issue one
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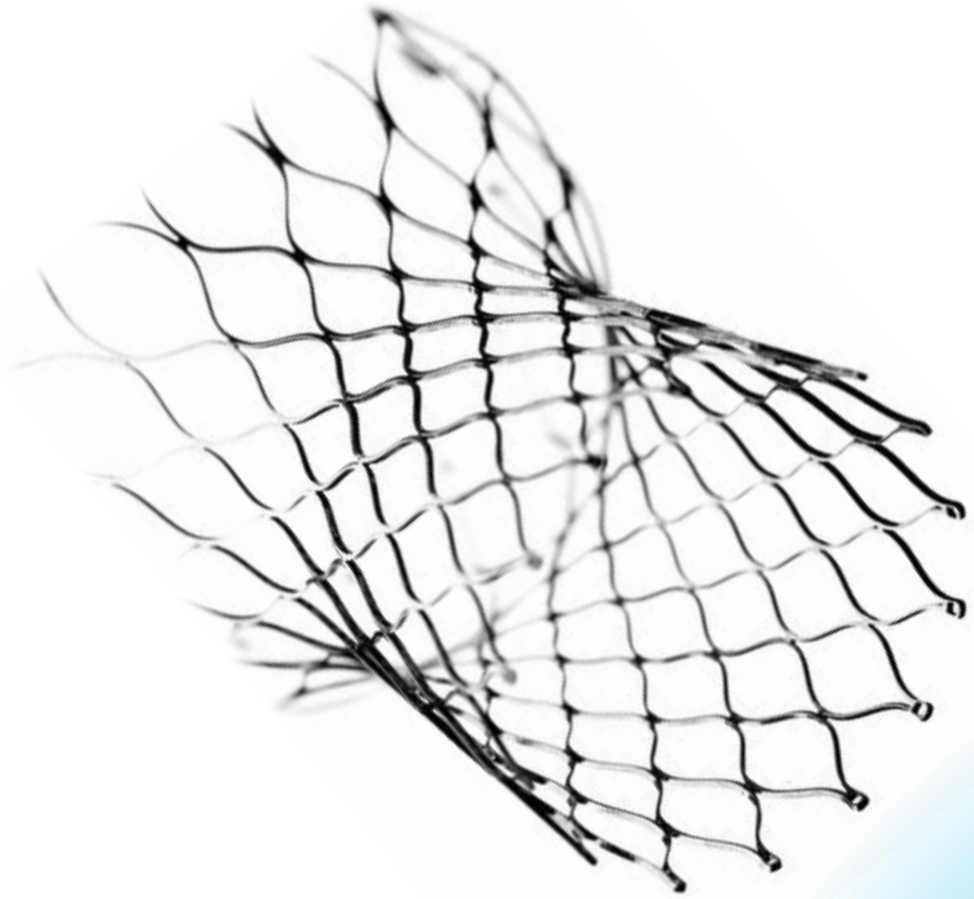
confluence

concepts and opinions in invasive cardiology

Transcatheter aortic valve implantation: What lies ahead?



The role of polymers in drug-eluting stents

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Supported by an unrestricted educational grant from Medtronic, Inc

EDITOR-IN-CHIEF
CHRISTIAN W HAMM

Dear colleagues,

Welcome to the first issue of *Confluence: concepts and opinions in invasive cardiology*.

The word 'confluence' means 'a bringing together of two or more streams', 'a place of junction' and 'a coming together of people or things' – all these definitions underpin our goals for this new publication. Our aim is to bring together cardiologists, cardiac surgeons and interventionists to discuss all issues around invasive cardiology that are of current interest.

Every issue of *Confluence* contains clinically relevant expert opinion pieces and review articles, topical interviews with thought leaders and reports from the most important global cardiology/cardiac surgery meetings. Our ultimate goal is to develop a diverse and easily digestible newsletter that will be of clinical benefit to you and your peers, as well as becoming a valuable and highly respected educational resource for cardiology and cardiac surgery communities alike.

We hope that we have achieved these goals in this first issue. Please let us know what you think of this issue and what you would like to see in future issues by emailing us at **confluence@axon-com.com** – your feedback is very important to us.

With best wishes,

Christian W Hamm

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Transcatheter aortic valve implantation: What lies ahead?


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It is forecasted that by 2012 transcatheter valve (TCV) therapies will account for approximately 40% of the total heart valve procedures performed in Europe (fig. 1)[1,2]. The absolute number of surgical valve procedures, however, is projected to rise during this period. Thus, TCV therapies will expand the total pool of treatable patients with heart valve disease. Although transcatheter aortic valve implantation (TAVI) has become recognised as a viable alternative for high-risk or inoperable patients, many important questions remain unanswered. The goal of this opinion piece is to highlight areas where further research and advancement is needed in this burgeoning field. More specifically, we will address issues related to patient selection and risk scores, procedural complications and standardisation of the definition of clinical endpoints.

Patient selection and surgical risk scores

TAVI is currently reserved for high surgical risk or inoperable patients. Surgical risk scores (SRS), such as the Society of Thoracic Surgeons (STS) predicted risk of mortality (PROM) and logistic EuroSCORE, are used commonly to identify such patients for clinical trials[3,4]. Furthermore, these SRS are used as benchmark performance measures for TAVI procedures. The application of SRS for transcatheter procedures can be associated with significant limitations. Firstly, it is important to appreciate the surgical population that was used to develop the risk score. For example, the logistic EuroSCORE was based on a general cardiac surgery population whereby 60% of patients had coronary artery bypass surgery, 30% had valve surgery and 10% had other cardiac-related

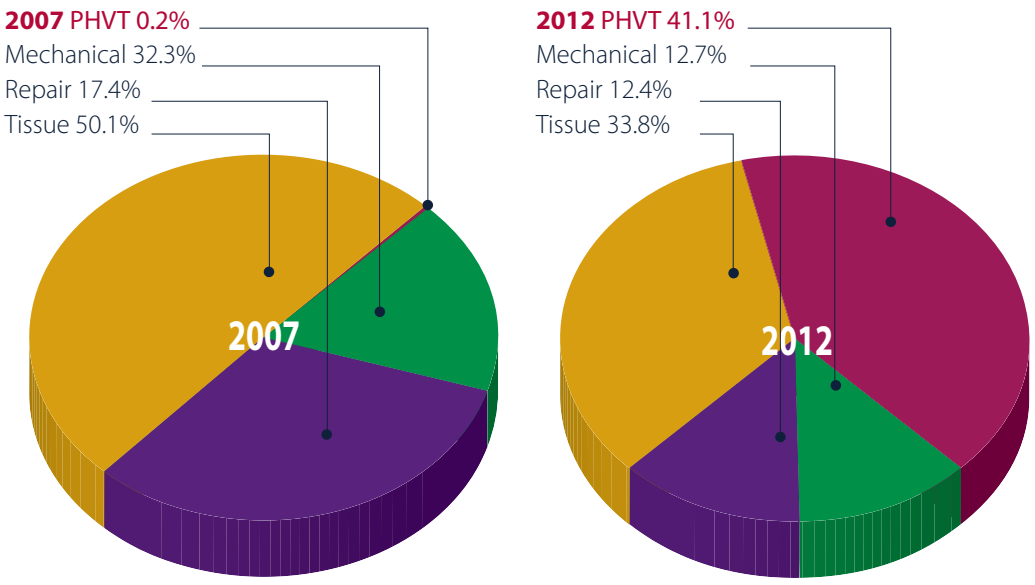


fig. 1

Heart valve market forecast... get ready for the storm!

