TREATMENT STRATEGIES

Cardiology

Volume 4 Issue 2

- Cardiac Imaging
- Congenital Heart Defect
- Heart Failure
- Hypertension
- Interventional Cardiology and Surgery

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TREATMENT STRATEGIES Cardiology

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Welcome...

I am delighted to welcome you to volume four issue two of *Treatment Strategies – Cardiology*. This issue will focus on the key topic areas in cardiovascular medicine and will provide readers with an exciting collection of papers from the leading cardiology professionals. In this edition we hope to again provide you with a comprehensive review of the latest updates and advances from the field.

This edition of *Treatment Strategies – Cardiology* will include a review of the recent ESC Congress that took place in Munich. The Cambridge Research Centre this year enjoyed a successful visit to the German city that hosted the Congress and was really impressed by the wealth of information on display at the event. The ESC Congress continued to provide attendees with all the latest updates in cardiovascular medicine.

The European Society of Cardiology (ESC) is the leading European association of cardiologists. The Society represents over 75,000 cardiovascular professionals from across Europe and the Mediterranean. Close to 28,000 professionals attend the annual Congress which is the largest medical meeting in Europe. The ESC comprises 6 Associations, 5 Councils, 18 Working Groups, 55 National Societies and the distinguished ESC Fellows and Nurse Fellows all collaborating to further cardiovascular research.

We do hope that you will find this fourth volume second issue as informative as the previous editions and we look forward to hearing your comments and feedback. Your contribution will help us to ensure that *Treatment Strategies – Cardiology* continues to be one of the most interesting cardiology healthcare publications dedicated to bringing you all the latest cardiology-related updates and developments.

I look forward to meeting you at ESC 2013 in Amsterdam.
Nigel Lloyd

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

Foreword

Steffen Desch
Department of Cardiology, The Herzzentrum Leipzig – University Hospital, Leipzig

This issue of *Treatment Strategies - Cardiology* features a cutting-edge potpourri of reports across a broad spectrum of cardiovascular topics, among them two articles on the exciting new field of device-based treatment for high blood pressure. A historical look at hypertension may serve as a prime example of the remarkable changes in cardiovascular medicine during the last decades. When former US president Franklin D. Roosevelt died of cerebral hemorrhage secondary to severe uncontrolled blood pressure in April 1945 just before the end of World War II, there was practically no effective anti-hypertensive treatment with an acceptable side effect profile. Although the dangers of an extremely high blood pressure values were well recognised at that time, less severe elevations were not considered an indication for treatment. As stated in 1937 by renowned cardiologist Paul Dudley White, it was widely believed that "hypertension may be an important compensatory mechanism which should not be tampered with, even were it certain that we could control it." However, a new era was already on the horizon as it became evident that even mildly elevated blood pressure is a risk factor for stroke, heart failure and death. In the late 1950s chlorothiazide was introduced as the first anti-hypertensive agent with an acceptable side effect profile. Several other classes of blood pressure lowering drugs including beta blockers, calcium channel antagonists and inhibitors of the renin–angiotensin–aldosterone system followed leading to impressive reductions in clinical events. Lifestyle interventions and drug therapy are now the cornerstones of anti-hypertensive treatment.

Despite these advances hypertension continues to be a major cause of cardiovascular events. Some patients are simply not treated because they are not diagnosed. Others are truly refractory to medical treatment or will not tolerate drug side effects. It is in these subgroups where devices for blood pressure control are particularly promising. Given the overwhelming success of device-based treatment in other areas such as arrhythmias, it seems almost surprising why it is only now that we see the first clinical studies in the field of hypertension. A word of caution: The magnitude of attention from cardiologists and media worldwide is in sharp contrast to the still very limited scientific data of these new technologies. Devices for the treatment of hypertension must meet the same high evidence-based requirements and undergo the same rigorous clinical evaluation as their drug counterparts.

We hope that you enjoy the latest edition of *Treatment Strategies – Cardiology* and the papers that have been included. Cardiology is one of the most thought-provoking areas of medicine, in which new discoveries and developments are constantly being made. We hope that the publication gives an in-depth overview of some of the most important and interesting topics within the field today.

Steffen Desch began his medical career at the Medical School at the University of Würzburg, Germany. His chosen topic for his doctoral thesis was The Treatment of Chronic Hepatitis C. Following this Dr. Desch carried out clinical research into platelet inhibition at Sanofi-Synthelabo, Munich. Dr. Desch has worked as a physician at both the University of Wurzburg and the University of Leipzig Heart Centre, where he currently acts as senior physician internal medicine and cardiology. He is also head of the cardiac catheterisation laboratory and his main clinical focus is interventional cardiology. His research areas include magnetic resonance imaging in acute coronary syndromes, clinical trials in acute myocardial infarction and cardiogenic shock. In 2012, Dr. Desch won the prestigious German Cardiac Society Award - the Andreas-Gruntzig Research Prize. He is reviewer on numerous international cardiovascular journals including, the *Journal of the American College of Cardiology*, the *European Heart Journal* and the *American Journal of Cardiology*. Dr. Desch has also had his work featured in a variety of publications.

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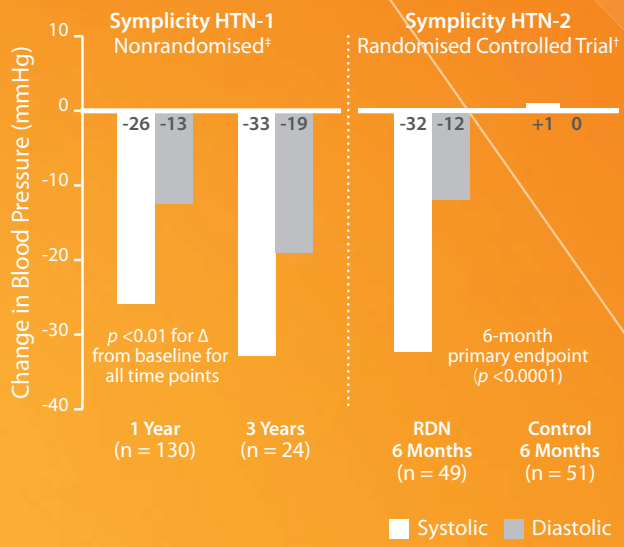

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* Based on published data from a randomised, controlled study and long-term data beyond two years.
† Symplicity HTN-2 Investigators. *The Lancet*. 2010.
‡ Symplicity HTN-1 Investigators. *Hypertension*. 2011. Expanded results presented at the American College of Cardiology Annual Meeting 2012.

ESC 2012 Annual Conference Review

25 - 29 August 2012 - Munich

Annual Meeting of the European Society of Cardiology (ESC)

INSIDE...

The Meeting

The Exhibition

Lauran Elsden, *Treatment Strategies*, takes a look over a number of key sessions, as well as spotlighting several stands and products being demonstrated at the exhibition. We then follow with papers and reviews which give a brief insight from a number of sessions highlighting findings that will have direct repercussions on clinical practise that are still very much being discussed.

The European Society of Cardiology (ESC) Annual Congress is the definitive meeting for those in the Cardiology field and represents more than 75,000 cardiology professionals across Europe and the Mediterranean. The ESC Congress is the largest medical meeting of its kind in Europe and is also recognised internationally as being the largest cardiology meeting in the world. This year, one third of the participants travelled to Munich from non-ESC countries. Professor Komajda, 2010-2012 President of the ESC, commented 'This confirms that the European Society of Cardiology is becoming truly global.' This year Japan was the main abstract submitter, whilst Germany had the most abstracts selected and presented.

Delegates travelled to Germany from afar to hear about the latest research, which will change their practice. The ESC Congress is a forward looking and interactive event bringing the best in cardiology to

***Introduction** continues on page R2*

ESC 2012 was hosted by the beautiful Bavarian city of Munich.

continued from page R1

delegates. Cardiologists who attend the ESC congress will leave with useful information and new contacts. This year close to 28, 000 participants from 140 countries registered at the ESC Congress. Professor Komajda went on to say, "These figures show that the ESC has become an international forum. In addition, Munich 2012 focused on developments in medical education. We are proud to have launched the ESC e-Learning platform here. This is a unique tool for self evaluation which will be extremely useful to cardiologists and has been well received by our National Cardiac Societies."

Each year it is the Hot Lines sessions that are most eagerly anticipated. These sessions cover an eclectic range of topics to suit the diverse nature of the cardiology field. Many of the Hot Lines sessions attracted the attention of visiting cardiologist; presenting information on recent study outcomes and findings, this included the WOEST study, which is the first study to demonstrate that the omission of aspirin in patients treated with oral anticoagulants and having coronary stent, is safe. The TRILOGY-ACS trial showed no difference in serious bleeding complications between prasugrel and clopidogrel, whilst the German Aortic Valve Registry (GARY) confirmed the good results of recent studies reflecting the growing experience in treatment and perioperative management of aortic valve disease. The high procedural success of more than 97% and the low rate of valve-related reinterventions (less than 0.5%) are also indicative of the latest improvements.

This year's choice in location was the beautiful city of Munich in Germany. Located on the River Isar, north of the Bavarian Alps and with a population of over 1.4 million, Munich is the third largest city in Germany, behind Berlin and Hamburg. Munich is a major European cultural centre, providing a wealth of things to do and sights to see. The National Theatre is Munich's opera house that boasts a long and prestigious history; being the venue chosen to premiere many significant operas, including Richard Wagner's *Tristan and Isolde* and Richard Strauss' *Friedenstag*. Munich is also home to the Deutsches Museum or German Museum, located on an island in the River Isar, it is the largest and one of the oldest science museums in the world. Every year Munich sees the arrival of Oktoberfest, a 16 day festival running from late September until Early October. Oktoberfest is one of the most famous events in Germany and one of the world's largest fairs, attracting over 5 million visitors each year. Whilst the festival is known primarily for the variety of beer to sample, there is also the chance to indulge in traditional German delicacies including Würstl sausages, pretzels and Reiberdatschi, potato pancakes. Another 'must see' sight of Munich is the beautiful Nymphenburg Palace, a Baroque place built in 1675, and the main summer residence of the Bavarian rulers. The ESC itself was hosted by Munich's International Congress Centre, a venue more than equipped to welcome the 28, 000 cardiology delegates in attendance.

The ESC saw the announcement that recent data has prompted updates of two ESC Clinical Practice Guidelines: the *ESC Clinical Practice Guidelines on the Management of Valvular Heart Disease* and a *Focused update of ESC Clinical Practice Guidelines for the Management of Atrial Fibrillation* recommending the use of novel oral anticoagulants.

As the ESC drew to a close Professor Komajda handed over the presidency of the ESC to Professor Panos Vardas from Greece stating, "There is still much work to do, to convince decision makers to take action and coordinate efforts in order to encourage people to live healthier lives. Efforts also need to be made to foster a positive environment for cardiovascular innovation in Europe. I wish the new ESC Board success in the continuous fight to reduce the burden of cardiovascular disease."

Diagnostic Pedal Cardio: Measuring the Cardiovascular System During Exercise

This year's meeting saw Ergospect showcase their newly developed Diagnostic Pedal Cardio.

Cardiovascular diseases are, according to the World Health Organisation (WHO), the leading cause of death in the Western countries, being responsible for 35% of all deaths of people over the age of 65.

Cardiac magnetic resonance (CMR) imaging is the gold standard for the visualisation of pathological processes within the myocardium-like myocardial infarction, myocarditis and cardiomyopathies. Numerous studies have shown that CMR is the most reliable method to determine infarct size and tissue perfusion as well as contractility. In patients with coronary heart disease (CHD), myocardial perfusion is balanced during rest, but shows impairments during exercise resulting in thoracic pain. This situation reflects the coronary artery stenoses permitting sufficient perfusion during rest, but limiting the increased blood flow demand during exercise.

The evaluation of these conditions is nowadays performed by stress MRI of the myocardium. Due to the lack of suitable devices, usually drugs like Dobutamine and Adenosine are used to stress the cardiovascular system. However, the administration of these drugs for stress CMR is accompanied by complications and does not reflect the physiological reality of daily situations.

By contrast, the newly developed Diagnostic Pedal Cardio enables a step exercise inside the MR bore, which is comparable to physical activities. The device is compatible with all MRI scanners ranging from 1.5 – 7.0 Tesla and has 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 myocard during a dynamic exercise via magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS) in clinical routine examination.

Via a manual control unit the pressure can be set prior to an examination and adjusted during the stress test. Pressure, distance and frequency are recorded and saved in a data file, which enables the calculation of force and power for subsequent evaluations.

The control software provides the user with a software package that facilitates navigation through all workflow stages. After following the instructions for hardware calibration, the user either selects one of the predefined templates or creates an individual exercise protocol.

Parameters such as frequency, force, duration and energy can be set prior to an examination. Once the desired protocol is entered, the program automatically controls all the parameters. If the exercise protocol has to be changed during the examination, the user has the option to adjust the settings instantly via manual adjustment. All parameters are recorded digitally and saved for subsequent evaluations.

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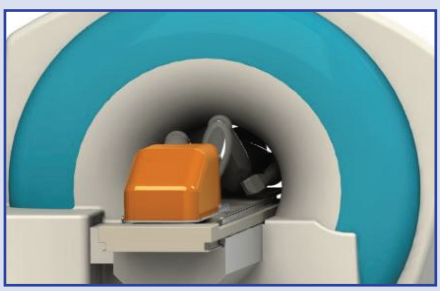
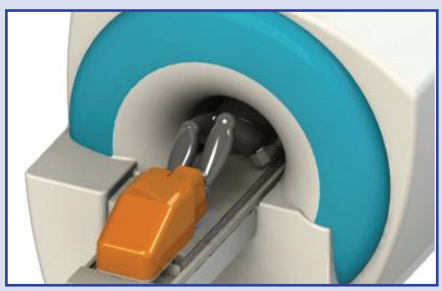
For more information on Ergospect please visit: www.ergospect.com





TAVI Improves Quality of Life in Patients with Severe Aortic Stenosis for at Least 1 Year

Transcatheter aortic valve implantation (TAVI) leads to meaningful improvements in health-related quality of life in patients with severe aortic stenosis that are maintained for at least 1 year, according to a study presented at ESC Congress 2012. The results from the German transcatheter aortic valve interventions registry were presented by Professor Till Neumann, MD, from Essen, Germany.

Aortic stenosis is the most common valvular heart disease with increasing incidence especially with regard to the ageing of the population. Today, the prevalence of aortic stenosis is estimated at about 2.5% of 75 year olds and 8.1% of people aged 85 years.

TAVI, introduced in 2002 by Dr Alain Cribier from France and 2005 by Dr John Webb from Canada, has been shown to improve survival compared with standard therapy in patients with severe aortic stenosis who cannot have surgery. In particular, older patients with aortic stenosis cannot always be offered conventional surgical aortic valve replacement at an acceptable risk. As a consequence, about 30% of these patients are presently not operated on. Therefore TAVI is currently an alternative treatment option.

The prospective multicentre German transcatheter aortic valve interventions registry includes patients with symptomatic, severe aortic stenosis since January 2009. "The registry was designed to monitor current use and outcome of transcatheter aortic valve interventions, including TAVI, in daily clinical routine, and to evaluate safety, effectiveness and health economic data," said Professor Neumann. "Therefore, the registry gives insight into a real world setting of using the TAVI procedure."

Health-related quality of life was assessed at baseline, at 30 days and 12 months with the EQ-5D questionnaire, a prominent instrument to measure health-related quality of life. The study used quality of life data for a total of 415 patients who survived 12 months after TAVI (average age 81.9 ± 5.9 years; men 37.3%).

> **"Our results demonstrate that the minimal invasive procedure of TAVI does not only save lives, but also leads to a remarkable improvement in health-related quality of life in a real world setting. This benefit in quality of life lasts for a long time period."**
>
> **Professor Till Neumann**
> **University Hospital Essen, Germany**

At 12 months, TAVI patients reported improvements with regard to each single dimension of the EQ-5D. In particular the distribution of the three levels (no problems, some problems, extreme problems) changed with regard to usual activities and discomfort after 12 months.

For usual activities, the proportion of patients with no problems rose from 17.5% to 48.6%, with some problems decreased from 72.5% to 39.7%, and with extreme problems increased slightly from 10.1% to 11.7%. For discomfort, the proportion of patients with no problems rose from 22.7% to 61.9%, with some problems decreased from 69.1% to 33.3%, and with extreme problems decreased from 8.3% to 4.8%. Professor Neumann said: "Patients gain improvements in their usual activities and feel more comfortable."

He added: "One of the main findings of our study is a remarkable increase in patients' self-ratings of quality of life after TAVI." Scores on the visual analogue health scale (EQ VAS), which records the patient's self-rated health on a vertical, visual analogue scale, significantly improved from a mean value of 44.7% ± 16.5 at baseline to 62.9% ± 17.4 at 30 days. However, even more important was the fact that this benefit in quality of life was sustained, as indicated by the patient's self-rated health status after one year (65.1% ± 20.6).

"Our results demonstrate that the minimal invasive procedure of TAVI does not only save lives but also leads to a remarkable improvement in health-related quality of life in a real world setting," said Professor Neumann. "This benefit in quality of life lasts for a long time period."

He continued: "Patients with severe aortic stenosis can profit from TAVI – the gain in health-related quality of life confirms this. Our findings regarding quality of life could give further impetus to the argument for performing TAVI in older patients with severe aortic stenosis."

NayaMed Showcase Medical Devices and Services at ESC 2012

NayaMed showcased their broad range of products and services at this year's ESC meeting. NayaMed, a Swiss medical device company, provides Implantable Cardiac Pacemakers and Implantable Cardioverter Defibrillators to European customers. Those CE Marked devices are manufactured in Switzerland based on proven technology and are already implanted in hundreds of patients all over Europe.

NayaMed entered the European market in 2011 and are the only medical device company having a business model which focuses on a web based, online commerce, which offers the opportunity to order devices online. It is also the only cardiac device company providing an Inventory System powered by an RFID scanning system implemented in every device box. Participating hospitals can manage their inventory online and are on top of their stock thanks to a re-ordering option on critical stock level reached.

The company offers its customers a personalised access to the NayaMed portal where, in just a few clicks, the customer is able to :

→ browse the NayaMed offering
→ order and track the arrival of the devices in the centre
→ manage the inventory
→ get Remote Technical Support

Remote Technical Support (RTS) is an important aspect on which NayaMed is focusing, being the only device company providing permanent Remote Technical Support for all the NayaMed implant and follow-up procedures all over Europe. The NayaMed RTS box simply connects the clinicians in the hospitals to the NayaMed Customer Care Centre through an audio and video connection. A NayaMed Technical advisor will answer and guide them throughout the implant or follow-up procedure. This service is ensured by highly experienced technical consultants with years of practice in the device industry and provided by NayaMed 24 hours 7 days a week. At any moment of day or night a customer can connect the RTS box to the programmer and get instant support.

ESC 2012 constituted NayaMed's first official participation at a medical congress and was consequently a tremendous success. As an internet based company, leveraging its services via the web, NayaMed sponsored the Twitter spot at this year's ESC, promoting, via Twitter, the importance of messages and customer awareness,

The second part of NayaMed's presence in ESC was the Remote Technical Support demonstration booth. Here the customers were able to experience, live, NayaMed's RTS System. A real, follow-up procedure was organised using a virtual patient, and the Programmer used to perform the follow-up was connected to the NayaMed Customer Care Centre via the RTS system. By simply clicking one button, the doctor could get in contact with one Technical Advisor from the NayaMed office based in Lausanne, Switzerland. The screen of the Programmer is also transmitted live to the NayaMed Customer Care Centre. An additional webcam was installed in the NayaMed Customer Care Centre and, from the NayaMed booth, the physicians could see the Technical Advisors supporting them live in all their requests.

Many physicians from all over the World came to try the RTS system and they were impressed by the simplicity with which they could get instant technical support within seconds, without having a Medical Rep next to them in the hospital.

The NayaMed RTS is already successfully used in a number of hospitals in Italy, Germany, UK and soon in France and Spain.

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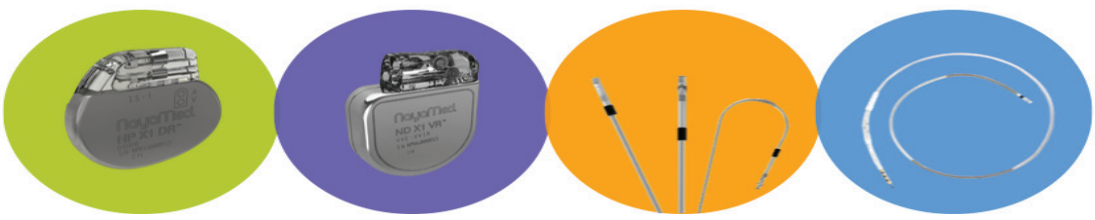

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Non-Smokers Benefit Most from Smoking Ban

After the smoking ban was introduced in Bremen, Germany, the rate of ST-elevation myocardial infarction (STEMI) diminished by 26% in non-smokers but remained almost constant in active smokers, according to research presented at the ESC Congress 2012. The results were presented by Dr Johannes Schmucker from Germany.

Many European countries have passed anti-smoking legislation which bans smoking from restaurants, bars and public buildings. After implementation of such a smoking ban on 1 January 2008 in the metropolitan area of Bremen in northwest Germany (800,000 inhabitants) a 16% decline in ST-elevation myocardial infarction (STEMI) was observed. STEMI is the severest form of myocardial infarction.

For the study, 3,545 STEMIs in the Bremen-STEMI-Registry which occurred between 2006 and 2010 were analysed. For the total population in 2006 and 2007, before the smoking ban was passed, averages of 65 STEMIs were registered per month. In 2008 to 2010, after the smoking ban was passed, the number fell by 16% to an average of 55 STEMIs per month. "This confirms that the smoking ban had a positive impact on the population as a whole by decreasing the number of STEMIs," said Dr Schmucker.

A nearly constant rate of STEMIs was observed in active smokers during 2006-2010. In 2006-2007 active smokers had an average of 25 STEMIs per month. In 2008-2010, they had an average of 26 STEMIs per month, a 4% increase. Dr Schmucker said: "Active smokers are inhaling such high doses of tobacco smoke that being exposed to less passive smoke in public venues is not going to change the risk for that particular group."

In non-smokers there was a 26% decrease in STEMIs, from an average of 39 STEMIs per month in 2006-2007 to an average of 29 STEMIs per month in 2008-2010. The steepest decline in the non-smoking group was detected in young non-smokers; in this group the average number of STEMIs per month was 31% lower in 2008-2010 compared to 2006-2007.

"The reduction in the occurrence of this severest and deadliest form of myocardial infarction in the metropolitan area of Bremen can be partially attributed to the commencement of anti-smoking legislation," said Dr Schmucker. "Non-smokers and especially non-smokers under the age of 65 benefited most from the implementation of the law, indicating the harmful effects of passive smoking. This suggests that expanding anti-smoking legislation could reduce the occurrence of STEMIs even further in the future."

Obesity Triggers Atrial Fibrillation in Fertile Women

Obesity triggers atrial fibrillation in fertile women, according to research presented at the ESC Congress 2012 by Dr Deniz Karasoy from Denmark.

Atrial fibrillation and obesity are among the largest public health related challenges in the western world today. Atrial fibrillation is the commonest heart rhythm disorder and is associated with increased mortality and morbidity. Previous studies have demonstrated that obesity increases the risk of new-onset atrial fibrillation in individuals with known risk factors for developing atrial fibrillation such as advanced age or cardiovascular comorbidity.

Atrial fibrillation is rare in young, healthy individuals and precipitating factors remain controversial. A growing body of evidence suggests that genetic predisposition, inflammation, obstructive sleep apnea, excessive alcohol consumption, and excessive physical exercise may cause atrial fibrillation in these individuals. However, it is unknown whether obesity increases the risk of atrial fibrillation in young people without other risk factors. The aim of this study was to use the unique opportunity provided by the consistency of nationwide registers of childbirth and hospitalisation in Denmark to examine the risk of atrial fibrillation related hospitalisations with respect to body mass index (BMI) among fertile women.

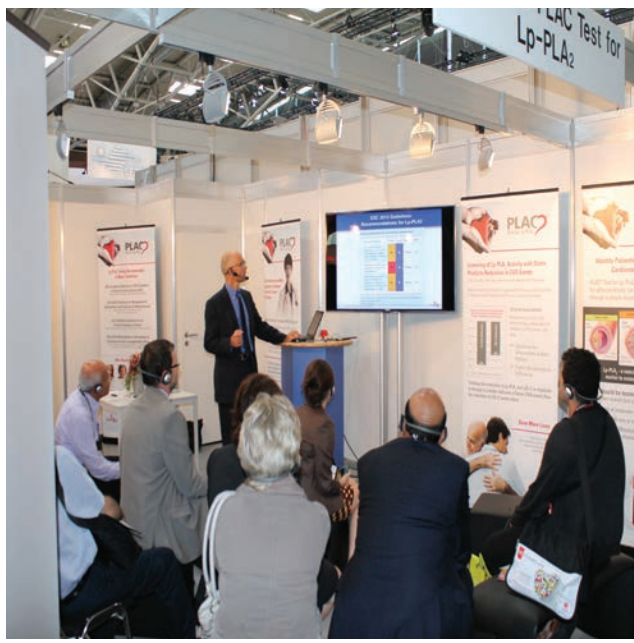
> **"The burden of both obesity and atrial fibrillation has clearly intensified, reaching epidemic levels and rising to the top of public health related concerns. Strategies that comprehensively promote weight loss may also decrease the burden of atrial fibrillation."**
>
> Dr Deniz Karasoy,
> Cardiovascular Research Centre, Gentofte

The present study was a register-based nationwide cohort study, comprising a population of approximately 271,000 seemingly healthy Danish women aged 20-50 years who had given birth during 2004-2009. They were followed for an average of 4.6 years.

The researchers adjusted the results for age, comorbidities, smoking status and pharmacotherapy received during pregnancy. They found that compared to healthy weight women with a body mass index (BMI) of 18.5-25 kg/m^2, the risk of developing atrial fibrillation was 2-fold higher in obese (BMI: 30-35 kg/m^2) and more than 3-fold higher in very obese (BMI > 35 kg/m^2) women.

"We have found that obesity increases the risk of new-onset atrial fibrillation in seemingly healthy fertile women," said Dr Karasoy, a research fellow at the Cardiovascular Research Centre, Gentofte, which is a highly specialised centre in nationwide epidemiologic research in Denmark.

He continued: "Atrial fibrillation in young individuals with no known risk factors is called 'lone atrial fibrillation'. Identifying risk factors in young individuals will contribute to understanding the nature of atrial fibrillation. Dietary modifications combined with physical exercise are warranted in obese fertile women to decrease their risk of atrial fibrillation."



ESC HIGHLIGHTS: NEW PRESIDENT ELECT AND AWARD WINNERS

The 2012 Annual Congress saw the ESC Presidency transferred from Professor Michel Komajda to Professor Panos Vardas from Greece.

Paying tribute to the outgoing President, Vardas said that he "had done a tremendous job as a visionary who has protected this historical society in the best way".

With Professor Vardas beginning his term of office, it was formally announced that the next President Elect would be Professor Fausto Jose Pinto from Portugal.

Additionally, Jeroen Bax, Martin Borggrefe and Geneviève Derumeaux were elected Vice Presidents of the ESC. Steen Dalby Kristensen was elected secretary treasurer and Claudio Ceconi was elected to the Audit Committee.

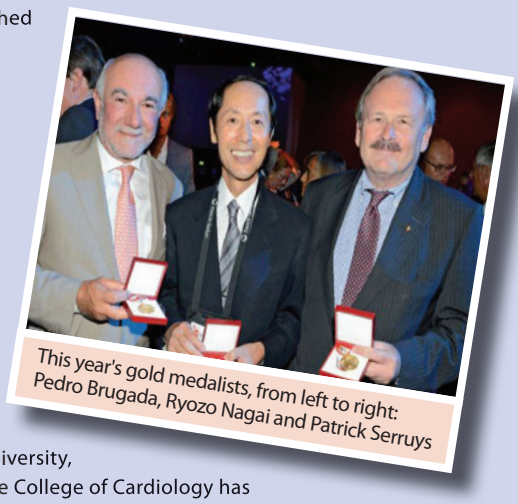
The following Councillors were elected: Piotr Ponikowski, Dan Atar, Carlo Di Mario, Francesco Cosentino, Stephan Achenbach and Davor Milicic.

> **"In order to survive, every organism needs to show the ability to adapt and this applies especially to large bodies and large organisations."**
>
> ESC President, Panos Vardas

Providing insights into his future plans for the ESC, incoming President Panos Vardas told the General Assembly that he intends to focus on maintaining success, organising new projects and respecting the new regulatory environments. such a strategy, he said, will include the promotion of unity between the ESC constituent bodies, transparency, innovative ideas and adapting to the constantly changing conditions.

THREE NEW ESC GOLD MEDALS AWARDED

This year's ESC saw three distinguished cardiologists recieve the prestigious Gold Medal Award, which were presented by Michel Komajda at the opening cerenomy. The recipients were Patrick Surreys of the Erasmus University, Rotterdam, who currently acts as the senior consulting editor of the *European Heart Journal*; Pedro Brugada of the University of Brussels, whose medical investigating led to the discovery of the condition Brugada's syndrome, which bears the cardiologists' name; and Ryozo Nagai, of the Jichi Medical University, the former president of the Japanese College of Cardiology has played a key role in promoting collaborations between scientists and the industry.



This year's gold medalists, from left to right: Pedro Brugada, Ryozo Nagai and Patrick Serruys

ESC AWARD WINNERS

At Monday's Award Ceremony, ESC President Michel Komajda and President elect Fausto Pinto presented the winners of the Young Investigators Awards (YIA), Challenging Case Reports, Best Abstract from ESC Affiliated Cardiac Societies, Moderated Posters and Best Poster awards:

YIA in Basic Science
Francesco Paneni

YIA in Clinical Science
Darren Mylotte

YIA in Coronary Pathophysiology and Microcirculation
Fabio Mangiacapra

YIA in Population Sciences
Mattis Flyvholm Ranthe

YIA in Thrombosis
Erik Walter Holy

Best Abstract from ESC Affiliated Cardiac Societies
Naveen Garg, Pai-Feng Hsu, Kunihiro Nishimura, Melinda Carrington and Malcolm Arnold

Moderated Posters Awards
Constantinos O'Mahony, Alexander Leuten, Ismo Anttila

Best Posters Awards
Patrick Houthuizen, Delvac Oceandy, Erik Skobel, Gianluigi Savarese, Aranzazu Gonzalez Miqueo, Payal Kohli, Masao Imai, Kentaro Hayashida, Steffen Just, Anders Ulvenstam

Challenging Case Report Award
Aammar Killu

Nursing/Allied Professional Investigator Award
Kaat Siebens

BIOTRONIK Demonstrates its Commitment to Heart Failure Solutions with World's First MR Approved CRT Devices

BIOTRONIK, a leading manufacturer of innovative medical technology, highlighted its broad, innovative and MRI (magnetic resonance imaging) approved implantable heart failure devices at the European Society of Cardiology Congress.

The latest BIOTRONIK cardiac resynchronisation devices, the Lumax 740 HF-T and Evia HF-T are the world's first CRT-D and CRT-P devices on the market approved for MR scans due to BIOTRONIK's innovative ProMRI® technology. The BIOTRONIK ProMRI® portfolio, which also includes the Lumax 740 ICDs, Evia and Estella pacemakers and compatible leads, sets new standards in quality and innovation by allowing cardiac device patients to undergo vital MR scans for the first time.

According to the European Society of Cardiology, heart failure affects approximately 30 million people in Europe, and its incidence continues to increase. Data from the United States show that heart failure is responsible for more hospitalisations than all forms of cancer combined and that it is the most frequent cause of hospitalisation in patients aged 65 years and older. Rehospitalisation rates during the six months following discharge are as high as 50%.

In both the Lumax 740 HF-T and Evia HF-T devices, BIOTRONIK's Heart Failure Monitor enables continuous, advanced heart failure monitoring. BIOTRONIK Home Monitoring® uses technology that automatically transmits patient status and device data from the patient to the physician on a daily basis.

The Heart Failure Monitor has a number of settings, including a thoracic impedance feature that predicts imminent cardiac decompensation, heart failure and helps physicians to prevent hospitalisation. "Heart failure patients tend to be older, aged 65 years or older, with more comorbidities," commented Professor Dr. Wolfgang Bauer, cardiologist and expert in diagnostic imaging techniques from Germany's University of Würzburg. "There is a clear advantage when using a device such as the Evia HF-T or Lumax 740, which will enable physicians not only to monitor the patient remotely but also enable them to have MR scans — a likely occurrence in heart failure patient populations."

The latest BIOTRONIK cardiac resynchronisation devices.

The BIOTRONIK CRT portfolio contains a number of MR compatible leads and lead introducers to complement the devices, allowing physicians to choose the optimal device and lead combination for each patient. Selectra, BIOTRONIK's introducer system, has a streamlined hub with a fully integrated hemostatic valve that minimises handling complexity and maximises the working length of the sheath during implant. The hydrophilic inner coating and low- friction valve are designed to reduce resistance and facilitate maneuverability of the lead.

BIOTRONIK's CRT portfolio includes cutting-edge technologies such as ProMRI® and the BIOTRONIK Heart Failure Monitor that enable physicians to choose the optimum combination for each patient and indication, and BIOTRONIK invests in landmark trials such as the EchoCRT trial to identify and answer open questions in the heart failure population and pave the way for continued clinical excellence."

"Heart failure is a growing public health problem and we are committed to developing innovative solutions such as our new state-of-the-art HF-T devices to support physicians in treating this condition."

Christoph Böhmer,
President International, BIOTRONIK

For more information please visit www.biotronik.com

Normal Weight Individuals with Belly Fat at Highest CVD Risk

"We knew from previous research that central obesity is bad, but what is new in this research is that the distribution of the fat is very important even in people with a normal weight," said Dr Francisco Lopez-Jimenez, senior author on the study and a cardiologist at the Mayo Clinic in Rochester, Minnesota. "This group has the highest death rate, even higher than those who are considered obese based on BMI. From a public health perspective, this is a significant finding."

