**Oration***

# First-in-man interventions in interventional cardiology

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## Introduction

Catheter-based cardiac interventions were developed to save lives and improve the quality of life for cardiovascular patients. Although the history of current cardiac interventions dates to the 1980s and '90s, a series of crucial steps from the 1920s onward made a successful cardiac intervention a reality. These advances were brought about by the creativity and determination of physicians and scientists who often had to persist against mainstream medical thinking before their ideas were ultimately embraced by the profession.

Interventional cardiology addresses cardiovascular problems through catheter-based procedures. A thin, flexible catheter is inserted into a patient's blood vessel and advanced to the heart along the blood vessel under fluoroscopic guidance. A range of cardiac procedures can be performed and devices can be delivered to correct cardiac defects through these catheters without an open-heart surgery. As a result, the morbidity of the procedure is limited and the patients have prompt recovery from the procedure with greatly reduced hospital stay.

Angioplasty and stenting and other catheter-based procedures were developed and continue to be refined by physicians seeking innovative solutions to problems encountered when treating cardiovascular patients.

A first-in-man intervention is an intervention or a medical procedure, previously developed and assessed through in vitro or animal testing, or through mathematical modeling, is used on human subjects for the first time.

## A brief history of catheter-based cardiac interventions

The foundation stone of the current interventional cardiology was laid in 1929 when it was proven that a catheter could be safely advanced

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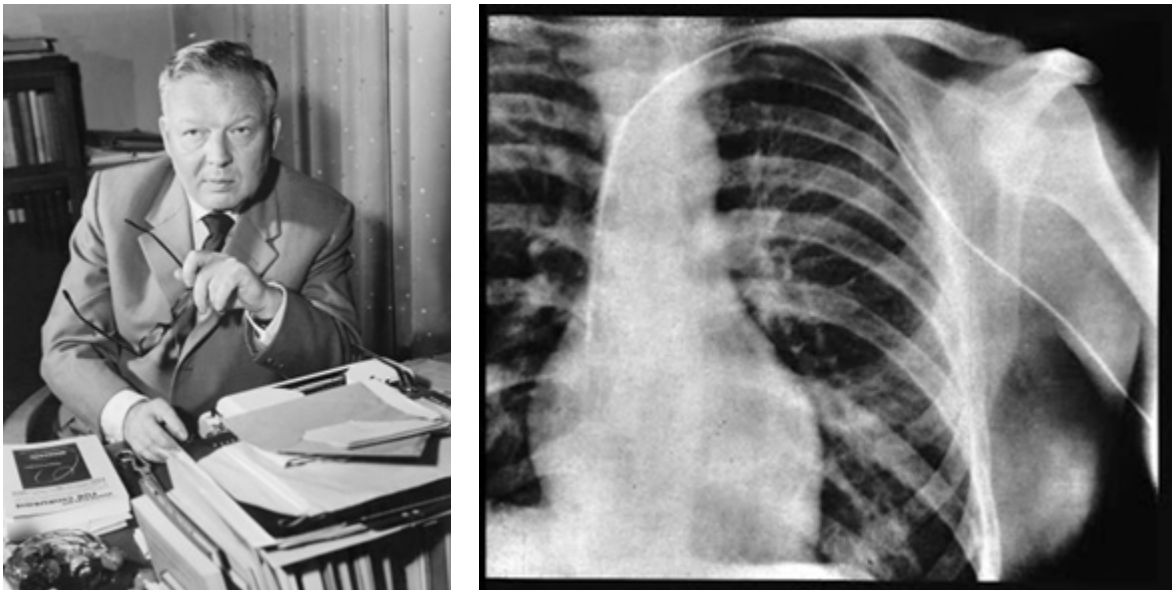
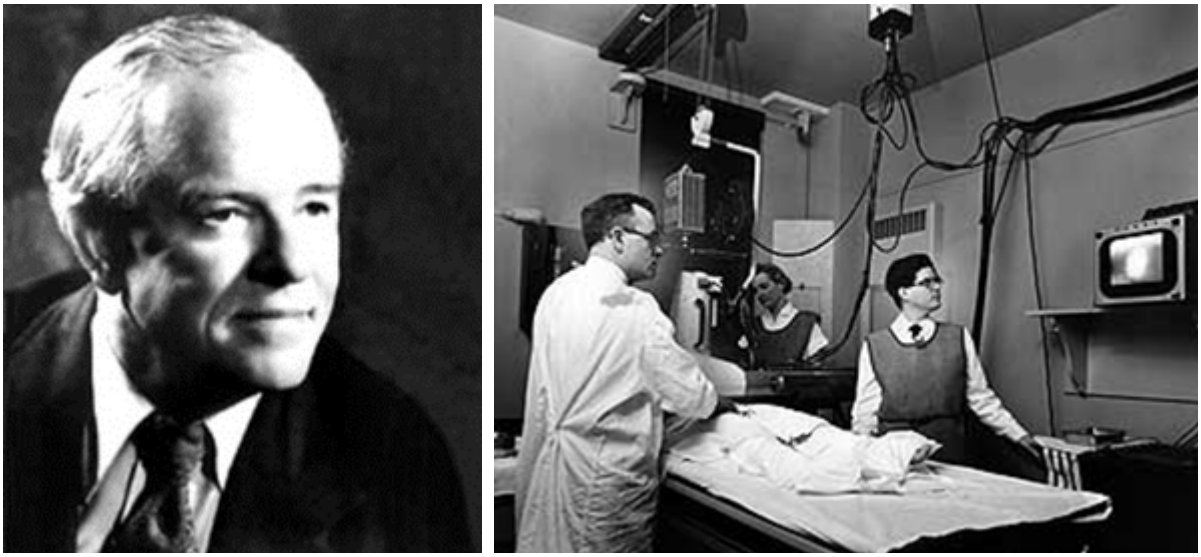
into a *living* human heart. This discovery was made by Dr. Werner Forssmann, a German doctor who inserted a catheter into his own heart and proved it with X-ray images. Dr. Forssman's accomplishment was dismissed by medical professionals as reckless, but when the significance of his work was realized, he was later awarded the Nobel Prize in 1956.



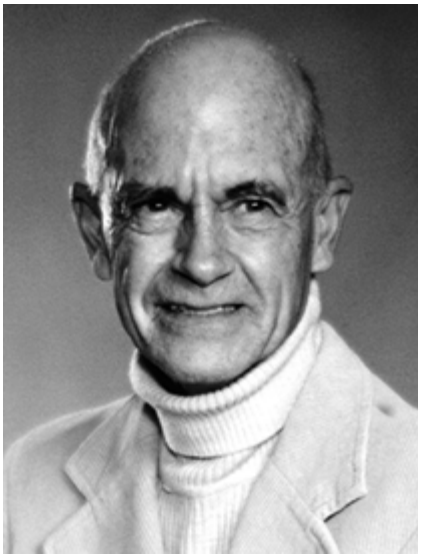
**Left: Dr. Warner Forssmann. Right: Dr Forssmann's first confirmation radiograph of inserting a catheter into his own heart**

Another significant breakthrough in interventional cardiology was the accidental discovery of cardiac angiography. This discovery was made by Dr. F. Mason Sones at the Cleveland Clinic in 1958 when a catheter slid and entered a chamber of the patient's heart while performing a cardiac procedure. Contrast media was safely injected into the chamber.[1] Until this time; it was thought that contrast media could not be safely injected into the heart.



