

Transcatheter aortic valve implantation for aortic stenosis

1 Guidance

- 1.1 The evidence on transcatheter aortic valve implantation for aortic stenosis is limited to small numbers of patients who were considered to be at high risk for conventional cardiac surgery. It shows good short-term efficacy but there is little evidence on long-term outcomes. There is a potential for serious complications; however, the patients on whom this procedure has been used have a poor prognosis without treatment and are at high risk if treated by open heart surgery. Clinicians wishing to use this procedure should do so only with special arrangements for clinical governance, consent and for audit or research.
- 1.2 Clinicians should take the following actions:
- Inform the clinical governance leads in their Trusts.
 - Ensure that patients understand the uncertainty about the procedure's long-term efficacy and its risks, which include death and the potential need for emergency cardiac surgery. They should provide patients with clear, written information. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG266publicinfo).
- 1.3 Patient selection should be carried out by a multidisciplinary team including an interventional cardiologist, a cardiac surgeon and a cardiac anaesthetist.
- 1.4 This is a technically challenging procedure that should be performed only by clinicians and teams with special training and experience in interventional cardiology. Units undertaking this procedure should have both cardiac and vascular surgical support for emergency treatment of complications.

- 1.5 The NHS Information Centre for Health and Social Care runs the UK Central Cardiac Audit Database, and clinicians should enter details about all patients undergoing transcatheter aortic valve implantation for aortic stenosis onto this database (www.ccad.org.uk).
- 1.6 Further publication of safety and efficacy outcomes will be useful. The Institute may review the procedure upon publication of further evidence.

2 The procedure

2.1 Indications and current treatments

- 2.1.1 Aortic stenosis (narrowing of the aortic valve) causes impaired outflow of blood from the heart, and is usually progressive. It requires the left ventricle to pump harder to maintain a normal circulation. Over time, left ventricular hypertrophy and heart failure may develop. Symptoms of aortic stenosis typically include exertional chest pain, breathlessness, dizziness and fainting.
- 2.1.2 Management of aortic stenosis depends on the severity of the condition, the presence of comorbidities, the age of the patient and their operative risk. Treatment is only usually needed if aortic stenosis is severe or symptomatic. In these patients, conventional treatment is surgical aortic valve replacement. This involves replacement of the diseased valve with an artificial (biological or mechanical) prosthesis through a median sternotomy approach and using cardiopulmonary bypass. Percutaneous balloon valvuloplasty is usually considered as palliative treatment and may be undertaken in very ill patients who cannot safely undergo surgery.

Interventional procedure guidance 266

Interventional procedures guidance makes recommendations on the safety and efficacy of a procedure. The guidance does not cover whether or not the NHS should fund a procedure. Decisions about funding are taken by local NHS bodies (primary care trusts and hospital trusts) after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS.

Interventional procedures guidance is for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland. This guidance is endorsed by NHS QIS for implementation by NHSScotland.

- 2.1.3 Transcatheter aortic valve implantation has been undertaken in patients in whom conventional aortic valve replacement would carry a high mortality risk due to advanced age and/or the presence of concomitant illnesses.

2.2 Outline of the procedure

- 2.2.1 Transcatheter aortic valve replacement may be carried out under general anaesthesia or under local anaesthesia with sedation. Access to the aortic valve can be achieved transluminally, via the femoral artery or vein (percutaneous or endovascular approach), or surgically, via a minithoracotomy and apical puncture of the left ventricle (transapical or transventricular approach). When the femoral vein is used for a transluminal approach, the interatrial septum is punctured in order to gain access to the left ventricle via the left atrium and mitral valve. When the femoral artery is used, surgical exposure and closure may also be required. The method chosen for catheter access to the aortic valve may be dictated by the presence of peripheral arterial disease, as the transluminal approach may not be feasible in these patients.
- 2.2.2 Whichever approach is used, a balloon catheter is advanced into the left ventricle over a guidewire and positioned within the opening of the aortic valve. The existing aortic valve is dilated in order to make room for the prosthetic valve. Rapid right ventricular pacing may be used to reduce cardiac output through the existing aortic valve and to reduce cardiac movement during implantation. The new valve, mounted on a metal stent, is manipulated into position and is either self-expanding or deployed using balloon inflation. Deployment leads to obliteration of the existing aortic valve.

Sections 2.3 and 2.4 describe efficacy and safety outcomes which were available in the published literature and which the Committee considered as part of the evidence about this procedure. For more details, refer to the Sources of evidence.

2.3 Efficacy

Transluminal approach

- 2.3.1 In three case series of 86, 50 and 36 patients, a transluminal approach was carried out successfully in 88% (76/86), 86% (43/50) and 75% (27/36) of patients, respectively. Causes of failure were reported as device misplacement in 9% (8/86) and 4% (2/50) of patients and inability to cross the diseased valve in 6% (3/50), 3% (1/36) and 2% (2/86) of patients.
- 2.3.2 Three case series of 50, 13 and 36 patients treated by a transluminal approach reported survival to be 81% (35/43), 45% (5/11) and 41% (11/27) at follow-up of 359 days (median), 305 days (median) and 6 months, respectively. These figures included only those patients in whom the procedure was completed successfully.
- 2.3.3 Four case series of 86, 50, 36 and 13 patients treated by the transluminal approach reported a significant decrease in mean aortic valve gradient from baseline: from 44 to 9 mmHg, 46 to 11 mmHg, 37 to 9 mmHg and 51 to 9 mmHg, respectively, at follow-up periods ranging from discharge to 1 month.
- 2.3.4 Three case series of 50, 36 and 13 patients reported a significant increase in mean aortic valve area from baseline: from 0.6 to 1.7 cm² ($p = 0.0001$), 0.6 to 1.9 cm² ($p < 0.0001$) and 0.6 to 1.3 cm² ($p < 0.0001$), respectively, at follow-up periods ranging from discharge to 1 month.
- 2.3.5 Four case series of 86, 50, 36 and 13 patients reported that mean New York Heart Association (NYHA) functional class improved: from 2.85 at baseline to 1.85 at 30-day follow-up ($p < 0.001$); by at least one class in 50% (25/50) of patients ($p < 0.0001$); to class I in five patients, class II in 14 patients and class III in two patients surviving beyond 33 days (baseline NYHA not reported); and by at least one class in all survivors at 1-month follow-up (9/11; $p = 0.006$), respectively.

Transapical approach

- 2.3.6 Using the transapical approach, all seven patients in one case series were successfully treated. In two further case series of 59 and 50 patients using the transapical approach (which included duplicate reporting of some patients), conversion to sternotomy was required in 7% (4/59) and 6% (3/50) of patients, respectively. This was due to incorrect valve positioning in all four patients in the first study, and proximal valve dislocation, aortic root dissection and severe calcification of one of the native aortic valve cusps in the second study.
- 2.3.7 The case series of 59 and 50 patients reported mean aortic gradients of 9 mmHg in 40 patients at discharge and 8 mmHg in all survivors at 6-month follow-up, respectively (baseline values not reported).
- 2.3.8 A case series of seven patients reported the mean aortic valve area to be 0.7 cm² at baseline (n = 7), 1.8 cm² at 1-month follow up (n = 6) and 1.5 cm² at 6-month follow-up (n = 4).
- 2.3.9 The case series of seven patients treated by the transapical approach reported that symptoms relating to aortic stenosis had resolved or significantly improved at 1- and 6-month follow-up.

Transluminal and transapical approach

- 2.3.10 The Specialist Advisers considered key efficacy outcomes to include procedural success, haemodynamic improvement, reduction of symptoms and short- and long-term survival.

2.4 Safety

Transluminal approach

- 2.4.1 Three case series of 86, 50 and 36 patients treated by the transluminal approach reported a 30-day mortality of 12% (10/86; five were intraprocedural), 12% (6/50; one was intraprocedural) and 22% (6/27), respectively. A case series of 13 patients reported in-hospital mortality to be 18% (2/11).

- 2.4.2 A case report on transluminal implantation via the femoral vein described the death of a patient 5 days after the procedure, due to guidewire-induced mitral valve leaflet laceration leading to severe mitral regurgitation and cardiogenic shock.
- 2.4.3 The incidence of stroke within 30 days was reported to be 12% (9/76), 4% (1/27), 9% (1/11) and 2% (1/43) of patients treated by a transluminal approach. The two patients from the latter two studies died within 30 days of the procedure. Additional complications reported within 30 days in these four case series included bradyarrhythmia in 36% (4/11) of patients, major bleeding in 18% (2/11), cardiac tamponade in 10% (9/86), iliac injury requiring vascular repair in 5% (2/43) and access site infection requiring antibiotics in 5% (2/43).

Transapical approach

- 2.4.4 The reported rates of in-hospital and 30-day mortality in two case series using the transapical approach were 14% (8/59) and 8% (4/50), respectively. A third case series of seven patients reported 30-day mortality to be 14% (1/7).
- 2.4.5 In a case series of seven patients, moderate paravalvular regurgitation was reported in two patients; this decreased after redilation.
- 2.4.6 The case series of 59 patients treated by the transapical approach reported pleural effusion in 31% (18/59) of patients, supraventricular tachyarrhythmia in 31% (18/59), pericardial effusion in 5% (3/59) and stroke in 3% (2/59), and the need for haemofiltration in 14% (8/59), tracheostomy in 14% (8/59), rethoracotomy in 14% (8/59) and cardiopulmonary resuscitation in 7% (4/59).

Transluminal and transapical approach

- 2.4.7 In addition to outcomes reported in the literature, the Specialist Advisers considered additional theoretical adverse events to include thromboembolic complications; valve embolisation, migration or misplacement; access site complications; the need for conversion to conventional surgery; the need for a permanent pacemaker; early device failure and uncertain durability of the implanted artificial valve.

2.5 Other comments

- 2.5.1 The Committee noted that there are a number of devices in use for the approaches to this procedure. They also noted that the devices and techniques used for the procedure are evolving.
- 2.5.2 The Committee noted that patient selection was limited to those at high risk of mortality from conventional valve replacement in the studies considered. More evidence on patient selection may be useful in reviewing the guidance.

3 Further information

- 3.1 The Institute has published interventional procedures guidance on balloon valvuloplasty for aortic valve stenosis in adults and children (www.nice.org.uk/IPG078) and percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction (www.nice.org.uk/IPG237).