The study included 12, 785 subjects aged 18 years and older from the Third National Health and Nutrition Examination Survey (NHANES III) and provided a representative sample of the United States population. The surveys recorded body measurements such as height, weight, waist circumference and hip circumference, as well as socioeconomic status, comorbidities, physiological and laboratory measurements. Baseline data were matched to the National Death Index to assess deaths at follow up.

Subjects were divided into three categories of BMI (normal: 18.5-24.9kg/m^2; overweight: 25.0-29.9kg/m^2; and obese: >30kg/m^2) and two categories of waist-to-hip ratio (normal: <0.85 in women and <0.90 in men; high: =0.85 in women and =0.90 in men). Analyses were adjusted for age, sex, race, smoking, hypertension, diabetes, dyslipidemia and baseline BMI. Subjects with chronic obstructive and the risk of death from all causes was 2.08 times higher in normal weight obese people as compared with subjects with normal BMI and normal waist-to-hip ratio.

"To our knowledge it is the first study that evaluated nationwide estimates of death in central obesity even in the absence of obesity as measured by BMI," said Dr Sahakyan, who is a cardiology research fellow at the Mayo Clinic in Rochester. "The high risk of death may be related to a higher visceral fat accumulation in this group, which is associated with insulin resistance and other risk factors, the limited amount of fat located on the hips and legs, which is fat with presumed protective effects and to the relatively limited amount of muscle mass."

"Many people today know their BMI," added Dr Lopez-Jimenez. "Our research shows that if a person has a normal BMI, this by itself should not reassure them that their risk for heart disease is low. Where their fat is distributed on their body can mean a lot, and that can be determined easily by getting a waist-to-hip measurement, even if their body weight is within normal limits."

Dr Sahakyan concluded: "Health professionals need to educate patients about the importance of having a healthy weight and a normal weight-to-hip ratio. Promotion of healthy lifestyle including healthy eating and exercise is perhaps the best strategy."

ESC Acute Cardiovascular Care Association Launched ACCA - The Newest and 6th ESC Association

ACCA was previously the ESC Working Group on Acute Cardiac Care. During ESC 2012 it became one of six ESC Associations, whose presidents are invited to ESC Board meetings. "It will be easier to inform the ESC Board about the activities of the association," said Professor Christiaan Vrints (Belgium), outgoing chairman of the Working Group on Acute Cardiac Care. "We will also have a bigger impact on the policies and the development of the ESC as an organisation."

The Working Group on Acute Cardiac Care had the largest and fastest growing membership of ESC working groups. Over the past 2 years it grew from just below 700 to more than 1,100 members. One in five of all members of ESC working groups belong to acute cardiac care.

"We're confident that we have the critical mass in terms of members to be a successful association," said Professor Peter Clemmensen (Denmark), ACCA's first president. "We will be more visible as an association and our vision and hope is that we will attract even more members."

The new association will expand its scope beyond the activities of the intensive cardiac care unit (ICCU), which was the original focus of the working group. Professor Vrints said: "The focus has been expanded to the first seven days of acute cardiovascular disease starting from the initial symptoms at home or work until the seventh day of hospitalisation. Nowadays, to improve the quality of care we have to focus on every aspect of acute cardiovascular care starting before admission to the hospital."

The expanded scope will see ACCA become involved in the pre-hospital phase of acute cardiovascular diseases, the diagnosis and treatment of patients in the emergency department, the transfer to the cath lab, the ICCU, and the cardiology department. This process of care involves many subspecialists beyond cardiology including emergency physicians, paramedics working in ambulances, and nurses working in the emergency department and ICCU. "We want to stimulate the participation of allied professions in the activities of this new association" said Professor Vrints.

Professor Clemmensen said: "Acute cardiac care, to be successful, has to be an integrated patient oriented approach starting from the first sign of symptoms and initial diagnosis. We will put a great deal of emphasis on the system of care and the flow of the patient, making sure that these acutely ill cardiovascular patients get into the right hospital beds and that we have the proper facilities in intensive care to save their lives."

He added: "While some of the other ESC associations are focused on a particular disease state, diagnosis, or single methodology, ACCA will concentrate on systems of care."

ACCA will hold an annual congress, and the first will be held 20-22 October 2012 in Istanbul, Turkey. The association's interdisciplinary membership and approach to disease management will be reflected in the main theme, "Integrative approach and management of Acute Cardiovascular Diseases".

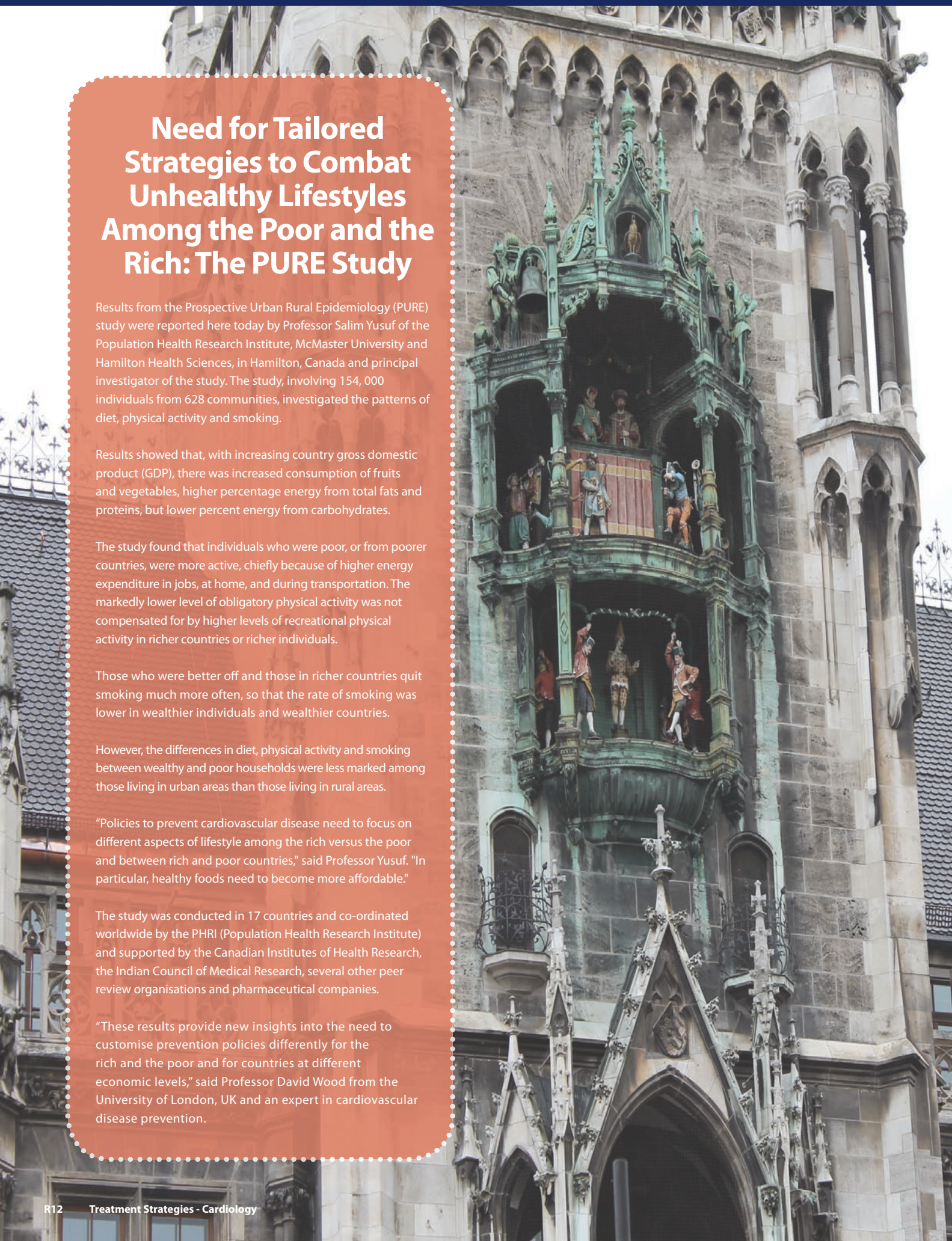
Professor Clemmensen said: "It's important that the congress becomes part of the yearly agenda of all our potential members."

Education and certification of the qualifications necessary to be an acute cardiac care physician have been important priorities for the working group over the past few years. It produced the ESC Textbook of Intensive and Acute Cardiac Care in 2011, a reference manual that was co-authored by internationally recognised scientists.

ACCA's official journal is *European Heart Journal - Acute Cardiovascular Care (EHJ-ACVC)* which, like the association, combines the expertise of the different subspecialties of cardiology, emergency and intensive care medicine in the management of patients with acute cardiovascular syndromes. The journal joined the family of ESC journals in March.

"The textbook encompasses the entire curriculum needed to provide the best care in this field. It engulfs patient care at the pre-hospital phase, the flow through the emergency room and to the coronary care unit and intensive care unit. As ACCA we will be updating the textbook and publishing a new version."

Professor Peter Clemmensen, ACCA's First Preseident



Need for Tailored Strategies to Combat Unhealthy Lifestyles Among the Poor and the Rich: The PURE Study

Results from the Prospective Urban Rural Epidemiology (PURE) study were reported here today by Professor Salim Yusuf of the Population Health Research Institute, McMaster University and Hamilton Health Sciences, in Hamilton, Canada and principal investigator of the study. The study, involving 154, 000 individuals from 628 communities, investigated the patterns of diet, physical activity and smoking.

Results showed that, with increasing country gross domestic product (GDP), there was increased consumption of fruits and vegetables, higher percentage energy from total fats and proteins, but lower percent energy from carbohydrates.

The study found that individuals who were poor, or from poorer countries, were more active, chiefly because of higher energy expenditure in jobs, at home, and during transportation. The markedly lower level of obligatory physical activity was not compensated for by higher levels of recreational physical activity in richer countries or richer individuals.

Those who were better off and those in richer countries quit smoking much more often, so that the rate of smoking was lower in wealthier individuals and wealthier countries.

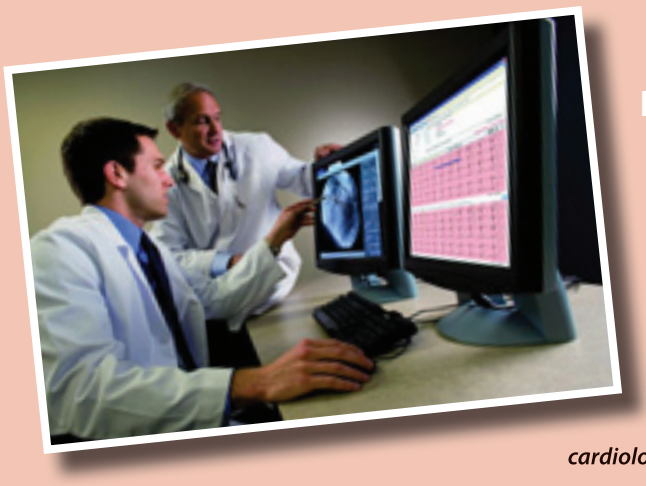
However, the differences in diet, physical activity and smoking between wealthy and poor households were less marked among those living in urban areas than those living in rural areas.

"Policies to prevent cardiovascular disease need to focus on different aspects of lifestyle among the rich versus the poor and between rich and poor countries," said Professor Yusuf. "In particular, healthy foods need to become more affordable."

The study was conducted in 17 countries and co-ordinated worldwide by the PHRI (Population Health Research Institute) and supported by the Canadian Institutes of Health Research, the Indian Council of Medical Research, several other peer review organisations and pharmaceutical companies.

"These results provide new insights into the need to customise prevention policies differently for the rich and the poor and for countries at different economic levels," said Professor David Wood from the University of London, UK and an expert in cardiovascular disease prevention.

Agfa HealthCare to Demonstrate its IMPAX Cardiovascular IT Solutions at ESC Congress 2012



Agfa HealthCare Delivers a Comprehensive and Integrated Cardiology Product Portfolio Providing Patient-Centric Data Consolidation on a Shared True Enterprise Platform

- *Innovative and comprehensive portfolio of cardiovascular IT solutions*
- *Patient-centric consolidation of relevant cardiology procedures on a shared true enterprise platform*
- *Agfa HealthCare's cardiology portfolio accommodates various clinical workflows by consolidating images and data across the wide range of cardiology sub-specialties*

Agfa HealthCare demonstrated its cardiovascular IT solutions at the 2012 Congress of the European Society of Cardiology (ESC) in Munich. Agfa HealthCare's IMPAX cardiovascular solutions provide a patient-centric consolidation of all relevant cardiology procedures on a shared true enterprise platform, with a true clinical workflow mapping and in-depth clinical content, and with refined clinical tools.

A Single Platform Integrating All Cardiovascular Clinical Procedures

At the ESC Congress 2012, Agfa HealthCare demonstrated how its innovative portfolio of cardiovascular solutions deliver the benefits of digital cardiology at the cardiologist's fingertips. New tools within the portfolio are designed to provide in-depth procedure-oriented clinical content, while sharing a common platform with the rest of the clinical procedures (coronary and peripheral angiography, PCI, shunt closure, adult echocardiography, stress testing, electrophysiology, ablation and device therapy - PM, ICD, CRT). One-click front-end image-data integration, clinical workflow integration from report elaboration to report distribution and a unified clinical back-end for research data complete the consolidation of images and data across the wide range of cardiology sub-specialties.

For more information visit www.agfahealthcare.com

Premier Heart Feature in Emergent Technology Showcase Area at ESC

Premier Heart showcased their latest technological advances in the Emergent Technology Showcase Area at this year's ESC. Premier Heart have been developing advanced cardiac diagnostic systems since 1998, and continue to expand the frontier of quality and accuracy in detecting coronary artery disease through their MCG technology.

Premier Heart's Multifunction Cardiogram (MCG) is a revolution in cardiac care, leveraging the principles of Computational Biology and Systems Analysis to assist physicians in the detection of coronary ischemia.

Premier Heart's goal is to revolutionise cardiology, raising the standard of care by combining a strong commitment to the practice of evidence-based medicine with cutting-edge research and feedback from our clinical users to deliver timely, accurate and cost-effective diagnostic information.

Coronary Artery Disease (CAD) is the leading cause of death worldwide, accounting for over 7 Million deaths annually — more than any other disease category.

Premier Heart's Multifunction Cardiogram is the only non-invasive online diagnostic testing tool designed to assist physicians in quickly and accurately detecting heart diseases, including CAD ischemia. When compared to traditional methods MCG has consistently been able to more accurately detect ischemia at earlier stages, enabling physicians to intervene and save lives.

The results from MCG have been validated in double-blind clinical studies where our system has demonstrated accuracy comparable to coronary angiography (90% overall sensitivity, 85% specificity). This level of accuracy results from advanced techniques in signal processing and systems analysis combined with our unmatched clinical database which allows MCG to provide quantitative, evidence-based results to assist in reaching a diagnosis.

MCG (Multifunction Cardio Gram) Technology.

For more information please visit www.premierheart.com

ESC 2012 At A Glance...

"One third of participants at the ESC Congress 2012 in Munich did not come from ESC countries. This confirms that the European Society of Cardiology is becoming truly global," said Professor Komajda, 2010-2012 President of the ESC. Japan was the main abstract submitter, although Germany had the most abstracts selected and presented.

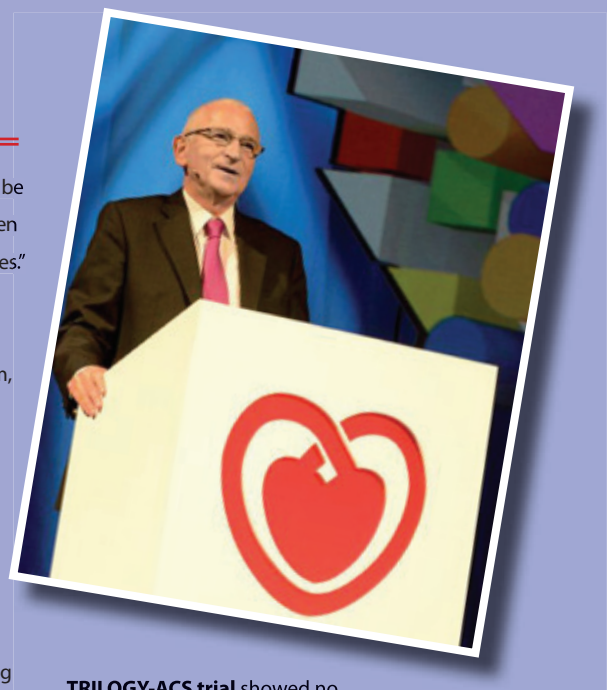
"Delegates come from afar to hear about the latest research, which will change their practice. The ESC Congress is a forward looking and interactive event bringing the best in cardiology to delegates. Cardiologists who attend our congress will leave with useful information and new contacts."This year close to 28 000 participants from 140 countries registered at the ESC Congress. "These figures show that the ESC has become an international forum. In addition, Munich 2012 focused on developments in medical education. We are proud to have launched the ESC e-Learning platform here. This is a unique tool for self evaluation which will be extremely useful to cardiologists and has been well received by our National Cardiac Societies."

"The most awaited sessions each year are the Hot Lines," said Professor Michael Böhm, Chairperson of the Congress Programme Committee. "WOEST, TRILOGY-ACS, GARY, IABP-SHOCK, and FAST-MI attracted the most attention in Munich."

WOEST is the first study demonstrating that the omission of aspirin in patients treated with oral anticoagulants and having coronary stent, is safe.

The IABP-SHOCK II trial ever performed in cardiogenic shock, was unable to show a benefit for the currently most widely used mechanical support device in cardiogenic shock.

FAST-MI (data from four French nationwide STEMI registries) showed increasing success of management of ST-elevation myocardial infarction, with mortality rates decreasing by 68% over 15 years. A worrying result of this study showed a substantial increase in the proportion of younger patients (i.e. below 60 years of age), especially women suffering from MI. The proportion of women under 60 years of age doubled (from 12% to 25%) and that of women under 50 years triples (from 3.7% to 11.1%). A fast growing proportion of young women were smokers (37% in 1995, 73% in 2012) and/or obese (18% to 27%).



TRILOGY-ACS trial showed no difference in serious bleeding complications between prasugrel and clopidogrel.

The German Aortic Valve Registry (GARY) confirmed the good results of recent studies reflecting the growing experience in treatment and perioperative management of aortic valve disease. The high procedural success of more than 97% and the low rate of valve-related reinterventions (less than 0.5%) are also indicative of the latest improvements.

FRANCE 2, the French Aortic National Registry confirmed a high success rate using both Edwards and Corevalve bioprosthesis, with excellent clinical improvement.

FAME-II showed that fractional flow reserve (FFR) should become the standard of care for treating most patients with stable coronary artery disease and significant coronary narrowings.

Key Findings:

→ ESC: a global society and a truly international congress

→ People are not making the necessary lifestyle changes to prevent cardiovascular disease

→ More efforts should be directed at making decision makers, healthcare providers and the general public more aware of the urgency of adopting healthy habits

→ Growing proportion of younger females among STEMI patients. Future preventive measures should be specifically targeted towards this group

" Munich 2012 is over. It was an excellent meeting with innovations for our attendees. Munich shows that the ESC annual congress has become an international forum. It is the biggest cardiovascular forum at the moment with one third of our attendees coming from non ESC countries and also there was a focus on education with the launch of the ESC e-learning platform."

Professor Michel Komajda FESC, ESC President 2010-2012

continued from page 15....

Renal Denervation and TAVI were also hot topics in 2012. Transcatheter aortic valve implantation (TAVI) is a new technique leading to meaningful and sustained improvements in health-related quality of life in patients with severe aortic stenosis. The EORP registry on TAVI presented today, showed that in the majority of cases, patients are very old and very sick, with co-morbidities which would have made their journey to surgery a nightmare. Renal Denervation (RDN) is a novel procedure for patients for resistant hypertension. When traditional pharma fails, RDN has been proven successful in reducing blood pressure and improve quality of life.

New ESC Clinical Practice Guidelines for the Management of Acute Myocardial Infarction in patients presenting with ST-segment elevation were announced at ESC Congress 2012. They stated that the prevention of delays was 'critical' to the management of patients with STEMI and recommend that centres equipped to perform primary PCI should deliver care on 24/7 basis and within 60 minutes of an initial call. Ambulance teams, therefore, should be trained and able to administer initial therapy, including fibrinolysis.

Recent data also prompted updates of two ESC Clinical Practice Guidelines: the ESC Clinical Practice Guidelines on the Management of Valvular Heart Disease and a Focused update of ESC Clinical Practice Guidelines for the Management of Atrial Fibrillation recommending the use of novel oral anticoagulants.

"Statistics presented at the ESC Congress 2012 (PURE, EHRA White Book) pointed to the fact that there are still very big inequalities in treatment across Europe", said Professor Komajda who handed over the presidency of the ESC to Professor Panos Vardas from Greece at the end of ESC Congress 2012.

"There is still much work to do, to convince decision makers to take action and coordinate efforts in order to encourage people to live healthier lives. Efforts also need to be made to foster a positive environment for cardiovascular innovation in Europe. I wish the new ESC Board success in the continuous fight to reduce the burden of cardiovascular disease."

Professor Michel Komajda FESC,
ESC President 2010-2012

Annual Congress of the European Society of Cardiology (ESC)
31 August — 04 September 2013
Amsterdam, The Netherlands

The ESC Congress 2013 spotlight is "The heart interacting with systemic organs, in other words, the heart may initiate or potentiate cardiovascular disease by interacting with systemic organs. This interaction may be part of the original disease mechanism or may be responsible for disease amplification and clinical syndromes."

Some of the main topics ESC 2013 will focus upon will include arrhythmias, heart failure, ischaemia, rehabilitation, congenital heart disease and paediatric cardiology.

The ESC 2013 will be hosted by the beautiful city of Amsterdam. the city centre. Amsterdam's main attractions include its historic canals, the Rijksmuseum, the Van Gogh Museum, the Anne Frank House, its Red Light District as well as its famous coffee houses which draw more than 3.66 million international visitors every year.

For more information please visit
www.escardio.org

STROKE PREVENTION

The first new oral anticoagulant for stroke prevention in atrial fibrillation in 50 years

Pradaxa® 150mg b.d. More effective stroke prevention vs warfarin is now available for adult patients with nonvalvular atrial fibrillation plus one or more risk factors.[1,2]

Compared to warfarin, Pradaxa® 150mg b.d. provides:

- 35% reduced relative risk of stroke or systemic embolism (p=0.0001, ARR†[3] per year 0.60%)[1]
- Similar rates of major bleeding[4,5]
- 59% reduced relative risk of potentially devastating intracranial bleeding (p<0.001, ARR†[3] per year 0.44%).[4,5]

† ARR = Absolute risk reduction

It's time for Pradaxa® 150mg b.d.

Pradaxa® 110mg b.d. For patients over 80 years or taking concomitant verapamil and could be considered for patients with an increased risk of bleeding.[2]

Please refer to the Prescribing Information for a full list of dosing scenarios.

Prescribing Information (SPAF – UK) PRADAXA® (dabigatran etexilate)

Capsules containing 110 mg or 150 mg dabigatran etexilate (as mesilate) **Action:** Direct thrombin inhibitor **Indication:** Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors: Previous stroke, transient ischemic attack, or systemic embolism (SEE); Left ventricular ejection fraction < 40 %; Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2; Age ≥ 75 years; Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension **Dose and Administration:** Renal function should be assessed by calculating CrCL prior to initiation to exclude patients with severe renal impairment (CrCL < 30 ml/min). Recommended daily dose 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term. In case of intolerability to dabigatran, patients should be instructed to immediately consult their doctor. Elderly: Aged ≥ 80 years 220 mg taken as one 110 mg capsule twice daily; 75 – 80 years consider 220 mg taken as one 110 mg capsule twice daily. As renal impairment may be frequent in the elderly (> 75 years), assess renal function by calculating CrCL prior to initiation to exclude patients with severe renal impairment (CrCL < 30 ml/min). Renal function should also be assessed at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate. Patients with an increased risk of bleeding: closely monitor clinically looking for signs of bleeding or anaemia. Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test may help identify increased risk patients. Patients with gastritis, esophagitis, or gastroesophageal reflux consider 220 mg taken as one 110 mg capsule twice daily due to the elevated risk of major gastro-intestinal bleeding. Renal impairment: contraindicated in severe renal impairment (CrCL < 30 ml/min); patients with renal impairment and a high risk of bleeding consider 220 mg taken as one 110 mg capsule twice daily. Close clinical surveillance is recommended in patients with renal impairment. As above assess renal function prior to initiation to exclude patients with severe renal impairment and assess renal function at least once a year or more frequently as needed. Concomitant verapamil 220 mg taken as one 110 mg capsule twice daily; Pradaxa and verapamil should be taken at the same time. No dose adjustment required but close clinical surveillance in patients < 50 kg. Not recommended if liver enzymes > 2 Upper Limit of Normal (ULN). If switching from Pradaxa to parenteral anticoagulant wait 12 hours after the last dose of Pradaxa; if switching from parenteral anticoagulants to Pradaxa then Pradaxa should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment; if switching from Pradaxa to VKA adjust the starting time of the VKA based on CrCL; if switching from VKA to Pradaxa stop VKA and give Pradaxa once INR <2.0. Cardioversion patients can stay on Pradaxa whilst being cardioverted. Not recommended aged < 18 years. Pradaxa should be swallowed whole with water, with or without food. Patients should be instructed not to open the capsule as this may increase the risk of bleeding. **Contraindications:** Hypersensitivity to any component; severe renal impairment (CrCL < 30 ml/min); active clinically significant bleeding; organic lesion at risk of bleeding; impairment of haemostasis; hepatic impairment or liver disease expected to have any impact on survival; concomitant systemic ketoconazole, cyclosporine, itraconazole, tacrolimus. **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; diseases/procedures associated with a risk of bleeding such as coagulation disorders, thrombocytopenia or functional platelet defects, active ulcerative GI disease, recent GI bleeding, recent biopsy or major trauma, recent ICH or brain, spinal or ophthalmic surgery, bacterial endocarditis. 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 agents which may increase the risk of haemorrhage. 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. Procedures such as spinal anaesthesia may require complete haemostatic function. The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate; these patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma. Treat with caution patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events. Myocardial infarction. Contains Sunset Yellow (E110) which may cause allergic reactions. **Interactions:** Anticoagulants and antiplatelet aggregation agents; Strong P-gp inhibitors e.g. amiodarone, quinidine, verapamil, clarithromycin co-administration (close clinical surveillance); verapamil co-administration - reduce Pradaxa dose to 220 mg (see above); not recommended for concomitant treatment posaconazole, dronedarone, protease inhibitors including ritonavir and its combinations with other protease inhibitors; avoid with P-gp inducers e.g. rifampicin, St John's wort, carbamazepine, phenytoin. Dabigatran etexilate and dabigatran are not metabolised by cytochrome CYP450 system, therefore related medicinal product interactions not expected. Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with Pradaxa in clinical trials and concomitant PPI treatment did not appear to reduce the efficacy of Pradaxa. Ranitidine administration together with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran. **Fertility, pregnancy and lactation:** Avoid pregnancy during treatment. Do not use in pregnancy unless clearly necessary. Discontinue breast-feeding during treatment. **Undesirable effects:** Most commonly reported adverse reactions are bleedings occurring in total in approximately 16.5 % in patients with atrial fibrillation treated for the prevention of stroke and SEE. Common (≥ 1/100, <1/10): anaemia; epistaxis; gastrointestinal haemorrhage; abdominal pain; diarrhoea; dyspepsia; nausea; hepatic function abnormal/liver function test abnormal; genitourological haemorrhage (150 mg). 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, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** April 2012.

Boehringer Ingelheim

Pradaxa®
dabigatran etexilate

Stroke prevention in atrial fibrillation

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).

References: 1. Boehringer Ingelheim. Pradaxa® 150mg hard capsules Summary of Product Characteristics. **2.** Boehringer Ingelheim. Pradaxa® 110mg hard capsules Summary of Product Characteristics. **3.** BMJ Clinical Evidence – How to calculate risk. http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665075.html Accessed March 2012. **4.** Connolly S, Ezekowitz MD, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009; 361:1139-1151. **5.** Connolly S, Ezekowitz MD, et al. Newly identified events in the RE-LY trial. N Engl J Med 2010; 363:1875-1876.

Date of preparation: April 2012 **Job code:** UK/DBG-121259•

For more information, including an educational pack, go to www.pradaxa.co.uk/SPAFeducationalpack or call the Pradaxa® information line on 0845 601 7880

Optimal Treatment Strategy Based on Platelet Reactivity Testing

Introduction

The satellite symposium titled 'Optimal Treatment Strategy Based on Platelet Reactivity Testing' was held in Munich on 27th August 2012. The meeting was chaired by Bernhard Witzenbichler, Charité University of Medicine Berlin, Berlin.

Aspirin and P2Y12-inhibitors are antiplatelet drugs used for the secondary prevention of cardiovascular disease. There is increasing recognition that not all patients respond adequately to these agents.[1] Clopidogrel is a thienopyridine, and used in conjunction with aspirin has a central role in the treatment of patients with acute coronary syndrome (ACS) and/or undergoing percutaneous coronary intervention (PCI). The pharmacokinetic and pharmacodynamic responses to clopidogrel are highly variable, leaving up to one third of patients with inadequate platelet inhibition or with high on-treatment platelet reactivity (HTPR).[2] The GRAVITAS trial linked HTPR while receiving clopidogrel to cardiovascular events after PCI, but did not define a treatment strategy.[3] The use of other thienopyridines has been shown to be effective in platelet inhibition in patients with HTPR.[4] The VerifyNow system is the first clinically available, rapid, and easy to use point-of-care system for measuring platelet reactivity to multiple antiplatelet agents. This provides a good tool to identify hyporesponsiveness; however an algorithm is still required to guide therapy decision making for these patients.

Optimal Treatment Strategy Based on Platelet Reactivity Testing
Accumetrics sponsored Satellite Symposium at the European Society of Cardiology (ESC) Congress, Munich, Germany, August 27, 2012

Chair: Bernhard Witzenbichler, Charité University of Medicine Berlin, Berlin

The Role of Platelet Reactivity Testing for Optimising Treatment Strategies
Bernhard Witzenbichler, Charité – University Medicine Berlin

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Platelet Function Testing in Daily Clinical Practice - Key Clinical Cases
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The Role of Platelet Reactivity Testing for Optimising Treatment Strategies

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The optimal treatment strategy is based on platelet reactivity testing. This not only measures platelet function, but guides treatment strategies in patients. There are different treatment modalities available for platelet inhibition, including clopidogrel. The principle concept is HTPR based on the variable response of patients to clopidogrel, which is caused by genetic polymorphism in the *f CYP2C19* allele. This polymorphism can lead to production of a number of different metabolites, resulting in a wide pharmacodynamic response that ranges from 'some hyper-responsiveness' to full non-responsiveness.

Therefore, the amount of platelet aggregation inhibition (PI) in a patient is very important (the optimal response is 40-60% PI in the maintenance phase on chronic P2Y12-inhibitors), but such tests usually take a couple of hours in the laboratory. However, the VerifyNow Assay is a cartridge based system requiring a small amount of blood that can be done at the bedside with results obtained in 2-5 minutes.

HTPR has been linked to ischaemic events.[5] The definition of hypo-responsiveness differs between trials; the most accepted definition for hypo-responsive patients is >230 platelet reactivity units (PRU) however, more liberal trials set the cut off at >208 PRU. Patients with the best PI are in the lowest quartiles of PRU, have the best outcomes, and the lowest incidences of death, myocardial infarction, and stent thrombosis.[6] The ADAPT-DES study[7] was a large-scale, prospective, multicentre registry study, examining the relationship between platelet responsiveness and stent thrombosis after drug-eluting stent implantation. The study had no clinical or anatomic exclusion criteria and enrolled 8,575 patients to assess the platelet response in different risk groups using the VerifyNow Assay. One third of the patients were hypo-responsive (35% of patients had a value of >230 PRU and 40% had a value of >208 PRU). The study showed a relationship between platelet response and subsequent definite or probable

stent thrombosis, although it is noted that only 30 days' data were presented. Patients with ACS had a much higher rate of stent thrombosis compared with elective cases, and in ACS patients, 40-60% of stent thrombosis events were attributed to hypo-responsiveness to clopidogrel. This study concurs with the assertion that HTPR is associated with an increased rate of ischaemic events. It should be noted that the European Society of Cardiology guidelines recommend consideration of platelet function testing in selected cases: diabetics; ACS; bifurcations; and patients with more than one stent or left main stenting (level IIb/B recommendation).

In conclusion, the suggested treatment of hypo-responsive patients with a platelet measurement of >230 PRU comprises a treatment compliance check, followed by testing for *CYP2C19* allele polymorphism. Once hypo-responsiveness is confirmed, the dose of clopidogrel can be doubled to 150 mg/daily, (although this suggestion is not supported by the GRAVITAS trial) and then platelet function re-measured. Alternatively, treatment could be switched to prasugrel or ticagrelor. In all cases, bleeding risk should be considered in this 'tailored therapy' for the patient.

Overcoming Hyporesponsiveness to Clopidogrel

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Hypo-responsiveness to clopidogrel is important in predicting events after ACS and PCI. A study by Brar *et al.*[8] reported the clopidogrel failure rate by PRU quartiles: patients in the upper quartile of platelet reactivity showed an event rate of 15.8%, almost 3 times the event rate of patients in the lower quartile who had a 5.8% event rate.