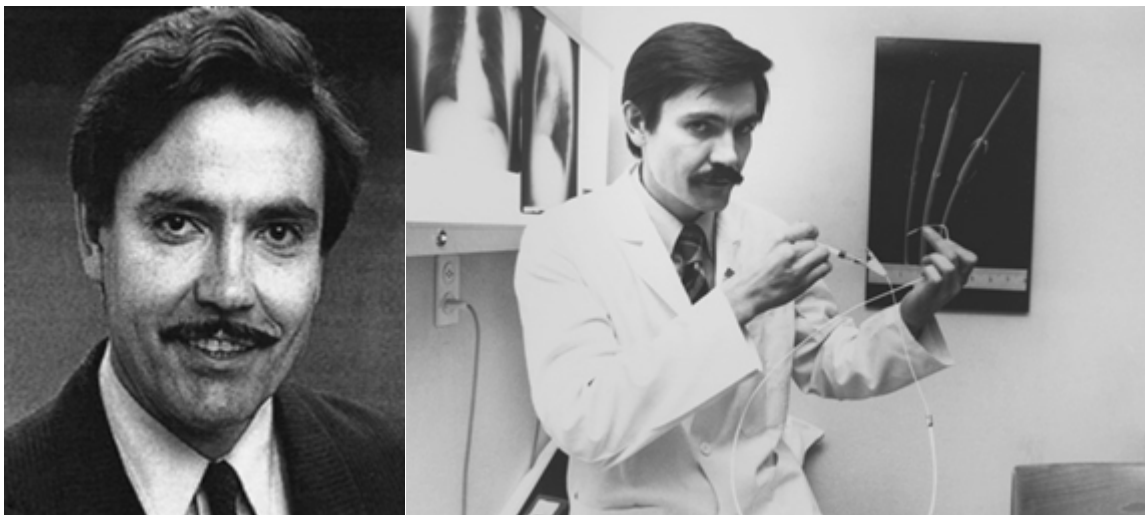
**Left: Dr. Mason Sones. Right: Dr. Sones performing coronary angiography at Cleveland Clinic**

In 1964, Dr. Charles Dotter in Portland, Oregon, pioneered the use of catheters to reopen blockages in the peripheral arteries. He advanced progressively wider catheters in the blood vessel and through the blockage. While this technique was dismissed by the larger medical community in the United States, doctors in Europe continued to develop an interest in the gains made by Dr. Dotter.

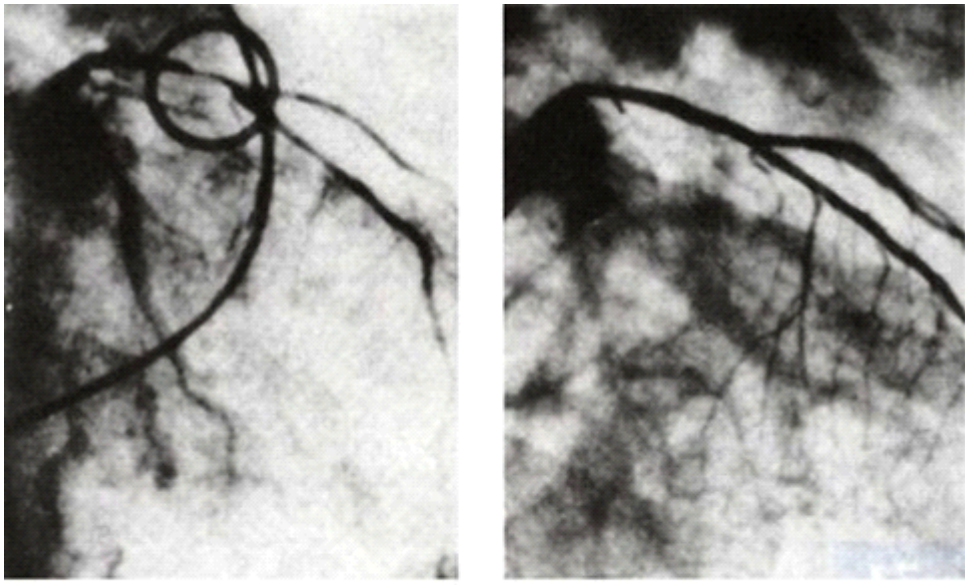


**Dr. Charles Dotter**

The major breakthrough of interventional cardiology was made when Dr. Andreas Gruentzig, in Zurich, Switzerland, in the mid-1970s, learned methods first introduced by Dr. Charles Dotter a decade earlier. Dr. Gruentzig built upon this advance by adding a balloon to a catheter and using it in the coronary arteries to treat heart disease. Because no appropriate medical device existed, Dr. Gruentzig began carefully crafting balloon catheters at home in his kitchen. His early research testing the procedure on animals was not broadly accepted at first in the cardiology field. However, his accomplishments were finally recognized after he performed a successful balloon angioplasty on a human patient in 1977.[2] A new era of interventional cardiology began after this first successful percutaneous coronary intervention.



**Left: Dr. Andrea Gruentzig. Right: Dr. Gruentzig demonstrates his technique**




**Angiographic pictures of First-In-Man percutaneous balloon coronary angioplasty procedure: Before and 10 years after the procedure**

There were a couple of common complications in early angioplasty procedures: the artery would sometimes collapse at the blockage site after a balloon catheter had cleared the blockage, or in about a third of patients the artery would become blocked again by the growth of scar tissue, a process called restenosis. A search for innovative solutions within the field of interventional cardiology led to the development of the metal coronary *stent* which, was inserted along with a catheter to fit inside an artery to prop it open and prevent it from collapsing.

The first stent was approved for use in the United States by the Food and Drug Administration (FDA) in 1994. These bare metal stents (BMS) were highly effective at preventing an artery from collapsing after angioplasty. However, these stents were only slightly effective in inhibiting the growth of scar tissue causing restenosis of inside the stent. The answer came in the form of drug-eluting stents (DES), which dramatically reduce the risk of restenosis. These stents, which were approved by the FDA in 2003, are coated with a drug to inhibit the growth of scar tissue.

In addition to coronary interventions, percutaneous balloon valvuloplasty for stenosis of heart valves, closure of intracardiac shunts using closure devices, and catheter-based delivery of alcohol for interventricular septal ablation in patients with hypertrophic obstructive cardiomyopathy developed alongside with the technical advancement of percutaneous coronary interventions. In 1982, Kanji Inoue, a Japanese cardiac surgeon, first developed the idea that a degenerated mitral valve could be inflated using a balloon made of strong yet pliant natural rubber.[3] The first transcatheter device closure of an atrial septal defect was performed in 1976 by Mills and King at Ochsner Medical Institutions.[4] However, percutaneous closure of intracardiac shunts including closing atrial septal defects, ventricular septal defects, patent foramen ovale and anomalous coronary fistulae became widely practiced after the invention of Amplazter closure devices. Alcohol septal ablation was first performed in Britain at the Royal Brompton Hospital by Ulrich Sigwart in 1994.[5] Since that time, it has quickly gained favor among physicians and patients alike due to its minimally-invasive nature, avoiding general anesthesia, lengthy recuperation and other complications associated with open heart surgery for septal myectomy.