Information for patients

NICE has produced information on this procedure for patients and their carers ('Understanding NICE guidance'). It explains the nature of the procedure and the decision made, and has been written with patient consent in mind. See www.nice.org.uk/IPG266publicinfo

Sources of evidence

The evidence considered by the Interventional Procedures Advisory Committee is described in the overview, available at www.nice.org.uk/IP685overview

Ordering printed copies

Contact NICE publications (phone 0845 003 7783 or email publications@nice.org.uk) and quote reference number N1602 for this guidance or N1603 for the 'Understanding NICE guidance'.

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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Understanding NICE guidance

Information for people who use NHS services

Catheter insertion of a new aortic valve to treat aortic stenosis

NICE 'interventional procedures guidance' advises the NHS on when and how new procedures can be used in clinical practice.

This leaflet is about when and how catheter insertion of a new aortic valve can be used in the NHS to treat people with aortic stenosis. It explains guidance (advice) from NICE (the National Institute for Health and Clinical Excellence).

Interventional procedures guidance makes recommendations on the safety of a procedure and how well it works. An interventional procedure is a test, treatment or surgery that involves a cut or puncture of the skin, or an endoscope to look inside the body, or energy sources such as X-rays, heat or ultrasound. The guidance does not cover whether or not the NHS should fund a procedure. Decisions about funding are taken by local NHS bodies (primary care trusts and hospital trusts) after considering how well the procedure works and whether it represents value for money for the NHS.

NICE has produced this guidance because the procedure is quite new. This means that there is not a lot of information yet about how well it works, how safe it is and which patients will benefit most from it.

This leaflet is written to help people who have been offered this procedure to decide whether to agree (consent) to it or not. It does not describe aortic stenosis or the procedure in detail – a member of your healthcare team should also give you full information and advice about these. The leaflet includes some questions you may want to ask your doctor to help you reach a decision. Some sources of further information and support are on the back page.

What has NICE said?

There is not much evidence about how well this procedure works or how safe it is, especially in the long term. There are serious safety concerns; however, patients who require this procedure are also at a high risk of death or serious complications if they are not treated or if they are treated with standard open heart surgery. If a doctor wants to use this procedure to insert a new aortic valve, they should make sure that extra steps are taken to explain the uncertainty about how well it works, as well as the uncertainty surrounding potential risks of the procedure. This should happen before the patient agrees (or doesn't agree) to the procedure. The patient should be given this leaflet and other written information as part of the discussion. There should also be special arrangements for monitoring what happens to the patient after the procedure.

Further information on the safety of this procedure and how well it works will be helpful. NICE is asking doctors to send information about everyone who has the procedure and what happens to them afterwards to a central store of information at the NHS Information Centre for Health and Social Care (www.ccad.org.uk) so that the safety of the procedure and/or how well it works can be checked over time. NICE may look at this procedure again if more information becomes available.

A team of healthcare professionals, including specialist doctors who are experienced in the management of aortic stenosis, should decide which patients are suitable for this procedure. The team should include a heart surgeon, a heart anaesthetist and a specialist in heart procedures using catheters (known as an interventional cardiologist).

NICE has also said that this is a difficult procedure. It should only be carried out by doctors with special expertise/training in interventional cardiology. The procedure should be carried out in units with specialists in heart and blood vessel surgery available in case emergency treatment is needed.

Other comments from NICE

In the studies that NICE looked at, the patients selected for this procedure were at high risk of death if treated with conventional open heart surgery. Further studies may be helpful.

There are different types of devices and techniques used for this procedure, which continue to change as doctors become more experienced in the procedure.

Catheter insertion of a new aortic valve

The medical name for this procedure is 'transcatheter aortic valve implantation'.

The procedure is not described in detail here – please talk to your doctor for a full description.

Stenosis means narrowing, and in aortic stenosis, the aortic valve in the heart has become narrow. Normally, this valve lets blood flow forward and out of the heart, and stops it from flowing backwards. But when the valve becomes narrow, it doesn't open properly, so blood can't flow so easily out of the heart. This puts a strain on the heart, and over time the heart muscle may get thicker in an attempt to push the blood harder through the partly open valve. People with aortic stenosis may have chest pain, feel breathless and dizzy, and may faint. Eventually some people develop heart failure.

A new valve may be inserted to replace the narrow aortic valve. In transcatheter aortic valve implantation, the valve is inserted via a thin tube (called a catheter) into the heart. The catheter can be inserted into the body through a large blood vessel, usually in the groin, under a local anaesthetic. Alternatively, it can be inserted directly into the heart through a small cut to the chest, under a general anaesthetic.

The standard operation for aortic stenosis involves opening up the chest (this is called open heart surgery) and putting the patient onto a heart and lung machine (heart–lung bypass). The valve can then be replaced.

The new procedure has been used in older patients and/or patients with additional illnesses, who might not survive open heart surgery.

This procedure may not be the only possible treatment for aortic stenosis. Your healthcare team should talk to you about whether it is suitable for you and about any other treatment options available.

What does this mean for me?

If your doctor has offered you catheter insertion of a new aortic valve, he or she should tell you that NICE has decided that the benefits and risks are uncertain. This does not mean that the procedure should not be done, but that your doctor should fully explain what is involved in having the procedure and discuss the possible benefits and risks with you. Your doctor should tell you that the long-term benefits are uncertain and that there may be some serious risks, including the possibility of death or the need for emergency heart surgery. You should only be asked if you want to agree to this procedure after this discussion has taken place. You should be given written information, including this leaflet, and have the opportunity to discuss it with your doctor before making your decision.

NICE has also decided that more information is needed about this procedure. Your doctor may ask you if details of your procedure can be used to help collect more information about this procedure. Your doctor will give you more information about this.

You may want to ask the questions below

- What does the procedure involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits? Could having the procedure make me feel worse?
- Are there alternative procedures?
- What are the risks of the procedure?
- Are the risks minor or serious? How likely are they to happen?
- What care will I need after the operation?
- What happens if something goes wrong?
- What may happen if I don't have the procedure?

Summary of possible benefits and risks

Some of the benefits and risks seen in the studies considered by NICE are briefly described here. NICE looked at eight studies on this procedure.

How well does the procedure work?

In three studies of patients who had the procedure through a large blood vessel, a total of 146 out of 172 replacement valves were inserted successfully. One of these studies reported that 35 out of 43 patients who had a successful procedure were still alive a year later, and another reported that 11 out of 27 patients were still alive 6 months after the procedure. A further study found that 5 out of 11 patients were still alive 10 months after the procedure. Tests to measure blood flow across the valve and the size of the valve were carried out on patients before and after the procedure, and symptoms of breathlessness were assessed. Overall, patients were found to have less severe aortic stenosis and reduced breathlessness.

In a study of seven patients who had the procedure through a small cut in the chest, the patients' symptoms improved or disappeared. All seven patients were found to have less severe aortic stenosis after 1 month and still showed improvement after 6 months.

In two other studies using this technique, 4 out of 59 and 3 out of 50 patients had to have open heart surgery because of problems during the procedure. Of the patients who had a successful procedure and who were still alive 6 months later, all were found to no longer have severe aortic stenosis using tests of blood flow.

As well as looking at these studies, NICE also asked expert advisers for their views. These advisers are clinical specialists in this field of medicine. The advisers said that how well the procedure works can be assessed by the successful replacement of the valve, an improvement in blood flow across the valve and in the valve area, an improvement in the patient's symptoms and by the initial and longer term survival of the patient.

You might decide to have this procedure, to have a different procedure, or not to have a procedure at all.

Risks and possible problems

Of 172 patients (in three studies) who had valve replacement through a large blood vessel, 22 died within 30 days of the procedure. Two patients died in hospital after the procedure in a study of 13 patients. One study reported that a patient died after the mitral valve of the heart was damaged during the procedure. Twelve out of 157 patients in four studies had a stroke within 30 days of the procedure. Other serious problems were reported in 19 patients, including a slow heart rate (in four patients), serious bleeding (in two), a build up of fluid around the heart (in nine), injury to the blood vessels carrying blood to the legs needing repair (in two) and infection of the catheter insertion site needing antibiotic treatment (in two).

In three studies of patients who had valve replacement through a small cut in the chest, 8 out of 59, 4 out of 50 and 1 out of 7 patients died within 30 days of the procedure. In the study of seven patients, two had leaking around the new valve, which improved after a further procedure. In the study of 59 patients, 18 had a build up of fluid around the lungs, 18 had an abnormal heartbeat, 3 had a build up of fluid around the heart and 2 had a stroke. Additionally, 18 patients needed to have temporary support using a kidney machine, 8 needed an opening made through the neck into the windpipe to allow air to pass, 8 patients needed further surgery through another small cut in the chest, and 4 patients needed emergency resuscitation.

As well as looking at these studies, NICE also asked expert advisers for their views. These advisers are clinical specialists in this field of medicine. The advisers said that possible problems include blockages in blood vessels caused by blood clots, problems at the place of entry of the tube, the need for open heart surgery or a permanent pacemaker, and movement, incorrect placement, and uncertain lifespan of the artificial valve.

More information about aortic stenosis

NHS Direct online (www.nhsdirect.nhs.uk) may be a good starting point for finding out more. Your local Patient Advice and Liaison Service (PALS) may also be able to give you further advice and support.

About NICE

NICE produces guidance (advice) for the NHS about preventing, diagnosing and treating different medical conditions. The guidance is written by independent experts including healthcare professionals and people representing patients and carers. They consider how well an interventional procedure works and how safe it is, and ask the opinions of expert advisers. Interventional procedures guidance applies to the whole of the NHS in England, Wales, Scotland and Northern Ireland. Staff working in the NHS are expected to follow this guidance.

To find out more about NICE, its work and how it reaches decisions, see www.nice.org.uk/aboutguidance

This leaflet is about 'Transcatheter aortic valve implantation for aortic stenosis'. This leaflet and the full guidance aimed at healthcare professionals are also available at www.nice.org.uk/IPG266

You can order printed copies of this leaflet from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1603).

We encourage voluntary sector organisations, NHS organisations and clinicians to use text from this booklet in their own information about this procedure.