Percentage of total heart valve procedures; expected to rise substantially from 2007–2012.

PHVT: percutaneous heart valve therapy. Adapted from [1,2].

surgeries. On the other hand, the STS risk score was based on patients undergoing valve surgery. Furthermore, 'inoperable patients' were obviously excluded during model development and high-risk patients likely accounted for a minority of those included in the analysis.

Although not particular to the STS or logistic EuroSCORE, several measurable and unmeasurable risk factors known to influence mortality are not factored into the equation[5,6]. For example, both models fail to include porcelain aorta and, more importantly, the frailty of the patient[7]. Also, using these surgical risk scores as benchmark performance measures for an unrelated procedure, such as TAVI, is not scientifically sound. This can lead to complacency on the part of the treating physician, especially when the SRS grossly overestimates the actual mortality risk of the TAVI procedure. In summary, two risk scores would be needed[8]:

- A SRS (developed using surgical patients) to help identify high-risk patients.
- A transcatheter risk score (developed using transcatheter patients) to act as a performance measure and improve patient-informed consent.

Procedural complications

The acute efficacy results are fostering the necessary enthusiasm and support for further development of the technology. What is perhaps of greater interest and importance is to understand the mechanisms behind the complications, to develop treatment strategies that either mitigate or prevent the complications and, finally, to appreciate the acute and long-term clinical implications of the complications. Conduction abnormalities and the need for permanent pacemaking, paravalvular aortic regurgitation, stroke and vascular complications have received particular attention and will be further discussed below.

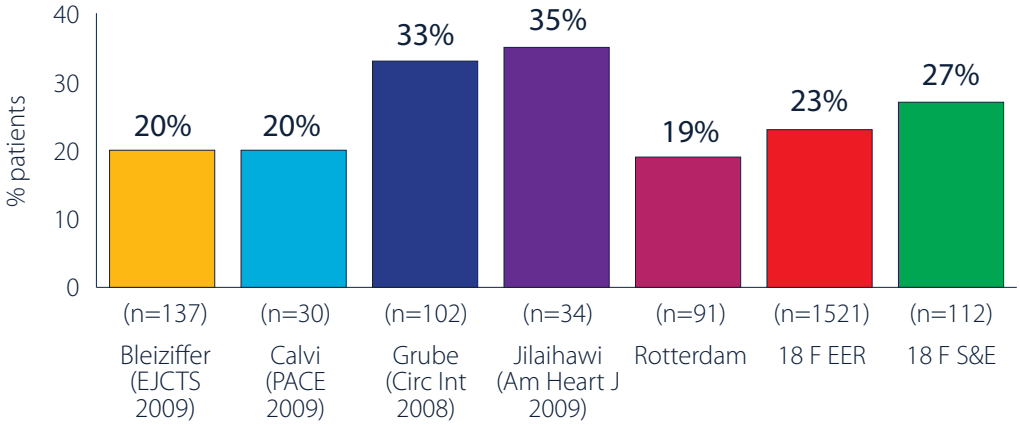
Conduction abnormalities and permanent pacemaker requirement

New-onset left bundle branch block (LBBB) has been reported in up to 40% of patients implanted with the CoreValve device (Medtronic, Inc, Minneapolis, MN, USA) and in 7% of patients implanted with the Edwards SAPIEN device (Edwards Lifesciences, Irvine, CA, USA)[9-11]. In parallel with these figures is the need for permanent pacemaking.

After implantation of the CoreValve device, the need for new permanent pacemaking has been reported to be in the range of 19–35% (fig. 2a)[9,10,12-15]. In contrast,

fig. 2a

Percentage of new permanent pacemaker implantations after CoreValve (Medtronic, Inc) implantation...



approximately 4–7% of patients are in need of permanent pacemaking after implantation of the Edwards device (fig. 2b)[16-19]. It must be highlighted that some centers implant permanent pacemakers on a 'prophylactic' basis (e.g. new-onset LBBB or asymptomatic bradycardia) or for administrative logistical purposes (e.g. promote earlier discharge). This may partly explain the wide range of observed permanent pacemaker implantation rates.

We have previously shown that the depth of implantation of the CoreValve device is associated with the development of LBBB (10.3 mm in those patients with new-onset LBBB vs. 5.3 mm in those without)[9]. Thus, we hypothesise that a more superior positioning of the CoreValve device within the left ventricular outflow tract may mitigate conduction abnormalities and reduce the need for permanent pacemaking. To put this into perspective, the Edwards SAPIEN device is implanted approximately 4–6 mm below the aortic valve annulus, whereas the CoreValve device, in our experience, is implanted a mean of 9–10 mm below the aortic valve annulus. Currently, it is being recommended to position the CoreValve device approximately 6 mm below the aortic annulus.

Paravalvular aortic regurgitation

Moderate-to-severe paravalvular aortic regurgitation is poorly tolerated after TAVI. In these cases, patients typically experience recurrent heart failure and longer lengths of stay in the intensive care units. According to the Expanded Evaluation Registry with the CoreValve device (n=1378) and the SOURCE registry with the Edwards SAPIEN device (n=1308), grade 3 or grade 4 paravalvular aortic regurgitation was observed in 3% and 5% of patients, respectively[17,20]. Of the remaining patients, approximately one-fifth had grade 0 paravalvular aortic regurgitation, two-thirds had grade 1 and one-fifth had grade 2. Anecdotal experience suggests that patients with grade 1 or 2 aortic regurgitation have a benign clinical course but this observation needs to be confirmed in larger clinical studies. The pericardial skirt of the Edwards and CoreValve device is 10–11 mm and 12 mm in height, respectively, and, together with the radial force of the device, functions to create a seal against the native aortic valve leaflets and left ventricular outflow tract, thereby mitigating paravalvular aortic regurgitation (fig. 3[21]).

Potential mechanisms of aortic regurgitation include:

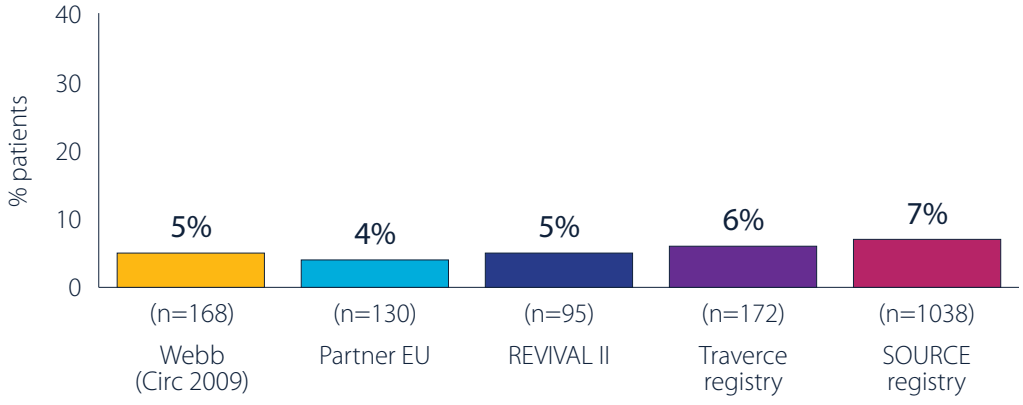


fig. 2b

...and after Edwards SAPIEN (Edwards Lifesciences) implantation.