## Recent first-in-man interventions to help advancement of new catheter-based cardiac procedures

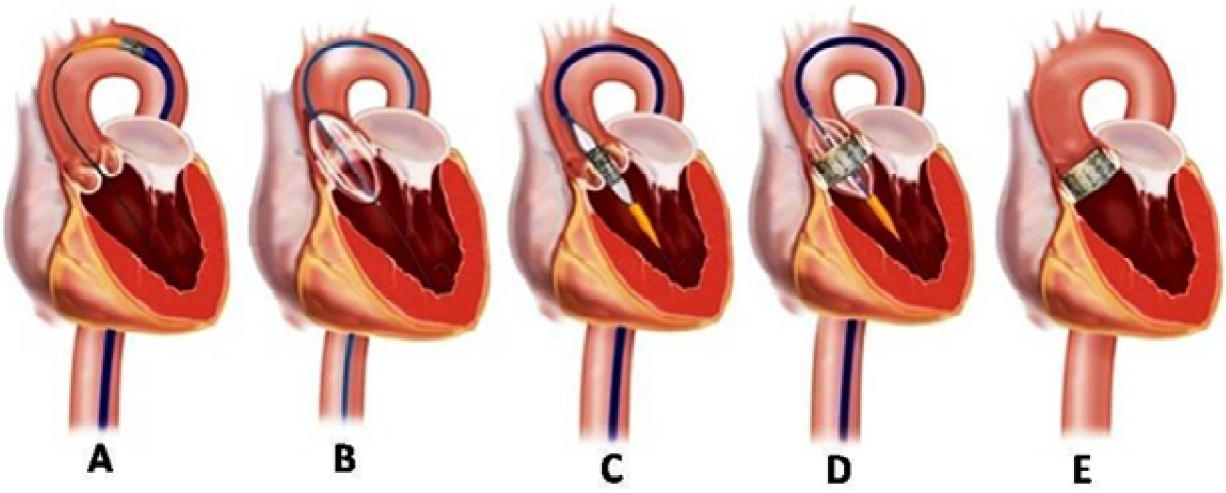
### 1. Trans catheter aortic valve replacement

For patients with symptomatic critical aortic stenosis, aortic valve replacement improves survival. However, the risks of open-heart surgery have prompted investigation of alternative therapies, including balloon aortic valvuloplasty and transcatheter aortic valve replacement.

The risk of aortic valve replacement increases with age and other co-morbidities, including emergency and prior cardiac surgery, lung and renal disease, small body surface area, history of stroke, atrial fibrillation, heart failure, and the need for associated coronary revascularization.[6] Some patients may be truly inoperable or denied surgery because of the presence of a porcelain aorta, prior radiation, cirrhosis, generalized frailty, or physician or patient preference.[7] A nonsurgical alternative for these patients was needed.

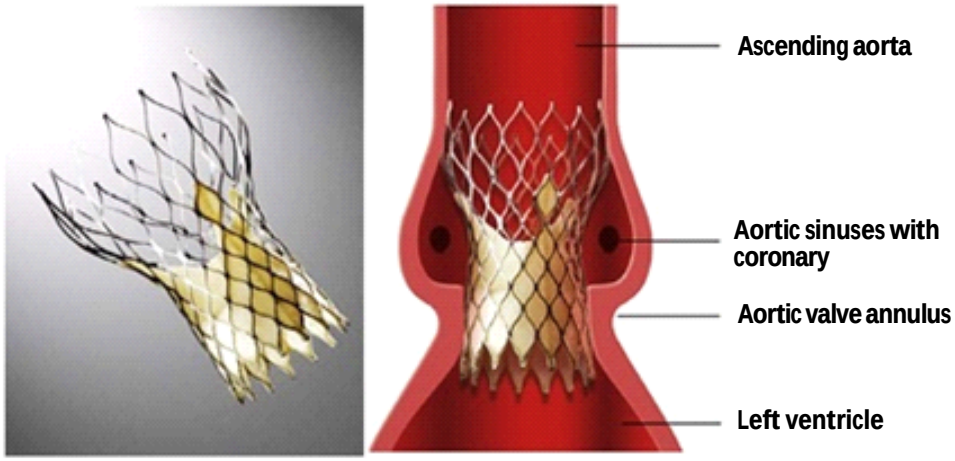
In the past, high-risk, and inoperable patients were offered balloon aortic valvuloplasty. This procedure remains an important palliative option but does not alter the natural history of aortic stenosis nor provide an improvement in survival.[8] The current era of transcatheter aortic valve replacement built on this procedure and began with the first demonstration of feasibility in 2002 by Prof Alan Cribrier.[9] He advanced the aortic valve along the femoral artery to the right atrium and then through the inter-atrial septum and mitral valve to the aortic valve position (anterograde approach). The first aortic valve implantation via femoral artery (retrograde approach) was done in 2005 by Dr David Paniagua.[10] However, the transcatheter aortic valve replacement by retrograde approach was pioneered and popularized by Dr. John Webb in Vancouver, Canada.

The transcatheter aortic valve replacement using a retrograde flex catheter system to implant an Edwards balloon-expandable percutaneous heart valve became popular since 2007. The procedure was more challenging initially, with the available large caliber delivery systems and earlier valves but the companies soon developed smaller caliber, more user-friendly delivery systems. The operator's skills and experiences were also improved along with the improvement of technology.[11] The long-term outcome appeared favorable even among the patients who were declined for aortic valve replacement surgery due to advanced age and multiple co-morbidities.[12] These outcomes were assessed by guidelines which, were developed to evaluate efficacy and safety outcomes of balloon-expandable transcatheter aortic valve replacement (Valve Academic Research Consortium (VARC) guidelines.[13] Various other imaging modalities including multi-slice CT were also developed to study the anatomy of the aorta and stenosed valve and also to find optimal implantation angles.[14]