National Institute for Health and Clinical Excellence

660 – Surgical repair of vaginal wall prolapse using mesh

Consultation Comments table

IPAC date: 17 April 2008

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Cook Medical, Manufacturer	1.1	In point 1.1, the statement “There is a risk of complications that can cause significant morbidity” makes no distinction regarding the complications expected with different types of meshes, even though section 1.1 says that both efficacy and safety vary with different types of mesh. Clinicians be advised to discuss how different meshes (i.e., biologic versus synthetic and	There is more detail of the different types of mesh in the efficacy and safety sections of the guidance document and the systematic review.
2	Individual patient	1.1	The evidence considered is of comparative studies only. Both Perros and Linda Brubaker have gone into print with their opinions that mesh should <u>not</u> be used for pelvic floor repairs, as contact with sensitive vaginal tissue should not be risked. Petros advocates a ‘bridge’ using patients’ own vaginal tissue that would otherwise be discarded. This method does not appear to feature in any of the research material considered in this exercise.	While the recommendation makes a comparative judgment, evidence from non-randomised controlled trials and case series studies were also reviewed.
3	Individual patient	1.2	I applaud this recommendation. Clear written information, adequate time to consider it and an opportunity to ask questions is preferable to a patient being told ‘we will use mesh’.	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
4	Individual patient	1.3	<p>This statement seems imprecise. What degree of special expertise is recommended? One study does point to a co-relation between erosion and the inexperienced surgeon. Other studies seem to hint at it. As these are all short-term follow-ups – experienced surgeons may be linked to later date erosion – we just don't know.</p>	<p>Thank you for your comment. NICE Interventional Procedures guidance highlights the requirement for training where appropriate, but it is the role of the relevant Royal Colleges and other professional organisations to prepare details of the content of that training.</p>
5	Individual patient	1.4	<p>The level of follow-up and details of adverse outcomes are very limited. Problems experienced by patients might be better understood if there were fuller reporting of problems within the professional literature.</p> <p>There is blatant sexual discrimination in the research studies, in that a woman's pain and quality of life is deemed to be of no account unless it is in relation to a randy male. If a woman is not sexually active this is marked N/A and discounted. I hope that NICE is able to influence such reporting.</p> <p>I include a sheet detailing some of the activity areas which cause me difficulty and which could usefully be included in quality of life postal surveys which could be done 5 and 10 years post op.</p>	<p>Thank you for your comment. Section 1.4 now highlights the importance of patient-reported outcomes.</p>
6	Individual clinician	1	<p>Would completely agree with this. These procedures offer a chance of cure where conventional techniques have or would fail. They should only be used by people who understand the options, potential problems and technique fully. There is not a one size fits all solution to prolapse and knowledge of many techniques is useful.</p>	<p>Noted. Thank you for your comment.</p>

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
7	Boston Scientific, Manufacturer	1	Equal consideration should be provided to open observational studies/registries for pelvic floor reconstruction. Mesh and graft implants are challenged by the modest amount of RCTs, which is made more problematic in analysis by further dissection by anterior, posterior, and/or combined anterior-posterior repair. The wide range of materials, location, placement and technique that may be associated with their use, disables any practical or realistic opportunity for comparative effectiveness. Registry data should be extended the same consideration as RCTs. Registries reflect the	All relevant sources of evidence were included in the systematic review, which analysed registry data in conjunction with other sources of evidence. Section 2.5.1 of the guidance now reads: 'The Committee noted that interpretation of the evidence was made particularly difficult due to the different meshes used and the variation in surgical approaches.'
8	Individual patient	2.1.3	I query whether mesh should be the procedure of first choice for an active woman. I would not recommend mesh repair of the vaginal wall for any woman unless she had recurrent prolapse and was already in residential care (or prepared to accept that lifestyle and quality of life). For an active woman mesh can be a disaster!	Thank you for your comment. Section 2.1.2 lists current treatment options for women with anterior and/or posterior vaginal wall prolapse – mesh is not included here but referred to in section 2.1.3 in terms of recurrence of prolapse.
9	Individual patient	2.2.3	A choice of anaesthetic was suggested and I chose spinal block. Saddle block, used for the 3 rd operation, proved to be the most comfortable as it allowed me full use of the intercostal muscles and thus no need for oxygen. I prefer to remain fully conscious.	Noted. The text says that this is 'usually' done under general anaesthesia.
10	Individual patient	2.2.4	I was surprised that the mesh was being cut to size in the theatre – rather than preformed with all the chisel like points of the edges properly smoothed. (I have used polypropylene mesh for splint making – it is rough!)	Noted, thank you. Section 2.2.4 states that the technique for implanting the mesh varies.

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11	Individual patient	2.3.17	<p>The timescale of follow-up is far too short for proper evaluation. As you rightly point out, almost none of the studies allow the patients' views to be heard. What is the point of repair unless the patient is able to feel a real improvement.</p> <p>Postal survey at 5 or 10 years would help as I think that there is likely to be considerable underreporting of problems – which take time to appear. There may be no referral to the original surgeon, or to any surgeon at all.</p>	Noted. Thank you for your comment.
12	Individual patient	2.4.1	This is presumably the injury/damage done during the operative procedure. For the result of damage due to mesh movement over time see Ginger Isom-Batz and Philippe Zimmern.	Noted. This is a review/editorial article and would not have been included among the relevant evidence in the systematic review
13	Individual patient	2.4.2	Mesh does not have to come out (erode or exposure) right through the skin to cause acute pain. In fact, once the skin has been penetrated, the pressure eases. No one records or reports on this.	Noted. Thank you for your comment.
14	Individual clinician	2: Indications	Could comment on high failure rate and high rate of dyspareunia with conventional surgery particularly if the prolapse is 3rd degree or recurrent.	The Committee considered this comment but decided not to alter the guidance.
15	Individual clinician	2.2.1	I would disagree with 2.2.1 certainly as far as synthetic mesh is concerned. Excising any tissue is almost certainly to be avoided. Once the pressure is taken off the vaginal wall, the mucosa shrinks over the next few weeks to its original state. If tissue is excised then the risk of shrinkage and mesh	This section now reads ' <i>some excess tissue may be excised</i> '.
16	Cook Medical, Manufacturer	2.2.1	This section is limited to the traditional treatment technique colporrhaphy, even though it is acknowledged in section 2.1.2 that site-specific defect-repair can be performed. We suggest to include other techniques as well.	The Committee added a sentence to the end of 2.2.3 about other procedures. 'Other site specific procedures such as paravaginal repair may also be undertaken using methods similar to colporrhaphy'

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17	Boston Scientific, Manufacturer	2: Outline of procedure	Excluded from consideration in the systematic review (see Sources of Evidence) used to make the provisional recommendations was Boston Scientific's absorbable biological xenograft called Xenform™ Soft Tissue Repair Matrix. Xenform™ Matrix is an acellular, non-crosslinked, bovine dermal matrix which promotes revascularization and regeneration as opposed to scarring and encapsulation	Noted. Thank you. Boston Scientific was contacted by the Review Body for relevant data at the outset of the systematic review - the peer-reviewed data was not supplied by at the time of the review. The guidance now says at section 2.5.2: "The Committee noted that there is a rapidly accumulating evidence base for this procedure. A number of further studies on mesh repair have been published since the systematic review was carried out, or are in progress with initial results to be made available in the near future. The updated evidence base will inform the review of this guidance in due course."
18	Individual clinician	2.3.1-7: Efficacy - Anterior repair	No real problems with this. However please note that the risk of dyspareunia (de novo) is considerable with conventional repairs as they almost always involve narrowing to achieve a reasonable result. Also there are many cases where sexual activity is not desired but freedom from prolapse symptoms is. A colpocleisis is one solution but mesh is another. These comments refer to posterior repairs also.	Noted. Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
19	Cook Medical, Manufacturer	2.3.1-7: Efficacy - Anterior repair	This sections' initial paragraph, i.e. item 2.3.1, splits the types of mesh which can be used, into four possible categories: absorbable biological, absorbable synthetic, combined biological and synthetic and non-absorbable synthetic. The term absorbable used in combination with biological mesh is misleading, implying that the product degrades leaving nothing behind. Another problem is that all biological meshes were included under this category, and therefore the analysis makes no distinction between different types of biological meshes. For example "Permacol/pelvicol" is a cross-linked "non-absorbable" biologic mesh, yet included under the heading of absorbable biological meshes in this document. The term absorbable is limited and does not reflect the nature of the materials. Rather, biological meshes should be split into "interactive or tissue inductive" on the one hand and "permanent or non-tissue inductive" on the other. This is an issue that applies to the remaining paragraphs of the document.	Biological mesh has a spectrum of absorbability and differs significantly to synthetic mesh. Due to the variability in terminology, the Review Body considered totally or partially absorbable mesh under the blanket 'absorbable' term. The Committee considered this comment but decided not to alter the guidance. It is not the purpose of the review to compare individual meshes.
20	Individual clinician	2.3.8-11: Efficacy - Posterior repair	See above. My experience is that repair of the posterior wall with mesh is easier, more effective, less prone to mesh protrusion (0/45 in my hands) and anatomically better than the anterior	Noted. Thank you for your comment.
21	Cook Medical, Manufacturer	2.3.8-11: Efficacy - Posterior repair	Same concerns as stated for Anterior Repair and Posterior Repair.	See response to comment 19.
22	Individual clinician	2.3.12-17: Efficacy - Anterior and/or posterior repair	See above. Combining traditional anterior and posterior repairs is much more likely to result in narrowing and dyspareunia if the repairs are of any size.	Noted, thank you.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
23	Boston Scientific, Manufacturer	2.3.12-17: Efficacy - Anterior and/or posterior repair	A study titled	See response to comment 17.
24	Individual clinician	2.4.1-4: Safety - Anterior repair	Safety comments apply to all 3 sections as described below. Points 1) These techniques have been found to give higher rates of non healing and mesh protrusion when used at the same time as a vaginal hysterectomy 2) The techniques are incredibly operator dependant. 3) Attention to detail is vital. Whilst complications will occur they can be kept to a minimum by fastidious attention to detail eg: not excising mucosa, the least avascular suturing technique, use of packs, care with tissue, knowledge of anatomy, knowing when to give up and when not to use technique 4) They are not an operation for an occasional surgeon the more you do the better you get.	Thank you for your comments. Taking each in turn:1) This will be covered in our guidance on surgical repair of vaginal vault and uterine prolapse repair using mesh for which a systematic review is currently being completed. 2) This is captured in section 1.3. 3) This is captured in section 1.3. 4) This is captured in section 1.3.
25	Cook Medical, Manufacturer	2.4.1-4: Safety - Anterior repair	Same concerns as stated in the Efficacy Section.	See response to comment 19.
26	Individual clinician	2.4.5-8: Safety - Posterior repair	See above	Noted. Thank you for your comment.
27	Cook Medical, Manufacturer	2.4.5-8: Safety - Posterior repair	Same concerns as stated in the Efficacy Section.	See response to comment 19.
28	Individual clinician	2.4.9-14: Safety - Anterior and/or posterior repair	One major advantage of kits using support via the obturator route anteriorly or via a buttock approach posteriorly is that they provide support for the vault also. Almost always when dealing with a post-hysterectomy prolapse, vault and wall prolapse are combined. These techniques provide a way of dealing with this in combination.	Noted. Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
29	Cook Medical, Manufacturer	2.4.9-14: Safety - Anterior and/or posterior repair	Same concerns as stated in the Efficacy Section.	See response to comment 19.
30	Boston Scientific, Manufacturer	2.4.9-14: Safety - Anterior and/or posterior repair	A study titled – Xeniform.	See response to comment 17.
31	Individual clinician	2.5: Other comments	<p>The overwhelming evidence from TOT and TVT procedures is that a monofilament macroporous mesh is the least troublesome. This is borne out by reports of the use of different materials used in these repairs (NB original TYCO posterior IVS with high rate of problems). Any other synthetic mesh should be avoided. Animal data on Pelvicol etc shows a very patchy and unpredictable absorption rate borne out by widely differing results from pt to pt. At least systems such as Prolift, Avaulta etc give a standardised approach which has been assessed to a degree, & can be audited refined and compared. I feel also that you should separate ad hoc use of a reinforcing patch over the conventional repair from the Prolift/Avaulta/AMS systems which provide a hammock supporting effect without narrowing or shortening whilst at the same time supporting the vault. They can give a very anatomically correct appearance. The latter have been the major advance in my opinion and are in a different league to reinforcing patches which seem to add little to the results</p>	Noted. Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
32	Individual patient	General	<p>As I walked and regained my normal stride the mesh flexed and snapped back. One stitch was also a source of problems so a year after insertion of the mesh, this stitch was removed and the mesh trimmed back. 8 months later, sitting was increasingly difficult and I struggled with normal tasks, using paracetamol, TENS and Lidocaine (locally applied anaesthetic). I spent time flat on the bed most days.</p> <p>Two years after insertion, the mesh was again trimmed back. This gave no real improvement. The mesh is so abrasive that it feels like a pan scourer under the skin of the vagina, with the edges that act like serrated knife blades. Normal walking results in swelling from this internal chafing – which causes pressure which results in pain – often hours after the activity that has been the cause of this reaction. I am usually reduced to a slow short-stepped waddle – and sitting can be truly painful and a problem. I spend periods each day flat on the bed. Basic household tasks are possible with additional analgesics. I have dropped out of almost all my activities and driving is now painful.</p> <p>Mesh that was barely palpable 6 months ago is, I am told, now visible through the skin. It is on the move!</p> <p>Currently I am losing muscle bulk and struggle to maintain general fitness.</p>	Noted. Thank you for your comment. Sections 1.1 and 1.4 of the guidance highlight the long-term morbidity and quality of life issues in relation to this procedure. NICE is revising its processes for the incorporation of patients' perspectives into Interventional Procedures Guidance, and plans to consult on its proposals during 2008.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
33	Individual patient	General	<p>References</p> <p>The female pelvic floor: Function, Dysfunction and Management – Peter Petros ISBN 9783540224105</p> <p>Multidisciplinary Management of the female Pelvic Disorders –Chapple, Zimmen, Brubaker et al. (NB Read the foreword as well as the main sections) ISBN 9780443072727</p> <p>Systematic review of the efficacy and safety of using mesh or grafts in surgery for anterior and posterior vaginal wall prolapse October 2007</p> <p>Vaginal mesh for incontinence and/or prolapse: caution required! – Ginger Isom-Batz, Philippe Zimmern Expert review of medical devices September 2007 www.future-drugs.com</p>	<p>Thank you for bringing these references to our attention.</p> <p>This is a book and would not have been included in the systematic review.</p> <p>This is a review chapter from a book and would not have been included in the systematic review.</p> <p>This is included in the systematic review commissioned by NICE</p> <p>This is a review/editorial and would not have been included in the systematic review.</p>