- malpositioning of the device (too high or too low)
- incomplete expansion of the device or malapposition against the native aortic valve leaflets or left ventricular outflow tract due to bulky calcifications
- undersized prosthesis
- aggressive pre-implant balloon aortic valvuloplasty
- malcoaptation of prosthetic valve leaflets due to the guide wire or pigtail catheter across the valve
- prolapse of native aortic valve leaflets or calcific debris into the prosthetic valve impeding normal leaflet excursion (particular to Edwards SAPIEN device)
- diastolic hypotension resulting in insufficient closing pressure.

Corrective measures may include post-implant dilatation, valve-in-valve technique, and particular to the CoreValve device, the use of a goose-neck snare to reposition the device in a slightly higher position (typically 1–4 mm)[22]. Currently, there are no preprocedural screening methods to predict the occurrence or severity of paravalvular aortic regurgitation.

Stroke

Stroke can be a catastrophic complication even after a so-called 'uneventful' TAVI procedure. Stroke has been reported to occur in 2.9%–6.3% of patients undergoing transfemoral TAVI (with both the Edwards SAPIEN or CoreValve device)[12,13,15–18] and 1.8%–5% of patients undergoing transapical TAVI (Edwards SAPIEN)[17,18,23–25]. Some advocates suggest that the transapical approach is associated with lower stroke rates than the transfemoral approach. Data from prospective, multicenter, adjudicated, feasibility and postmarket trials, however, suggest comparable stroke rates between the two vascular approaches. The SOURCE registry, for example, reported a stroke rate of 2.4% and 2.6% for the transfemoral (n=463) and transapical approach (n=575), respectively[17]. Similar stroke rates were reported for the PARTNER EU trial (3.2% transfemoral [n=61] vs. 2.9% transapical [n=69])[18].

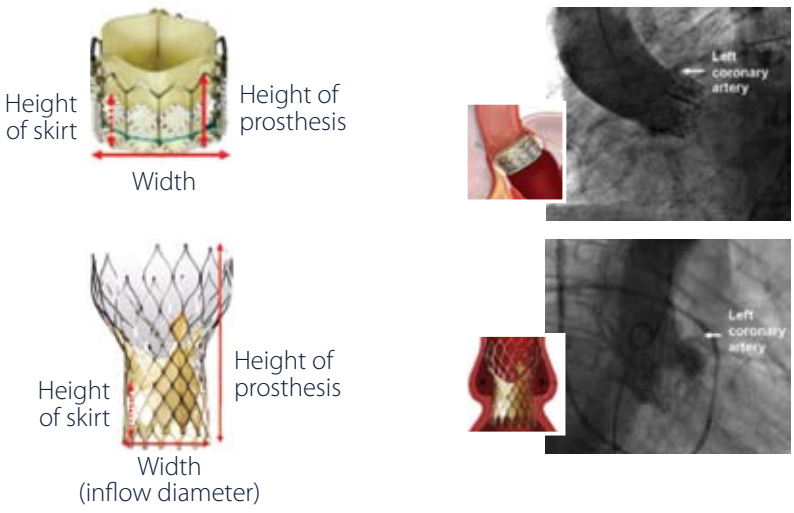
More recently, attention has focused toward the potential merits of using embolic protection devices. These devices are intended to divert embolic clots or debris away from the major neck vessels and

fig. 3

Edwards SAPIEN (Edwards Lifesciences) and CoreValve (Medtronic, Inc) devices

The pericardial skirt, in addition to the radial force of these devices, functions to create a seal against the native aortic valve leaflets and left ventricular outflow tract to mitigate paravalvular aortic regurgitation.

Adapted from [21].



towards the descending aorta. Clinical studies using the Aortic Embolic Protection Device (AEPD; SMT Research and Development, Ltd., Herzliya, Israel (figs. 4a+b) and the Embrella Embolic Deflector (Embrella Cardiovascular™, Inc., Malvern, PA, USA) will likely initiate by Q4 of 2009. In addition to these devices, it hoped that a more detailed assessment of the aorta, improved techniques and less traumatic catheters will decrease the occurrence of stroke.

Vascular complications

Given the large-bore catheters used for TAVI procedures, vascular complications are of particular concern. Imaging techniques such as fluoroscopic angiography, computed tomographic angiography and magnetic resonance angiography can provide objective information of the peripheral arterial system – salient features include vessel diameter, degree of calcification and atherosclerosis, obstruction, tortuousity and ulceration. The 18 F CoreValve Safety and Efficacy trial reported a vascular complication rate of 12%, whereas the Edwards PARTNER EU trial (22 F and 24 F devices) reported a rate of 27%[15,18,26]. Previous analyses have demonstrated that vascular complications are associated with increased in-hospital mortality (36% with vascular complications vs. 10.3% without)[27]. Cautious preprocedural screening (e.g. excluding patients with circumferential calcification of ilio-femoral vessels) is essential to reduce these complications. Edwards has recently introduced the 18 F Edwards SAPIEN XT device (associated with a cobalt-chromium alloy-stented valve and RetroFlex 4 delivery catheter) with the expectation that it will reduce vascular complications.

Standardisation of the definition of clinical endpoints

One complicating factor when trying to analyse and compare available TAVI data stems from the great heterogeneity involving the definition of clinical endpoints[28–30]. A number of organised societies have alluded to the need for standardised reporting practices[31–33]. Furthermore, any valid treatment comparisons between TAVI and surgical aortic valve replacement will require some common ground for clinical endpoint reporting. Thus, this endeavour should involve the mixed perspectives of interventional cardiologists, cardiac surgeons, clinical valve specialists, manufacturers and regulatory bodies located on both sides of the Atlantic. This framework was successfully adopted by the Academic

fig. 4a

The Aortic Embolic Protection Device (AEPD) from SMT Ltd.

This device is currently available in 8 F and is inserted via the transfemoral arterial route. The device spans the three major neck vessels.

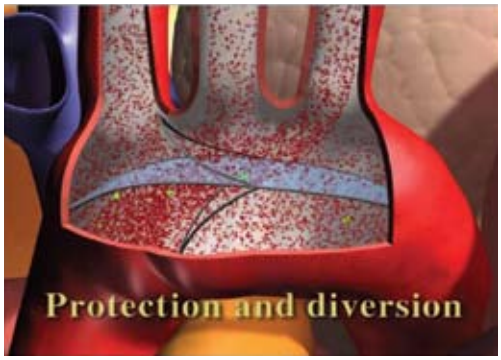


fig. 4b

Pictorial representation of the transverse aortic arch with major neck vessel

SMT filter device in situ functions to divert debris away from the major neck vessels.

Research Consortium (ARC) to standardise the definitions of clinical endpoints for stent trials[34]. Along these lines, the cardiology and cardiac surgery communities are currently working towards a Valvular Academic Research Consortium (VARC)[29].

The future

The future and widespread adoption of TAVI will rely on a number of inter-related factors, including long-term durability and safety data, randomised controlled trials comparing TAVI with surgical aortic valve replacement and reimbursement for the technology.

