Healthy Heart

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Dr. Parloop Bhatt

From the Desk of Hon. Editor:

Dear Friends,

Although Pulmonary arterial hypertension (PAH) is relatively a rare disease, its incidence is substantially higher in certain group of patients.

No published estimates are available on the expected magnitude of the incidence of idiopathic PAH in India; however, overall magnitude is likely to be substantial if the data on incidence (1-4 per million per year) from industrialized countries are to be extrapolated. Associated conditions responsible for increased prevalence in India include portal hypertension, HIV associated PAH, and PAH associated with respiratory system disorders. Pulmonary venous hypertension is common in India due to high prevalence of rheumatic valvular heart disease contributing to development of severe pulmonary hypertension. Pathologies like collagen vascular disorders, drugs/toxins, persistent pulmonary hypertension of the new born, and PAH caused by chronic thrombotic or embolic disease would be other contributors to development of PAH.

Until few years ago PAH was considered a rapidly progressive disorder, ultimately resulting in death. Today, we definitely have entered into an explorative new era with number of new medications available to treat this condition, improving functional quality of life of these patients and lengthening their life span.

- Dr. Keyur Parikh

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance, is a severe hemodynamic abnormality common to a variety of diseases and syndromes. Elevation in pulmonary arterial pressure causes an increase in right ventricular afterload, impairing right ventricular function and ultimately leading to heart failure and death.

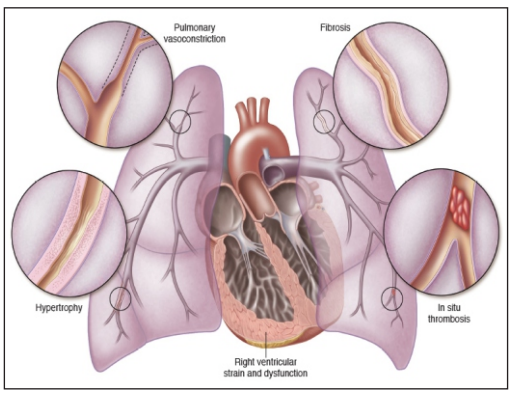
The three major factors thought to contribute to the increased pulmonary vascular resistance are:

i) Vasoconstriction

ii) Remodeling of the vessel wall and

iii) Thrombosis

There are a number of metabolic pathways which contribute to these changes that involve vasoactive mediators such as the vasodilators nitric oxide and prostacyclins and vasoconstrictor endothelin-1. These substances affect both vascular tone and



remodeling leading to their use as pharmacologic targets.(Fig.1)

Diagnosis

Though no specific diagnosis for PAH is available, physical examination in early stages of the disease may help to combat the disease. Certain diagnostic parameters required to confirm the presence of pulmonary hypertension include:

- Chest X-Ray
- Electrocardiogram
- Echocardiogram
- Right-heart catheterization
- Pulmonary function tests
- Perfusion lung scan
- Six-minute walk test