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
34	American Medical Systems, Manufacturer	General – Anterior and posterior repair	<p>1) Follow-up after polypropylene mesh repair of anterior and posterior compartments in patients with recurrent prolapse Gauruder-Burmester, Koutouzidou, Rohne, Gronewold, Tunn Int Urogynecol J (2007) 18:1059-1064</p> <p>Summary: Retrospective analysis of 120 patients at one year with recurrent cystocele and/or rectocele or with combined vaginal vault prolapse who were treated by either posterior or anterior mesh interposition depending on defect. Findings suggest that the interposition of a monofilament polypropylene mesh by the vaginal route seems to be an excellent procedure for definitive repair of recurrent anterior/posterior vaginal wall prolapse or combined prolapse, has low morbidity and is well tolerated by the patients.</p> <p>Note: <i>The Consultee also mentioned a confidential abstract. The Committee’s attention was drawn to its existence, but details of it have not been included in this consultation comments table.</i></p>	The guidance now says at section 2.5.2: “The Committee noted that there is a rapidly accumulating evidence base for this procedure. A number of further studies on mesh repair have been published since the systematic review was carried out, or are in progress with initial results to be made available in the near future. The updated evidence base will inform the review of this guidance in due course.”
35	American Medical Systems, Manufacturer	General – Anterior prolapse	<p>1) Low-Weight Polypropylene Mesh for Anterior Vaginal Wall Prolapse – A Randomized Controlled Trial Hiltunen, Nieminen, Takal, Heiskanen, Merikari, Niemi, Heinonen Obstetrics & Gynecology, Vol. 110, No. 2, Part 2, August 2007 455-462</p> <p>Summary: Study compared 201 women who were randomly assigned to anterior colporrhaphy with or without a tailored mesh. Primary outcome was recurrence of anterior vaginal prolapse at 12 months. Conclusion: Anterior colporrhaphy reinforced with tailored mesh significantly reduced the rate of recurrence of anterior vaginal wall prolapse compared with the traditional operation but was associated more</p>	Thank you for these references. See response to comment 34.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			<p>often with SUI (stress urinary incontinence).</p> <p>2) Note: <i>The Consultee also mentioned a confidential abstract. The Committee's attention was drawn to its existence, but details of it have not been included in this consultation comments table.</i></p> <p>3) Prospective, Multi-center Trial Evaluating the Perigee™ System with Polypropylene Mesh for Cystocele Repair: Estrogenicity and Outcomes Moore, et.al. Abstract AUGS 2007 Scientific Meeting Summary: Ongoing, prospective, multi-center study to evaluate the safety and effectiveness of the Perigee System and whether there is a correlation between vaginal estrogen levels and extrusion rates. Ninety eight women underwent the procedure to repair a cystocele and were seen for follow up at 6 wks, 3, 6, 12, & 24 months and an objective assessment of vaginal estrogenicity and atrophy was made. It was found that the Perigee System with polypropylene mesh is safe and effective and resulted in a low extrusion rate in a mostly post-menopausal population with mild atrophy (moderate estrogenicity). There did not seem to be a correlation between vaginal estrogen levels and the incidence of an extrusion.</p> <p>4) Note: <i>The Consultee also mentioned a confidential abstract. The Committee's attention was drawn to its existence, but details of it have not been included in this consultation comments table.</i></p>	
36	Johnson & Johnson Medical, Manufacturer	General	Johnson & Johnson Medical broadly agree with the conclusions reached by IPAC and support the position suggested on the use of mesh in the treatment of Pelvic Organ Prolapse (POP).	Thank you for these references. See response to comment 34.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			<p>We would like to draw to your attention additional data we have identified which we believe further supports the role of mesh in this disease area. This evidence was either not included in the ReBIP systematic review or has been published subsequently:</p> <ol style="list-style-type: none"> 1. Abdel-fattah M, Ramsay I on behalf of the West of Scotland Study Group. Retrospective multicentre study of the new minimally invasive mesh repair devices for pelvic organ prolapse. BJOG 2008;115:22-30 2. Al-Nazer MA, Ismai, WA, Gomaa IA. The incidence of recurrent cystourethrocele after anterior vaginal wall repair with and without reinforcement with polypropylene mesh (Gynemesh PS) :1-year follow-up. Int Urogynecol J (2007) 18 (Suppl 1):S49-50 3. Altman D, Väyrynen T, Engh ME, Axelsen S, Falconer C; For the Nordic Transvaginal Mesh Group. Short-term outcome after transvaginal mesh repair of pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Dec 12 [Epub ahead of print] 4. Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008;115:391-397. 5. De Vita D, Araco F, Gravante G, Sesti F, Piccione E. Vaginal reconstructive surgery for severe pelvic organ prolapses: A 'uterine-sparing' technique using polypropylene prostheses. European Journal of Obstetrics & Gynecology and Reproductive Biology 	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			<p>6. Neuman M, Friedman M. [Advanced mesh implants for vaginal pelvic floor reconstruction: report of 100 prolift operations] Harefuah. 2007;146(12):923-7, 999-1000</p> <p>Additionally, a number of conference abstracts were identified and provided to ReBIP. Again, we believe this data set adds further credibility to the evidence base supporting the role of mesh in POP surgery. We have attached a summary for consideration by the IPAC.</p>	

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcatheter aortic valve implantation for aortic stenosis

Aortic stenosis occurs when the aortic valve, which separates the main pumping chamber of the heart from the circulation, becomes partially narrowed. This reduces the flow of blood out of the heart. Transcatheter aortic valve implantation is an alternative to surgical valve replacement. The procedure is performed through a tube, which is inserted into either a blood vessel at the top of the leg (transluminal approach) or into the apex of the heart (transapical approach). Through this tube, a replacement valve is inserted and deployed over the faulty native valve.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in December 2007.

Procedure name

- Transcatheter aortic valve implantation

Specialty societies

- Society of Cardiothoracic Surgeons of Great Britain and Ireland
- British Cardiovascular Intervention Society
- Society of Clinical Perfusionists

IP overview: Transcatheter aortic valve implantation for aortic stenosis

Description

Indications

Aortic stenosis involves the progressive narrowing of the aortic valve causing impaired outflow of blood from the heart. This requires the left ventricle to pump harder to maintain a normal circulation. Over time, left ventricular hypertrophy and heart failure may develop. Symptoms of aortic stenosis include exertional chest pain, breathlessness, dizziness and fainting.

Outcome measures that are normally used to assess the severity of the condition include:

Clinical assessment:

- New York Heart Association (NYHA) heart failure classification: is used to classify the severity of breathlessness: from class I, in which the patient has no limitation in daily physical activity, to class IV, in which the patient is breathless at rest.
- Haemodynamic assessment (usually by echocardiography and Doppler):
 - Aortic valve area (cm^2) or aortic valve area index (relative to body surface area; cm^2/m^2). Aortic valve area $<0.6 \text{ cm}^2/\text{m}^2$ indicates severe aortic stenosis.
 - Transaortic gradient (mmHg). Peak transaortic valve gradient $>64 \text{ mmHg}$ and mean transaortic valve gradient $>40 \text{ mmHg}$ indicates severe aortic stenosis.