The effectiveness of clopidogrel depends on its conversion to an active metabolite by cytochrome P450 (CYP) - principally *CYP2C19*. Cytochromes are important in this process as they ensure adequate levels of the active metabolite and subsequently the adequate action of clopidogrel. The simplest way to overcome clopidogrel hypo-responsiveness is to double the dose, which has been shown to be effective[9,10] but there still remains a considerable proportion of patients with hypo-responsiveness.[11] The GRAVITAS study was rather disappointing, reporting no difference in outcome between standard therapy (placebo loading dose, then clopidogrel 75 mg/day) and tailored therapy (600 mg loading dose then clopidogrel 150 mg/day). However, a tailored approach for poor responders with repeated loading doses of clopidogrel (comprising a 600 mg loading dose and an additional 600 mg bolus to a maximum of 2400 mg), given until a therapeutic target is reached, produced a better outcome.[12] Another approach to overcoming clopidogrel hypo-responsiveness is to target genetic resistance rather than clopidogrel hypo-responsiveness. Carriers of a dysfunctional allele of *CYP2C19* (*CYP2C19*2*) who were heterozygotes responded well to an increased loading dose of 900 mg of clopidogrel. However, this approach did not work in homozygotes.[13] This finding was supported by the long term ELEVATE 56 trial[14] which showed that tripling the clopidogrel dose in heterozygous patients (up to 225 mg) achieves reactivity comparable with that achieved by a 'normal' dose in patients not carrying the dysfunctional *CYP2C19* allele. However, this approach has no effect in homozygotic patients.

Prasugrel is also a thienopyridine but has a simpler metabolic activation in the liver than clopidogrel. Therefore, the amount of active metabolite presented to the receptor itself is predictable. Mega *et al.*[15] treated 6 patients with clinical clopidogrel resistance by increasing the clopidogrel dose. This increase in dose had no effect, but the addition of prasugrel immediately reduced platelet activity in these patients. In carriers of the dysfunctional allele prasugrel has been shown to be more effective than doubling the clopidogrel dose.[16] Additionally, prasugrel has also been shown to overcome high on-clopidogrel platelet reactivity in chronic coronary artery disease patients more effectively than high dose (150 mg) clopidogrel. The results are similar in patients with acute coronary syndrome, ST segment elevation myocardial infarction (STEMI) patients, and patients with chronic kidney disease.[17, 18]

A third thienopyridine, ticagrelor by-passes the liver and acts directly on the P2Y receptor, and is very effective in treating clopidogrel-resistant patients undergoing maintenance haemodialysis.[19] In ACS patients, ticagrelor produces significantly higher platelet inhibition[20] and lower platelet reactivity than prasugrel, however both agents treat high platelet reactivity effectively.[21]

A phosphodiesterase stage 3 inhibitor, cilostazol, has been tested in countries outside Europe and the USA. The ACCEL-RESISTANCE study showed that cliostazol produces much better results in patients with clopidogrel hypo-responsiveness in triple therapy (aspirin, clopidogrel, cilostazol) compared with high maintenance dose clopidogrel.[22]

Overall, hypo-responsiveness to clopidogrel can be identified and treated - particularly using the new anti-platelet agents prasugrel and ticagrelor. However, several questions remain about which patients should be treated.

Platelet Function Testing in Daily Clinical Practice - Key Clinical Cases

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In clinical practice, VerifyNow testing is useful - especially in patients with ACS and STEMI – as an adjunctive to identifying and mitigating HTPR, and in identifying non-compliance and unauthorised treatment changes. VerifyNow testing in Dr Bauriedel's clinic led to treatment modification in 7 of 69 patients (10%), and confirmation of low platelet reactivity not requiring further action in 62 of 69 patients (90%). He explained that platelet function testing for the individualisation of antiplatelet therapy, to mitigate HTPR, may be considered in selected

patients with stent thrombosis or those undergoing high-risk PCI. The same tool may be cost effective by shortening recovery time after antiplatelet discontinuation and associated pre-surgical length of stay. The VerifyNow Assay also facilitated the personalised choice of P2Y12 antiplatelet therapy while still allowing compliance to treatment guidelines. It is already known that HTPR shows a clear association with adverse clinical event outcomes. A cut-off value of 235 PRU is prognostic for subsequent thrombotic events, although various cut-off values have been proposed in the literature,[23, 24, 25, 26, 27, 28] up to a maximum by Ahn *et al*.[29] who reported a sub-group of STEMI patients with a higher cut-off value of 272 PRU.

Dr Bauriedel presented 6 case reports, 5 of which illustrated the use of the VerifyNow Assay in a clinical setting (1 patient did not have a VerifyNow Assay). 4 of the patients presented with STEMI, 1 had a posterior infarction and 1 had a stent at the proximal left anterior descending artery (LAD).

Case 1

A 77-year old female patient with diabetes and a recent history of GI bleeding presented with acute STEMI. Recanalisation of the occluded artery was performed and the right coronary artery, which showed a high grade proximal lesion, was treated. Due to the patient's history of recent GI bleeding the patient was continued on clopidogrel therapy according to the guidelines. No VerifyNow testing was done in this case.

Case 2

A 73 year-old patient presented with acute STEMI which included a posterior infarction. The ECG showed pronounced alterations and the beginning of high grade atrioventricular block. A pace maker was implanted and an angiogram performed which showed ischaemic cardiomyopathy and proximal occlusion of the circumflex artery, in addition the right coronary artery was diffusely deceased and showed 2 high grade proximal lesions. Initially the occlusion was crossed and a good result achieved by stent implantation. The patient was stabilised, and an additional ECG showed complete resolution of the ST elevation. This indicated that the prognosis for the patient was good. The patient was being treated with clopidogrel, a VerifyNow Assay indicated a value of 302 PRU and consequently clopidogrel was changed to ticagrelor. The right coronary artery was repaired and the patient remained on ticagrelor. The follow up VerifyNow Assay value was significantly decreased at 82 PRU.

Case 3

A 61 year-old patient presented with a posterior infarction. The patient was pre-loaded with clopidogrel 600 mg in the emergency room. An angiogram was performed and revealed a peripheral occlusion which could be easily corrected with stents. 11 hours post the clopidogrel 600 mg loading dose, a VerifyNow Assay value was found to be 310 PRU. The patient was given 2 x 90 mg of ticagrelor, aiming to reduce this PRU value. The VerifyNow Assay value 5 hours after the administration of the ticagrelor dose was markedly reduced to 6 PRU, showing a 98% reduction.

Case 4

A 77 year-old patient presented with acute STEMI due to stent thrombosis. The patient had undergone a stenting of the proximal left anterior descending (LAD) 10 days previously and was being treated with clopidogrel and aspirin. At the time of the proximal LAD stent the VerifyNow Assay value was 202 PRU.

The patient's immediate problem was acute stent thrombosis. A re-test with the VerifyNow Assay revealed a marked elevation of the value to 341 PRU. This raised the possibilities of lack of patient compliance, or clopidogrel absorption problems. Accordingly, the patient underwent recanalisation of the LAD, was given ticagrelor and sent for Coronary Artery Bypass Graft (CABG) surgery. The patient stabilised after the LAD procedure, but several days later refused CABG surgery and was discharged. However, 18 days post LAD recanalisation the patient was re-admitted with re-stent thrombosis at the proximal LAD. A VerifyNow Assay revealed a relatively high value of 275 PRU, and since the patient was being treated with ticagrelor and aspirin, this again raised concerns about the patient's compliance and/or absorption problems. The patient was sent for CABG surgery the same day and is currently doing well.

Case 5

This was a complicated case concerning a 57 year-old patient who suffered from myasthenia gravis and was having immunosuppressive therapy. The patient had undergone stenting of the LAD 1 year previously. In addition, 6 months ago the patient had undergone stenting of the circumflex artery. Subsequently the patient was admitted with acute STEMI due to stent thrombosis. At the time of the circumflex bifurcation, the patient was treated with prasugrel, but this had recently been substituted by the general physician for clopidogrel and aspirin. On admission the patient had a VerifyNow Assay value of 314 PRU. The angiogram displayed the target lesion of the circumflex and a severe LAD in the stent region. This was successfully re-constructed. The patient was re-commenced on prasugrel and aspirin and the VerifyNow Assay showed very good results - a value of 12 PRU. The patient was clinically stable. A follow up angiogram 3 months later revealed an excellent result from the circumflex and the marginal arch, and very good filling of the LAD compared with the previous angiogram. This indicated that the prasugrel and aspirin therapy had probably helped to remove the thrombus material at the LAD. The VerifyNow Assay showed clear reduction of the PRU value to 9 PRU.

14 months later the patient presented with cardiogenic shock due to another stent thrombosis. The circumflex artery and the marginal branch were occluded and there was a very high grade LAD stenosis. Unfortunately, the patient presented very late at the hospital, and

although the LAD and the marginal branch were repaired, there was an excessive thrombus formation and the patient died. The patient had stopped taking prasugrel 10 days previously, following advice from the general physician. This case illustrates the importance of careful follow-up of patients.

Case 6

This patient required abdominal surgery but had undergone stenting of the proximal LAD 3 weeks previously. The patient was being treated with ticagrelor, and guidelines state that the drug should be withdrawn for 5 days before surgery is permitted. The VerifyNow Assay enabled the patient's PRU values to be monitored closely and on day 3 the PRU value was 200 PRU. This meant that the operation could take place on day 3 rather than waiting the full 5 day period recommended by the guidelines.

To conclude, in these case reports, the VerifyNow Assay had helped to either highlight compliance and absorption problems, reduce waiting times for surgery, or identify hypo-responsiveness to clopidogrel.

Chairman's Summary

These cases illustrate how helpful platelet function testing can be, especially in sick patients. We can summarise that platelet function testing is now simplified. There is overwhelming evidence that high on-treatment platelet reactivity is linked to poor outcome. We now have a good tool to identify hyporesponsiveness. However, we are still not completely sure how to treat patients identified as low responders, and we need an algorithm to guide our decision-making. For this, we will need more intervention therapy studies in the future.

Disclaimers

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Leading the Revolution: Stroke Prevention in Patients with Atrial Fibrillation – Different Perspectives and Practical Approaches

Introduction

The satellite symposium titled 'Leading the Revolution: Stroke Prevention in Patients with Atrial Fibrillation – Different Perspectives and Practical Approaches' was held during the European Society of Cardiology (ESC) Congress on Monday 27 August 2012 at the ICM – Internationales Congress Center München, Munich, Germany.

The meeting was co-chaired by Professor Michael Böhm, Saarland University, Homburg/Saar, Germany, and by Professor Gregory Lip, University of Birmingham, Birmingham, UK.

Atrial fibrillation (AF) is the most common cardiac arrhythmia and confers a substantial mortality and morbidity from stroke and thromboembolism.[1] Patients with AF are 5-times more likely to experience a stroke, and approximately 20% of all strokes are due to AF.[1] Interestingly, AF-related strokes are associated with a high recurrence rate and worse survival compared with strokes from other aetiologies.[2]

Oral anticoagulation (OAC) therapy with vitamin K agonists (VKA) were first introduced approximately 60 years ago and were until recently the only available OACs for stroke prevention in AF. Warfarin, the most commonly used VKA, reduces the risk of stroke by approximately 60% in patients with non-valvular AF.[3] There are, however, several limitations to warfarin treatment including a significantly increased risk of haemorrhage. More recently, novel oral anticoagulants (NOAC), which target specific components of the coagulation cascade, have been developed to overcome limitations seen in VKA therapy. Among these new drugs, dabigatran, a specific thrombin inhibitor, has been shown in clinical trials to be as effective as warfarin in the reduction of stroke, with a reduced risk of bleeding.[4,5] NOACs therefore represent attractive alternatives to standard warfarin treatment in patients with AF.

Leading the Revolution: Stroke Prevention in Patients with Atrial Fibrillation – Different Perspectives and Practical Approaches
Boehringer Ingelheim Sponsored Satellite Symposium at the European Society of Cardiology (ESC) Congress, Munich, Germany, August 27, 2012

Chair: Professor Michael Böhm, Saarland University, Homburg, Germany and Professor Gregory Lip, University of Birmingham, Birmingham, UK

Welcome and Introduction
Michael Böhm, Saarland University, Homburg, Germany

Navigating a Changing Landscape: What Factors Should we Consider when Choosing an Anticoagulant for Stroke Prevention: Focus on Primary Prevention
Gregory Lip, University of Birmingham, UK

Navigating a Changing Landscape: What Factors Should we Consider when Choosing an Anticoagulant for Stroke Prevention: Focus on Secondary Prevention
Matthias Endres, Charité Universitätsmedizin Berlin, Germany

Choosing the Right Path: What is the Evidence Supporting Dabigatran Etexilate and How can we Optimise Use in Clinical Practice?
Stuart Connolly, Hamilton Health Sciences/McMaster University, Canada

Choosing the Right Path: What is the Evidence Supporting Dabigatran Etexilate and How can we Optimise Use in Clinical Practice?
Paul Dorian, University of Toronto, Canada

Let Our Audience Lead the Way: Panel Discussion
Gregory Lip, University of Birmingham, UK

Moving Forward Together: Summary and Close
Gregory Lip, University of Birmingham, UK

Meeting Objectives

- To review the factors that need to be considered when choosing an OAC for stroke prevention
- To describe the evidence base that exists for dabigatran in stroke prevention
- To explore the practical considerations associated with the use of dabigatran for stroke prevention in patients with AF

Navigating a Changing Landscape: What Factors Should we Consider when Choosing an Anticoagulant for Stroke Prevention: Focus on Primary Prevention

Gregory Lip
(University of Birmingham, UK)

Patients with AF are at particularly high risk of ischaemic stroke and intracranial haemorrhage. As AF is so common, occurring in

1:4 patients over 40 years of age with a history of heart attack and in 1:5 otherwise healthy adults, this area has generated great interest and a wealth of clinical data is now available. Clinical research in AF continues at a fast pace and the landscape is changing rapidly. Therefore, there are a number of factors to consider when choosing an anticoagulant for stroke prevention, including consideration of the risks associated with the OAC.

An historic meta-analysis found that patients receiving warfarin had an overall 64% reduction in risk of stroke compared to controls and a significant (26%) reduction in risk of all-cause mortality.[3] In contrast, patients receiving anti-platelet therapy (eg aspirin) compared with controls had a 22% reduction in risk of stroke, with only a minor reduction (14%) in risk of all-cause mortality. To date, the majority of studies support the use of OACs rather than aspirin in patients with AF.

For patients receiving warfarin, it is both important and necessary for them to be closely monitored and to be under good therapeutic control as assessed by International normalised ratio (INR). The recommended therapeutic range is INR 2.0–3.0 and it was found that patients who spent more than 70% of their time within this range had a 79% reduced risk of stroke compared with patients spending less than 30% of their time within this range.[6] Interestingly, this study also found that the outcome for patients with poor control while on warfarin was worse than for patients receiving no warfarin.[6]

The 2010 ESC Guidelines for the Management of AF have recently been updated to reflect findings from clinical experience which has been gathered in the last two years.[7] An important recommendation from these guidelines is for a practice shift towards a greater focus on identification of 'truly low-risk' patients with AF (ie men and women age <65 years with lone AF, who do not require any antithrombotic therapy) rather than the traditional approach focusing on identification of 'high-risk' patients.

The simplest risk scheme is the $CHADS_2$ score (2 points for previous embolic event and 1 point each for congestive heart failure, hypertension, age ≥75 years and diabetes mellitus); however, a recent study by Olesen *et al.* demonstrated that patients with a $CHADS_2$ score of 0 were not truly at low-risk of stroke, with one-year event rates ranging from 0.84 to 3.2.[8] Therefore continued use of the $CHADS_2$ scoring system may put many patients with AF at risk of devastating strokes. The ESC guidelines therefore make a class I recommendation for use of the CHA_2DS_2-VASc score (2 points for previous embolic event and age ≥75 years, and 1 point each for congestive heart failure, hypertension, diabetes mellitus, age 65–74 years, vascular disease, and female sex) to help improve classification of AF patients at low-risk.[7]

In terms of bleeding risk, ICH is the most feared complication of OAC with a high mortality and morbidity.[9] Although historical trials showed higher ICH rates in patients treated with warfarin compared with aspirin, recent studies have shown the risk of ICH to be similar in both groups.[10] Friberg *et al.* showed that in almost all patients with AF, the risk of ischaemic stroke without anticoagulant treatment is higher than the risk of ICH with anticoagulant treatment.[10] Thus, the net benefit indicates that more patients may benefit from anticoagulant treatment, with the exception of patients with a CHA_2DS_2-VASc score of 0, reflecting the fact that they are truly low-risk.

In conclusion, OACs confer the best AF thromboprophylaxis and should be used where possible to prevent strokes in AF patients with more than one risk factor. Furthermore, in line with the recommendations from the updated ESC guidelines, there should be a concerted effort to identify 'truly low-risk' patients who do not require anticoagulant therapy.

Navigating a Changing Landscape: What Factors Should we Consider when Choosing an Anticoagulant for Stroke Prevention: Focus on Secondary Prevention

Matthias Endres

(Charité Universitätsmedizin Berlin, Germany)

Untreated stroke patients with AF are at increased risk of a second stroke compared with other stroke subtypes, with a 50% chance of experiencing a second stroke within 5 years. Furthermore, stroke due to AF is typically more severe than stroke due to other aetiologies, with a mortality of up to 50% after 1 year.[2]

From a neurologist's perspective, OACs are considered to be very effective for the prevention of stroke. The European Atrial Fibrillation Trial (EAFT) showed that warfarin reduces the risk of stroke by almost 70% compared with placebo, whereas treatment with aspirin showed only a 14% reduction in stroke risk compared with placebo.[11] These data suggest that aspirin is not sufficiently protective for secondary stroke prevention and instead support the use of OACs. As such various NOACs have been developed, including dabigatran, rivaroxaban, and apixaban that show non-inferior (or even better) efficacy than warfarin in clinical trials.[4, 12, 13]

The efficacy and safety profile of dabigatran, demonstrated by the RE-LY trial, together with practical advantages over VKAs, have led to its rapid uptake in clinical practice. However, some areas of uncertainty in everyday clinical practice remain. A specific concern for neurologists is whether to treat ischaemic stroke with thrombolysis, particularly since the use of thrombolysis in patients receiving concurrent dabigatran has not been studied and may be associated with increased bleeding. In the setting of acute ischaemic stroke, intravenous administration of recombinant tissue plasminogen activator can be given to eligible patients within 4.5 hours of symptom onset, but only if the relevant anticoagulant activity can be excluded.

Another area of concern is when to initiate NOAC therapy after an acute stroke in patients with newly diagnosed AF. Unfortunately, in the

Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, patients with transient ischaemic attack (TIA) or ischaemic stroke were excluded if the event had occurred within the previous two weeks. Therefore, the recommendations for timings of dabigatran administration are based on anecdotal reports. In patients with a TIA, we recommend that, dabigatran should be started as soon as imaging tests have excluded a cerebral haemorrhage. Furthermore, we recommend that treatment is initiated 3–5 days after a mild stroke, 5–7 days after a moderate stroke and two weeks after a severe stroke.[14]

One of the major challenges of stroke prevention comes from the prominent observation that patients with the highest risk of stroke are undertreated with anticoagulants.[15] A study by Häusler *et al.*, which analysed 2390 stroke patients in Berlin demonstrated that only 23% of these patients received OACs according to guideline recommendations, and only 6% had an INR value of 2.0–3.0.[15] It is therefore important to consider why approximately 50% of eligible patients do not receive effective anticoagulant therapy and how this can be improved. One reason for this may be that physicians are influenced more by events that induce bleeding than those that induce stroke. Evidence also suggests that there is a the lack of OAC use in older patients, despite the findings that the net clinical benefit of OACs in patients over 80 years old is higher than in younger patients.[16]

In conclusion, stroke patients with AF have high mortality and high risk for ischaemic strokes and intracranial bleeding and should therefore receive OACs. Given that NOACs have a favourable safety profile with lower risk of ICH compared with warfarin, these should be considered as the first choice therapy for secondary stroke prevention.

Summary

For patients who are well-controlled on warfarin, the decision to change to a NOAC should be discussed between the physician and the patient, but the reduced risk of ICH conveyed by NOAC should be emphasised. A concerted effort to identify 'truly low-risk' patients who do not require OACs should be made.

Choosing the Right Path: What is the Evidence Supporting Dabigatran Etexilate and How can we Optimise Use in Clinical Practice?

Stuart Connolly

(Hamilton Health Sciences/McMaster University, Canada)

Dabigatran and other NOACs have been available in Canada for nearly two years; therefore this provided an ideal opportunity to share this experience with the drug. There are a number of factors that need to be considered when deciding how to treat a patient with AF. These include the decision to treat the patient with warfarin or whether to switch them to a NOAC such as dabigatran and subsequently, what dose of dabigatran should be administered. The RE-LY trial assessed the efficacy of two doses of dabigatran (110 mg or 150 mg twice daily) compared with warfarin in 18,113 patients with AF and a risk of stroke.[4,5] The results demonstrated that both doses reduced ischaemic stroke: the 110 mg dose was associated with rates of stroke and systemic embolism similar to those associated with warfarin, whereas the 150 mg dose was associated with lower rates of stroke and systemic embolism, but similar rates of major haemorrhage compared with warfarin. More importantly, these data showed that dabigatran significantly reduced the risk of haemorrhagic stroke caused by warfarin. This effect was seen in all patient subgroups including those that were well-controlled on warfarin, those with previous history of stroke and both warfarin-experienced and warfarin-naïve patients.[4]

The RE-LY study also assessed the risk of major bleeding and found that the lower dose of dabigatran significantly reduced the risk of bleeding compared to warfarin, while the higher dose was only slightly reduced the risk compared with warfarin.[4] Moreover, both doses of dabigatran significantly reduced the risk of ICH. This is of particular interest as 1.5% patients on warfarin experience ICH within the first 2 years of therapy.

Another important factor influencing the decision on dosing, which has also influenced the labelling in almost every country, is the observed age interaction seen with dabigatran such that the greatest reduction in haemorrhage occurs in patients younger than 65 years old. This effect was shown to be diminished as patients get older and was essentially lost in elderly patients (≥75 years) in whom the rates of major bleeding were the same with the 110 mg dose as warfarin, and were slightly increased with the 150 mg dose.[17] Interestingly, this age-specific relationship was observed primarily for extracranial bleeds, where both doses of dabigatran consistently reduced the risk of ICH compared with warfarin across all age ranges.[4] In addition, it has been shown that high plasma concentrations of dabigatran are associated with an increased risk of bleeding and this is of particular concern for patients with impaired renal function.[4]

Direct comparison of the dabigatran doses based on the data obtained from the RE-LY trial showed that there was a significant reduction (~25–30%) in the risk of ischaemic stroke in the 150 mg dose compared with the 110 mg dose; however, there is a slight increase in the risk of haemorrhage (~16% increase) with the higher dose.[4] Finally, in terms of net clinical benefit, there were no differences in mortality rates or hospitalisations between the two doses. Therefore the decision about which dose to use should be at the discretion of the prescribing physician and is dependent on the risk for the individual patient. For example, in patients at high risk of ischaemic stroke the 150 mg dose should be used, whereas if the physician is more concerned about safety and bleeding, the 110 mg dose may be more appropriate.[17]

In conclusion, it is relatively easy to switch a patient from warfarin to NOACs but there are a number of factors that need to be assessed before doing so. These include assessment of the INR, which needs to

be between 2.0–2.3, and assessment of renal function. In terms of choosing a dose, it is important to remember that dabigatran is affected by kidney function and is associated with an increased risk of bleeding in older patients, thus highlighting the need for continued assessment and patient follow up.

Choosing the Right Path: What is the Evidence Supporting Dabigatran Etexilate and How can we Optimise Use in Clinical Practice?

Paul Dorian

(University of Toronto, Canada)

Recently there have been a number of articles published that raise concerns about the potentials risks of NOACs and in particular dabigatran. In a letter to the editor of the *New England Journal of Medicine*, Cotton *et al.* recently stated that they 'have cared for several injured patients receiving dabigatran, all of whom had poor outcomes', suggesting that dabigitran in practical use is associated with a higher risk of bleeding than was seen in clinical trials.[18] By contrast, a group in New Zealand assessed 7000 dabigatran patients over 2 months and found that there was a lower risk of bleeding than was predicted in clinical trials. Importantly, this study showed that the majority of patients with bleeding were either over 80-years-old or had impaired renal function, suggesting that these risks could be mitigated by careful consideration of age and renal function prior to initiation of treatment with anticoagulants.[19] Post-marketing surveillance performed by the European Medicines Agency suggests that fatal bleeding is seen less frequently in patients receiving dabigatran than clinical trial data would suggest.

In an attempt to define the tolerability of warfarin among elderly patients with AF, Hylek *et al.* demonstrated that age ≥80 years was associated with increased bleeding risk despite careful anticoagulation control.[20] Although these issues also apply to NOACs, these data highlight the difficulties in managing bleeding risk when using warfarin, particularly when initiating therapy. Historically, warfarin antidotes such as fresh frozen plasma and cyroprecipitate have been used to reduce risk of bleeding caused by VKAs, however, these tend to be limited by small sample sizes and thus the clinical benefit of warfarin reversal is unclear.[21]

It is often thought that with careful management of warfarin it is possible to reduce the bleeding risk; however a subgroup analysis of the RE-LY study found that there was a substantial risk of bleeding even with higher time spent in therapeutic range. Furthermore, the relative risk favours the use of dabigatran even in the subgroup with the best warfarin control.[22]

Another subgroup analysis of the RE-LY trial comparing the periprocedural bleeding risk of patients treated with dabigatran and warfarin showed that the risk of periprocedural bleeding was no greater in the dabigatran group compared with the warfarin group, despite the use of a warfarin antidote where possible.[23] As expected, there was a significantly lower rate of bleeding with dabigatran in patients undergoing surgery within 48 hours of anticoagulation interruption. Similarly, patients in which anticoagulation was stopped less than 24 hours before surgery were found to have a 15.4% risk of bleeding when receiving warfarin compared with a 6.8% or 2.8% risk of bleeding if receiving 150 mg or 110 mg dabigatran, respectively. As such recommendations for the timing of treatment interruption prior to surgery suggest that the greater the risk of bleeding, the earlier treatment with dabigatran should be stopped. The risk of bleeding can be assessed in these patients using activated partial thrombin time or hemoclot tests, and management decisions can be made utilising clinical algorithms.[24]

In conclusion, all anticoagulants will occasionally cause bleeding; however, the risk of bleeding is lower with NOACs compared with warfarin. Therefore NOACs should be considered as first choice therapy, especially in patients who are naive to anticoagulants. In patients that are already receiving anticoagulation therapy the risk remains, but these can be mitigated with patient education, monitoring renal dysfunction and careful assessment of dosing.

Summary

Overall, it is important to understand that there is always a risk of bleeding with anticoagulants. However, this risk is lower with NOACs compared with warfarin. Careful consideration of dosing and timing of initiation of treatment is required when prescribing anticoagulants, especially in higher risk patients (including the elderly, those with impaired renal function, diabetes, hypertension or those with history of recent bleeding).

Let Our Audience Lead the Way: Panel Discussion

Gregory Lip

(University of Birmingham, UK)

Drug indication is determined by randomised clinical trial data, but registries are also very important for assessing drug uptake, interactions and adverse events post-launch. The GLORIA-AF is a worldwide registry following antithrombotic therapy and outcome in patients with AF that currently includes 56,000 patients. This registry has helped to consolidate the knowledge gained in large randomised trials, such as the RE-LY trial, and has provided important 'real-world' insight into the uptake of anticoagulants.

How Should NOAC be Managed in the Setting of Acute Coronary Syndrome?

It is widely accepted that dabigatran should be stopped immediately in patients with acute coronary syndrome and thrombolysis should not be used. More problematic however, is how to manage these patients after an acute episode, as these patients will continue to be at risk of stroke and will therefore require anticoagulant therapy. In addition, very often these patients have been fitted with a stent and will therefore require antiplatelet

therapy. However, combination of OACs with antiplatelet therapy is known to increase the risk of bleeding by approximately 50%, with a further 50% increase in the risk of bleeding when combined with dual antiplatelet therapy. These bleeds include gastrointestinal and cerebral haemorrhage and therefore present a significant challenge in the management of these patients. As such, it is recommended that a bare metal stent is used in these patients as these require less time on dual antiplatelet therapy. Furthermore, more data is required to investigate the need for dual antiplatelet therapy in these patients. The choice of whether to use dabigatran depends on the relative risk of stroke and myocardial infarction and should be made on an individual patient basis.

How can we Know Whether Patients are Adhering to Therapy?

Adherence to treatment is a major issue in the cardiovascular field, with high rates of discontinuation of therapy for chronic prevention of cardiovascular outcomes. For example, 50% of patients discontinue warfarin for AF within 3 years. One way to counteract this problem is to monitor INR in patients taking warfarin, however in cases where INR is not within range (~50% of the time) it is difficult to determine if this is due to lack of compliance. In addition, the relationship between the patient and the physician can often be instrumental in ensuring optimal adherence and patient outcome. Continued discussion between the patient and the physician for example can help the patient overcome their concerns and improve compliance.

Moving Forward Together: Summary and Close

Gregory Lip

(University of Birmingham, UK)

Ischaemic stroke and ICH remain a feared risk of OAC therapy in patients with AF. However, NOACs such as dabigatran offer an alternative demonstrating better efficacy and an improved safety profile in terms of bleeding and stroke risk compared with warfarin. These agents may therefore improve clinical outcomes for patients with AF who are at high risk of stroke. There are a number of practical considerations when prescribing OACs and it is important that the dosing and timing of initiation of treatment is monitored carefully, especially in elderly patients and those with impaired renal function. The latest ESC guidelines strongly recommend a paradigm shift towards identification of 'truly low-risk' patients who do not require OACs and the use of the CHA_2DS_2-VASc scoring system. Finally, although the uptake of NOACs has been slower than expected due to physician uncertainty over bleeding risks in a clinical setting and the lack of an antidote, recent clinical trial data and 'real-world' analyses based on large registries showing a lower risk of stroke and ICH than predicted in clinical trials should help improve uptake.

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Reducing the Risk of Stroke in Atrial Fibrillation: A Risk Benefit Approach

Introduction

The satellite symposium titled, "Reducing the risk of stroke in atrial fibrillation - A risk benefit approach" was held during the European Society of Cardiology (ESC) Congress 2012 in Munich, Germany.

The meeting was co chaired by Gunter Breithardt, Professor Emeritus of Medicine and Cardiology at the University of Munich, Germany and Elaine Hylek, Associate Professor of Medicine at Boston University School of Medicine, Director of the Thrombosis Clinic and Anticoagulation Service and Associate Director of the Boston University Clinical Translational Science Institute of Education and Training Division.

Atrial fibrillation (AF) is a rapid, irregular heart rhythm originating in the atrial chambers of the heart, commonly causing palpitations and fatigue. It is the most common significant cardiac rhythm disorder arrhythmia, with a prevalence that increases with age. The trend for an improved population life expectancy with the likelihood of more people living beyond their seventies means the prevalence of AF is predicted to rise by 2020.[1] This is of concern because AF is a strong independent risk factor for stroke.

Reducing the Risk of Stroke in Atrial Fibrillation: A Risk Benefit Approach
Satellite Symposium at the European Society of Cardiology (ESC) Meeting, Munich, Germany, August 26, 2012

Chair: Gunter Breithardt, Professor Emeritus of Medicine and Cardiology, University of Munich, Germany and Elaine Hylek, Associate Professor of Medicine, Boston University School of Medicine, Director of the Thrombosis Clinic and Anticoagulation Service and Associate Director of the Boston University Clinical Translational Science Institute of Education and Training Division.

Lecture 1 - Clinical Challenges in the Practice of Stroke Prevention in AF
Elaine Hylek, Boston University School of Medicine, United States

Lecture 2 - The Benefit and Risk of Antithrombotic Therapy in AF Patient Populations: Lessons Learned From Antiplatelet Trials
Stuart Connolly, McMaster University, Canada

Lecture 3 - The Benefit and Risk of Anticoagulation in AF Patient Populations: Lessons Learned from Warfarin Trials
Lars Wallentin, Uppsala Clinical Research Centre, Sweden

Lecture 4 - Anticoagulation for Cardioversion and Ablation in AF: Current Practices and Evolving Knowledge
John Camm, St George's University of London, United Kingdom

There are a number of antithrombotic (antiplatelet) or anticoagulant (warfarin) agents used for stroke prevention in AF (SPAF). Warfarin, a vitamin K antagonist (VKA), is currently the most commonly used oral anticoagulant (OAC). The associated presumed and actual risks with these agents lead to under treatment especially in patients at greatest need, which include the elderly. Furthermore there is evidence of a high discontinuation rate of antithrombotic treatment despite knowledge of persistent stroke risk.[2, 3]

The clinical management of SPAF is complex, however the availability of new treatment modalities offer improved choices enabling more individualised treatment.

New or novel oral anticoagulants are no longer "on the horizon", but a reality. The aims of this symposium were threefold:

- To identify current challenges in clinical practice for SPAF
- To understand clinical trial evidence for emerging therapies
- To compare emerging therapies to current antithrombotic or anticoagulant treatment strategies

Clinical Challenges in the Practice of Stroke Prevention in AF

Elaine Hylek

(Boston University School of Medicine, United States)

The biggest clinical challenge in the practice of SPAF is that AF becomes increasingly prevalent as populations age. By 2040 the population of over 75 year olds in the US will outnumber those in the 65-74 year age group.[4, 5] The incidence of bleeding also increases with age and this presents a particular problem in the management of SPAF. Over 70% of acute upper gastrointestinal (GI) bleeding occurs in the over 60 years age group, and the incidence of lower GI bleeding increases 200 fold from the third to the ninth decade of life.[6, 7] Furthermore, the pharmacokinetic and pharmacodynamic changes that occur with age complicate treatment. Clearance of drugs is decreased resulting in the need for lower drug dosages.[8, 9] Decreased kidney function means that increased vigilance is required when treating these patients.[10]

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Anticoagulation with the VKA warfarin is used in SPAF. However its narrow therapeutic index means that the intensity of anticoagulation needs to be maintained within the international normalised ratio (INR) range of 2.0 to 3.0 to optimise efficacy. An INR of <2 increases the risk of ischaemic stroke (IS) and an INR>3 increases intracranial haemorrhage (IH) risk.[11, 12] Warfarin dosing is complex with many factors, including the patient's age, body surface area, sex, weight and interactions with multiple drugs and food, influencing the dose.[13, 14] This makes maintenance of the INR within the 2-3 range difficult to achieve without close monitoring and frequent dose adjustments.

