaution, because Acute Myocardial Infarction (AMI) could not be reliably ruled out, which reduces the risk of discharging patients from hospital with an unrecognised AMI. Patients with missed AMI also have a higher risk of a further adverse cardiac event.

In many cases, patients that are admitted stay longer than the initial 10-12 hours, and frequently stay longer than 24 hours. These kinds of extended hospital stays are a frequent cause of hospital overcrowding, as well as the addition to the potential complications that can be caused by a delayed patient diagnosis.

Distinguishing patients with ACS from the large proportion of patients with suspected cardiac pain remains a major diagnostic challenge for clinicians, especially in individuals without clear symptoms or electrocardiogram (ECG) features.

The early release mechanism of H-FABP following myocardial ischemia means that it is a highly effective biomarker in the diagnosis and management of patients with suspected ACS, especially when used in combination with Troponin.

The H-FABP test is a laboratory-based clinical chemistry assay and can be used on a wide range of commercial biochemistry analysers. It does not require any dedicated instrumentation or equipment to run.

Using a combination of H-FABP and Troponin has been shown to significantly improve the diagnostic sensitivity for MI/ACS during the early hours after symptom onset, compared to using Troponin alone. Prognostically, a number of large trials have illustrated the value of H-FABP in stratifying long-term ACS risk in both Troponin positive and Troponin negative patients. H-FABP has also be shown to be an incrementally additive to Troponin, diagnostically and prognostically, even when a highly sensitive Troponin assay is used.

H-FABP has been found to be clinically useful in a range of other applications, such as pulmonary embolism, coronary artery bypass surgery and cerebrovascular disease.

This is the worlds first CE marked automated chemistry assay for Heart-type Fatty Acid Binding Protein, a highly sensitive & specific marker of myocardial ischemia.

For more information please visit
www.h-fabp.com

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Telemonitoring Systems - custo kybe center

Custo med, is one of the leading suppliers of cardiopulmonary computer-aided diagnosis systems. They are the only company world wide to offer a unified platform for all cardiopulmonary examinations.

Custo Med showcased their custo kybe centre which is a part of their telemonioring system and includes: custo belt, custo guard and the software module custo kybe center.

Custo Kybe stores ECG data continuously over months, detects arrhythmia and sends these events to the custo kybe center automatically. The type of transmitted events can be freely configured via the custo kybe center. The patient can trigger the sending of an additional event by pressing a button. The system provides continuous sending of live ECG to the custo kybe center via the function ECG online streaming.

Data are transmitted via mobile telephone, USB or WLAN. When using the mobile telephone version, a direct communication with custo kybe user is possible by calling or by sending an SMS via the custo kybe center. The custo kybe is designed as a multi-parametric monitoring system and in addition to the ECG other sensors such as SpO, blood glucose and blood pressure will be integrated in the near future.

The medical operating system custo diagnostic is the intelligent link between medical technology and administrative software. The consistent design of the user interface allows working efficiently in all diagnostic modules. Via standardised interfaces medical data can be exchanged with the superordinate Hospital Information System in a bi-directional manner.

For more information please visit www.customed.de

Award Winning Automated External Defibrillators

Earlier this year Defibtech received the 2013 "Exporter of the Year" Award on Capitol Hill from ThinkGlobal Inc., publisher of Commercial News USA, the official export promotion magazine of the U.S. Department of Commerce.

Creator and manufacturer of automated external defibrillators (AEDs) Defibtech's product line includes the Lifeline™ and ReviveR™ families of AEDs, which the company were displaying at the ESC Congress 2013.

These AEDs treat sudden cardiac arrest, the most common cause of death worldwide. About 7 million people die worldwide from sudden cardiac arrest each year, most because an AED is not available to treat them. As a result an increasing number of AEDs are being placed in workplaces, schools, transportation hubs, public gathering areas, and other locations where large numbers of people congregate.

Defibtech's reliable, ground-breaking, easy-to-use, and affordable AEDs can be operated successfully by virtually anyone and have become a popular choice worldwide.

Symposia Highlights

Satellite Symposia

Stroke Prevention in AF 2013: Registry Insights and Perspectives

The GARFIELD (Global Anticoagulant Registry in the FIELD) Registry presentations at the ESC congress provided data outcomes on real-world treatment patterns of at-risk AF populations. One-year outcomes data from the first cohort of the Global Anticoagulant Registry in the FIELD (GARFIELD), an innovative, independent academic research initiative, provided insights into the elevated stroke risk among subpopulations of patients with atrial fibrillation (AF). The findings from eight abstracts presented at the ESC Congress 2013, collectively show that anticoagulant therapy, which is known to significantly lower stroke risk in AF patients, is consistently under-utilised among those at-risk AF patients.

GARFIELD is led by an international steering committee under the auspices of the Thrombosis Research Institute (TRI), London. It is an international, observational, multi-centre, prospective study designed to understand the global burden of AF, a common condition in which the two upper chambers of the heart (the atria) quiver rather than beat rhythmically and can lead to life-threatening complications, including stroke. Up to 2% of the population has AF. Despite the availability of highly effective preventive treatments, AF-related stroke remains a major and increasing clinical and societal burden.

"These 1-year data from GARFIELD illustrate that evidence-based stroke prevention guidelines are not always followed in everyday clinical practice," said Prof. The Lord Ajay Kakkar, Prof. of Surgery at University College London and Director of the TRI, London UK. "Taken together, these new findings re-emphasise what has been observed in clinical trials regarding stroke risk in AF patients. The research suggests there are opportunities to improve patient outcomes through more consistent application of best practice and adoption of the many innovative therapies to prevent stroke in high-risk AF patients."

The data presented at ESC Congress 2013 are from the first of five GARFIELD cohorts. The first cohort includes a total of 10,614 patients with non-valvular AF and at least one investigator-determined additional risk factor for stroke, recruited from 540 randomly-selected sites in 19 countries. Of these patients, 5,089 were recruited retrospectively as a validation cohort and 5,525 were recruited prospectively and comprise the study populations in these abstracts. ESC Guidelines for the management of atrial fibrillation recommend that all patients at high risk of stroke be prescribed anticoagulation therapy with vitamin K antagonists (VKAs), unless contraindicated. High stroke risk is defined as a score >/=2 on the CHA2DS2-VASc risk score. Previously reported baseline data showed that in Cohort 1, 82.6% of patients had CHA2DS2-VASc >/=2 but only 62% of these patients received anticoagulant therapy.

Data for the stroke-risk stratification research presented at ESC Congress 2013 were available in 5,523 patients enrolled prospectively between December 2009 and October 2011.

The 1-year data - which are preliminary and should be interpreted with caution - were included in one oral presentation and seven poster abstracts. The oral presentation was featured at the State of the Art: Acute Coronary Syndromes - Current Guidelines and Future Prospects, a session that spotlighted the four highest-rated abstracts in this topic.

Positive Phase III Results for New Anticoagulant Edoxaban

During the first Hot Line session of ESC 2013 on 1st September, Daiichi Sankyo released the first Phase III data for its novel oral anticoagulant, Lixiana (edoxaban), in any indication. Positive phase III results for this new anticoagulant have put the product firmly on course for regulatory filings early next year.

In the Hokusai-VTE trial, which studied the drug's effect in venous thromboembolism (VTE), the factor Xa inhibitor demonstrated superior safety and non-inferior efficacy versus warfarin in 8,292 patients with either acute symptomatic deep vein thrombosis, pulmonary embolism, or both.

The once daily, oral Factor Xa inhibitor was shown to be non-inferior to injectable warfarin for treatment and prevention of recurrent symptomatic venous thromboembolism (VTE) in the phase III trial, which was reported at the European Society of Cardiology (ESC) Congress.

Importantly edoxaban also outperformed warfarin on the principal safety measure in the study and was significantly less likely to cause clinically-relevant bleeding.

The results - which have simultaneously been published in the New England Journal of Medicine - set Daiichi Sankyo on track to file for approval of edoxaban in VTE by the first quarter of 2014 in the US, Europe and Japan, according to the company's global R&D head Glenn Gormley.

Edoxaban was first approved in Japan in 2011 under the Lixiana brand name for the prevention of VTE in patients undergoing orthopaedic surgeries, and is also in a phase III trial involving atrial fibrillation (AF) patients, with results due later this year.

The results of the phase III Hokusai-VTE study are largely in line with trials of other Factor Xa inhibitors in this setting. These drugs have been tipped as potential replacements for warfarin and, with their oral dosing and the fact that they do not require such close dose titration and monitoring making them suitable for out-of-hospital use, could open up a multi-billion dollar market.

However the success of this drug will be somewhat challenging, firstly due to the increasingly saturated market and also as it is anticipated to launch as the fourth-to-market novel oral anticoagulant and third-to-market oral factor Xa inhibitor in VTE.

Pradaxa® - Novel Oral Anticoagulant

At the ESC Congress 2013 new data provide evidence for the positive safety and efficacy profile of Pradaxa® in various atrial fibrillation patient populations

Boehringer Ingelheim presented new data on the novel oral anticoagulant (NOAC) Pradaxa® (dabigatran etexilate) during the ESC Congress 2013. The new data will add to the extensive body of knowledge already available on Pradaxa®'s positive safety and efficacy profile.

Data presented at the ESC Congress 2013 complemented the on-going clinical trial programme of Pradaxa®, including results from the pivotal RE-LY® trial and the only long-term NOAC study, RELY-ABLE®, as well as new preclinical research on the company's investigational antibody fragment antidote for dabigatran.

"The breadth of data being presented for Pradaxa® at this year's ESC Congress 2013 demonstrates Boehringer Ingelheim's continued dedication to improving the lives of patients with cardiovascular disorders. Our extensive and ongoing investment into clinical research will provide additional evidence on the positive efficacy and safety profile of Pradaxa® as well as important insights on its use in a wide range of patients and clinical settings", said Prof. Klaus Dugi, Corporate Senior Vice President Medicine, Boehringer Ingelheim.

Boehringer Ingelheim remains committed to advancing the cardiology field and supporting physicians in their search for optimal stroke protection.

Finding the Disease in Heart Failure Concept, Status and Path Forward

Philips unveiled the latest in a series of innovations aimed at helping cardiologists to improve patient outcomes and enhance clinical workflows at ESC 2013. Developed in close collaboration with leading cardiologists, Philips' new solutions span the entire continuum of care - from diagnosis to treatment and aftercare - through the deployment of advanced diagnostics, patient-centric informatics and advanced interventional imaging to guide minimally invasive interventions. Closely following the introduction of important innovations such as Philips' AlluraClarity low-dose interventional X-ray imaging system and EchoNavigator navigation tool, the new introductions at ESC 2013 are further evidence of Philips' commitment to working with cardiologists to transform cardiology together.

"Bringing meaningful innovation to healthcare across the continuum of care, in terms of clinical value, improved workflows, increased efficiency and cost containment, means working closely with clinical experts at the forefront of their field," said Deborah DiSanzo, CEO Philips Healthcare. "That makes ESC 2013 an ideal place not only to show the world's cardiac care specialists what we have achieved so far, but also to engage with them in helping to create the future of cardiology."

Philips' new EPIQ ultrasound platform, which was unveiled at ESC 2013, is the latest example of the integrated solutions that Philips is developing. For the first time, Anatomical Intelligence, a rich database of anatomic computer models and adaptive system technology, has been built into an ultrasound system, creating an "active" ultrasound device achieving exceptional clinical results in less time.

Gene Saragnese, CEO Imaging Systems at Philips Healthcare said "EPIQ is a perfect example of what you can achieve when you combine the latest technological developments with real user insights to move an imaging technology into a completely new level of performance."

Philips was showcasing several new products at ESC 2013 that demonstrated its 'Transforming Cardiology, Together' approach of engaging with cardiologists to identify user needs, addressing customers' top-of-mind, real-life issues and concerns.

ESC e-Learning Opportunities

The ESC e-Learning (ESCeL) platform is an online collaborative tool, aiming to deliver their curricula and facilitate the harmonisation of cardiovascular training across sub-specialties of cardiology. It is a tool dedicated to cardiologists in training as well as to experienced cardiologists. Tracks include; knowledge and skills; assessment; professional development; and the laboratory accreditation process.

Launched at ESC Congress 2012 in Munich, the ESCeL platform aims to provide the highest standard of training and education to as many cardiologists as possible at the lowest possible costs. 'Our idea is to harmonise training throughout Europe so that cardiologists receive the same quality of education regardless of where they're from,' explained Lino Gonçalves.

The ESCeL programme has evolved into an on-going project that is currently recruiting users. 'We're really excited that proof of concept has been established, showing that it's possible to deliver high standards of training and education and be both easily accessible and user friendly,' said Lino Gonçalves, leader of the ESCeL project. Such standardisation of training, he added, has been made even more important by recent EU directives on the free movement of patients and healthcare professionals throughout Europe, expected in 2014.

Each of the national Accreditation Authorities (NAAs) will need to take individual decisions over whether they wish to use the ESCeL platform as the basis for national cardiology training programmes or not. 'We do know that the NAAs are currently considering ESCeL as the basis for accreditation processes,' said Lino Goncalves. 'Some will find that the platform caters for all their national requirements, while others may choose to add in their own local requirements.'

Designed for flexibility each of the six ESC Associations having autonomy to supply their own content. 'Some Associations have chosen to utilise the full potential of the platform, with content on knowledge, practical skills, and professional assessments; while others have opted just to offer knowledge assessments,' said Lino Gonçalves.

Storming ahead is the EAPCI ESCeL programme, which went live in February 2013 and covers all three options. For the knowledge module a total of 48 courses are offered, covering seven topics corresponding to the seven chapters of the EAPCI core curriculum. For the skills module, participants are required to upload cases, and also keep procedural logbooks recording minimum numbers of procedures on a monthly basis and their experiences of patient safety issues. Additionally, trainees are required to undergo Direct Observation of Practical skills (Dops) at the beginning, middle and end of the programme, with local trainers specially appointed to evaluate their practical skills and other aspects such as how they interact with patients and other health professionals.

Finally, EAPCI trainees can opt to undergo '360 degree peer appraisal', where clinicians, nurses, and technicians evaluate different characteristics of their working style at the beginning, middle, and end of the programme.

THE HFA went live in May 2012, and has developed six highly interactive educational courses on various aspects of heart failure, including diagnosis, symptoms, diuretics, Ace inhibitors and ArBs, beta blockers, anaemia and iron deficiency, with more to follow.

The EAPCR, which launched in August 2012, now offers several courses on cardiovascular risk factors, rehabilitation and secondary intervention on the platform.

The ESCeL programme in general cardiology will be presented for the first time at this congress. 'This will be useful not only for trainees who want to become general cardiologists, but also for qualified cardiologists who want to keep updated' said Lino Gonçalves.

Future plans for ESCeL include linking the platform to the ESC Textbook and other educational resources, including ESC Guidelines, ESC Congress 365, webinars and clinical cases. Next spring, ESCeL version 2.0 will be introduced with innovative features such as facilities for translation and the possibility of introducing national educational products in parallel with those from the ESC.

Looking to the long term, the ESCeL platform plans to develop strong social networking capabilities, and evolve into a more personalised educational space.

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Ablation of Ventricular Tachycardias in Structural Heart Disease

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Introduction

Ventricular tachycardia (VT) is a potentially life-threatening arrhythmia. Pharmacological treatment can reduce recurrences of sustained arrhythmia, but it is associated with pro-arrhythmic reactions, frequent toxic effects and long-term adverse effects.[1]

Implantable cardioverter-defibrillators (ICDs) provide significant protection against the risk of sudden death;[2-4] however, they do not prevent arrhythmia recurrences or the occurrence of electrical storm (ES), which are independent predictors of cardiac mortality. Despite proven survival benefit, ICD treatment still has drawbacks, one of the most important being inappropriate shocks. The treatment with shocks has been associated to an increased cardiac mortality as an independent factor.[5-7] It is still to be remarked that a pooled analysis of all randomised ICD trials showed an ICD-unresponsive sudden cardiac death rate of 5%. Yet, despite 25 years of advances in ICD technology, the frequency of ICD-unresponsive SCD has not declined.[6,8]

These problems have prompted a search for alternative approaches to decrease recurrence of potentially lethal ventricular arrhythmias. Recent studies have shown the benefits of catheter ablation (CA) for VTs. In the VTACH trial,[9] CA was applied after the first tolerated VT episode, prolonging the time to VT recurrence and reducing its incidence, although no survival benefit was observed in the ablation group. Sauer *et al.*[10] reported a beneficial effect of CA on survival in patients according to CA result. The study showed that the presence of renal disease, poor left ventricular ejection fraction, advanced age, VT tolerance, and VT inducibility are independent mortality predictors. Notably, VT ablation performed after the year 2003 (with the implementation of electroanatomic mapping and irrigated radiofrequency technologies) was demonstrated to be more effective than those previously performed.

A recent study by our group[11] indicates that CA favourably affects VT recurrences, hospitalisation and survival in a large cohort of patients with VT. The study showed that a successful VT ablation procedure (defined as the achievement of non-inducibility of any VT at programmed ventricular stimulation after the ablation) decreased arrhythmia recurrences and cardiac mortality in the largest series of VT patients with structural heart disease up-to-date. We also supported CA as treatment for high-risk patients (ie patients with ES, hypotensive VT, chronically occluded left anterior descending coronary artery, chronic kidney disease, left ventricular ejection fraction ≤30%, severe pulmonary disease) who were not previously considered candidates for invasive therapy. The non-inducibility of index VT is not only acutely life-saving, but can also increase the patient's survival. The subsequent cardiac hospitalisation rate was also markedly decreased.[11]

This review will focus on the ablative treatment of VT using a substrate mapping approach in patients with structural heart disease.

Ablation Strategies for Ventricular Tachycardias

The majority of patients that suffer from VTs have an arrhythmia substrate defined by areas of ventricular scar. It can be the result of necrosis due to prior myocardial infarction (MI) in the setting of coronary artery disease (CAD), but it can also result from the replacement of myocardial tissue by fibrosis in nonischemic cardiomyopathy (NICM), previous myocarditis or surgical incisions.[12]

Re-entry is the responsible mechanism of most VTs in the context of structural heart disease. The re-entrant circuit components include at least an entrance site, an isthmus of slow conduction occurring through viable myocardial cells within the scar, and an exit site. Catheter ablation of VT relies on the identification of these critical components of the circuit, with the aim of interrupting the conduction of the impulse in crucial parts of the circuit.[12] Many strategies have been proposed to identify target ablation sites. Not only activation and entrainment mapping techniques performed during tachycardia, but also the more recent strategies of substrate mapping in sinus rhythm, are now currently used in many centres.

Conventional Strategies

Conventional mapping techniques are based on activation mapping and entrainment mapping during ongoing tachycardia. Activation mapping is based on the determination of local electrogram timing in relation to the QRS onset during tachycardia, allowing the acquisition of activation sequence maps. The zone of slow

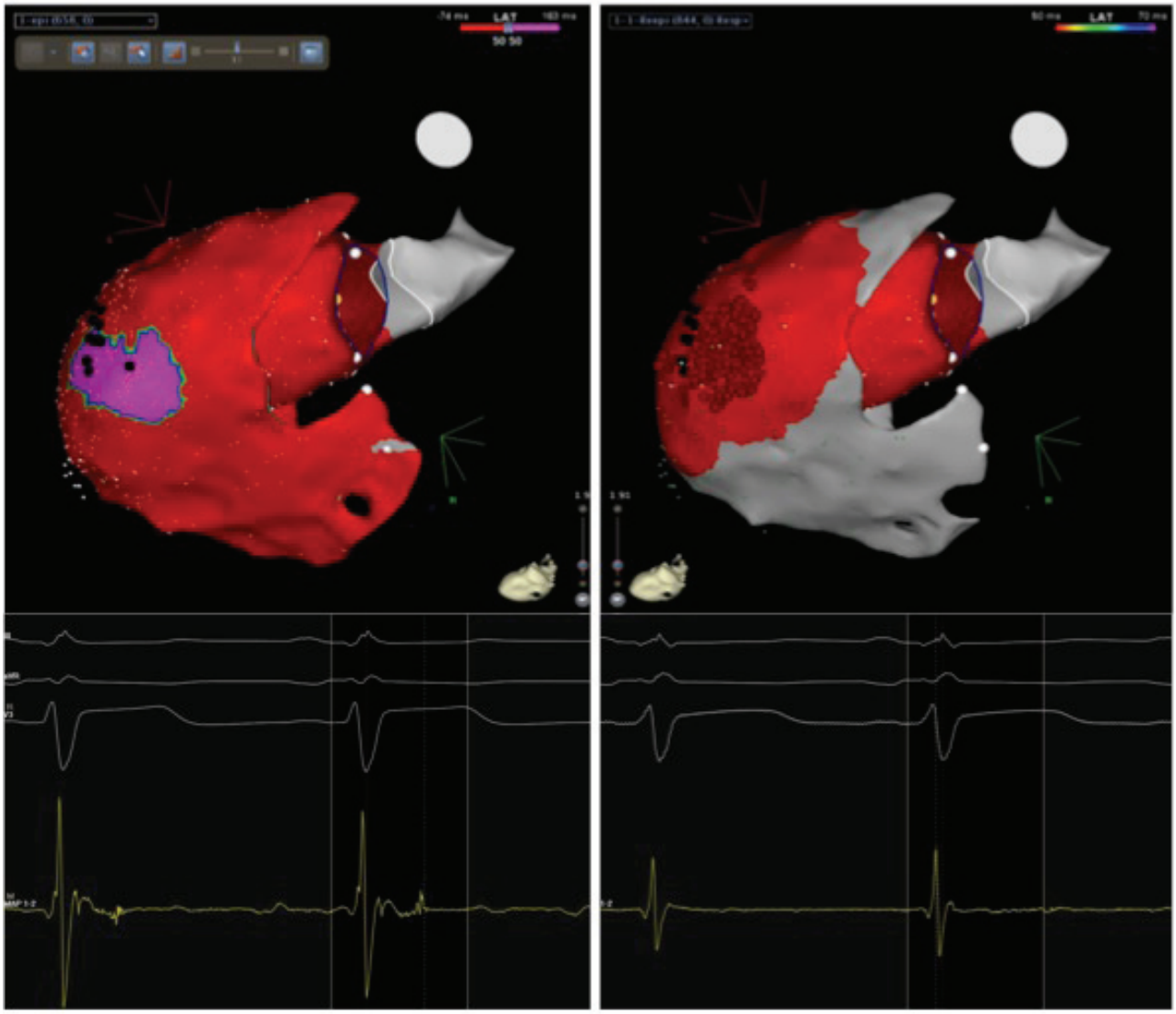

Figure 1. Endocardial and Epicardial electroanatomical late potentials localisation and demonstration of their disappearance after ablation. Basal mapping (left panel) showed a large area with late potentials (pink areas) in the epicardial surface of the left ventricular apex. Remap after the ablation (right panel) on the same geometry showed the complete disappearance of all late potentials previously mapped.

conduction can be identified by mid-diastolic potentials and the exit site by the earliest presystolic ventricular signal from the mapping catheter.[12] To distinguish these critical sites from bystanders, entrainment mapping with concealed fusion can be used as an electrophysiological manoeuvre. By measuring the post-pacing interval and the stimulus-QRS/electrogram-QRS interval,[13] one can prove that a slow-conducting area is critical to the circuit, if the former is within 30 ms of the VT CL and the latter is within 20 ms of the VT CL.

The prerequisite of mapping during ongoing tachycardia is an important limitation of conventional mapping techniques. Those techniques are not feasible if: 1. the clinical VT is not inducible with programmed ventricular stimulation; 2. the clinical VT is inducible but poorly tolerated or haemodynamically unstable, requiring cardioversion or defibrillation shock; 3. mechanical block of the induced VT by catheter manipulation occurs repeatedly during the procedure;[5] 4. inability to reproducibly induce the VT.[14, 15]

Some experiences have previously been published with the use of intra-aortic balloon pump or percutaneous haemodynamic support devices that, by improving systemic perfusion, could help to overcome those limitations; those techniques, however, are not applicable to all patients and require a multidisciplinary team with surgical back-up in experienced centres.[16]

Another important limitation of conventional techniques is their limited applicability in patients experiencing multiple VT morphologies.[8] Identification of all VT circuits requires extensive mapping in tachycardia. It is still debatable whether non-spontaneously occurring VTs should be targets of ablation or if ablation should mainly target the clinical occurring VT.[12]

Substrate Mapping Strategies

Substrate mapping strategies are based on the characterisation of the abnormal myocardial substrate in sinus rhythm by 1. careful identification of the scar area by voltage criteria and 2. targeting

abnormal electrograms suggesting slowing conducting myocardium.[17]

During voltage mapping in sinus rhythm "normal" ventricular myocardium is defined by bipolar endocardial voltage ≥1.5 mV and bipolar epicardial voltage ≥1 mV, "scar" by areas with a signal amplitude ≤0.5 mV, and the "border zone" as an area with a bipolar voltage 0.5-1.5 mV within the endocardium and 0.5-1.0 mV in the epicardium.[18] Several techniques have been proposed for substrate mapping ablation based on voltage criteria. Marchlinski *et al.*,[18] proposed the application of linear lesions extending from the dense scar to the normal myocardium or anatomic barriers, or at sites with a good pacemapping.[18] These linear ablation lesions along the infarct border zone were proved to be effective in controlling unmappable VTs. Less extensive ablation lesions were suggested by Soejima *et al.*;[15] short ablation lines were applied under the guide of short periods of entrainment mapping during VT or by pace mapping maneuvers. When an isthmus could be identified by entrainment mapping, persistence of VT inducibility was significantly inferior and shorter ablation lines where needed, comparing with pacemapping guided ablation.[15] Arenal *et al.*,[19] by stepwise reducing voltage cut-offs for scar definition from 0.5 to 0.1 mV, described a method to recognise conducting channels that corresponded to areas of higher voltage inside the scar. Transection of these channels by radiofrequency applications was able to suppressed VT inducibility in 88% of cases.[19]

Substrate Mapping Targeting Late Activity

Abnormal electrograms in sinus rhythm suggesting slow conduction have been recognised as possible targets of ablation.[17] In the era of surgical therapy for VTs, subendocardial resection of endocardial late potentials was associated to suppression of VT inducibility at programmed stimulation.[20] Later studies[21] showed that the presence of pathological signals (defined by amplitude <1 mV, duration ≥ 40 msec, and presence of more than four deflections), predicted a successful VT ablation site with 86% sensitivity and 94% specificity.[21] Recently, late activity has drawn a lot of attention. "Late potentials" are fractionated, low amplitude, multiple component electrograms occurring after the end of the surface QRS complex that can represent conduction on the reentry circuit isthmus.[22-24] Ablation in sites where LP were recorded in sinus rhythm, resulted in 84% freedom from VT recurrences.[24, 25] An LP-targeted ablation strategy was effective in both Ischemic Cardiomyopathy and non- Ischemic Cardiomyopathy patients.[26, 27]

Recently, LPs abolition was used as an additional endpoint to the VT ablation procedure[28] in 64 patients with CAD or idiopathic dilated cardiomyopathy. Electrical activity recorded after the off-set of the surface QRS in SR was tagged on the anatomical map of the left ventricle and the "late potential" colour-coded map obtained was then repeated after ablation to compare the location and extension of LPs areas, aiming at the complete late activity abolition[28] (Figure 1).

Inducibility at the end of the procedure was significantly lower (16%) in patients with complete than those with incomplete LPs abolition (62 %, $p < 0.01$). VT recurrence during a medium of 13 months follow-up period was also significantly lower (9.5%) in patients with complete than those with incomplete LPs abolition (75 %, $p < 0.0001$). Complete LPs abolition provided a higher sensitivity and positive predictive value than post-ablation inducibility on programmed stimulation.[28] Jais *et al.*[29] proposed the elimination of "local abnormal ventricular activities" (LAVAs) during SR or ventricular pacing as a useful end-point for VT substrate based ablation. LAVAs are sharp high-frequency ventricular electrograms distinct from the far-field ventricular electrograms, occurring anytime during or after the far-field ventricular electrograms in sinus rhythm or before the far-field ventricular electrograms during VT. The ablation targeting LAVAs using a Pentaray mapping catheter was performed in 70 patients with structural heart disease and LAVAs abolition was associated with a significant reduction in VT recurrence or death during a 22 months follow-up period.[29] The strategy of late or abnormal potential mapping in sinus rhythm and their complete abolition has thus proved to reduce VT recurrence and can additionally be used as an end-point for VT ablation procedures. Additionally, it actually allows an objective way of quantification of substrate modification.

Defining the Strategy

Currently no randomised studies have directly compared conventional mapping with substrate mapping techniques, and data is also lacking on the best method for substrate mapping. The success of VT ablation depends on the identification of the VT circuit components, that can be elegantly achieved with conventional EP activation and entrainment mapping during tachycardia if the tachycardia is stable and mappable.