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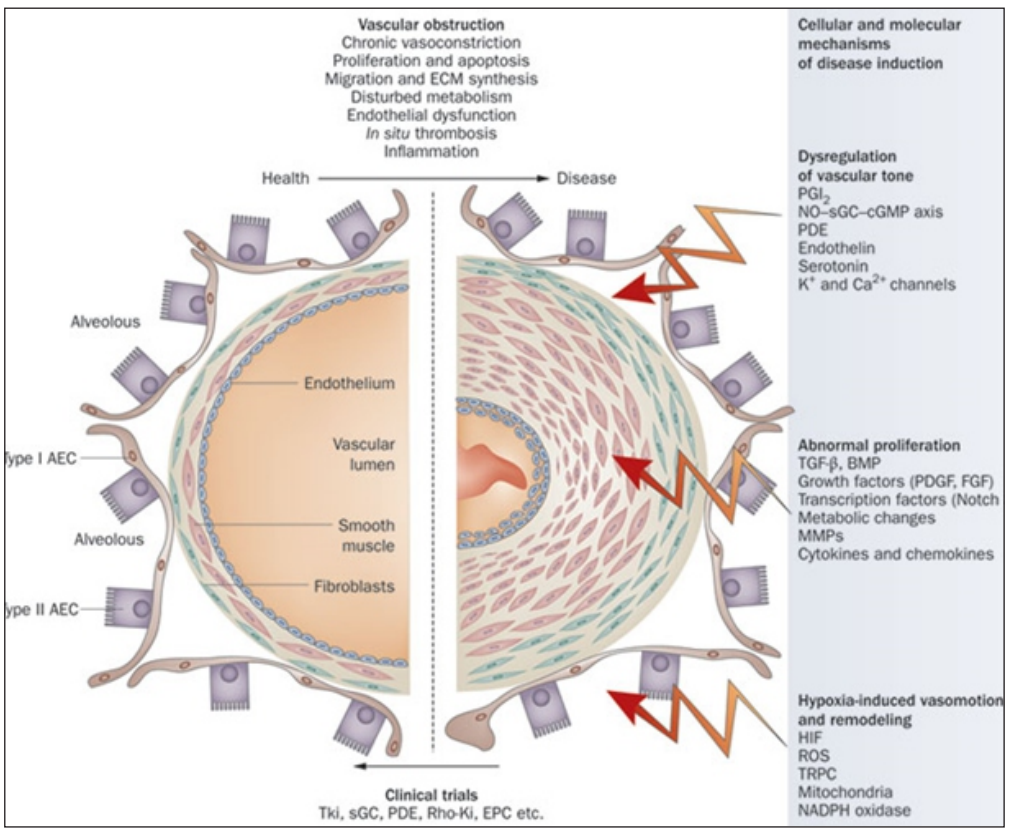
Figure-1 : Mechanism of Disease: Pulmonary Arterial Hypertension



In approximately a third of patients with PAH, echocardiography demonstrates right-to-left shunting across a patent foramen ovale .

Note the flattened interventricular septum due to right ventricular overload.

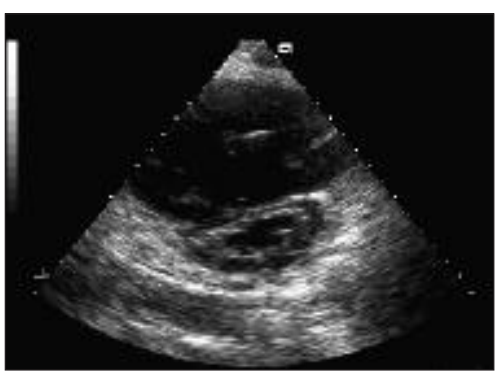


Figure-2 : Two-dimensional short-axis echocardiogram image.

Signs and Symptoms

Symptoms of IPAH are nonspecific and commonly include the following:

Dyspnea, Weakness, Recurrent syncope

Cardiovascular examination in patients with PAH often reveals the following findings:

- The pulmonic component of the second heart sound is usually increased, which may demonstrate fixed or paradoxic splitting in the presence of severe right ventricular dysfunction; occasionally, the second heart sound may be palpable
- A pulmonic regurgitation (Graham Steell murmur) may be apparent
- A murmur of tricuspid regurgitation can be present, and a right ventricular lift (heave) may be noted
- Jugular venous pulsations may be elevated in the presence of volume overload, right ventricular failure, or both; large V waves are often present because of the commonly present severe tricuspid regurgitation
- Right-sided S3 gallop

Other findings may include the following:

- Hepatomegaly with palpable pulsations of the liver
- Abnormal abdominal-jugular reflex
- Ascites - Not uncommon in untreated patients and in patients with worsening decompensated right heart failure
- Pitting edema - In the extremities
- Presacral edema - In patients who are bedridden

Treatment Approaches

Treating idiopathic PAH requires significant education regarding, and exposure to, the available therapies for IPAH and their potential complications. Note that there are no therapies approved for use as primary prevention of IPAH. All approved treatments are for use in patients that have already developed clinical manifestations of IPAH.