There is strong evidence based data to show that time in the therapeutic range (TTR) matters in the management of SPAF. The Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF III and V) trials showed that patients receiving warfarin whose TTR was <60% had increased mortality (4.2%) and occurrence of bleeding (3.85%) compared with those who had a TTR of over >75%, who had the best outcome (1.69% mortality and 1.58% bleeding).[15] Evidence from the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W) trial (discussed later in more detail by Stuart Connolly) suggests that the minimum threshold TTR necessary to realise the benefit of warfarin is ≥58-65%.[16] The mean TTR figures achieved in the other three key trials: the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY),[17] the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)[18] and the Apixaban for Reduction in Stroke and Other Thrombotic Events in Atrial Fibrillation (ARISTOTLE) trials[19] were 64%, 55% and 62% respectively and are in the region of this minimum threshold. Also, an assessment of US warfarin management from QUEST diagnostics health trends database showed a mean TTR of 57.7%. However, the lower median TTR figure indicates that many patients are not achieving the minimum threshold TTR, and this is a clear unmet need.[20]

A careful risk benefit approach is needed when administering warfarin in AF therapy. The use of anticoagulants, especially amongst the elderly requires careful balancing of antithrombotic efficacy against the risk for haemorrhage. In one study the prothrombin time ratio (PTR) was the dominant risk factor for IH along with increased age. Patients of 80 years or older had an almost three-fold increase in IH, and in two thirds of these the IH occurred even when patients had an INR within the 2-3 range. These results emphasise the need for careful use of warfarin in the elderly.[11] However it is important to remember that IH is rare in younger patients with AF who are treated with warfarin.

An appreciation of risk factors associated with warfarin medication was highlighted through a case study of a 79 year old man with a history of hypertension on warfarin therapy and daily aspirin. This patient presented with worsening right-sided weakness and aphasia and an admission INR of 2.1. The concomitant use of aspirin with warfarin anticoagulation therapy, along with the patient's hypertension may have contributed to the complications. Concomitant aspirin and warfarin increases the likelihood of IH by about 40%, while controlling blood pressure is also known to reduce IH and IS.[21]

Warfarin medication can be hazardous. In 2007-2009 warfarin medication was the most commonly implicated medication in emergency hospitalisation for adverse drug events in older US adults, with 46% of emergency department visits resulting in hospitalisation being attributable to warfarin. Approximately 5% of these were due to IH, which unsurprisingly results in about 99% hospitalisation. 40% were attributable to GI bleeding which although does not have the same morbidity and mortality as IH still led to over 80% hospitalisation. 23% presented with elevated INR which results in about 60% admission to hospital.[22]

Although warfarin is effective in SPAF, it is under used in clinical care. Within the first year, 26% of patients of 80 years of age stopped taking warfarin for various reasons. Real or perceived safety issues accounted for 81% of the discontinuations. This discontinuation and also low adherence to warfarin presents a challenge in the management of SPAF.[23] The underutilisation of anticoagulation therapy in AF is a worldwide issue. According to recent data from 2006, 47%, 46% and 69% of patients with AF in the US, Sweden and China, respectively, were not receiving warfarin therapy.[24, 25, 26]

Antiplatelet agents such as acetylsalicylic acid (aspirin) in SPAF, although not as effective as warfarin, also have modest effects in SPAF.[27] The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial assessed whether warfarin reduced risk of major stroke, arterial embolism or other IH compared with aspirin in elderly patients. The primary analysis showed that the yearly risk of stroke was lower at 1.8% for warfarin than for aspirin at 3.8% (Hazard ratio (HR) 0.48, 95% CI 0.28-0.80, p=0.003). However there was no statistical difference in the yearly risk of major haemorrhage with warfarin (1.9%) versus aspirin (2.2%) (Relative risk 0.96, CI 0.53-1.75).[28]

The 2012 focused update of the ESC Guidelines for the management of AF recommends the use of anticoagulation therapy in AF over antiplatelet agents.

The Benefit and Risk of Antithrombotic Therapy in AF Patient Populations: Lessons Learned From Antiplatelet Trials

Stuart Connolly
(McMaster University, Canada)

Patients with AF for whom VKA therapy is unsuitable may be treated with antiplatelet therapy. The antiplatelet agent aspirin reduces the risk of stroke by 22%. Dual antiplatelet therapy with aspirin and clopidogrel

leads to greater stroke reduction and reduced the rate of major vascular events from 7.6% per year to 6.8%.[30]

A meta-analysis of 6 trials on the efficacy and safety of antiplatelet agents for SPAF compared to placebo demonstrated that aspirin does reduce stroke in patients with AF, although warfarin is substantially more efficacious than aspirin.[31]

In the ACTIVE trial programme, patients with AF and one or more additional risk factors for stroke were enrolled in one of two trials. If they were considered suitable candidates for warfarin therapy, they were enrolled in ACTIVE-W, a comparison of warfarin with the combination of clopidogrel and aspirin. The results of ACTIVE-W showed that use of a VKA reduced the risk for stroke by 42% over clopidogrel and aspirin. The primary endpoints of the study at follow up were the rates of vascular events, (defined as stroke, embolism, MI and vascular death). These were significantly higher in the clopidogrel/aspirin group than in the warfarin group, a difference of 1.7% per year. Major bleeding events were similar between the two therapies and the occurrence of IS and haemorrhagic stroke were reduced under warfarin therapy.

Those considered unsuitable for warfarin therapy were enrolled in ACTIVE-A and were randomised to receive clopidogrel (75 mg/day) or placebo on a background of aspirin therapy. It was hypothesised that, in these patients, the addition of clopidogrel to aspirin would reduce the risk of major vascular events with an acceptable risk of major bleeding. The primary outcome (a composite of major vascular events, including stroke, MI, non-central-nervous-system systemic embolism or death from vascular causes) was significantly reduced by 11% with the combination of clopidogrel and aspirin, which was largely due to a 28% reduction in stroke. However this came at a cost. The rate of major bleeding was significantly increased, from 1.3% to 2.0% per year, with treatment and there was a trend to increased fatal bleeding. There were also significant increases in intracranial and extracranial bleeding.

The annual rates of stroke in ACTIVE A and ACTIVE W for VKA, clopidogrel and aspirin and aspirin alone were 1.4, 2.4 and 3.3, respectively.[32]

The 2011 Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) double blind study of 5999 patients investigated whether the oral anticoagulant apixaban, a novel factor Xa inhibitor, offered another alternative to patients unable to use VKA.[33] The mean follow up period was 1.1 years and the primary outcome was the occurrence of stroke or systemic embolism. Apixaban reduced the risk of stroke or systemic embolism by more than 50% without significantly increasing the risk of major bleeding or IH compared to aspirin. Secondary and other efficacy outcomes, including cardiovascular hospitalisation and death, were also reduced in the apixaban group. Thus, the net clinical benefit to these patients was substantial.

In conclusion, there is very strong evidence to suggest that antiplatelet therapy reduces the risk of stroke in AF. Single antiplatelet therapy reduces stroke by about 20% compared to the placebo/control. The use of dual antiplatelets gives an additional 30% reduction in stroke but the benefit is substantially offset by bleeding risk. Both single and dual antiplatelet therapies are considerably less effective than oral anticoagulation.

The Benefit and Risk of Anticoagulation in AF Patient Populations: Lessons Learned from Warfarin Trials

Lars Wallentin
(Uppsala Clinical Research Centre, Sweden)

Warfarin is a long established medication used in the management of SPAF. However there are patients for whom it is unsuitable. New alternative treatment options to warfarin in SPAF are now becoming available. However these treatments need to address a number of unmet needs. Ideally they should have at least the same antithrombotic effect as current treatments, be associated with a lower risk of intracranial and other bleedings, have few unexpected side effects and few food or drug interactions. Equally, good oral bioavailability (once or twice daily), a broad therapeutic window at standard dosing and predictable anticoagulation without lab monitoring will enable ease of use in practice, and an enhanced patient acceptability and long term tolerance.

The new oral anticoagulants offering additional options for patients with AF include direct thrombin inhibitors and factor Xa inhibitors: dabigatran, rivaroxaban, apixaban and edoxaban. Three Phase III clinical trials have reported the efficacy of dabigatran, rivaroxaban and apixaban in patients who have AF and risk factors for stroke or embolic complications.[17, 18, 19] The phase III study Effective Anticoagulation with factor Xa next Generation in Atrial Fibrillation) (ENGAGE AF-TIMI 48) trial for edoxaban is still on going.[34] Although trial designs between the studies differed, all three of the agents were efficacious in reducing the primary endpoint of stroke or systemic embolism by demonstrating non-inferiority to warfarin therapy; dabigatran and apixaban also demonstrated superiority to warfarin. Dabigatran, rivaroxaban and apixaban were associated with similar bleeding when compared with warfarin and published data suggest that all 3 agents are at least as efficacious as dose-adjusted warfarin, with similar major bleeding profiles. Furthermore, they do not require dietary restrictions and have few drug-drug interactions and less intensive laboratory monitoring.

The RE-LY study reported dabigatran 150 mg was associated with a lower rate of stroke and systemic embolism when compared with warfarin, whereas dabigatran 110 mg was associated with a similar rate for such events (relative risk = 0.66; 95% CI 0.53–0.82; $p<0.001$; and relative risk = 0.91; 95% CI, 0.74–1.11; $p=0.34$, respectively).[17] CHADS(2) scores (a simple, validated risk score for predicting the risk for stroke in patients with AF not treated with anticoagulants) were lower with dabigatran than with warfarin. In addition, the

advantages of dabigatran over warfarin were unaffected by concomitant antiplatelet (aspirin) use[36] and were consistent irrespective of centres' quality of INR control.[37, 38]
From the intention-to-treat analysis of the ROCKET-AF study, rivaroxaban was reported to be noninferior to warfarin in reducing stroke or systemic embolism (2.1% vs 2.4% per year; HR = 0.88; 95% CI, 0.75–1.03; p<0.001).[18] This was true also for AF patients with moderate renal insufficiency who have higher rates of stroke and bleeding than those with normal renal function.[39]

The ARISTOTLE trial reported that apixaban reduced stroke or systemic embolic events by 21% when compared with warfarin (1.27% versus 1.60% per year, respectively; HR = 0.79; 95% CI, 0.66–0.95; p<0.001), and reduced major bleeding by 31% (2.13% versus 3.09% per year, respectively; HR=0.69; 95% CI: 0.60-0.80; p<0.001).[19, 40]

The effects of apixaban versus warfarin were consistent in patients with AF with and without previous stroke or transient ischaemic attack (TIA). Owing to the higher risk of these outcomes in patients with previous stroke or TIA, the absolute benefits of apixaban might be greater in this population.[41]

When compared with warfarin, apixaban treatment reduced the rate of stroke, death and major bleeding, regardless of renal function. Patients with impaired renal function seemed to have the greatest reduction in major bleeding with apixaban.[42]

For patients who are unwilling to adhere to regular coagulation monitoring or whose therapeutic effect using warfarin is not optimal despite adequate monitoring and management, the inhibitors of direct thrombin or factor Xa may provide alternative choices in anticoagulation.

In conclusion, there are a number of challenges ahead in the optimisation of anticoagulant management in AF populations. This includes the selection or prioritisation of patients for therapy with novel agents, managing the transition between agents, and establishing follow- up on an individual and system level, including the determination of the long term effects of therapy. Finally there is a need to analyse the effects, and cost effectiveness of these new agents in different real life settings.

Anticoagulation for Cardioversion and Ablation in AF: Current Practices and Evolving Knowledge

John Camm
(St George's University of London, United Kingdom)

AF is a common arrhythmia that may be treated with cardioversion (controlled electric shock) or ablation.

Anticoagulation in AF before, during and after cardioversion (pharmacologic and electrical), and left atrial ablation, including long term anticoagulation after successful left atrial ablation, were addressed in this presentation along with the latest guideline changes.

A flowchart summary of the 2010 guidelines of *The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology* highlighted three different strategies for the management of cardioversion in AF. These included a treatment route for recent onset AF (AF onset <48 hours), the conventional route for oral anticoagulation (OAC) in AF for cardioversion and the transoesphageal echocardiogram (TOE) strategy.[43]

The use of the novel anticoagulant dabigatran was investigated in a large clinical trial involving a total of 1983 cardioversions performed in 1270 patients.[44] The frequencies of stroke and major bleeding within 30 days of cardioversion on two doses of dabigatran (110 mg BID and 150 mg BID) were low and comparable to those on warfarin with or without TOE guidance. Thus, in this trial dabigatran was considered a reasonable alternative to warfarin in patients requiring cardioversion.

Recent guidelines on antithrombotic therapy for AF have incorporated dabigatran in their 2012 recommendations. The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (ACCP 9) recommends the use of dabigatran along with adjusted dose VKA therapy in patients with AF of >48 hours for at least 3 weeks before cardioversion.[45] The changes to the ESC guidelines in 2012 also include the incorporation of dabigatran in their recommendations for anticoagulation pericardioversion.[29]

AF ablation requires optimal periprocedural anticoagulation for minimising bleeding and thromboembolic complications. The use of anticoagulants for left atrial ablation was considered in a 2012 consensus document by experts that anticipated that anticoagulation, including the use of new anticoagulants will be utilised before, during and after left atrial ablation.[46]

The current situation in Europe on the use of anticoagulation before and after AF ablation is seen from the results of the EP Wire survey on the use of antithrombotic therapy in relation to device implantation and AF ablation.[47] 71 centres were involved and a median of 330 ablations were performed per year per centre. In this study 40% of the patients were on OAC, 20% on antiplatelet therapy and 40% on no antithrombotic therapy prior to ablation. The use of anticoagulation continued for 6 to 12 months in patients with CHAD scores ≥1 or CHAD scores >2.

The 2012 ESC guideline recommendations for anticoagulation during left atrial ablation prefer the use of OAC with a VKA during the procedure, while the 2012 HRS/EHRA/ECAS guidelines recommend considering anticoagulation along with warfarin.[29, 46]

A recent publication found that dabigatran compared favourably with warfarin when used in AF ablation.[48] A total of 211 patients were

studied and the results showed no periprocedural deaths or symptomatic thromboembolic complications in either group, and total bleeding complications occurred less frequently in the dabigatran group (4.5%) than in the warfarin group (12.9%; p<0.05), suggesting that it may be a suitable alternative to warfarin.

However a multicenter, observational study indicated different results.[49] 145 patients undergoing AF ablation took periprocedural dabigatran and an equal number took uninterrupted periprocedural warfarin. In this study the use of dabigatran significantly increased the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy. However, the difference in approach to the periprocedural use of dabigatran for AF ablation must be taken into account when considering these studies.[50] A multicentre study, which showed a variety of periprocedural anticoagulation procedures are used for AF ablation, highlighted the importance of establishing an optimal strategy.[51]

Although AF ablation appears to eliminate the increased risk of death and stroke associated with AF,[52] central to the best management of AF patients is the question of what causes stroke in AF patients. On one hand it is possible a trigger causes AF which then results in a stroke. If this is the case, then eliminating AF will eliminate the risk of stroke. On the other hand, if the trigger causes both AF and/or a stroke, then treating the AF alone may not reduce the likelihood of stroke.

Three studies of anticoagulation after successful left atrial ablation have been conducted. In the first study, the risk of a thromboembolic event (TE) after left atrial ablation was 1.1%, with most events occurring early within 2 weeks after the procedure. Interestingly, long term results showed that discontinuation of anticoagulant therapy appeared to be safe both in patients without risk factors for stroke and in patients with risk factors.[53]

A nonrandomised study of 3355 patients found that the risk-benefit ratio favoured the suspension of OAC after successful AF ablation even in patients at moderate-high risk of TE.[54]

In a large propensity matched community sample, AF ablation was associated with a reduced risk of stroke/TIA and no significant difference in heart failure hospitalisations compared with antiarrhythmic drug therapy.[55]

Current guidelines on long term anticoagulation post ablation recommend the continuation of OAC.[45, 46]

In conclusion, careful anticoagulation management in patients undergoing AF ablation and cardioversion procedures is crucial to minimise the risk of stroke. There is a range of approaches to anticoagulation management pre and post AF ablation and cardioversion and further clinical trial evidence will be required to guide future therapeutic decisions in this field.

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How High-sensitive Cardiac Troponin T and NT-proBNP Impact Clinical Practice

Introduction

The satellite symposium titled, "How high-sensitive cardiac troponin T and NT-proBNP impact clinical practice" was held during the European Society of Cardiology (ESC) Congress on Monday 27 August 2012 in Munich, Germany.

The meeting was chaired by Professor Dr Hugo Katus from the Heidelberg University Hospital, Germany and Professor Dr Harvey White from Auckland City Hospital, New Zealand.

Cardiac troponins play a pivotal role in the universal definition of acute myocardial infarction (AMI) and natriuretic peptides have become one of the key tools in diagnosis and heart failure (HF) therapy guidance. In this symposium, experts in cardiac biomarkers shared the latest scientific knowledge on the diagnostic performance of the new high sensitivity cardiac troponin T (cTnT-hs) assay in the early diagnosis of AMI and their routine experience in cTnT-hs rise and/or fall interpretation for rapid rule-in and rule-out of AMI. The prognostic importance of detectable cTnT-hs value in acute coronary syndrome (ACS) patients and the benefits of natriuretic peptide to guide HF therapy for patients with chronic left ventricular (LV) systolic dysfunction was also presented.

How High-Sensitive Cardiac Troponin T and NT-proBNP Impact Clinical Practice
Roche sponsored Satellite Symposium at the European Society of Cardiology (ESC) Congress, Munich, Germany, August 27, 2012

Chair: Professor Dr Hugo Katus, Heidelberg University Hospital, Germany and Professor Dr Harvey White, Auckland City Hospital, New Zealand.

The Benefits of High-sensitive Cardiac Troponin T for the Early Diagnosis of Acute Myocardial Infarction
Christian Müller, University Hospital Basel, Switzerland

How Positive High-sensitive Cardiac Troponin T Results Predict Long Term Prognosis in Patients with an Acute Presentation
Evangelos Giannitsis, Medical Department III, Heidelberg University Hospital, Germany

Towards a Better Understanding of Biomarker Guided Heart Failure Care: The PROTECT Study
James Januzzi, Massachusetts General Hospital, United States

The Benefits of High-sensitive Cardiac Troponin T for the Early Diagnosis of Acute Myocardial Infarction

Christian Müller
(University Hospital Basel, Switzerland)

The rapid and reliable diagnosis of AMI is a major unmet clinical need and is critical for the initiation of effective evidence-based medical treatment and management.

Patients with symptoms suggestive of AMI account for about 10% of all emergency department (ED) consultations, however only 10–20% of them eventually suffer from AMI.[1] Electrocardiography (ECG) and troponin testing form the diagnostic cornerstones and complement clinical assessment in the evaluation of chest pain patients.[2, 3, 4]

ECG by itself is often insufficient to diagnose an ACS or AMI, since ST-segment deviation may be observed in other conditions. Although troponin assays are very helpful in clinical practice for identifying patients with ACS who are at high risk, standard conventional troponin assays are limited by their low sensitivity at the time of presentation. This is due to a delay of 3-4 hours in increased troponin circulating levels. The diagnosis of AMI consequently requires prolonged monitoring over a period of 6-12 hours and serial blood sampling in a significant number of patients.[2, 3, 5] The 2011 European Society of Cardiology (ESC) guidelines recommend monitoring for troponin levels using contemporary assays for 6-8 hours after the onset of acute chest pain to safely rule out AMI.[6] This places a huge burden on the ED.

The cTnT-hs assay has now been introduced clinically for earlier diagnosis of AMI. This has enabled measurement of cTnT concentrations not reliably detected with prior generations of tests.[7] The new tests can measure cTnT levels in healthy individuals and have the ability to measure minor elevations in cTnT levels, so enabling the shortening of the monitoring time post-AMI. In addition, the superiority of the cTnT-hs assay has been found to be most pronounced among patients with recent onset of chest pain.[8] Among patients who presented within 3

hours after the onset of chest pain, the diagnostic accuracy, as quantified by the area under the receiver-operating-characteristic curve (AUC), was significantly higher with four sensitive cTn assays than with the standard conventional assay.[8] Based on these results, it was concluded that the sensitive assays in conjunction with ECG and clinical assessment could improve the early diagnosis of AMI. These data were so convincing that they were included in the 2011 ESC guidelines as evidence for the use of the more sensitive cTn assays in the early diagnosis of AMI, with a first sampling on admission (T0) followed by a second sampling within 3 hours in patients with chest pain <6 hours).[6] Two recent reports have provided useful guidance on the application of the cTn-hs assays in daily clinical practice.[4, 9] This requires the differential diagnosis of an elevated cTn, as well as all available tools to differentiate AMI from other causes of acute chest pain.

The cTnT-hs assay has a high precision at lower concentration ranges with an analytical coefficient of variation <10% at the 99th percentile concentration of the reference population (URL).[8, 10] Therefore, the cTnT-hs assay should be used at a quantitative level and changing values should be used to distinguish acute from stable disease. This is particularly important as elevations above the 99th percentile URL are common in patients with structural heart disease, including patients with stable coronary artery disease. It should be remembered that cTnT is a specific marker of myocardial necrosis but does not inform about the cause(s) of necrosis. An AMI may only be diagnosed with a rise and/or fall of cTnT together with characteristic symptoms, and/or ECG changes indicative of ischaemia and/or imaging evidence of acute myocardial ischaemia. Other causes of myocardial necrosis, (e.g. acute HF or myocarditis) when an elevated cTnT-hs test result is obtained, should also be considered.

A simple algorithm incorporating levels of cTnT-hs at presentation and absolute changes within the first hour optimised sensitivity and negative predictive value (NPV) at 100% for myocardial infarction rule-out.

Recently, a prospective multicentre study, which included 872 unselected patients with acute chest pain presenting to the ED, designed to develop and validate an algorithm for rapid rule-out and rule-in of AMI, was published.[11] The cTnT-hs assay was used in a blinded fashion at presentation and after 1 hour. The final diagnosis was adjudicated by two independent cardiologists. A cTnT-hs algorithm incorporating baseline values, as well as absolute changes within the first hour, was derived from 436 randomly selected patients and validated in the remaining 436 patients. The primary prognostic endpoint was death during 30 days of follow up. AMI was the final diagnosis in 17% of patients. After applying the cTnT-hs algorithm developed in the derivation cohort to the validation cohort, 259 patients (60%) were classified as "rule-out," 76 patients (17%) as "rule-in" and 101 patients (23%) as in the "observational zone" within 1 hour. Overall, this resulted in a sensitivity and NPV of 100% for rule-out, a specificity and positive predictive value of 97% and 84%, respectively, for rule-in, and a prevalence of AMI of 8% in the observational zone group. Cumulative 30 day survival was 99.8%, 98.6% and 95.3% ($p<0.001$) in patients classified as rule-out, observational zone and rule-in, respectively. Using this simple algorithm incorporating cTnT-hs baseline values and absolute changes within the first hour could negate the need for prolonged monitoring and serial blood sampling in around 75% of patients in clinical practice.

In conclusion, the use of the guideline recommended cTnT-hs assay allows the rapid and reliable diagnosis of AMI in the ED and enables the ability to appropriately treat all patients presenting with acute chest pain.

How Positive High-sensitive Cardiac Troponin T Results Predict Long Term Prognosis in Patients with an Acute Presentation

Evangelos Giannitsis
(Heidelberg University Hospital, Germany)

The introduction of cTn-hs assays has changed the quality of diagnosis by improving the analytical sensitivity and detection of signals indicative of cardiovascular (CV) disease.[12] Around 30% of patients diagnosed with CV disease using the highly sensitive cardiac troponin I (cTnI-hs) have been shown to have AMI.[13] A total of 20.4% and 9.1% had type 1 and type 2 AMI, respectively, and 65.8% did not meet criteria for AMI. An increased cTnI level of 0.28 ng/ml had a 70% sensitivity and specificity for AMI diagnosis.

In Patients With Chest Pain With or Without ACS

cTnT measured with the cTnT-hs assay also provides better diagnostic and prognostic information compared to conventional cTnT assay in both patients with evidence ACS and in those with generalised chest pain.[14] In particular, cTnT-hs provides independent prognostic power for mortality within 6 months.

Even among patients with a standard fourth generation cTnT result below the 99th percentile cut off (0.01 ng/mL), cTnT-hs has been shown to improve risk assessment, providing useful diagnostic information in patients with ACS, and strong and independent predictive power for adverse long term outcomes even after early invasive strategy.[15] This was independent of other determinants of risk (e.g., old age, reduced glomerular filtration rate and TIMI risk score).

In Patients With Pulmonary Embolism (PE)

The use of cTnT-hs in the risk assessment of normotensive patients with acute pulmonary embolism, with a cut off value of 14 pg/mL, provides excellent prognostic sensitivity and NPV (both 100%).[16] In comparison, as many as 50% of the patients with an adverse early outcome would have been misclassified as low risk by traditional cTnT measures (cut-off 0.03 ng/mL). Patients with elevated cTnT-hs levels had a reduced probability of long term survival ($p=0.029$) and cTnT-hs was shown to be the only laboratory biomarker capable of predicting an

elevated risk of death over the long term.

In Patients With Acute Aecompensated HF

In hospitalised patients with acute decompensated HF, a positive hscTn test (both cTnT and cTnI) has been shown to be associated with lower systolic blood pressure on admission, a lower ejection fraction (EF) and higher in-hospital mortality (8.0% vs. 2.7%, p<0.001) than those who were negative for troponin, independently of other predictive variables. In another study, 98% of HF patients had detectable cTnT-hs at the limit of the blank (LoB = 3 ng/L).

In Patients With A Non-Cardiac Cause of Chest Pain

It is unknown to what extent non-cardiac causes, including renal dysfunction, may contribute to cTnT-hs levels. An observational international multicentre study of 1181 patients assessed the prognostic significance of cTnT-hs (0.014 µg/L; 99th percentile) in patients with non-cardiac causes of chest pain.[19] Among the known covariates, age was found to be the most important determinant of cTnT-hs, followed by renal failure, chronic HF, advanced valvular disease, pulmonary hypertension and diabetes. However, cardiac and non-cardiac factors, including renal dysfunction, only explain <50% of cTnT-hs levels among patients with a non-cardiac cause of chest pain. Therefore, unknown or underestimated cardiac involvement during the acute presenting condition seems to be a major cause of elevated cTnT-hs.

In Conclusion

In conclusion, there is a high prevalence of elevated cTn-hs among patients presenting with acute symptoms to an ED. Approximately 50-65% of cTn-hs elevations are not due to an ACS. Elevated cTnT-hs levels are associated with adverse long term outcomes, regardless of an acute presentation as ACS or non-ACS, and represent an independent risk factor. Comorbidities, including old age, renal failure and chronic HF, among others, are more prevalent in the presence of elevated cTnT-hs. Elevated cTnT-hs in patients without ACS is not a limitation, but a chance to identify patients with severe comorbidities at risk for further adverse outcomes.

Towards a Better Understanding of Biomarker Guided Heart Failure Care: The PROTECT Study

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Despite successes in the development of therapies for chronic HF, affected patients are still suffering significant morbidity and mortality. The current standard of care (SOC) for chronic HF includes pharmacological and non-pharmacological treatment that aims to improve symptoms and cardiac function. However, the titration of pharmacological treatments is often suboptimal, and even when optimal, higher risk patients may go unrecognised. This has led to interest in how to improve monitoring of patients with chronic HF in order to better guide therapy.

Biomarkers, especially natriuretic peptides such as B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP), are a valuable addition to standard clinical assessment in the diagnosis and prognosis of HF. [20]

BNP and NT-proBNP levels are increased in HF, and correlate well with ventricular wall stress and severity of HF. Among HF syndromes, systolic dysfunction and HF with preserved EF may cause elevated BNP or NT-proBNP. In addition, other relevant cardiac diagnoses, including right ventricular failure, valvular heart disease and arrhythmias, such as atrial fibrillation, may cause elevation of BNP or NT-proBNP.

The Valsartan Heart Failure Trial (Val-HeFT) examined whether differences in the biological characteristics of BNP and NT-proBNP modified their clinical correlates and prognostic performance in HF and found that, although they had similar relationships with age, LVEF and internal diameter and creatinine clearance, NT-proBNP was superior to BNP for predicting mortality and morbidity (p=0.032) or hospitalisation for HF (p=0.0143).[21] When measurements at randomisation and after 4 months were compared, it was found that patients could be stratified into four categories according to NT-proBNP levels at these two time points.[22] Patients with high NT-proBNP values at both time points had the highest risk for mortality and hospitalisation, followed by the low-high, high-low and low-low categories. Thus, serial determinations of NT-proBNP concentration and classification into these categories of changes according to threshold levels offers a strategy for risk stratification of patients with chronic and stable HF.

Therapies that are favourable for chronic HF (such as diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β-blockers and aldosterone antagonists) tend to lower concentrations of BNP or NT-proBNP. Thus, there has been increasing interest in guiding HF therapy with BNP or NT-proBNP, with the goal of lowering concentrations of these markers (and maintaining their suppression) as part of the therapeutic approach in HF. However, it remains unclear whether HF care with a goal to maximise medical therapy and also lower NT-proBNP concentrations is superior to SOC alone.

Over the past few years, a number of studies with heterogeneous inclusion criteria, methods and results have been performed.[23] However, there is an increasing amount of evidence to suggest that natriuretic peptide–guided HF management may improve mortality and morbidity.

The Pro-B Type Natriuretic Peptide Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study was designed to evaluate the hypothesis that a HF strategy guided by NT-proBNP could reduce CV events versus SOC.[24] In both groups, therapy was adjusted to achieve optimal drug targets, and in the NT-proBNP group, NT-proBNP was also maintained below 1000 pg/L. The primary endpoint of the trial was total CV events for a 1 year period.

In follow up, patients in the NT-proBNP group were more likely to have up titration of mineralocorticoid inhibition and substantial down titration of loop diuretics. The use of all treatments increased in the NT-proBNP group, with a significant increase in use of β-blockers and aldosterone antagonists versus SOC.

The NT-proBNP concentrations fell from 2344 to 1135 pg/mL in the NT-proBNP group and from 1946 to 1844 pg/mL in the SOC group (group comparison, p=0.03). Over 40% of NT-proBNP patients achieved a NT-proBNP concentration <1000 pg/mL. In terms of the primary endpoint, there were 100 CV events in the SOC group and 58 events in the NT-proBNP group (group comparison, p=0.009). There was an early and sustained divergence of the hazard curves out to 1 year follow up for the time to first event in favour of the NT-proBNP group (p=0.03). When the mean number of events was analysed by NT-proBNP concentration, a proportional linear increase was observed. In addition, the longer the NT-proBNP level stayed below 1000 pg/mL, the better the outcome.

Not only did biomarker guided therapy benefit younger patients in the PROTECT study, but benefits were also found in the elderly population. Elderly patients with HF have a worse prognosis than younger patients, and results from PROTECT showed that in patients ≥75 years of age, NT-proBNP values increased in the SOC arm (2570 to 3523 pg/mL, p=0.01), but decreased in the NT-proBNP-guided arm (2664 to 1418 pg/mL, p=0.001).[25] Elderly patients treated with SOC management had the highest rate of CV events, whereas the elderly with NT-proBNP management had the lowest rate of CV events (1.76 events per patient versus 0.71 events per patient, p=0.03); the adjusted logistic odds for CV events related to NT-proBNP-guided care for the elderly was 0.24 (p=0.008), whereas in those <75 years, the adjusted logistic odds for events following NT-proBNP-guided care was 0.61 (p=0.10).

NT-proBNP guided therapy was also shown to significantly improve patient quality of life versus SOC over a 1 year period (p=0.01).

NT-proBNP is not only associated with prognosis but it is also associated with ventricular remodelling. In the PROTECT study, the final NT-proBNP value was strongly associated with the likelihood for worsening LV volumes or a fall in LVEF.[26] These improvements in LV, as well as diastolic function from baseline, were seen in the NT-proBNP group.

In conclusion, the care of patients with HF can be challenging, with few objective tools available to assist in therapy decision making. Natriuretic peptides are powerfully prognostic biomarkers in patients with HF and may represent an objective target for therapy. Chronic HF therapy guided by a goal to reduce natriuretic peptide concentrations below prognostically meaningful levels results in more aggressive HF care, is well tolerated and is associated with superior outcomes.

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Latest Advances in 3D Echocardiography

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Introduction

In the latest years three-dimensional echocardiography (3DE) presented a remarkable evolution, regarding imaging resolution, speed of use and easier tools. Currently, 3DE is already integrated into daily medical practice and it is recognised as an important clinical tool, superior to 2D echocardiography for right and left ventricular (LV) function analysis,[1] for valvular heart disease evaluation and for patient selection and guidance of new invasive cardiac interventions.

Left Ventricle

LV function is one of the cores for echocardiography use, having an enormous impact on medical decisions. 3DE imaging has improved the accuracy in the evaluation of LV volumes, ejection fraction (EF), and wall motion analysis, regardless of ventricular shape.[2] However there is a significant underestimation of 3DE LV volumes, when compared with CMR, which[3] can be explained by echocardiography image quality[4] and by the ability for clear differentiation between the myocardium and the trabeculae.

LV volumes used to be assessed by several (4 to 7) heart beats acquisitions, which by the stitching artefacts represented a significant limitation for the study of patients with irregular heart rhythm or respiratory distress. At present time, LV volumes can be assessed by one heart beat with appropriate frame rate. Moreover some software recognise LV endocardium automatically in every frame of the cardiac cycle, presenting LV global and segmental volumes, stroke volume, ejection fraction and regional function analysis in few seconds.[5] The final report presents time–volume curves quantifying regional function and the LV systolic dyssynchrony index (SDI),[6] the most widely studied tool for 3DE assessment of dyssynchrony. It is defined as the standard deviation of time to minimal regional volume, expressed as a percentage of cardiac cycle duration. Simultaneously, the parametric "bulls eye" displays the timing of LV contraction and LV relaxation. This methodology examines regional LV contraction/ relaxation at approximately 700–800 points over the endocardial surface and the colour coding is used to identify which regions are contracting last (Figure 1). Simultaneously, 3DE wall motion–tracking systems have been developed, assessing 3DE strain, twist and displacement. The first model came from Toshiba Artida system®, requiring 7 heart beats for LV reconstruction and analysis. Using 3DE, data can be acquired and analysed in less time and the global results are comparable between 3D and 2DE, but 3DE has shown superior accuracy and reproducibility over previously used 2D-speckle tracking echocardiography.[7] Lately, one-heart beat 3DE wall motion–tracking software (4D) has been developed by Siemens® and GE Medical Systems®. The former uses automatic endocardial and epicardial borders contouring and tracking with consequent "voxel" deformation computing. The latter automatically generates 4D Strain ROI in the end diastolic frame, built up from an endocardial and an epicardial mesh, using a tracking algorithm based on frame-to-frame block matching (Figure 2). Both systems have been validated in simulated datasets,[8-9] but its clinical value remains to be established.