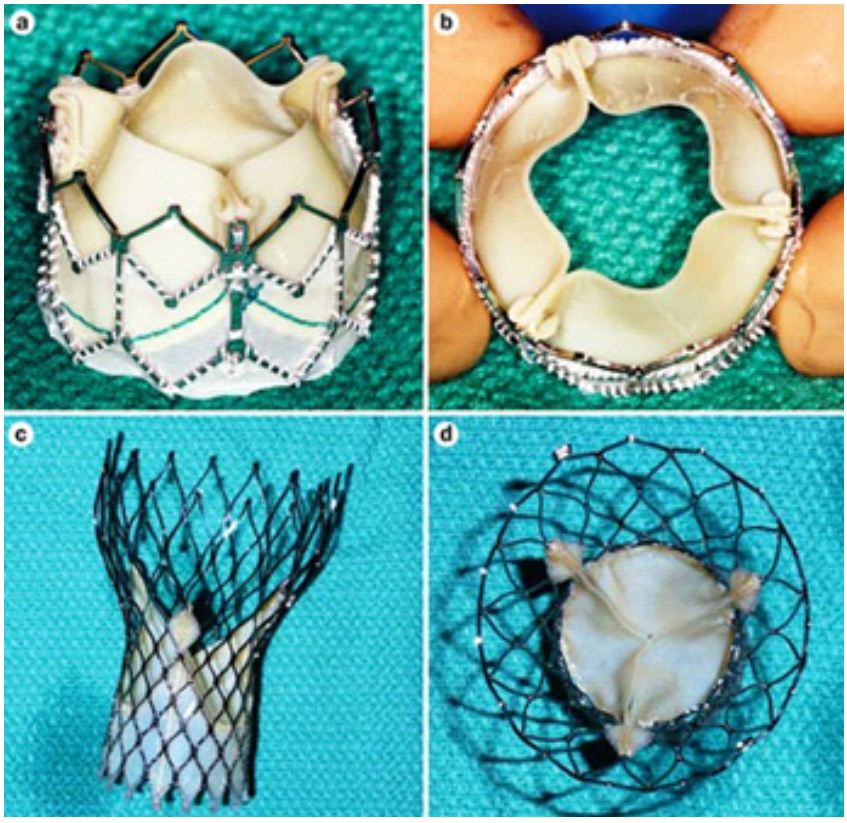



**Retrograde transcatheter aortic valve replacement technique; A – Crossing the stenosed aortic valve with a guide wire; B – Balloon aortic valvuloplasty; C – Positioning of the balloon-expandable heart valve; D – Deployment of the valve; E – Post valve replacement**

A self-expanding aortic valve prosthesis intended for retrograde delivery across the aortic valve has been developed (Core Valve, Paris, France). The stent design may simplify the implantation procedure, reduce paravalvular leaks, and facilitate the treatment of aortic insufficiency and stenosis. After evaluation in animal models, this device was subsequently successfully implanted in a human being,[15] and its use has been expanded across Europe and many other countries in the world. Favorable efficacy and safety outcomes have been reported when this valve was implanted in high-risk patients who had been declined for surgery due to their co-morbidities.[16]




**Left: Medtronic CoreValve. Right: CoreValve positioned at the aortic valve.**



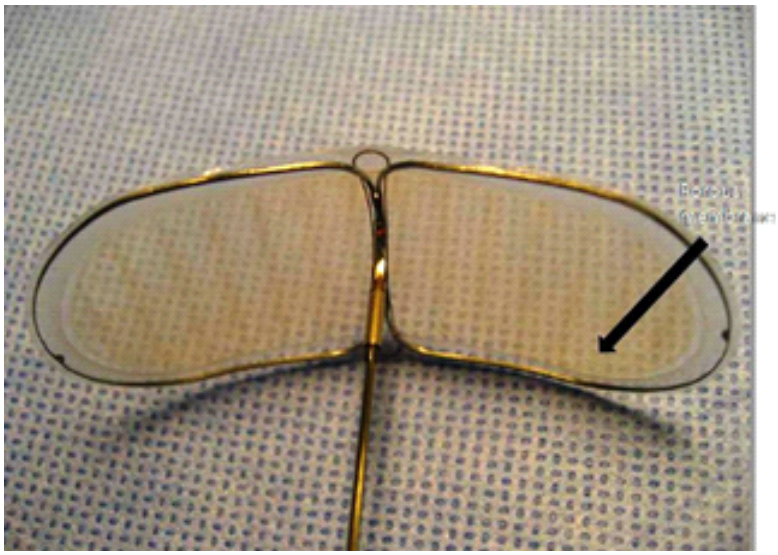

**Percutaneous heart valves: A – Edwards Sapien valve; B – Edwards Sapien valve with open leaflets; C – Medtronic CoreValve; D – Medtronic Core Valve with closed leaflets**

## 2. Embolic protection during cardiac interventions

Transcatheter aortic valve replacement is associated with a risk of cerebral embolism and stroke. Atheroembolism may occur because of the traumatic passage of wires and catheters around an atheromatous aortic arch. Calcific embolism may occur when the endothelial covering of a degenerated aortic valve is disrupted. Thromboembolism may occur during any interventional procedure. Transcatheter aortic valve replacement has been associated with a stroke rate of 1.9-4.2%. [17,18]

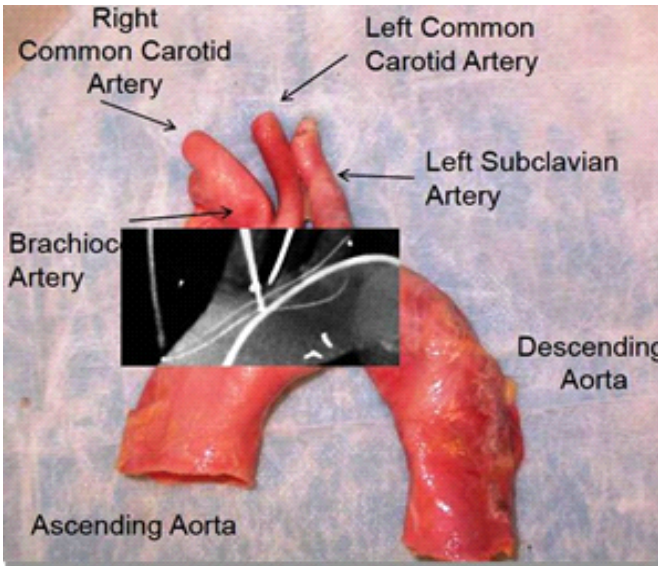
Clinical stroke may represent one end of the spectrum of cerebral embolism. Recent studies suggest that subclinical cerebral embolic events are common.[19] Crania magnetic resonance imaging has demonstrated new cerebral lesions in 22% of elderly high-risk patients undergoing diagnostic catheterization with crossing of the aortic valve[19] and recent studies found that 73-84% of patients undergoing transcatheter aortic valve replacement had new cerebral lesions on cranial magnetic resonance imaging.[20] The clinical importance of asymptomatic new magnetic resonance imaging lesions is unknown, but remains a concern.[21]

The first-in-man use of the Embrella Embolic Deflector™ device showed a significant reduction in the subclinical cerebral emboli during the transcatheter aortic valve replacement procedure.[22] Also, the use of this device was safe and required only minimal additional time.

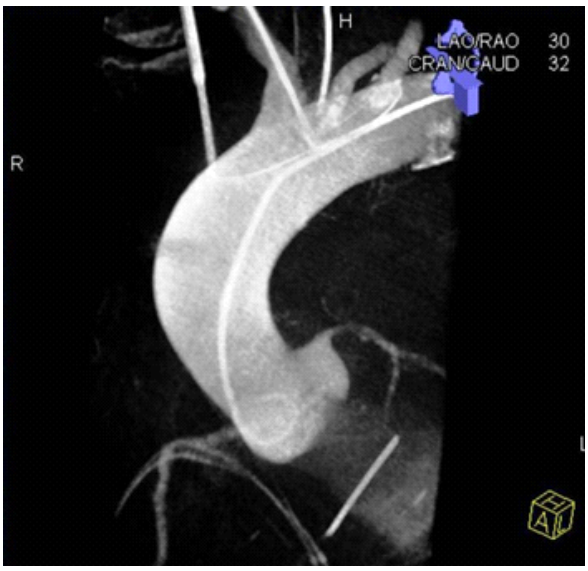


**Embrella Embolic Deflector™ device**

The Embrella device has several advantages. It can be introduced easily from the radial artery with minimal interference with the course of the TAVR procedure. A single device provides protection for the right carotid and right vertebral branches of the brachiocephalic artery and the left carotid artery. In some patients, the device may also overlie the left subclavian ostium, providing protection for the left vertebral. As the device is not positioned within the cerebral vessels, the risk of arterial spasm, injury, thrombosis, or transiently impaired cerebral perfusion appears minimal.