Whenever VT inducibility in the EP Lab is not advisable or not obtained, substrate mapping techniques are helpful tools by allowing mapping and ablation to be performed in SR. Additionally, they provide the opportunity, not only to map the arrhythmogenic substrate in detail, but also to compare pre- and post-ablation substrate maps, allowing a complete evaluation of the substrate modification achieved. Targeting late activity and abnormal ventricular electrograms simultaneously with the construction of the voltage anatomical map, can direct the operator to a more selective and critical area of interest in patients with extensive scar areas. Eliminating slow conducting abnormal electrograms, even if bystander for a specific tachycardia, might eliminate other critical sites of additional circuits in patients with multiple VT morphologies.[23]

Substrate mapping during SR targeting late and abnormal activity has been shown to be a successful technique for VT ablation, since it was proved to reduce arrhythmia recurrences and mortality during the follow-up.

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Wire Tricks for PCI of Bifurcation Lesions

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Introduction

Coronary artery bifurcation lesions are encountered in up to 15–20% of all percutaneous coronary interventions (PCI).[1-6] Compared with simple lesions, bifurcations have been associated with lower procedural success rates, higher adverse event rates, longer procedures, and worse angiographic and clinical outcomes.[5-8] The less favourable outcomes associated with bifurcation treatment compared with non-bifurcation lesions may in part result from the inability of current devices and techniques to adequately scaffold and preserve the side-branch (SB) ostium, which is a common location of restenosis.[5, 6, 9]

Stenting using drug-eluting stents (DES) is currently the default approach to treat bifurcation PCI due to their superior angiographic and clinical outcomes as compared to bare metal stents (BMS).[10-14] Refinement of the various techniques used (high-pressure stent deployment or postdilatation, kissing balloon inflation, intravascular ultrasound guidance –IVUS-), better selection of lesions to be treated with a 2-stent technique, and deferral of treatment of SB ostial lesions with an angiographically suboptimal result after main branch (MB) stenting but functionally non-significant have led to even better outcomes, narrowing the gap with non-bifurcation PCI.[15] Bifurcation PCI with DES is associated with a higher stent thrombosis rate (ST).[5, 15-18] Contemporary randomised studies have shown that routine stenting of both branches offers no benefit over stenting of the MB only with provisional stenting of the SB,[1, 4, 5] making the provisional strategy the preferred approach. However, there are conditions where a more complex strategy of treatment might be needed.

Bifurcation Techniques

1-stent Techniques

"Keep it Open" Strategy

This strategy is employed when the SB is not suitable for stenting because of a small size or clinical insignificance, and has no severe ostial disease.[2] It is performed as follows: wire both branches and dilate the MB if needed but not the SB. Deliver and postdilate the stent in the MB with a properly selected high pressure balloon to adjust its diameter to the MB distal and proximal segments, leaving only the jailed wire in the SB for protection. Once this has been achieved and there is adequate flow in the SB irrespective of the ostial severity the procedure is considered complete. The side branch is not rewired or postdilated unless it develops symptomatic occlusion or slow flow.

Provisional Stenting

This strategy consists of implanting a stent in the MB first, only proceding to SB stenting if its appearance after MB stenting is considered suboptimal (Figure 1). Bifurcation lesions where the SB is suitable for stenting (expected diameter equal or greater tan 2.25 mm) and has minimal disease ("non-true" bifurcation) or significant disease but confined to the ostium or extending <5 mm from the ostium ("true" bifurcation) are tackled with this strategy. Generally, SB predilatation must be performed only if the lesion is very severe, angulated or highly calcified. However, it must be remembered that SB predilatation does not ensure SB rewiring and angiographic success. On the contrary, by avoiding SB predilatation we avoid carina shifting towards the SB ostium, which increases the chances of recrossing the SB through a distal strut (carina cell), thereby facilitating optimal ostial SB scaffolding after kissing balloon dilation.[19] SB predilatation may also lead to ostial dissections and subintimal wiring of the SB.

An optimal proximal MB stent expansion and apposition with Proximal Stent Optimisation (POT) prevents the wire from passing outside the proximal MB stent during wire exchange. If the result in the SB is satisfactory (stenosis<75% or fractional flow reserve [FFR]>0.80),[20] then the procedure is complete. In case the result in the SB is suboptimal, rewire the SB and remove the jailed wire only when recrossing has been completed. A final kissing inflation (FKI) can then be performed

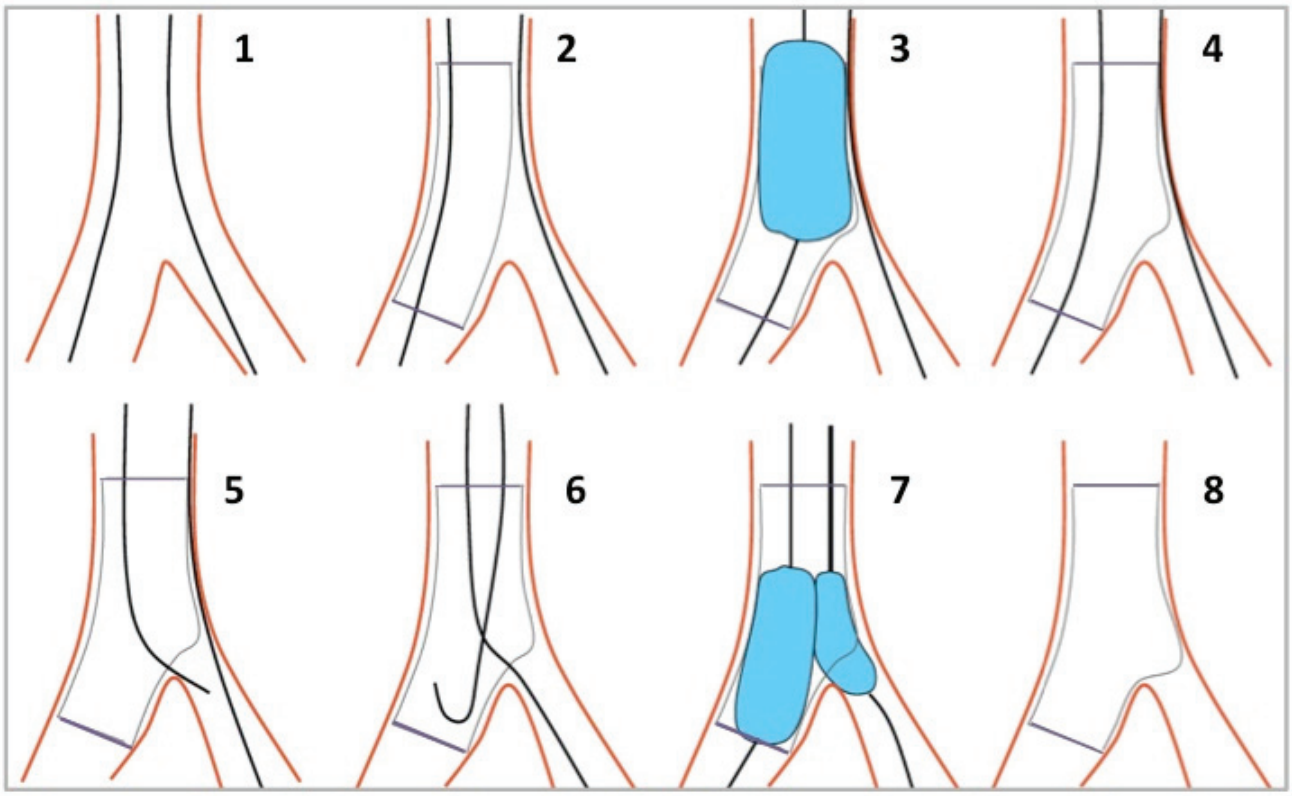

Figure 1. Provisional stenting strategy procedural steps. 1. Wiring of both branches; 2. Predilatation of MB and stenting the MB; 3. Proximal optimisation technique; 4. Stent apposition; 5. Recrossing MB guidewire through the most distal strut; 6. Jailed wire in SB removed and placed in distal MB with a loop; 7. Final kissing inflation; 8. Final result (if SB result is not satisfactory, T stenting, TAP, inverted crush or culotte strategies can be performed) (Adapted from reference 9).

with a moderate pressure in the SB. The MB balloon is then inflated to correct the MB stent deformation caused by the dilation of the SB ostium. If the result in the SB is still suboptimal (>75% residual stenosis and/or TIMI flow <3, FFR <0.75, flow-limiting dissection, abrupt vessel closure) proceed with SB stenting. A T-stent or T-And-Protrusion (TAP) technique is most frequently used, although culotte, and reverse or internal crush may also be employed (see below for a description of these techniques).[2, 5, 21]

2-stent Techniques

Evolution of the Treatment of Bifurcations

Currently, bifurcation PCI with two stents is mainly performed as a crossover from a provisional strategy in the case of a suboptimal result in a large-sized SB (abrupt closure, flow-limiting dissection, >75% stenosis, TIMI flow <3). Bifurcations involving large-sized SBs with severe disease extending beyond the ostium or originating at steep angles are not likely to be treated optimally with a one-stent technique. It is estimated that approximately 30% of true non-left main bifurcation lesions encountered in every day practice warrant treatment with a two-stent technique.[15, 22, 23]

A two-stent strategy as an intention to treat should be considered in "true" bifurcations (Medina 1.1.1, 1.0.1, and 0.1.1)[24] (Figure 2) when a significant SB is involved (>2.5 mm, large amount of myocardium subtended, disease extending >5 mm from the ostium).
It is estimated that approximately 70% of true non-left main bifurcations are currently being tackled with a provisional stenting approach.[5] However, it should be noted that the comparison of single versus complex strategies is often limited, as complete randomisation is difficult and a high cross-over rate is generally observed between groups. Such bias is induced in almost all bifurcation studies, with operators selecting a 2-stent approach in more complex lesions while treating simple lesions with 1-stent.

Conventional 2-stent Techniques

Culotte, Crush and SKS

Culotte and crush techniques have been designed to provide complete scaffolding of the SB and the MB. These techniques are usually employed for large SB (>2.5mm) with relatively low take off-angles since SBs with a 90 degree angle are easily treated with a classical T approach.[25] In the culotte technique, a first stent is deployed in one of the branches, usually across the most angulated of the two, which is most often the SB. The second branch is then rewired through the strut of the first stent and dilated with a non-compliant balloon. The second stent is implanted followed by FKI.

In contrast, using the crush technique a stent is first positioned in the SB and retracted to protrude in the MB (>5 mm in the classical crush or 1-2 mm in mini-crush). The protruding portion of the SB stent is then crushed against the wall by deployment of the MV stent or dilatation with a NC balloon. The procedure needs to be completed with the rewiring of the SB and FKI post-dilatation. Rewiring is made

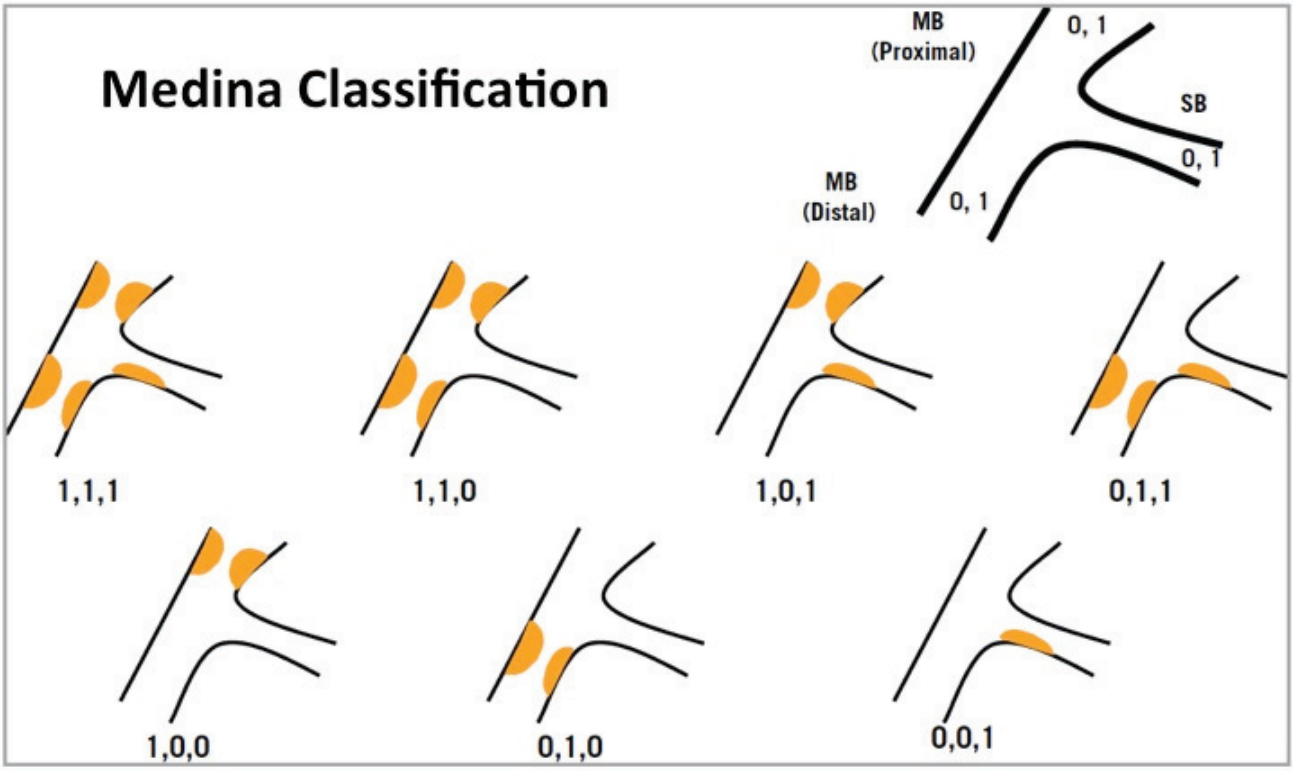

Figure 2. Classification for bifurcated lesions proposed by Medina A *et al*. Adapted from reference 22.

difficult by the presence of three layers of struts, and *in vitro* and clinical studies suggest that this technique takes advantage from a further step of crushing the first stent with a balloon, doing a first kissing dilatation and then proceeding to the final stent implantation and FKI. This complex technique requires more steps than culotte and has more limited anatomical applications, explaining why the crush technique is rarely used nowadays.

In the Nordic stent technique study (Randomised Comparison of Coronary Bifurcation Stenting With the Crush Versus the Culotte Technique Using Sirolimus Eluting Stents), a total of 424 patients with a bifurcation lesion were randomised to crush (n=209) and culotte (n=215) stenting. At 6 months there were no significant differences in major adverse cardiac event rates between the groups. Both the crush and the culotte bifurcation stenting techniques were associated with similar MACE: 4.3 % in crush and 3.7 % in culotte (P=0.87). Angiographic in-stent restenosis of main vessels and/or side branches after 8 months, however, were higher in the crush group and were found in 12.1% versus 6.6% (P=0.10) and in 10.5% versus 4.5% (P=0.046) in the crush and culotte groups, respectively.[26]

In the recent CACTUS study (Coronary bifurcations: Application of the Crush Technique Using Sirolimus-eluting stents), a randomised prospective trial comparing crush stenting to provisional T-stenting in true bifurcation, Colombo *et al*. found that angiographic restenosis rates were not different between the crush and the provisional group with respectively 4.6 % and 6.7 % restenosis in the main branch (p=ns) and 13.2 % and 14.7 % restenosis in the SB.[25] MACE rates were also similar with 15.8% in the crush group versus 15% in the provisional stenting group (p=ns).

Another technique for complex bifurcation treatment is the Simultaneous Kissing Stent (SKS) technique. Both SB and MB stent are deployed either simultaneously or sequentially to form a double-barrel stent with a neocarina in the MB. Such technique has the advantage of not requiring the recrossing of the stent, but SKS technique raises concern over the potential risk of stent thrombosis induced by the long

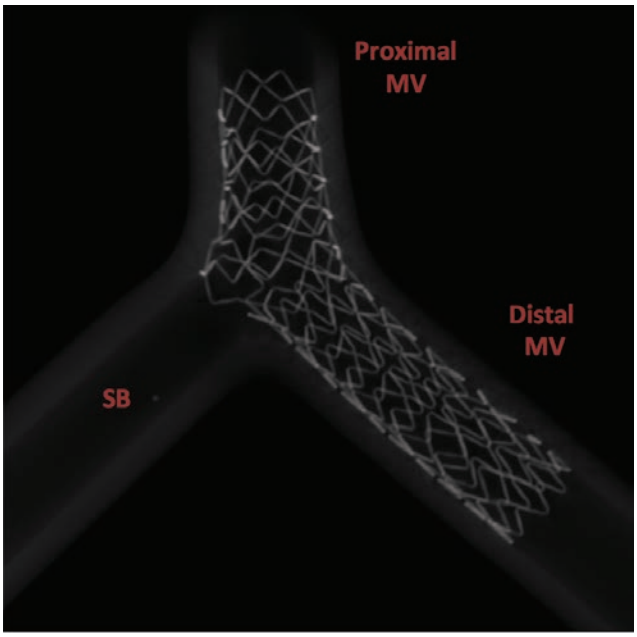

Figure 3. 3D micro-CT reconstruction of a 3.0 Biomatrix® stent deployed in the MB of the bifurcation after POT and FKI.

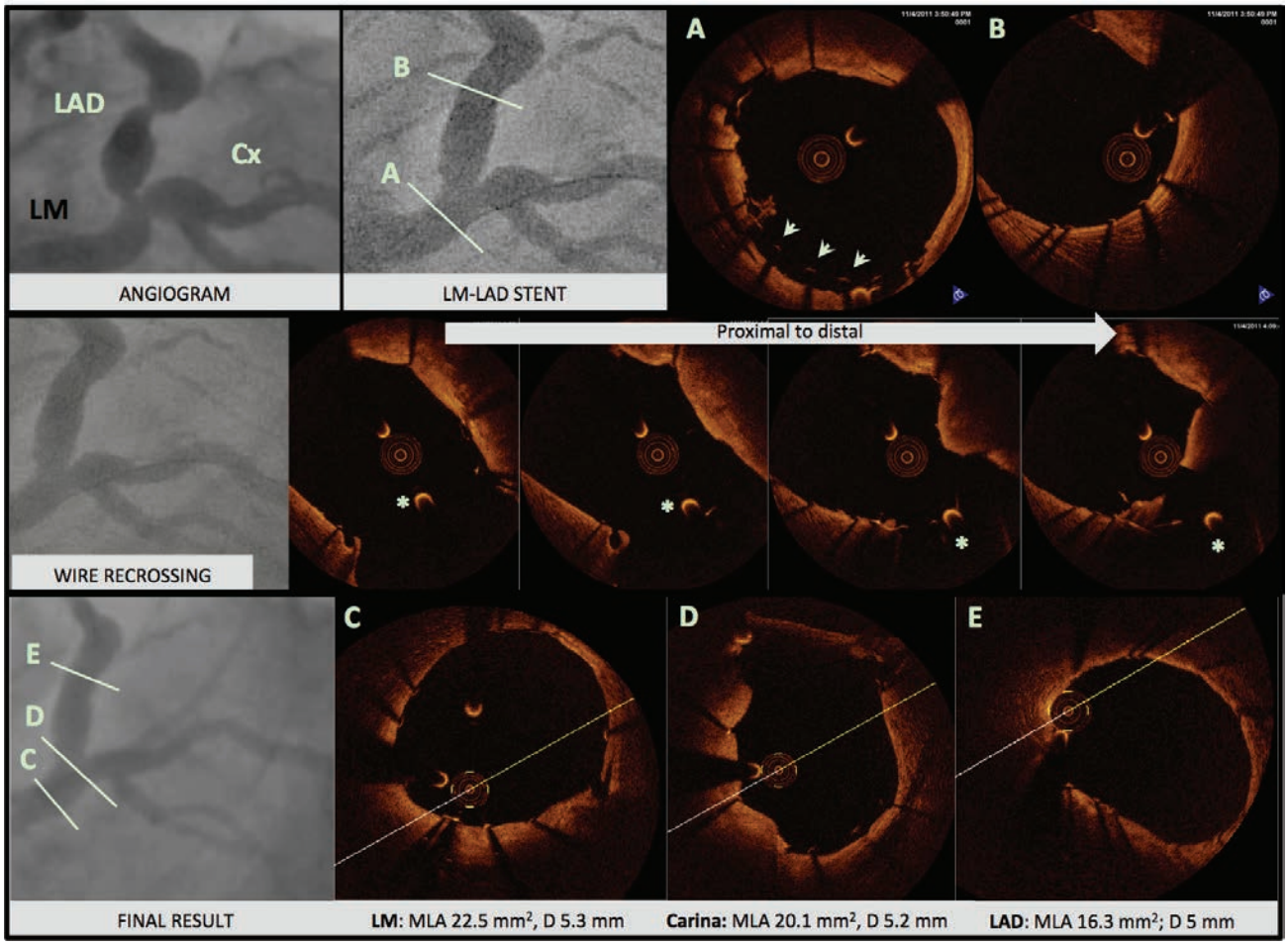

Figure 4. OCT guidance of bifurcational stenting. The images belong to a 62 years-old male, hypertensive, hypercholesterolemic patient, complaining of exertional dyspnoea. Upper panel: left caudal angiographic view of a bifurcated lesion involving the distal left main (LM) (Medina 0,1,0), before and after stenting the MB with a 4.0 x 38 mm Resolute Integrity stent (Medtronic) and postdilated with a 4.5 mm NC balloon. Optical coherence assessment revealed significant malappositoin in the left main (A) and good apposition in the proximal left anterior descending (LAD). Then, left main was postdilated with a 5.0 NC balloon. Medium pannel: OCT assessment of guidewire recrossing. Consequtive "proximal-to-distal" OCT frames demonstrating optimal distal cell recrossing with the guidewire into the side branch (left circumflex, LCx). Lower pannel: final assessment of bifurcational stenting after final kissing inflation with 4.5 mm (LAD) and 4.0 mm (LCx) NC balloons. Good apposition was documented at the level of the LM (C), carina (D) and proximal LAD (E). MLA, minimal lumen area; D, diameter.

double neocarina in the MB.

T and TAP

In the classical T-stenting technique, a stent is implanted in the SB up to the SB ostium. A second stent is then deployed in the MB and the procedure is completed by FKI. It is a popular approach for wide angle (>70°) T-shaped bifurcation because it provides coverage of the SB with minimal stent protrusion in the MB.

For an angle of less than 70°, the T-stenting technique is limited by the gap in scaffolding at the SB ostium. A popular adaptation of the T-stenting that offers good strut coverage at the expense of a predictable increase of malapposition of the ostium is the T-and-protrusion technique (TAP). The SB stent is advanced and left with a minimal protrusion (1-2 mm) into the MB. The aim of the TAP technique is to provide a full continuity of scaffolding between the MB stent and the SB stent. Good clinical results have been observed with TAP-technique and long term TLR rate as low as 6.8% have been reported.[2] The main limitation of TAP remains the risk of misplacing the SB stent and producing a neocarina, extensively protruding in the MB lumen.

Wire Tricks for Bifurcation PCI

Certain anatomical conditions increase complexity when treating bifurcation lesions, such as extreme vessel tortuosity, extreme angulation of the origin of the SB or severe stenosis of both MV and SB. Those conditions increase the rate of failing while trying to wire both MV and SB, leading to procedural failure.

Difficulties accessing SB are common. Critical steps during bifurcation PCI face potential difficulties avoiding "under stent" rewiring, accessing the best strut (distal) or even difficulty to cross the strut with the balloon after rewiring.

Proximal Optimisation Technique

Proximal postdilatation of MB stent ensuring optimal apposition of the stent significantly enables a correct rewiring of the MB. Moreover, distal strut deformation of the MB stent facilitates and optimises SB access

for FKI.[28, 29] It should always be performed when experiencing trouble rewiring or advancing the balloon (Figure 3).

Following a provisional stenting strategy, after MV stenting adjusting size to distal MV diameter, proximal postdilatation with bigger balloons adjusted to proximal MV diameter (preferably non-compliant) ensure correct apposition of the stent struts in the proximal segment.

Wire-control Catheters

Wire-control catheters are steerable deflectable-tip (up to 90º) devices that can be useful to access the SB in complex bifurcation lesions with unfavourable anatomy, specifically sharp angulated SB uptake. They can be advanced to the lesion in its straight configuration and then the tip can be deflected and rotated, orientating the guidewire towards the SB, providing with excellent support.

Ojeda S *et al*.[30] reported the use of a wire-control catheter to access difficult side branches after conventional techniques have failed. In 85% of the patients, the catheter led to the success of the procedure with no complications.

OCT Guidance

Optical coherence tomography (OCT) is a high resolution intravascular imaging tool used to assess coronary lesions and evaluate the results of stenting. In particular, OCT allows accurate assessment of the position of stent struts overlying the SB ostium.[31, 32] For example, final kissing balloon inflation (FKI) is a widely recommended final step for the majority of bifurcation stenting strategies. It requires a wire recrossing into the SB, which can be performed within several stent cells overriding the SB ostium. Wiring a proximal stent cell leads to incomplete scaffolding of the stent/s at the origin of the SB and the displacement of multiple struts, which remain malapposed near the carina, potentially increasing the risk of stent thrombosis. OCT can easily demonstrate that an appropriate guidewire recrossing into the side branch through a distal cell has been achieved, leading to proper stent scaffolding in the carina (Figure 4).[18, 33, 34]

Reversed Wiring Technique

When dealing with very complex side branch access, advanced wiring techniques may be needed. Kawasaki T *et al*.[35] described a technique that aims to access highly angulated SB. Insertion into the guiding catheter requires the disconnection of the "Y-shaped" connector and the manipulation of the guidewire to obtain a 180-degree bend 2-5 cm proximal from the tip. Thus, the guidewire advances completely folded into the coronary artery distally to the bifurcation. Then, it is withdrawn smoothly to point towards SB origin. Additional support might be needed and soft-tip mother-in-child catheters have been successfully used in this setting.[36]

Szabo Technique

When SB is stented first ("S" strategies),[37] optimal ostial coverage is critical. Szabo and colleagues described an anchoring technique to accurately position an ostial stent without relying on conventional angiographic landmarks.[38-40] Despite its potential, the complexity of the technique and recent reviews[40] suggesting incomplete ostial coverage and stent deformation, it is rarely used nowadays.

Conclusions

Although provisional stenting is the current recommended strategy for bifurcated lesions, "true" bifurcation lesions (Medina 1.1.1, 1.0.1, 0.1.1) with long stenosis in the side branch cannot be successfully treated by provisional approach in all patients. Complex rewiring techniques may facilitate the achievement of optimal results in adverse anatomical conditions.

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Circulatory Support in Cardiogenic Shock: Complicating Acute Coronary Syndromes

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Introduction

Cardiogenic shock (CS) can be defined as the inability of the heart, due to impaired pumping function, to provide adequate blood flow to meet resting metabolic demands.[1] Patients therefore have evidence of reduced cardiac output (CO) and tissue hypoxia despite preserved intravascular volume. If haemodynamic monitoring is available, CS can be defined as an elevated arteriovenous oxygen difference, a cardiac index below 2.2l/m^2 and a pulmonary capillary wedge pressure >15mmHg. The diagnosis is usually made on clinical grounds with evidence of reduced cardiac output and organ perfusion manifested as altered mental status, cold, clammy extremities and oliguria.[2] It is important that left ventricular (LV) dysfunction is confirmed and non-cardiac causes of shock, such as hypovolaemia, are excluded.

CS has many aetiologies, however it is most commonly caused by LV failure following an acute coronary syndrome (ACS). When cardiogenic shock is suspected in the absence of significant left ventricular impairment, there should be a high index of suspicion for mechanical complications of an acute coronary syndrome (ACS) (Table 1). Without intervention, progression of CS is rapid and fatal.[3]

The initiating event in CS is nearly always new or worsening LV dysfunction, which is usually severe. This dysfunction sets up a downward spiral of events with worsening coronary flow, exacerbation of myocardial ischaemia and further reduction in CO. This low CO state leads to organ hypoperfusion and the initiation of complex neurohormonal pathways. Catecholamines are released along with elevated levels of vasopressin and angiotensin II, which have the net effect of peripheral vasoconstriction leading to an increased afterload state, salt and water retention with exacerbation of pulmonary oedema. It is well recognised that many patients have an ineffective change in systemic vascular resistance (SVR) with normal or even low SVRs.[4] This inappropriate vasodilatation may be a secondary systemic inflammatory response syndrome (SIRS) initiated by the ACS itself. This is a particularly catastrophic physiological state to be in as organ perfusion is further impaired and intestinal vasodilatation leads to gut ischaemia, bacterial translocation and subsequent sepsis.[5] Many patients with inappropriate vasodilatation are resistant to catecholamines and vasopressin may be the most effective vasopressor in this scenario.[6]

CS complicates approximately 5% of ACS[7] and there is evidence that the incidence has fallen over the last 10 years. This declining incidence over time is likely to be multifactorial due to improved pharmacotherapy, patient monitoring and most importantly the widespread adoption of early revascularisation. Despite rapid advances in the management of ACS, the in-hospital mortality rate remains unacceptably high, ranging from 47.9% to 59.4%.[8] Hospitality mortality is significantly lower in patients who undergo revascularisation and those who had CS on presentation as opposed to those who developed CS during their hospital admission.[7, 9]

Management

Key to the management of CS is rapid diagnosis and treatment before myocardial and other organ damage is irreversible. The cause should be identified and precipitants and confounding factors should be treated (such as anaemia, arrhythmias and vasodepressor drugs). Once the diagnosis of CS complicating ACS has been made, management should simultaneously focus on myocardial revascularisation and the optimisation of cardiac output and organ perfusion.