AUTHOR, BIO

Right Ventricle

The right ventricle (RV) has a particular morphology and a distinctive functionality with two main sections of fibres contracting perpendicular to each other, as the proximal inflow contract longitudinally and the distal, at RV outflow, circumferentially. Dedicated 3DE software for RV quantification has overcome some of the 2D echocardiography limitations, enabling RV geometry, volumes and ejection fraction. The most recent software for RV analysis is based on volumetric

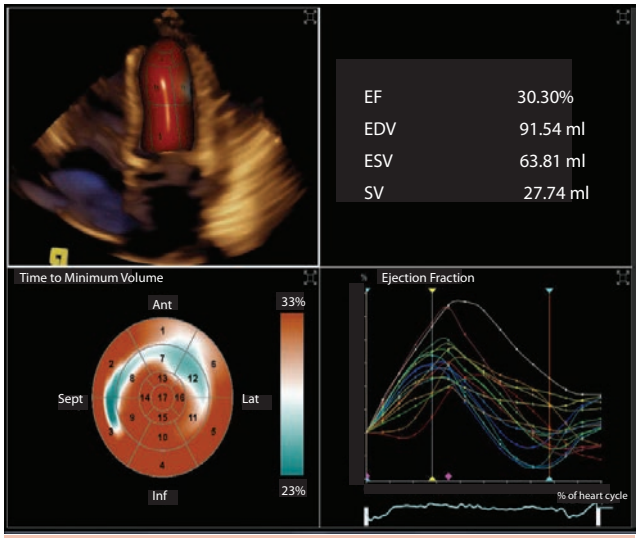

Figure 1. 3D transthoracic echocardiography one heart beat - left ventricular (LV) ejection fraction and contraction timing evaluation.

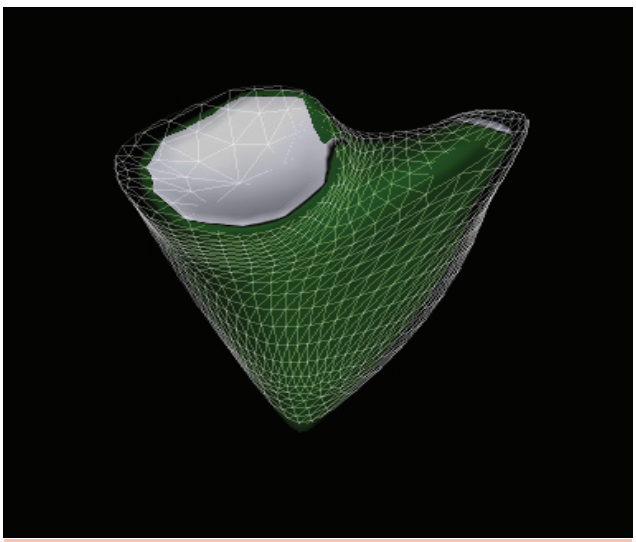

Figure 2. 3D transthoracic echocardiography-right ventricle ejection fraction.

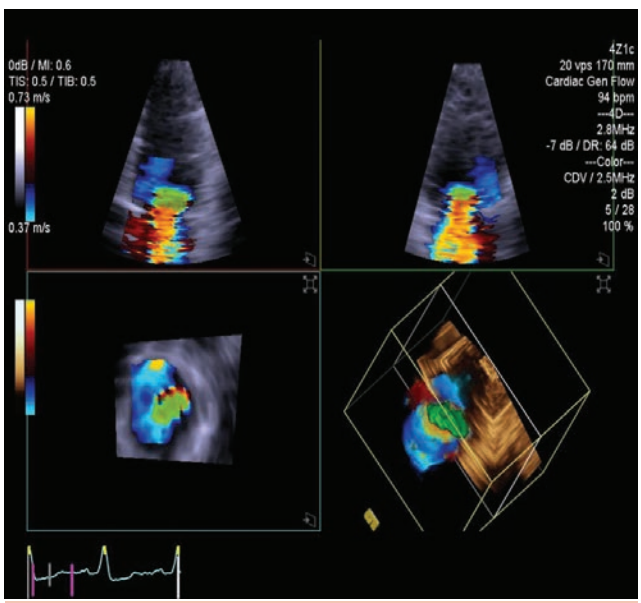

Figure 3. 3D transthoracic echocardiography – semiautomatic recognition of 3D PISA volume in mitral regurgitation.

semiautomatic endocardial border detection at end diastole and end-systole (Figure 2) and it has been validated by contrast CMR and radionuclide ventriculography.[10] Similarly to LV volumes, RV volumes calculated by 3DE are underestimated, when compared with CMR RV volumes.[11] Nevertheless, RV analysis requires very good quality windows and the dedicated software is still not available on cart.

Valvular Heart Disease

3DE has demonstrated to be superior to 2DE for detailed evaluation of morphology, function and at the time of guiding interventions.

Considering mitral valve (MV) apparatus, 3DE has the ability to represent structures in detail, enabling both LV perspective and the generation of the "surgeon's views" facilitating the progress of anatomic and functional interpretation. 3D transthoracic echocardiography[12] has similar accuracy for precise anatomic localisation of prolapsing MV segments when compared to 2D transesophageal echocardiography (TEE)[13] and 3D TEE is superior to 2D and to direct inspection during surgery, for diagnosing the location and the extent of complex MV disease.[14] The quantification-dedicated software (QLAB® software, Phillips Medical Systems, MA, USA) precisely measures the size, shape, degree of nonplanarity of the MV annulus, mitral leaflet surface area and prolapse height, mitral annular dimensions, and papillary muscle location. It provides an accurate measurement of MV ring and assists on the assumption of MV repair feasibility. Moreover, 3DE improves the diagnostic confidence for selecting patients for percutaneous interventions, as MitralClip™ and during the effective performance of these procedures.[1]

Additionally in respect to mitral regurgitation evaluation 3DE shown that the true proximal flow convergence region is generally more hemielliptical than hemispheric and that erroneous assumption of spherical proximal isovelocity surface area (PISA) or circular vena contracta underestimates mitral regurgitation severity,[15] especially in those with functional mitral regurgitation.[16] However, most systems present 3D colour Doppler imaging with restricted frame rate, even when using several heart beats and these often result in stitching artefacts. The Acuson Sc2000™ (Siemens Medical Solutions®) launched instantaneous full-volume colour Doppler echocardiography with quantitative software on-cart. It is performed with one heart beat and it has dedicated software for visualisation and recognition of 3D PISA surface, allowing effective regurgitant orifice area calculation (Figure 3).[12] *In vitro* experiments established the accuracy of this method[12] and *in vivo* validation of this technique was recently reported.[17] Moreover, it presents dedicated semi-automatic software for stroke volume estimation, through each of the valves. This can be useful for regurgitant volumes measurement particularly in complex situations as after mitral clip implantation.[18] However, up to now there is no validated reference standard for comparison between 2DE and 3DE findings.

Regarding mitral stenosis (MS) quantification 3DE planimetry is already the recommended method of evaluation as 2DE is performed in absence of an anatomical landmark to ensure that the short-axis view used to

trace the orifice is the smallest one. 3DE allows detailed visualisation and characterisation of mitral valvular and subvalvular involvement which has particular interest in candidates to balloon mitral valvotomy.[19]

The aortic valve 3DE analysis might be challenging by its thin leaflets and because imaging is obtained with an oblique angle of incidence of the ultrasound. 3DE provides additional data on the spatial relationship with the surrounding structures and it allows face alignment of the cut plane of the aortic annulus orifice, irrespective of the spatial orientation of the aortic root in the body. This facility showed that aortic annulus and LV outflow tract are mostly elliptical and not circular and that 2DE parasternal long-axis view often underestimates its area.[20] Providing a proper aortic annulus diameter measurement, 3DE is an accurate tool for prosthesis size selection in patients referred to transcatheter aortic valve implantation (TAVI).[1, 21]

During TAVI 3D TEE helps guiding the procedure, can confirm the optimal prosthesis position, and provide additional data for visualisation of the paravalvular aortic regurgitation jets. The best method for accurate quantification of paravalvular aortic regurgitation is still in discussion, but 3D TTE vena contracta planimetry use has been recently reported, showing an accurate capability for quantitative evaluation of paravalvular AR after TAVI.[22]

Chronic aortic regurgitation can also be evaluated by 3DE vena contracta planimetry. This method does not make assumptions of geometry, improves precision and had a good correlation with aortography grading of aortic regurgitation[23] and with the CMR.[24] Nevertheless, up to now, the final interpretation should follow the principle of comprehensive evaluation and integrated approach.

3DE also developed imaging interpretation in normal and abnormal TV anatomy, and 3DE measurements of the tricuspid annulus are accurate compared with CMR imaging, which may have an important implication in the surgical decision making processes.[25]

Conclusion

Echocardiography is changing rapidly and significant evolution and software improvements are foreseen in close future. Better quality imaging, high frame rate, 3DE by single-beat and automatic quantification software on-cart are overcoming 3DE limitations, improving medical knowledge of cardiac morphology and function, and establishing a place clinical routine.

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Moving the Goalposts: Pulmonary Hypertension Associated with Congenital Heart Disease

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Introduction

Congenital heart disease (CHD) is a frequent birth defect with a birth prevalence of 0.8%.[1] A significant proportion of patients with systemic-to-pulmonary shunts will develop pulmonary arterial hypertension (PAH) of variable severity,[2] and its presence in CHD patients negatively affects quality of life, morbidity and mortality.[3-6] The extreme end of PAH associated with CHD is known as Eisenmenger syndrome, a clinical phenotype first described by Dr. Paul Wood and characterised by suprasystemic pulmonary artery pressures causing shunt reversal and central cyanosis.[7]

The prevalence of PAH associated with CHD is estimated between 1.6 and 12.5 per million adults, with 25%-43% having Eisenmenger syndrome.[2, 8, 9] Fortunately, due to better diagnostic tools and earlier defect repair, evolution to Eisenmenger syndrome has declined from ±8% in the 1950s to 1-2% today.[8, 10] Presumably a shift will occur with fewer patients having PAH associated with simple cardiac lesions (atrial septal defect (ASD), ventricular septal defect (VSD) or patent ductus arteriosus (PDA)) and more patients having PAH associated with complex congenital heart defects (such as single-ventricle physiology who underwent palliative procedures).[11]

Pulmonary hypertension is defined as an invasively measured mean pulmonary artery pressure above 25 mmHg.[12] Left-sided heart problems (post-capillary pulmonary hypertension) or an increase in pulmonary blood flow (hyperkinetic pulmonary circulation) may also cause pulmonary hypertension but an increase in pulmonary vascular resistance (pre-capillary pulmonary hypertension or PAH) is considered most frequent in CHD patients.

In patients with an intracardiac shunt, increased pulmonary blood flow and/or pressure leads to endothelial dysfunction which alters pulmonary vascular proliferation and apoptosis, but also endothelial homeostatic functions with subsequent vasoconstriction, thrombosis and inflammation, all contributing to increased pulmonary vascular resistance.[13] The earlier stages of shunt-induced pulmonary vascular disease, as first described by Heath and Edwards, present with medial hypertrophy and/or intimal proliferation and are largely reversible after closure of the defect.[14, 15] However, when occlusive fibrotic lesions have developed later in life, closure of the defect may not result in complete normalisation of pulmonary artery pressures and may even cause right heart failure.[16, 17]

Non-modifiable Risk Factors and Classification

Although the histopathological end-result (so called plexiform lesions) are similar irrespective of shunt location, the underlying pathophysiology may differ. Some defects, such as an unrestricted AVSD, VSD, a large PDA, D-transposition of the great arteries with VSD and truncus arteriosus invariably lead to pulmonary vascular remodelling during the first one or two years of life and the clinical syndrome of PAH. By contrast, pre-tricuspid systemic-to-pulmonary shunts, as in the ASD, will only evolve to PAH in 10-20% of the cases.[18, 19] Important systemic to pulmonary artery shunts performed as palliative procedures in certain CHD patients may also cause pulmonary hypertension. In order to account for the heterogeneity in PAH associated with CHD, an updated classification was proposed at the Dana point meeting. Type and dimensions of the defect are relevant in assessing the risk and rate of developing PAH. Moreover, in small defects (ASD<2 cm and VSD<1 cm), the role of the defect in the development of PAH is uncertain. Direction of the shunt provides information whether the patients has evolved to Eisenmenger physiology. Extracardiac abnormalities and repair status also give additional prognostic information. Apart from data included in the classification, older patients and patients with complex underlying heart defects will have a worse prognosis.[6, 20]

Modifiable Risk Factors and Goal-oriented Therapy

The current practice guidelines for patients with idiopathic PAH include a practical table, including parameters with established importance in pulmonary hypertension and defines treatment goals for these patients.[21] Up until now, the only treatment that has proven to improve outcome in CHD patients with PAH are three classes of disease targeting therapy: prostanoids, endothelin-receptor antagonists and phosphodiesterase-5 inhibitors.[22] As they target the 3 main pathways

involved in the pathophysiology of PAH, combining 2 or more drugs is increasingly used in patients with CHD-PAH. The effect of these therapies has been evaluated mainly through surrogate endpoints evaluating exercise intolerance (mainly 6 minutes walk distance). More conventional treatment, including digitalis, diuretics, oral anticoagulation, and oxygen supplementation, is predominantly used on an empirical basis, but the effect on survival rate remains unclear.

Recently, there is increased interest in goal-oriented strategies. By identifying treatment targets in order to facilitate early intervention these strategies aim to reduce morbidity and prolong life. We would like to elaborate on parameters that can be used as an indication for starting or escalation of treatment and to assess the effect of treatment. These parameters should correlate strongly with deterioration and mortality. Not only risk factors at baseline (before treatment initiation), but also risk factors that are relevant during treatment are important to assess the patient's status.

1. Impaired Exercise Intolerance

Exercise capacity can be evaluated using New York Heart Association class (NYHA) assessment, 6 minute walk distance or a cardiopulmonary exercise test. Eisenmenger patients have a severely reduced exercise tolerance with a peak oxygen consumption between 10 and 14 mL/kg/min.[3] Six minute walk distance in these patients syndrome is usually between 290 and 430 meters in recent reports and clinical trials.[23-25] Although NYHA class is widely used in CHD to distinguish those with mild from moderate exercise intolerance, there is only a mild correlation with 6 minute walk distance and peak VO2, indicating that most patients with CHD underestimate their exercise intolerance.[4, 26]

NYHA class ≥3 and a deterioration in NYHA class have been related with adverse outcome in Eisenmenger patients.[6, 27, 28] Although termination of exercise may be more related to increased right-to-left shunt and cyanosis than to poor ventricular function or myocardial ischaemia (which have a more profound effect on prognosis), 6 minute walk distance is also related with outcome[26] (similar to idiopathic PAH[29-31]).

Several studies have indicated a positive effect of disease targeting therapies (such as endothelin receptor antagonists and phosphodiesterase-5 inhibitors) on NYHA class and 6 minute walk distance (range +28 till + 119 meters). However, Diller *et al.* reported that 20-30% of patients fails to increase 6 minute walk distance and up to 33% fails to improve NYHA class.[23] It has not been shown whether the change in NYHA class or 6 minute walk distance itself has additional prognostic relevance.

The authors added that whereas 6 minute walk distance may be more sensitive to detect the effect of treatment initiation in patients with low baseline distance, NYHA class may be more effective in evaluating the effect in patients with higher baseline walk distance.[23] Recently, a study evaluating the validity of 6 minute walk distance in patients with PAH, indicated that an improvement of 6 minute walk distance with 42 meters is clinically relevant (most studies in CHD-PAH patients report an average improvement of 57 meters).[32]

2. Right Ventricular Dysfunction

Although deterioration of the right ventricle is much slower in Eisenmenger patients when compared to patients with idiopathic PAH,[33] preservation of RV function is a major determinant of survival.[34] Clinical signs of right heart failure,[6] the degree of right ventricular hypertrophy on electrocardiography[28] and qualitative echocardiographic assessment of right ventricular function[35] have been related with adverse outcome. More recently, quantitative assessment of longitudinal right ventricular function using tricuspid plane annular systolic excursion (TAPSE) showed that patients with TAPSE <16 mm had a worse prognosis.[36] These findings are in line with the treatment goals for idiopathic PAH, indicating patients with TAPSE<15 mm as unstable and deteriorating.[12]

There is scarce evidence that treatment with disease targeting therapy may improve right ventricular function.[37] Interestingly, in patients with idiopathic PAH referred for treatment, the change in right ventricular ejection fraction after initiation of disease targeting therapy was related with outcome, whereas change in pulmonary vascular resistance was not.[38] Whether a direct effect of the medication on the right ventricle or other factors are responsible for improvement of right ventricular function remains unclear. However, 25% of patients, despite improvements in pulmonary vascular resistance, presented with progressive right ventricular deterioration after initiation of therapy. In patients with Eisenmenger syndrome, it is unknown whether a change in right ventricular function has prognostic relevance. Recently, Diller *et al.* indicated that elevated plasma BNP levels are related with increased mortality. Interestingly, the initiation of disease targeting therapies resulted in a reduction of plasma BNP levels.[26]

3. Central Cyanosis

In Eisenmenger patients, persistent venous to arterial mixing at the atrial, ventricular, or arterial level because of suprasystemic pulmonary artery pressures results in chronic hypoxemia. A reduced tissue oxygenation causes hypoxic damage to other organs.[39] In order to increase arterial oxygen content a secondary erythrocytosis develops. Nevertheless, the combination of cyanosis with PAH makes Eisenmenger patients the most limited CHD subpopulation.[4]

Although there was an initial concern that disease targeting therapies would lower oxygen saturation (due to a decrease in systemic vascular resistance and increased right-to-left shunt),[24] most studies evaluating the effect of these therapies report an increase in resting transcutaneous oxygen saturation (range +2% till +10%).[23, 24] Patients with the lowest baseline saturations are likely to benefit most from disease targeting therapy initiation and the effect is more

pronounced during exercise.[23] Although the improvement in oxygen saturation increases functional capacity, its relationship with outcome has not been shown.

In Eisenmenger patients, the diversion of venous blood into the systemic arterial circulation is the main factor causing hypoxemia. However, these patients may also present with ventilation/perfusion mismatching, which increases arterial desaturation and may in part explain that oxygen therapy improves saturation.[40] However, the only randomised trial evaluating the use of nocturnal oxygen therapy in adult patients showed no significant survival benefit of nocturnal oxygen therapy.[41]

A reduced tissue oxygenation causes a physiological increase in erythropoietin production resulting in secondary erythrocytosis and increased oxygen carrying capacity.[42] In order to increase haemoglobin levels (and oxygen carrying capacity) and to stimulate adequate erythropoiesis, sufficient iron stores are required. Although iron deficiency is related with generalised symptoms, impaired exercise capacity and quality of life[43] and has been identified as a risk factor for cerebrovascular events,[44] up to one third of Eisenmenger patients still present with iron deficiency.[45] Iron deficiency may have broader clinical consequences, not only related to impaired haemoglobin metabolism, but also to impairment of oxidative metabolism and cellular immune mechanisms.[46] Inappropriate phlebotomies have been shown to cause iron deficiency, and have therefore been discouraged in Eisenmenger patients.[44] Iron deficiency, defined as a ferritin level <30 pmol/L or a ferritin level 30-100 pmol/L and a transferrin saturation <20% is related with adverse outcome.[20] Interestingly, in absence of iron and vitamin deficiency, an optimal relationship between resting oxygen saturation and haemoglobin level can be described.[47] The indication for a phlebotomy is limited to patients with hyperviscosity symptoms who have a haematocrit >65%, no iron deficiency and who are treated with disease targeting therapies.[48]

4. Pulmonary Artery Thrombosis versus Haemoptysis

Haemoptysis is a feared complication in patients with Eisenmenger syndrome. Haemoptysis was reported in 11%-100% of patients and as the cause of death in up to 30% of patients.[7, 28, 35, 49, 50] However, in more recent cohort description haemoptysis as a cause of death has decreased and was not related with prognosis.[20, 51] Nevertheless, when significant haemoptysis occurs therapeutic possibilities are often very limited.[52] It is believed that haemoptysis is caused by pulmonary infarction secondary to pulmonary artery thrombosis or the development of collateral bronchial circulation. The prevalence of pulmonary artery thrombosis in this patient cohort is estimated between 13% and 31%[49, 50] and is associated with biventricular dysfunction.[36, 50] The main cause for the occurrence of pulmonary artery thrombosis is low-flow due to pulmonary vascular obstruction and not coagulation abnormalities.[50]

Although anticoagulation for treatment and prevention of pulmonary artery thrombosis appears logical, its use in clinical practice is far more complicated due to the possibility of severe bleeding complications.[52] Some have advocated the use of aspirin,[39] others hospitalisation and heparinisation in case of a thrombus[53] and others anticoagulation in patients with thrombus and no or mild haemoptysis.[52] In contrast to idiopathic PAH, where there is modest evidence for a survival benefit in anticoagulated patients,[54, 55] there is no long-term survival difference between anticoagulated and non-anticoagulated patients.[56] The presence of large aneurysms, clotting abnormalities in cyanotic heart disease and the risk for iron deficiency[20, 39] further complicate the decision to initiate anticoagulant therapy. Possibly, there may be a role for new oral anticoagulants with a lower risk of bleeding.[57]

5. Renal Dysfunction

High creatinine levels have been related with increased mortality.[26, 35] Increased uric acid levels may be caused by enhanced urate reabsorption due to abnormal intrarenal haemodynamics,[58]

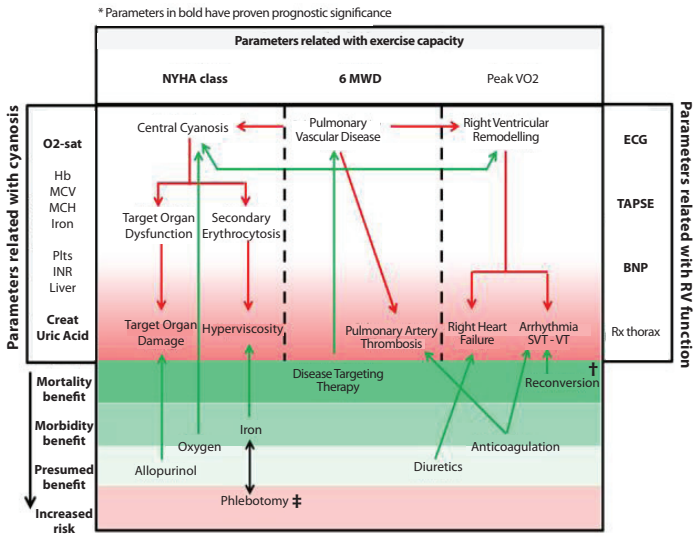

Figure 1. In CHD patients and associated shunt lesions, increased pressure and/or volume load will cause progressive pulmonary vascular disease. Once pulmonary artery pressure exceed systemic pressure, shunt-reversal occurs. Pulmonary vascular disease, right ventricular remodeling and central cyanosis are the main hallmarks of Eisenmenger syndrome. This figure gives a simplified overview of the main pathophysiological targets for therapy. There is a gradual evolution from what can still be considered a physiological adaptation to central cyanosis (secondary erythrocytosis) and increased right ventricular afterload (preservation of a right ventricular phenotype with hypertrophy) to a real pathological state (right heart failure, pulmonary artery thrombosis, renal dysfunction, arrhythmias). Based on the pathophysiology, the main parameters that should be assessed regularly in every patients (and which may also be important to evaluate prognosis and treatment effects) are added. There are treatment options with proven mortality benefit (dark green), proven morbidity benefit (light green), presumed benefit (white) and with proven adverse effects (red). †Individualized (pharmacological, electric cardioversion, ablation), but very difficult. ‡Isovolumic fluid replacement (750–1000 mL of isotonic saline while removing 400–500 mL of blood). O2-sat: oxygen saturation – Hb: hemoglobin – MCV: mean corpuscular volume – MCH: mean corpuscular hemoglobin – Plts: platelets – INR: international normalized ratio – Creat: creatinine – NYHA: New York Heart Association – 6MWD: 6 minute walk distance – Peak VO2: peak oxygen consumption – ECG: electrocardiogram – TAPSE: tricuspid annulus plane systolic excursion – BNP: brain natriuretic peptide.

	Parameter	Baseline related with prognosis	Value	Deterioration related with prognosis	R/	Improvement	Improvement related with prognosis	Proposed Target value
Exercise capacity	**NYHA**	Yes	NYHA≥3	Yes	DTT	Yes	?	NYHA2
	6 MWD	Yes	<250 m	?	DTT	Yes	>42 m	>300 m
	Peak VO2	?	?	?	DTT	?	?	?
RV function	**TAPSE**	Yes	<16 mm	?	DTT?	?	?	?
	BNP	Yes	30 pmol/L	Yes	DTT	Yes	?	<30 pmol/L
Cyanosis	**O2-sat**	Yes	<80%	?	DTT	Yes	?	>80%
					O2	Yes	No	?
	Iron def	Yes	†	?	Iron	Yes	?	†
	Hb	No	-	?	Iron	Yes	?	‡
Renal	**Uric acid**	Yes	>8 mg/dL	?	Allopurinol	Yes	?	?
	Creatinine	Yes	1.3 mg/dL	?	N/A	N/A	N/A	N/A
Arrythmia	**SVT**	Yes	N/A	N/A	Reconversion	Yes	Yes	Sinus
PAT	**PAT**	?	N/A	N/A	Antico	?	?	?

Table 1. This table demonstrates which variables should be evaluated at regular time intervals, their relationship with outcome (increased mortality). It also demonstrates whether the changes obtained with initiation of therapy have been related with outcome and if a target value can be formulated.
NYHA: New York Heart Association – 6 MWD: 6 minute walk distance – TAPSE: tricuspid plane annular systolic excursion – BNP: brain natriuretic peptide – O2: oxygen – Hb: haemoglobin – DTT: disease targeting therapy ‡ Ferritin <30ng/mL or ferritin 30-100 ng/mL and transferring saturation <20% ‡Predicted haemoglobin = -0.44*(O2-sat) + 57.5.

decreased excretion due to hypoxia[59] or even increased production due to tissue ischaemia[60] and is related with increased mortality.[60] Allopurinol, a purine analogue, can be used to lower uric acid levels. However, it is unknown whether this is related with improved survival.

6. Arrhythmias

Daliento *et al*. reported supraventricular tachyarrhythmias in 36% of patients and ventricular tachyarrhythmias in 22% of patients.[35] A history of clinical arrhythmias is related with adverse outcome.[6] Supraventricular tachyarrhythmias, such atrial flutter or fibrillation, are usually poorly tolerated, and restoration of sinus rhythm may related with a better outcome.[61]

Figure 1 provides a simplified overview of the pathophysiology in patients with shunt lesions evolving to Eisenmenger syndrome. Pathophysiological targets for therapy and related parameters that should be regularly checked in clinical practice are mentioned. The relation of each parameter with outcome is summarised in Table 1. A treatment algorithm, similar to idiopathic PAH can be proposed and some of the aforementioned parameters can be used to assess clinical response to disease targeting therapies.

Conclusions

PAH associated with CHD is a progressive disease. Regular monitoring including relevant parameters facilitates early intervention in order to improve functional capacity and outcome. Based on the underlying pathophysiology, treatment goals in patients with CHD-PAH may differ from idiopathic PAH. More detailed data are required to identify the most relevant parameters in this patient population.

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The Treatment of Virus-associated Inflammatory Cardiomyopathy

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Introduction

Myocarditis is an inflammatory heart muscle disease caused by myocardial infiltration of immunocompetent cells following any kind of cardiac injury (Table 1). Frequently myocardial inflammation is caused by a viral infection that produces myocardial necrosis and triggers an immune response in order to eliminate the infectious agent. In addition to virus-induced necroses chronic myocardial injury may develop by postinfectious immune or autoimmune processes or be associated with systemic autoimmune diseases. In the long run, virus persistence, virus-associated and persisting post-infectious inflammatory processes, and myocardial defects which have developed at the initial stage of the disease may be responsible for persistent or progressive ventricular dysfunction, arrhythmias and symptomatic heart failure. The disease presents as an acute or chronic form of dilated cardiomyopathy (DCM) but due to its broad spectrum of presentation the clinical diagnosis is often misleading.

Early fulminant disease is associated with a high mortality rate despite in time intensive care. Such courses are occasionally seen in lymphocytic myocarditis but more frequent in giant cell or granulomatous myocarditis or cardiac involvement in sarcoidosis. Untreated giant cell and eosinophilic myocarditis have an extremely poor prognosis, with 4 year survival rates of less than 20%.[1] Granulomatous necrotizing myocarditis is lethal if overlooked and untreated.

AUTHOR, BIO

In recent years improvement in early intensive care, including mechanical support with biventricular assist devices, has improved prognosis of, and often allows complete recovery from, fulminant disease or bridging to transplantation. Patients who survive the critical phase have a fairly good prognosis and survival from myocarditis in children and adults is similar at around 70%. In the remaining patients progressive chronic heart failure and unpredictable sudden cardiac death remain a serious concern. In contrast to fulminant disease, non-fulminant myocarditis and inflammatory cardiomyopathy are more likely to result in a progressive course with death or transplantation being required (Figure 1A).

New pathogen specific quantitative molecular diagnostic tests and histochemical staining procedures have expanded the role for endomyocardial biopsy as the only reliable method to elucidate the true nature of the disease (Figure 1A-D) and to specify tailored treatment conditions for subgroups of patients.[2,3] If the underlying infectious or immune-mediated causes of the disease are carefully defined by clinical and biopsy-based tools, specific immunosuppressive or antiviral treatment options, in addition to basic symptomatic therapy, may avoid unnecessary interventions and improve prognosis in a number of patients with acute and chronic disease.[4]

Pathogenic Mechanisms and Course of Virus Associated Inflammatory Cardiomyopathy

Enterovirus and Adenovirus Associated Heart Disease

For many viruses the exact cardiac infection site and the underlying pathogenic mechanisms are unknown. Most information on the pathophysiology of viral heart disease and post-infectious autoimmune myocarditis in both rodent models and humans is known from enteroviral infections such as coxsackie virus B3. Enteroviruses enter the host through the gastrointestinal or respiratory tract, reside in the reticuloendothelial system, and attack heart tissue as a secondary target organ. After enterovirus internalisation the negative strand RNA is reversely transcribed into a positive strand for subsequent virus replication.[5,6] Virus-related cytolysis of cardiomyocytes is

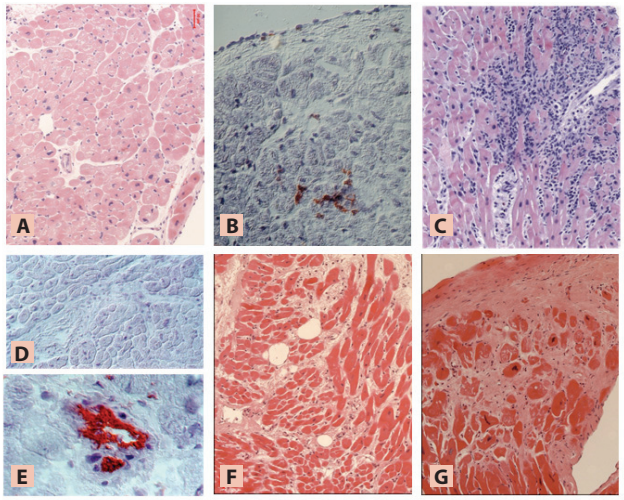

Figure 1A. Diagnostic evaluation of inflammation in a myocardial biopsy specimen (histology and immunohistology). a) normal myocardium, b) borderline-myocarditis with low-grade focal lymphocytic infiltration, c) acute lymphocytic myocarditis with focal cell infiltrates and necrosis of myocytes, d and e) VCAM-1 expression in non-inlamed (d) and inflamed (e) cardiac tissue, f and g) moderate (f) and advanced (g) postinflammatory dilated cardiomyopathy with hypertrophy of the cardiomyocytes and pronounced fibrosis/scarring.

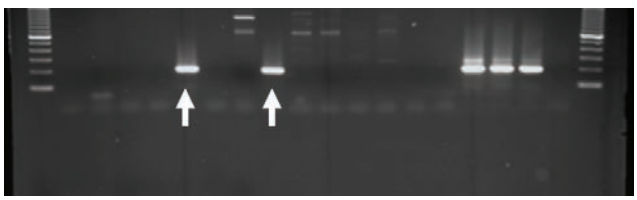

Figure 1B. Ultrasensitive detection of viral genome by nested polymerase chain reaction (nPCR) and gelelectrophoresis (arrows – enterovirus-positive patients).

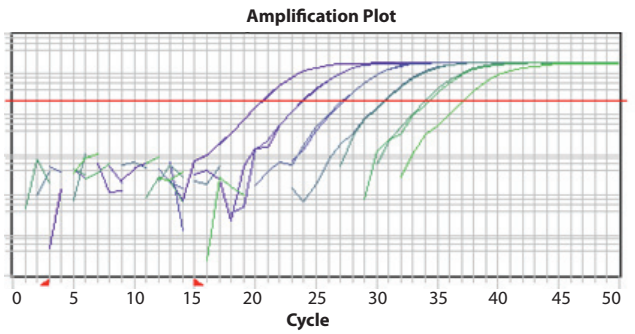

Figure 1C. (RT-)QPCR allowing quantification of the virus DNA load and viral transcripts.