**Embrella device positioned in transverse aorta**

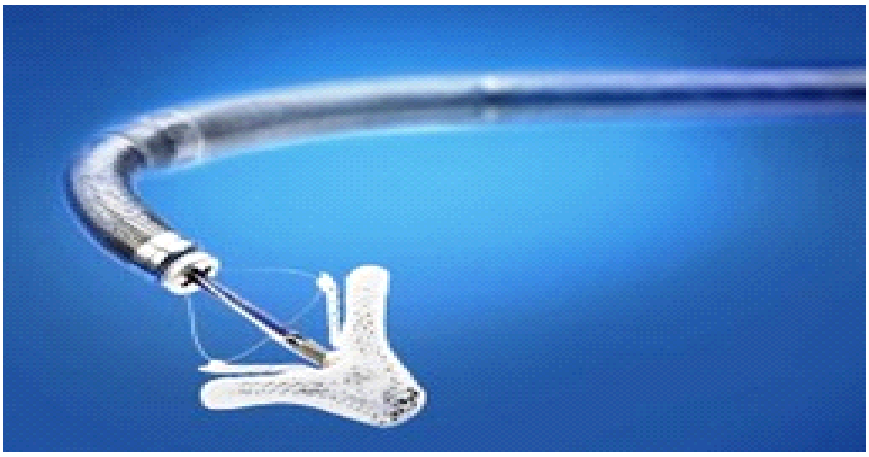



**Performing a TAVR while an Embrella device in place**

## 3. Mitral valve leaflet technology to treat mitral regurgitation

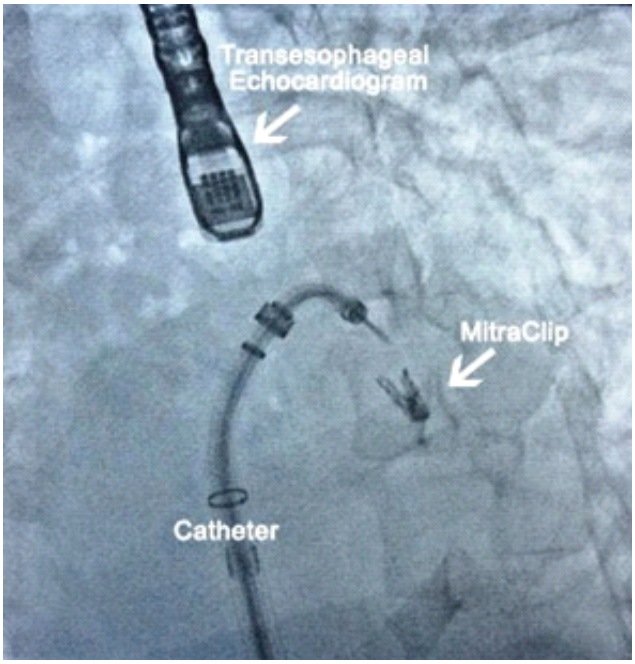
The standard method of treating severe mitral regurgitation is mitral valve repair or replacement through an open-heart surgery. Two percutaneous leaflet repair procedures have been evaluated to date. The Mobius device (Edwards Lifesciences, Irvine,) used a transeptal suction catheter to grasp the mitral leaflets and deploy percutaneous sutures. Although animal and human trials demonstrated feasibility, the procedure was complex and is not currently being pursued.[23]

The Mitraclip device has proven relatively safe and often effective. Using a multiaxial transeptal catheter system, a metallic clip is used to grasp and approximate the free edges of the 2 leaflets. Transesophageal echocardiographic guidance is used to position the implant and assess the effect. If not satisfactory, the clip can be removed or repositioned or an additional clip can be implanted.[24]



**Mitraclip device: The most popular device used for percutaneous mitral valve repair at present**

In EVEREST II trial, patients with moderately severe or severe mitral regurgitation were included in a randomized fashion for either percutaneous repair or conventional surgery for repair or replacement of the mitral valve respectively. The efficacy and safety end points of the two procedures were compared. The primary composite end point for efficacy was freedom from death, from surgery for mitral-valve dysfunction, and from moderately severe or severe mitral regurgitation at 12 months. The primary safety end-point was a composite of major adverse events within 30 days. Although percutaneous repair was less effective at reducing mitral regurgitation than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes.[25]




**Percutaneous mitral valve repair procedure**

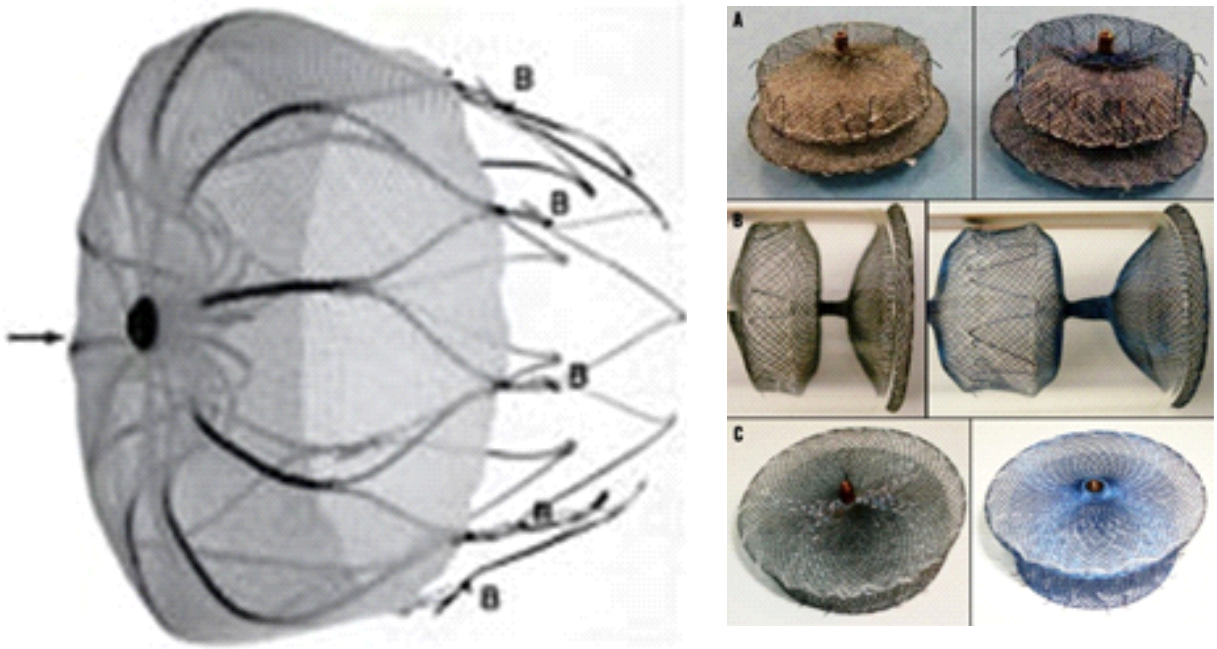
## 4. Left atrial appendage occlusion

Left atrial appendage occlusion is a treatment strategy to prevent thromboembolism in atrial fibrillation. The thrombus formation is in the left atrial appendage in 90% of the cases.[26]

Left atrial appendage occlusion can be used as an alternative for patients who cannot use oral anticoagulants, although it has been studied and approval is sought as an alternative in patients who are eligible for oral anticoagulants. Some patients cannot take anticoagulants because of a recent or previous bleeding, non-compliance, or pregnancy.