The following clinical guidelines on treatment of PAH have been published:

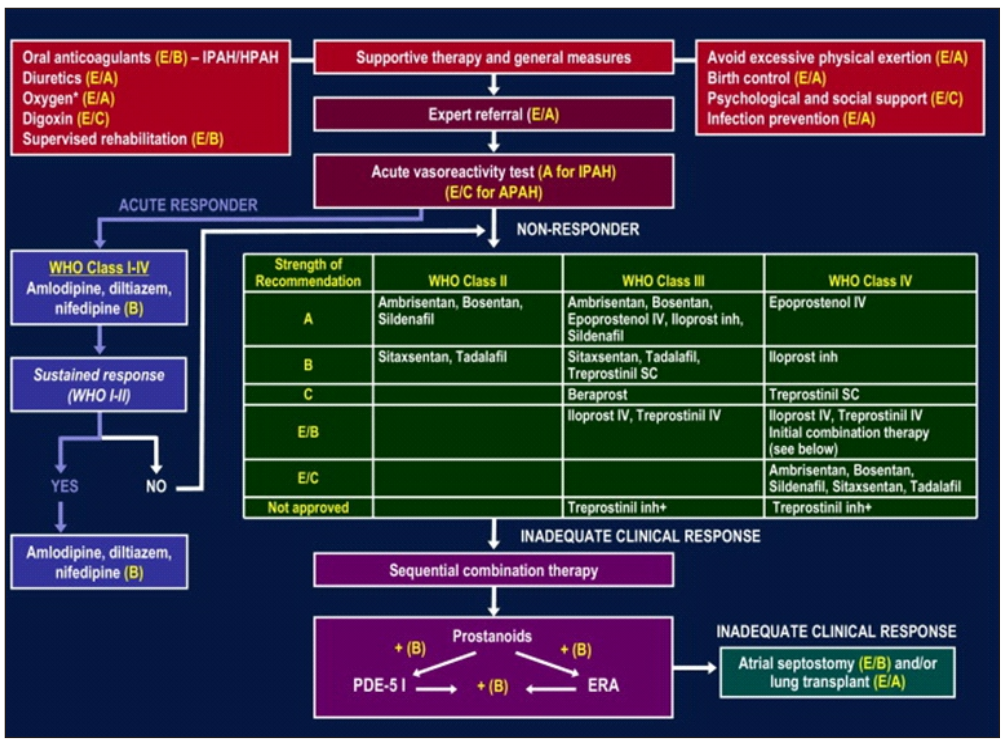
1. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines and the 2007 addendum
2. Guidelines on diagnosis and treatment of pulmonary arterial hypertension: The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology
3. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension

Treatment Modality

1. ***Calcium Channel Blocker Therapy:*** Until about 15 years ago, calcium channel blockers (CCBs) had been the most widely used class of drugs for IPAH. These drugs are thought to act on the vascular smooth muscle to dilate the pulmonary resistance vessels and lower the pulmonary artery pressure. The use of CCBs should be limited to patients without overt evidence of right-sided heart failure.
2. ***PAH-SpecificTherapy:*** Approved medications for PAH (including IPAH) currently available in the United States are as follows:

Epoprostenol - Intravenous, parenteral prostacyclin analogue, sometimes referred to as a "prostanoid

Figure 3 : Treatment Modalities



Treprostinil - Intravenous or subcutaneous, parenteral prostacyclin analogue, sometimes referred to as a prostanoid

Treprostinil inhaled - Nebulized inhalation; prostacyclin analogue

Treprostinil extended-release tablet - Twice-daily oral prostacyclin analogue

Iloprost - Nebulized inhalation; prostacyclin analogue, sometimes referred to as a prostanoid

Bosentan - Oral; endothelin receptor antagonist (ERA)

Ambrisentan - Oral ERA

Sildenafil - Oral phosphodiesterase type 5 (PDE-5) inhibitor

Tadalafil - Oral PDE-5 inhibitor

Riociguat - Oral soluble guanylate cyclase (sGC) stimulator (currently approved only for adults)

Macitentan – Oral ERA (also currently approved for adults])

3. ***Ancillary Treatment:*** Patients with idiopathic PAH may benefit from therapy with anticoagulants, digoxin, diuretics, or supplemental oxygen.