Myocardial Revascularisation

Emergency revascularisation in CS complicating AMI is the only intervention with robust randomised evidence of a prognostic benefit. This evidence comes from the seminal SHOCK trial, which randomised 302 patients to emergency coronary revascularisation (PCI or CABG) or initial medical stabilisation. The trial did not meet its primary endpoint of 30-day mortality, however at 6-months follow-up there was a significant difference in mortality (50.3% vs. 63.1%, p=0.027).[10] This difference in mortality persisted at 6-years follow-up, at which time almost two-thirds of hospital survivors with cardiogenic shock who were treated with early revascularisation were alive six years later, equating to a 13.2%

• Ventricular septal rupture
• Left ventricular free wall rupture
• Papillary muscle rupture and mitral regurgitation
• Right Ventricular Failure

Table 1. Mechanical Complications of AMI.

absolute and 67% relative improvement in six-year survival compared with initial medical stabilisation.[11]

Despite the well-established benefit of emergency revascularisation in CS, the choice of single vs. multi-vessel PCI is not clear. The majority of patients with CS have multi-vessel coronary artery disease (MVD).[12] MVD is more likely to induce global myocardial ischaemia, LV dysfunction and has been associated with worse long-term outcomes.[13, 14] Multi-vessel PCI has therefore been proposed as a strategy in the treatment of CS, however currently there is only registry data to supports its use, and there is a pressing need for a randomised control trial.[12]

Circulatory Support

In parallel to myocardial revascularisation, restoration and maintenance of adequate organ perfusion (including myocardial perfusion) via circulatory support is essential. It is important to note that organ perfusion and the prevention of tissue hypoxia are not only dependent on adequate CO but also on appropriate mean arterial pressure (MAP). Cardiac power output (CPO) is the product of simultaneously measured CO and MAP divided by the conversion factor of 451 to give the output in Watts. CPO provides a measure of cardiac hydraulic pumping ability and represents the energy input that the arterial system receives from the heart at the level of the aortic root.[15, 16] CPO has been shown to be the strongest haemodynamic indicator of mortality in patients with cardiogenic shock.[17] The myocardium in CS is invariably ischaemic and beyond myocardial revascularisation it is theoretically possible to strive for further "myocardial protection" through improving the mismatch between myocardial oxygen supply and demand. Myocardial contraction in systole impedes coronary blood flow and as a result the majority of coronary flow occurs in diastole. Diastolic flow is determined by the MAP and left ventricular filling pressures. Hence an increase in MAP and reduction in LV filling pressures would lead to improved coronary blood flow and myocardial oxygen supply. Modifiable determinants of myocardial oxygen demand include heart rate, preload and afterload. LV unloading leads to a reduction of preload and hence myocardial oxygen demand.

Circulatory support falls into two categories; pharmacological (inotropes and vasopressors) and mechanical support. Inotropes and vasopressor therapy are rapidly available and can quickly improve systemic haemodynamics, and as such are almost invariably used in the management of CS. Their use is not without drawbacks, as they increase myocardial ATP consumption and hence lead to increased myocardial oxygen demand, potentially exacerbating the already ischaemic myocardium.[18] Furthermore they are associated with an increased frequency of ventricular arrhythmias, contraction band necrosis and infarct expansion.[19] Inotropic and vasopressor support have not been shown to improve outcomes in randomised studies and may in fact lead to worse outcomes.[20-23] Many patients who develop cardiogenic shock may have pre-existing LV dysfunction and as such may have been prescribed negative inotropes and vasodilators such as angiotensin converter enzyme inhibitors (ACE-I), beta-blockers, morphine and nitroglycerin. These agents may cause further deterioration in haemodynamics and should be withheld until the resolution of shock.[24-27]

Mechanical Circulatory Support

Like pharmacological circulatory support, mechanical support aims to restore cardiac output to adequate levels and improve organ perfusion, but also aims to provide myocardial protection. In recent years an increasing number of devices have become available each with their own unique advantages and disadvantages (Table 2).

The intra-aortic balloon pump (IABP) is the most widely used mechanical circulatory support device has been used in clinical practice for over 40 years.[28] Physiological studies have demonstrated that the IABP acutely improves systemic haemodynamics, augments coronary flow, reduces myocardial oxygen demand and can sustain coronary patency following percutaneous revascularisation.[29-31] These sound physiological principles and a historical lack of alternative percutaneous devices has led to the widespread use of the IABP despite a paucity of adequately powered randomised evidence to support their use.

Until recently, evidence for IABP use in ACS complicated by CS came from the meta-analysis of cohort studies of this population. Strikingly this meta-analysis observed marked heterogeneity in the effect estimates of IABP therapy between the thrombolysis and the primary PCI studies. The overall effect estimate in the thrombolysis cohorts favoured IABP therapy, whereas the overall effect estimate in the primary PCI cohorts disfavoured IABP therapy.[32]

The IABP-SHOCK II was the first large randomised trial of IABP use in cardiogenic shock.[33] This multicentre, open-labeled, randomised study enrolled 600 patients with acute myocardial infarction (with or without ST-elevation) with cardiogenic shock, if early revascularisation was planned. Patients were randomised in a 1:1 ratio to intra-aortic balloon counterpulsation (IABP group) or no intra-aortic counterpulsation (control group). The primary study endpoint, 30-day all cause mortality, occurred in a similar proportion of the IABP and control groups (39.7% and 41.3%, relative risk with IABP 0.96, p=0.69), by an intention to treat analysis. The IABP-SHOCK II trial represents a real achievement to randomise 600 patients with CS, however it is not without some limitations. The mortality rate was

Strategy	Therapy/ Device	Mechanism	Advantages	Disadvantages
Medical Therapy	Inotropes	↑Contractility ↑HR	Ease of use Non-invasive	↑Myocardial oxygen consumption ↑Mortality
Counterpulsation	IABP	Diastolic pressure augmentation Systolic afterload reduction	Ease of use Availability ↓PCWP ↑Coronary flow	No active flow, relies on innate cardiac function Minimal impact on systemic haemodynamics
Extracorporeal bypass heart pump	Tandem Heart	LA to Aortic flow	↑CO ↑MAP ↓HR ↓EDP	Requires septal puncture Indirectly unloads LV
	ECMO	RA to Aortic flow	↑CO ↑MAP	↑Preload and afterload ↑Myocardial oxygen consumption
Intracorporeal transvalvular heart pumps	Impella devices	LV to Aortic flow	↑CO ↑MAP ↓HR ↓EDP ↑Coronary flow	Impella 5.0 requires surgical cut-down

Table 2. Adapted from reference 54. LA = left atrium, RA = right atrium, HR = heart rate, CO = cardiac output, MAP = mean arterial blood pressure, EDP = end diastolic pressure, IABP = Intraaortic balloon pump, ECMO = extracorporeal membrane oxygenation, PCWP = pulmonary capillary wedge pressure.

lower than anticipated and hence the study was underpowered for its primary endpoint. There was a crossover rate over 10% and as such the results of the intention to treat analysis are harder to interpret, and a treated analysis may be informative.

As suggested by IABP-SHOCK II, IABP therapy may not provide any clinical benefit in CS, particularly in those patients with the most severe shock. As stroke volume and blood pressure fall the IABP becomes progressively less effective as it can only augment and not generate flow.[34] This is where the percutaneous left ventricular assist devices may provide additional benefit over the balloon counterpulsation.

Currently, three percutaneous devices are commonly used, Impella (Abiomed Europe GmbH, Aachen, Germany), TandemHeart (Cardiac Assist Inc, Pittsburgh, Pennsylvania, USA) and extracorporeal membrane oxygenation (ECMO). These devices differ significantly with respect to mechanism of haemodynamic support, insertion technique and potential complications.

The Impella Recover System (Abiomed Europe GmbH, Aachen, Germany) is a recently-developed device designed for short-term circulatory support,[35] with encouraging clinical results in terms of feasibility of use and limited complication.[36-42] The Impella is a microaxial rotary flow device incorporated on a pigtail catheter and can be deployed percutaneously via a retrograde approach into the left ventricle (LV). The most distal end of the device is a 6F pigtail catheter that assists in stabilising the device once in the left ventricle. Proximal to the pigtail catheter is an inlet that has four openings that allow blood to be entrained into the cannula. The entrained blood passes through the cannula to the outlet that is positioned within the aorta where it is expelled. Three versions of the Impella exist providing increasing levels of circulatory support (Impella 2.5, CP and 5.0). They are driven by an electric motor and controlled from an external console.

Based on its operating principle, the major haemodynamic benefits of the Impella are generally promoted as direct LV unloading, improvement of coronary perfusion and increase in cardiac output.[43] Possibly because of its recent introduction in the clinical environment, there is limited hemodynamic data available during Impella support. These data support the notion of improved diastolic LV function, with decreased end-diastolic aortic pressure and end-diastolic wall stress and increased LV compliance.[44] With respect to coronary haemodynamics, initial data is supportive of improved coronary perfusion.[45]

The first direct comparison of Impella with IABP randomised 26 patients with cardiogenic shock secondary to AMI to either Impella or IABP. The primary endpoint was change in cardiac index (CI) at 30 minutes. The change in CI at 30 minutes was significantly greater in the Impella group however 30-day mortality was 46% in both groups. This study was the first to show that the use of Impella in patients with AMI complicated by cardiogenic shock is safe, feasible and leads to improved haemodynamics compared to IABP.[46] To date no study powered for hard endpoints comparing IABP to Impella exists in the CS population. The Danish Cardiogenic Shock trial is currently recruiting patients with ACS complicated by CS treated with Impella CP vs. conventional circulatory support. The primary end-point is all cause at 6 months.

The TandemHeart is a type of extracorporeal bypass pump that can

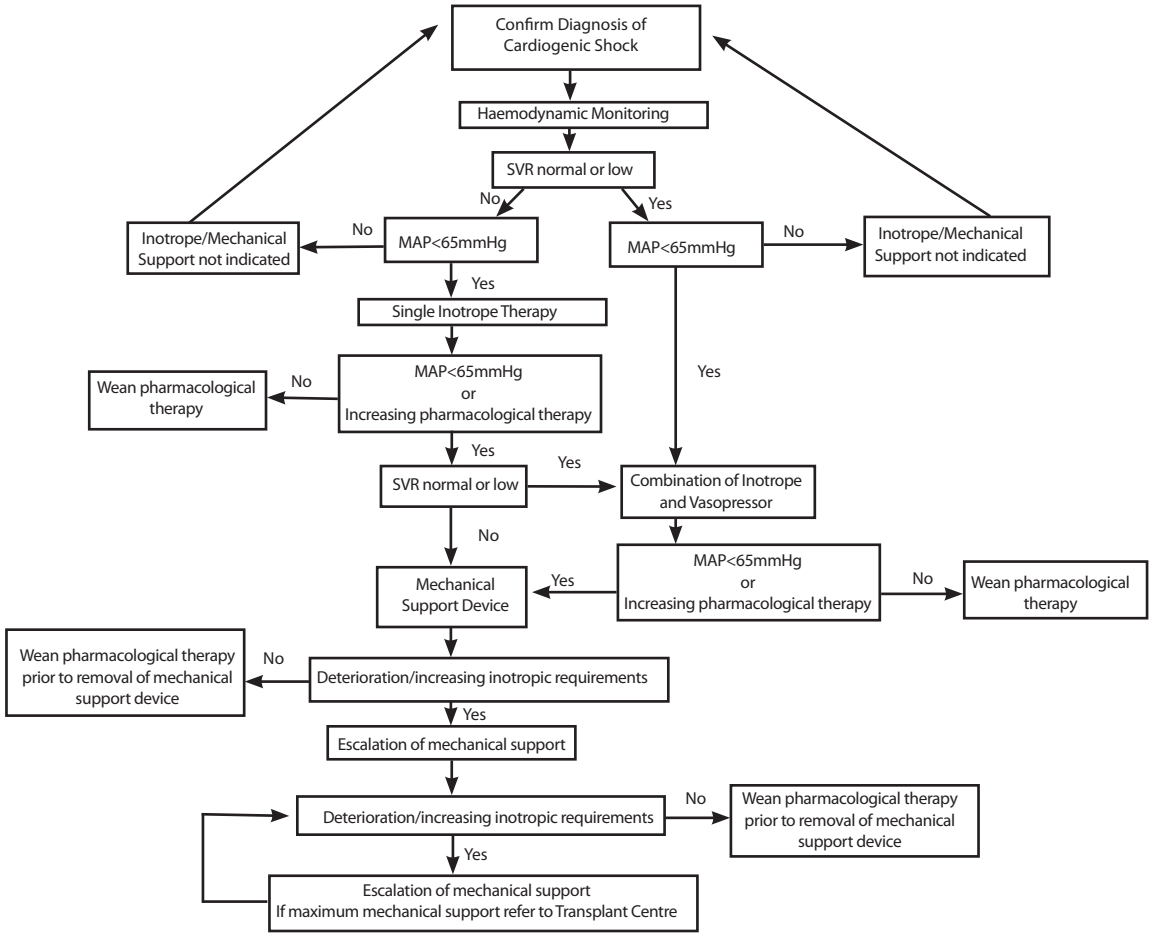

Figure 1. Suggested algorithm in the management of cardiogenic shock. SVR = systemic vascular resistance, MAP = mean arterial pressure.

be inserted percutaneously in the catherisation laboratory. The inflow catheter is inserted into the femoral vein and passed into the right atrium and finally into the left atrium via a puncture of the atrial septum. The outflow catheter is positioned via the femoral artery at the level of the aortic bifurcation. It is a continuous centrifugal pump that can deliver a flow rate of up to 4l/min powers the device. This is comparable to the Impella CP, although insertion is considerably more complex and as a result non-emergent insertion times exceed 30 minutes on average.[47] The transseptal puncture requires the operator to be experienced in this technique and carries the additional complication risk of cardiac tamponader and residual atrial septal defect (ASD). The TandemHeart has been shown to augment MAP and CO leading to a substantial increase in CPO.[48] The TandemHeart only indirectly offloads the LV and may increase LV afterload, and hence does not provide the same theoretical myocardial protective effects of the Impella devices.[19, 49]

TandemHeart has been shown in 18 CS patients to augment MAP while producing marked reductions in left ventricular end-diastolic pressure, stroke work, and resultant myocardial oxygen demand.[48] Direct comparisons of TandemHeart to other devices are scarce and, to date, there have been two small randomised trials comparing the TandemHeart with IABP in patients presenting with CS complicating AMI.[50, 51] Both studies demonstrated marked improvements in haemodynamic parameters although were not powered to assess impact on mortality.

Extracorporeal membrane oxygenation (ECMO) circuits consist of a centrifugal pump, membrane oxygenator and a circuit consisting of inflow and outflow cannulae. It is the only means of mechanical support that is also able to oxygenate the blood and hence may have a unique role in cardio-respiratory failure. Additionally, the right ventricle is bypassed and it may also have a role in biventricular failure. The inflow cannula is positioned in the right atrium via the femoral vein and the outflow catheter is placed in the descending aorta via the femoral artery. Depending on the cannulae size, flow rates of up to 4.5L/min can be achieved. Although ECMO is able to augment MAP, CO and CPO it does not directly offload the LV and in fact leads to increased preload and afterload. As a consequence myocardial oxygen consumption is increased.[52] ECMO has never been compared to the IABP or to any other percutaneous ventricular assist device (VAD) in a randomised setting, although retrospective comparisons have been performed. ECMO appears feasible to perform in CS of multiple aetiologies including complicating ACS.[53] ECMO has been associated with significantly higher blood product requirements and had a higher

incidence of thromboembolic complications. This may be secondary to the activation of inflammatory and clotting cascades induced by extracorporeal blood circuit.

Conclusion and Future Perspective

Progressive advancement in the management of ACS and most importantly the widespread adoption of early revascularisation has lead to a falling incidence of CS. Despite this, mortality remains unacceptably high. Currently there is surprisingly little outcome-based randomised evidence to guide the treatment of this complex condition. Early intervention with PCI is essential, however the role of single vs. multivessel PCI remains unresolved, and there is a pressing need for a randomised trial to assess this. The correct means of circulatory support is also unclear. There is substantial evidence that high doses and multiple inotropic and vasopressor agents worsen prognosis and these drugs should be minimised. Following this rationale the early introduction of mechanical support in CS complicating AMI is advised. At present none of the available percutaneous support devices have outcome data to support their use. Without this evidence it is difficult to be prescriptive with respect to which device is preferential. A decision on the choice of percutaneous circulatory support device should depend on operator experience as well as the individual patient. Both TandemHeart and ECMO can deliver similar flow rates of up to 4l/min. This was superior to the original percutaneous Impella 2.5 device that could only 2.5l/min. The Impella CP is now available and can deliver flow rates of up to 4l/min. The Impella devices directly unload the LV leading to a reduction myocardial afterload and hence, a theoretical reduction in myocardial oxygen demand with simultaneous improved systemic haemodynamics and coronary flow. ECMO should be considered in those patients with cardio-respiratory failure or biventricular failure. The recent IABP SHOCK II trial serves to highlight some of the inherent difficulties of enrolling and conducting a randomised trial in this incredibly high-risk cohort of patients. Despite these difficulties it is imperative that investigators continue outcome based research if we are to see a substantial reduction in mortality. Mechanical support has a firm physiological rationale for its use not only to support the systemic circulation but also to improve myocardial oxygen supply and demand mismatch. With the progressive refinement of percutaneous VADs and reduction in complication rates, they are likely to play an increasingly integral role in the management of CS in the future.

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Advanced Echocardiographic Tools for Early Detection of Chemotherapy-induced Cardiotoxicity

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Introduction

In the last few years, there has been important progression in cancer treatments, which has led to a significant reduction of morbidity and mortality of several types of cancer. The therapeutic management of patients with cancer includes multiple combinations of chemotherapy, radiotherapy, and surgery. However, many of these treatments can cause cardiovascular complications such as heart failure (HF), myocardial ischemia/infarction, hypertension, thromboembolism, and arrhythmias.[1, 2] Chemotherapy-induced cardiotoxicity is a rising concern for both cardiologists and oncologists. Therefore, identifying these effects is crucial to the successful management of cancer patients with cardiovascular complications. Current approaches to surveillance are often inadequate to detect myocardial disease, which can delay medical therapy and lead to symptomatic HF. Newer echocardiographic techniques have enhanced the capability at detecting cardiotoxicity at an early stage. The purpose of this review is to summarise the current state of echocardiographic assessement of cardiac toxicity induced by chemotherapy.

Types of Chemotherapy-induced Cardiotoxicity

Anthracyclines (Doxorubicin, Daunorubicin, Epirubicin, Idarubicin) and trastuzumab are the most commonly used antineoplastic drugs with known cardiotoxicity.[2] Cardiac toxicity can be divided into four types: acute, sub-acute, chronic and late-onset.[3] Acute complications are frequently observed after the first administration of high doses, in elderly patients, and are usually associated with few symptoms or may be asymptomatic, resolving spontaneously in hours or weeks. Sub-acute cardiotoxicity is rare, appears several days or weeks after the last dose of drug and is frequent manifested as pericarditis or myocarditis. Chronic cardiotoxicity is observed in patients exposed to repeated doses of chemotherapy and occurs several weeks or months after chemotherapy (within 1 year following treatment). It usually manifests as congestive HF due to left ventricular (LV) dysfunction and has a poor prognosis. Finally, late cardiotoxicity is diagnosed at >1 year following treatment, and may be manifested clinically as HF, arrhythmias and conduction abnormalities, but has a more favourable prognosis.

Electrocardiography

Electrocardiography is traditionally used as support in cardiotoxicity and is the final stage in clinical examination, however the electrical abnormalities found are often non-specific.[1, 2] Increased QT-interval dispersion has recently been found to be a predictor of acute HF after cyclophosphamide therapy.[1, 2]

Biomarkers

Natriuretic peptides have been used for the non-invasive assessment of LV function. Increased levels are produced mainly in response to LV wall pressure and volume overload, and are strongly related to symptoms, cardiac events and mortality.[3-5] In the setting of chemotherapy, however, data regarding the use of natriuretic peptides for monitoring are inconclusive.[3, 4] Although widely used in current oncology studies, their clinical value remains unproven.

Cardiac troponin is a powerful biomarker for the sensitive and specific detection of cardiac injury arising from various causes. Elevations of serum troponin levels have also been reported after chemotherapy, indicating myocardial damage and predicting

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subsequently subclinical and clinical cardiac morbidity and mortality.[3, 6, 7] The place of troponin and its clinical value in patients receiving anticancer drugs is also controversial.[3]

Conventional Echocardiography

The most appropriate method of assessing chemotherapy-induced cardiomyopthy is transthoracic echocardiography, which can measure cardiotoxicity in a quantitative, non-invasive manner. Standard echocardiography evaluates the global cardiac function. Recently, cardiotoxicity was defined as a reduction of LV ejection fraction (LVEF) of ≥5% to <55% in patients with symptoms of HF, or an asymptomatic reduction of the LVEF of ≥10% to <55%.[8] LVEF has been traditionally used in the assessement of the cardiac impact of chemotherapy, but its limitations require an identification of better measurement techniques.[3, 9-14] LVEF is susceptible to changes in loading conditions and has limited test-retest reproducibility. Deteriorations in LVEF represent a relatively late stage of systolic impairment, after the myocardium has exhausted its considerable functional reserve.[8] Despite its feasibility, LVEF is not sensitive enough to reveal subclinical or regional myocardial dysfunction.[13]

More recently, it has been established that HF can result from abnormalities of diastolic function, where LVEF is relatively preserved. Analysing patients who had developed cardiotoxicity, several authors reported that from conventional Doppler parameters, only isovolumic relaxation time (IVRT) showed significant prolongation after the initiation of chemotherapy.[14, 15] Parameters of diastolic function (transmitral early/late diastolic velocity ratio, IVRT, pulmonary venous flow pattern, etc.) can be easily measured with reasonable accuracy, but are highly sensitive to any change in the circulatory system and, thus, rather unspecific for cardiotoxicity evaluation.[3]

It has not been clearly established whether the LV diastolic dysfunction always precedes the systolic impairment or *vice versa*. Therefore, it seems reasonable to evaluate both systolic and diastolic function. Myocardial performance index, an accurate marker of global LV function, may be particularly useful here since it appeared significantly altered in patients receiving chemotherapy.[16, 17]

Advanced Echocardiographic Tools for Early Detection of Cardiotoxicity

Tissue Doppler Imaging (TDI) has emerged as a complementary method to standard echocardiography, as it is able to assess the velocity of LV segments. Published data regarding the utility of TDI to detect cardiotoxicity are contradictory. Early changes are more pronounced for most TDI measurements compared with standard Doppler or LVEF evaluation.[19] An IVRT on the mitral annulus below 80 ms, soon after the completion of chemotherapy, proved to be a good predictor of late LVEF impairment.[19] Recent studies reported that systolic mitral annular velocity (S') showed significant reduction during the first few months of treatment.[10, 18] Fallah-Rad noted that only S' was able to identify all patients who developed cardiomyopathy during chemotherapy.[10] In contrast, Tassan-Mangina *et al*.[19] reported that after 1-3 months of chemotherapy, only early diastolic mitral annular velocity decreased, while changes in S' occurred later. On the other hand, in patients under chemotherapy, significant early deteriorations were observed in TDI derived strain and strain rate without a significant reduction in LVEF and myocardial velocity measurements.[3, 9]

With technical improvements in the temporal and spatial resolutions of two-dimensional (2D) echocardiography, the myocardial deformation and rotation can now be measured using 2D-strain imaging. Tissue deformation is evaluated by a frame-by-frame tracking of individual speckles throughout the cardiac cycle. It requires lower frame rates (40–70 frames/second), is relatively angle independent and appears to be more reproducible.[20] 2D-strain technique can evaluate LV deformation in 3 planes (longitudinal, radial and circumferential strain). Recent reports showed that early decrease in LV global radial strain,[3, 10, 12, 13] global longitudinal strain (GLS)[3, 11-13] and twist (LVtw)[14] might be useful in detecting subclinical myocardial damage due to chemotherapy, earlier than conventional measurements (including 2D LVEF and 3D LVEF). As suggested by Sawaya *et al*.,[11] the superiority of the 2D-strain analysis over LVEF could be explained by the regional pattern of the chemotherapy-induced cardiotoxicity (in the early stages the function of some myocardial segments may compensate for others, leading to a preserved LVEF) and by the lower variability (especially in the longitudinal dimension).

LV function results from the contraction and relaxation of helically oriented myofibres.[21] GLS reflects LV long-axis function and is controlled predominantly by subendocardial fibres, while LVtw reflects the rotational LV deformation and is related predominantly to the subepicardial fibres.[21, 22] In drug-induced cardiotoxicity, both myocardial layers are damaged[22] as a consequence of titin (the largest protein and integral part of the myofilament system) degradation via the activation of calpains, which contributes to myofilament disorganisation.[14] These observations suggest that a precise assessment of LV function must take into account both rotational and longitudinal deformation. A recent study demonstrated that a newly combined parameter represented by the product of GLS and LVtw (GLS×LVtw) is able to unmask the small subclinical changes in myocardial deformation, with a better accuracy than other TDI and 2D-strain parameters,[23] before any LVEF decrease. This new index may help target patients who could benefit from closer cardiac monitoring, earlier initiation of cardioprotective medical therapy, or less anticancer drugs. The measurement using 2D-strain imaging requires off-line analysis, which is time consuming and involves additional training and expertise. Two dimensional-strain imaging itself continues to be

refined to overcome the actually limitations for clinical practice. Three-dimensional strain imaging will probable simplify the calculation of this combined index.

Conclusions

Transthoracic echocardiography and particularly TDI and 2D-strain imaging can be considerably valuable for the early detection of LV dysfunction induced by anticancer therapies. Myocardial deformation identifies preclinical myocardial dysfunction earlier than conventional measurements in patients undergoing treatment with antineoplastic therapy. Two dimensional-strain technique holds great promise for improving early detection of subclinical myocardial dysfunction due to chemotherapy, but further research is warranted in order to determine its role in this important clinical setting.

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Prognostic Role of Left Ventricular Dysfunction Evaluated by Two-dimensional Speckle Tracking Analysis

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Introduction

Estimating left ventricular (LV) systolic function in patients affected by cardiovascular diseases plays a key role in optimising therapeutic strategies. As a consequence, one of the earliest applications of clinical echocardiography was the detection of parameters able to provide a reliable measure of left ventricular size and function. Among the different echocardiographic parameters that have been proposed, the calculation of left ventricular ejection fraction (LVEF) is the measure most widely used for this aim.[1] Its relevance is even more evident in the management of patients affected by chronic heart failure (CHF), for which it is indispensable for diagnosis, prognostic stratification and therapeutic guidance.[1] However, LVEF has a number of limitations, such as the relevant intra- and inter-observer variability, the dependence from quality of imaging and from loading conditions.[2] Indeed, several alternative measures have been proposed over the last 20 years,[2] most of which are based on the analysis of longitudinal LV systolic function. Among these, the parameters obtained by two-dimensional (2D) speckle tracking analysis[3-5] seem to be particularly promising.

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Two-dimensional Speckle Tracking Echocardiography

Two-D speckle tracking is a technique which analyses conventional gray-scale B-mode recordings by tracking myocardial speckles, i.e. natural acoustic markers generated by the interaction between ultrasound beam and myocardium, frame by frame during the cardiac cycle.[4] The analysis of speckles movements provides information about the entity (strain) and the rate of myocardial deformation (strain rate). Two-D speckle tracking method has been validated by sonomicrometry and tagged magnetic resonance imaging[3] and, in comparison to strain analysis derived by tissue Doppler approach, it is characterised by fewer criticisms such as angle dependency, noise interference and intra- and inter-observer variability.[5]

Segmental and global strain measures of LV function can be obtained by analysing the three different directions of myocadial deformation, i.e. longitudinal, radial and circumferential myocardial deformation. However, when compared to circumferential and radial strain, the measure of evaluating global longitudinal strain (GLS) offers some advantages. First of all, it seems more reproducible. In fact, the evaluation of circumferential and radial strain needs a fixed short-axis tracking, which is not easily obtainable considering that LV shortens from base to apex with systole.[5] However, this limitation does not influence longitudinal tracking, which moves with the base to apex motion.[5] Moreover, GLS provides information about subendocardial longitudinal fibers that are considered the most vulnerable in many disease processes and whose deterioration is earlier than that observed for mid and epicardial fibers, whose function is reflected by radial and circumferential strains.