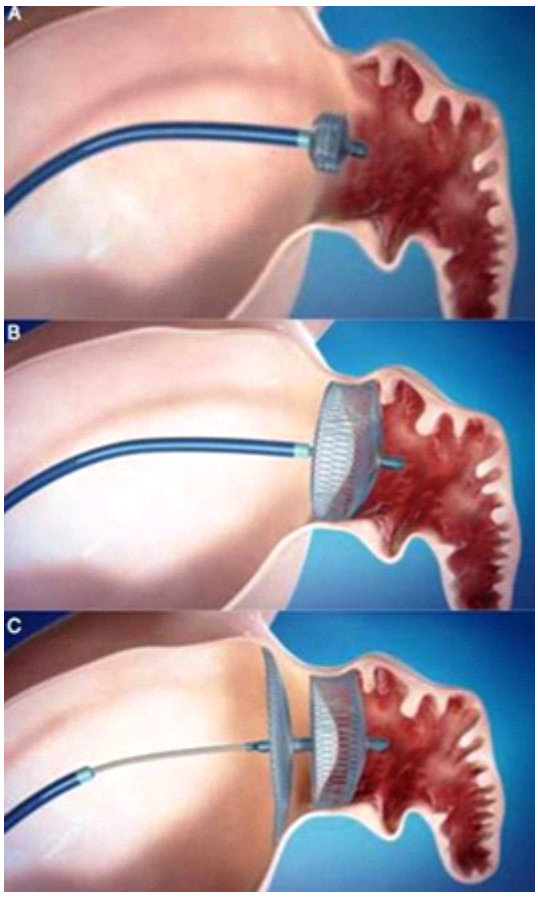
In 2009 the U.S. Food and Drug Administration Advisory panel approved the WATCHMAN left atrial appendage closure device for use in patients with non-valvular atrial fibrillation in centers with heart surgery backup. This decision was based on the results of the PROTECT-AF trial[27] which, showed less hemorrhagic stroke with the device compared to treatment with warfarin and the stroke and all-cause mortality outcomes were non-inferior.

Another device termed PLAATO (Percutaneous Left atrial Appendage Transcatheter Occlusion) was the first left atrial appendage occlusion device. In 210 patients receiving the PLAATO device, there was an estimated 61% reduction in the calculated stroke risk.[28]



**Left: Watchman left atrial appendage occluder. Right: Amplazter cardio plug device for left atrial appendage occlusion**

Both left atrial appendage occlusion systems are introduced into the right atrium and are then passed into the left atrium through a patent foramen ovale or through a puncture hole. These small iatrogenic atrial septal defects usually disappear within six months. Although these are catheter-based techniques, they are generally performed under general anaesthesia.



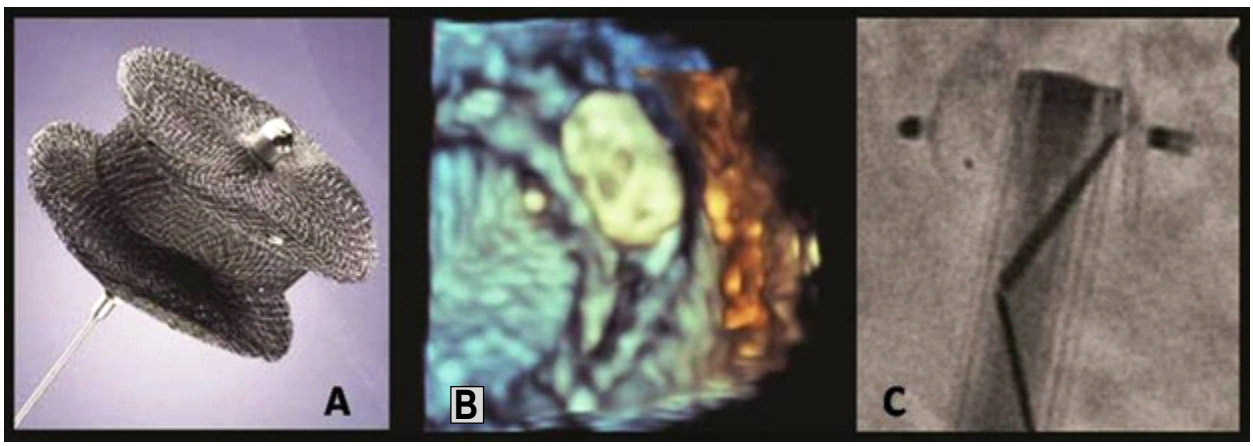

**A. Exposure of the anchoring lobe in the left atrial appendage landing zone**

**B. Confirmation of stability and location of the lobe implantation after complete exposure of the lobe**

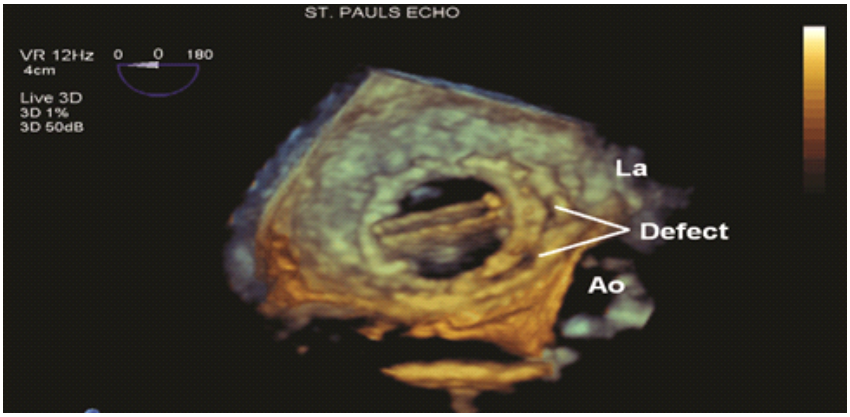
**C. Exposure of the atrial disc occluding the orifice of the atrial appendage**