Current treatment and alternatives

Surgical aortic valve replacement involves replacing the diseased valve with a artificial one (made of biological tissue or metal) through a median sternotomy and using cardiopulmonary bypass. This procedure carries a very high risk for some patients, particularly those who are elderly and/or who suffer from concomitant illnesses.

Percutaneous balloon valvuloplasty may be used to treat aortic stenosis, usually in a palliative context for very ill patients who cannot undergo surgery.

What the procedure involves

Transcatheter aortic valve replacement may be carried out under general anaesthesia or under local anaesthesia with or without sedation. Imaging guidance, including fluoroscopy, angiography and transoesophageal echocardiography is required. Prophylactic antibiotics and anticoagulation medication are administered before and during the procedure. Temporary

IP overview: Transcatheter aortic valve implantation for aortic stenosis

peripheral extracorporeal circulatory support (usually via the femoral vessels) may also be used.

The procedure aims to implant a bioprosthetic aortic valve at the site of the native aortic valve. Access to the aortic valve can be achieved transluminally, with entry to the circulation usually achieved via the femoral artery or vein (sometimes known as a percutaneous or endovascular approach); or surgically, with access to the aortic valve via apical puncture of the left ventricle using a minithoractomy approach (transapical, or transventricular approach). In the transluminal approach, when the femoral vein is used, the interatrial septum is punctured in order to gain access to the left ventricle via the left atrium and mitral valve; when the femoral artery is used, surgical exposure and closure may be required. The choice of how catheter access to the aortic valve is achieved may depend on the existence of factors that make passage through the circulation difficult such as peripheral vascular disease.

Regardless of the approach, a balloon catheter is advanced into the left ventricle over a guidewire and positioned at the opening of the aortic valve. Dilatation of the native aortic valve is carried out, in order to make room for the implantable valve. In order to provide a stable platform for aortic valve implantation, rapid right ventricular pacing is used to temporarily interrupt cardiac output through the native aortic valve. The new valve is mounted on a metal stent which is either self-expanding or deployed using inflation of a large balloon on which the stented valve has been crimped. Deployment leads to obliteration of the native aortic valve.

Efficacy

There were four case series and one case report of patients who underwent transcatheter aortic valve replacement via a transluminal approach^{1,2,3,4,5} and three case series of patients who underwent the procedure via a transapical approach^{6,7,8}.

Technical success

The transluminal procedure was carried out successfully in 88% (76/86), 86% (43/50), and 75% (27/36) of patients in three case series^{1,2,3}. One case series of this approach did not report the procedural success rate⁴.

The most common causes of technical failure in the transluminal approach were misplacement (or suboptimal placement) of the device which occurred in 4% (2/50) and 9% (8/86) in two case series^{2,1} and inability to cross the diseased valve which occurred in 2% (2/86), 3% (1/36) and 6% (3/50) in three case series (1/36, 2/86 and 3/50)^{1,3,2}.

A case series of seven patients reported a 100% procedural success rate for the transapical approach⁸. In two other case series of 30 and 59 patients who

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underwent the transapical procedure (which included duplicate reporting of some patients), conversion to sternotomy was required in one patient (3%) and four patients (7%) respectively^{7,6}. In the former study, sternotomy was required because the patient had severe calcification of one of the native aortic valve cusps which did not allow safe implantation of the new valve. In the latter study, all conversions to sternotomy were due to incorrect positioning of the valve⁷.

Haemodynamic improvement

Mean aortic valve gradient improved significantly after the procedure in all four case series of the transluminal approach. It decreased from 46 mmHg at baseline to 11 mmHg at discharge in one case series ($p = 0.001$)², from 37 mmHg at baseline to 9 mmHg 24 hours after the procedure in another ($p < 0.0001$)³, from 51 mmHg at baseline to 9 mmHg 1 month after the procedure in a third ($p < 0.00001$)⁴, and from 44 mmHg at baseline to 9 mmHg 1 month after the procedure in the fourth ($p < 0.001$)¹.

For the transapical approach, the case series of 59 patients reported a mean post-procedural aortic gradient of 9 mmHg in 40 patients at discharge from hospital (baseline value not reported)⁶. In the case series of 30 patients, mean aortic gradient improved from 43 mmHg at baseline to 8 mmHg at discharge from hospital⁷. In the case series of seven patients, echocardiographic follow-up was completed in six patients at 1 month and four patients at 6 months. At baseline, 1-month and 6-month follow-up, mean aortic gradient was 32 mmHg, 10 mmHg and 11 mmHg respectively⁸.

In three case series of the transluminal approach, mean aortic valve area improved significantly after the procedure. Mean estimated aortic valve area increased from a baseline of 0.6 to 1.7 cm² at discharge in one case series ($p = 0.0001$)², from 0.60 to 1.9 cm² 24 hours after the procedure in a second ($p < 0.0001$)³ and from 0.56 to 1.3 cm² 1 month after the procedure in a third ($p < 0.0001$)⁴.

Only one case series ($n = 7$) of the transapical approach reported aortic valve area at follow-up. At baseline ($n = 7$), 1-month ($n = 6$) and 6-month ($n = 4$) follow-up, mean aortic valve area was 0.7 cm², 1.8 cm² and 1.5 cm² respectively⁸.

Symptomatic improvement

In one case series of transluminal aortic valve replacement, all survivors (9/11) improved by at least one NYHA class after the procedure ($p = 0.006$) and in another case series, half of the 43 patients who had successful procedures improved by at least one NYHA class ($p < 0.0001$)². A third case series of 21 patients who survived beyond 33 days reported that 5 patients improved to NYHA class I, 14 to class II and 2 to class III³.

One case series of 86 patients, who also underwent the transluminal approach, reported that mean NYHA functional class improved from 2.85 at baseline to 1.85 at 30-day follow-up ($p < 0.001$)¹.

Only one case series ($n = 7$) of the transapical approach reported symptomatic outcomes. The authors stated that symptoms related to aortic stenosis were either resolved or significantly improved at 1- and 6-month follow-up. They also reported that postoperative NYHA class was unchanged in one patient who had end-stage lung disease preoperatively⁸.

Survival

In three case series of the transluminal approach, longer term survival was 81% (35/43; median follow-up at 359 days)², 45% (5/11; median follow-up at 305 days)⁴ and 41% (11/27; follow-up at 6 months)³.

Safety

In two case series of the transluminal approach, 30-day mortality was 12% (10/86 and 6/50). Five of the ten deaths in the first study and one of the six in the second were intraprocedural¹. In another two case series, among patients for whom the transluminal procedure was technically successful, 30-day and in-hospital mortality were 22% (6/27) and 18% (2/11) respectively⁴.

The rates of in-hospital mortality in two case series of the transapical approach were: 14% (8/59) and 10% (3/30)^{6,7}. A third case series of seven patients treated with the transapical approach reported 14% (1/7) 30-day mortality and 2 further cancer-related deaths during a 6-month follow-up⁸.

There was an additional case report of a patient in whom antegrade transluminal valve implantation was abandoned because of guidewire-induced mitral regurgitation and cardiac arrest. After resuscitation, the procedure was performed via a retrograde approach. Despite improved valve function, the patient died secondary to guidewire-induced mitral valve leaflet laceration, severe mitral regurgitation and cardiogenic shock, five days after the procedure⁵.

Incidence of stroke within 30 days was reported in 12% (9/76)¹, 4% (1/27)³, 9% (1/11)⁴ and 2% (1/43)² of patients who underwent successful transluminal procedures. The latter two patients subsequently died within 30 days of the procedure. Other complications within 30 days reported in these four case series included: bradyarrhythmia in 36% (4/11) of patients, major bleeding in 18% (2/11)⁴; cardiac tamponade in 10% (9/86)¹; and iliac injury requiring major vascular repair in 5% (2/43) and access site infection requiring antibiotics in 5% (2/43)².

In one case series of the transapical approach ($n = 7$), one patient each had pleural effusion and lower urinary tract infection and two patients had moderate paravalvular regurgitation which reduced after redilation and further expansion of the prosthesis⁸.

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The two case series of 30 patients and 59 patients (which included duplicate reporting of some patients) the incidence of pleural effusion was 37% (11/30) and 31% (18/59) of patients respectively and supraventricular tachyarrhythmia was 30% (9/30) and 31% (18/59) respectively^{7,6}. In both studies, the transapical approach was used.

The case series of 59 patients also reported two (3%) strokes, eight patients (14%) with transient hemofiltration, eight patients (14%) who required tracheostomy for weaning off ventilation, eight patients (14%) who required rethoracotomy, four patients (7%) requiring cardiopulmonary resuscitation, and three patients (4%) with pericardial effusion⁶.

The case series of 30 patients also reported the following complications: transient hemofiltration (13%), tracheostomy (10%), cardiopulmonary resuscitation (7%) and other nonspecified complications (47%)⁷.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous aortic valve implantation. Searches were conducted via the following databases, covering the period from their commencement to 13/11/07: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See appendix C for details of search strategy.)