GLS: From the Assessment of Myocardial Dysfunction to Prognosis

Different studies have demonstrated the ability of GLS in more accurately detecting mild myocardial dysfunction in the presence of hypertension, diabetes, severe aortic stenosis, ischemia and in both

First author (year)	Clinical setting	Number of patients	Strain measures	End-points (mean follow-up)	Results	Cut-off proposed
Stanton T (2009)[9]	Unselected patients	546	GLS	- All-cause mortality (Follow-up 5.2-1.2 years)	Independent association with death	GLS > -12%
Dahl JS (2012)[10]	Aortic stenosis	125	GLS	- Composite end-point (cardiovascular mortality and cardiac hospitalisation due to worsening of heart failure) - Cardiovascular mortality. (Follow-up up to 4 years)	GLS was the only predictor of major arrhythmic cardiac events in multivariate model	-
Munk K (2012)[11]	Acute myocardial infarction	162	GLS	- Composite end-point (all-cause mortality, hospitalisation for cardiac cause, outpatient clinical visit for CHF) (Follow-up median 24 months)	Independent association of GLS in predicting events	GLS > -10% for highest risk group
Bertini M (2012)[12]	Chronic ischemic cardiomyopathy	1060	GLS	- Composite end-point (all-cause mortality and heart failure hospitalisation) - All-cause mortality (Follow-up 31months)	Independent association of GLS in predicting events	GLS > -11.5%
Sarvari SI (2012)[13]	Heart transplantation	176	GLS	1-year mortality	GLS was the only non-invasive predictor of death	-
Cho GY (2009)[14]	ADHF	201	GLS GCS	- Composite end-point (readmission for heart failure, and cardiac death) (Follow-up: 39±17 months)	Independent role of GCS but not of GLS in predicting events	GCS > -10.7%
Mignot A (2010)[15]	CHF patients	147	GLS	- Composite end-point (ADHF hospitalisation and death for cardiac events) (Follow-up 12 months)	- Independent role of GLS in predicting events - Greater GLS ROC curve than LVEF	GLS > -7%
Nahum *et al.* (2010)[16]	CHF patients	125	GLS GLSR	- Composite end-point (cardiovascular death, hospialisation and cardiac transplantation or mechanical support) (Follow-up 283 days)	- Independent association of global systolic strain with events	GLS > -9%
Iacoviello *et al.*[17]	CHF patients	308	GLS GLSR	- All cause mortality, cardiovascular mortality and/or heart transplantation and major ventricular arrhythmic events (follow-up of 26 ± 13 months)	Independent association of global systolic strain and strain rate with all the considered events	GLS >-10%

Table 1. Studies evaluating longitudinal strain prognostic role. GCS: Global circumferential strain; GLS: global longitudinal strain; GLSR: Global longitudinal strain rate. LVEF: left ventricular ejection fraction.

left and right ventricular cardiomyopathies.[6-8]

Moreover, as summarised in Table 1, over the last few years the possible role of 2D strain measures as prognostic markers in several clinical conditions has been shown, i.e. in unselected patients,[9] in patients undergoing transcatheter aortic valve replacement,[10] in patients with acute myocardial infarction[11] and chronic ischemic cardiomyopathy,[12] in patients who have undergone heart transplantation[13] and in heart failure patients.[14-16]

In a recent study, we have further demonstrated the relevance of GLS in stratifying chronic heart failure (CHF) patients prognosis by evaluating, for the first time, its role in predicting death, all of the events related to heart failure progression (cardiovascular death, heart transplantation, hospitalisation due to acute decompensated heart failure) and the occurrence of ventricular arrhythmic events.[17] We studied 308 CHF patients who had shown LVEF < 45% at the time of diagnosis, who were in a stable haemodynamic status, and who were receiving conventional medical and electrical therapy. As shown in the

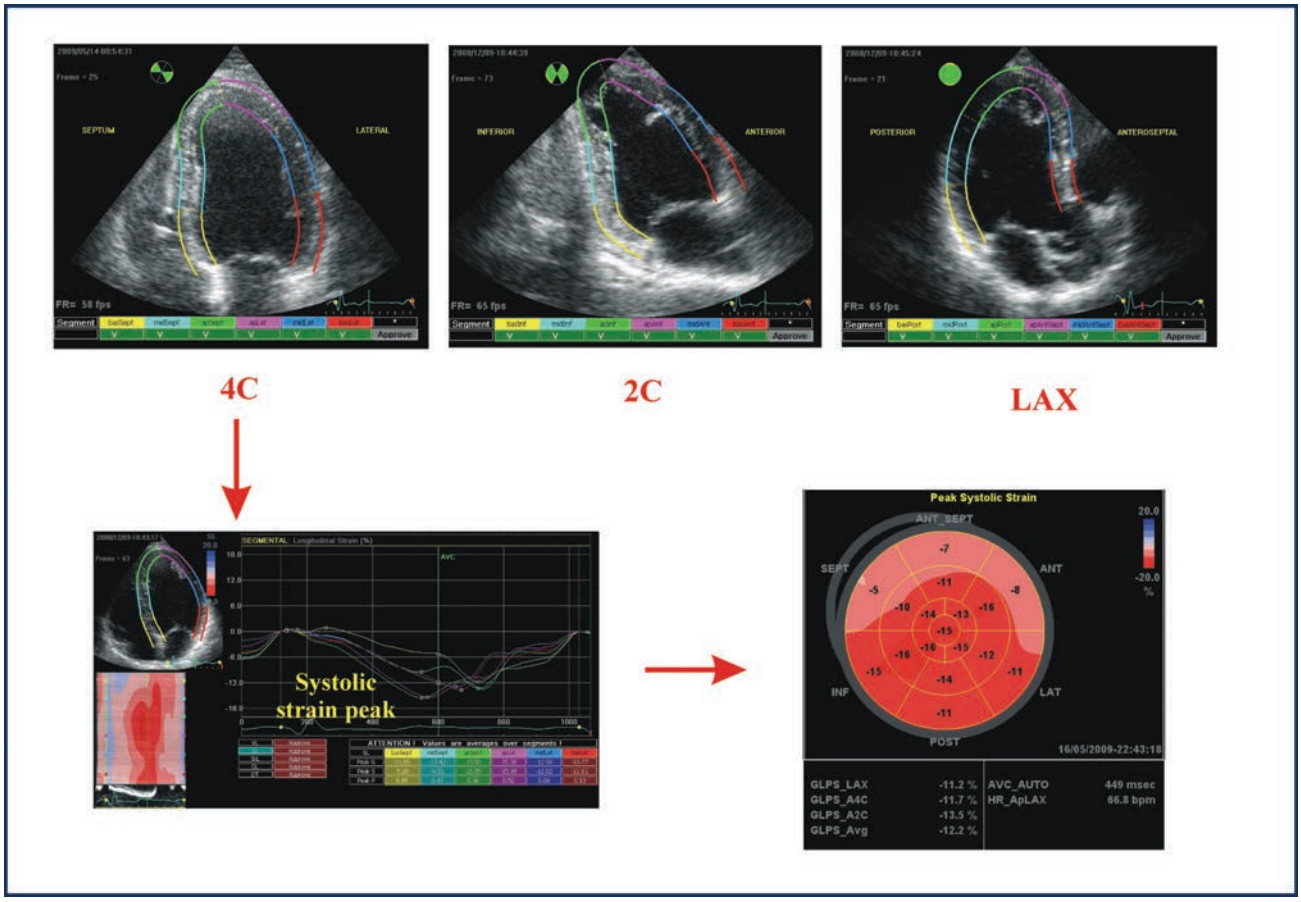

Figure 1. Global systolic strain evaluated by EchoPAC PC version (GE Vingmed Ultrasound, General Electric, Milwaukee, WI). Standard apical views acquired at a frame rate of 50-70 frame/sec are analysed by using 2D speckle tracking technique. GLS has been calculated as the mean values obtained in all the apical views.

figure, we evaluated GLS by analysing the standard apical views acquired at a frame rate of 50-70 frame/second off-line by using 2D speckle tracking technique (EchoPAC PC version, GE Vingmed Ultrasound, General Electric, Milwaukee, WI). GLS has been calculated as the mean values obtained in all the apical views.

During a mean follow-up of 26 ± 13 months, 37 patients died (29 due to cardiovascular causes), 10 patients underwent heart transplantation, and 75 patients experienced at least one episode of hospitalisation due to acute decompensated heart failure (ADHF). Thirty-one patients without a history of major ventricular arrhythmic events experienced the occurrence of ventricular fibrillation and/or tachycardia or sudden death. At multivariate Cox regression analysis, GLS remained significantly associated with all-cause mortality (HR: 1.15; 95%CI: 1.02-1.30; p: 0.026), cardiovascular death (HR: 1.20; 95%CI: 1.04-1.39; p: 0.011), cardiovascular death or heart transplantation (HR: 1.24; 95%CI: 1.09-1.41; p: 0.001), ADHF-related hospitalisations (HR: 1.15; 95%CI: 1.05-1.25; p: 0.003), after correction for the most widely used CHF prognostic markers (after correcting for age, ischemic cardiomyopathy, NYHA class, mean arterial pressure, natremia, glomerular filtration rate, haemoglobin, logarithm of NT-proBNP). Moreover, it remained significantly associated to arrhythmic events (HR: 1.17; 95%CI: 1.03-1.33; p: 0.018) after correction for the presence of non-sustained ventricular tachycardia, NYHA class, logarithm of NT-proBNP. Finally, when c-index was considered, strain measures showed values very similar to those observed for LVEF, thus suggesting a predictive power equivalent to that of the most widely used parameter reflecting LV systolic function.

Limitation of 2D Speckle Tracking Technique

Although the results of available studies make 2D strain measures seem particularly promising as parameters of systolic function, the limitations of this technique should be also taken into account. Having a good quality image strongly influences the accuracy of 2D strain measures, because speckle tracking of poor quality recordings may lead to false-positive results. Although progress is being made, for the present, accurate strain is limited by frame rate and heart rate. Finally, to date, only one manufacturer seems to be producing reliable strain data in multiple laboratories and it is responsible for the vast majority of strain data in the literature.

A recently developed 3-dimensional speckle-tracking (3D-STE) technique showed promising preliminary results in analyses of 3-dimensional images data sets.[18] 3D-STE technique, compared with the quantitative tissue velocity imaging and two-dimensional speckle tracking imaging, has great advantages because it is independent of angle and does not ignore the

characteristics of three-dimensional cardiac wall motion. On the other hand, 3D strain parameters are obtained by using low frame rates (between 18 and 25)[19] and are closely dependent from the quality of 2D images used for acquisition. Finally, there are few data validating 3D-STE as a technique with prognostic value.

Conclusions

Two-D speckle tracking analysis is a new echocardiographic technique able to provide measures of segmental and global LV function. In particular, global longitudinal LV systolic strain is a measure which is easy to be obtained, characterised by a high intra- and inter-observer reproducibility. In our recent study we have demonstrated the independent role of GLS in predicting heart failure progression and major arrhythmic events among patients affected by CHF, thus strengthening the potential usefulness of this parameter in current clinical practise.

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Novel Interventional Strategies to Address Reverse Left Ventricular Remodeling in Advanced Heart Failure

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Introduction

Heart failure is one of the leading causes of mortality and morbidity in the western world and is associated with increasing socio-economic costs. The causation of this mortality and morbidity is the loss of myocytes that are being replaced by fibrotic tissue, leading to increased haemodynamic stress. The rise in mechanical load activates a cascade of deleterious neurohumoral signaling pathways and multiple cellular and molecular abnormalities, such as alterations in the extracellular matrix and vascular elements, occur with left ventricular remodeling as a final result. The term left ventricular remodeling reflects changes in ventricular mass, its composition, overall volume, geometry and shape. During the process of remodeling, the left ventricle becomes less elliptical and ventricular sphericity increases. These changes in shape contribute to the reduction in radial, circumferential and longitudinal strains. Furthermore, the torsion mechanics are being altered, apical segments do not retain maximal curvature and the apex is no longer an optimum fulcrum for ventricular contraction.

Given the causal relationship between remodeling and reduced pump function, therapies that decrease the elevated stress are of the utmost important in the management and treatment of heart failure. In this regard, the term of "reverse remodeling" has been adopted to reflect the beneficial effects of therapeutic interventions that induce a leftward shift in the ventricular pressure-volume relationship in parallel with ventricular size reduction. This remodeling process has also been linked to favourable changes in the molecular and cellular portrait and is distinct from cardiac recovery, which is defined as the best achievable clinical outcome of a patient with heart failure, namely being free from future heart failure events.[1] Although not all therapies inducing reverse remodeling alter long-term prognosis, every therapy associated with a positive long-term outcome and cardiac recovery has been paralleled by a reduction in ventricular volumes.

Multimodal treatments have been introduced to alleviate the symptoms or reverse the progression of heart failure. Besides the lifestyle management and pharmacological therapies, various device-based interventions have been proposed to induce reverse remodeling. Among them, cardiac resynchronisation improved morbidity and mortality in defined subsets of heart failure patients. Despite these undisputable advances, a gap persists in therapeutic options for patients with advanced heart failure. Recent developments in device-based treatment of chronic heart failure are designed to target various components in the cascade heart failure progression and to try to fill the therapeutic gap. From a didactic point of view, potential targets can be divided into 3 groups: mechanical, electro-mechanical and neuro-modulatory targets (Figure 1 and Table 1). Here, we focus particularly on devices targeting systolic left ventricular restoration.

Systolic Left Ventricular Restoration

Left ventricular enlargement initially serves to sustain the stroke volume and ventricular function. However, as outline above, in the long-term it is associated with increased wall stress, precipitating a vicious cycle of progressive ventricular enlargement and functional worsening. Specific but common subsets of patients prone to this development are those with anterior myocardial infarction. Here, the extensive damage with thinning of the anterior and apical segments favours scar expansion, ventricular elongation and dilation. In accordance with Laplace law, the altered ventricular geometry increases regional wall stress and regional overload, which not only further aggravates abnormal local mechanics but also adversely affects remote myocardial segments and perpetuates further ventricular dilation. This self-perpetuating cycle viciously affects not only spherical chamber remodeling, but also cardiac mechanics and efficiency.

Reduction of wall stress by shrinking the ventricular cavity has typically been attempted surgically, and various surgical strategies have been investigated. Among them is the Revivent™ Myocardial Anchoring System, which is a novel technology for left ventricular plication that is minimal invasive. Through a mini-thoracotomy access, multiple stitches

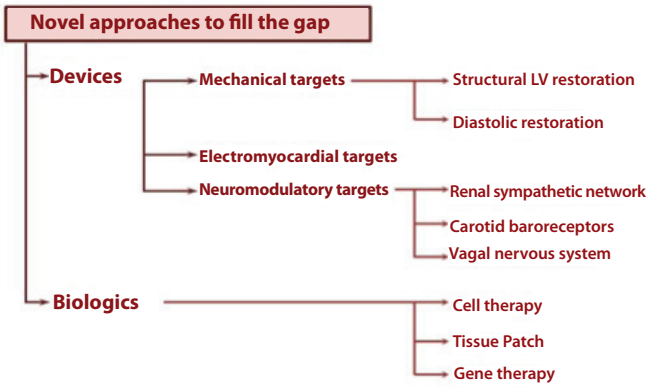

Figure 1. Novel potential concepts to fill in the currently existing therapeutic gap in the treatment of chronic heart failure. Adapted from Toth G., Vanderheyden M., Bartunek J., Novel based strategies in treatment of chronic heart failure. In Batunek J., Vanderheyde M., (Eds) *Translational Approach to Heart Failure*, Springer 2013;425-436.

are placed along the border of the scarred anterior and apical segments, plicating the infarcted ventricular segments, and reshaping the ventricle.[2] The review of standard ventricular restoration therapies including aneurysmectomy or constraining devices is beyond the scope of the current review.

Percutaneous Approach to Ventricular Restoration

Percutaneous left ventricle partitioning approach with Parachute™ (CardioKinetix Inc., Menlo Park, CA, USA) has emerged as an alternative percutaneous procedure to restore left ventricular geometry. The concept and associated intervention aims to partition those distal dysfunctional segments that are non-contributory to the ventricular mechanics and that reduce efficiency of pump function by creating a space with a non-circulatory blood volume. The partitioning is achieved using an umbrella or parachute-shaped device excluding dysfunctional apical segments from mid and basal segments with preserved contractile function (Figure 2). In other words, the Parachute™ partitions

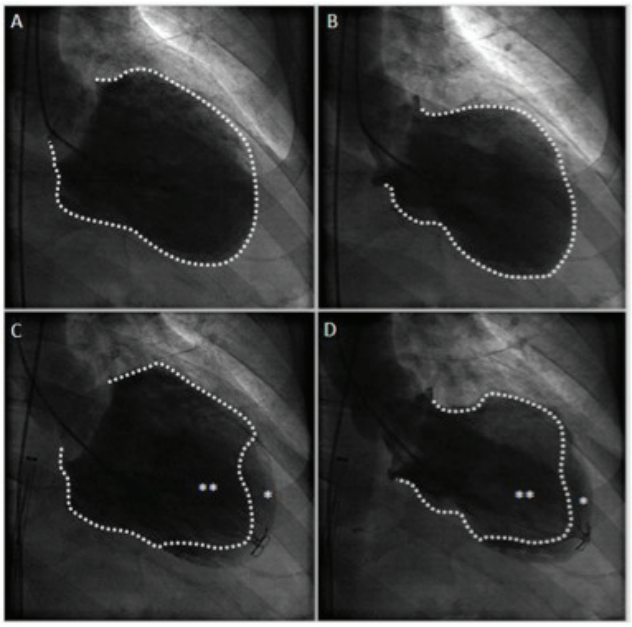

Figure 2. The extensive a/dyskinesis after anterior myocardial infarct results in a functional-geometrical mismatch. (Panel A, B) Parachute™ device is designed to partition the enlarged ventricle into a "dynamic" (**) and a "static" (*) chamber to restore the normal functional-geometrical relation (Panel C, D). Adapted from Toth G., Vanderheyden M., Bartunek J., Novel based strategies in treatment of chronic heart failure. In Batunek J., Vanderheyde M., (Eds) *Translational Approach to Heart Failure*, Springer 2013;425-436.

the enlarged ventricle into a "dynamic" and a "static" chamber. The "static" chamber is that portion of the left ventricle which is separated from the systemic circulation after positioning of the device in the apical region. The dynamic chamber proximal from the device which forms the new apex is not only smaller but also aims at partial geometrical normalisation of the apical segments. The device consists of an umbrella-like flexible nitinol frame, covered with poly-tetra-fluoro-ethylene surface. The nitinol frame not only provides a stable and well-expanded position below the papillary muscles, but with its flexibility it allows the device to follow the contractions of the rest of the

Target	Device	Principle
Mechanical-systolic	Parachute™	Percutaneous left ventricle partitioning device for patients with big antero-apical scar
	Revivent™	Surgical left ventricle plication device for patients with big antero-apical scar
	CorCap™	Mesh-like device placed surgically around the heart in order to reshape the ventricle and prevent further dilation
Mechanical-diastolic	ImCardia™	Epicardially placed metallic coils using the bowstring to restore effect to restore diastolic function diastolic function
	CORolla™	Endocardially placed metallic coils using the bowstring effect to restore diastolic function
	IASD™	Interatrial shunt device for reduction of therapy resistant increased left atrial pressure
Electro-myocardial	Optimizer™	Cardiac contractility of the myocardium modulation with non-excitatory stimuli
Neuro-modulatory	RDN	Renal denervation therapy for reducing baseline sympathetic activity in *systolic* CHF
	BaroStim™	Continuous stimulation of the carotid baroreceptors for reducing sympathetic activity in *systolic* CHF
	CardiowFit™	Chronic vagal nerve stimulation modulation of the autonomic imbalance

Table 1. Novel approaches, designed to fill in the currently existing therapeutic gap in the treatment of chronic heart failure. Adapted from Toth G., Vanderheyden M., Bartunek J., Novel based strategies in treatment of chronic heart failure. In Batunek J., Vanderheyde M., (Eds) *Translational Approach to Heart Failure*, Springer 2013;425-436.

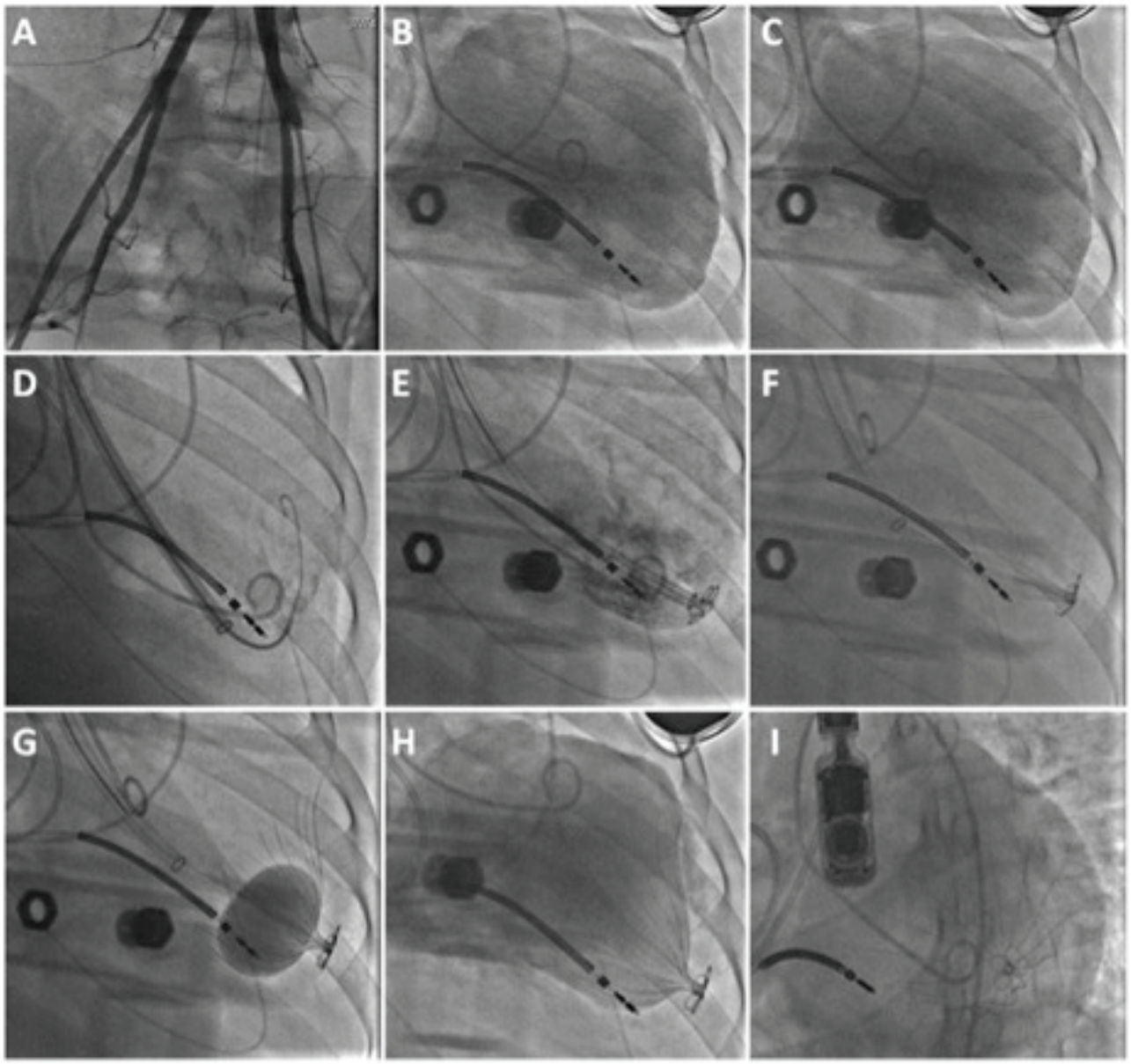

Figure 3. Procedure flow of Parachute™ device implantation. Panel A – Checking of appropriate femoral access. Panel B and C – defining the dyskinetic segments and identification of the the aimed landing zone. Panel D – Dedicated 16Fr sheathless guiding catheter is advanced into the left ventricle over a diagnostic pigtail catheter in the direction of the dyskinetic apex. Panel E and F – Pulling back the guiding catheter allows the release of the nitinol frames and opening of the Parachute™. Panel G – Inflating a balloon enhances the full deployment and the anchoring of the nitinol frame in the myocardium. Panel H and I – Final position and its impact on the ventricular chamber reshaping. Adapted from Toth G., Vanderheyden M., Bartunek J., Novel based strategies in treatment of chronic heart failure. In Batunek J., Vanderheyde M., (Eds) *Translational Approach to Heart Failure*, Springer 2013;425-436.

myocardium, thereby imitating the native movements of the apex. Conceptually, this should facilitate ventricular torsion mechanics.

Patient Selection and Procedural Aspects

Proper selection of the patient for this procedure is critical. From a clinical point of view, patients with persisting NYHA III-IV stage heart failure symptoms despite optimal therapeutic regimen represent a population with unmet clinical need. Patients should be presenting with dysfunctional apical segments. At screening, both echocardiography and computed tomography are instrumental in identifying potential contraindications for this procedure such as the presence of false chordae, which may interfere with appropriate device positioning, intraventricular thrombus or extensive ventricular calcification. In addition, a CT scan allows the exact sizing of the device, which is important not only to ensure appropriate partitioning and exclusion of the distal dysfunctional segments but also appropriate insertion distal to the papillary muscle head. Since the device is introduced through a 15 F sheet the patient should have a good femoral access.[3]

The implantation itself is straightforward. The device is inserted using a dedicated sheathless guiding catheter (Figure 3, Panel A). A left-ventricular angiogram helps to delineate the akinetic or dyskinetic apical regions and define the intended position of the device (Figure 3, Panel B and C). The insertion of the guiding catheter to the left ventricle is facilitated by the pigtail catheter which is used as support when crossing the aortic valve to avoid valve damage stiff guide-wires. Various guiding

catheters designed to facilitate the device delivery to the apical region are being proposed (Figure 3, Panel D).

After achieving the intended and stable guiding position, the pigtail catheter is removed and the device is advanced carefully into the guiding catheter, thereby avoiding aspiration of air bubbles in the delivery system. Once advanced into the tip of the guiding catheter, the landing position is checked and adjusted if needed. Next, the device is further advanced until it shoulders against the apex with its soft, flower-shaped foot. At this point, when the final position is checked with angiography, the entire system is to be held fixed in the position and the delivery guiding is slowly retrieved to release the Parachute™ device. Step-by-step, this movement will free the nitinol frame, which starts to open up (Figure 3, Panel E and F). Nitinol is an alloy which can be prepared to have various physical properties. Unlike most other nitinol devices used in structural interventions, Parachute™ is much softer and opens to its final shape much more slowly. Therefore the expansion is facilitated by balloon inflation to ensure the full deployment and stable anchoring of the nitinol frame in the myocardium (Figure 3, Panel G). As soon as the whole frame opens up completely, the hooks are fixed in the wall of the ventricle and the Parachute™ device acquires a stable position. The final impact on the ventricular chamber reshaping is checked by a control left-ventricular angiogram (Figure 3, Panel H and I).

Structural and Haemodynamic Effects

As described above, the device partitions the infarcted left ventricle into a 'static', afunctional chamber and into a 'dynamic', functional chamber. Thanks to its position and the physical properties of the nitinol, the stress on the weakened myocardial segments generated during the heart cycle can be easily released and transformed into supportive work. In addition, replacement of dysfunctional apical segments with partitioning of the "non-contributory" apical blood volume by the compliant parachute may conceptually improve diastolic filling. In this regard it can contribute to the restoration of the twisting and untwisting contractile mechanics and together with the unloading of the basal segments and reduction of the intraventricular wall stress improve myocardial efficiency. Animal studies support these data and demonstrate a leftward shift in the pressure-volume relationships.[4] In patients, reduction of left ventricular filling pressure was demonstrated, however, further human studies should determine the effects on cardiac mechanics and efficiency using the pressure-volume loops assessment.

Clinical Experience

Clinical experience has been gathered initially in the feasibility and safety study with the Parachute™ including 38 patients. The procedure was performed in 34 cases and implantation was performed successfully and safely in 31 patients (79% of all patients). During the 6-month follow-up, 5 adverse events were observed. In patients with completed 12 months follow-up (n=28), a significant improvement in functional status (New York Heart Association class 2.5 ± 0.6 to 1.3 ± 0.6, $p < 0.001$) and in quality-of-life score (38.6 ± 6.1 to 28.4 ± 4.4, $p < 0.002$) were observed. However no significant change in 6-minute hall walk distance (from 358.5 ± 20.4 m to 374.7 ± 25.6 m, ns) was observed.