Given the obvious requirement for long-term follow-up data, the number of patients with ≥3 years' clinical follow-up is severely limited[35]. It is unlikely, given the age and multiple comorbidities of patients currently undergoing TAVI, that robust long-term follow-up data (i.e. >10 years) will become available. Furthermore, the long-term effects of either crimping the valve into a delivery catheter, performing a post-implant balloon dilatation or valve-in-valve procedure are currently unknown.

Undoubtedly, randomised controlled trials will be needed to establish the noninferiority or superiority of TAVI (versus surgical aortic valve replacement) and its eventual acceptance into medical practice as evidence-based medicine. At this time, a legitimate question may follow: "Has TAVI has reached an appropriate level of maturity to be subjected to a randomised, controlled clinical trial?" The pivotal randomised PARTNER US trial may shed light onto this important question – enrolment should be complete by Q4 2009 with the primary endpoint being all-cause mortality at 1-year.

As a result of its novelty, lack of comparative data (to surgical aortic valve replacement) and a lack of cost-effectiveness data, reimbursement policy makers may be skeptical about the potential merits of TAVI. The road to reimbursement can be summarised in the following points:

- CE mark approval is required from governmental regulatory bodies.
- Evidence-based medicine must prove the efficacy and safety of the technology.
- The risk/benefit ratio must be in favour of the individual patient.
- The cost-effectiveness must be established on a societal level.

Owing to limited financial resources, many TAVI programmes across Europe and Canada are restricted in the number of TAVI procedures they can perform. Despite these restraints, it is notable that approximately 8000 TAVI procedures have been performed since CE mark approval was obtained for the CoreValve (April 2007) and Edwards SAPIEN devices (June 2007).

In 2007, TAVI actually represented approximately 1.2% of all aortic valve procedures in Europe (including surgical aortic valve replacement); this percentage increased to 6.5% in 2008. With an expectation of ~9000 TAVI procedures to be performed in 2009, TAVI may represent nearly 13% of all aortic valve procedures (fig. 5).

It is unquestionable that refinements in the technique and technology (lower profile devices, ability to reposition and retrieve) will provide those patients with aortic valve disease with new hopes and aspiration in the future to come.

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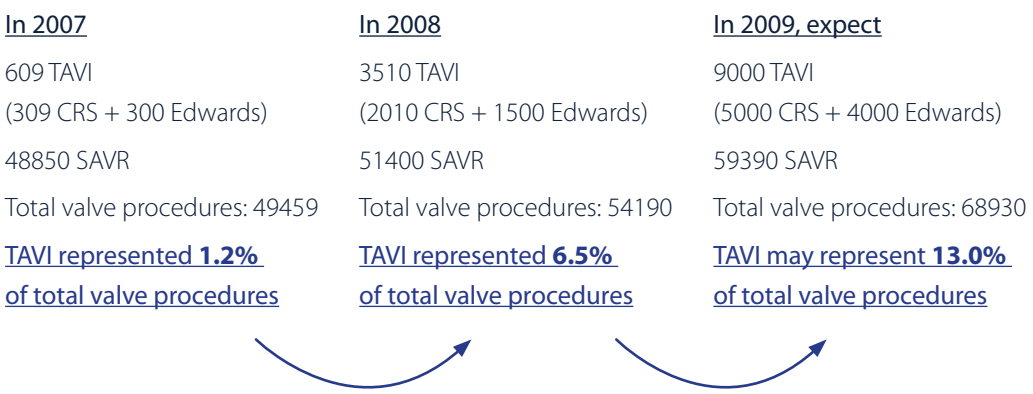

fig. 5

SAVR procedures continue to increase

This figure demonstrates that the number of surgical aortic valve replacement (SAVR) procedures continues to increase. Also, since CE mark approval, the percentage of total heart valve procedures represented by TAVI increased considerably from 2007 to 2008. A similar trend is expected for 2009.

DISCLOSURES: The opinions and factual claims herein are solely those of the authors and do not neccesarily reflect those of the publisher, editor-in-chief, editorial board and supporting company. NP is a consultant for Medtronic, Inc, PdJ is a proctor for Medtronic, Inc and AT and PWS have no relevant disclosures.

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The role of polymers in drug-eluting stents

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Introduction

Drug-eluting stents (DES) have proven to be highly beneficial in that they dramatically reduce the restenosis rates relative to bare metal stents (BMS). Local delivery of antirestenotic drugs from stent scaffolds is achieved through polymeric coatings. The polymers employed are either biostable or bioabsorbable, although, currently, most of the DES that are on the market are based on biostable polymers (Table 1). Such coatings have to be robust, offer effective drug-release kinetics and, above all, be biocompatible. The following article discusses the role played by polymers in providing these various DES attributes.

Background

The concept behind DES technology is the controlled release of a chemotherapeutic agent from a structurally supportive metallic or organic stent backbone. Arguably, the choice of drug, control of its release kinetics and subsequent tissue effects are the most important components of this technology, and it is the polymer coating that dictates the release kinetics. To date, two different classes of drugs have been successfully employed on DES platforms in order to inhibit neointimal overgrowth[1]:

- The 'limus' family of antimitotic drugs – such as sirolimus, zoratolimus and everolimus – which halt cell-cycle progression in the G1 phase.
- Paclitaxel, a microtubule-stabilising drug that interrupts mitotic division in late metaphase, resulting in cell-cycle arrest.

Table 1

The various DES currently on the market and the biostable polymers used therein.

DES	Biostable polymer
Cypher™	Polybutyl methacrylate and ethylene-vinyl acetate copolymer
Taxus™	*TransLute* (styrene-isobutylene-styrene block copolymer)
Xience V™	Copolymer of hexafluoropropylene and vinylidene fluoride
Endeavor™	*PC polymer* (phosphorylcholine-based copolymer)
Resolute™	*BioLinx™* (copolymer blend based on butyl methacrylate, hexyl methacrylate, vinyl acetate and vinyl pyrrolidinone)

Polymer coatings utilised in coronary drug-release systems

Medically, like other implantable biomaterials, polymers are used typically to provide mechanical support or to serve as a vehicle for the delivery of bioactive agents. In coronary stenting, polymers have been tried as a lone component of a stent backbone[2], though generally this use has been limited due to inferior radial strength compared with metal alloy stents. On the other hand, since the inception of DES therapy, polymer coating has been the most favoured vehicle for both drug-loading and control-of-release kinetics.

Although biostable polymers are employed in most DES, some newer DES systems employ bioabsorbable polymers, which generally comprise of polymers such as polylactic acid (PLA), polyglycolic acid (PGA) and PLGA copolymers. These polymers degrade and get metabolised in the body leaving behind a BMS. However, PLA degrades over 2–3 years and PLGA, depending on the glycolic acid content, can degrade rather too rapidly to result in significant inflammation. As such polymer composition determines degradation kinetics, which in turn largely determines the utility of bioabsorbable polymers.