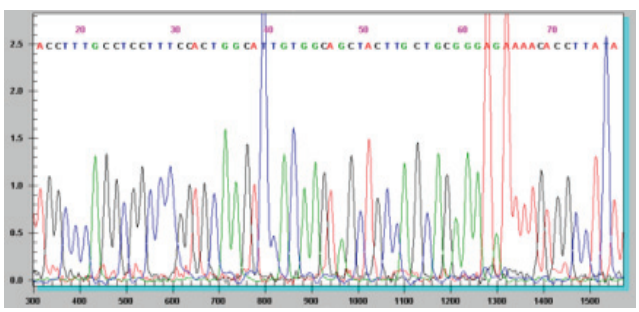

Figure 1D. Determination of virus types and virus subtypes by sequencing (e.g. sequence fragment of Coxsackievirus B3).

Frequent virus infections infiltrating cardiomyocytes and interstitial cells picornaviruses (coxsackie A/B, echo), adenovirus (A 1, 2 ,3 and 5)
Frequent virus infections infiltrating vascular endothelial cells Erythrovirus genotypes 1 (B19V) and 2, Human herpesvirus 6 A/B
Virus infections infiltrating yet undefined target cells Erythrovirus genotypes 1 (B19V) and 2, picornaviruses (echovirus, poliovirus), orthomyxovius (influenza), paramyxoviruses (RSV, mumps togaviruses (rubella), flaviviruses (dengue fever, yellow fever), cytomegalievirus Epstein-Barr virus, varicella-zoster virus, retrovirus (HIV), Hepatitis virus
Bacteria chlamydia (c. pneumonia/psittacosis), haemophilus influence, legionella, pneumophilia, brucella clostridium, francisella tularensis, neisseria meningitis, mycobacterium (tuberculosis), salmonella, staphylococcus, streptococcus A, S. pneumonia, tularemia, tetanus, syphilis, vibrio cholera
Spirocheta borrelia recurrentis, leptospira
Postinfectious autoimmunity
Autoimmune diseases Dematomyositis, inflammatory bowel disease, rheumatoid arthritis, sjögren syndrome, systemic lupus erythematodes, wegner's granulomatosis, giant cell myocarditis
Systemic diseases Churg-Strauss syndrome, collagen diseases, sarcoidosis, Kawasaki disease, scleroderma
Drugs aminophyllin, amphetamine, anthracyclin, catecholamines, chloramphenicol, cocain cyclophosphamid, doxorubicin, 5-fluoruracil, mesylate, methylsergit, phenitoin, trastuzumab, zidovudine
Hypersensitivity reactions (drugs) azitromycin, benzodiazepines, clozapine, cephalosporins, dapsone, dobutamin, lithium, diuretics, thiazide, methyldopa, mexiletine, Streptomycin, sulfonamides, nonsteroidal antiinflammational drugs, tetanus toxoid, tetracycline, tricyclic antidepressiva

Table 1. Infectious and inflammatory causes of myocarditis and inflammatory cardiomyopathy.

already detected before any inflammatory infiltrate develops and appears to be decisive in fulminant cases of myocarditis.

In the short run, spontaneous virus clearance is associated with clinical and haemodynamic improvement not observed in patients with persisting infection.[7] Long-term follow-up of such patients has revealed that patients who get rid of the virus in time during the first weeks or months after onset of the disease (50-60%) may avoid progression of heart failure with long-term improvement.[7, 8] Untreated patients with persisting enterovirus infection have a significantly higher risk of death.[8-10]

Therefore, the current challenge of antiviral therapy in patients with chronic viral cardiomyopathy is the timing of treatment in order to prevent further virus spreading and to achieve in time virus clearance before chronically infected heart tissue has been damaged irreversibly.[4]

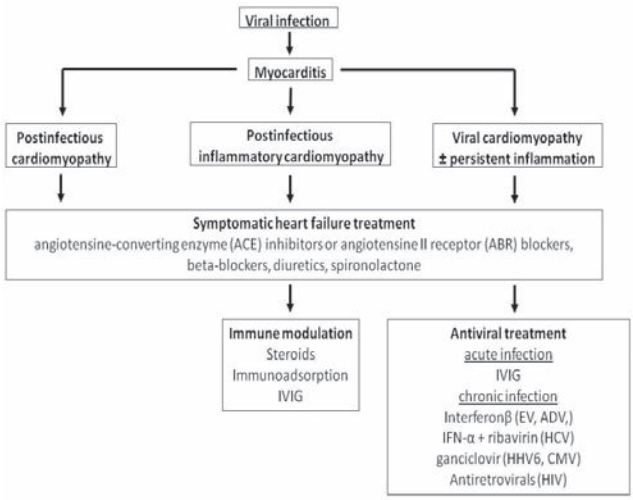

Figure 2. Figure legend needed.

Parvovirus and Herpesvirus Associated Heart Disease

Following primary infection in childhood, erythroviruses including its genotype 1 (B19V) may develop life-long persistence and reside asymptomatically in the bone marrow of a vast majority of the adult population. The *in vivo* tropism of erythrovirus infection is regulated by a number of determinants and persistent infection and replication is mainly restricted to erythroid progenitor cells, but also endothelial cells.[11, 12]

In contrast to enteroviruses and adenoviruses which primarily infect and injure cardiomyocytes, erythroviruses from the bone morrow infect vascular endothelial cells (EC) and their genomes have been localised in endothelial cells (EC) of venuoles, small arteries or arterioles in fulminant myocarditis or sudden onset heart failure.[13] In chronic inflammatory cardiomyopathy erythrovirus genotype 1 (PVB19) infection is predominantly detected in ECs of small capillaries and clinically associated with vasospasms and endothelial dysfunction.[14-17]

The same holds true for cardiac herpesvirus type 6 (HHV6) infection.[18] The great majority of the population becomes infected with HHV6 in the first two years of life, with the virus establishing latency in a small fraction of mononuclear cells. Of note, HHV-6 is the only human herpesvirus known to be integrated into germ line chromosomal telomeres in about 0.8% of the general population (ciHHV-6).[19] In HHV6 associated heart disease, viral antigens, DNA and viral particles were identified preferentially in vascular endothelial cells and occasionally in single degenerating cardiomyocytes.[18] An endothelial dysfunction and microvascular disease is discussed as possible pathogenesis of HHV-6 associated cardiovascular diseases. Although the vast majority of low-level HHV-6 reactivations in cardiac patients are asymptomatic, the condition may be associated with increased cardiac symptoms not responding to heart failure medication.

Since both viruses infect the vascular endothelium, they constitute different cardiac diseases than entero- or adenoviruses. Therefore, their clinical presentation and pathogenicity and course is different and must not be equalised with that of the latter two pathogens which infect and injure contractile cardiac tissue structures thereby leading to severe systolic left ventricular dysfunction. Data on the long-term course of B19V and HHV6 associated cardiomyopathies are not available.

Treatment

Symptomatic Treatment of Heart Failure

Although conventional pharmacotherapy does not influence specific causes of acquired diseases of viral or immune origin, it remains the hallmark of any heart failure therapy.[20] It does not depend on the etiology of the disease and remains primarily supportive (Figure 2). Despite routine use of angiotensine-converting enzyme (ACE) inhibitors or angiotensine II receptor (ABR) blockers, beta-blockers, diuretics, and spironolactone in patients with heart failure due to DCM, these patients still have a considerable annual mortality rate of 5-10%. A survival benefit has been demonstrated for ACE-inhibitors, β-blockers, and spironolactone which should be administered routinely started with low doses in all patients with New York Heart Association (NYHA) class II to IV heart failure.[21] Diuretics may improve heart failure symptoms without significant effect on long term outcome. Despite improvements in the treatment of heart failure in the last 15 years, clinical outcome following the onset of symptoms has not substantially changed.

Cardiac transplantation has been considered the last treatment for end-stage heart failure with DCM as one of the leading causes diagnosed at the time of the operation. Since the necessary numbers of organs stagnate or have even declined in some countries over the past years, mechanical left ventricular assist device (LVAD) has been introduced as one promising option to improve prognosis until recovery from fulminant acute disease or to bridge to transplantation in endstage disease.

Biopsy-based Specific Treatment of Acquired Disease

The gold standard of diagnosing the underlying causes of infectious myocarditis and DCMI is the histological, immunohistological and PCR-based analysis of endomyocardial biopsies if its time-dependent and methodological limitations are kept in mind.[4] Both persistent viral infections and infection-associated or post-infectious inflammatory processes of the myocardium have been recognised as independent prognostic parameters, in addition to left and right ventricular dysfunction, in myocarditis and DCM.[8, 22-25] Therefore, specific treatment options in addition to conventional pharmacotherapy are required which directly address the underlying viral or inflammatory causes of the disease (Figure 2).

Antiviral Treatment

Treatment of Acute Viral Heart Disease

Prevention of viral translation, transcription, and proliferation with the

use of antiviral medications that target viral attachment to host-cell receptors, virus entry, or virus uncoating such as Pleconaril, WIN 54954, or soluble CAR-Fc are effective in the early stage, only. In clinical practice, however, such agents are of limited use since most patients with virus associated heart disease are diagnosed at a time when the viruses have established a chronic infection of myocardial cells.

Interferons serve as a natural defense against many viral infections. Their innate production is associated with clinical recovery and subsequent sequelae while exogenous administration is protective. Type I interferons (IFN-α/β) therefore constitute a promising choice to treat the chronic disease.

Treatment of Chronic Viral Heart Disease

Interferons

Currently, there is no approved antiviral treatment for patients with chronic viral heart disease, but data from uncontrolled open labeled phase II studies have demonstrated that subgroups of patients, who have not improve upon heart failure medication, get significant long-term benefit even years after onset of the disease.[8] The drug is usually administered subcutaneously every other day in addition to constant heart failure medication for a six months' period.[26] In order to limit interferon-specific side effects the patient should enter a run-in period to improve tolerance following a stepped regimen, during which the patient receives 2x106 IU IFN-β per application every other day for 1 week. Within the following two weeks, the study medication can be elevated to 4x106 IU and 6x106 IU IFN-β, respectively, and continued for the following 21 weeks.

In a first biopsy-based treatment study, patients with chronic enterovirus and adenovirus infections of the myocardium responded well to a six months' interferon-beta (IFN-β1a) course.[26] Complete elimination of enteroviral and adenoviral genome was proven by follow-up biopsies taken three month after termination of the antiviral therapy. Virus clearance was paralleled by an improvement of mean left ventricular function, a decrease in ventricular size, an amelioration of heart failure symptoms and a decrease of infiltrating inflammatory cells. Of note, no patient deteriorated and patients with severely affected left ventricular dysfunction gained most benefit.[26]

Long-term follow-up of IFN-β treated patients recently showed that the ten year outcome of treated patients is markedly improved in comparison to untreated enterovirus infection.[8] Since adenoviruses are cleared effectively from the myocardium upon IFN-treatment, the same may hold true for chronic adenovirus infection of the heart but at present respective data on the long-term effect of treatment are not available.[26]

Currently, effective treatment conditions for viruses other than enterovirus and adenovirus have not yet been tested consequently. Other cardiotropic viruses frequently associated with chronic heart failure, e.g. parvovirus B19 (B19V) or human herpes virus type 6 (HHV6), respond less well upon IFN-β treatment with respect to virus clearance and haemodynamic changes, although such patients, too, improve clinically despite incomplete virus clearance.[27] Complete clearance may need longer treatment intervals, higher doses or even a complete change of the anti-viral treatment regimens. In a recent pilot trial, clinical improvement of parvovirus positive patients was associated with reduction of virus load and improvement of endothelial dysfunction.[28]

Similar insufficient information is available on HHV6 treatment conditions. There are no drugs approved by the Food and Drug Administration (FDA) for the treatment of HHV-6 infections but most strains of HHV-6 are susceptible to both ganciclovir and foscarnet.[19] Upon ganciclovir treatment, symptomatic improvement has been reported in few patients with reactivated ciHHV6 infection.[29] Whether these drugs constitute a reliable treatment condition in patients with symptomatic heart disease is currently unknown.

Treatment of Autoimmune and Post-infectious Inflammation

Myocardial inflammatory processes or autoimmunity may survive myocardial virus elimination and warrant immunosuppressive treatment in order to prevent later immune-mediated myocardial injury.[9, 30, 31] Immunosuppressive treatment demands biopsy-based exclusion of virus from treated patients since virus-positive patients do not improve or even deteriorate upon anti-inflammatory treatment while virus-negative patients with post-infectious or auto-immune inflammatory processes responded well in clinical trials.[9, 30-33]

Frequently administrered anti-inflammatory drugs are immunoglobulins, corticosteroids, azathioprine and cyclosporine, which are administered on top of regular heart failure medication. Generally the treatment is started on prednisolone (1 mg/kg body weight) for 2-4 weeks. During the following weeks it is reduced in increments of 10 mg bi-weekly until a maintenance dose of 10 mg is reached. Depending on the body weight, azathioprine may be added at a dose of 100 to 150 mg daily. The treatment duration should last for 3 to 6 months. Actual data of first randomised trials confirm efficacy of those treatment regimens in carefully selected patients.[30, 31]

Actually it is not proven that patients with acute virus-negative myocardial inflammation (< 6 months) get any benefit from immunosuppressive treatment.[33] Two randomised studies showed, however, that patients with chronic inflammation have a significant treatment advantage compared with patients receiving purely symptomatic treatment.[30, 31] The TIMIC study investigated patients with chronic active myocarditis and restricted LV function (LV ejection fraction [EF] less than 45%) who had displayed symptoms of chronic heart failure in spite of having received symptomatic medication for heart failure for more than 6 months. Viral infection was excluded by molecular biology tests before treatment was started.[9]

38 out of 43 patients on immunosuppressive therapy (88%) showed a

improvement of cardiac function and dimensions, defined as an increase of >10 percentage points in the absolute EF and a reduction of LV end diastolic volume (EDV) or LV end diastolic diameter (EDD) 10% (i.e. LVEF from 26.4±6.9 to 48.0±7.3%, LVEDV from 258.0±52.5 to 125.9±29.6, LVEDD from 68.6±7.4 to 52.8±6.3 mm). None of the untreated patients show at six month improvement of LVEF, that significantly worsened compared with baseline. In particular, 35/42 patients (83%) showed further impairment of cardiac. By the course of placebo group the TIMIC study confirmed that persistent inflammation exerts a harmful effect on the myocardium.[30]

The second study showed that a 3 month regimen may equally be effective as previous trials that used 6 months of immunosuppression, and that beneficial effects last for an extended period of time (2 years).[31] Furthermore, this trial validated the diagnostic sensitivity and accuracy of cell adhesion molecule (CAM) abundance for DCMi even in the absence of lymphocytic infiltration, possibly due to the close functional association between CAM induction and immunocompetent infiltration and cytokine induction and thus constitutes an important criterion for selecting those patients who will likely benefit from immunosuppression.[34]

Currently available data show that immunosuppressive therapy in patients with biopsy-proven, virus-negative inflammatory cardiomyopathy is an effective and safe option in addition to supportive treatment for recovery of cardiac failure. Furthermore, the TIMIC study confirmed that persistent inflammation exerts harmful effects on the myocardium in untreated patient. No data are available for the long-term survival rate after immunosuppression, although mortality in the US myocarditis trial after four years showed a trend towards a treatment advantage.[35]

Intravenous Immunoglobuline (IVIG) Treatment

The first data of acute myocarditis treated with intravenous immunoglobulin (IVIG) suggested that use of high-dose IVIG for treatment of acute myocarditis is associated with improved recovery of left ventricular function and with a tendency to better survival during the first year after presentation.[36] Later investigations and randomised studies which compared IVIG and cortisone treatment revealed that the treatment with intravenous immune globulin in children was not effective.[37] Freedom from death or transplantation was 81% at 1 year, and 74% at 5 years, with no difference between the modes of treatments. The median time to recovery of function was also comparable between the groups. Thus, treatment with intravenous immune globulin appear to confer no advantage to steroid therapy alone.[38]

Immunoadsorption

The rationale for immunoadsorption is to lower cardiotoxic antibodies in the patient's plasma, and with serial treatments over 5 or more days, extract antibodies and immune complexes from the heart as well.[39-41] The plasma is separated from cellular components by a centrifuge or column and passed through an immunoadsorbtion column. IgG and to a lesser degree IgA and IgM are non-specifically adsorbed during repetitive sessions. Plasma IgG levels are partially restored by infusion of 0.5 g/kg polyclonal IgG over 18 or more hours after the last apheresis treatment. The favourable haemodynamic results of immunoadsorption in patients with DCMi may be related to removal of functionally active cardiac autoantibodies or other immunologically active compounds, since immunoadsorption leads to biopsy-proven decrease in lymphocytic infiltration and CAM expression.[42, 43]

Conclusion

Viral infections are the most common triggers of inflammatory myocardiopathies and can, if persistent, damage the myocardium even without accompanying inflammation. Cases of subacute myocarditis that initially are accompanied by non-specific symptoms are often identified and myocardial biopsy performed only at an advanced stage. Because the clinical course of myocarditis is unpredictable, all patients with etiologically unexplained heart failure have to undergo myocardial biopsy, before irreversible and thus untreatable damage to the myocardium has developed. Since the pathophysiological processes in myocarditis take place at the cellular and subcellular levels, myocardial biopsy is the only method by which the causative strain can be identified and/or inflammation can be confirmed - both of which are important for differential treatment. Only if the underlying infectious or immune-mediated causes of the disease are carefully defined by clinical and biopsy-based tools, specific immunosuppressive and antiviral treatment options in addition to basic symptomatic therapy may improve prognosis of subgroups of patients with acute and chronic disease.

Conflict of Interest Statement

The authors declare that no conflict of interest exists. The research projects used as the basis for the review article were funded by the German Research Foundation (DFG) in the context of Sonderforschungsbereich-Transregio (SFBTR19), inflammatory cardiomyopathies.

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Renal Denervation is Coming of Age

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Introduction

Arterial hypertension remains the single largest contributor to death worldwide.[1] Every 20 mm Hg increase in systolic blood pressure correlates with a doubling of 10 year cardiovascular mortality.[2, 3] Epidemiological data clearly demonstrate that even small decreases in systolic blood pressure (SBP) result in a significant reduction of cardiovascular mortality (2 mm reduction of SBP reduces stroke mortality by 10% and mortality due to ischaemic heart disease by 7%).[2] Despite lifestyle and pharmacologic intervention, many patients with hypertension do not achieve blood pressure control.[4-6] The incidence of true treatment resistant hypertension is estimated to be in the range of 5 to 15% among all hypertensive patients. Sympathetic overactivity is frequently observed in that patient cohort.[7] Renal denervation (RDN) therapy offers a catheter based therapeutic tool that directly tackles overactivity of the sympathetic nervous system.

Interventional treatment of resistant hypertension was the topic of this year's "Great Debate" at the Euro PCR meeting in Paris. The following article briefly summarises the current clinical data and gives an update on new registry data and developments in RDN technology, as presented at EuroPCR.

Symplicity Trial Program

Worldwide more than 5000 patients underwent renal denervation therapy with the Symplicity™ system up to date. RDN was shown to be a safe and effective treatment option in patients with poor blood pressure control, despite poly-pharmacologic treatment (Figure 1).[8-13] Initial information regarding feasibility and efficacy of the method were obtained in a first-in-man study.[8] Following those early encouraging experiences, a series of pilot studies were conducted. Results from the first-in-man experiment and from a series of pilot studies were combined to the Symplicity HTN-1 study.[9, 10] Latest follow-up data demonstrated a sustained blood pressure response for up to 3 years (Figure 1) and an increasing response rate over time (Figure 2). To rule out potential observational bias, an open-label randomised controlled multi centre trial, the Symplicity HTN-2 study, was performed.[11] Results also confirmed that RDN is safe and that the blood pressure lowering effects are sustained also up to 12 months after treatment in a controlled randomised setting[12] (Figure 3). The Symplicity HTN-3 study, a double blind, randomised, controlled multi centre trial, recently started enrolment in the United States.[14]

Beyond Blood Pressure Control

Since over-activity of the central sympathetic nervous systems plays an important role in a variety of conditions, RDN was also shown to display beneficial effects beyond blood pressure control, such as in patients with diabetes,[15] obstructive sleep apnoe,[16] polycystic ovarian syndrome,[17] and atrial arrhythmia.[18] Whether RDN might also be beneficial in patients with chronic kidney disease or heart failure is going to be evaluated in future clinical trials.

While reduction of cardiovascular endpoints following RDN has not been proven yet, early data indicate favourable effects on left ventricular mass and diastolic function in patients with resistant hypertension.[19]

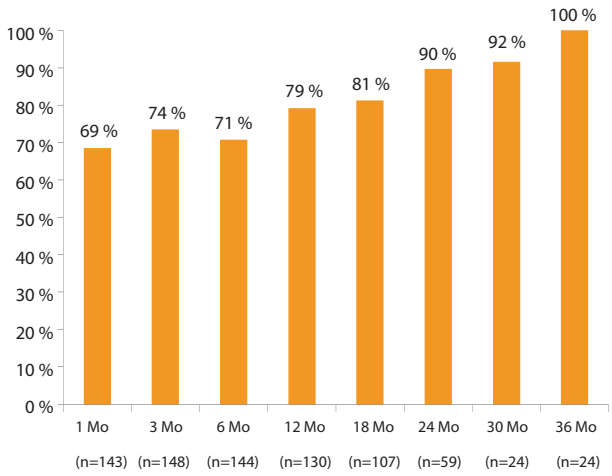
Registry Data

Whether those favourable results of clinical trials can be reproduced in the real-world setting is of great interest to the hypertension community. First, numerous exclusion criteria prevented a significant number of patients from enrollment in clinical trials. For instance, patients with significant renal anatomy abnormalities or prior renal artery interventions were not eligible for participation in the Symplicity trial program.[9-11] 30 out of the 190 patients (16%), initially assessed for eligibility, did not undergo randomisation in the Symplicity HTN-2 study due to unfavourable renal anatomy.[11]

Second, adherence to antihypertensive medications is expected to differ between randomised controlled trials and the real world. In the Symplicity HTN-trial program, patients were asked to stay on their antihypertensive regimen. Number and/or dosage of antihypertensive agents were therefore reduced in only 10 out of 49 patients in the HTN-2 study.

Results from the ALSTER hypertension registry support the concept of

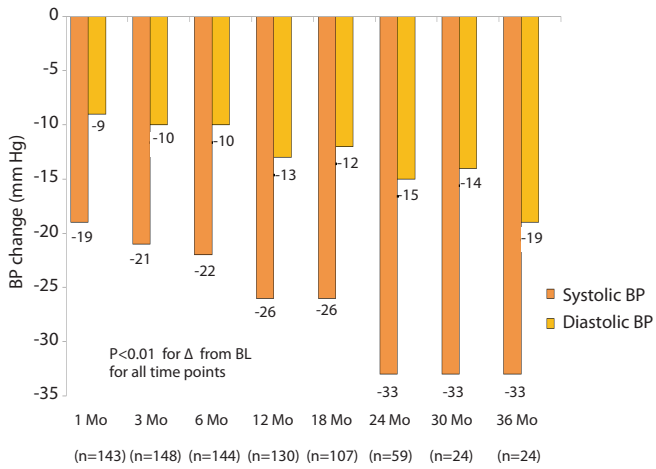
Symplicity HTN-1: Percentage Responders Over Time
Responder was defined as an office SBP reduction ≥ 10 mmHg



*Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

Figure 1. Response rate in the Symplicity HTN-1 trial increases over time.

Symplicity HTN-1: BP Reductions Through 3 years



*Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

Figure 2. Symplicity HTN-1 trial shows sustained blood pressure response up to 3 years.

RDN in a real world setting. 6 months follow up data were available in 31 from 125 treated patients with resistant hypertension. Office systolic blood pressure significantly improved after 3 and 6 months despite reduction of antihypertensive medication in 27% of patients after 6 months.[20]

Another group presented their experience with RDN under standard of care conditions. Treatment of resistant hypertensive patients (n=35) was proven to be safe and resulted in a significant reduction of both office (-30/-15 mm Hg) and ambulatory blood pressure (-23/-10 mm Hg) after 6 months.

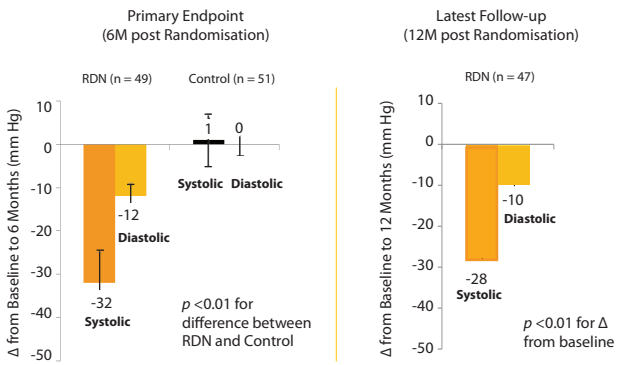
In the same line, a group from Utrecht also presented a significant reduction in office systolic blood pressure after 6 (-24 mm Hg) and 12 months (-27 mm Hg) in 45 patients. ABPM data were available in 14 patients after 6 months, showing a small but significant reduction of 9 mm Hg in systolic blood pressure.

Since not all patients seem to response equally to RDN, efforts are made to potentially identify indicators of treatment success. In the Halle registry (n=61 patients), the drop in 24 h systolic ABPM was comparable to the published Symplicity data (-9 vs. -11 mm Hg), while patients with the poorest blood pressure control at baseline (>180 mm Hg) benefit by far the most (-40/-16 mm Hg) at 6 months.

Interestingly, another single centre registry reported that the efficacy of RDN seems to depend on the number of ablation points per artery. Authors therefore recommend 7 to 8 ablation points per artery (if technically feasible) and also report of a significant benefit after a repeated RDN procedure in non-responders. (Note: repeated procedures are currently not recommended by the authors or by the manufactures of RDN devices).

Whether results of randomised controlled trials can be reproduced in a large-scale real-world setting is also currently evaluated in the

Symplicity HTN-2: Primary Endpoint and Latest Follow-up



Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Esler, M.)

Figure 3. Latest Symplicity HTN-2 trial results confirm sustained blood pressure response after 12 months follow up.

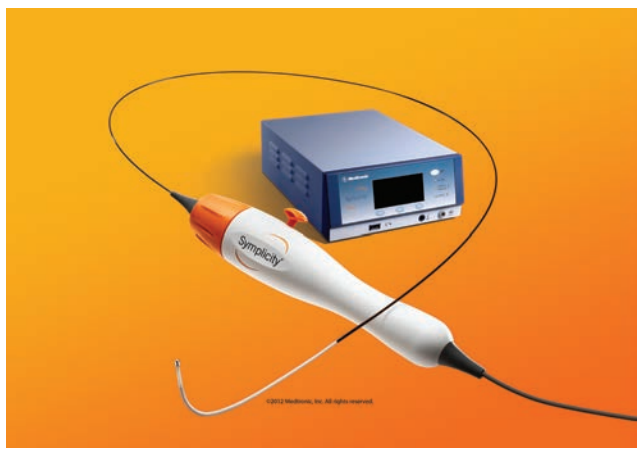


Figure 4. Symplicity™ Renal Denervation System.

prospective Global Symplicity™ Registry.

New Approaches to Renal Denervation

The vast majority of clinical trial data were obtained using the radiofrequency (RF) based Symplicity™ System (Medtronic). Results from other RF as well as from non RF-based therapies (ultrasound) were presented at this year's Euro PCR meeting in Paris.

A multi-electrode RF catheter (EnligHTN™, St. Jude) (Figure 4) demonstrated an office BP reduction of -28/-10 mm Hg already 30 days after treatment in a first-in-man study with 46 patients.

The RHAS trial is a small (n=8) single center first-in-man study with a balloon mounted helical RF electrode (One-Shot™, Covidien), aiming for a significant reduction of procedural time (average 33.5 min) and potentially less (shorter) pain sensations. Office BP reduction was reported to be -31/11 mm Hg at 30 days.

The REDUCE-HTN trial, another small first-in-man trial with 7 patients, evaluated safety and efficacy of a balloon mounted catheter (Vessix Vascular), delivering bi-polar RF energy. Office BP reductions were reported to be -30/-11 mm Hg after 30 days.

Finally, results of a first non RF-based study, the REDUCE FIM trial were reported. Average drop of office blood pressure in 15 patients was -32/-16 mm Hg 3 month after treatment with a catheter based ultrasound technology (PARADISE™, Recor).

Conclusions

Recent data presentations expand the evidence for the long-term safety and efficacy of the Symplicity renal denervation system. Several small, non randomised, first-in-man trials also demonstrated short-term safety and efficacy of other RF- and non RF-based devices, supporting the general concept of renal denervation in patients with treatment resistant hypertension. However, randomised controlled trials are required to demonstrate sustained results for these newer devices before they meet the benchmark set by the Symplicity™ system, but their entry promises to brighten the future of the interventional treatment of arterial hypertension.

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Device-based Therapies for Resistant Hypertension

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Introduction

Hypertension is universally considered the most detrimental among cardiovascular risk factors. The worldwide prevalence of hypertension in adults aged 25 and over was around 26.4% in 2000 and it is calculated that in 2025 it will increase by 60%, corresponding to around 1.56 billion of hypertensive people.[1-2] Both systolic and diastolic blood pressure (BP) values are directly and continuously associated with an increased incidence of coronary and cerebrovascular events, peripheral artery disease, heart failure and chronic kidney disease.[3] In 2007, hypertension was the highest ranked cause of death in the USA, being responsible of 17.4% of total mortality.[2] Despite this overwhelming evidence, BP control in the worldwide hypertensive population is still unsatisfactory.[4] Sympathetic nervous system (SNS) is known to play a major role in development and maintenance of essential hypertension,[5] thus it is not surprising that during the past decades several efforts have been made to counteract its overactivation.[6-7] In the last few years, novel non-pharmacological, promising approaches targeting SNS have been developed, including renal denervation (RDN) and baroreceptor-activating therapy (BAT) (Figure 1).

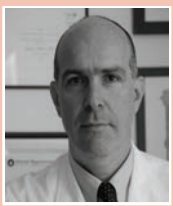
Resistant Hypertension: Clinical Aspects

According to the currently accepted definition, RH is defined when a therapeutic plan that has included adherence to lifestyle measurements and the prescription of at least 3 drugs, including a diuretic, in adequate doses, has failed to lower systolic and diastolic BP to goal.[8-9] Thus, RH category includes patients with uncontrolled BP in spite of the use of 3 or more drugs, as well as patients whose BP is controlled with 4 or more drugs.

The real prevalence of RH has been by now investigated by few studies. The NHANES study estimated that 12.8% of drug-treated hypertensive patients met the criteria of definition of RH.[10] The prevalence among drug-treated hypertensive patients referred to a specialist Hypertension Unit is even higher.[11] Resistant hypertensive patients have a greater prevalence of associated cardiovascular risk factors (such as older age, obesity and diabetes), of target organ damage (such as albuminuria, reduced renal function, and left ventricular hypertrophy) and of previous history of cardiovascular events.[10, 12-14] These features translate to a worse cardiovascular prognosis: patients with true resistant hypertension, that is confirmed by 24-hours BP monitoring, had an almost 3-fold increased risk in comparison to patients who had both office and 24-hours BP controlled.[15]

Another peculiarity of RH patients, with crucial consequences for their diagnostic work-up, is the high prevalence of secondary hypertension.[16] Amongst others, primary aldosteronism and the obstructive sleep apnoea (OSA) are the most frequent forms of secondary hypertension among RH, with an estimated prevalence of 11.3%[17] and up to 60%[16] respectively. For these reasons, it is mandatory that secondary causes of hypertension are investigated and excluded in RH patients.

Different clinical conditions may often mimic RH, leading to the definition of pseudoresistant hypertension. Amongst causes of pseudoresistant hypertension, it is possible to recognise lifestyle factors, such as excessive dietary salt or heavy alcohol intake; chronic use of drugs that can raise BP values (FANS, oral contraceptives); inaccurate BP measurements; isolated office (white-coat) hypertension; poor patient compliance to therapeutic plan or inadequate therapy; and secondary causes of hypertension.[9] Thus, initially the approach to a patient with a putative RH should be directed to confirm a true drug-treatment resistance. In particular, the assessment of out-of-office BP



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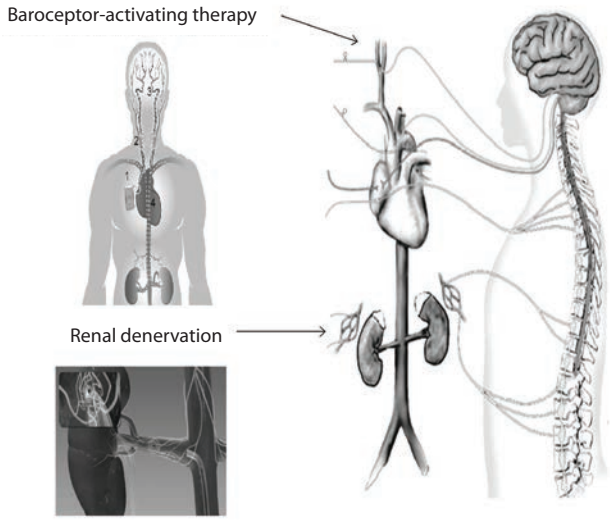

Figure 1. New non-pharmacological BP-lowering treatments targeting sympathetic nervous system.

values by using 24-hour ambulatory BP monitoring is mandatory.[9] In a recent study, 24-hour ambulatory BP monitoring revealed that about one third of patients classified as having RH on the basis of office BP had instead white-coat RH.[14] In addition to this, screening for secondary causes of hypertension, as already mentioned, is imperative in these patients. In this diagnostic work-up, referral to the appropriate specialist Hypertension Unit is recommended, especially when BP values remain out of goal in spite of 6 months of adequate drug treatment and with a high suspicion of secondary hypertension.[9]

Renal Denervation: Current Evidence

In humans bilateral ablation of renal nerve afferents is achieved using a radiofrequency ablation catheter inserted endovascularly through the femoral artery and connected to a generator. The procedure, performed bilaterally, has a total duration of about 1 hour, requires intravenous analgesia and sedation and has short recovery times. By now, safety and effectiveness of this procedure in humans was investigated in two clinical trials: Symplicity Hypertension (HTN)-1[18] (with extended follow-up),[19] which is an in-man proof-of-concept, efficacy and safety study, and the Symplicity HTN-2 study, a multicentre, prospective, randomised clinical trial.[20] Key characteristics and results of the clinical trials performed by now are summarised in Table 1. These studies demonstrated a significant reduction in BP, sustained for at least 2-years.[18-20] Particularly relevant are the results of the Symplicity HTN-2 study, including 106 participants randomly assigned to RDN immediately (treatment group) or after 6 months (control group).[17] Office BP values decreased significantly by 32/12 mmHg in the treatment group, whereas no changes occurred in the control group.[19] Safety profile appeared to be quite favourable: in the extended Symplicity HTN-1 cohort, 97% of patients (149 of 153) had no complications. Adverse events were mainly related to the renal angiography procedure.[19] The complications rate was similarly low in the Symplicity HTN-2.[20]

Clinical trials	Trial design	Study population	BP / drugs at baseline	BP reduction at the end	24-hours BP monitoring
Symplicity HTN-1 study[18]	proof-of-concept efficacy and safety study	50 patients with severe RH (office systolic BP >160 mmHg with three or more antihypertensive medications, including a diuretic	177/101 mmHg on BP-lowering 5.1 drugs	- 27/17 mmHg after 12 months	Not performed
Symplicity HTN-1 study - extended follow-up[19]	efficacy and safety study	153 patients with severe RH	176/98 mmHg on 5.1 BP-lowering drugs	- 32/14 mmHg at 24 months	Not performed
Symplicity HTN-2 study[20]	multicentre, prospective, randomised clinical trial	106 patients with RH and office systolic BP >160 mmHg (or >150 mmHg for patients with type 2 diabetes)	178/96 mmHg	-32/12 mmHg at 6 months	Performed in a subgroup: BP reduction -11/-7 mmHg (p<0.05)
DEBuT-HT trial[25]	multicentre, prospective, non-randomised feasibility study	45 patients with severe RH	179/105 mmHg on 5 BP-lowering drugs	-21/12 mmHg at 3 months, -33/22 mmHg in 17 subjects followed up for 2 years	Performed: -6/4 mmHg after 3 months; -4/13 mmHg after 2 years
Rheos Pivotal Trial[26]	double-blind, randomised, placebo-controlled trial	265 patients with RH	169/101 mmHg on 5.2 BP-lowering drugs	-25 mmHg (systolic BP) at 12 months from month 0, -35 mmHg from pre-implant	Not performed

Table 1. Main characteristics of clinical trials performed by now using renal denervation (in grey) and baroreceptor-activating therapy (in white).