4. ***Surgical options*** available include:

- Atrial septostomy
- Lung transplantation
- Pulmonary thromboendarterectomy

Future Therapies

Clinical trials are under way to determine the safety and efficacy of several new therapies for IPAH. These include oral and inhaled prostanoids, phosphodiesterase inhibitors, tyrosine kinase inhibitors, and other novel agents. Efforts are currently focused on prostacyclin analogues, newer endothelin antagonists, and PDE-5 inhibitors.

Essential update: US FDA approved treprostinil extended-release tablets for pulmonary arterial hypertension in WHO group I patients

In December 2013, the FDA approved orally administered treprostinil (Orenitram) extended-release tablets for the treatment of pulmonary arterial hypertension in WHO group I patients to improve exercise capacity. Approval was based on an efficacy study in which patients treated with twice-daily treprostinil improved their median 6-minute walk distance by 23 meters (P =0.013), as compared with those who received placebo FREEDOM study (to evaluate oral treprostinil) was a 16-week, multicenter, double-blind, placebo-controlled study in 350 patients with PAH randomized to placebo or oral treprostinil. All patients in the study were already on background therapy with an ERA, PDE-5 inhibitor, or both. While there was an 11m placebo-corrected median increase in six minute walk in the treprostinil cohort, this did not reach statistical significance (p=0.07).

The FREEDOM-C2 study was also a multicenter, double-blind, placebo-controlled study in 310 patients with PAH all of whom were already on background therapy with either a phosphodiesterase 5 inhibitor (PDE5i) or ERA. Patients were randomized to either oral treprostinil or placebo for 16-weeks.

Another multicenter, randomized, placebo controlled trial of 349 PAH patients who were not receiving any background PAH therapy was performed over a 12 week duration (treprostinil monotherapy, n=233; placebo, n=116). The primary endpoint of 6 minute walk distance favored treprostinil with a 23m increase compared to placebo (p=0.125).

Care Institute of Medical Science (CIMS) has initiated a Phase 3 clinical trial in patients with Pulmonary Arterial Hypertension (PAH) involving Sustained Release Oral Treprostinil (a Prostacyclin analogue). This placebo controlled study will evaluate the study drug in combination with any approved background oral monotherapy.

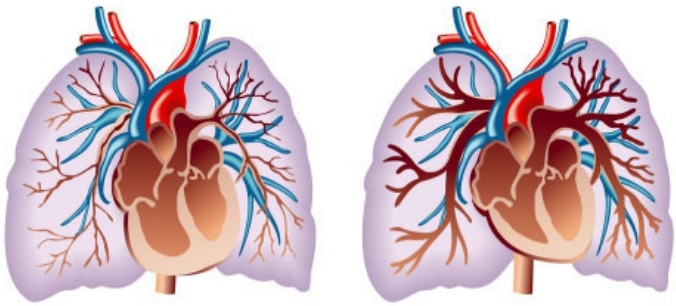
The patients completing (per protocol) the first part of the research may be eligible for a long term efficacy study in which the patient will have life-long access to oral treprostinil at no cost to them.

Further Readings

1. [Guideline] Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. Jul 2004;126(1 Suppl):35S-62S. [Medline].
2. [Guideline] Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest. Jun 2007;131(6):1917-28. [Medline].
3. [Guideline] McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation. Apr 28 2009;119(16):2250-94. [Medline].

Phase 3 Clinical Research on Pulmonary Arterial Hypertension

Care Institute of Medical Science is initiating a Phase 3 clinical trial in patients with Pulmonary Arterial Hypertension (PAH) involving Sustained Release Oral Treprostinil (a Prostacyclin analogue). This placebo controlled study will evaluate the study drug in combination with any approved background oral monotherapy.



Oral treprostinil (Orenitram®) was recently approved by US-FDA in December 2013 for the treatment of WHO group I PAH. Treprostinil is also currently approved in the United States and other territories for the treatment of PAH when administered by subcutaneous or intravenous infusion (Remodulin), or by inhalation (Tyvaso). The sponsor is now continuing the development of the oral formulation administered three times daily, which offers an easier mode of administration for patients. A previous randomized, double blind, placebo controlled study of oral treprostinil administered as monotherapy (which included Indian patients), demonstrated a statistically significant improvement in exercise capacity in PAH patients after 12 weeks therapy.