Polymers may also be classified as hydrophilic or hydrophobic. The former exhibit affinity to water and the latter tend to be averse to water. In the aqueous environment of the body it is only reasonable to expect a

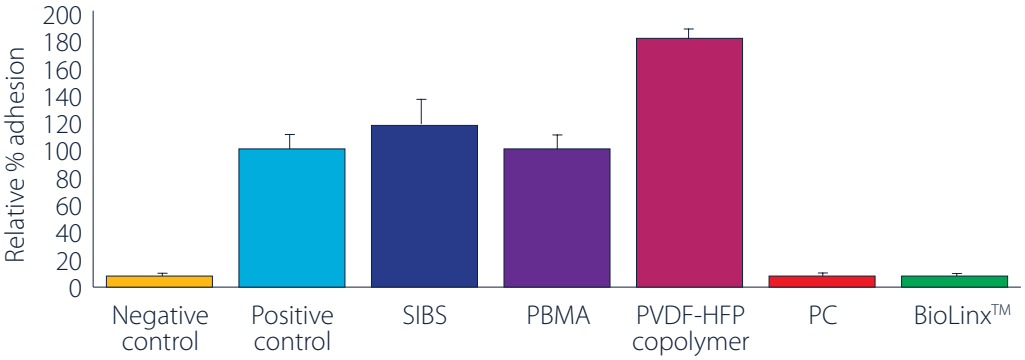


fig. 1
Relative adhesion of activated monocytes

Adhesion of activated monocytes is indicative of an inflammatory surface. Hydrophobic polymers exhibit higher adhesion relative to hydrophilic polymers.

PBMA: polybutylmethacrylate; PC: phosphorylcholine; PVDF-HFP: copolymer of vinylidene fluoride and hexafluoropropylene; SIBS: styrene-isobutylene-styrene. Adapted with permission from Medtronic, Inc.

hydrophilic polymer to generate less interfacial tension relative to a hydrophobic polymer and therefore be more acceptable to the body. However, antiproliferative drugs, such as paclitaxel or sirolimus and its analogues, are highly hydrophobic and it is not feasible to incorporate a hydrophobic drug in a hydrophilic polymer and obtain a controlled and sustained release. As such, it is not surprising that Cypher™ (Cordis Corporation), Taxus™ (Boston Scientific) and Xience V™ (Abbott) were formulated with hydrophobic polymers and attain a controlled and sustained drug release. It is apparent from Table 1 that the constituent monomers that comprise these polymers are all hydrophobic.

Nevertheless, it is possible to design polymers with a combination of hydrophobic and hydrophilic monomers such that the hydrophobic components hold and elute the hydrophobic drug in a controlled manner but present a hydrophilic surface in the aqueous body environment to potentially elicit minimal inflammatory response. Indeed, polymers employed in Endeavor™ (phosphorylcholine [PC] polymer) and Resolute™ (BioLinx™ polymer) (both Medtronic, Inc) are more hydrophilic relative to other DES polymers since they contain substantial amounts of water-soluble monomers such as PC and vinyl pyrrolidinone, respectively. The zwitterionic PC head groups associate with a large number of water molecules to provide the hydrophilicity[3,4] and hence are favoured in the body environment[5]. Similarly, BioLinx has been designed to present a hydrophilic surface with adequate hydrophobic component incorporated to offer a controlled and sustained elution of the drug zotarolimus[6]. Evidence of biocompatibility of PC and BioLinx polymers was borne out in *in vitro* studies of interactions of activated monocytic and vascular smooth muscle cells (VSMCs) using real-time-based gene profiling and FACS-BD cytokine array[7] (fig. 1). In addition, the polymer system also promoted viability of endothelial and VSMCs[7].

fig. 2

A deployed Resolute™ stent with BioLinx™ polymer after tracking three times in a 5 F guide catheter.

The molecular architecture of the polymers is important in providing a robust coating, and it is imperative that a polymer coating is tough and adheres well to the stent surface (fig. 2). It should not crack or peel when the stents are often tracked through hard calcified lesions in the vasculature. Softer, elastomeric segments in the coating polymer eliminate cracking but, in excess, can also lead to a balloon-sticking problem. Those hard glassy blocks in the polymer not adequately compensated with elastomeric components can lead to brittle coatings that crack. Regarding drug elution,

softer polymers enhance the drug-elution rate, whereas hard polymers can either sequester the drug or drastically impede the elution rate[8]. Furthermore, it is important that if a polymer blend is employed, the component polymers are either miscible, or mutually compatible, so as not to phase separate. Phase-separated polymer systems are often unable to provide diffusion-controlled kinetics because of preferential migration of drugs into phases of different physicochemical characteristics.

The importance of drug-release kinetics to DES efficacy

The control of drug release is central to the effectiveness of DES technology and the main reason behind the incorporation of polymer coating into DES devices. Evidence on the importance of release kinetics can be seen in the comparative performance of a number of current DES platforms. The history of DES development provides some insights into the importance of this dynamic to antirestenotic efficacy.

Limus-eluting stents

Early clinical trials with sirolimus-eluting stents compared fast-release stents (FRS; 100% drug release at <15 days) with slow-release stents (SRS; 80% at 30 days) using otherwise identical stent platforms and drug dosages. Although the FRS showed somewhat superior NIH suppression at initial 4-month follow-up, the durability of this antirestenotic efficacy to 12 months appeared more sustained with SRS – which was ultimately the product chosen to come to market (the Cypher stent)[9-11]. Comparison of the next-generation limus-eluting DES also confirms the importance of early release kinetics. On one hand, the Endeavor stent employs a fast-release protocol (~95% at 10 days)[12] to deliver its drug load to the arterial tissue early where it is retained for 28 days owing to its relatively high lipophilicity. Against this, Resolute, with the same drug load (1.6 µg per mm^2 of stent surface) as Endeavor, elutes 85% of its zotarolimus content over the first 60 days post-procedure, and the remainder of the drug by 180 days[13]. The gradual release of drug from Resolute stent produces a more tightly constrained drug level in the tissue, but sustaining it for a longer duration resulting in low TLR rates, low late loss and zero thrombosis at 2 years in the Resolute I clinical trial[14]. Similarly, the Xience V stent displays a slower drug-release profile (40–50% at 10 days; 80% at 30 days)[15] and displays a very similar degree of antirestenotic efficacy to the Cypher stent[16].

The ISAR-TEST-3 trial also provided an interesting illustration of the importance of early drug-release kinetics[17]. This study randomised patients to otherwise identical fast-release polymer-free sirolimus-eluting stents or slow-release biodegradable polymer stents and compared their performance with those of Cypher stents. Although both investigative stents release a similar proportion of drug (80–90%) at 30 days, a more rapid release of sirolimus in the first 10 days resulted in an inferior performance efficacy compared with the Cypher stent; whereas a slower early release of sirolimus resulted in a similar antirestenotic efficacy to Cypher.

Paclitaxel-eluting stents

The Taxus stent operates to a very different and much slower drug-release model compared with the limus-agent platforms already considered[18]. The Taxus II trial tested slow- (10% at 30 days; remainder sequestered indefinitely) and moderate-release (25% at 30 days; remainder sequestered indefinitely) DES platforms. The moderate-release formulation had a rapid initial burst, with an eight-fold higher release of paclitaxel in the first 10 days. Overall, however, the antirestenotic performance of both was very similar, indicating that a dosing threshold for NIH inhibition had been reached with the slow-release model; this was the formulation subsequently brought to market[19].