Recently, a pooled analysis of 91 patients was reported at EuroPCR.[4, 5] Overall, device implantation was successfully performed in 86/91 patients with a favourable safety profile. In this regard, the use of traditional pigtail catheter is required to prevent aortic valve damage during the transition of the guide to the ventricle. Likewise, given the size of the device, assessment of the peripheral vascular disease is mandatory to avoid vascular complications. Several encouraging surrogate and clinical efficacy signals, including the reduction of end-systolic volumes provide the basis for the larger randomised trial. In this regard, a large pivotal US-based trial Parachute IV has recently been initiated to address the clinical value of the intervention in patients with advanced systolic heart failure on top of the optimal medical treatment

Future Steps and Leads to Clinical Translation

Clinical adoption of any device requires a continuous surveillance of the safety, device development while addressing the clinical efficacy in target population based on the mechanistic impact of the intervention. The Ongoing Parachute IV trial will determine the role of the device in patients with chronic heart failure. The current generation of the device already offers a reasonable variety of sizes and shapes, which allows it to target a broad spectrum of left ventricular sizes. As clinical experience is expanded, future development is likely to focus on refinement as regards to its placement with further development of guides, their size and shapes. Sizing of the device and "geometrical match" in relation to the ventricular size is critical, as it can result in a portion of the patients being excluded.[6] On the one hand this may represent the inherent limitation when targeting grossly remodeled and dilated failing ventricle. On the other hand, whether Parachute-based intervention with apical partitioning may be beneficial in the earlier stages of remodeling shortly after the ischemic insult remains to be addressed. In current experience, the median time of implant is more than 3 years after the infarction,[5] and questions remain as to whether earlier interventions might be clinically more efficacious, and whether they would interfere with the remodeling process. It also remains to be determined whether the degree of the wall motion in the basal to mid segment can affect the final haemodynamic and clinical outcome.

Conclusions

Catheter-based LV reconstruction is an innovative approach aimed to restore ventricular geometry and efficiency. Early clinical experience with the Parachute™ device has demonstrated favourable safety and encouraging efficacy signals. The ongoing pivotal trial will determine the clinical efficacy in comparison with optimal medical treatment in patients with ischemic heart failure. Further development should streamline patient selection and optimal timing of this intervention after myocardial infarction with apical wall motion abnormalities.

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Lead Extraction: A Single Centre Experience A Critical Reappraisal of Techniques and Results

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Introduction

Over the last few years, an increasingly widespread use of cardiac implantable electronic devices for the treatment of cardiac rhythm disturbances[1-3] has been closely followed by an increase of device-related complications, mainly infections and malfunctions. The prevalence of cardiac device-related infections ranges between 0.5% and 1.6%,[4, 5] with incidence of 1.9-4.8/1000 device-year,[6, 7] which has virtually tripled in last decade.[8, 9] Clinical presentation of device-related infection may be local, systemic or both, and the intravascular segment of the lead is frequently involved in all these clinical settings.[10-12] Some cases can be severe and potentially life-threatening: 10-21% mortality is frequently observed in cases of cardiac device-related endocarditis,[13-16] and complete healing can be obtained only by the complete removal of the hardware.

Moreover, lead failure due to construction defects has recently become disurbingly frequent.[17, 18] The only way to avoid lead-to-lead interaction and to gain vascular access lies in lead extraction, and this is particularly advisable when further need of the CIED is expected to be long, which is common in young patients. Therefore the necessity arose to define more effective and safe techniques for device removal in case of complications. Specific techniques and tools are requested to perform lead extraction, due to adherences, fibrotic and sometimes calcific tissue ingrowth binding the leads to vessel or cardiac wall. These adherences can occur whenever the lead comes into contact the vessel and cardiac structures.[19, 20]

Direct traction can be inconsistent due to scar tissue bonding sites along lead length. Pulling a lead without support can cause stretching, breakage or fracture. The force required to extract tined electrodes may be enough to risk avulsion of the myocardium. Open heart surgery is associated with significant morbidity and mortality. Intravascular lead extraction requires an high level of experience, specific techniques (counter-traction,[21, 22] single sheath[23]), dedicated tools (locking stylets,[24] mechanical[23] and powered dilators, employing laser,[25-32] radiofrequency,[33] rotational handle-driven cutting forces[34, 35]), different approaches (via the access vein, transjugular,[23, 36] transfemoral[37-41]) and ancillary retrieval instruments.[19, 39, 42-51]

Pier Giorgio Golzio graduated in Medicine with a first class honours degree at University of Turin in 1983 and achieved a postgraduate qualification in Cardiology, with first class honours at the same university in 1988. Since 1991, he has been a full-time staff physician in the Cardiology and Cardiovascular Surgery Department at the University of Turin, where he has gained experence in thrombolytic therapy, non-invasive and invasive diagnostic techniques, ICD implants and biventricular pacing techniques. Dr. Golzio is currently Chief of the Electrophysiology and Cardiac Pacing Unit at the University of Turin, and is a teacher of Electrocardiography on the Post Graduate Fellowship Course in Internal Medicine at the University of Turin. He has previously acted as a tutor in Cardiology for the Post Graduate Fellowship Course in Geriatrics, as well as in Clinical Cardiac Pacing for the Post Graduate Fellowship Course in Cardiology at the University of Turin. Dr. Golzio's research interests include lead malfunction and extraction, infections of cardiac implantable electronic devices, and surgical AF ablation. He is also a Fellow of the European Society of Cardiology (ESC) and the American College of Cardiology (ACC), as well as a member of the National Board of Associazione Italiana di Aritmologia e Cardiostimolazione (AIAC), the European Heart Rythum Association (EHRA) and the ESC/EHRA Task Force on Accreditation for Lead Extraction.

Aims

We believed that it was appropriate to proceed with a quality assessment of the procedures carried out at our centre. The decision to carry out this assessment comes from the awareness, supported by the Guidelines on lead extraction, that in every specialised centre the optimisation of the operating methods and the necessary level of experience to perform delicate operations are directly proportional to the number of treated patients. This study reports our experience in lead extraction.

Materials and Methods

Study Population

The study population was entirely composed of consecutive patients referred to our university department for lead extraction between April 2003 and November 2011. All patients with infective indications were on long-term antimicrobial suppressive therapy and have been

→ Cardiothoracic team on duty
→ Typed and cross-matched blood
→ Continuous monitoring of ECG
→ Continuous monitoring of invasive arterial blood pressure and oxygen saturation
→ Back-up temporary pacing
→ Echocardiograph (TT-TE)
→ Intravascular U/sound (not always)
→ Pericardiocentesis set
→ General or local anaesthesia/working anaesthesia equipment

Table 1. Lead extraction protocol.

evaluated by transthoracic and transesophageal echocardiography the day before or the same morning of the procedure.

Extraction Protocol

Lead extraction was performed under local anaesthesia in the electrophysiology lab, with a cardiac surgery team on active duty and with anaesthesiology support. Extraction protocol (Table I) required cardiothoracic team on duty, with support of an anaestesiologist and with a working anaesthesia equipment in the room. We had four typed and cross-matched blood units disposable, and continuously monitored ECG, oxygen saturation and invasive arterial blood pressure. We always had a working echocardiograph in the room, and everything that was needed to perform an emergency pericardiocentesis.

Temporary transvenous back-up pacing was always established, and this was maintained, when indicated, until reimplantation of a permanent pacing system could be safely performed. In cases of pacemaker dependency, a variable approach was used: surgical

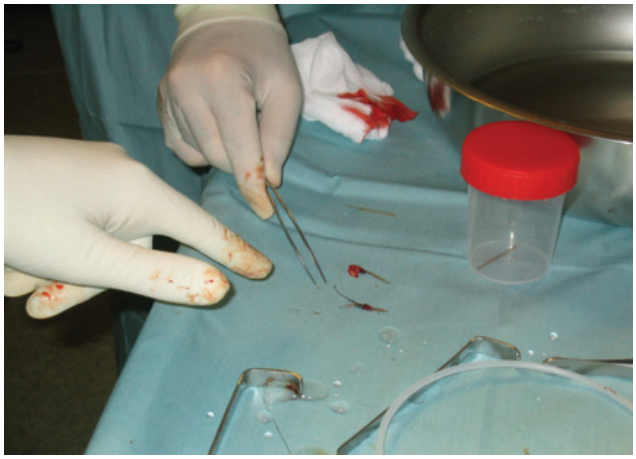

Figure 1. The tip and the connector of each lead were sectioned following the extraction, held in reserve in sterile containers in a 4° C controlled temperature fridge and consequently sent to the Microbiology Department.

extraction and concomitant epicardial lead placement, or transvenous lead extraction concomitant with percutaneous implantation of a conventional screw-in lead connected to an external device, to bridge to the subsequent definitive implant.

Lead Extraction Techniques

We used a manual traction with conventional and locking stylets, and dilation with polypropylene sheaths. The size of the sheaths ranged from 7 to 14 F. We used the single-sheath technique described by Bongiorni. Ancillary retrieval tools (Lassos, Osypka GmbH, Grentzig-Whylen, Germany; Needle's eye snare, Cook Vascular; Amplaz gooseneck snare) were also used, if needed. The superior approach (via the venous implant access route) was followed in the majority of cases, but in rare cases we used the superior transjugular or the

Major Complications	1. Death 2. Cardiac avulsion or tear requiring thoracotomy, pericardiocentesis, chest tube, or surgical repair 3. Vascular avulsion or tear (requiring thoracotomy, pericardiocentesis, chest tube, or surgical repair) 4. Pulmonary embolism requiring surgical intervention 5. Respiratory arrest or anesthesia related complication leading to prolongation of hospitalisation 6. Stroke 7. Pacing system related infection of a previously non-infected site
Minor complications	1. Pericardial effusion not requiring pericardiocentesis or surgical intervention 2. Hemothorax not requiring a chest tube 3. Haematoma at the surgical site requiring reoperation for drainage 4. Arm swelling or thrombosis of implant veins resulting in medical intervention 5. Vascular repair near the implant site or venous entry site 6. Haemodynamically significant air embolism 7. Migrated lead fragment without sequelae 8. Blood transfusion related to blood loss during surgery 9. Pneumothorax requiring a chest tube 10. Pulmonary embolism not requiring surgical intervention

Table 2. Classification of complications.[52]

Patient Population	
Patients, n	154
Males	122 (78.7)
Leads extracted, n	318
Age (years)	69.9±14.2
Number of leads extracted	2.2±0.7
Dwelling time (months)	43.2±43.1
Number of previous conservative treatments	0.8±1.1
Infective indications	136 (88)
chronic draining sinus	60 (39)
local infection	32 (21)
systemic infection	44 (28)
Recent (<3 months)	42 (31)
Chronic (>3 months)	94 (69)
Non infective indications	18 (12)
Manual traction alone	132/318 (41.5)
Traction and dilation	186/318 (58.5)
Transjugular	1/318 (0.3)
Transfemoral	2/318 (0.6)
Complete procedural success	305/318 (96)
Complete clinical success	316/318 (99.4)

Table 3. Descriptive characteristics, clinical indications of lead extraction, techniques employed and results for the 154 patients and 318 leads treated during the study period. Data are presented as mean ± standard deviation (SD) and counts (and percentages).

transfemoral approach.

Bacteriological Analysis

Bacteriological swabs were collected from the pocket: preoperatively in cases of local infection and, in all patients, during the procedure, from the deep portion of the pocket. A tissue specimen was also excised. After the extraction of each lead, the tip and the pin were cut and all tissue specimens and every fragment of the lead pin and tip were immediately collected into a sterile dry container and sent to the microbiology laboratory for analysis (Figure 1).

Intraprocedural Data Collection

During the procedure we recorded the procedural times, and we defined:

- Preparative time: from entry into the operating room to skin incision;
- Operation time: "skin to skin" procedural time;
- Mobilisation time: from skin incision to complete mobilisation of the lead up to the entry into the vascular space;
- Extraction time: from complete mobilisation of the lead up to the entry into the vascular space to complete extraction. It includes two times: manual traction time, from complete mobilisation of the lead

		N	%
Polarity	Monopolar	50	15.7
	Bipolar	268	84.3
Insulation	Silicon	229	72
	Polyurethane	89	28
Fixation	Pins	268	84.3
	Screw-in, retractable	13	4.1
	Screw-in, fixed	37	11.6
Type	Atrial	109	34.3
	Ventricular	117	36.8
	VDD	5	1.6
	Coronary sinus	32	10.1
	ICD	55	17.3
Access vein	Left Cephalic	87	27.3
	Right Cephalic	25	7.9
	Left Subclavian	194	61
	Right Subclavian	12	3.8

Table 4. Lead characteristics.

Times	Min	Max	M	SE	SD
Operating room time	0:50:00	6:15:00	3:49:30	0:11:24	1:21:24
Preparative time	0:10:00	3:05:00	1:22:20	0:06:18	0:45:02
Operation time	0:20:00	3:45:00	1:53:10	0:08:00	0:57:10
Mobilisation time	0:05:00	1:50:00	0:45:01	0:03:59	0:28:33
Extraction time	0:00:10	2:05:00	0:26:53	0:04:39	0:33:18
Manual traction time	0:00:05	0:05:00	0:00:51	0:00:08	0:00:59
Dilatation time	0:02:30	0:45:00	0:16:31	0:02:24	0:11:49
Fluoroscopy time	0:01:00	0:42:00	0:13:52	0:01:32	0:10:59

Table 5. Procedural times. Values are expressed as hours:minutes:seconds.

	Type of Complication	N	%
Acute complications	None	140	90.9
	nsVT > 7 beats	2	1.3
	Symptomatic hypotension	2	1.3
	Asymptomatic hypotension	9	5.8
	Pericardial effusion	1	0.6
	Cardiac tamponade→ thoracotomy required	1	0.6
	Cardiac tamponade→thoracotomy required→DIC→death in 2nd post-operative day	1	0.6
Chronic	None	148	96.1
	Fever	6	3.9
Treatment	Volume expansion	22	14.3
	Drugs	17	11.1
	Transfusions	5	3.2

Table 6. Different types of complications. nsVT: non sustained ventricular tachycardia; DIC: disseminated intravascular coagulation.

up to the vascular access to complete extraction or stopping of the traction due to failure and change to dilatation, and dilation time, from stopping of the manual traction to complete extraction.

Definition of Outcomes

The procedural success of device removal and its complications were defined according to Heart Rhythm Society Consensus.[52]

• Complete procedural success was defined as the removal of all targeted leads and lead material from the vascular space, with the absence of any permanent complication.

• Clinical success was defined as the removal of all targeted leads and lead material from the vascular space, or retention of a small portion of the lead that did not negatively impact the outcome goals of the procedure.

• Failure was the inability to achieve either complete procedural or clinical success, or the development of any permanently disabling complication or procedure related death.

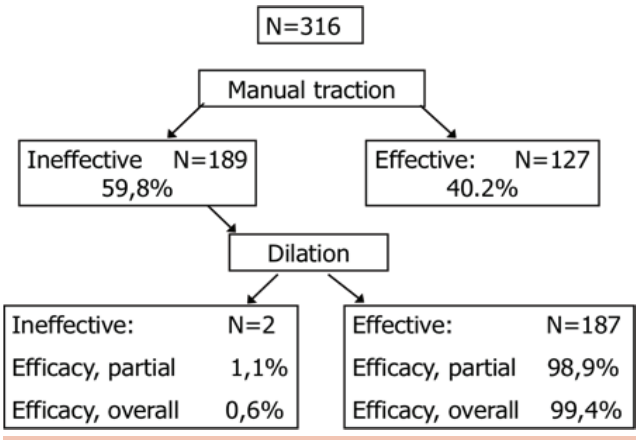

Figure 2. Sequential results of manual traction alone and followed by dilation. N = number of leads.

Complications were divided into major complications and minor complications, according to HRS Expert Consensus (Table 2).[52]

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as counts and percentages of the respective strata. The continuous variables were analysed by independent-samples T-tests and one-way ANOVA when degrees of freedom were greater than one (Bonferroni test for multiple comparisons). Nominal variables were compared using the chi square test or, for multiway tables, the Pearson chi-square, the likelihood-ratio chi-square and contingency coefficient. Hazard Ratios (HR) were presented with 95% confidence interval (CI). All tests of significance were two-tailed, and a p value < 0.05 was

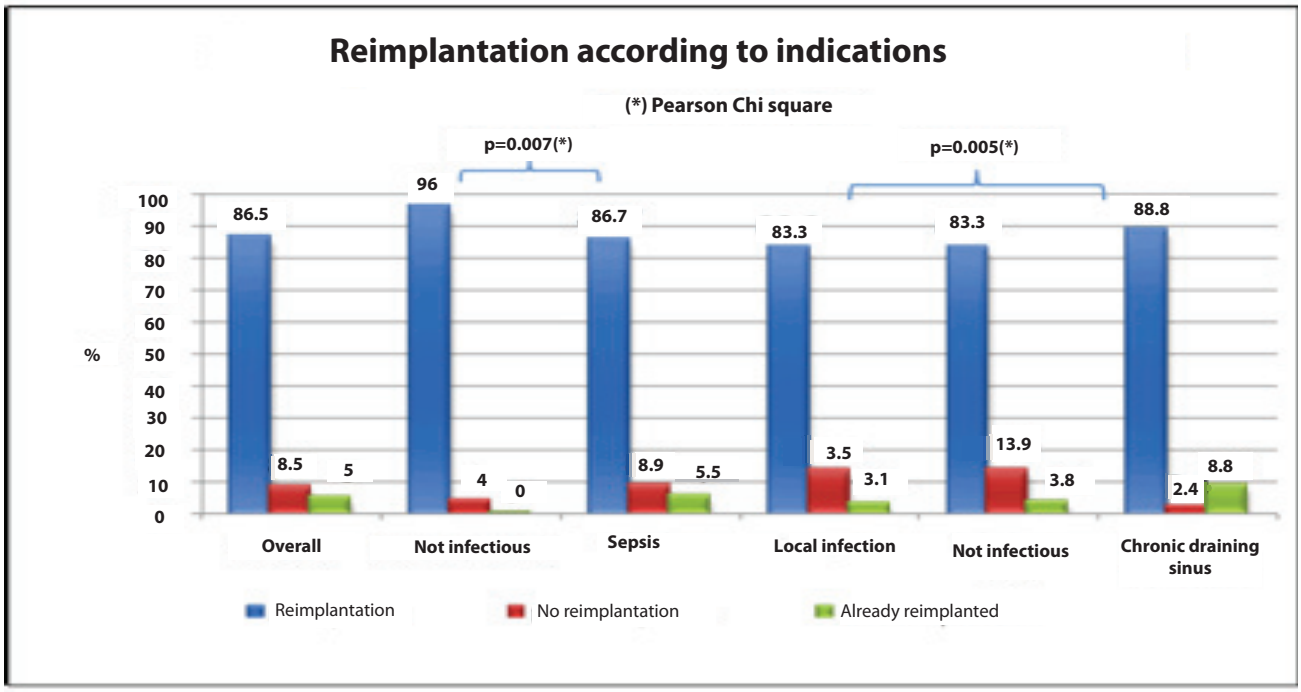

Figure 3. Reimplantation rates in the whole population, and split according to non infective and infective indications, and further in cases of sepsis, local infection and chronic draining sinus. Blue bars shows real reimplantations, and red bars real cases in which reimplantation had not been performed. The green bars refer to these patients in which a new device had been yet reimplanted, waiting for lead extraction.

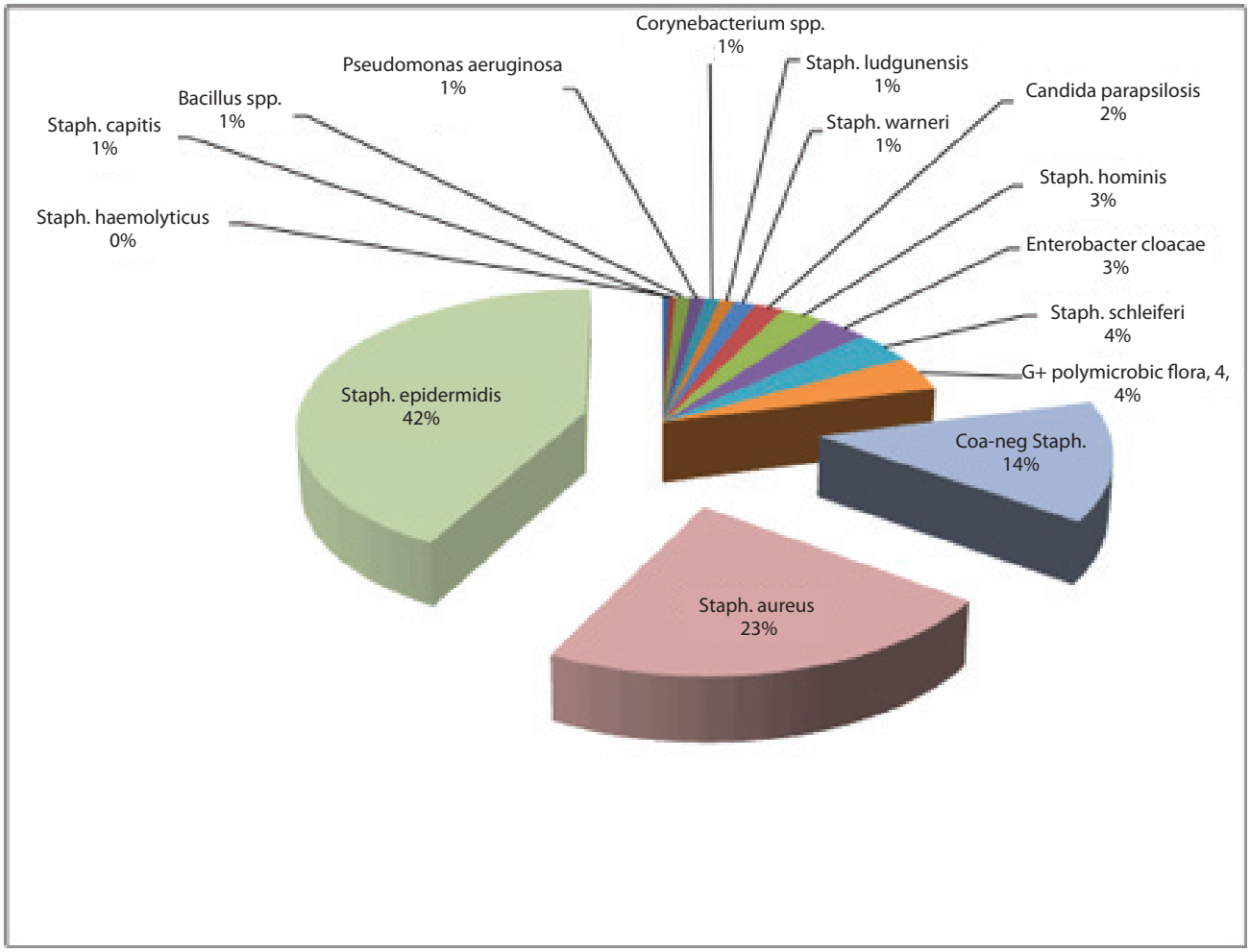

Figure 4. Prevalence (in percentages) of the bacterial strains identified from culture examination of the 293 leads extracted with infective indications.

Study	# of Patients(Pts) and leads (L)	Dwellig time, years	Success, %			Major Complications,%	Death, %
			T	P	F		
1988 – 93 First cases[19]	1299 Pts 2195 L	4.7±3.8	86	8	6	2.5	0.6
1994-95 Accufix[54]	985 Pts 1237 L	3.1±2.0	94	4	2	1.4	-
1994-95 Non-Accufix[54]	1011 Pts 1743 L	4.5±4.1	91	6	2	1.5	-
1994-96 Mechanical dilators Dilation/ countertraction[54]	2338 Pts 3540 L	3.9±3.4	93	5	2	1.4	0.4
1997-2007 Mechanical dilators. Single sheath, Pisa[23]	1193 Pts 2062 L	5.75 (0.1-28)	98.4	0.9	0.6	0.8	0.3
1995-99 Laser Registry, USA[38]	1684 Pts 2561 L	5.8±4.0	90	3	7	1.9	0.8
1996-2001 Laser, European[25]	292 Pts 383 L	6.1 (0.2-30)	90.9	3.4	5.7	3.4	-
2003-2007 Laser (LEXICON)[55]	1449 Pts 2405 L	6.8 (0.1-29.7)	96.6	2.3	1.2	1.4	0.28
1999-00 EDS[56]	265 Pts 459 L	8.4±5.0	95.9	3.5	0.6	2.6	0.6
2003-2006 EDS[33]	120 Pts 161 L	6.1±1.2	93	3.3	3.7	6.6	-
2009-2011 Evolution[57]	66 Pts 140 L	55 (22-240)	88		12	1.5	0
Evolution[58]	14	73 (12-244)	92.9		8.1	0	0

Table 7. Results, complications and mortality with different techniques.

considered significant.

Data were analysed using the Statistical Package for Social Sciences (SPSS, version 18.0.0, SPSS Inc., Chicago, IL, USA). All included patients gave written informed consent for participation in the study, which was approved by the institutional ethic committee and was performed according to the principles of the Declaration of Helsinki.

Results

During the study period, 154 patients with 318 leads underwent lead extraction. Descriptive characteristics, clinical indications requiring lead extraction, techniques employed and concise results are summarised in Table 3. Lead characteristics are described in Table 4, and procedural times are described in Table 5.

The sequential results of manual traction alone, and of manual traction followed by dilation are reported in Figure 2. Complete procedural success occurred in 303 leads (95.9%), partial in 11 (3.5%) and procedural failure was observed for two leads (0.6%). Acute complications occurred in 9.1% of cases: ventricular non-sustained tachycardia >7 beats in 1.3%, symptomatic hypotension in 1.3%, asymptomatic hypotension in 5.8%, pericardial effusion in 0.6%, cardiac tamponade in 0.6%. The patient that required urgent thoracotomy was treated with extraction due to lead vegetations, but died in the second post-operative day because of disseminated intravascular coagulation, a complication probably due to overwhelming sepsis. Chronic complication occurred in 3.9% of cases, with fever (Table 6). Transfusions were needed in 3.2% of patients, and volume expanders in 14.3%.

Reimplantation was performed in 86.5% of patients. According to the indications for lead extraction, reimplantation was performed in 96% of patients with non-infective indication, and in 85.7% of patients with infective indication (p=0,007). Within the group of infective indications, reimplantation was performed in 83.3% of patients with sepsis, in 83.3% of patients with pocket infection, and in 88.8% of patients with chronic draining sinus (p=0.005) (Figure 3).

Our microbiological data confirmed the importance of

Factor			RR	Significance
Operator related	# of procedures	< 30 procedures (Laser)[59]	NR	0.005
	Experience, years	> 3 years[60]	2.8	NS
Procedure related	Dwelling time	> 10 years[38]	NR	
		> 5 years[55]	3,25	NS
		For each year[61]	1.16/year	0.0001
	# of leads	# of leads, overall[59]	NR	0.005
		# of leads, incremental[60]	3.51	0.013
	Type of leads	ICD vs pacing[60, 62]	2.52	0.053
		ICD double coil,[60, 63, 64] unless coated[65]	NR	
		Ventricular vs atrial	NR	
		Not isodiametric vs isodiametric[62]	NR	
	Type of dilator	Laser vs mechanical[27]	3	NS
		Laser vs mechanical[61]	9.14	0.0119
		Laser, double coil, superior vena cava[66]	+++	NV
Patient related	Gender	Female vs male[59]	NR	0.01
		Female vs male[55]	1.37	NS
	BMI	> 25[55]	4	0.016
	Age	Young age[67]	NR	
	Heart disease	Congenital HD: size, tortuos veins, shunts;[60, 68, 69] GUCHD[70]	NR	
	Comorbilities	Renal failure, creatinine > 2.5[55]	2.5	0.0164
	Infection, endocarditis	WBC increased at time of procedure[2]	1.52	0.005
		Endocarditis[55]	1.9	0.001
		Endocarditis+diabetes[55]	4.0	0.0001
		Endocarditis+diabetes+ renal failure[55]	6.3	0.0001

Table 8. Risk of major complications. NR: not reported, NS: Not significant; ICD: implantable cardioverter defibrillator; HD. Heatt disease; GUCHD: grown-up congenital heart disease.

Staphylococcus strains as causative pathogen. The prevalence of the bacterial strains identified in cultural examination of the 293 leads extracted in 136 patients with infective indications is reported in Figure 4.

Discussion

Success in lead extraction is observed in approximately 93-98% of cases, and it is total in 91-95.9% and partial in 3-6%. Failure accounts for 2-8.5% of cases, with differences related to different centres, the techniques employed and the period (Table 7). Moreover, results, complications and mortality are strictly influenced by factors operator, procedure and patient-related (Table 8, and Reference 53). Therefore, results should be weighed according to many different variables.

Conclusion

The results obtained show that the procedure of lead extraction in our centre was rewarded by a high success rate both in terms of a high percentage of success and a limited number of recorded complications, comparable with literature data. The methods employed, involving manual traction with the use of a locking stylet, dilation with the use of polypropylene sheaths and transjugular approach were able to treat and resolve even the most complex cases.

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Remote Diagnosis and Management of Paediatric Heart Murmurs at John Radcliffe Hospital, Department of Paediatric Cardiology

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Background

I was encouraged to investigate the possibilities of tele-auscultation because, from a study performed by Mayo clinic and data reported in the *Journal of Telemedicine and Telecare* back in 2004, I knew that telemedicine-directed auscultation of patients is just as successful as an "in-person" assessment for the detection of cardiac arrhythmias.[2]

Though the yield of echocardiograms is virtually zero,[3, 4] and there is little doubt that with a careful clinical examination and good auscultation innocent murmurs can be correctly identified, there are growing requests to perform echocardiograms on patients who present with an innocent murmur.