The patients completing (per protocol) the first part of the research may be eligible for a long term efficacy study in which the patient will have life-long access to oral treprostinil at no cost to them.

For further information, please contact any of our team members listed below if you think that your PAH patient may benefit from this research.

Please contact Dr. Keyur Parikh +91-98250 26999 or
any CIMS Cardiologist listed on front page to enroll in this trial

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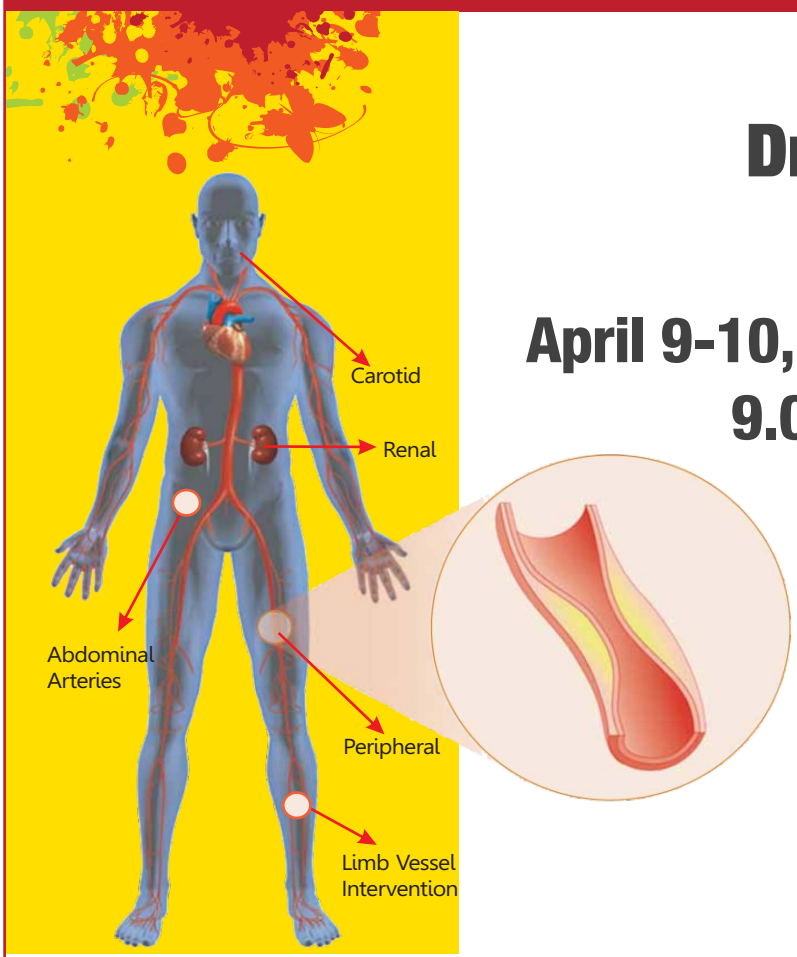

by

Dr. Ashit Jain

(USA)

April 9-10, 2015, Thursday & Friday
9.00 am to 3.00 pm

Patients who are eligible :

- Carotid Artery Stenosis
- Renal Artery Stenosis
- Acute Limb Ischemia
- Critical Limb Ischemia
- Varicose Veins
- Dialysis Access Procedures
- Pulmonary Embolism
- Thoracic Outlet Syndrome
- Uterine Fibroids
- Vascular Malformations
- Venous Insufficiency and Venous Ulcers
- Claudication
- Aortoiliac Occlusive Disease
- Femoropopliteal Disease
- Brachiocephalic Arterial Disease
- Venous Thromboembolic Disease
- Thoracic Abdominal Aortic Aneurysms
- Mesenteric Disease
- Catheter-Based Interventions for Failing Hemodialysis Accesses
- Infrapopliteal Peripheral Arterial Disease
- Intracranial Arterial Stenotic Disease
- Vertebral Arterial Disease

Kindly refer your PVD, AAA patients for consultation (complimentary) and intervention.