## 5. Trans catheter closure of para-valvular leaks

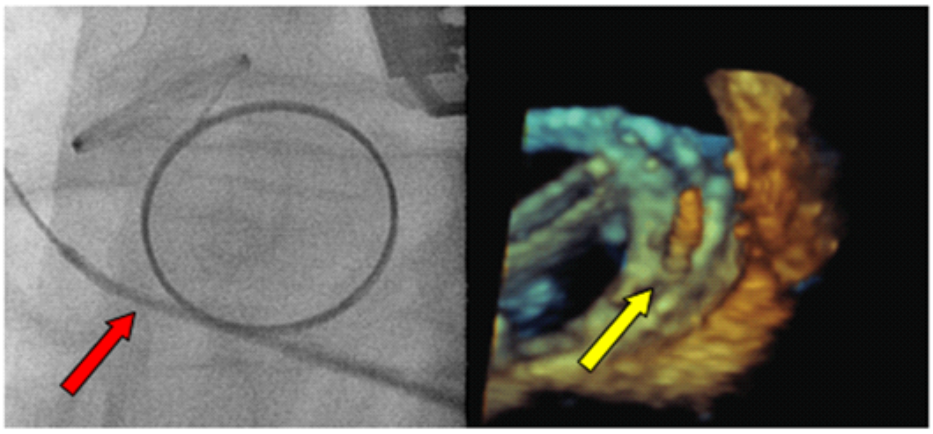
Para-valvular regurgitation (PVR) after surgical valve replacement may occur when there is an incomplete seal between a prosthetic valve and the surrounding cardiac tissue. Typically, this is associated with the dehiscence of sewing ring sutures, often precipitated by infection, annular calcification, or technical factors. Re-operation for a para-valvular leak is associated with an increased likelihood of a recurrent leak, morbidity, and mortality. Transcatheter closure of para-valvular leaks has been hampered by technical challenges, the limitations of available imaging modalities and the lack of closure devices specifically designed for this purpose. The initial experience with para-valvular leak closure using a device specifically designed for this purpose has been described.[29] In patients with mitral para-valvular leak a transapical approach and real-time 3D transesophageal echocardiography have been used, whereas in patients with aortic para-valvular leak, a retrograde approach with 3D transesophageal echocardiography guidance have been used.



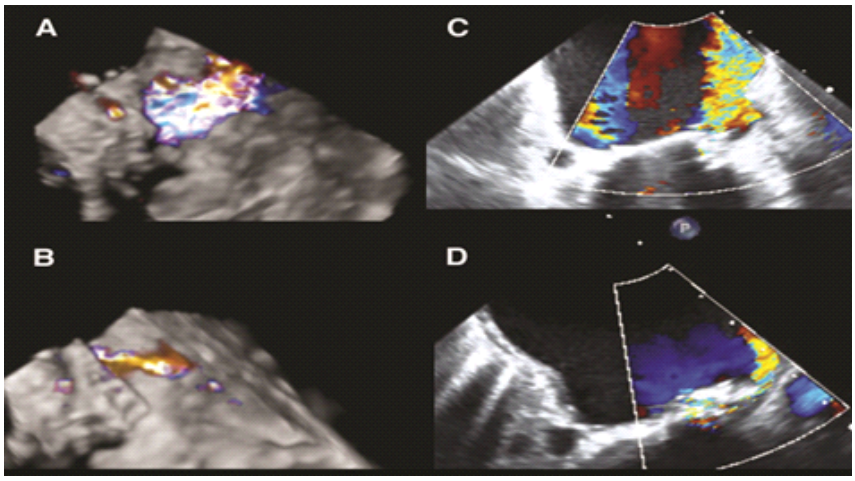

**The new purpose specific device for para-valvular leak closure. The Amplatzer Vascular Plug III with the extended proximal and distal rims for optimal fixation in an area with high flow. (A) ex vivo; B. 3-D transesophageal cardiography guidance image; C. fluoroscopic image**




**Localization of the para-valvular leaks with 3D-transesophageal echocardiography guidance. Real-time live 3D-transesophageal echocardiography guidance image of the mitral annulus and mechanical prosthesis en-face from the left atrium in diastole. The para-valvular defect is located along the anterolateral border of the prosthesis ring, La - left atrial appendage, Ao - aorta**



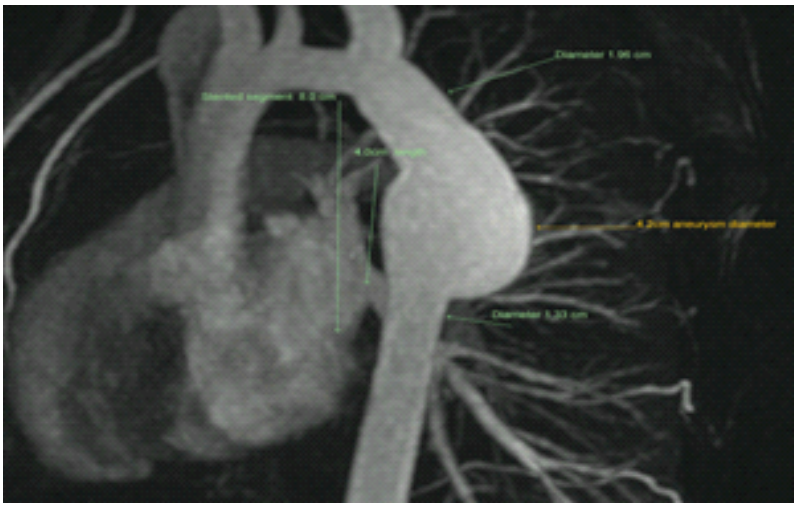
**Procedural guidance using fluoroscopy and 3D-transesophageal echocardiography guidance. Left: fluoroscopic image of a posterior leak wired (red arrow); Right: real-time live 3D-transesophageal echocardiography guidance of the mitral annulus and mechanical prosthesis en-face from the left atrium in diastole. The catheter (yellow arrow) can be seen through the para-valvular defect located along the border of the mitral prosthesis ring**




**Significant reduction of mitral regurgitation. Improvement of mitral regurgitation from severe (A and C) to trivial degree (B and D) on 3D-transesophageal echocardiography guidance (A and B) and 2D-transesophageal echocardiography guidance (C and D)**

## 6. Custom-made endovascular stent grafts for treatment of aneurysms after coarctation repair

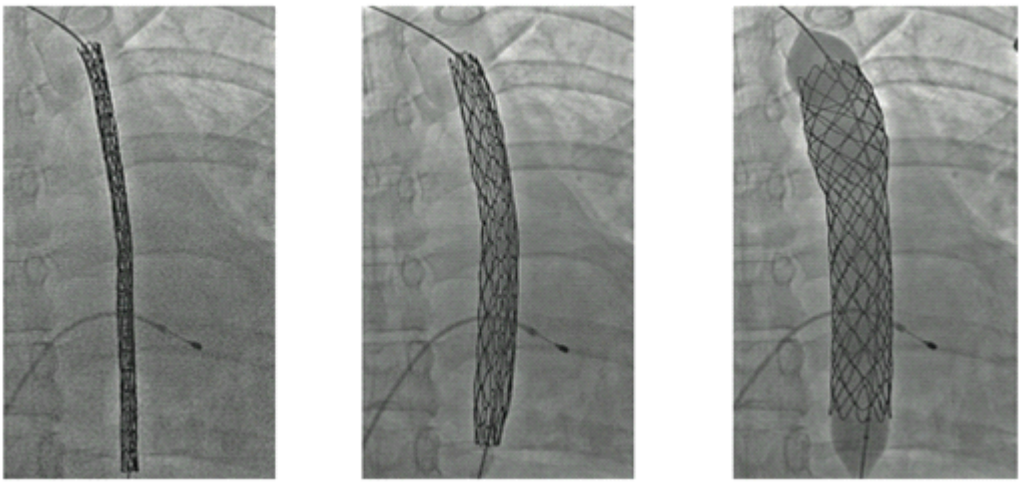
Aneurysm formation is known to occur in about 5-30% of patients late after surgical repair for coarctation.[30] Small (<5 cm), asymptomatic aneurysms without the tendency to rapidly enlarge can be treated conservatively.[30] This is reflected by the low overall mortality risk from a ruptured aortic aneurysm.[30] However, as the aneurysm increases in size, the risk of rupture increases. In some long-term follow-up studies, conservative (medical) therapy for aneurysms carried a very high mortality.[31] In patients who develop aneurysm after coarctation repair, treatment is justified for either symptom relief (chest pain, haemoptysis in case of erosion into the lung) or to improve survival (in aneurysms >5 cm diameter or fast-growing aneurysms).