In 2012, cardiology services at John Radcliffe took referrals for 1020[5] such patients. The patients were examined by the cardiologist, who provided a confirmation of an innocent murmur by means of auscultation. There is an expectation from GP's and patients that a consultation will include an echocardiogram. It is explained to parents that there is a possibity that incidental findings may arise, which will have no bearing on the management of the child but could significantly impact on them later in life, simply due to the knowledge of a pre-existing condition. In spite of this, it is rare for an echocardiogram to be declined.

Proposal

The basic question that I asked is whether we would ultimately be able to reassure referring paediatricians, general practitioners and parents about an innocent murmur and, in doing so, avoid a full consultation and echocardiogram. I also wanted to establish if we could offer a reporting service, similar to that provided for echos, in which our referring sites will send us their auscultatory files for assessment. I wanted to determine whether a diagnosis can be arrived at remotely, and if this information can be conveyed back in a timely manner.

Objectives

The objectives of this investigation were:

- To immediately reassure general practitioners and parents of a non-pathological finding.
- To decrease the anxiety currently experienced by parents and patients.
- To avoid secondary care referral, where there is an average waiting time of 90 days.[5]
- To greatly improve the service provided to the patients who need an intervention from the cardiology services.
- Significantly impact on the cost associated with providing a confirmed diagnosis.

Reasoning

The cost of the current service is met by the referring practitioner, but the additional burden to the secondary care environment has taken on a greater significance with the ever growing local and national drives to deliver patient care in a more appropriate manner. In the UK, QIPP – Quality, Innovation, Productivity and Prevention Challenge[6] – has placed a requirement upon the NHS to improve the quality of care it delivers, whilst at the same time making up to £20billion of efficiency savings by 2014-15. This is to be reinvested in frontline care.

Our proposed service meets these objectives head on, and once our

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Figure 1. 3M™ Littmann® TeleSteth™ Server System.

providers are equipped, several additional opportunities to change care pathways are available:

- Delivering primary care in the community.
- Reducing patient movement in secondary care.
- Delivering cost benefits for primary and secondary care.

In parallel, I believe that auscultation sounds captured from patients presenting with a pathological condition can be assessed for the purposes of triage and monitoring post-intervention.

Most importantly perhaps, we can deliver additional patient and service benefits once the technology is in place, for example in the monitoring of low-grade systolic murmurs discovered in otherwise healthy middle-aged men, and for whom there is an increased risk of AVR but no increase in risk of CVD death.[7]

The Technology

The technology required to provide such a service had been thoroughly assessed throughout 2012 from within the hospital, however this was focused upon real-time sessions connecting two locations. Experience with our tele-echocardiography facilities made it clear to us that a robust service would require the use of a "store and forward" model to be implemented successfully and without insurmountable service requirements from the consultancy standpoint.

The 3M™ Littmann® portfolio was principally able to meet our needs but, due to the ever-shifting regulations surrounding the security and hosting of patient data, the final "server-based" solution for tele-auscultation, TeleSteth™, only finally became available to us in June 2013. The 3200 model comes with Heart and Lung Visualisation Software 3M™ StethAssist™, which allows auscultations to be recorded and played back whilst being displayed as a phonocardiogram, and has the ability to switch between bell, diaphragm and extended range modes, even after the file is saved. Essentially, stethoscopes are connected to a personal computer via a Bluetooth[8, 9] wireless link.

The hosted server solution TeleSteth™ simply provides a secure mechanism for these files to be referred to a consultant with the minimum amount of effort, and then for a return of the files with the added consultancy information and report. Importantly, whilst we wanted to focus on a "store and forward" solution, the ability to perform a real-time streaming session is preserved within the 3M™-hosted TeleSteth™ solution.

Proof of Concept

During 2012, we had satisfied ourselves that the sound captured by the stethoscope chest piece at the patient site can be heard equivalently at both the patient and consulting sites through the stethoscope's binaural headset, using "real-time streaming". I wanted to confirm that the server-based solution did not in any way alter the files from a sound perspective, and that we could assess the auscultation sounds in isolation, and arrive at the right diagnosis with a "store and forward" solution. Our pilot study set out therefore to answer the following questions:

- Are the auscultation sounds transferred through TeleSteth™ solution identical to the originals?
- Can referring GPs and paediatricians easily produce recordings?
- Are the sounds of sufficient quality to facilitate accurate diagnosis?
- Can the sounds be assessed remotely, and used to produce a robust diagnosis?
- What is the cost of the existing service to primary and secondary care?
- What is the cost of the newly proposed service to primary and secondary care?

Design

A group of local GPs were engaged to commence use of the 3M™ Littmann® 3200 Digital Electronic Stethoscope and the associated StethAssist™ software. Sound profiles were captured by recording auscultations made from patients who were found to present with a murmur. From the offset, I found a great enthusiasm and desire to engage in this exercise. This provided a rare opportunity to capture a deep knowledge of the complete and detailed roadmap from the first meeting of the GP and patient, through to the concluding discharge and communication. Twenty second recordings were captured from each of the following standard auscultation positions.

- Aortic
- Pulmonary
- Tricuspid
- Mitral (Apex)
- Left Infraclavicular
- Left 3rd/4th Parasternal

The StethAssist™ software allows entry of free-text data which is

user, time and date-stamped on entry. Each patient assessed also had the following information captured:

- Indication
- Symptoms
- Pulse (Radial and femoral)
- BP

The length of each appointment was logged by the practice IT systems, and this was compared to pre-existing data to ascertain the additional requirements and cost implications for the GP. Additionally, the individual component activities which occur in the GP practice were mapped and costs calculated, and the costs incurred in the secondary care service were derived from existing tariffs (Figure 2, 3). The sound recordings were transferred through the TeleSteth™ server according to standard operating instructions and, in parallel, were transferred between the collecting PC and the consultant's PC using physical media. Sounds were compared to check for any perceivable difference in quality. The assessment of each recording was logged so that a record of the time spent on each assessment was produced.

Results

Children presenting to their GP's with innocent systolic murmurs, and who will be referred to a cardiologist, as normal, for confirmation, were assessed using the TeleSteth™ hosted server solution. All but two of the referrals contained a complete sound profile as prescribed in the procedure. (These referrals had a

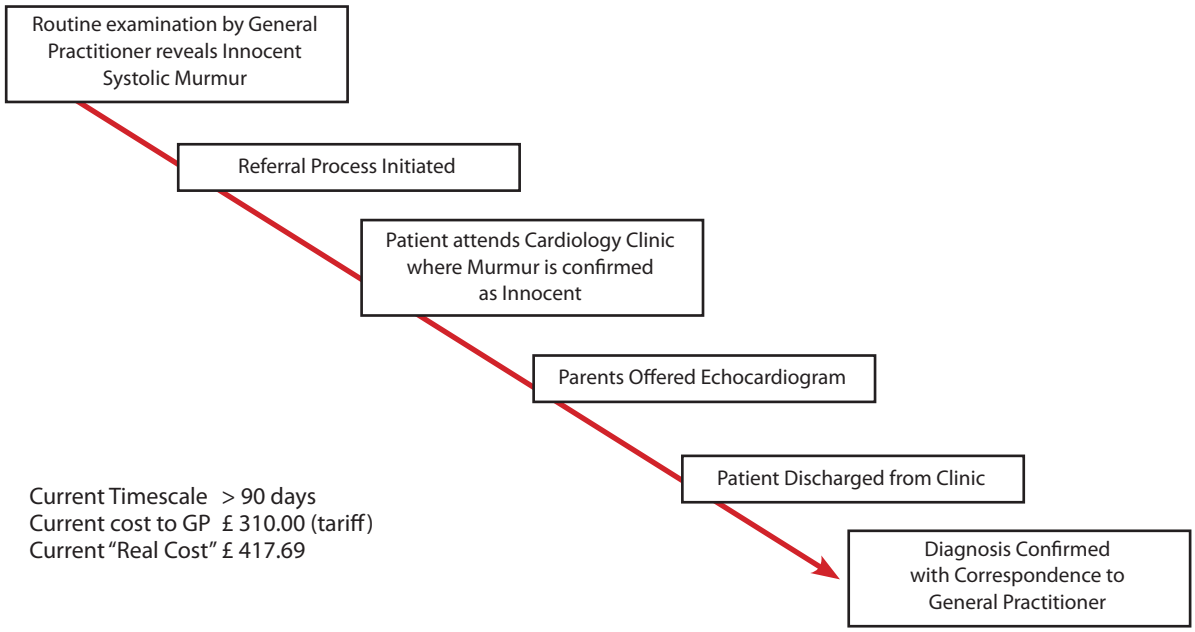

Figure 2. Existing Patient Journey

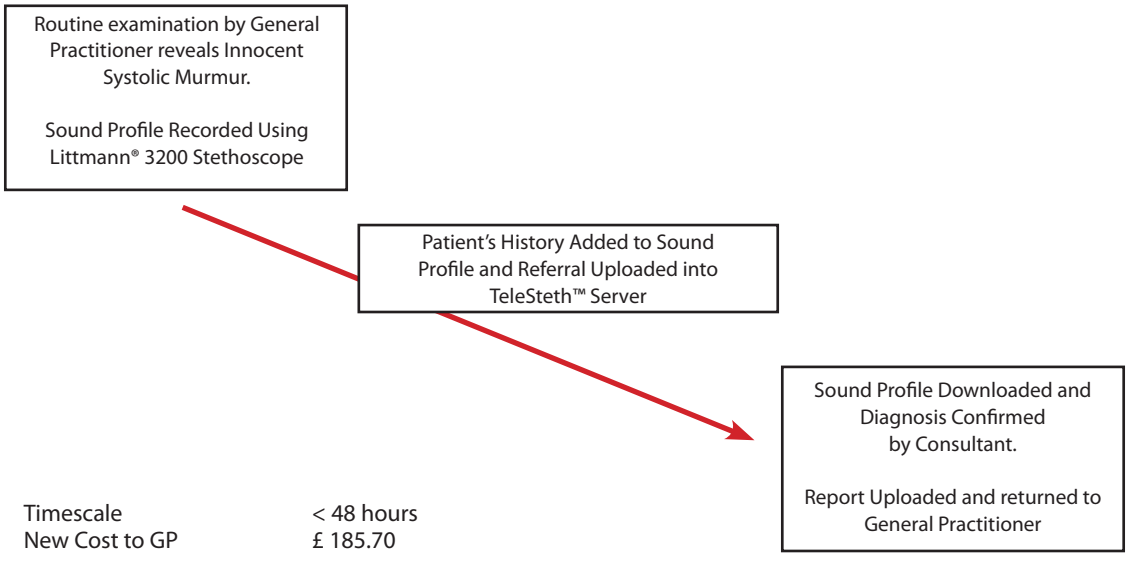

Figure 3. New Proposed Patient Journey.

General Practice:	
Physician	£ 234.60 per hour
Administration	£ 27.00 per hour
Tariffs:	
Referral to Cardiologist	£ 230.00
Simple Echocardiography	£ 80.00
Cost of current patient pathway to manage innocent systolic murmurs in children:	
Physician	£ 89.93
Administration	£ 17.76
Tariffs	£ 310.00
Total	£ 417.69
Cost of new patient pathway to manage innocent systolic murmurs in children:	
Physician	£ 105.57
Administration	£ 8.64
TeleSteth Referrals	£ 25.00 (assumes 20 patients per annum)
New Tariff	£ 46.49 (derived as component of current tariff)
Total	£ 185.70
Secondary Care:	
Cardiologist	£ 460.00 per hour
Current Tariffs	
Consultation	£ 230.00 (30 minutes)
Simple Echocardiogram	£ 80.00

Table 1. Health Economics data collected during the trial.

reduced number of recordings, due to difficulties gaining cooperation from the young patient). In all cases, I felt able to confirm the diagnosis of the GP by assessing the sound files. It remains our belief that with appropriate use of tele-auscultation, we could discharge a patient without the need for a face to face appointment in a clinic.

Conclusions

Recordings of auscultations delivered through the TeleSteth™ server solution appear to be identical to those heard live and digital copies maintained on the local PC.

The introduction of a reporting service for innocent systolic murmurs would allow us to reassure referring paediatricians, general practitioners and parents about a large proportion of children with an innocent murmur, and in so doing, avoid a full consultation and echocardiogram. This is particularly appropriate when the characteristic still's murmur is encountered in pre-school assessments.

We can remotely arrive at a diagnosis and convey this information back in a timely manner, reducing the discharge of the patient from in excess of 90 days, to 48 hours or less. We can reduce the direct cost to the general practitioner from £417.69 per patient, to a maximum of £185.70 per patient (Table 1). We can also introduce a triage process for all new murmurs leveraging the TeleSteth™ server and significantly improve the current process of referral.

A full clinical study will now be pursued in order to demonstrate the statistical sensitivity and specificity of the service, and establish the extent to which the service can be used to introduce benefit. This will be run as a retrospective comparison using the patients who have been enrolled into the pilot phase and further subsequent patients, until a suitable size cohort has been achieved.

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1. "New NHS Network" - N3 is a Wide Area Network (WAN) for the NHS in England and Scotland. It is an Internet Protocol (IP) Network. Each node (user/computer) on an IP network has a unique IP address. N3 is an IP version 4 (IPv4) network. IPv4 networks have IP addresses that are normally shown in an x.x.x.x format, where x is between 0 and 255. For example 192.168.0.1.
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8. Bluetooth is a registered trademark of the Bluetooth SIG, Inc
9. The USB dongle device complies with Part 15 of the FCC Rules. Operation is subject to the following two conditions: 1. This device may not cause harmful interference; 2. This device must accept any interference received, including interference that may cause undesired operation.

Optimal Antiplatelet Treatment Strategy Based on Platelet Reactivity Testing after Coronary Stent Implantation: A Single-centre Experience

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Thrombus formation is a major driver for stent thrombosis, myocardial infarction and cardiovascular mortality.[1-3] Accordingly, a large body of evidence, primarily based on *ex vivo* measurements, shows a close correlation between high on-treatment platelet reactivity (HTPR) and the occurrence of adverse ischemic events among patients treated with clopidogrel following percutaneous coronary interventions.[3-6] This is the rationale for an increasing demand for platelet function testing to detect individuals with prothombotic status (identified by HTPR), to allow individualisation and monitoring of antiplatelet therapy. On the contrary, however, routine measurement of platelet reactivity has not yet been widely implemented in the guidelines, since there have been no large-scale trials demonstrating that adjustment of antiplatelet treatment based on *ex vivo* platelet reactivity testing leads to an improved clinical outcome.[7-10]

Of note, cardiac morbidity and mortality in eastern Germany are known to have increased by 10-20% above average levels, independent of patient age.[11] Since coronary thrombus formation and its precursors play a key role at the site of angioplasty and contribute to major adverse cardiac and cerebrovascular events, we performed additional platelet function testing by use of the VerifyNow assay in our clinical practice.

The present report deals with platelet reactivity of a total of 103 patients with symptomatic coronary artery disease and subsequent clinical events. Forty-five patients suffered from acute coronary syndromes (ACS), including 22 patients with acute STEMI, nine with NSTEMI and fourteen with unstable angina, whereas 58 patients had no ischemia at rest. The age of patients was between 39 and 85 years. All patients were treated at our institution by percutaneous coronary stent implantation and by specific antiplatelet medication according to the guidelines.[12, 13] VerifyNow testing (Accumetrics Inc., San Diego, California) was carried out 2-4 hours after prasugrel (60mg) or ticagrelor (180mg) loading, and 4-24 hours following clopidogrel (600mg) application, in accordance to recent protocols.[4, 7-10, 14, 15] Platelet function testing was not systematically performed in each consecutive patient. Rather, indications for testing were clinically driven. Among them were in-stent-thrombosis, rapid arteriosclerosis progression, staged PCI procedures, severe myocardial infarction, and coronary disease without apparent risk factor. High on-treatment platelet reactivity (HTPR) was indicated by a cut-off value > 208 P2Y12 reaction units (PRU) measured by the VerifyNow test, as recently reported.[9, 14]

As a central finding, high on-treatment platelet activity (HTPR) was identified in 29 of 103 (28%) coronary patients that had been found eligible for additional VerifyNow testing. HTPR was most present (40%) in ACS patients (18 of 45 patients), especially with STEMI (11 of 22 patients; 50%). Presence was lower, but still apparent in 10 of 58 stable coronary patients (17%). Mean PRU value amounted to 278±12 (n=29, x±SEM) for all HTPR patients; mean values (±SEM) for the ACS, STEMI and the non-ACS subsets were 290±17 (n=18), 271±12 (n=11) and 250±10 (n=10), resp. Of note, all patients of the STEMI subgroup were male and six were heavy smokers, but only one patient had diabetes; the frequency of smoking and of diabetes was low in each other subgroup. The incidence of 28% for HTPR, including a staged increase of up to 50% in acute STEMI as revealed by the present study, is confirmed by previous work in the field. Parodi and colleagues described HTPR in 14% of ACS patients undergoing PCI[6] and, while the same authors found an increased frequency of 44% and 60%, resp. in acute STEMI,[15] others reported 31% in elective coronary stenting[5, 16] or 29% for ACS patients switched back from prasugrel to clopidogrel.[14]

In the present study, HTPR in ACS may be even higher than 40%, since some of the 45 patients were taken directly into the cath lab and a priori treated by new platelet inhibitors as recommended by the guidelines,[12, 13] thereby possibly masking HTPR in the presence of clopidogrel. Also, there were patients with considerable comorbidities and bleeding risks, in whom we did not automatically "booster" the 600 mg clopidogrel loading that was already given in the emergency department or pre-hospital. As a result, our present HTPR data lend direct support to the current guidelines that recommend new antiplatelet drugs preferable to clopidogrel.[12, 13] In addition, it should be known that in ACS patients treated with PCI,

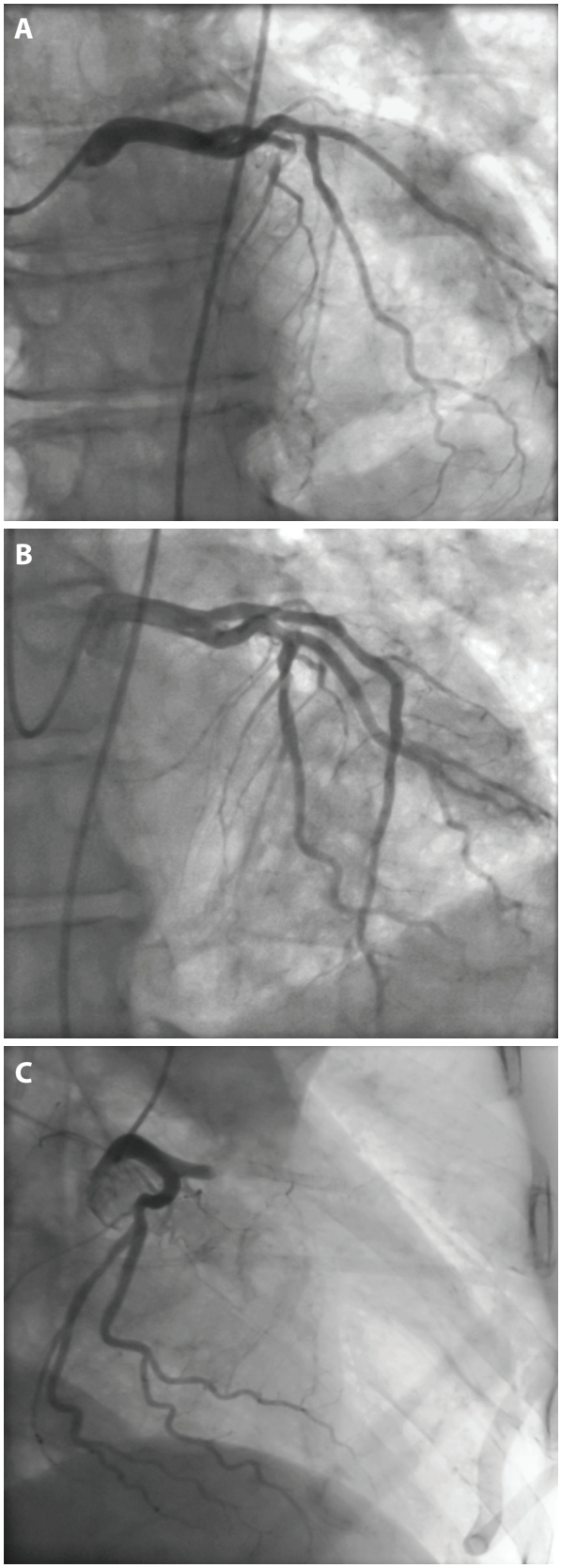

Figure 1. Coronary angiogram of the left coronary artery of a 77-year-old man with acute STEMI due to IST of the proximal LAD before A and after successful recanalisation, B. Eighteen days later, another acute IST at the proximal LAD occurred, resulting in complete occlusion of the artery; see the stent struts at the site of previous stent application. Of note, VerifyNow testing on dual antiplatelet ticagrelor and aspirin therapy was 275 PRU, indicative of ongoing HTPR.

morphine use may be associated with a delayed activity of the new oral antiplatelet agents, possibly related to impaired muscular activity of the stomach and the intestine, with the ultimate consequence of delayed drug absorption.[15] We can confirm these observations by two STEMI patients who showed significant platelet inhibition no earlier than eight hours post intake of ticagrelor.

Modification of antiplatelet therapy by prasugrel or ticagrelor in our patients led to a prompt and pronounced decrease in HTPR, in accordance with previous reports.[9, 14, 15] However, this does not necessarily mean the initiation of an adequate response to these novel drugs in each HTPR patient. In this important aspect, the clinical consequences observed in two patients highlight adjunctive platelet function testing to be extremely useful. The first patient was 83 years old, and was admitted to our hospital for an acute STEMI due to in-stent thrombosis (IST). Both target lesions could be reopened and reconstructed and the patient was stabilised, whereas VerifyNow measurements of 249 and 243 PRU 3h and 24h later, resp. demonstrated persistent HTPR on ticagrelor. The patient died the next day.

The story of the second patient is illustrated by Figure 1. Again, a 77-year-old man suffered from an acute STEMI due to in-stent thrombosis (Figure 1A). Ten days before, the proximal LAD had been stented and the patient was treated with clopidogrel and aspirin; PRU at that time was 202. We repaired the occluded stent (Figure 1B) and adjunctive VerifyNow testing revealed a value of 341 PRU. Thus, we questioned the compliance of the patient, and considered absorption problems due to a genetic disposition or malfunctioning metabolism. With regards to the course of PRU data and the private conditions of the patient, insufficient compliance with regular intake of his dual antiplatelet medication was considered the more probable reason for the worsened platelet inhibition. We switched from clopidogrel to ticagrelor and sent the patient to heart surgery. However, since he was in a stable condition and without angina after the stenting procedure, the patient refused the planned bypass surgery and was finally sent home. Again, however, 18 days post-recanalisation of the LAD-IST, the patient came back with another acute thrombosis at the proximal LAD (Figure 1C). VerifyNow testing on ticagrelor (and aspirin) was 275 PRU, still indicative of persistent HTPR. Therefore, the concern about the patient's compliance arose once more. We immediately sent the patient to coronary bypass surgery; he was operated the same day and now has no need for regular dual antiplatelet medication.
In conclusion, both cases report underscore the high value of adjunctive platelet reactivity testing to exclude persistent HTPR on novel antiplatelet agents. Apparently, this constellation is strongly indicative of impending MACCE.

The following case report is complex and complicated, thereby underlining the severe consequences of unauthorised treatment changes. A 57-year-old man had undergone stent implantation of the

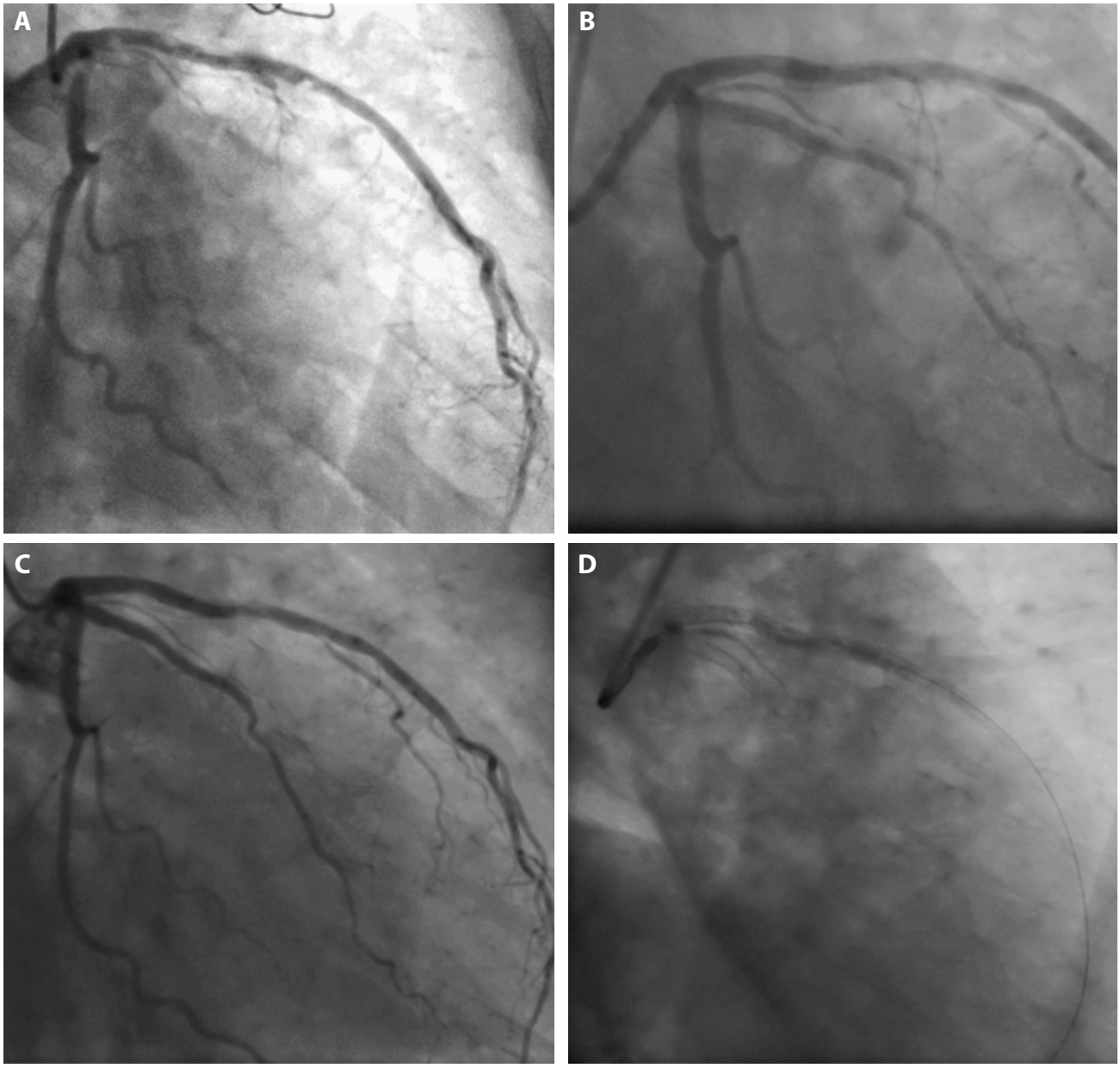

Figure 2. Coronary angiogram of the left coronary artery of a 57-year-old man with severe recurrent IST of the LAD and the circumflex artery (left main stem equivalent). Acute STEMI due to IST of the first marginal branch (occluded), and the endangium inside the circumflex artery (Cx) and the LAD before A and after successful reconstruction of the first marginal branch and the proximal Cx, B. Three months later, ongoing excellent clinical and angiographic result, C. Fourteen months later, cardiogenic shock due to another (lethal) IST of the Cx, first marginal branch and the LAD, D. Importantly, prasugrel medication had been stopped ten days before.

LAD one year before and of the circumflex artery six months before. Since that time he had been treated with prasugrel. In addition, the patient suffered from myasthenia gravis and received immunosuppression. The patient was admitted to our hospital with acute STEMI. The VerifyNow assay value was 314 PRU, indicating HTPR. Importantly, prasugrel had recently been substituted for clopidogrel by the general physician. The angiogram displayed complete occlusion of the marginal branch and severe lesions at the proximal circumflex artery and LAD due to in-stent thrombosis (Figure 2A). All lesions could be reopened and successfully reconstructed (Figure 2B). The patient was re-commenced to prasugrel and aspirin and the VerifyNow test showed a value of 12 PRU. Subsequently, the patient was clinically stable; a follow-up angiogram 3 months later confirmed an ongoing excellent result of the circumflex artery and the marginal branch, and a very good filling of the LAD in contrast to the previous angiogram (Figure 2C). This indicated that the prasugrel and aspirin therapy had probably helped to protect the LAD from thrombus formation. The VerifyNow test revealed persistent reduction of platelet reactivity by a value of 9 PRU.