The assessment of DES polymer effects

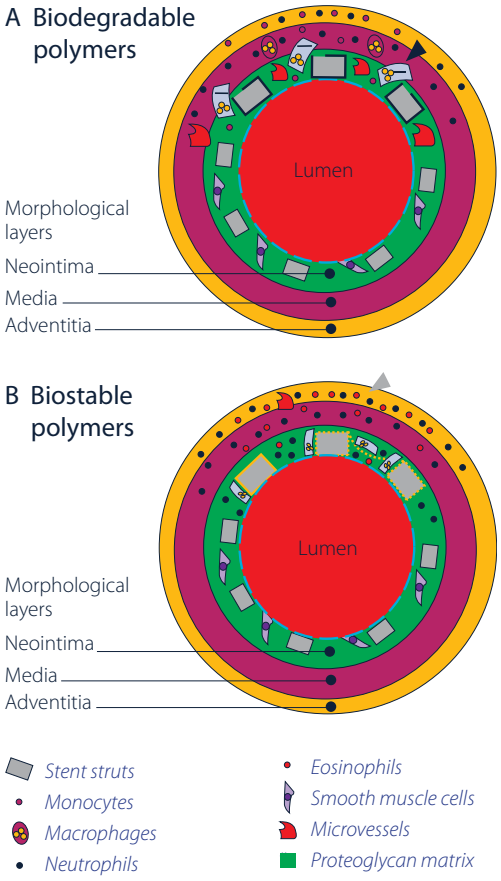
A number of limitations should be considered when assessing the accumulated evidence on vascular responses to DES implantation in both animals and humans.

Firstly, due to the limited resolution of conventional angiography and intravascular ultrasound, as well as the practical constraints of direct angioscopy, there are a limited number of methods available to directly assess the long-term effects of DES and nonerodable polymers on arterial healing. Most of our information comes from two sources: preclinical animal models (in particular rabbit and porcine) and human autopsy studies. There have been recent advances in imaging techniques – specifically regarding optical coherence tomography – which are certainly encouraging and will likely provide important information on vascular responses to stent implantation in the future[20].

Secondly, much of the available clinical data, and to a lesser extent preclinical studies, compared DES platforms (i.e. stent plus polymer plus drug) with BMS (stent only) controls. As such it is often difficult to definitively attribute an observed 'DES effect' to either active drug or carrier polymer.

Differences in inflammation between biodegradable and biostable polymer-coated stents

The inflammatory response to most biodegradable polymer-coated stents is dictated by their biological sequences of degradation. For example, PLA-based polymer stents show a considerably low inflammatory response early after implantation in different animal models (fig. 3)[21-24]. As soon as the polylactide chain starts to degrade into shorter fragments or its monomers, a dramatic change in the biological vascular environment is observed[25-27]. Due to chemical reactions with the polymer and pH changes in the vascular tissue surrounding the polymer, the



cellular and acellular responses to the polymer are accumulating. It is likely that proinflammatory growth factors and cytokines induce inflammatory cell recruitment and infiltration to the tissue adjacent to the degrading polymer. The primary goal is to reduce the burden of foreign body; thus, the predominant inflammatory reaction is a nonspecific immune reaction dominated by monocytes and macrophages. Many of these macrophages form multinucleated giant cells to cope with the bulk of polymer fragments. As a consequence of persisting inflammation and sustained release of pro-inflammatory cytokines, a new formation of microvessels, termed neovascularisation, is commonly observed. The result of this is frequently a reinforcement of the already existing inflammatory response until the resorption process is completed. Ultimately, the inflammatory response is reduced as the polymer has degraded. The histopathological

fig. 3

Diagram illustrating the fundamental differences of histopathological reactions occuring after implantation.

A

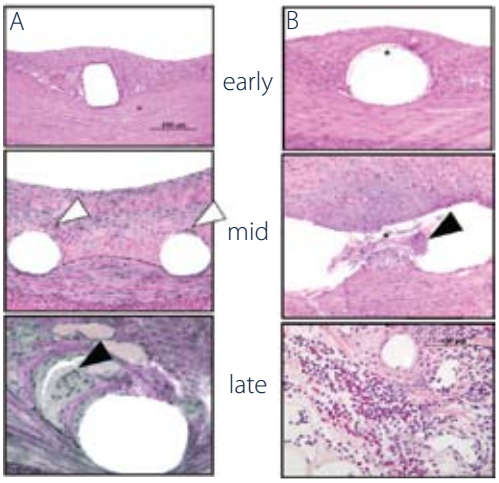
There is a predominance of chronic inflammation including monocytes, macrophages and giant cells (black arrowhead) in the surrounding of the degrading stent struts, with some of the giant cells incorporating pieces of degrading polymer.

B

Biostable polymers show a predominance of chronic inflammation including neutrophils and sometimes eosinophils within the surrounding of stent struts but also within the media and adventitia (grey arrowhead). Few giant cells are seen close to polymer fragments in the surrounding of stent struts.

fig. 4

Representative images of biodegradable (A) and biostable (B) polymer-coated stents. At early time points, biodegradable coatings show little inflammation, while there is ongoing chronic inflammation including monocyte infiltration (white arrowhead)) at mid-term time points and giant cell formation at later time points (black arrowhead) depending on the pace of degradation.



differences among other biodegradable polymers are mainly characterised by the differences in the pace of degradation and the biocompatibility of the individual monomers (fig. 4).

In contrast, most biostable polymers vary in their degree of inflammation early after stent implantation (fig. 3)[28-30]. There has been a large variety of different biostable polymers that have been adopted by cardiovascular device companies for the use as drug carriers on stents[31-35]. They can be grouped in many ways, starting from the chemical structure of their respective monomers to their complex three-dimensional structure, which determines their biochemical behaviour. Lately, they have been divided into polymers with a predominance of hydrophilic versus hydrophobic surface characteristics likely to render them more or less biocompatible. However, the type and degree of the inflammatory response to biostable polymers is determined by various factors, including the stability of the polymer *in vivo*, the inertness at relevant biological conditions and the capability of allowing a regenerative tissue growth. Hence, most of the biostable polymers provoke an inflammatory process dominated by leukocytes. Early after stent implantation, neutrophils get deposited at the polymer sites that ultimately strengthen the pro-inflammatory milieu in the surrounding tissue. Monocytes and macrophages are commonly observed, however, and limited mostly to the polymer coating itself. In contrast to most biodegradable polymers, the inflammatory reaction persists, and is likely to find a balance after the nonspecfic immune response has resolved, or leads to a prolonged, more specific hypersensitivity response involving T lymphocytes and eosinophils (fig. 4)[31,36]. To date, the detailed factors resulting in a hypersensitivity response remain to be elucidated.

Clinical data

Initial reports of late adverse events following DES therapy were anecdotal in nature. An early pathological case report from Virmani et al concerned a 58-year old patient who died of acute circumflex vessel stent thrombosis 18 months following Cypher implantation[31]. Sectioning of the coronary arteries revealed the absence of neointimal regrowth and signs of significant arterial wall toxicity at the stented segment, such as malapposition and aneurismal dilatation of the vessel wall, and diffuse predominantly T lymphocyte and eosinophil infiltration with occasional giant cells. Collectively, these changes were consistent with a hypersensitivity reaction, although an isolated giant-cell reaction was also noted adjacent to polymer fragments which had become detached from the stent backbone. In general, however, such a marked hypersensitivity reaction is not typical for DES-associated delayed vascular healing.