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good-quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty in appraising methodology.
Patient	Patients with aortic stenosis.
Intervention/test	Transcatheter aortic valve implantation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on seven case series^{1-4,6,7} and one case report⁵.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures

- Balloon valvuloplasty for aortic valve stenosis in adults and children. NICE interventional procedures guidance 78 (2004). Available from www.nice.org.uk/IPG078
- Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction. NICE interventional procedures guidance 237 (2007). Available from www.nice.org.uk/IPG237

Technology appraisals

- None

Clinical guidelines

- None

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Public health

- None

Table 2a Summary of key efficacy and safety findings on transcatheter aortic valve implantation (transluminal approach)

Abbreviations used: AVR, aortic valve replacement; CAD, coronary artery disease; NYHA, New York Heart Association; TEE, transesophageal echocardiographic.																				
Study details	Key efficacy findings		Key safety findings	Comments																
<p>Grube et al (2007)¹ <i>Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second and current third-generation self-expanding CoreValve prosthesis.</i></p> <p>Study design: prospective case series Country: Canada and Germany (multi-centre) Study period: Aug 2005–Feb 2007</p> <p>Population: high-risk patients with severe symptomatic aortic valve disease (stenosis with or without regurgitation) who could not be considered for open heart surgery n = 86 Mean age: 82 years. Male: 35%. Mean EuroSCORE: 22% Comorbidities: hypertension (72%), CAD (56%), diabetes mellitus (31%), congestive heart failure (22%)</p> <p>Technique: aortic valve replacement via a retrograde percutaneous transvascular approach. A size 21-F device was used in the first 50 patients and a size 18-F device was used in the latter 36 patients. Device: CoreValve Inc, USA</p> <p>Mean follow-up: not reported</p> <p>Disclosure of interest: two authors were consultants to the device manufacturer.</p>	<p>Procedural success: 88% (76/86) Reasons for technical failure:</p> <ul style="list-style-type: none"> Valve misplacement requiring open conversion (n = 6) Device could not cross calcified native valve so balloon valvuloplasty was performed (n = 2) Suboptimal placement of prosthesis requiring second implantation of a similar prosthesis (n = 2) <p>Clinical follow-up (30 days) Baseline NYHA functional class:</p> <ul style="list-style-type: none"> I and II: 17% (15/86) III and IV: 83% (71/86) Mean: 2.85 ± 0.73 <p>Postoperative NYHA functional class:</p> <ul style="list-style-type: none"> Mean: 1.85 ± 0.60 Difference between baseline and postoperative: p-value <0.001 <p>Echocardiographic follow-up (30 days)</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>Postoperative</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td>Mean aortic transvalvular gradient (mmHg)</td> <td>44 ± 15</td> <td>9</td> <td><0.001</td> </tr> <tr> <td>Mean calculated aortic valve area (cm²)</td> <td>0.60 ± 0.16</td> <td>Not reported</td> <td></td> </tr> <tr> <td>Mean left ventricular ejection fraction (%)</td> <td>54.1 ± 16.3</td> <td>Not reported</td> <td></td> </tr> </tbody> </table> <p>Aortic regurgitation grade (of 76 successful procedures)</p> <p>Postoperative: Unchanged or reduced: 66% Worsened: 20% (all due to paravalvular leakage) No cases of severe regurgitation.</p>			Baseline	Postoperative	p-value	Mean aortic transvalvular gradient (mmHg)	44 ± 15	9	<0.001	Mean calculated aortic valve area (cm ²)	0.60 ± 0.16	Not reported		Mean left ventricular ejection fraction (%)	54.1 ± 16.3	Not reported		<p>Procedural complications (see also 'reasons for technical failure' in efficacy column):</p> <ul style="list-style-type: none"> Suboptimal placement of the prosthesis requiring second implantation of a similar prosthesis (n = 2) Valve misplacement requiring conversion to open surgery (n = 6) <p>30-day mortality: 12% (10/86) Procedural mortality: 6% (5/86) Periprocedural mortality: 6% (5/86)</p> <ul style="list-style-type: none"> After conversion to balloon valvuloplasty (n = 1) After conversion to surgical aortic valve replacement (n = 1) Due to pericardial tamponade (n = 3) <p>30-day complications</p> <ul style="list-style-type: none"> Stroke: 10% (9/86) Myocardial infarction: 1% (1/86) Cardiac tamponade: 10% (9/86) (six cases were likely to be procedure-related) 	<p>Study objective: to evaluate the feasibility, safety and clinical outcome of implantation of the self-expanding CoreValve aortic valve prosthesis in high-risk patients with aortic valve disease.</p> <p>EuroSCORE: method of calculating predicted operative mortality for patients undergoing cardiac surgery Risk factors are weighted and added to give an approximate percent predicted mortality.</p>
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IP overview: Transcatheter aortic valve implantation for aortic stenosis

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<p>Webb et al (2007)² <i>Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis.</i></p> <p>Study design: case series Country: Vancouver, Canada Study period: not reported</p> <p>Population: high-risk patients with severe symptomatic aortic valve disease who could not be considered for open heart surgery n = 50 Mean age: 82 ± 7 years. Male: 60%. Mean EuroSCORE: 28% Comorbidities: CAD (72%), moderate to severe regurgitation (48%), prior thoracotomy (34%), severe lung disease (32%)</p> <p>Technique: percutaneous transfemoral transarterial valve replacement. A balloon-mounted valve was passed retrogradely through the aorta and positioned within the native aortic annulus under fluoroscopic, aortographic and TEE guidance. Device: Edwards Lifesciences Inc, USA</p> <p>Mean follow-up: not reported. Clinical outcomes assessed at 1, 6 and 12 months.</p> <p>Disclosure of interest: two authors were consultants to the device manufacturer.</p>	<p>Procedural success: 86% (43/50) Reasons for technical failure: inability to pass iliac artery (n = 1), inability to cross aortic valve (n = 3), defective prototype delivery catheter (n = 1), malpositioning (n = 2).</p> <p>Clinical follow-up (30 days) Baseline NYHA functional class:</p> <ul style="list-style-type: none"> • II: 10% (5/50) • III: 64% (32/50) • IV: 26% (13/50) <p>Postoperative NYHA functional class:</p> <ul style="list-style-type: none"> • 50% of patients (who had successful procedures) improved by ≥ 1 NYHA functional class (p < 0.0001) (<i>no further details reported</i>). <p>Echocardiographic follow-up (at discharge)</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>Postoperative</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td>Mean transaortic gradient (mmHg)*</td> <td>46 ± 17</td> <td>11 ± 5</td> <td>0.001</td> </tr> <tr> <td>Mean estimated aortic valve area (cm²)*</td> <td>0.6 ± 0.2</td> <td>1.7 ± 0.4</td> <td>0.0001</td> </tr> <tr> <td>Mean left ventricular ejection fraction (%)*</td> <td>53 ± 15</td> <td>57 ± 13</td> <td>0.0001</td> </tr> <tr> <td>Median mitral regurgitation grade*</td> <td>2 (moderate)</td> <td>1 (mild)</td> <td>0.01</td> </tr> <tr> <td>Median aortic regurgitation grade</td> <td>1 (none/trivial)</td> <td>1 (mild)</td> <td>0.57</td> </tr> </tbody> </table> <p>No patients had more than mild prosthetic valvular insufficiency. Most patients had some paravalvular insufficiency. *Improvements maintained at 1 year</p> <p>Subsequent valve operations: 6% (3/50) All were due to ongoing symptomatic aortic stenosis after unsuccessful transcatheter procedure.</p>		Baseline	Postoperative	p-value	Mean transaortic gradient (mmHg)*	46 ± 17	11 ± 5	0.001	Mean estimated aortic valve area (cm ²)*	0.6 ± 0.2	1.7 ± 0.4	0.0001	Mean left ventricular ejection fraction (%)*	53 ± 15	57 ± 13	0.0001	Median mitral regurgitation grade*	2 (moderate)	1 (mild)	0.01	Median aortic regurgitation grade	1 (none/trivial)	1 (mild)	0.57	<p>30-day mortality: 12% (6/50) One intraprocedural death (2%) due to aortic injury. Five periprocedural deaths during 30 days due to:</p> <ul style="list-style-type: none"> • Ventricular arrhythmia • Left main occlusion • Iliac injury • Stroke • Multiorgan failure <p>30-day complications (of 43 successful procedures)</p> <ul style="list-style-type: none"> • Iliac injury requiring major vascular repair: 5% (2/43, first patients in series). One patient subsequently died • Abdominal aorta perforation: 3% (1/43). Patient subsequently died • Retroperitoneal bleeding from iliac artery perforation: 3% (1/43). Patient was successfully treated with a covered stent • Antibiotics for access site infection: 5% (2/43) • Periprocedural stroke: 2% (1/43). Patient died on day 29 <p>Late outcomes</p> <ul style="list-style-type: none"> • 3 deaths after 30 days due to respiratory failure, myocardial infarction, renal failure • 81% (35/43) of patients who had successful operations were alive at time of publication (median follow-up: 359 days) 	<p>Study objective: Not stated.</p> <p>The authors also compared results for the first and last 25 patients in the series, which demonstrated a significant learning curve (rates of procedural success, malposition, intraprocedural and periprocedural mortality were lower on the latter group).</p>
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IP overview: Transcatheter aortic valve implantation for aortic stenosis

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Study details	Key efficacy findings		Key safety findings	Comments																				
<p>Cribier et al (2006)³ <i>Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience.</i></p> <p>Study design: case series Country: France Study period: Aug 2003– (unknown)</p> <p>Population: elderly patients with symptomatic severe aortic valve stenosis ($\leq 0.7\text{cm}^2$) who were refused for standard AVR n = 36 Mean age: 80 ± 7 years. Male: 57%. Mean EuroSCORE: 12% Comorbidities: CAD (76%), hypertension (70%), severe lung disease (41%), renal failure (38%), pulmonary hypertension (38%), diabetes mellitus (32%), mitral valve disease (32%)</p> <p>Technique: percutaneous heart valve implantation via a an antegrade trans-septal approach (n = 26) or retrograde approach (n = 7) Device: Edwards LifeSciences Inc, USA</p> <p>Mean follow-up: not reported Range of follow-up: 9–26 months)</p> <p>Disclosure of interest: study was funded by the device manufacturer.</p>	<p>Procedural success: 75% (27/36) (One patient died before the procedure, one procedure was cancelled after predilation due to large annulus size, one patient died during predilation)</p> <p>Reasons for technical failure: procedure aborted as patients could not haemodynamically tolerate the guidewire across the mitral valve (n = 2), valve migration immediately after implantation (n = 2), catheter too short to reach aortic valve (n = 1), valve could not be crossed retrogradely due to extensive calcification (n = 1).</p> <p>Clinical follow-up (of 21 patients who survived beyond 33 days) Follow-up duration and baseline NYHA class not reported</p> <ul style="list-style-type: none"> Improvement to NYHA class I (n = 5) Improvement to NYHA class II (n = 14) Improvement to NYHA class III (n = 2) <p>Echocardiographic follow-up (24 hours post-procedure)</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>Postoperative</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td>Mean aortic gradient (mmHg)*</td> <td>37 ± 13</td> <td>9 ± 2</td> <td>< 0.0001</td> </tr> <tr> <td>Mean aortic valve area (cm^2)*</td> <td>0.60 ± 0.09</td> <td>1.9 ± 0.11</td> <td>< 0.0001</td> </tr> <tr> <td>Mean left ventricular ejection fraction (%) (n = 22)</td> <td>45 ± 18</td> <td>53 ± 14</td> <td>0.02</td> </tr> <tr> <td>Aortic regurgitation grade (n)</td> <td><i>Baseline values not reported</i></td> <td>Mild (≤ 1): 10 Moderate (2): 10 Moderate to severe (> 2): 5</td> <td></td> </tr> </tbody> </table> <p>*n = 25 patients surviving at 24 hours. Postoperative improvements in aortic gradient and aortic valve area were sustained at 1, 3, 6 12 and 24 months</p>			Baseline	Postoperative	p-value	Mean aortic gradient (mmHg)*	37 ± 13	9 ± 2	< 0.0001	Mean aortic valve area (cm^2)*	0.60 ± 0.09	1.9 ± 0.11	< 0.0001	Mean left ventricular ejection fraction (%) (n = 22)	45 ± 18	53 ± 14	0.02	Aortic regurgitation grade (n)	<i>Baseline values not reported</i>	Mild (≤ 1): 10 Moderate (2): 10 Moderate to severe (> 2): 5		<p>Procedural complications (see also 'reasons for technical failure' in efficacy column):</p> <ul style="list-style-type: none"> Valve migration immediately after implantation (n = 2) <p>Major adverse cardiac and cerebrovascular events at 30 days</p> <ul style="list-style-type: none"> Death: 22% (6/27) <ul style="list-style-type: none"> Cardiac tamponade (n = 2) Urosepsis (n = 1), patient was on chronic steroids for rheumatologic disease Ventricular arrhythmia (n = 1) Brain death post resuscitation (n = 1) Death, unexplained at autopsy and not device-related (n = 1) Stroke: 4% (1/27) <p>Additional major adverse cardiac and cerebrovascular events at 6 months</p> <ul style="list-style-type: none"> Death: 3% (10/27) <ul style="list-style-type: none"> Renal failure (n = 3) Postoperative (n = 3) Pulmonary embolus (n = 1) Pneumonia (n = 1) Cancer (n = 1) Multi-organ failure (n = 1), patient suffered a procedural stroke and died 33 days postoperatively 	<p>Study objective: to evaluate the feasibility and safety of percutaneous heart valve implantation.</p>
	Baseline	Postoperative	p-value																					
Mean aortic gradient (mmHg)*	37 ± 13	9 ± 2	< 0.0001																					
Mean aortic valve area (cm^2)*	0.60 ± 0.09	1.9 ± 0.11	< 0.0001																					
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IP overview: Transcatheter aortic valve implantation for aortic stenosis