Transient intraprocedural bradycardia, sometimes requiring atropine, was quite frequent (13%). Renal function was preserved after 6 months.[20] RDN appeared to have a positive effect also on cardiac organ damage, with a significant reduction in left ventricular mass index and an improvement in systolic and diastolic function after 6 months,[21] and on glucose metabolism.[22]

However these results were blunted by several limitations. First of all, both studies were funded by the company producing the equipment, and the sponsor was involved in the study design and analysis. Second, only the HTN-2 study had a randomised controlled design; however, it was not blinded, since the control group had no sham intervention. Third, the main outcome variable, BP reduction, would have been better explored by a 24-hour BP monitoring, which was performed only in a subgroup of the Symplicity HTN-2 study. Interestingly, 24-h BP monitoring data showed a relevantly smaller BP reduction in comparison to that highlighted by office BP.[20] Long-term duration of the antihypertensive effect after RDN needs to be investigated, since renal nerve fibres may regenerate. Up to now, patients with dual renal arteries and accessory arteries have been excluded and there are no data on unilateral RDN effects. Efforts should be also made in order to identify pre-procedurally RH patients with high probability of good BP response to RDN, as well as to indicate immediate procedure success during the procedure.[23]

Although radiofrequency procedure appears to be overall safe in the short term, ongoing experimental studies are proposing less-invasive approaches for RDN other than radiofrequency, such as local delivery of neurotoxic drugs, cryoablation and ultrasound-induced denervation. Furthermore, the safety of long term SNS inhibition, and particularly of the irreversible disruption of renal efferences and afferences, and its possible consequences on cardiovascular homeostasis, is still an unsolved issue, that should be deeply investigated in mechanistic studies and in long-term follow-up of clinical trials.

Baroceptor-activating Therapy: Current Evidence

Baroceptor-activating therapy (BAT) is an innovative approach to treat resistant hypertension, which acts by increasing the depressor influences that physiologically modulate BP. In the past years an implantable device (Rheos System, CVRx, Inc., Minneapolis, Minnesota), acting by electrical stimulation of the carotid sinus, has been developed. The original procedure comprehended bilateral leads implant and general anaesthesia.[24] Very recently, the same company released a second-generation BAT device (Barostim), which is implanted mono-laterally in assisted local anaesthesia.

Until now, safety and effectiveness of BAT in humans have been investigated in two clinical trials: the Device Based Therapy in Hypertension (DEBuT-HT) Trial[25] and the Rheos Pivotal Trial,[26] whose main features are briefly exposed in Table 1.

Both studies demonstrated a consistent and sustained BP-lowering efficacy for BAT, comparable to that obtained by RDN.[25-26] Preliminary data of 4-year follow up indicated a sustained and even greater BP reduction over time.[27]

In the DEBuT-HT study, though limited by a non-randomised design, results are reinforced by 24-h BP measurements.[25] The Rheos Pivotal Trial was a double-blind, randomised, placebo-controlled trial, enrolling 265 subjects with RH. All patients were implanted with the device and subsequently randomised (2:1) 1 month after implantation to receive BAT immediately or delayed BAT initiation following the 6-month visit (control group).[26] The study, though demonstrating a great reduction in BP, missed the primary endpoint of acute efficacy, which aimed at obtaining, in a super-superiority design, a proportion of subjects that achieved at least a 10 mmHg drop in systolic BP at 6-month compared with activation visit, with a superiority margin of 20%. Only 54% of patients treated immediately with BAT versus 46% in the control group reached this endpoint. The sustained efficacy endpoint, considering the persistence of BP response after 12 months, was instead reached. Furthermore, the percentage of patients achieving systolic BP <140 mmHg after 6 months was significantly higher and almost doubled in the treatment than in the control group.[26] These results were flawed by an unexpected BP difference between pre-implant and 1-month after implant (activation visit), probably due to different recovery times from surgery. Furthermore, the control group was not subjected to any restriction in terms of drug therapy modification.[26] Considering these two issues, the super-superiority design appeared to be not adequate in testing BAT efficacy. Thus, design flaws make impossible to draw clear conclusions about BAT efficacy by these trials.

In a substudy of the DEBuT-HT and U.S. feasibility trials, patients treated with experienced left ventricular hypertrophy regression, comparable, if not superior, to that obtained with RDN,[21] and improvement in left diastolic and systolic function and ventricular geometry.[28] Preliminary data demonstrated also a decrease in central BP and augmentation index after acute BAT activation.[29] A sustained inhibition of cardiac adrenergic drive after 3 months, as assessed by power spectral analysis of the RR variability,[30] and an acute inhibition of muscle sympathetic nerve activity with BAT activation was also demonstrated.[31] Furthermore, BP-lowering effect is achieved without impairing cardiac baroreflex function, that is the ability of modulating heart rate in response to spontaneous BP changes.[31] The absence of new-onset orthostatic hypotension in the DEBuT-HT study confirmed this results.[25]

The safety issue appears to be the most critical one for BAT therapy. In the DEBuT-HT study, 7 out of 42 subjects experienced a procedure-related serious adverse event, including 1 death due to angioneurotic oedema (for suspected drug reaction).[25] In the Rheos-Pivotal study there were no procedure-related deaths,[26] and

adverse events involved transient (4.4%) or permanent (4.8%) nerve injury, general surgical complication (4.8%) or respiratory complaint / wound complication (2.6%). The majority (76%) of procedure-related adverse events resolved completely. Overall, adverse events were mainly related to carotid sinus lead placement or anaesthetic procedure, and compared favourably with that in the published carotid surgical literature. This limitation could be, at least in part, overcome by the second-generation device, which require a less invasive surgical approach: preliminary data demonstrated a much lower incidence of serious adverse events, with a similar efficacy compared to Rheos (*Hasenfuss G. Oral* presentation at ESH 2011, unpublished). Glomerular filtration rate stability, as well as no progression in carotid artery stenosis, were observed in 1-year-follow up.[25, 32] Given the invasive nature of the procedure, the demonstration of a good risk-benefit ratio with long-term studies with hard cardiovascular endpoints is required. Future research should also clarify possible predictors of BAT response in order to achieve pre-procedural patient selection.

Conclusions

In the past few years two different non-pharmacological, interventional approaches aimed at lowering BP were set up. These interventions were tested in resistant hypertensive patients, with promising results in terms of BP control. However, so far multiple doubts exist about both safety and efficacy in this selected population. In particular, their efficacy in reductions of cardiovascular morbidity and mortality needs to be demonstrated. Thus, at the moment these interventions should be recommended only in refractory hypertension when all the other therapeutic options were not tolerated or ineffective. In this case, given the very high cardiovascular risk of this population, the interventional approach would be ethically acceptable. Only randomised controlled trials with long-term follow-up and hard endpoints could rule out whether these procedures will be routinely recommended in resistant hypertensive patients or in other subsets of patients. Since novel pharmacological approaches to hypertension are also considered for use in resistant hypertension, head-to-head comparisons with other drugs are also warranted.[33]

Both BAT and RDN might potentially carry great benefits since they both target SNS, one of the most important pathophysiological mechanisms for cardiovascular disease. SNS inhibition could be useful not only for BP-lowering, but also, as suggested by pioneeristic studies, for target organ damage regression and metabolic control. SNS inhibition could represent a valuable therapeutic approach also in other cardiovascular diseases characterised by adrenergic overdrive: ongoing trials are evaluating BAT and RDN in heart failure, but chronic kidney disease, insulin resistance and many other conditions are potential targets. However, long-term follow-up is necessary to verify if the profound alterations induced in SNS modulation might not have also adverse consequences in terms of cardiovascular homeostasis. This issue is crucial particularly for not titratable and virtually irreversible approaches such as RDN. The possible benefits and caveats of long-term SNS inhibition should be deeply investigated in mechanistic studies.

As above described, BAT and RDN have their own advantages and limitations; however, among common advantages, it is important to remember that both can overcome poor compliance to treatment, one of the main causes of poor BP control.[34]

Technical advances are warranted in order to reduce the adverse events rate and improve the risk-benefit ratio of device-based treatment for RH, in order to imagine a possible extension of the treatment indication to lower-risk categories. A careful cost-effectiveness analysis is also necessary, weighting the high cost of device-based therapy against benefit in long-term cardiovascular prevention. Future research should also address other questions concerning patients' selection; particularly in the case of hypertension, a disease with multiple etiology, it is important to set up clinical tests or markers able to predict BP response to autonomic modulating therapies.

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Ischaemic and Bleeding Events after Percutaneous Coronary Interventions: The Role of Platelet Reactivity

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Introduction

In the past two decades percutaneous coronary intervention (PCI) has become the treatment of choice for patients with coronary artery disease (CAD),[1, 2] and every year an increasing number of PCI are performed.[3] Although, as a result of technological and pharmacological advances,[4] there has been a significant decline in the occurrence of major complications after PCI,[4] bleeding and thrombotic events are still frequent and associated with increased mortality risk after PCI.[5-11]

Dual antiplatelet therapy (DAPT) is the cornerstone of treatment for patients undergoing PCI. Current guidelines recommend treating those patients with a combination of aspirin and P2Y12 antagonist for at least 1 month in case of bare metal stent (BMS) implantation and 1 year after drug-eluting stent (DES) implantation.[12] Adding to aspirin an adenosine diphosphate (ADP) P2Y12 receptor antagonist, such as clopidogrel, or prasugrel and ticagrelor, in patients with acute coronary syndrome (ACS), leads to greater protection from long-term ischaemic events following PCI.[13-16] However, this beneficial effect is accompanied by an increased risk of bleeding during and after the procedure,[17] which is strongly associated with mortality at long-term follow-up.[5, 18] Of note, despite dual antiplatelet therapy, approximately 10% of patients experience recurrent cardiovascular events after PCI.[15, 16] This has been partially attributed to the fact that a substantial proportion of patients may have inadequate clopidogrel-induced antiplatelet effects leading to persistently high platelet reactivity.[19-22] Proposed mechanisms for inter-individual variability in responsiveness to clopidogrel include genetic (such as CYP polymorphisms), cellular (e.g. up-regulation of P2Y12 pathway) and clinical factors (e.g. drug interactions, ACS, diabetes mellitus and poor adsorption).[22] Several studies have demonstrated that the level of platelet reactivity during clopidogrel therapy is largely unpredictable, resulting in a highly variable reported prevalence of poor 'responders' to clopidogrel.[23] The prevalence of this phenomenon ranges from 4% to 30%, depending, in part, on the loading dose of clopidogrel and on the method used to assess responsiveness.[23-25] However, clopidogrel responsiveness should not be considered in a dichotomous way ('responders' or 'non-responders' patients), but as a continuous parameter following a Gaussian distribution. Despite this evidence, a 'one-size-fits all' strategy of dual antiplatelet treatment is common in clinical practice. As a result, a substantial proportion of patients treated with clopidogrel present either too high or too low residual platelet reactivity. Many studies have shown that in patients with decreased response to clopidogrel, high platelet reactivity (HPR) may result in increased risk of thrombotic complications after PCI.[26-34] On the other hand, in patients with increased response to clopidogrel, low platelet reactivity (LPR) may result in increased risk of bleeding complications.[17, 35]

Platelet Function Tests

In the last few years, different platelet function tests have been used to identify patients with inadequate platelet reactivity.[23, 36] Light transmittance aggregometry (LTA) is considered the gold standard for platelet function assessment. LTA measures the transmission of light through platelet-rich plasma after exposure to a platelet agonist (ADP in the case of assessment of thienopyridine efficacy) using platelet-poor plasma as reference.[36] Another valid test to evaluate clopidogrel responsiveness is the phosphorylation state of vasodilator-stimulated phosphoprotein (VASP), a specific intracellular marker of residual P2Y12 receptor reactivity in patients treated with P2Y12 inhibitors, which is measured by flow cytometry and recorded as platelet reactivity index (PRI).[36] However, LTA and the VASP phosphorylation test are labour intensive, require special training, and are not routinely available. Therefore, they are not considered a practical approach to risk-stratifying most patients undergoing PCI.[29] Instead, several bedside or near-bedside platelet function tests, such as the Verify-Now P2Y12 (Accumetrics Inc, San Diego, California), the Multiplate analyser (Dynabyte, Munich, Germany), the Platelet Function Assay-100 (PFA-100 System; Dade Behring, Miami, Florida) and Plateletworks (Helena Laboratories, Beaumont, Texas), are currently available.[36] In particular, the Verify-Now P2Y12 assay is a turbidimetry-based optical detection system that measures platelet-induced aggregation as an increase in light transmittance. The assay contains 20mol ADP and 22 nmol prostaglandin E1 (PGE1) to reduce the activation contribution from ADP binding to P2Y12 receptors. A second activator, isothrombin

receptor–activating peptide (iso-TRAP), is incorporated into a second channel of the assay device. The device provides an estimated inhibition (in percent) without a pre-clopidogrel sample by reporting the ratio of the results of the ADP-PGE1 and iso-TRAP channels.[36] Finally, it uses a proprietary algorithm to report values in P2Y12 reaction units (PRU). The lower the PRU value, the greater the degree of P2Y12 receptor inhibition by clopidogrel and viceversa.[36] Another point-of-care assay, multiple electrode platelet aggregometry (MEA), for rapid and standardised assessment of platelet function in whole blood, has been recently developed. Impedance with MEA is assessed on a device called the Multiplate analyser (Dynabyte, Munich, Germany) and transformed into arbitrary aggregation units (AU).[36]

Prediction of Adverse Events with Platelet Function Tests

Recent investigations aimed at establishing therapeutic thresholds to define optimal P2Y12 inhibition in clopidogrel-treated patients. Using the Multiplate Analyser, Sibbing *et al*. found that patients with low response to clopidogrel (>468 AU*min) had significantly increased risk of stent thrombosis.[37] Similarly, Patti *et al*.[30] prospectively evaluated the relationship between residual platelet reactivity, measured by the VerifyNow P2Y12 assay, and 30-day major adverse cardiovascular events (MACE) in 160 clopidogrel-treated patients undergoing PCI. In that study, 30-day MACE occurred more frequently in patients with pre-procedural PRU levels in the highest quartile versus those in the lowest quartile (20% vs 3%; P=0.034). On multivariable analysis pre-PCI PRU levels in the highest quartile were associated with 6-fold increased risk of 30-day MACE (OR 6.1; 95% CI 1.1-18.3, P=0.033). A PRU value ≥240 was found to be the optimal cutoff to predict 30-day outcome, providing a sensitivity of 81% and a specificity of 53%. In the same line of evidence, Price *et al*.[29] reported a PRU ≥235 as the optimal cut-off value to predict 6 month out-of-hospital cardiovascular death, non-fatal myocardial infarction (MI) or stent thrombosis (AUC 0.711; 95% CI 0.529-0.893, P=0.03) in 380 patients undergoing elective PCI. In the setting of ACS, consistent with the above-mentioned studies, Marcucci *et al*.[31] found a very similar optimal cutoff to predict 12-month cardiovascular death or nonfatal MI with a PRU value ≥240. More recently, the Popular Study (Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel-Pretreated Patients Undergoing Elective PCI) evaluated the ability of multiple platelet function tests in predicting atherothrombotic events, including stent thrombosis, in clopidogrel-pretreated patients undergoing PCI with DES implantation.[32] The study investigators observed that high on-treatment platelet reactivity, when assessed by light transmittance aggregometry (both 5 µmol/L and 20 µmol/L ADP), VerifyNow P2Y12 assay, and Plateletworks, was significantly associated with atherothrombotic events. Of note, the platelet reactivity threshold that best predicted ischaemic events using the VerifyNow P2Y12 assay was a PRU value of 240.

The message consistently emerging from these studies is that increasing the degree of platelet inhibition significantly reduces ischaemic events; however, this is at the price of higher bleeding complications, which in turn are associated with poorer outcomes after PCI.[5] Sibbing *et al*.[17] observed that the risk of major bleeding events in patients pretreated with 600 mg clopidogrel undergoing PCI was significantly higher in those with increased response to clopidogrel (<124 AU*min assessed with the Multiplate Analyser) as compared with those showing platelet reactivity ≥124 AU*min (2.2vs.0.8%, OR 3.5, 95% CI 1.6–7.3, p=0.001). Similarly, ARMYDA BLEEDS (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Bleeding Study)[35] showed that 30-day incidence of major bleeding or entry-site complications after PCI occurred more frequently in patients with pre-procedural PRU levels in the lowest quartile compared to those in the highest quartile (10.1% vs 1.3%, P=0.043). By ROC curve analysis, the optimal cutoff for the primary end point was a pre-PCI PRU value <189 (AUC 0.76, 95% CI 0.66-0.87, P=0.001).

Evidence for a Therapeutic Window of Platelet Reactivity

Overall, previous studies suggest the possibility of identifying a therapeutic window for platelet reactivity associated with the lowest risk for both thrombotic and bleeding complications. Using the Multiplate Analyser, it was found that the group of patients with pre-PCI platelet reactivity in the range of 189 to 467 AU*min had the lowest risk for the occurrence of both bleeding and ischaemic events.[37] However, in this analysis, only in-hospital bleeding and 30-day ST were considered.[37] Campo *et al*.[38] have also found a therapeutic window for platelet reactivity measured with the VerifyNow P2Y12 assay (between 86 and 238 PRU). However, in this study, platelet reactivity was measured 30 days after PCI, and the adverse events occurred within the first month were excluded from the analysis. More recently, in the ARMYDA-PROVE (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty–Platelet Reactivity for Outcome Validation Effort) study a PRU value ≥239 as the optimal cutoff point was shown to predict ischaemic events, whereas a pre-PCI PRU value ≤178 was found to be the optimal cutoff point to predict bleeding events.[39] In this study, when the population was divided into 3 groups based on the distribution of PRU values (low platelet reactivity for PRU ≤178; normal platelet reactivity for PRU between 178 and 239; high platelet reactivity for PRU ≥239), the incidence of net adverse clinical events (NACE, defined as the occurrence of ischaemic or bleeding events) was significantly lower in those patients with intermediate platelet reactivity.

Therapeutic Options and Future Perspectives

As outlined in these studies, pre-PCI evaluation of platelet reactivity carries important prognostic information and may guide the therapeutic approach to those patients that do not fall within the described therapeutic window. In particular, in patients with a low response to clopidogrel and higher ischaemic risk, more aggressive antiplatelet strategies might be useful in obtaining platelet reactivity

values that fall within the desired range. These include higher clopidogrel doses, the use of inducers of clopidogrel metabolism (i.e., cilostazol), or newer, more potent P2Y12 receptor blockers.

In this regard, various trials were designed to investigate the potential benefit of tailored antiplatelet therapy according to on-treatment platelet reactivity assessed by VerifyNow assay.[40-42] The GRAVITAS (Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety) trial sought to determine whether high-dose clopidogrel was superior to standard-dose therapy for the prevention of cardiovascular events after PCI in patients with high on-treatment platelet reactivity (HTPR), defined as 230 PRU or higher, according to a point-of-care platelet function assay. The study investigators reported that prolonged high-dose clopidogrel therapy provides a modest pharmacodynamic effect but does not reduce the rate of death from cardiovascular causes, nonfatal MI or stent thrombosis at 6 months follow-up compared with the standard maintenance dose of 75 mg daily (2.3% vs 2.3%; HR 1.01; 95% CI 0.58-1.76; P=0.97).[40] Many reasons for these disappointing negative results have been proposed. First, the population enrolled in the study was at very low risk, making any benefit from intensive antiplatelet treatment difficult to be proven. Second, simply doubling the dose of clopidogrel could not be effective in reducing thrombotic risk in patients with HPR. Third, platelet reactivity was measured 12-24 hours post-PCI, a timeframe during which this parameter could be increased by the procedure itself.[41] Concerning the management of patients with HPR on clopidogrel, new more potent P2Y12 inhibitors have been tested in larger trials. The TRIGGER-PCI (Testing platelet Reactivity In patients underGoing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel) trial investigated the effectiveness of prasugrel versus clopidogrel in this subset of patients after elective PCI with DES implantation.[42] This trial failed to demonstrate the clinical utility of this strategy given the low rate of adverse ischaemic events after PCI in stable coronary artery disease. However, the results of the TRIGGER-PCI trial impact on the concept of personalised antiplatelet therapy demonstrating that HPR can be reliably corrected by switching from clopidogrel to prasugrel.[42] Consistently with these findings, the RESPOND (Response to Ticagrelor in Clopidogrel Nonresponders and Responders and the Effect of Switching Therapy) trial demonstrated that ticagrelor therapy was associated with uniform and superior platelet inhibition in both previously identified clopidogrel 'responders' and 'non-responders'. Nearly all patients enrolled in the study, irrespective of clopidogrel response status, after switching to ticagrelor had platelet reactivity below the cutoffs associated with ischaemic risk.[43]

On the other hand, in patients with increased response to antiplatelet therapy and higher bleeding risk, it could be reasonable to adopt the following strategies: deferring PCI until platelet reactivity falls within the desired range; utilising individualised preventive pharmacological measures such as restricted use of glycoprotein IIb/IIIa inhibitors, more extensive use of bivalirudin and of gastroprotective agents; preferring the radial approach and limiting the use of drug-eluting stents, thereby obviating the need of prolonged dual antiplatelet therapy. The potential benefit of this personalised approach is however yet to be demonstrated.

In addition, there may be an indication for monitoring platelet reactivity in the long term, i.e. as long as the patient continues DAPT, in order to assure the maintenance of an adequate therapeutic window.

Conclusions

A large body of evidence outlines the impact of pre-procedural platelet reactivity on short- and long-term outcomes of patients undergoing PCI. However, given the limited data available to support that managing therapy based on platelet function assessment could actually improve outcomes, the routine measurement of platelet reactivity has not been widely implemented and recommended in guidelines. Nevertheless, a tailored therapeutic approach based on the results of platelet function tests could be reasonable in high-risk patients with a history of stent thrombosis or severe bleeding, or in those undergoing complex PCI.

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Remote Patient Assessment, Monitoring and Diagnosis via Telemedicine at Oxford John Radcliffe Hospital Department of Paediatric Cardiology

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Introduction

Being ever conscious of the real benefits we had delivered at Oxford John Radcliffe, with the introduction of a real-time consultancy for echocardiology into our Telemedicine services, and having assessed the 3M™ Littmann® Electronic Stethoscopes Model 3200, it was clear that there might be an opportunity to extend our services, leveraging the ability of the 3200 to connect with a second stethoscope in a remote location – the interesting concept of TeleAuscultation.

The 3M™ Littmann® Connected Solutions portfolio provides both TeleAuscultation and tools designed for advanced education of auscultation and we have embarked upon a programme to introduce the portfolio, and assess the benefits which it offers.

1999 and the dawn of a new millennium, saw the introduction of telemedicine to the Oxford John Radcliffe Hospital. All referring district general hospitals were equipped with videoconferencing equipment, initially using ISDN connection, but ultimately adopting N3/IP[1] connections through the UK National Health Service's dedicated broadband infrastructure.

Initially we utilised the videoconferencing for real-time imaging of echocardiography or tele-echocardiography. We would guide paediatricians in referring hospitals with regards to positioning of echo probes etc, so that we were then able to provide instant diagnosis in most of the patients. Routine transfer for echo was no longer necessary, and parents were able to witness the consultations via videoconferencing, the cardiac diagnosis was explained, and immediate treatment was then initiated where necessary, or necessary actions taken to transfer the patient. If immediate transfer was not necessary, then patients were stabilised and cared for in their own district general hospital delivering real patient benefits and cost savings. A full clinical audit of the services[2] investigated the benefits to the department and the region, with the telemedicine links from six district general hospitals being studied, over a period of one year. Patients assessed remotely by videoconference and using tele-echocardiography presented with a variety of symptoms (figure 1), and the audit data revealed that we were able to accurately diagnose remotely (figure 2 and figure 3).

As a result of the remote assessments by videoconference, and use of tele-echocardiography, we were able to successfully avoid transfers to the hospital and also to instigate immediate and urgent transfers where these were appropriate, either to Oxford John Radcliffe, or indeed to Great Ormond Street Hospital in London (table 1).

Overall, from the cohort of patients assessed remotely, immediate and urgent transfers were reduced by over 50% and we were able to reduce the incidence of delayed transfer by 50%. Impacted by our activities, we witnessed a five-fold increase in referrals from out of the region, but our out-patient clinic attendances from referrals also increased five-fold, mirroring this change, and further reinforcing that remote assessment has a direct positive impact on referrals and admissions.

Interestingly, having firmly established tele-echocardiography into our routine, we have since witnessed a complete change in the way that this consultancy was requested and provided.

All our referring district general hospitals of course have telemedicine facilities, and we have also trained a lead person in every location, initially on our in house echo course and subsequently during our outreach clinics. Initially most of the consultations were real time, but over time there has been a gradual shift to the use of 'store and forward'.

Dr. Adwani commenced his cardiology training in Mumbai. Before joining John Radcliffe Hospital in Oxford, as a substantive consultant, he trained in Pune, Melbourne, Birmingham, London, Los Angeles and Newcastle, before becoming a consultant at the John Radcliffe Hospital in Oxford. His interests include heart failure, transplantation, Marfan syndrome and telemedicine applications. Since his appointment at John Radcliffe Hospital, Dr. Adwani has been the lead for telemedicine applications in the paediatric cardiology department. Dr. Adwani has also overseen significant improvements to the hospital's tele-echocardiology facilities.

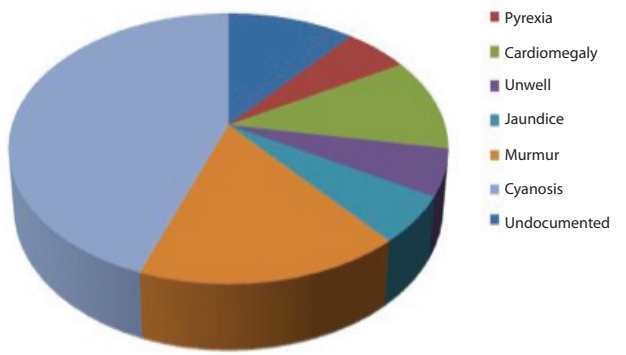

Figure 1. Presentations from tele-echocardiography.

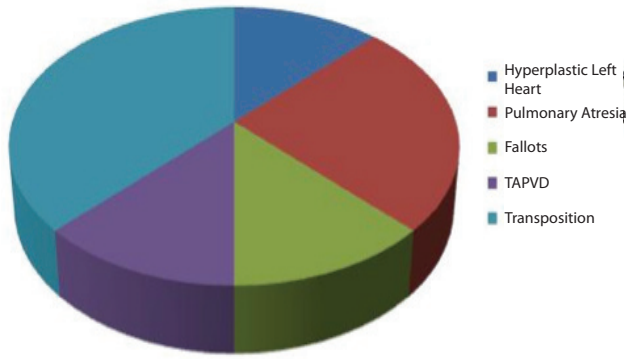

Figure 2. Cyanotic Heart Lesions.

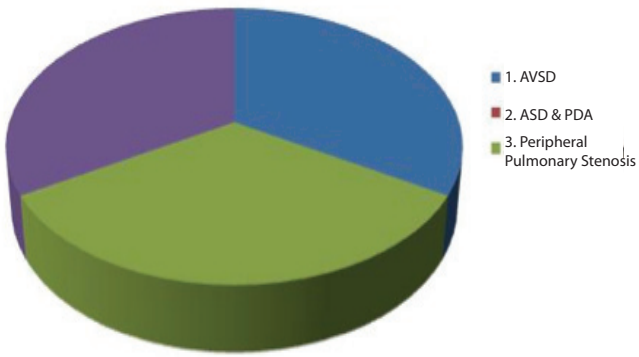

Figure 3. Heart Murmurs.

Cyanotic Heart Lesions	Upgraded to Immediate Transfer	38%
	Delayed to Non-Urgent Transfer	38%
	Immediate Transfer to GOS (London)	24%
Pyrexia	No Transfer / Referral	100%
Jaundice	No Transfer / Referral	100%
Cardiomegaly	Upgraded to Immediate Transfer	50%
	No Transfer / Referral	50%
Unwell	No Transfer / Referral	100%
Murmurs	No Transfer / Referral	100%

Table 1. Referral / Transfer Outcomes.

Today, our referring hospitals send us the pictures via archiving system, and we rarely resort to real time guided sessions, yet we are still able to provide instant diagnosis and start immediate treatment and significantly avoid transfers to Oxford John Radcliffe just for the purpose of diagnosis. We have the opportunity to explain the diagnosis and implications to parents, who never fail to be impressed with the connection to 'remote expert', and the added burden of having children being assessed in a hospital, which is quite remote from their home, is frequently avoided.

Littmann Connected Solutions at Oxford John Radcliffe

Soon after the launch of the 3M™ Littmann® Electronic Stethoscopes Model 3200 (figure 4), the opportunities for leveraging the features of the stethoscope were recognised, and the model 3200 was immediately put to use in the paediatric cardiology department.

The model 3200 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 with the ability to switch between bell, diaphragm and extended range modes, even after the file is saved.

We knew from a study performed by the Mayo clinic and reported in the *Journal of Telemedicine and Telecare* back in 2004, that telemedicine-directed auscultation of patients is just as successful as an 'in-person' assessment for detection of cardiac arrhythmias.[3] The significant quality improvements in the new Littmann® 3200 electronic stethoscope, gave us confidence that TeleAuscultation might be able to deliver much more.

We commenced testing of TeleAuscultation early in 2011 by linking examination rooms so that the more junior doctors were able to call in an instant, real-time auscultatory report from the consultant cardiologist. We of course had to satisfy 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, and this is absolutely the case.

Essentially, both site's stethoscopes were connected to a Windows®-based personal computer[4] via a Bluetooth®[5, 6] wireless link. The two PC's are then connected to each other over a TCP/IP[7] data network. We have since tested the feasibility of this from various different locations, including the outpatient clinics, accident and emergency department and the neonatal intensive care units.

3M™ Littmann® TeleSteth™

The TeleSteth Online Auscultation System (figure 5) was developed to extend the practice of auscultation into situations and environments where face-to-face encounters are not always convenient or feasible. This platform further allows healthcare professionals to share heart, lung and other body sounds with colleagues by means of a 'Store and Forward' facility. Auscultations can be uploaded to the server for a later

Figure 4. 3M™ Littmann® Electronic Stethoscopes Model 3200.

download and reporting by a chosen consultant. An automatic email is generated to the referring site and also to the consultant, so that it is immediately apparent that there is a referral waiting for assessment.

The Local Client Server Solution means that all patient data remains within our systems. Of further interest to us, as we fully implement the Electronic Patient Record,[8] is the fact that the data file, which contains all of the digital information relating to the auscultation session, can be appended to the patient electronic record for future reference, and to assist in monitoring of progress.

So far, we have been able to provide useful diagnosis on a selection of murmurs uploaded for us via this 'store and forward' component of the TeleSteth server. The quality of the recorded sounds is good, and the graphical display is very educative. We now intend to test this with our referring paediatricians and general practitioners.

A question we have been asked is whether we will ultimately be able to reassure referring paediatricians, general practitioners and parents about an innocent murmur, and in so doing, avoid a full consultation and echocardiogram.

Though the yield of echocardiograms is virtually zero,[9, 10] and there is

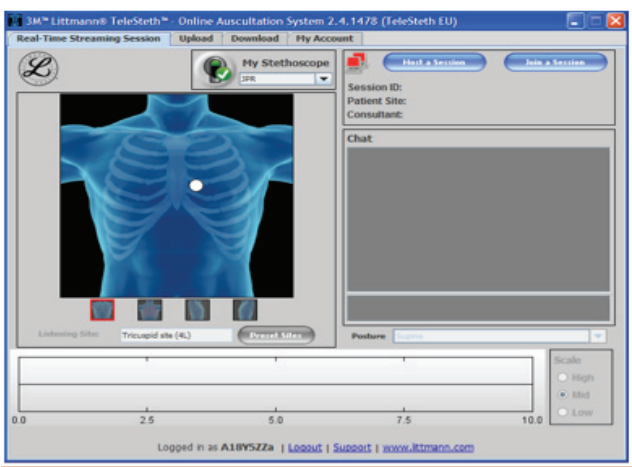

Figure 5. 3M™ Littmann® TeleSteth™ - Online Auscultation System.