Please contact
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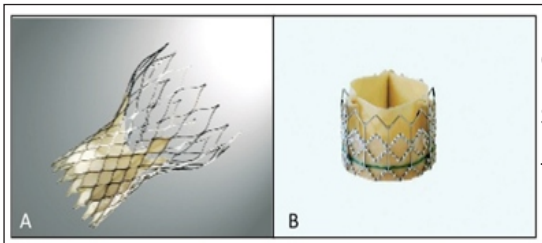
TRANSCATHETAR AORTIC VALVE IMPLANTATION (TAVI)

INTRODUCTION

Rising life expectancy results in an increase of degenerative and neoplastic diseases. Population-based observational studies report that 1% to 2% of patients older than 65 years have moderate-to-severe aortic stenosis (AS) . Surgical aortic valve replacement (AVR) dates back to 1960 and is currently the only treatment option for severe AS that has been shown to improve survival, regardless of age . In the ideal candidate, surgical AVR has an estimated operative mortality of 4% (Kvidal et al., 2000). Unfortunately, up to one-third of patients with severe AS are ineligible for corrective valve surgery, either because of advanced age or the presence of multiple comorbidities . Current treatment options for those patients not offered surgery include medical treatment or percutaneous balloon aortic valvuloplasty, although neither has been curative and has high mortality. Medically treated patients with symptomatic AS have 1- and 5- year survival of 60% and 32%, respectively. With the introduction of percutaneous aortic valve implantation in 2002, there seems to be an alternative for these patients.

Selection of patient

Due to the existence of tried and tested surgical AVR with good long-term results, the selection of patients for transcatheter aortic valve implantation (TAVI), which should done in a multidisciplinary consultation between cardiologists, surgeons, imaging specialists, and anesthesiologists, involves several critical steps. Candidates considered for TAVI must have severe symptomatic AS in addition to a formal contraindication to surgery or other characteristics that would limit their surgical candidacy because of excessive mortality or morbidity . The procedure should be offered to patients who have a potential for functional improvement after valve replacement. It is not recommended for patients who simply refuse surgery on the basis of personal preference.



Profile of the Core Valve Revaving System (A) and Edward SAPIEN Transcatheter Heart Valve (B)

ASSESSMENT FEASIBILITY FOR TAVI

Indication for Transcatheter aortic valve implantation

- Severe aortic stenosis (AVA: <1cm2,mean gradient >40mmHg, severe symptoms)
- Contraindication for surgical valve replacement

Contraindication for Transcatheter aortic valve implantation

- Mild to moderate aortic stenosis
- Asymptomatic patients
- Life expectancy <1 year
- Surgical aortic valve replacement possible, but patient refused
- Aortic anulus <18 or >25mm (balloon-expandable) and <20 or >27mm (self-expandable)
- Bicuspid aortic valve
- Asymetric heavy valvular calcification
- Aortic root >45mm at the aortotubular junction
- Presence of left ventricular apical thrombus

Contraindication for transfemoral approach

- Severe calcification, tortuosity, small diameter of the iliac arteries
- Previous aortofemoral bypass
- Severe angulation, severe atheroma of the aorta
- Coarctation of the aorta
- Aneurysm of the aorta with protruding mural thrombus

Contraindication for transapical approach

- Previous surgery of the left ventricle using a patch
- Calcified pericardium
- Severe respiratory insufficiency
- Non-reachable left ventricular apex

Table : Actually proposed indications and contraindications for TAVI

Conclusion

Transcatheter aortic valve implantation was developed to provide an alternative and less invasive method of treating aortic valve stenosis. Actually, it has been proved that the method is feasible, with results that have been reproduced by many physicians in many centers. TAVI should be restricted to a limited number of high-volume centers, that have both cardiology and cardiac surgery departments as well as expertise in structural heart disease intervention and highrisk valvular surgery. Because of excellent results with surgical valve replacement, patient selection, which should be done in multidisciplinary conferences, is of utmost importance.

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