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<p>Berry et al (2007)⁴ <i>Novel therapeutic aspects of percutaneous aortic valve replacement with the 21F CoreValve Revalving system.</i></p> <p>Study design: case series Country: Quebec, Canada Study period: Mar 2005–Feb 2007</p> <p>Population: patients with severe aortic valve disease (aortic area index $\leq 0.6\text{cm}^2/\text{m}^2$) who were declined for surgical valve replacement n = 13 (2 patients were subsequently found to have unsuitable peripheral vascular access) Mean age: 82 ± 7 years. Male: 46%. Median EuroSCORE: 36% Comorbidities: chronic renal insufficiency (70%), pulmonary hypertension (69%), hypertension (54%), pulmonary hypertension (38%), diabetes mellitus (23%), moderate to severe mitral regurgitation (45%)</p> <p>Technique: percutaneous aortic valve replacement Device: CoreValve Inc, USA</p> <p>Median follow-up: 305 days (in survivors)</p> <p>Disclosure of interest: study was funded by the device manufacturer.</p>	<p>Clinical follow-up (1 month) Baseline NYHA functional class:</p> <ul style="list-style-type: none"> • III: 77% (10/13) • IV: 23% (3/13) <p>Postoperative NYHA functional class:</p> <ul style="list-style-type: none"> • NYHA class improved by two classes in one patient and one class in all other survivors ($p = 0.006$) (<i>no further details reported</i>). <p>Echocardiographic follow-up</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>Postoperative (1 month)</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td>Mean estimated aortic valve area (cm^2)</td> <td>0.56 ± 0.19</td> <td>1.3 ± 0.4</td> <td>< 0.0001</td> </tr> <tr> <td>Mean aortic valve gradient (mmHg)</td> <td>51 ± 19</td> <td>9 ± 4</td> <td>< 0.00001</td> </tr> <tr> <td>Mean left ventricular ejection fraction (%)</td> <td>49 ± 17</td> <td>56 ± 11</td> <td>Not reported</td> </tr> <tr> <td>Aortic regurgitation grade (n)</td> <td></td> <td>Mild (≤ 1): 7 Moderate (2): 4</td> <td></td> </tr> </tbody> </table>				Baseline	Postoperative (1 month)	p-value	Mean estimated aortic valve area (cm^2)	0.56 ± 0.19	1.3 ± 0.4	< 0.0001	Mean aortic valve gradient (mmHg)	51 ± 19	9 ± 4	< 0.00001	Mean left ventricular ejection fraction (%)	49 ± 17	56 ± 11	Not reported	Aortic regurgitation grade (n)		Mild (≤ 1): 7 Moderate (2): 4		<p>Safety outcomes are reported for the 11 patients who underwent the procedure.</p> <p>In-hospital mortality: 18% (2/11)</p> <ul style="list-style-type: none"> • Stroke following operation due to iatrogenic iliac artery endarterectomy ($n = 1$) • Cerebral haemorrhage 20 days postoperatively ($n = 1$), patient had a mitral valve prosthesis <p>30-day complications</p> <ul style="list-style-type: none"> • Stroke: 9% (1/11) (patient died on postoperative day 20) • Major bleeding: 18% (2/11) • Bradyarrhythmia: 36% (4/11) <p>Long-term mortality: 38% (3/8 surviving patients) Deaths due to:</p> <ul style="list-style-type: none"> • Cardiac failure 101 and 118 days postoperatively respectively ($n = 2$) • Chest infection 75 days postoperatively ($n = 1$) 	<p>Study objective: to investigate whether novel therapeutic approaches may facilitate aortic valve replacement outcomes for high-risk patients.</p>
	Baseline	Postoperative (1 month)	p-value																						
Mean estimated aortic valve area (cm^2)	0.56 ± 0.19	1.3 ± 0.4	< 0.0001																						
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Study details	Key efficacy findings	Key safety findings	Comments
<p>Hanzel et al. (2005)⁵ <i>Retrograde percutaneous aortic valve implantation for critical aortic stenosis.</i></p> <p>Study design: case report Country: Michigan, USA Study period: not reported</p> <p>Patient: 84-year old man with critical aortic stenosis, refractory severe congestive heart failure, failure of prior balloon aortic valvuloplasty and refused surgical aortic valve replacement n = 1</p> <p>Technique: percutaneous aortic valve implantation via an antegrade transseptal approach was attempted and subsequently changed (to a retrograde approach) during the procedure. Initial balloon valvuloplasty was performed to predilate the valve.</p> <p>Follow-up: 5 days</p> <p>Disclosure of interest: none stated</p>	<p>Successful implantation.</p> <p>Aortic valve area increased from 0.55 to 1.7 cm² with only mild paravalvular aortic regurgitation.</p>	<p>Patient died on postoperative day 5 secondary to guidewire-induced mitral valve leaflet laceration, which occurred during the antegrade approach leading to severe mitral regurgitation and cardiogenic shock.</p>	<p>Antegrade implantation was attempted but retrograde placement was performed because of complications.</p>