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. It is possible that this might change in the future, and it is not our opinion that the two technologies should be mutually exclusive in any case, but for now there is no doubt that the ability to provide a remote consultation with TeleAuscultation is a pivotal requirement for this to happen.

Our objective is to establish if we can offer a reporting service, similar to that provided for Echo's, in which our referring sites will send us their auscultatory files for assessment. We will determine if we can remotely arrive at a diagnosis and convey this information back in a timely manner. In doing so we can immediately reassure general practitioners and parents, and decrease the anxiety currently experienced, as they await an appointment in the cardiology clinics, where there is an average waiting time of 1-2 months.

It remains to be seen if this might change the landscape regarding subsequent referral for echo.

When we first started to use the 3M™ Littmann® 3200, it immediately became clear that one of the huge benefits provided by the stethoscope, was the opportunity for students to play back auscultation sessions from existing and previous patients and to cement their education with exposure to stored data.

3M™ Littmann® Listen-In®

Since one of our key functions at Oxford John Radcliffe is medical education, we were very pleased to hear about development of an educational package which allows clinical educators to share a simultaneous auscultation sound experience with up to four students.

When we were introduced to the 3M™ Littmann® Listen-In system (figure 6), it instantly became a hot favourite for medical students during ward rounds. The child is auscultated by the consultant and a group of medical students can quite simply – 'listen in'. One stethoscope acts as the presenting stethoscope, while the others act as listening stethoscopes. The concept is wonderfully simple, but the benefits enormous. Now, on our teaching rounds, we can perform just one auscultation on a patient, rather than needing multiple attempts, and in paediatric medicine the value of this cannot be overstated.

We now know how the sound is presented to the student, since the lead or presenting stethoscope controls the functions of all connected stethoscopes. The direct change associated with a switch from Bell to Diaphragm mode for example, might not be immediately obvious for a student, but when the difference is fully demonstrated using the Listen-In System, the importance of the filter settings, and indeed how these different modes are used on a

Figure 6. 3M™ Littmann® Listen-In System.

mechanical stethoscope, are made crystal clear. Sounds which might not have been heard using traditional teaching methods, are shared with the full confidence of the presenter. Auscultation remains a skill which is practiced all over the world, and which continues to provide basic but vital information about the patient.

There is a phenomenal amount of multimedia, readily available to assist students learning normal and abnormal sounds which can be heard using auscultation, and no-one more can fail to acknowledge the importance of resources such as these. We acknowledge that intensive repetitive listening of around 400 to 600 times[11, 12] is required for the human brain to master a new sound, but there is little doubt that before you can recognise and then go on to master a sound, you must first be introduced to it. Central to all of this is the correct positioning of the stethoscope chest piece, and the posture which should be adopted by the patient in order to optimise the sounds. Our education programme will now undergo a review to determine how best we could leverage use of the 3M™ Littmann® Listen In bedside teaching, along with stored auscultation sessions which can be reviewed through the visualisation software StethAssist.

There is little doubt that telemedicine at Oxford John Radcliffe will continue to develop and grow, and that TeleAsucultation will add an extra dimension to the service. Junior doctors are regularly listening to murmurs and appreciate senior review. This will not only reassure them, but also the patients and their parents, as they witness us providing accurate auscultatory diagnosis by a cardiologist. We will continue to make use of this facility to better understand how this can improve the patient journey and the services which we provide.

Finally we will establish and pilot a reporting service in which our referring sites will send us their auscultatory files for assessment. We will determine if we can remotely arrive at a diagnosis and convey this information back in a timely manner, and if, in so doing, we can immediately reassure general practitioners and parents, and decrease the anxiety currently experienced, as they await an appointment in the cardiology clinics.

A key metric for the value of this component will be its impact upon the cardiology clinics as we 'triage' referrals and reduce re-visits for ongoing assessment. Of course we need to audit this service, in the same way that we did the tele-echocardiography, and we are actively engaged in producing the necessary study proposals and objectives ready for ethical approval, and look forward to reporting our findings in 2013.

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Telerehabilitation in the Treatment of Coronary Artery Disease

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Introduction

The effectiveness of cardiac rehabilitation (CR) for patients suffering cardiovascular diseases has been proven.[1, 2] Traditionally, the CR programs are hospital based (ambulatory or in-patient) and are supported by a multi-disciplinary team. Core components of CR are physical activity and exercise training, behaviour-modification strategies and risk-factor management, nutritional counselling and psychosocial management.

The impact of exercise training has been investigated for patients suffering from all different manifestations of coronary artery disease (infarction, PCI, CABG) and for patients with heart failure (HF). Exercise training influences the main pathophysiological mechanisms that induce exercise intolerance and has a positive influence on risk factors and endothelial function.[3] Several studies[4] also demonstrate that abnormalities of both skeletal muscle and vasomotor tone, characteristic of HF, can be reversed with exercise training. Furthermore, regular physical activity increases the vascular expression of anti-oxidative radical scavenger enzymes in patients with coronary artery disease[5] and decreases the sympathetic nerve activity in HF patients.[6] Besides neurohormonal adaptations exercise training also effects inflammation by reducing the level of cytokines within the blood.

Why is Cardiac Rehabilitation Underused?

Despite the overwhelming evidence that supports the effectiveness of in-hospital CR, uptake rates remain poor. A variety of patient and provider factors contribute to these poor uptake rates. Patients regularly choose not to attend the rehabilitation sessions in the hospital due to a lack of access to transport, ill-health, time and scheduling commitments associated with returning to work or reimbursement issues.[7] However non-compliance with lifestyle and risk factor recommendations in CR is associated with adverse outcomes. For example, Van der Wal *et al.*[8] demonstrated that non-compliance with exercise training was associated with an increased risk for mortality and HF readmission.

Another worrisome finding concerns the progressive worsening of various cardiovascular disease risk factors during the months after in-clinic CR. Hansen *et al.*[9] found that in patients with coronary artery disease following a three month program of in-clinic CR, the cardiovascular disease risk profile worsened significantly during the 18 months after the in-clinic CR as a result of non-adherence to the recommended minimal physical activity level.

Cardiac Telerehabilitation as Alternative

During the last decade however researchers started to search for potential alternatives to overcome the problems with hospital based CR described above.

One alternative is the home based CR, where the patient exercises at home and is in contact with his medical supervisor by means of telephone calls, video conferencing, the internet or other communication media.

Researchers from the NHS in Cornwall, the Peninsula Medical School, the Agency for Health Technology Assessment in Warsaw and the University of Birmingham have analysed 12 studies relating to cardiac rehabilitation.[7] This systematic review, which included data from 1938 participants, found that there was no difference between home based and centre based rehabilitation for a number of issues including mortality, cardiac events, exercise capacity, risk factors that can be modified (such as smoking, high blood pressure, total cholesterol) and quality of life in people at a low risk of further events after myocardial infarction or revascularisation. The study also found some evidence that home based CR participants were more likely to stick to their rehabilitation regime. This is an important point, because poor participation can be a weakness in some cardiac rehabilitation programmes delivered from centre based settings such as hospitals or gyms.

Furthermore, the concept of telerehabiltation has been introduced recently. In telerehabilitation, the patient's exercise is monitored from a distance, with regular feedback. This monitoring is done using several different monitoring devices (accelerometers, pedometers, online questionnaires etc) and is transmitted by mobile phone or the internet. The recent advances in information and communication technologies (ICT) can be used to enhance the delivery of a telerehabilitation program.

Formative research results indicated that telerehabilitation could have numerous advantages over conventional CR. Cardiac patients can be reached in an effective way, even if they can not attend the rehabilitation centre due to a lack of time or transport, or due to ill-health.[7]

One possible drawback for telerehabilitation is the difficulty in monitoring adverse reactions by patients from a distance. Fortunately, in the selected patients, the risk of adverse reactions during the rehabilitation program is very low, allowing to introduce this kind of supervision to the majority of patients. Also while the younger patients are used to working with ICT applications, most of the older patients are not acquainted with this technology. They sometimes do not have mobile phones or do not know how to access the internet properly. Therefore age is sometimes considered a potential barrier for telerehabilitation.

Numerous devices have been described in the literature that can be used in a telerehabilitation setting such as a cardiac patient training companion (CPTC). The CPTC is a theoretical concept, defined as the ideal apparatus specifically designed for the cardiac patient. It is able to record and store the patient's data accurately and to transfer these data automatically to a platform that is available for the patient's caregivers.

Requirements for a Cardiac Patient Training Companion

A CPTC (Figure 1) should preferentially have the following characteristics:[11]

Feedback: the patient should receive encouragement that their efforts pay off to reduce the risk that they could relapse. Therefore the CPTC should give the patient easy understandable feedback on their progress and this is preferable in real time. This feedback also helps for those patients who do not believe that they will succeed (lack of self-efficacy) to enhance their health condition. The Telerehab II study (currently conducted in the Jessa Hospital, Belgium) uses a motion sensor with automated feedback by email or SMS. The effect of this feedback on the activity level of the participating patients will be investigated in this study.

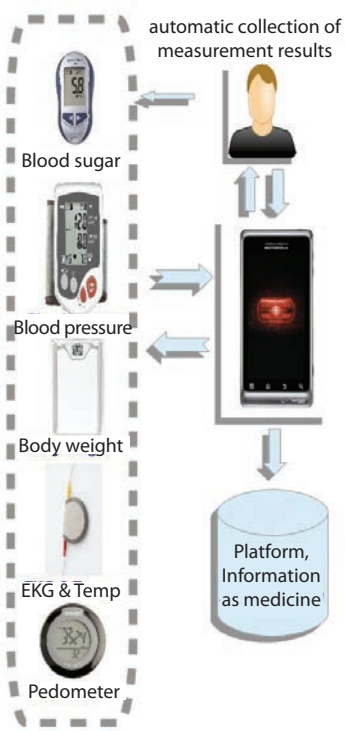

Figure 1. Concept of a cardiac patient training companion.

Low tech: most of the CR patients that can benefit from the CPTC are older and have less experience with complex technical devices and computers. In addition these patients can also suffer from ageing deficiencies such as bad sight making the manipulation of these devices more difficult. A CPTC should therefore be easy to use, possibly remotely configurable.

Accurate: accuracy of the collected data, such as heart rate, the number of steps, the energy expenditure etc. is primordial. The CPTC serves as a tool to remotely provide the caregivers with patient data. Based on those data, caregivers will make decisions and provide feedback to their patients.

Convenience: if the patient needs a long preparation to "wire up" the devices, such as a heart beat strap that has to be mounted directly on their breast, the solution is often too cumbersome for the patient resulting in a partial or complete abandoning of the use of such devices. Patients convenience will increase if the CPTC has additional functionalities such as a watch or mobile phone.

Low power: it is frustrating when a car or cell phone cannot be used because of an empty battery. This is also the case for the CPTC. Most current designs run out of power quite quickly. One day of autonomy is often not enough. Autonomy is another characteristic to consider when comparing CPTC alternatives.

Alarm: Cardiac revalidation patients have a severe heart condition. Therefore, alarming caregivers when the recorded data from the patient go out of predefined limits is an additional requirement. An example of such a functionality is found in the device with a tele-event-Holter ECG feature used by Piotrowicz *et al*.[14, 15] that enabled the patient to register an ECG recording immediately whenever a worrying symptom occurred.

Large storage capacity: the rehabilitation process takes a long time. Often the patient can do revalidation exercises such as staircase climbing from time to time, not necessarily each day following a regular training scheme. A CPTC with sufficient on board memory to do precise book keeping over longer periods, possibly months or years, constitutes an advantage for the patient and the caregiver.

Automated data transfer: today's follow-ups of a patient often have the format of regular counseling. The cardiologist only has the sparse information they can collect during the visit of the patient. This leads to more difficult analyses then would be the case if they had access to all the data that could have been collected by the CPTC. Therefore remote data transfer from the CPTC to a centre managed by caregivers is preferable. This remote data transfer can be completely automated, partly automated with some data collected and transmitted by the patient themself or completely manual requiring the patient to keep a diary.

Mobility: patient's ability to combine the rehabilitation process with work, vacation, family visits etc. will increase if this remote data transfer can be done using a mobile device and is not tied to a

preconceived environment such as their home.

Security: patient's data is personal information within the European Data Protection Directive (95/46 EC). This directive classifies health related information as the most personal information of an individual. A CPTC needs to be conform to this European legislation and this implies that collected information is secured in a way that access to this information is restricted to the patient and caregiver.

Affordable: of course the solution needs to be affordable for the patient and this implies a low cost for the CPTC or the availability of an entry level solution that has the most important functionalities.

Two way communication: When the CPTC raises an urgency that triggers an intervention of caregivers, a two way communication of the caregiver with the CPTC can be useful to avoid unnecessary interventions. If the caregiver can use the CPTC to inform the patient about this urgency, it is still possible for the patient to flag the incident for example as the result of a wrong manipulation of the device if this would be the case.

Findings of Cardiac Telerehabilitation Studies

Mattila *et al*.[12] developed a measurement system and implemented the necessary software tools on a mobile phone platform enabling patients to participate in a home-based CR program. The framework they proposed is composed of a patient sensor and the mobile exercise application TuneWalk. The patient sensors were able to acquire ECG readings and movement activity from the patient by means of a three-channel acceleration signal along the X, Y and Z axes. These registrations could be transferred to a mobile phone via Bluetooth. TuneWalk was the mobile exercise application that communicated with the sensor device, stored the accumulated data and sent them to a web application server for remote exercise performance analysis and consultation by the patient's personal mentor. A randomised controlled trial (RCT) using the TuneWalk application is now being conducted.

The Care Assessment Platform (CAP) is a model for out-patient CR developed by Varnfield *et al*.,[1] which integrates home-based CR with mobile phones and web-services. Walters *et al*.[13] performed a RCT to compare the CAP model with the standard in clinic CR model. In the CAP model, a mobile phone that has an integrated accelerometer application for recording exercise information, is given to the patients. All data are synchronised to a remote web portal. Mentors view and assess patient's measurements and health data on the portal and use this information for individual feedback and goals setting during weekly telephone monitoring sessions. A RCT of the CAP program versus an in-clinic CR program is being conducted to compare clinical outcomes, adherence to the technology and the cost-benefit ratio.[13] The preliminary results already show high usage rates and acceptance of the CAP model by participants. The participant's average usage rate of the mobile phone was between 91.5% and 97%, depending on the health variable that was measured. The patients reported that the mobile phone was easy to use. 91% of the participants found the phone consultations with the mentors motivating and helpful to reach their goals.

Piotrowicz *et al*.[14, 15] assessed ECG's recorded during home-based CR for 75 stable patients with heart failure. In the 8-week programme a mini device recorded ECG's automatically at preset moments that were coordinated with exercise training. The mini device also had a tele-event-Holter ECG feature that enabled the patient to register an ECG recording immediately whenever a worrying symptom occurred. These fragments were then transmitted via mobile phone to a monitoring centre. Following the 8-week exercise training programme, the mean (SD) peak VO2 in cardiopulmonary exercise treadmill test increased from 17.8 ml/kg/min (4.1) to 19.7 ml/kg/min (5.2) ($P< 0.0001$). The distance in the 6-min walking test increased from 418 m (92) to 462 m (91), ($P< 0.0001$). In all, 11.534 ECG fragments were transmitted and evaluated. Most ECG fragments originated from the automatic recordings, but 20 ECG fragments were recorded by 8 patients when they felt unwell. The heart failure patients undergoing the home-based telemonitored CR did not develop any arrhythmia which required a change of the procedure, confirming it was safe. Piotrowicz *et al*. concluded that CR at home can be improved when patients used the tele-event-Holter ECG facility.

Guiraud *et al*.[16] explored the efficacy of telephone support guided by accelerometer measurements, on the adherence to physical activity (PA) recommendations in cardiac patients not achieving PA recommendations. In this prospective randomised study stable non-compliant cardiac patients were randomised into an intervention group and a control group. The intervention included PA recording for 8 weeks with an accelerometer and regular telephone calls by the kinesiologist to give feedback on the amount of PA performed and to provide strategies to increase the daily amount of PA. The researchers[16] found that this intervention appeared to be effective to improve adherence to PA in non-compliant cardiac patients. In the intervention group, the mean (SD) time spent at moderate-intensity PA increased from 95.6 (80.7) to 137.2 (87.5) min per week between the 1st and 8th week ($P=0.002$), with 36.8 % of the sample achieving the target amount of moderate-intensity PA. During the 8th week, the active energy expenditure averaged 543.7 (144.1) kcal and 266.7 (107.4) kcal in the intervention group and control group, respectively ($P=0.004$). Reid *et al*.[17] compared the CardioFit internet-based expert system with usual CR to assess its effects on PA following hospitalisation for acute coronary syndromes. A total of 223 participants were recruited for this RCT. The patients randomised to the CardioFit group had access to a secure website for activity planning and tracking (PA was measured by a pedometer). Usual care consists of PA guidance from the cardiologist. They noticed that patients in the CardioFit group were more physically active at 6 months as well as at the 12 month follow-up. At 6 months follow-up the mean (SD) amount of moderate and vigorous PA (min/week) for the patients from the CardioFit group was 201.0 (153.2),

compared to 163.4 (151.3) for the patients from the usual care group. At 12 months follow-up 201.4 (179.8) and 169.6 (152.6) min/week of moderate and vigorous PA were recorded for the CardioFit and usual care group, respectively. This translated in an increased health-related quality of life (QOL) measured by the MacNew instrument[17] at 6 and 12 months of follow-up. Körtke *et al*.[18] came to the same conclusion for patients that had undergone cardiac surgery such as bypass surgery, valve replacement, valve reconstruction and aortic aneurysm surgery.

The telerehab II trial (currently conducted in the Jessa Hospital, Belgium) is aiming to evaluate whether the addition of a motion sensor with automated feedback by email or SMS to the conventional rehabilitation program could result in an increase in daily activity among coronary artery disease patients. It investigates the impact of the intervention with the motion sensor on the patient's VO_2 peak (measured during ergometry), haemoglobin A1C and lipid profile as well as the feasibility of the telerehabilitation program.

A total of 80 patients are participating in the trial. They are monitored during a period of 18 weeks. Preliminary results already show a significant increase in daily activity and VO_2 peak between week 1 and week 6 as compared to conventional CR alone. In the intervention group, the daily steps increased with 94.55 % and the VO_2 peak increased with 13.09 % from week 1 to week 6. In the control group, the daily steps increased with 14.08 % and the VO_2 peak increased with 7.55 % from week 1 to week 6. Analysis of patient data after 18 weeks in the program and program results will be available soon.

Conclusion

Recent findings documented in literature suggest that telerehabilitation programs can overcome the barriers of hospital-based CR programs. Evidence is already mounting that telemedicine can be more effective than conventional CR in improving patient's physical activity level and QOL.

However, further research is required to determine the impact of a telerehabilitation intervention on patient's fitness (for example VO_2 peak, ventilatory threshold), physical activity level, rehospitalisation rate and mortality in the long-term.

Also, the value of a telerehabilitation program including other core components of CR such as nutritional counselling and psychosocial management needs to be studied.

Even though different telemedicine designs have been developed, it still needs to be determined what type of sensor/web application is most feasible for today's cardiac patient and considering the characteristics of a perfect cardiac patient training companion described in,[11] further sensor research and development is needed.

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New Challenges for Cardiac Rehabilitation

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Introduction

Cardiac rehabilitation (CR) is defined as a multidisciplinary programme consisting of exercise training, risk factor modification and psychosocial intervention. It is intimately linked with the concept of 'secondary prevention', which corresponds to a comprehensive risk factor management to reduce cardiovascular risk as assessed by a variety of outcomes, including improved survival, reduced recurrent events and improved quality of life.

The 2008 ESC guidelines on acute myocardial infarction state that "rehabilitation should be offered to all patients after ST-elevation myocardial infarction" with the aim of "restoring the patient to as full a life as possible, including return to work" by taking into account "physical, psychological and socio-economic factors".[1]

Modern cardiac rehabilitation centres combine restoration of one's health from an acute affection with secondary prevention, which implies that patient care is not restricted to patients after an acute event like a myocardial infarction, cardiac surgery or decompensated heart failure, but includes a variety of 'non-acute' cardiovascular disease states such as stable coronary heart disease, peripheral obstructive artery disease and patients with cardiovascular risk factors, especially metabolic syndrome or diabetes mellitus.

Systematic reviews have shown that compared to usual care alone, exercise based CR improves exercise tolerance, health related quality of life and the cardiovascular risk factor profile and reduces mortality in coronary heart disease patients.[2, 3] The long term benefit of CR is thereby driven by the successful implementation of a favourable behavioural change. This fact is acknowledged in the most recent European guidelines on cardiovascular disease prevention in clinical practice,[4] where multimodal interventions, integrating education on healthy lifestyle and medical resources, exercise training, stress management, and counselling on psychosocial risk factors, are recommended with a class I, level A evidence in individuals at a very high cardiovascular disease risk. The initiation of behavioural change however, is often difficult. Nevertheless, the adherence to some principles of communication can facilitate treatment and prevention of cardiovascular disease (Table 1).

Most effective in the assessment of the individual's thoughts, attitudes, and beliefs concerning their perceived ability to change behaviour, have been shown to be cognitive-behavioural strategies . Thereby the most important tools needed to achieve a positive outcome are to respect the environmental context in which life style changes have to be implemented, to set realistic goals and to monitor their own behaviour. The practice of these specific clinical skills, needs however a special communication training, which should be offered regularly in a CR institution. Table 2 lists some strategic steps which make counseling on behavioural change effective.

Although the recommendations in the guidelines are clear, their implementation is hampered by several barriers, which have been identified recently:

1) The quality of CR service.
The recently published RAMIT trial,[5] a pragmatic trial to analyse the effectiveness of CR as provided 'in real life', concluded that "in this trial, comprehensive rehabilitation following myocardial infarction had no important effect on mortality, cardiac or psychological morbidity, risk factors, health-related quality of life or activity." Besides the fact, that the trial was largely

•	Spend enough time with the individual to create a therapeutic relationship - even a few more minutes can make a difference.
•	Acknowledge the individual's personal view of his/ her disease and contributing factors.
•	Encourage expression of worries and anxieties, concerns, and self-evaluation of motivation for behaviour change and chances of success.
•	Speak to the individual in his/ her own language and be supportive of every improvement in lifestyle.
•	Ask questions to check that the individual has understood the advice and has any support they require to follow it.
•	Acknowledge that changing life-long habits can be difficult and that gradual change that is sustained is often more permanent than a rapid change.
•	Accept that individuals may need support for a long time and that repeated efforts to encourage and maintain lifestyle change may be necessary in many individuals.
•	Make sure that all health professionals involved provide consistent information.

Table 1. Principles of effective communication to facilitate behavioural change.[4]

underpowered to allow any conclusion about its primary endpoint (mortality), it nevertheless revealed large differences in the delivery of CR between centres. A huge variation was noted in staffing levels and multi-disciplinary involvement (e.g., dietetics, physiotherapy, psychology, occupational therapy), duration and frequency (e.g., 4 to 20 weeks, once or twice weekly), intensity of exercise prescribed, methods used to change health behaviour (e.g., lectures, cognitive behavioural methods, written materials), method of delivery (e.g., individual, group based, group based with 'home exercise', outpatient, self-management at home, home-based and menu based).[6] This trial therefore reminds us that clinical audit of CR programmes is an essential safeguard to ensure effective delivery of the services. It is therefore the responsibility of each national working group on CR to establish an audit system and to draw the necessary conclusion from its analysis.

2) Prescription of CR in stable coronary artery disease.
Admittance of patients to CR after an elective PCI is low. In a registry of 2,395 consecutive patients who underwent PCI, only 40% of the patients were sent to CR.[7] However CR participation was associated with a 45% to 47% reduction in 5-year all-cause mortality rate compared with non-participation. Therefore, CR participation should be encouraged as part of an evidence-based secondary prevention plan also for patients who have undergone elective PCI.

3) Attendance rate and completion of CR programmes.
Hammill *et al*. addressed the relationship between the number of sessions attended during CR and long-term risks of death and myocardial infarction. They revealed a gradual loss of effect of CR on cardiovascular death and myocardial infarction of 22% and 23% respectively, when the attendance was 12 instead of 36 sessions and 14% and 12% respectively when only 24 of 36 sessions were attended. Interruption of CR resulted even in a 41% relative risk increase on cardiac death, a 23% increase of all cause hospitalisation and a 32% increase in cardiac re-hospitalisation rate in non-completers vs. completers over 13 yrs.[8]

To preserve the achievements of CR during the last decades, a tight control of the standards of care delivered in CR services and the implementation of core components is urgently warranted. Furthermore, the clinical effectiveness and the achievement of sustainable health outcomes have to be demonstrated.

The British Association for Cardiovascular Prevention and Rehabilitation recently published the second edition of *Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation* (www.bacpr.com), which can serve as an example on how to ensure clinical effectiveness and sustainable health outcomes for patients. It sets out the core standards that patients, health care professionals and commissioners could expect from a high quality cardiac rehabilitation programme. Seven standards and seven core components for CR are formulated:

1) The delivery of the seven core components employing an evidence-based approach.
1.1 Health behaviour change and education

•	Develop a therapeutic alliance.
•	Counsel all individuals at risk of or with manifest cardiovascular disease.
•	Assist the individuals to understand the relationship between their behaviour and health.
•	Help individuals assess the barriers to behaviour change.
•	Gain commitments from individuals to own their behaviour change.
•	Involve individuals in identifying and selecting the risk factors to change.
•	Use a combination of strategies including reinforcement of the individual's capacity for change.
•	Design a lifestyle modification plan.
•	Involve other healthcare staff whenever possible.
•	Monitor progress through follow-up contact.

Table 2. 'Ten strategic steps' to enhance counseling on behavioural change.[4]

1.2 Lifestyle risk factor management (physical activity and exercise, diet, smoking cessation)
1.3 Psychosocial health
1.4 Medical risk factor management
1.5 Cardioprotective therapies
1.6 Long-term management
1.7 Audit and evaluation

2) An integrated multidisciplinary team consisting of qualified and competent practitioners, led by a clinical coordinator.

3) Identification, referral and recruitment of eligible patient populations.

4) Early initial assessment of individual patient needs in each of the core components, ongoing assessment and re-assessment upon programme completion.

5) Early provision of a cardiac rehabilitation programme, with a defined pathway of care, which meets the core components and is aligned with patient preference and choice.

6) Registration and submission of data to a national database.

7) Establishment of a business case including a CR budget which meets the full service costs.

CR in the modern cardiology era has become more challenging. A lot of programmes however do not keep pace with changing trends and increasing exigencies. The biggest challenge for CR in defending its achievements today is therefore to assure the highest standards of care. Continuous instruction of involved healthcare professionals, (e.g. how to induce behavioural changes) as well as reporting and evaluation of outcome data are essential. National working groups on CR are called upon to take their responsibility in the implementation of this call.

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Upcoming Congresses and Meetings

European Association of Echocardiography Congress 2012 (EUROECHO 2012)

05 – 08 Dec 2012

Athens, Greece

The aim of the EAE is to promote excellence in clinical diagnosis, research, technical development and education. Consequently, over the past few years, EUROECHO has become one of the largest and most definitive scientific meetings on non-invasive cardiovascular diagnosis in the world. This year's symposia will have a particular focus on valvular heart disease and left ventricular function. It is a unique opportunity to meet the greatest experts in the world, to exchange ideas with colleagues with the same professional interest and to visit one of the largest exhibitions on cardiovascular imaging and related products.

6th World Congress of Paediatric Cardiology & Cardiac Surgery 2013

17 - 22 Feb 2013

Cape Town, South Africa

The 6th World Congress will build on the solid scientific foundations established through previous World Congresses from Paris in 1993, through Cairns 2009. Cape Town provides the meeting place for the global coalition of doctors, nurses and health scientists who use research and technological development to provide better care for babies, children and adults with heart disease. This is the major international scientific event for our global community and an opportunity to highlight and review four years of research and technological developments in basic sciences, clinical research and therapeutic interventions. The best international faculty promises an exceptional scientific programme across the different disciplines, from interventions, procedures and operations through critical care.

EuroHeartCare

22 - 23 March 2013

Glasgow, UK

The planned programme offers opportunities to develop practical skills, debate important issues in practice and education, exchange ideas, and learn from experts. During the two days of scientific sessions, attendees will hear the latest updates on acute cardiac practice, heart failure, prevention, diabetes, surgery, interventions and devices, psychosocial and behaviour issues, and interact with colleagues from around the globe. Delegates will have the possibility to participate in oral, moderated poster and poster abstract presentations and share their research and clinical projects. The meeting will also provide a unique opportunity by which our Industry Partners may network with attendees from across the world.

Euro PCR 2013

21 – 24 May 2013

Paris, France

Join more than 12,500 delegates at the definitive congress for healthcare professionals in the cardiology community. EuroPCR provides an invaluable space for cardiology specialists from around the globe to come together to discuss and debate the latest clinical trials, data and treatment strategies in the field. Open-mindedness, innovation and a patient-centred approach are the winning elements that make up EuroPCR, with discussion and debate on the different treatment options in a constructive manner. Bringing together the entire cardiovascular community, EuroPCR 2013 will provide attendees with a richly educational experience and an international platform for expression.

VI Congress of Cardiologists and Angiologists of Bosnia and Herzegovina and the II Congress of Nurses and Technicians of Bosnia and Herzegovina

Tuzla, Bosnia and Herzegovina

23 - 25 May 2013

The VI Congress provides an excellent opportunity for angiologists, cardiologists and other experts in the field of internal medicine and cardiac surgery, from around the world, to exchange experiences and current information in this field of medicine.

Heart Failure Congress 2013

25 – 28 May 2013

Lisbon, Portugal

The Heart Failure Congress 2013 which will be held in Lisbon this year and will be organised by the Heart Failure Association of the European Society of Cardiology (HFA of the ESC) in conjunection with the European Section of the International Society for Heart Research and the ESC Working Group on Myocardial Function. The aim of the joint Scientific Committee is to create an exciting forum for both clinicians and scientists to present, hear, exchange, and discuss the most up-to-date research and clinical findings in heart failure. The programme has been carefully planned to provide state-of-the art information about all aspects of heart failure - from basic science, through diagnostic strategies, pharmacological and device therapy, disease monitoring and organisation of

care, with a special focus on the role of nurses, pharmacists and remote monitoring.

British Cardiovascular Society (BCS) Annual Conference 2013

03 – 05 June 2013

London, UK

The BCS' Annual Conference is the largest cardiovascular event in UK, with over 2,000 members in attendance. The Conference provides cardiovascular professionals with the chance to witness the latest cutting-edge developments in the world of clinical cardiology, and network with cardiology experts from around the world. The Conference enables delegates to interact with world-wide experts, providing the most innovative information in cardiovascular science with a UK focus.

Multidisciplinary European Endovascular Therapy Congress (MEET) 2013

09 – 11 June 2013

Rome, Italy

This year's MEET conference will be held in Rome. Over three days, the symposium will present an extensive programme dedicated to endovascular techniques, focusing on Veins, EVAR, TEVAR, CAS, Lower limbs, SFA, BTK, AAA, and 18 F and above access management. The event will enable cardiology and radiology specialists from a wide range of disciplines to come together and debate the various scientific sessions.

23rd European Meeting on Hypertension and Cardiovascular Protection - ESH 2013

14 – 17 June 2013

Milan, Italy

The 2013 ESH meeting will contain a broad range of clinical and experimental research papers presented in numerous state-of-the-art lectures, plenary sessions, debates, how-to and other teaching sessions, breakfast workshops, integrated sessions for ESH working groups and satellite symposia, as well as oral and poster presentations. The European Society of Hypertension has developed its educational activities in cooperation with the European Society of Cardiology. Thus, at this year's ESH 2013 Meeting in Milan widespread EBAC accreditation for continuous medical education will be requested for those attending.

European Heart Rhythm Association (EHRA) EUROPACE 2013

23 - 26 June 2013

Athens, Greece

In June 2013 the lovely city of Athens will host EHRA EUROPACE 2013, the seventeenth edition of the official Meeting of the European Heart Rhythm Association (EHRA). EHRA EUROPACE is an established, international conference attracting key opinion leaders, well-recognised scientists, physicians, allied professionals and industry, who all enjoy scientific exchange of the highest level in an informal atmosphere. A record-breaking 5560 participants attended our last meeting. The steadily growing international attendance confirms the relevance of EHRA EUROPACE within the worldwide scientific community.

Catheter Interventions in Congenital & Structural Heart Disease – CSI 2013

27 – 29 June 2013

Frankfurt, Germany

CSI invites adult and paediatric interventionalists, cardiovascular surgeons and cardiology specialists to come and share the latest innovations and medical breakthroughs in cardiac surgery and catheter therapy of congenital and structural heart disease. The programme will include lectures from leading experts and professionals from across the globe, live case demonstrations and industry exhibitions.

European Society of Cardiology (ESC) Congress 2013

31 Aug – 04 Sept 2013

Amsterdam, The Netherlands

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 held annually in Europe and 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 chosen spotlight 'controversies in cardiovascular medicine promises stimulating debate of today's most prevalent topics. The 2013 programme 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.

Heart Rhythm Congress

20 - 23 Oct 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. After the most successful year in 2012, with 3000 delegates in attendance, the next congress will be held in Birmingham and promises to be another triumph.

XV WSA - World Congress Cardiac Arrhythmias, Pacing and Electrophysiology

17-20 Sept 2015

Beijing, China

The mission of the WSA - World Congress of Cardiac Pacing and Electrophysiology is to be very educative, underlining the evidence-based clinical practice in the field of arrhythmology for clinical cardiologists and young electrophysiologists. On the other side, the Congress will also touch the most advanced topics in invasive electrophysiology and pacing. Therefore in 2015 we will give to the top level electrophysiologists the opportunity to show and discuss new diagnostic and therapeutic strategies.

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