As the resolution of clinically practicable invasive and noninvasive imaging techniques is insufficient to characterise the extent of vascular healing, most of our understanding of impaired vascular healing post-DES implantation comes from autopsy studies of patients who succumbed for cardiac or noncardiac reasons at a time point following coronary stenting. A report from Joner et al compared autopsy specimens from 23 patients with prior DES implantation (at >30

days) with 25 matched controls with a previously implanted BMS[37]. All cases came from a registry of 484 stent specimens submitted to the CVPath (Gaithersburg, MD, USA) for pathological consultation. DES specimens (Cypher and Taxus) showed greater delayed healing compared with BMS: fibrin deposition score (2.3±1.1 vs. 0.9±0.8; p≤0.001) and endothelial coverage (55.8±26.5 vs. 89.8±20.9; p≤0.001). In addition, DES specimens were more likely to have evidence of late stent thrombosis (LST; 14/23 patients vs. 2/25 patients). In all 14 DES patients with late thrombosis, delayed healing appeared to be a principal contributing factor. Interestingly, however, 11 of 14 patients had evidence of a second pathological risk factor for LST, suggesting that a 'dual-hit' was often necessary to provoke a thrombotic event.

The contribution of drug and polymer to these cases of delayed healing is difficult to definitively define. In three of 11 cases there was evidence of a full-blown chronic hypersensitivity reaction, which may have been a direct response to residual polymer. In the remainder of cases the relative contribution of drug effects and response to nonerodable polymer are unclear.

Information relating to the prevalence of delayed arterial healing in patients who remain well post-coronary intervention is beyond the scope of an autopsy study. Indirect evidence, however, may be construed from a large-scale serial angiographic follow-up study[38]. In this study patients receiving Cypher, Taxus and ISAR polymer-free DES underwent surveillance coronary angiography at two time points post-DES implantation, namely 6–8 months and 2 years. In 1580 lesions with paired follow-up, delayed late luminal loss was a systematic feature of DES therapy (0.12±0.49 mm between 6–8 months and 2 years) – a finding which illustrates that across large numbers of DES-treated patients, arterial healing is an ongoing process beyond 6–8 months. This contrasts markedly with data from the BMS era where neointimal volume peaked at 3–6 months and thereafter volumes of restenotic plaque tended to remain stable or indeed contract slightly due to completion of vessel wall healing[39-41]. Interestingly, there seemed to be device-specificity to this phenomenon; late NIH progression was not observed with the polymer-free DES platform.

Conclusion

Polymers, as either biostable or biodegradable multimers of complex molecules, have revolutionised interventional cardiology by introducing the possibility of a controlled release of antirestenotic compounds for the treatment of obstructive atherosclerotic coronary lesions. The necessity of controlled drug release was impressively shown in a series of early preclinical studies evaluating precursors of currently available DES. While a landmark improvement was achieved with the advent of polymer science in interventional cardiology, initial attempts at controlled drug release were hampered by the concerns regarding biocompatibility and delayed vascular healing. Without a doubt, the further improvements with second-generation DES were among those factors attributable to advancements in polymer chemistry that partly resumed the trust of interventional cardiologists.

To date, we have just started to learn about the complex interactions in vascular biology that are likely to play a major role in the long-term success of any interventional treatment, and the diversity of therapeutic potentials offered by polymeric DES will certainly continue to determine the evolution of interventional cardiology.

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REFERENCES: See page 17

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'Stent for Life' initiative: Interview with Jean Fajadet

What is the 'Stent for Life' initiative and what are its aims?

The 'Stent for Life' initiative is a project initiated early in 2009 by the EAPCI – the European Association for Percutaneous Cardiovascular Interventions (Professor William Wijns is the first president), the European Society of Cardiology (ESC) working group on Acute Cardiac Care, EuroPCR and Eucomed.

The mission of this initiative is to promote the life-saving indication of percutaneous coronary intervention (PCI) and to reduce mortality rates for patients with acute coronary syndromes (ACS). The main objectives are to:

- define those regions/countries in Europe who have an unmet medical need for the optimal treatment of ST-elevated myocardial infarction (STEMI)
- define those regions/countries where the use of primary PCI can be encouraged, and thereby the quality of care improved
- implement an action programme to increase patient access to primary PCI.

During the 2008 ESC meeting, Professor Petr Widimsky (Czech Republic) gave a presentation on the impact of primary PCI for STEMI in Europe, and it was very interesting to see that among the European countries, there were major differences concerning the use of primary PCI in STEMI. He showed that in some countries more than 80% of the patients had a successful recanalisation and, conversely, in other countries the majority of patients could not have a successful recanalisation of an infarct-related vessel. It was interesting to see that when primary PCI was the 'dominant' treatment compared with thrombolysis, the results were better.

> " The mission of this initiative is to promote the life-saving indication of PCI and to reduce mortality rates for patients with ACS „

What we are looking at now is how our 'champion' countries (Czech Republic, The Netherlands, Denmark, Sweden and Austria) actually work (primarily, how their network works) and the quality of collaboration between emergency medical services (EMS), non-PCI hospitals and PCI centres (whilst always remembering the important fact that these hospitals are working 24 hours a day, 7 days a week). This is demonstrated perfectly in a recent paper from Jiri Knot published in *Eurointervention* in August (Knot J et al: 5; 299–309). The initiative is in line with the ESC guidelines, which designate primary PCI as class 1 for STEMI and class 1 for high-risk ACS. Our goals are to promote the best way of treating patients with STEMI and high-risk ACS in Europe, to improve the delivery and patient access for this life-saving indication of PCI and to reduce mortality and morbidity.

Who are the main people involved in this initiative?

Petr Widimsky, William Wijns and I are mainly involved in this initiative. We also have representatives from the ESC working group on acute cardiac care, Nicolas Danchin and Marco Tubaro. Adriaan Podgieter and Nadav Tomer, who are two representatives from Eucomed – a Brussels-based association representing the medical device industry

– are actively participating in this initiative. And last, but not least, the whole initiative is managed by Zuzana Kaifoszova, our excellent project manager.

What next for the initiative and what are your goals?

At EuroPCR 2009 in May we put out a 'call for action' involving all the national working groups for interventional cardiology and national cardiology societies of Europe, and we have now identified six pilot countries (Bulgaria, France, Greece, Serbia, Spain and Turkey), in which we will start this programme.

We have three main goals:

- To increase the use of primary PCI towards 70% or more among STEMI patients.
- To achieve primary PCI rates over 600 per million inhabitants per year in most European countries. Currently, in some countries we have more and in some countries we have less, but the average is around 300 or 400.
- To empower PCI centres to offer 24 hour, 7 day a week services for primary PCI, which is not evident in many countries. This is the main point of the initiative.

At whom are you aiming the initiative?

This is very important. Of course, our target is the cardiology community, but we also target the noncardiology medical community (i.e. general practitioners), the general public, the political authorities and the healthcare payors as well.

What other activities have you planned in 2009 and 2010?

As already mentioned, we sent the first call for action during the EuroPCR meeting. The next important event will take place during the ESC meeting in Barcelona in August. The representatives of the six Stent for Life pilot countries are invited to sign a declaration that will officialise the start and implementation of the programme in their countries.

> " It was interesting to see that when primary PCI was the 'dominant' treatment compared with thrombolysis, the results were better „

For how long will you run the programme in these pilot countries?