Fourteen months later, the patient suffered from cardiogenic shock due to another stent thrombosis. The circumflex artery and the marginal branch were occluded; also the LAD showed high-grade lesions (Figure 2D). Unfortunately, the patient had arrived into the hospital very late, and although the LAD and the marginal branch were repaired, the excessive thrombus formation could not be stopped and

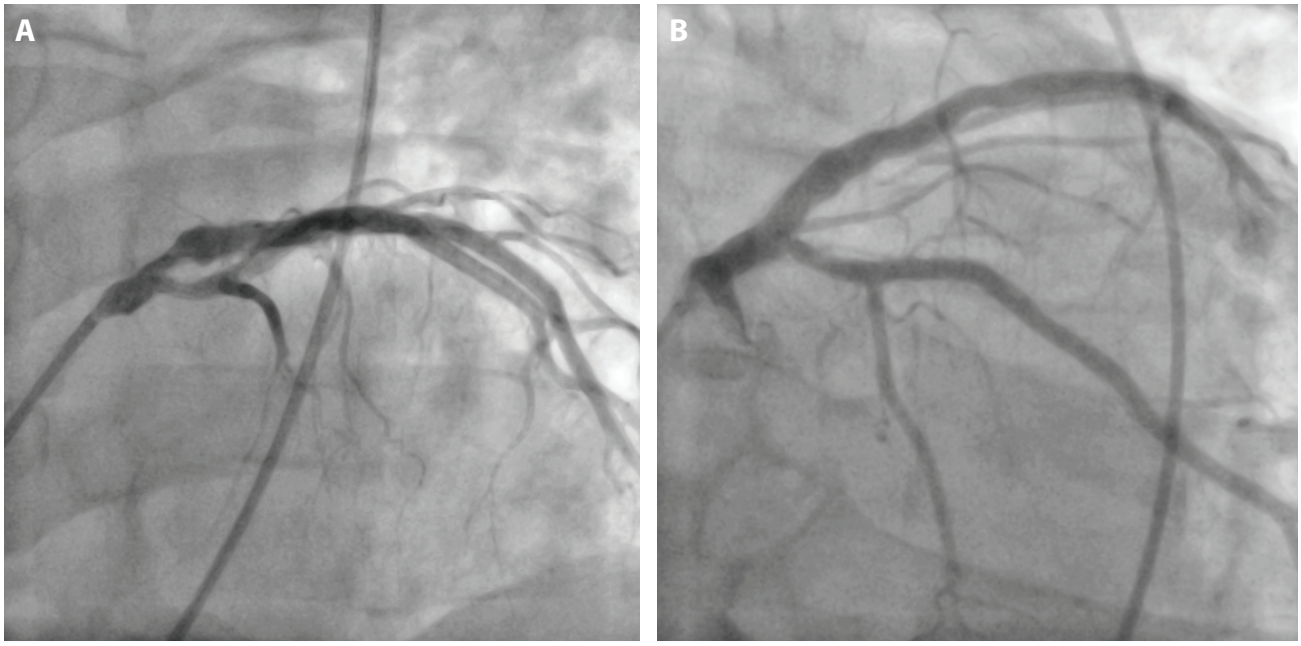

Figure 3. Coronary angiogram of the left coronary of a 76-year-old unstable patient. The high-grade complex proximal LAD stenosis (A) is treated by stent implantation (B), without compromising the left main stem.

finally caused the death of the patient. Later, we were informed that the patient had stopped taking prasugrel ten days before, following advice from the general physician. At this time, we might discuss the time limit for dual antiplatelet therapy of 12 months that is manifested in the guidelines and reconsider its usefulness in selected cases. Furthermore, this case does not only illustrate the importance of careful follow-up of patients, but also underscores the catastrophic sequelae of unauthorised treatment changes.

The following case report is an example for tailored antiplatelet treatment in four subsequent clinical scenarios in the same patient, again emphasising the role of adjunctive VerifyNow testing. A 76-year-old man with unstable angina due to a complex 80% proximal LAD stenosis was successfully treated by the implantation of a 4,0 mm drug eluting stent. Representative coronary angiograms pre- and post-stent implantation are depicted by Figure 3A and B. His comorbidities were an infrarenal aortic prosthesis and a mixed connective tissue syndrome treated by corticosteroids, known for their prothrombotic effects. Twelve hours after stent implantation and 600 mg clopidogrel loading, platelet reactivity was found

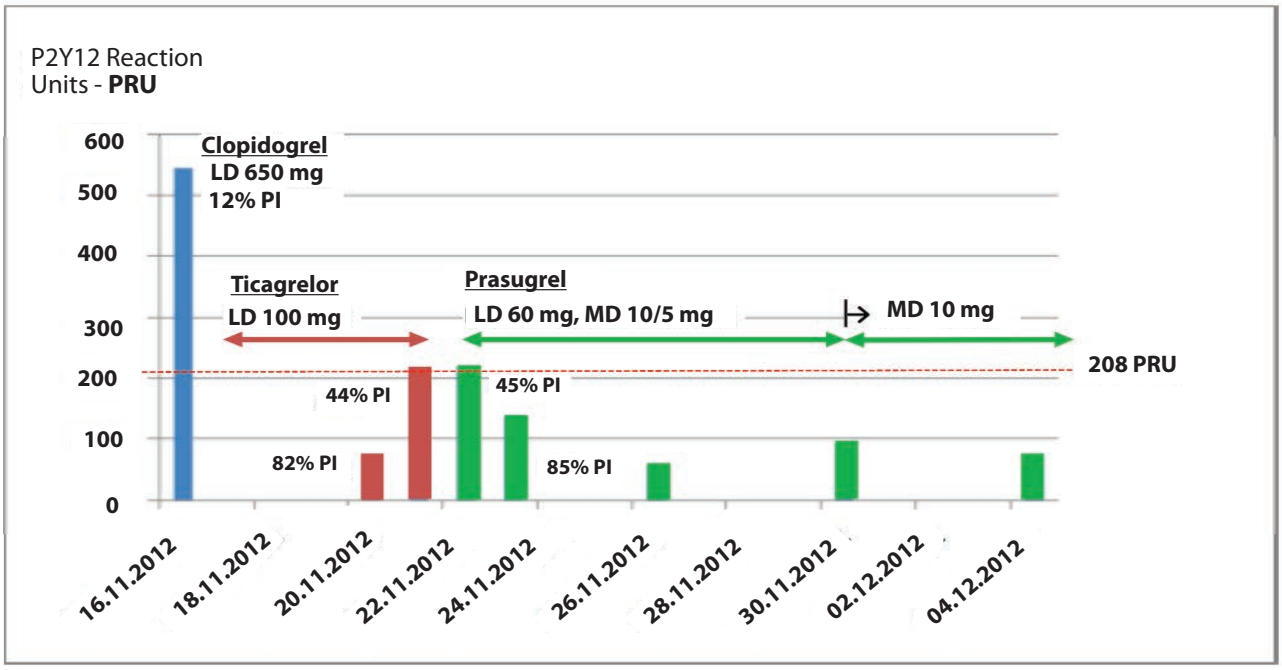

Figure 4. Individual antiplatelet treatment strategy based on VerifyNow testing with HTPR constellation. The cut-off value >208 PRU is indicated by the dotted red line. For further details of the clinical course, respective VerifyNow measurement data and subsequent differential antiplatelet treatment see the text. LD, loading dose; MD, mean dose; PI, platelet inhibition.

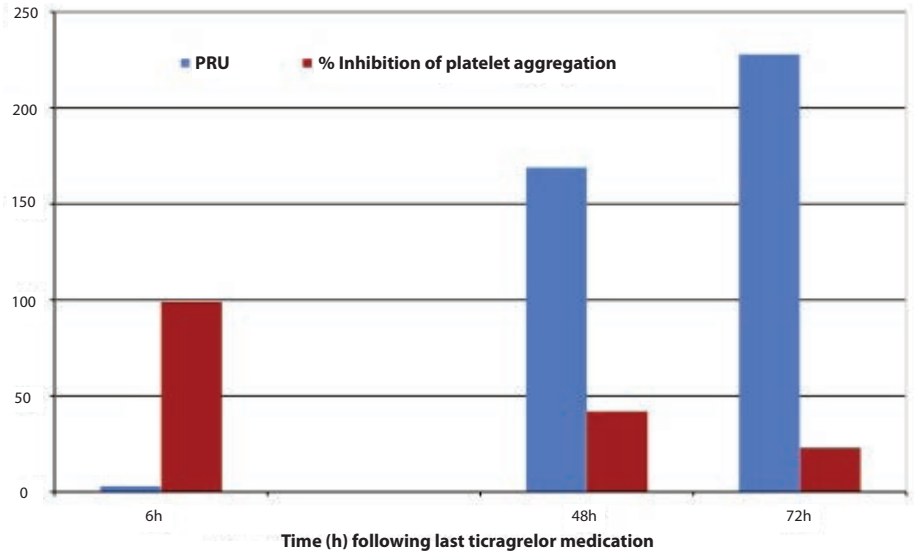

Figure 5. Recovery of platelet reactivity after tricagrelor withdrawal. See the inhibition of platelet aggregation (red bars) already below 50% 48 hours following the last ticagrelor medication, while platelet reactivity (blue bars) increased to a value of 169 PRU. Note that due to VerifyNow testing abdominal surgery was performed on day 3 (72 hours) rather than waiting the full 5-day period commonly recommended.

markedly increased, with 544 PRU by additional VerifyNow assessment (Figure 4).

To antagonise the apparent HTPR, ticagrelor was started. Subsequently, four days later, VerifyNow testing showed a value of 73 PRU, indicating effective inhibition of 82% (Figure 4). However, the patient increasingly suffered from new-onset dyspnoea, a known side-effect of the drug.[12] Therefore, ticagrelor was stopped, which was followed by complete resolution of dyspnoea within 48 hours. Taking the ongoing effect of P2Y12 receptor binding into account, the decision for further antiplatelet treatment was difficult due to threads by either increased bleeding or thrombotic complications in the stented coronary artery. When the VerifyNow testing revealed a value of 213 PRU the following day, we felt the dose of 10 mg prasugrel suitable to continue antithrombotic treatment, high enough to avoid stent thrombosis and low enough to avoid excessive bleeding (Figure 4). A further decrease in platelet inhibition was stopped or even corrected by 10 mg prasugrel daily, as outlined by VerifyNow values of 219 and 139 PRU, resp. However again, age-related limitations of prasugrel use in patients > 75 years that had prevented its application a priori had to be considered. In summary, a decreased prasugrel dose of 5 mg as advised for patients >75 years was too low to yield sufficient platelet inhibition efficacy. As outlined, by the subsequent VerifyNow data, the daily dose of 10mg proved to be adequate for effective antiplatelet treatment (Figure 4). In summary, this case report confirms VerifyNow testing to be a valuable tool for individual tailored antiplatelet therapy in different clinical scenarios.

Platelet function testing may also be useful to monitor the recovery of platelet reactivity after the withdrawal of platelet medication before surgical interventions. Surgery guidelines are widely based upon empirical data on the time of terminating antiplatelet medication before surgery. For ticagrelor, the recommendations state that drug intake should cease for 5 days before surgery is permitted.[12, 13] This is shown in Figure 5 in the 74 year-old patient who required abdominal surgery but had undergone coronary stent implantation at the proximal LAD three weeks before. The VerifyNow assays allowed the patient's PRU values to be monitored closely, and on day 3 the value has reached 228 PRU, whereas inhibitions decreased to 42% (48h) and 23% (72h). This meant that the operation could take place on day 3 rather than waiting the full 5-day period recommended by the guidelines, thereby saving 2 days of hospitalisation.

In summary, our experience with the VerifyNow system clearly demonstrates that adjunctive platelet function testing in selected patients, especially in those with ACS/STEMI, is useful to identify and mitigate HTPR, to individualise and monitor antiplatelet treatment, to identify non-compliance and unauthorised treatment changes. Specifically, use of VerifyNow testing detected HTPR and lead to treatment modification in 29 of 103 patients (28%), beyond confirmation of low platelet reactivity not requiring further action in 74 of 103 patients (72%). Regarding the waiting period for surgery, the same tool may be cost-effective by shortening recovery time after antiplatelet discontinuation and associated pre-surgical length of stay. In conclusion, in a single-centre analysis of a real world application of platelet function testing, the VerifyNow test facilitates the personalised choice of P2Y12 antiplatelet therapy, while still allowing compliance to treatment guidelines. However, a still unresolved concern is that several studies using platelet function tests provide (low and very low) platelet reactivity data, which have shown to be surrogates of worse outcomes in larger investigations.[7, 14] Therefore, additional basic science as well as clinical work is necessary to make antiplatelet treatment safe and effective for all patients.

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Childhood Obesity; Top Priority in Preventive Cardiology?

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Introduction

Childhood obesity is evolving into a pandemic that jeopardises the health of middle-aged and even young adults. Associated co-morbidities are numerous and range from cardiovascular diseases (CVD) and diabetes to sleep apnoea, asthma and emotional disturbances caused by stigmatisation. Fortunately, timely intervention leading to normal weight in adult life restores cardiovascular risk to a level that is no different from those who have never been obese.[1]

The advent of non-invasive techniques that allow assessment of peripheral endothelial function has changed our understanding of the sequential steps that underlie the pathophysiology of CVD related to childhood obesity.

The endothelial cell layer, long underappreciated as a simple inert barrier, plays a crucial role in maintaining vascular tone, thereby regulating blood flow in relation to demand. The process of Vascular Smooth Muscle Cell (VSMC) relaxation is governed by nitric oxide (NO) (Figure 1). In response to increased shear stress or as a result of insulin signalling, increased phosphorylation of endothelial Nitric Oxide Synthase (eNOS) will increase NO formation. NO activates guanylyl cyclase, which induces VSMC relaxation, through increased production of cyclic Guanosine MonoPhosphate (cGMP).

Healthy endothelium, however, also guarantees atheroprotection through the control of platelet aggregation, of VSMC proliferation, and of adhesion and diapedesis of leukocytes. However, the maintenance of normal endothelial function requires a balance between vasodilating (NO-related) mechanisms and vasoconstrictive factors, which mainly result from damage imposed on endothelial cells. The latter for instance include classical risk factors, which are associated with obesity.

During the past decade it has become clear that endothelial dysfunction, which is the earliest demonstrable step in the process of atherosclerosis,[2] could serve as a major target and even a surrogate endpoint of interventional studies which aim to reverse the detrimental effects of long-standing obesity in children.

Factors Responsible for Obesity-related Endothelial Dysfunction

Hypertension is highly prevalent in obese children[3] and is associated with multiple factors that adversely affect endothelial function, including an overactive renin-angiotensin aldosterone and sympathetic nervous system, leading to impaired eNOS activity, peripheral vasoconstriction and increased oxidative stress.

The PEP Family Heart Study,[4] conducted in 3038 adolescents (12 to 18 years) has demonstrated that central obesity promotes hyperlipidemia, with elevated triglycerides, LDL-cholesterol, non-HDL cholesterol, triglyceride/HDL-cholesterol ratio and low HDL-cholesterol. Physical activity and physical fitness are increasingly recognised as independent determinants of longevity. Physical inactivity in obese children is manifest and a relation between physical activity/fitness and endothelial dysfunction has been demonstrated.[5]

Adipocytes are no longer considered a simple storage for free fatty acids. It is now generally accepted that adipose tissue is an endocrine organ, responsible for the release of a whole series of so-called adipokines (adipocyte-derived cytokines).[6] In addition, hypertrophic adipose tissue releases pro-inflammatory cytokines such as Tumour Necrosis Factor alpha (TNF-α), leading to enhanced expression of Intercellular Adhesion

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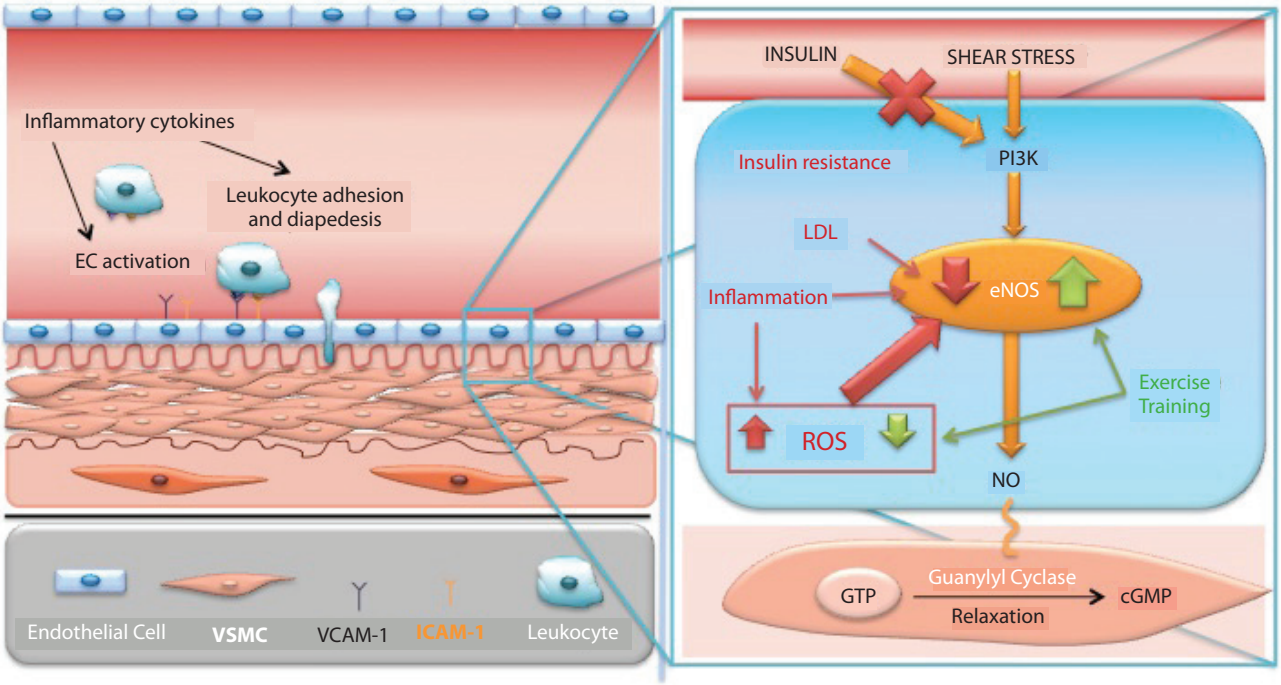

Figure 1. Left side: upon activation by inflammatory cytokines endothelial cells express adhesion molecules (i.e.; VCAM-1 and ICAM-1), which allow leukocytes to adhere, transmigrate and initiate a cascade of inflammatory reactions. Right side: schematic overview of nitric oxide (NO) production and relaxation of Vascular Smooth Muscle Cells (VSMC). In response to increased shear stress or as a result of insulin signaling, the phosphoinositol 3 kinase (PI3K)/akt pathway is activated leading to phosphorylation of endothelial Nitric Oxide Synthase (eNOS). eNOS converts L-arginine to L-citrulline and NO. NO activates guanylyl cyclase, which induces smooth muscle relaxation, through increased production of cyclic Guanosine MonoPhosphate (cGMP). Superoxide reduces NO bioavailability by reacting with NO to form peroxynitrite (ONOO-), which has strong oxidant properties.

Endothelial dysfunction in obese children is characterised by insulin resistance impairing insulin mediated NO production and subsequent vasodilation. Furthermore LDL and inflammatory cytokines are inhibitors of eNOS activation. Localised chronic inflammation leads to increased reactive oxygen species (ROS) generation, which also contributes to reduced bioavailability of NO and vasoconstriction. Finally, exercise training up regulates both eNOS protein expression and eNOS phosphorylation, and increases anti-oxidative mechanisms.

EC, Endothelial Cell; VSMC, Vascular Smooth Muscle Cell; VCAM-1, Vascular Cell Adhesion Molecule 1; ICAM-1, InterCellular Adhesion Molecule 1. PI3K, PhosphatidylInositol 3-Kinase; LDL, Low Density Lipoprotein Cholesterol; ROS, Reactive Oxygen Species; eNOS, endothelial Nitric Oxide Synthase; GTP, Guanosine TriPhosphate; cGMP, cyclic Guanylyl MonoPhosphate.

Molecule-1 (ICAM-1), InterLeukin (IL)-6, and Macrophage Chemo attractant Protein-1 (MCP-1). As a consequence, leucocytes adhere to the endothelium and diapedesis of monocytes from the circulation to adipose tissue is stimulated. As such, the stage for a chronic low grade inflammatory status is set, leading to enhanced oxidative stress and the subsequent inhibition of the vasodilating effects of NO, impaired generation of NO and eNOS uncoupling. Firstly, the production and secretion of adiponectin, a cytokine with anti-inflammatory, insulin-sensitising and anti-atherogenic properties, is reduced. Lower adiponectin levels affect endothelial function by reducing NO bioavailability and through its effect on circulating angiogenic cells.[7] Secondly, leptin is mainly secreted by white adipose tissue. It suppresses appetite, increases energy expenditure and has pro-angiogenic effects, including enhanced eNOS phosphorylation and the stimulation of endothelial cell proliferation. However, the benefits of increased leptin levels in obese individuals are mitigated by a selective leptin resistance for both central (appetite) and peripheral (pro-angiogenic) effects.[8]

Insulin resistance, and especially type II diabetes, are feared complications of childhood obesity. Since insulin is a potent vasodilator, the co-occurrence of endothelial dysfunction with insulin resistance comes as no surprise. In addition, insulin resistance is associated with increased levels of endothelin-I, a potent vasoconstrictor, and the upregulation of adhesion molecules. Diabetes mellitus leads to increased levels of reactive oxidant species (ROS) and Advanced Glycation End products (AGE), which further compromise NO bioavailability.

Finally obesity is an independent risk factor for sleep apnoea. Both in children and adults, sleep apnoea predisposes to the development of endothelial dysfunction,[9] through mechanisms that include hypertension and altered autonomic cardiovascular control.

Established and Novel Techniques to Assess Endothelial Dysfunction

Assessment of flow-mediated dilation (FMD) at the level of a large conduit artery, usually the brachial artery, is still the gold standard for evaluation of peripheral endothelial function, also in children.[10] It implies the use of high-resolution ultrasound to measure the internal diameter of the artery, from lumen-intima interface on the near and far vascular wall.[11] Thereafter, the brachial artery is occluded during 5 minutes using an inflated sphygmomanometer. After release, increased flow causes endothelial-dependent dilation through raised shear stress.[12] An

impaired proportional response (i.e., related to baseline diameter) is the signature of NO-dependent impaired endothelial dysfunction. Despite its universal application, the use of FMD is hampered by inter- and intra-observer variety and requires high levels of experience. Moreover, correct assessment of endothelial function demands strict technical and environmental standardisation, as well as patient adherence to diet and abstinence from smoking.

More recently, peripheral arterial tonometry (PAT) has been put forward as an alternative technique, which is semi-automated and less subject to interpretation. It involves probes that are placed on the index finger of both hands and by which pressure differences secondary to dilating arterioles in the fingers are measured. Similar to FMD, the brachial artery is occluded during 5 minutes. Following release of the cuff, the Reactive Hyperemia Index (RHI) is calculated after 90 to 150 seconds during the hyperemia phase and defined as the mean Pulse Wave Amplitude (PWA) divided by the pre-occlusion period. The ratio is corrected for the ratio measured at the contralateral hand and multiplied by a correction factor. Despite its clinical and outcome correlates, RHI is a measure of microvascular endothelial function and therefore, contrary to FMD, it does not solely depend on NO.[13] Other factors such as the vasodilator prostacyclin (PGI2), as well as Endothelium-Derived Hyperpolarising Factor (EDHF) and sympathetic tone play a significant role.

How Should we Approach Childhood Obesity and the Associated Endothelial Dysfunction?

The obvious goal of the management of childhood obesity is to achieve weight loss. In order to ensure a sustained adaptation of lifestyle, a multi-disciplinary approach is essential. Besides significant diet changes, the introduction of physical activity is an essential component of such a strategy. Mental coaching, psychological evaluation and family counselling are increasingly evaluated for their additive value in order to achieve long-term success.

Weight Loss

Weight loss ameliorates CV risk factors, such as hypertension, lipid abnormalities and glucose metabolism, all of which are known to be associated with endothelial dysfunction. It is difficult to tease out the absolute net effect of weight loss in terms of improved endothelial function, since the available literature mainly deals with multi-disciplinary approaches. In a small single-centre study, Kaufman *et al*. demonstrated that a 5 to 8% decrease in total body mass obtained with diet alone led to a significant decrease in weight, body fat percentage and BMI, with a trend towards improvement of endothelial function.[14] Comparing combined diet and 6 weeks of exercise training to diet alone in 82 overweight children, 9 to 12 years of age, Woo *et al*. saw improved endothelial function in both groups, albeit significantly more pronounced in the diet plus exercise group.[15]

Exercise Training

Based on a large study involving 6000 children between 11 and 19 years, De Bourdeaudhuij *et al*. concluded that overweight children are significantly less active than their healthy counterparts. Significant differences were also noted for vigorous and moderate physical activity.[16]

Exercise training is a potent adjunct treatment modality when it comes to improving endothelial function in obese children. As little as eight weeks of exercise training consisting of three 1-hour sessions of circuit training each week led to a significant improvement in endothelial function, even without weight loss in a randomised cross-over study involving 19 obese adolescents.[17] Two other studies confirmed the effect of exercise alone on endothelial function. Meyer *et al*. investigated the effects of 1 hour of training, 3 times a week during 6 months and noted a significant improvement of endothelial function and a reduction in IMT in young (14.7 ± 2.2 years) obese children.[18] Tjønna *et al*. demonstrated that 3 months aerobic interval training outweighed a multidisciplinary treatment programme of 1 year in terms of improved endothelial function and reduction in CV risk factors.[19]

Besides the modulatory effect of regular physical activity on CV risk factors, exercise directly impacts endothelial function by increasing endothelial shear stress. In adult patients undergoing coronary artery bypass surgery (CABG), exercise training prior to CABG led to upregulation of eNOS mRNA and higher eNOS protein and phosphorylation in arterial segments.[20] ROS generation was significantly lower in the training compared with the control group. On a functional level, exercise training resulted in improved acetylcholine-mediated vasodilatation of the arterial segments obtained from the left internal mammary artery.

Pharmacological Treatment

The available literature on pharmacological treatment of obese children with respect to the effect on endothelial function is limited. Since the withdrawal of both rimonabant and sibutramine, due the increased risk of psychiatric adverse events[21] and increased CV risk[22] respectively, orlistat, a reversible blocker of lipase, is the only drug still available to aid weight loss in Europe. Based on a recent meta-analysis of data obtained in children, it appears that a drug-related weight loss of 5 kg and 5 cm reduction in waist circumference after at least 6 months of therapy, did not improve lipid abnormalities nor insulin levels.[23] In an open-label trial conducted in adults and consisting of a calorie-restricted diet and 120 mg of orlistat, there was no demonstrable effect on FMD.[24]

Metformin is approved in many countries to treat insulin resistance in obese children. Despite its benefit in adults with metabolic syndrome, adding metformin to a structured lifestyle intervention did not reverse insulin resistance in obese children.[25]

Psychological Approach

Obesity in children is associated with both psychological and social problems. Psychosocial distress and eating disorders are more

prevalent[26] and are associated with a generally worse quality of life, further aggravating obesity. Therefore many treatment programs successfully included cognitive behavioural therapy, leading to a longer lasting effect in terms of weight maintenance. The main goal of such programs is to educate children about energy balance, so they learn to understand how obesity develops. To achieve lifestyle modifications children are taught self-regulation skills and actively participate to set up a tailor fit personal plan.[27]

Parents are involved in helping their child obtain a new lifestyle, including changes in food preparation and organising exercise, since including the parents is not only effective in treatment,[28] but also in prevention of childhood obesity.[29] The current evidence for preventive programmes is strong and recommended by the European Society of Cardiology in their recent guidelines on cardiovascular disease prevention,[30] to start in early childhood and to continue throughout adulthood and senescence.

Although the association of anger and hostility and coronary artery disease related morbidity and mortality is proven in adults,[31] it remains to be determined whether these psychological traits, which are highly prevalent in obese children, impose an additional cardiovascular risk. Interestingly, Osika *et al*. were able to demonstrate in 248 healthy children, that scores for anger, depression and anxiety are inversely correlated to endothelial function as assessed with Endo-PAT.[32]

Conclusion

The prevalence of childhood obesity is rapidly increasing and exposes these children to a significant cardiovascular risk. Research has mainly focused on vascular alterations in adults who have been obese for several decades, yet obese children represent the other end of the spectrum with respect to the pathogenesis of atherosclerosis. Endothelial dysfunction has been demonstrated to be the first, reversible step towards atherosclerosis and more translational and clinical research is necessary to fully understand this *primum movens*.

Finally, intensifying the collaboration between researchers and clinicians is essential to both understand and efficiently tackle childhood obesity associated cardiovascular disease.