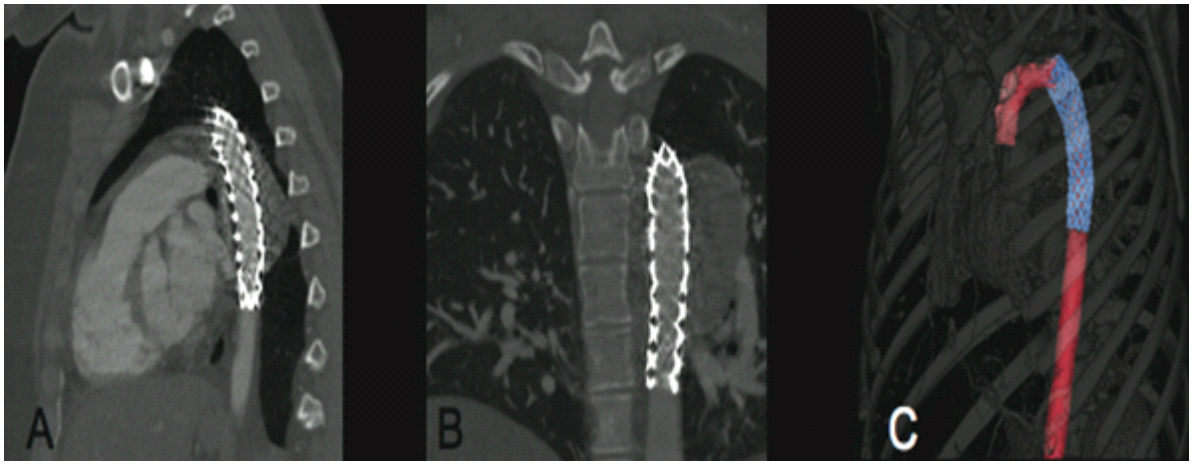
**Aortic aneurysm at the site of a previous coarctation repair**

Reoperation with resection of the aneurysm is considered standard treatment. However, this is associated with significant mortality (as high as 30%) and morbidity including paraplegia in 4-14%, bleeding, stroke cardiac events, and renal failure.[32]

Endovascular stenting is a promising alternative to surgery with good procedural and midterm outcomes. However, because coarctation often involves hypoplasia of the aortic arch, marked changes in the diameter of the aorta proximal and distal to the coarctation site are not uncommon and can present a challenge to ensure good stent apposition when the goal is to exclude an aneurysm. The first-in-man use of a custom-designed endovascular stent graft and delivery system has been developed for the treatment of an aneurysm following surgical coarctation repair, which enabled effective management of the marked change in aortic diameter between the proximal and distal limits of the aneurysm.[33]



**Deployment of the stent graft. Left – Positioning of the stent. Middle – Inflation of the inner balloon. Right – Inflation of the outer balloon**

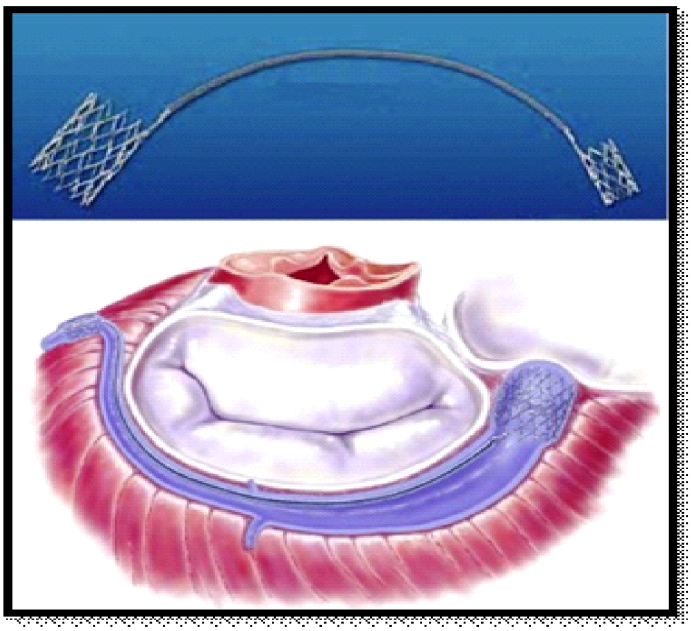



**CT appearance: Post stent graft deployment**

## 7. Coronary sinus annuloplasty for treatment of mitral regurgitation

Mitral annuloplasty using an undersized ring is a routine component of surgical mitral valve repair. Several percutaneous devices have attempted to reproduce the beneficial effects of surgical annuloplasty by taking advantage of the proximity of the coronary sinus to the mitral annulus.[34] The coronary sinus and its major tributary, the great cardiac vein, parallel the annulus of the mitral valve along its posterior and lateral aspect. The epicardial coronary venous system is readily accessible from the internal jugular vein as the confluence of the coronary sinus drains directly into the right atrium. Percutaneous approaches have generally used internal jugular or subclavian access to the right atrium to allow intubation of the coronary sinus. Various remodeling devices can be introduced into the coronary sinus, with the objective being to displace the adjacent posterior mitral annulus toward the anterior aspect of the annulus and thereby improve coaptation of the mitral leaflets.

The MONARC percutaneous transvenous annuloplasty device (Edwards Lifesciences) consists of a stent-like anchor placed in the great cardiac vein, a connecting bridge, and a second anchor located proximally at the coronary sinus ostium. The compressed device can be introduced from the jugular vein using a long sheath. Once positioned within the cardiac venous system, the sheath is withdrawn allowing the self-expanding nitinol alloy anchors to expand, providing fixation. Tensioning the device before deployment of the proximal anchor allows for acute shortening of the coronary sinus. In addition, the nitinol bridge segment is constructed like a spring with biodegradable spacers. Over a few weeks, the spacers dissolve and the bridge shortens, the anchors are drawn together and the coronary sinus shortens further. Thus, there is both an acute and delayed effect.



**Above: Monarc coronary sinus stent. Below: Deployment of monarc stent in the coronary sinus**

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