In the first six pilot countries we want to identify what are the real problems. For example, in some countries, the problem is not to drive the patient to the hospital in the very early phase because they have an excellent national emergency ambulance system, but, in other countries, that could be a problem. So, we must first identify the main issues in countries with a low or moderate rate of primary PCI: is it a problem with the population who are not aware of the severity of the disease, is it the ambulance system, is it the hospital system that does not have 'around the clock' facilities, is it an issue related to reimbursement? Once we have identified the problem, we will try to implement an action plan corresponding to the needs of those countries. I think this will take at least a couple of years.

How important will your relationship with the ESC be, and will you be partnering with any other cardiology societies or groups?

The EAPCI is a new association which is a registered branch of the ESC that was launched 3 years ago thanks to the joint venture between EuroPCR and the interventional cardiology working group (WG 10) of the ESC. William Wijns is the first president of the EAPCI, by September 2009 Carlo DiMario (London, UK) will be the

next one and I am the president-elect. The relationship between EAPCI and ESC is of course very important and I hope that we will work very closely with the Stent for Life initiative and the whole of the ESC.

What is important and unique with this initiative is that several organisations are participating: the EAPCI, the ESC Working Group on acute cardiac care,

> " Stent for Life is truly a pan-European initiative „

EuroPCR, EUCOMED and all the National Cardioloogy societies and Working Groups for Interventional Cardiology... truly, it is a pan-European initiative.

If the pilot studies work well, are you planning to roll-out this project globally at some point in the future?

We have currently identified six pilot countries and if the initiative is successful in those countries, we will of course extend the initiative to other countries.

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(Continued from page 14)

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Highlights from EuroPCR 2009

Barcelona, Spain, 18–22 May 2009

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EuroPCR 2009, the official annual meeting of the EAPCI, took place in Barcelona, Spain from 18–22 May, and provided over 10,000 attendees with an exciting programme covering the entire field of CV interventions. Through a variety of sessions (e.g. plenaries, late-breaking clinical trials, symposia and workshops), participants were able to gain insight to the latest CV news, discuss hot topics with opinion leaders and really understand how to implement these latest clinical advances into their own daily practice. In addition, there were a number of 'live in-a-box' sessions, which combined live cases with the most up-to-date data. This report highlights some of the key sessions from the meeting.

'Do it for the patient'

The clear message at EuroPCR 2009 was 'Do it for the patient', focussing on an interdisciplinary approach to the patient with the common objective of 'what is the best treatment for an individual patient?'. The implementation of a 'heart team' (cardiologists, surgeons, anaesthetists, nurses and technicians) working closely together in the process of clinical decision making was strongly advocated, despite the understanding that putting this principle into practice is challenging.

'Stent for Life'

Another novel important initiative presented was 'Stent for Life'. W Wijns (Belgium) highlighted that even in the face of strong scientific evidence for urgent revascularisation as a life-saving procedure for patients with acute CAD, there is a substantial underuse of it, with up to 85% of patients not receiving any kind of reperfusion therapy in certain EU countries. In light of this, the aim of this new initiative is "to improve the delivery and patient access to the life-saving indications of PCI and thereby reduce mortality and morbidity of patients suffering from ACS".

TAVI

It is agreed that transcatheter aortic valve implantation (TAVI) is an effective and acceptable alternative to conventional surgery for patients at high surgical risk. However, broadening the indication and accepting low-risk patients at that stage is still strongly discouraged. Furthermore, it was made clear that the patient's wish to refuse surgery is not an acceptable indication for TAVI.

There is an understanding that the currently available risk scores have shortcomings since they have never been designed for this particular cohort of patients. Despite this, using risk scores to evaluate the individual risk (i.e. the Euroscore or STS score) is considered mandatory. M Thomas (UK) stressed that optimal patient selection for TAVI also requires exact assessment of the aortic anatomy, valvular morphology and the vascular access site by imaging techniques. Similarly, M Leon (USA) highlighted the importance that the decision for TAVI and procedure management should always be made by a multidisciplinary heart team, and TAVI should only be performed in patients with whom a consensus between cardiologist, cardiac surgeon and anaesthesiologist can be reached.

The latest results from TAVI registries were also reported. V Schächinger (Germany) presented 1-year follow-up data from the PARTNER EU registry. In this nonrandomised registry, 130 patients were included (61 patients after transfemoral and 69 patients after transapical AVI with the SAPIEN valve [Edwards Lifesciences]). In both groups, comparably good long-term functional outcomes could be obtained with an overall 1-year survival rate of 62%.

L Buellesfeld (Germany) presented data on the 12-month safety and performance of TAVI using the 18 F CoreValve revalving prosthesis (Medtronic, Inc). In this analysis 112 patients were included. The mean age of the patients was almost 82 years and the mean logistic Euroscore was 23%. Technical success rate was 86.5% with an excellent acute, maintained haemodynamic and functional performance. All-cause mortality after 30 days and after 12 months was 15.2% and 28.6%, respectively, and thus lower than estimated.

M Thomas also presented the 30-day results of the SOURCE Registry – a European registry of TAVI using the SAPIEN valve. TAVI was performed via transfemoral (TF) access in 463 patients and via transapical (TA) access in 575 patients. However, results showed the TA group suffered from more comorbidities and a higher Euroscore. Overall technical success rate was 94% and mortality rate at 30 days was 8.5% (6.3% for the TF group and 10.3% for the TA group). Importantly, it was found in the registry that major vascular complications were not associated with an increased mortality.

The 'Great Debate' – treating the elderly

This session was chaired by J Fajadet (France). Even though no clear definition exists, an age of 75 years is a mostly accepted threshold among cardiologists and surgeons. Fundamental goals for the treatment of this particular patient cohort were depicted as prolonged survival, improved QOL and cost effectiveness of the treatment. It was emphasised that the best results, considering clinical outcome and cost effectiveness, can be obtained by a collaborative multidisciplinary team approach to the patient. However, post-procedural follow-up of the patients, which includes both rehabilitation and the family, is essential.

Glimpse into the future

As described by A Kappetein (The Netherlands), the SYNTAX score aims to characterise coronary anatomy and to predict outcome after PCI. While the score incorporates several previously described angiographic scores and has been validated in the SYNTAX trial (allowing good prediction of MACCE) it does not account for comorbidities.

A Colombo (Italy) presented 12-month follow-up data from the SYNTAX trial which compared surgery with interventional treatment in patients with three-vessel disease and focused on different subgroup analyses. Results showed that PCI works well for patients with low SYNTAX scores but CABG was superior in patients with high scores. No gender- or age-dependent differences in the overall outcome could be observed. However, in the elderly, the lower stroke rate seems to favour PCI.

N Pijls (The Netherlands) discussed the results of the FAME study in the context of the SYNTAX data. In FAME, patients with multivessel disease underwent fractional flow reserve (FFR)-guided interventional treatment. It was pointed out that in the FFR-guided group fewer stents per patient, procedural time was identical to non-FFR-guided group, costs for material were lower and the composite endpoint of death, MI, CABG or repeat PCI was significantly lower (13.2% vs. 18.4%; p=0.02). Therefore, these data represent the paradigm for functional revascularisation, stenting of ischemic lesions and medical treatment of nonischemic lesions.

Finally, P Serruys (The Netherlands) and F Mohr (Germany) considered the results of the SYNTAX trial and registry, and highlighted that 66% of the patients are best treated with CABG; however, for the remainder, PCI is an excellent alternative.

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