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Endovascular Strategies for Thrombus Management

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Background

Acute coronary syndromes (ACS) represent the commonly sudden, and often fatal, clinical manifestation of a pathologic phenomenon which consists of the rupture of a coronary plaque and a resultant occlusive thrombosis. Atherosclerosis has a central role in the pathophysiology of ACS and the presence of vulnerable plaque (VP) has been widely accepted as the primary cause of this life-threatening condition.[1,2] VP is a lesion made of several components such as large lipid necrotic core and thin fibrous cap with macrophage infiltration (Thin Cap Fibroatheroma), which predispose the plaque to a high risk of rupture.[3,4] This event is followed by the exposure of thrombogenic materials with simultaneous activation of primary and secondary haemostatic pathways. Platelets agglomeration and adhesion together with fibrin formation and red cell entrapment determine the size, shape and colour of the so developed thrombus. Thrombus composition and features have been associated with the severity of clinical presentation, accounting for poor prognosis especially when of recent formation and rich in red cells (red thrombus).[5-7] A non-occlusive or transiently occlusive thrombus most frequently underlies unstable angina with pain at rest and non-ST segment elevation myocardial infarction (non-STEMI), whereas a more stable and fully occlusive thrombus is most frequently seen in ST segment elevation myocardial infarction (STEMI), with possible adjunctive vascular tone modification and collateral flow development.[8-10] Moreover distal embolisation of particles deriving from the necrotic core of the vulnerable plaque or straightly from the thrombotic agglomerates seems to play a crucial role in determining the so called "no-reflow phenomenon" and, ultimately, the infarct size. (Figure 1, 2)

The presence of angiographically detected thrombosis in patients hospitalised with ACS is associated with a higher incidence of adverse events, with a reported rate of death or non-fatal myocardial infarction of 15.8% at 6 months.[11] Therefore, an appropriate and aggressive management of thrombus is needed to prevent distal embolisation and to achieve a better acute reperfusion result as well as a long-term result. Over the last two decades, the management of ACS has evolved through the findings of several large, randomised clinical trials, and advancements have included novel antiplatelet agents, anticoagulants and several devices for percutaneous revascularisation.

According to clinical presentation, thrombosis is distinguished in acute and chronic and, besides the coronary arteries system, it may also occur in a peripheral vessel. Thrombotic phenomena in coronary arteries tend to settle acutely, while the peripheral involvement is generally chronic. Despite this, there is a general agreement that treatment of this pathologic condition should focus on the acute presentation, granting higher benefits in terms of functional recovery.

At present the main strategies to overcome thrombosis and the subsequent risk of distal embolisation take advantage of pharmacological treatments, mechanical devices (divided into two categories, based on their mechanism of action, namely distal embolic protection devices and thrombectomy devices or catheters) and covered stents.

Pharmacological Strategies

Anticoagulant options in the setting of primary PCI (pPCI) include unfractioned heparin (UFH), enoxaparin and bivalirudin. UFH is an indirect thrombin inhibitor that represents the first line therapeutic agent for any catheter-based intervention and is used independently of the stable or unstable clinical presentation. However, UFH bears some limitations[12] such as its relative inability to inhibit clot-bound thrombin, its poor control of von Willebrand factor release, as well as

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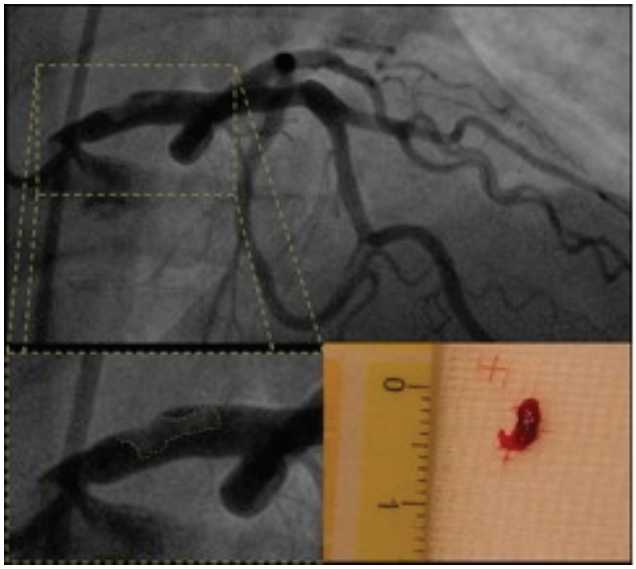

Figure 1. Angiographic image showing large thrombus in left main stem; right panel: thrombotic material subsequently aspirated.

platelet activation and rebound of thrombin generation after discontinuation, so that alternative anticoagulant agents were investigated. Enoxaparin has a more predictable pharmacological profile, showing good performance in the presence of ACS and in other PCI settings. One randomised, open-label trial, the Acute myocardial infarction Treated with primary angioplasty and intravenous enOxaparin or unfraction heparin to Lower ischemic and bleeding events at short- and Long- term follow-up (ATOLL) trial has investigated the short- and long-term benefits of the treatment with Enoxaparin versus UFH in patients undergoing pPCI.[12] Despite similar results in terms of peri-procedural events (30-day death, complication of myocardial infarction and major bleedings) the authors demonstrated a lower incidence of the composite main secondary endpoints (death, recurrent myocardial infarction or ACS or urgent revascularisation) suggesting that enoxaparin may be preferred over UPH when possible (European Society of Cardiology [ESC] guidelines 2012: Class of recommendation [COR] IIb, Level of Evidence [LOE] B).[14]

Bivalirudin is a direct thrombin (factor IIa) inhibitor that blocks the conversion of fibrinogen into fibrin and has a low attitude towards binding to plasmatic proteins, thus producing a predictable anticoagulant effect that can be checked with routine tests (ACT, aPTT). The ACUITY trial tested various anticoagulant regimens, showing non-inferiority of bivalirudin in respect to classical approaches in relation to cardiac events, with an advantage in major bleeding at the 30-day analysis.[15] Guidelines have included recommendation for bivalirudin instead of UFH plus IIb/IIIa glycoprotein inhibitors in patients with ACS undergoing early invasive treatment (American Heart Association/American College of Cardiology [AHA/ACC] and ESC: COR I, LOE B).[14,16]

Glycoprotein IIb/IIIa inhibitors (abiciximab, tirofiban and eptifibatide) are potent inhibitors of platelet aggregation frequently administered to patients with ACS undergoing PCI, especially in the setting of PCI with

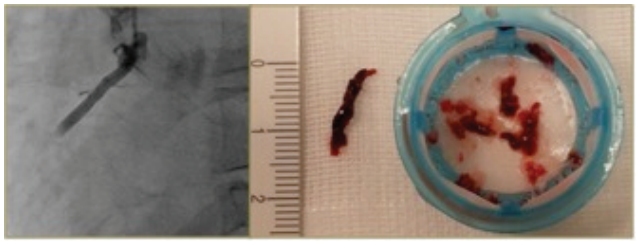

Figure 2. Occlusive thrombotic lesion of right coronary artery; right panel: thrombotic material subsequently aspirated.

highly thrombotic lesions.[17,18] They have rapid onset of action and result in a high level of inhibition of platelets aggregation with several randomised clinical trials supporting their use in pPCI.[19-22] De Luca *et al*. in a recent meta-analysis have shown the patients receiving abciximab in the setting of pPCI had lower 30 day mortality compared to the control group of patients not receiving abciximab (2.4% vs 3.4%, p=0.047), and this beneficial effect was also seen at 6 and 12 months follow-up (4.4% vs 6.2%, p=0.01).[23] The same authors have also reported a comparison in benefits between small molecules (tirofiban and eptifibatide) and abciximab, showing non-significant differences in clinical outcomes in terms of death, final TIMI flow grade and ST segment resolution after pPCI. In 2011 the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) PCI guideline executive summary stated that "In patients undergoing pPCI treated with UFH [unfractionated heparin], it is reasonable to administer a GPIIb/IIIa inhibitor (abciximab, double bolus eptifibatide or high bolus dose tirofiban), whether or not patients were pretreated with clopidogrel" as class IIa indication,[24] while the European Society Cardiology (ESC) guidelines on STEMI in 2012 suggest a COR IIb, LOE: B14. In recent studies, a proper time for GIPs administration has been investigated, but results showed conflicting data.[23,25] The issue still remains a matter of concern and the 2011 ACCF/AHA/SCAI PCI guideline executive summary indicated GPI administration as class III indication for routine pre-catheterisation laboratory (e.g. ambulance or emergency room) as part of an upstream strategy for patients with STEMI undergoing PCI.[24]

Mechanical Devices – Thrombectomy Devices

Thrombectomy devices have been developed to remove intracoronary thrombus by generating an active and strong suction force. Thrombotic material is fragmented into small particles and then aspirated as the thrombectomy catheter moves forward and backwards through the coronary lesion. They can be further classified into manual (Export, Pronto, Thrombuster II etc.) or mechanical (AngioJet Rheolytic Thrombectomy, X-Sizer etc.) thrombus aspiration devices (Figure 3). For manual devices, aspiration should start a few centimetres proximal to the target lesion, and then the catheter should then be moved forwards very slowly with continuous aspiration, with the lesion being gently crossed when possible. Several trials (EXPORT, EXPIRA, TAPAS)[26-28] demonstrated improved myocardial reperfusion and survival rates in patients with STEMI who underwent PCI plus thrombectomy compared with patients treated with PCI alone. In the TAPAS trial, the primary

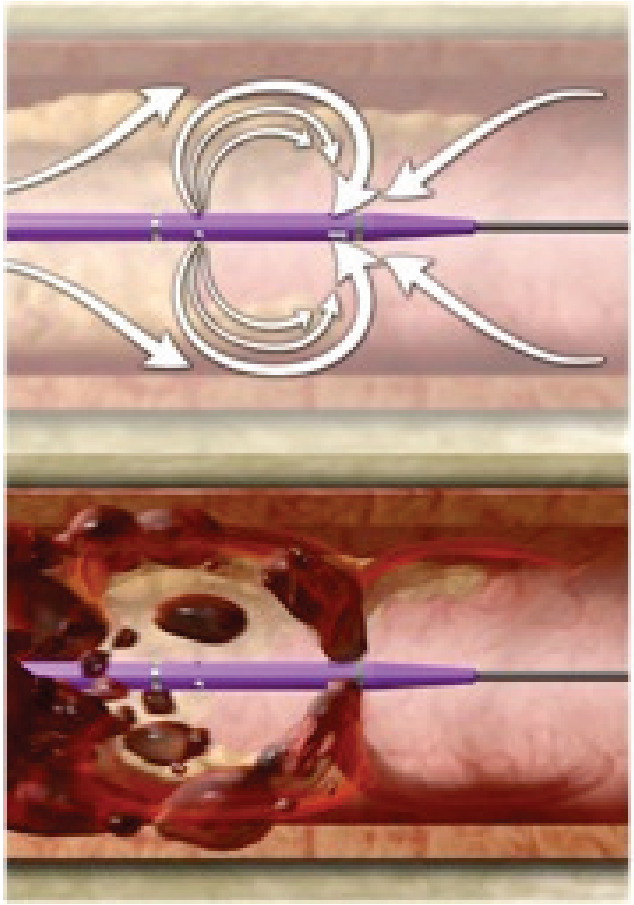

Figure 3. AngioJet Thrombectomy Catheter System, as an example of mechanical thrombectomy devices. Saline jets travel backwards to create a low pressure zone causing a vacuum effect, so that thrombus is drawn into the in-flow windows and pushed back down the catheter.

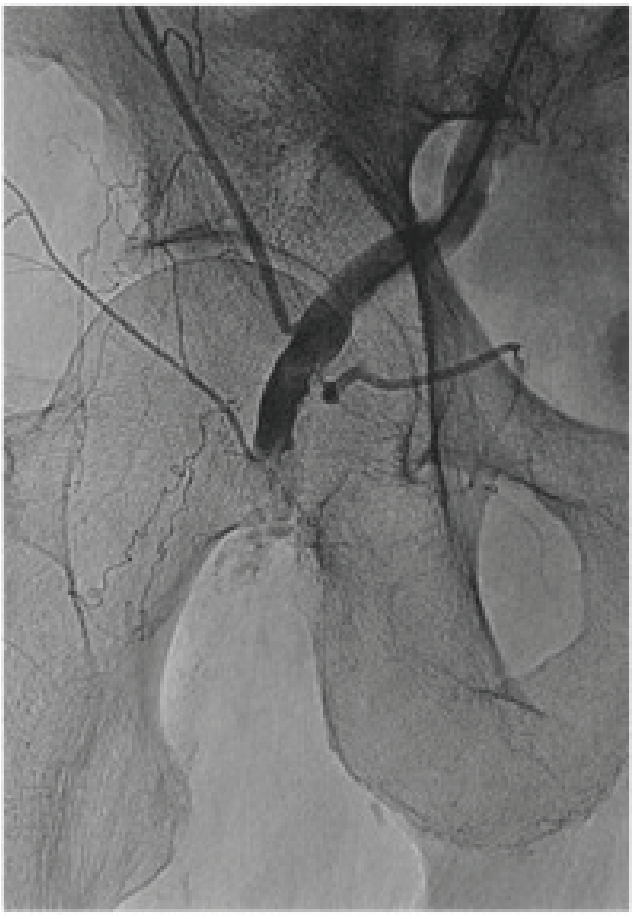

Figure 4. Thrombosis of right common femoral artery. A percutaneous treatment was adopted to restore patency.

endpoint consisted of myocardial bush grade (MBG) 0 or 1 (defined as absent or minimal myocardial perfusion after the procedure, respectively), which occurred in 17.1% of patients in the thrombectomy group and in 26.3% of those in the conventional PCI group (p<0.001). The secondary endpoints included the incidence of major cardiac events (as cardiac death and non-fatal re-infarction) at 1 year follow-up, which was shown to be less frequent in the study group (5.6% vs 9.9% p=0.009).[28] The encouraging results from this trial gave a strong drive to the use of manual thrombus aspiration devices, which are now widely adopted in almost all pPCI and recommended in the European Guidelines on STEMI revascularisation strategies (COR IIa, LOE B).[14]

Mechanical Devices – Distal Embolic Protection Devices

Distal embolic protection (DEP) devices were first developed in order to protect from embolisation during PCI in diseased saphenous vein graft (SVG). The Saphenous vein graft Angioplasty Free of Emboli randomised trial (SAFE) was the first trial that used the PercuSurge GuardWire, a transient distal balloon occlusion guidewire that allows the recovery of debris liberated during PCI by aspiration before restoration of anterograde flow.[29] Later, filter embolic protection devices were introduced, which consisted of a guidewire with an expandable filter that is positioned distally to the culprit lesion to capture and then retrieve embolic material that may be displaced at the moment of balloon angioplasty and stenting. Despite the strong plausibility behind the development of these devices, a certain number of trials have shown no real improvement in microvascular perfusion or clinical outcomes when DEP devices were used during pPCI.[30, 31] Indeed, these are not recommended in STEMI patients (ESC guidelines: COR III, LOE C),[14] but are beneficial during Carotid Artery Stenting (CAS), as assessed in some recent trials.[32-34]

Mechanical Devices – Mechanical Thrombectomy

Mechanical thrombectomy is performed with more complex mechanical devices and consists of thrombectomy with active thrombus defragmentation and aspiration (AngioJet, Figure 3). Mainly, thrombectomy is accomplished by the incorporation of a pressurised high velocity saline stream at the catheter tip. Once in the pathway of the jets, thrombus is fragmented into small particles, while the jets also provide the driving force for evacuation of the thrombus debris from the body through the catheter and associated tubing. Few studies support the use of AngioJet to face coronary thrombosis.[35, 36] However, according to two meta-analysis of pooled randomised clinical trials, simple manual aspiration has emerged as the only modality with clinical benefit in the setting of AMI, while the other modalities had either neutral benefit or even detriment (with rheolytic thrombectomy).[37, 38] A possible explanation for the disappointing results seen with mechanical devices may lay in a higher operative complexity, which also accounts for the

longer procedure time, if compared with manual aspiration devices.

In addition, the recent meta-analysis of Burzotta *et al*. has shown that IIb/IIIa GPIs administration together with thrombus aspiration results in a lower mortality rate when compared with thrombectomy alone, GPIs alone or neither GPIs/thrombectomy (3.3% vs 4.8% vs 5.00% vs 7.4%, p=0.02).[37]

Mechanical Devices – MGuard Stent

A novel alternative to face thrombotic lesion and to lower the risk of distal embolisation has been offered by the MGuard stent. This device has the capability to trap potentially embolic material at its source. It consists of a metal stent covered with an ultra-thin polymer mesh protective sleeve, wrapped around the stent itself. During deployment of the stent the flexible mesh freely expands over the stent struts, pushing embolic and prothrombotic material towards the intima, entrapping it. Promising short-term results have been shown in the MAGICAL and MASTER trials, but these data still need confirmation by other long-term studies.[39, 40]

Pulmonary Embolism and Deep Venous Thrombosis

In recent years endovascular strategies for thrombus treatment have also been introduced in the settings of peripheral vascular diseases. In the complex management of pulmonary embolism, among the fundamental role played by anticoagulation, systemic thrombolysis and surgical embolectomy, some percutaneous techniques may offer an alternative in selected cases. The potential advantages of an endovascular strategy with tools regularly used in the catheterisation laboratory (conventional JR or MP guide catheters together with syringes for manual thrombus aspiration) include the possibility to achieve invasive haemodynamic assessment, local thrombolysis (with 1/3 of the systemic dose) and thrombus aspiration with a simple and inexpensive procedure. Specifically designed catheters (e.g. AngioJet PE catheter) are now being produced and might improve the procedural success.[41, 42] Indications for this strategy, however, remain restricted. In patients with contraindications to fibrinolysis or who are still unstable after it, thrombus fragmentation and/or aspiration performed by an experienced team should be considered (ESC Guidelines: COR IIa, LOE: C).[43]

Similarly, patients presenting with iliofemoral deep venous thrombosis (IFDVP) may take advantage of catheter-directed thrombolysis (CDT) or pharmaco-mechanical CDT (PCDT) when limb-threatening circulatory compromise occurs (AHA guidelines: COR: I, LOE: C).[44] Finally, stent placement may be considered to treat vein occlusive lesion after CDT or PCDT (AHA guidelines: COR: IIa, LOE: C).[44]

Thrombus in Peripheral Arterial Disease

Thrombosis in a lower limb artery may be responsible for the clinical condition defined acute limb ischaemia (ALI) (Figure 4). A number of causes may be responsible for the sudden decrease of the arterial perfusion (artery disease progression, cardiac embolisation, thrombosis of popliteal aneurysm, trauma, iatrogenic complications of endovascular techniques) and urgent revascularisation is strongly recommended for ALI with threatened viability (ESC guidelines COR I, LOE A).[45] Patients with presence of vital signs of the limb, together with those presenting mild to moderate muscle weakness and sensory loss may benefit from a prompt revascularisation by means of thrombolysis, open surgery or endovascular therapy. Once the clinical diagnosis is established, treatment with UFH should be given (ESC Guidelines COR I, LOE C).[45] Revascularisation strategy will depend on lesion features (thrombotic or embolic, location and duration of ischaemia), but there is general agreement that, when possible, endovascular therapy should be the initial treatment of choice, thanks to its reduced morbidity and mortality. Different devices aiming at mechanical removal of the clot have been developed (e.g. AngioJet Thrombectomy System) and are commonly used alone or in combination with local thrombolysis, option strongly indicated to decrease delay to reperfusion (ESC COR I, LOE B).[45] Recent studies have suggested that a percutaneous strategy for ALI is safe, showing good performance of the endovascular tools in term of immediate result and long-term follow-up.[46-49]

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Further Reading

Please see the abstracts below for further reading on thrombosis. These articles plus others are available in previous editions of *Treatment Strategies - Cardiology*. Please see our website for more articles on thrombosis and a range of other topics within cardiology.

Platelet Function Testing to Identify Patients at High Risk for Coronary Stent Thrombosis: Absolute Requirement or Obsolete Myth?

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The treatment of obstructive coronary artery disease (CAD) has changed dramatically since the introduction of coronary stenting in the mid 1980s. The bare-metal coronary stent (BMS) was first introduced in 1985 to provide a mechanical scaffold for the coronary artery wall to prevent elastic recoil of the vessel wall and to seal dissections induced by balloon angioplasty. Further technological advances ultimately led to the introduction of drug-eluting stents (DES) in 2003. DES release anti-proliferative drugs that reduce neointimal formation thereby reducing in-stent restenosis rates to below 10%. As a result, the cardiology community embraced the DES with a subsequent broadening of indications for interventional treatment of CAD (e.g. multivessel disease, chronic total occlusions, small vessel diameters) far beyond those in the BMS era. This article will take an in-depth look into different methods of platelet function testing, and will explore how important, if at all, this is in the treatment of coronary stent thrombosis.

Understanding Stent Thrombosis in the Era of Drug-Eluting Stents

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The evolution of percutaneous coronary interventions (PCI) and the advent of new and more potent antiplatelet agents have substantially improved our ability to effectively manage coronary artery disease (CAD). Furthermore, the use of drug-eluting stents (DES) has significantly reduced the incidences of target vessel (TVR) and lesion revascularisation (TLR).[1-6] However, the reduced in-stent restenosis resulting from inhibition of excessive neointima formation with DES is associated with the rare, yet catastrophic, delayed endothelialisation and stent thrombosis (ST) which continues to represent a complex and difficult to elucidate phenomena.[7] Following multiple definitions of ST, the Academic Research Consortium (ARC) incorporated different timing and diagnostic certainty data to produce a unified definition.[8] ST is divided based on the time frame into early, late and very late; and based on diagnostic certainty into definite, probable and possible. This article looks at the stent thrombosis in more detail, and investigates different treatment strategies that can be implemented.

Upcoming Congresses and Meetings

Heart Rhythm Congress

20 - 23 October 2013

Birmingham, UK

The Heart Rhythm Congress aims to provide education and training to promote diversity and improved technology for all involved in the treatment of cardiac arrhythmia patients. The first heart rhythm event to include extensive arrhythmia patient day meetings, nurse education, primary care shared learning, clinical training service providers review and specialist further accreditation. With a trade exhibition running throughout, Heart Rhythm Congress focuses on improving patient outcomes by uniting all healthcare professionals. The Congress had a successful year in 2012, with over 3000 delegates in attendance, and the next congress promises to be another triumph.

Transcatheter Cardiovascular Therapeutics (TCT) 2013

28 October – 01 November 2013

San Francisco, USA

TCT is thrilled to be returning to San Francisco in 2013, and will once again be committed to evidence-based medicine, live case presentation learning, state-of-the-art didactic presentations, and late breaking clinical science. The event will offer the latest research in interventional vascular medicine, live clinical cases for using the latest investigational technologies, education and training in advanced cardiac CT imaging.

55th Annual World Congress of the International College of Angiology (ICA)

07 – 09 November 2013

New Haven, USA

The ICA World Congress offers a serious academic forum to those interested in the research, education and clinical investigation in the field of cardiovascular medicine and surgery. The Congress will provide an in-depth review of the entire spectrum of topics related to the management and treatment of patients with cardiovascular and vascular disease, and a special emphasis will be placed upon evolving trends, therapies and minimally invasive treatments. Live video case presentations, didactic lectures, panel discussions, debates and more will enable delegates to explore the programme's central focus: Surgical, Percutaneous, and Medical Management—From Peripheral Vascular Disease to Coronary and Cerebrovascular Disease and Abdominal Aortic Aneurysms.

EuroEcho-Imaging 2013

11 - 14 December 2013

Istanbul, Turkey

EuroEcho-Imaging 2013 is the official Annual Meeting of the European Association of Cardiovascular Imaging. The aim of this event is to create an exciting forum in which both clinicians and scientists can present and discuss the most up-to-date research and clinical findings on the broader spectrum of echocardiography together with the other cardiovascular imaging modalities. This year, the Meeting's main themes are 'Heart Failure' and 'Imaging in Interventional Cardiology', and the event will also have a focus upon education, with several teaching courses and specifically designed sessions being arranged. Additionally, the participation of young cardiologists and researchers will be encouraged through the organisation of two young investigator award sessions. The conference represents a unique opportunity for the cardiologist interested in the clinical and interventional applications of cardiovascular imaging to meet and interact with leading imaging experts from all over the world.

EuroHeartCare 2014

04 - 05 April 2014

Stavanger, Norway

The theme of EuroHeartCare 2014 will be 'Heart and Mind'. The idea that emotions might be tied to heart disease and that the heart and mind interact to promote and exacerbate disease is not new, and this conference will explore both the scientific and holistic viewpoints within cardiovascular medicine. Topics which will be covered include shared decision making, palliative care and e-health and applications in heart disease. Delegates will have the possibility to participate in oral, moderated poster and poster abstract presentations and share their research and clinical projects, as well as taking part in plenary sessions, symposia and more.

World Congress of Cardiology Scientific Sessions 2014

04 – 07 May 2014

Melbourne, Australia

The World Heart Federation is dedicated to leading the global fight against cardiovascular disease via a community of more than 200 member organisations. The Session offers a global platform for cardiovascular disease specialists and public health professionals to share their knowledge and network with others. 150 sessions on cardiology, policy and public health will be presented by world leading experts, and the latest scientific findings will be featured in over 1,000 new abstracts on the prevention, diagnosis and treatment of cardiovascular disease.

Heart Failure Congress 2014

17 - 20 May 2014

Athens, Greece

Heart Failure 2014 is the Annual Meeting of the Heart Failure Association of the ESC, and this year the theme will be 'Fighting Heart Failure:

From Prevention to Devices'. The conference is open to anyone who has an interest in heart failure. The aim of the event is to create an exciting forum for attendees to present, hear, exchange and discuss the most up-to-date research and clinical findings in heart failure, from basic science to diagnostic strategies and disease monitoring. Over 4,000 healthcare professionals attended the event in 2013, and this year looks set to be even bigger.

EuroPCR 2014

20 – 23 May 2014

Paris, France

EuroPCR provides delegates with the latest techniques, updates and breakthrough science, arming attendees with information which they can later turn into actions that will improve patient's quality of life. Bringing together the entire cardiovascular community, EuroPCR 2014 will provide a richly educational experience and an international platform for expression.

British Cardiovascular Society (BCS) Annual Conference 2014

02 – 04 June 2014

Manchester, UK

The BSC Annual Conference is one of the most highly attended and respected cardiovascular events in the UK. The Conference offers access to over 2,200 cardiovascular healthcare professionals, including top cardiologists, physicians and nurses through a number of different sessions, including symposia, educational sessions, workshops and more. The Conference will feature a number of different tracks, which will explore specially chosen topics and angles in more detail. The Exhibition is a crucial component of the Conference, and offers attendees the opportunity to learn about the latest breakthroughs and newest products within the field of cardiology.

8th World Research Congress of the European Association for Palliative Care (EAPC)

05 - 07 June 2014

Lleida, Spain

The European Association For Palliative Care aims to promote palliative care throughout Europe and represents thousands of members from across Europe both individually and as a collective. The EAPC World Research Congresses have been arranged on alternate years since the first Congress, which took place in Berlin in 2000. Each year the event grows larger, and it is now recognised as the most important meeting place for palliative care researchers. Indeed, in 2012 1,172 participants from 49 different countries attended the show, with a record 678 abstracts being submitted. The Congress will showcase cutting-edge research in formal sessions, as well as encouraging informal discussion outside of the lecture halls.

Multidisciplinary European Endovascular Therapy Congress (MEET) 2014

08 - 10 June 2014

Nice, France

This year's MEET conference will be held in Nice, and the packed three-day programme will include symposia, live case study sessions, plenary sessions and more. An extensive programme will be dedicated to endovascular therapy techniques, and the event will enable cardiology and radiology specialists from a wide range of disciplines to come together and discuss the latest research findings in this field.

Joint Meeting of the European Society of Hypertension (ESH) and International Society of Hypertension (ISH)

13 - 16 June 2014

Athens, Greece

The Joint Meeting of the ESH and the ISH will provide a full update of the most important achievements in the field of hypertension through state-of-the-art lectures, plenary sessions, meet-the-expert sessions, debates, workshops and more. The Meeting will also cover diseases that are related or connected to hypertension, including obesity, diabetes mellitus and COPD. Key opinion leaders and leading experts in hypertension will have a large presence at the show, which looks set to be a fantastic event.

Catheter Interventions in Congenital & Structural Heart Disease – CSI 2014

26 - 28 June 2014

Frankfurt, Germany

CSI 2014 will offer attendees a comprehensive overview of the major topics in catheter therapy of congenital and structural heart disease in both adults and children. The programme will include lectures given by leading experts in the field from all over the world, live case demonstrations and interactive debate. There will also be a varied programme of lunch and evening sessions which will enable direct interaction with these experts. The Congress will offer delegates the chance to learn about the latest techniques and the newest devices within the field of catheter therapy.

European Society of Cardiology (ESC) Congress

30 August - 03 September 2014

Barcelona, Spain

The ESC Congress is currently the world's premier conference on the science, management and prevention of cardiovascular disease. The European Society of Cardiology (ESC) represents 75,000 cardiology professionals across Europe and the Mediterranean. The ESC Congress is held annually in Europe and is dedicated to presenting the latest updates in the field of cardiovascular disease. It is the largest medical meeting in Europe, gathering nearly 30,000 participants every year. The comprehensive programme promises stimulating debate of today's most prevalent topics. The 2014 event will bring together everybody involved in cardiovascular medicine, from clinical practitioners to basic scientists, epidemiologists, nurses, technicians, healthcare industry, care opinion leaders and policy makers.

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