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<p>Walther et al (2007)⁶ <i>Transapical minimally invasive aortic valve implantation: multicentre experience.</i></p> <p>Study design: case series Country: Germany, Vienna, USA (multicentre) Study period: not reported</p> <p>Population: high-risk patients with severe symptomatic aortic valve stenosis; not considered for open heart surgery. n = 59 Mean age: 81 ± 6 years Male: 25% Euroscore estimated mortality risk: 27 ± 14% Mean NYHA class: 3.4 ± 0.5 Comorbidities: hypertension (74%), mitral incompetence (41%), CAD (37%), renal failure (34%), pulmonary hypertension (32%), diabetes mellitus (27%).</p> <p>Technique: transapical transcatheter aortic valve implantation via a left minithoracotomy using 23mm (n = 19) or 26mm (n = 40) diameter prostheses Device: Cribier-Edwards valve (Edwards LifeSciences Inc, USA)</p> <p>Mean follow-up: 110 ± 77 days</p> <p>Disclosure of interest: several authors were consultants to the device manufacturer</p>	<p>Intraoperative conversion to sternotomy: 7% (4/59). All were due to incorrect positioning of the valve (2 patients died in-hospital).</p> <p>Echocardiographic follow-up</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>Discharge (n = 40)</th> </tr> </thead> <tbody> <tr> <td>Mean aortic gradient (mmHg)</td> <td><i>Not reported</i></td> <td>9 ± 6</td> </tr> <tr> <td>Mean aortic valve area (cm²)</td> <td>0.5 ± 0.2</td> <td><i>Not reported</i></td> </tr> <tr> <td>Mean left ventricular ejection fraction (%)</td> <td>47 ± 16</td> <td><i>Not reported</i></td> </tr> <tr> <td>Aortic incompetence grade (number of patients)</td> <td><i>Not reported</i></td> <td>None: 14 Trace: 11 Mild (1): 12 Moderate (1-2): 2 Severe (> 2): 1</td> </tr> </tbody> </table>			Baseline	Discharge (n = 40)	Mean aortic gradient (mmHg)	<i>Not reported</i>	9 ± 6	Mean aortic valve area (cm ²)	0.5 ± 0.2	<i>Not reported</i>	Mean left ventricular ejection fraction (%)	47 ± 16	<i>Not reported</i>	Aortic incompetence grade (number of patients)	<i>Not reported</i>	None: 14 Trace: 11 Mild (1): 12 Moderate (1-2): 2 Severe (> 2): 1	<p>Mortality</p> <ul style="list-style-type: none"> Overall mortality: 22% (13/59) In-hospital mortality: 14% (8/59) 30-day mortality: 14% (8/59) <p>Complications</p> <ul style="list-style-type: none"> Stroke: 3% (2/59) Pleural effusion: 31% (18/59) Supraventricular arrhythmia: 31% (18/59) Transient hemofiltration: 14% (8/59) Tracheostomy: 14% (8/59) Cardiopulmonary resuscitation (successful): 7% (4/59) Pericardial effusion: 4% (3/59) Rethoracotomy: 14% (8/59) 	<p>The authors comment that no deaths were procedure- or valve-related (good valve function with patent coronary arteries was proven at autopsy)</p> <p>Early procedures were performed on-pump but with increasing experience femoral cannulation without cardiopulmonary bypass was used.</p>
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Mean aortic gradient (mmHg)	<i>Not reported</i>	9 ± 6																	
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<p>Walther et al (2007)¹ <i>Minimally invasive transapical beating heart aortic valve implantation: proof of concept.</i></p> <p>Study design: case series Country: Germany Study period: Feb 2006 – Sept 2006</p> <p>Population: high-risk patients with severe symptomatic aortic valve stenosis; not considered for open heart surgery (Euroscore estimated mortality risk > 11% and aortic annulus diameter ≤ 24mm). n = 30 Mean age: 82 ± 5 years Male: 30% Euroscore estimated mortality risk: 27 ± 12% Mean NYHA class: 3.5 ± 0.6 Comorbidities: hypertension (77%), renal failure (43%), diabetes mellitus (40%), CAD (23%), pulmonary disease or chronic obstructive pulmonary disorder (23%), mitral incompetence (20%).</p> <p>Technique: transapical transcatheter aortic valve implantation via a left minithoracotomy using 23mm (n = 8) or 26mm (n = 22) diameter prostheses Device: Cribier-Edwards valve (Edwards LifeSciences Inc, USA)</p> <p>Mean follow-up: 127 ± 63 days</p> <p>Disclosure of interest: none stated</p>	<p>Intraoperative conversion to sternotomy: 3% (1/30). Patient had severe calcification of one native valve cusp (conventional valve placement was successful).</p> <p>Echocardiographic follow-up</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>Discharge</th> </tr> </thead> <tbody> <tr> <td>Mean aortic gradient (mmHg)</td> <td>43 + 14</td> <td>8 ± 5</td> </tr> <tr> <td>Mean aortic valve area (cm²)</td> <td>0.5 ± 0.2</td> <td><i>Not reported</i></td> </tr> <tr> <td>Mean left ventricular ejection fraction (%)</td> <td>52 ± 13</td> <td>55 ± 12</td> </tr> <tr> <td>Aortic incompetence grade (number of patients)</td> <td><i>Not reported</i></td> <td>Trace: 3 Mild (1): 9 Moderate (1-2): 2</td> </tr> </tbody> </table>			Baseline	Discharge	Mean aortic gradient (mmHg)	43 + 14	8 ± 5	Mean aortic valve area (cm ²)	0.5 ± 0.2	<i>Not reported</i>	Mean left ventricular ejection fraction (%)	52 ± 13	55 ± 12	Aortic incompetence grade (number of patients)	<i>Not reported</i>	Trace: 3 Mild (1): 9 Moderate (1-2): 2	<p>In-hospital mortality: 10% (3/30) No deaths were valve-related. Due to:</p> <ul style="list-style-type: none"> • An acute abdomen followed by multiorgan failure (n = 2; on postoperative days 18 and 86) • Low cardiac output syndrome in patient with severe biventricular myocardial failure during induction of anaesthesia <p>Complications</p> <ul style="list-style-type: none"> • Pleural effusion: 37% (11/30) • Supraventricular tachyarrhythmia: 30% (9/30) • Transient hemofiltration: 13% (4/30) • Tracheostomy: 10% (3/30) • Cardiopulmonary resuscitation (both successful): 7% (2/30) • Others (no specified): 47% (14/30) 	<p>The patients in this study are also reported in the previous study (Walther et al 2007).</p> <p>Early procedures were performed on-pump (n = 22) but with increasing experience femoral cannulation without cardiopulmonary bypass was used (n = 8).</p>
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Abbreviations used: AVR, aortic valve replacement; CAD, coronary artery disease; NYHA, New York Heart Association; TEE, transesophageal echocardiographic.																																				
Study details	Key efficacy findings				Key safety findings	Comments																														
<p>Ye et al (2007)⁹ <i>Six-month outcome of transcatheter aortic valve implantation in the initial seven patients.</i></p> <p>Study design: case series Country: Canada Study period: not reported</p> <p>Population: high-risk patients with severe symptomatic aortic valve stenosis; not considered for open heart surgery and not suitable for percutaneous transfemoral aortic implantation because of atherosclerosis or unfavourable anatomy. n = 7 Mean age: 82 years Male: 35% Euroscore estimated mortality risk: 31 ± 23% NYHA class: 4 (n = 1), 3 (n = 4), (2 (n = 2)</p> <p>Technique: transapical transcatheter aortic valve implantation via a left minithoracotomy using a 26mm diameter prosthesis. Device: Cribier-Edwards valve (Edwards LifeSciences Inc, USA)</p> <p>Mean follow-up: not reported 6-month clinical follow-up completed in all patients</p> <p>Disclosure of interest: none stated</p>	<p>Procedural success: 100% (7/7)</p> <p>Clinical follow-up (1 and 6 months)</p> <ul style="list-style-type: none"> Symptoms related to aortic stenosis were either resolved or significantly improved at 1- and 6-month follow-up Postoperative NYHA class was unchanged in 1 patient who had end-stage lung disease <p>Echocardiographic follow-up</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>Immediately after procedure</th> <th>1 month (n = 6)</th> <th>6 months (n = 4)</th> </tr> </thead> <tbody> <tr> <td>Mean aortic gradient (mmHg)</td> <td>32 ± 8</td> <td>10 ± 7</td> <td>10 ± 5</td> <td>11 ± 8</td> </tr> <tr> <td>Mean aortic valve area (cm²)</td> <td>0.7 ± 0.3</td> <td>1.6 ± 0.6</td> <td>1.8 ± 0.7*</td> <td>1.5 ± 0.5</td> </tr> <tr> <td>Mean left ventricular ejection fraction (%)</td> <td>49 ± 9</td> <td>52 ± 13</td> <td>54 ± 8</td> <td>60 ± 9</td> </tr> <tr> <td>Median aortic regurgitation grade</td> <td>1</td> <td>1</td> <td>2</td> <td>1</td> </tr> <tr> <td>Median mitral regurgitation grade</td> <td>3</td> <td>2</td> <td>2</td> <td>2</td> </tr> </tbody> </table> <p>* Unable to calculate aortic valve area in 3 patients at 1-month follow-up</p>					Baseline	Immediately after procedure	1 month (n = 6)	6 months (n = 4)	Mean aortic gradient (mmHg)	32 ± 8	10 ± 7	10 ± 5	11 ± 8	Mean aortic valve area (cm ²)	0.7 ± 0.3	1.6 ± 0.6	1.8 ± 0.7*	1.5 ± 0.5	Mean left ventricular ejection fraction (%)	49 ± 9	52 ± 13	54 ± 8	60 ± 9	Median aortic regurgitation grade	1	1	2	1	Median mitral regurgitation grade	3	2	2	2	<p>Procedural complications</p> <ul style="list-style-type: none"> 1 patient had a pleural effusion requiring tube drainage 1 patient had lower urinary tract infection 2 patients had moderate paravalvular regurgitation which reduced after redilation resulted in further expansion of the prosthesis <p>30-day mortality: 14% (1/7)</p> <ul style="list-style-type: none"> 1 patient died on postoperative day 12 due to pneumonia <p>6-month mortality</p> <ul style="list-style-type: none"> 1 patient died on postoperative day 51 from end-stage lung cancer that existed preoperatively 1 patient died on postoperative day 85 from cancer 	<p>Study objective: to report 6-month outcomes for the first seven successful transcatheter aortic valve implantations.</p>
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Validity and generalisability of the studies

- The studies included only patients who were considered a high risk for conventional surgery because of advanced age (mean age of 80 years or above) and the presence of significant co-morbidities (for example, advanced lung disease, cerebrovascular disease and, renal failure).

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr Bernard Prendergast, Dr Martyn Thomas and Dr Olaf Wendler (British Cardiovascular Intervention Society) and Professor Tom Spyt (Society for Cardiothoracic Surgery in Great Britain and Ireland).

- All Specialist Advisers stated that this was a novel procedure and that the comparator was surgical aortic valve replacement.
- Theoretical adverse events included: death, stroke, pericardial tamponade, thromboembolic complications, valve embolisation, malplacement, prosthesis migration, paravalvular leak, access site complications, infection, need to convert to conventional surgery, need for permanent pacemaker implantation, early device failure, and impaired durability of the implanted bioprosthesis compared to bioprostheses which are used during conventional open heart surgery.
- Anecdotal adverse events included: one respiratory-related death (out of 12 patients from one centre) in a patient with severe pulmonary fibrosis, inadvertent implantation in an upside down position - remedied by second implantation (valve-in-valve), paraprosthesis leakage (of a mild degree in Specialist Advisor's own experience), and difficulty to control bleeding from the puncture hole in the left ventricle.
- All Specialist Advisers stated that there is uncertainty about the durability of the procedure (with the longest follow-up being about 4 years).

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- Key efficacy outcomes were procedural success, haemodynamic improvement, survival and reduction of symptoms.
- All Specialist Advisers stated that roll out of the procedure and training is very important and that a highly skilled multidisciplinary team is required.

Considerations for IPAC

- Procedure and device evolution; one study (Grube et al 2007) reported that original devices used were size 24F, now a size 18F device is available. In their study, a size 21-F device was used in the first 50 patients and a size 18-F device was used in the latter 36 patients. In addition, one author commented that the retrograde approach had been problematic because of the size of the delivery system and concomitant peripheral vascular disease.

References

1. Grube E, Schuler G, Buellesfeld L et al. (3-7-2007) Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. *Journal of the American College of Cardiology* 50: 69-76.
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3. Cribier A, Eltchaninoff H, Tron C et al. (21-3-2006) Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *Journal of the American College of Cardiology* 47: 1214-1223.
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6. Walther T, Simon P, Dewey T et al. (11-9-2007) Transapical minimally invasive aortic valve implantation: multicenter experience. *Circulation* 116: 1240-1245.
7. Walther T, Falk V, Borger MA et al. (2007) Minimally invasive transapical beating heart aortic valve implantation--proof of concept. *European Journal of Cardio-Thoracic Surgery* 31: 9-15.
8. Ye J, Cheung A, Lichtenstein SV et al. (2007) Six-month outcome of transapical transcatheter aortic valve implantation in the initial seven patients. *European Journal of Cardio-Thoracic Surgery* 31: 16-21.

Appendix A: Additional papers on transcatheter aortic valve implantation not included in summary table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bauer F, Eltchaninoff H, Tron C et al. (2004) Acute improvement in global and regional left ventricular systolic function after percutaneous heart valve implantation in patients with symptomatic aortic stenosis. <i>Circulation</i> 110: 1473-76.	n = 8 Follow-up: not reported Transluminal approach	Left ventricular global and regional systolic function improved immediately after percutaneous aortic valve implantation.	More recent study from the same centre included in table 2.
Berry C, Cartier R, and Bonan R. (2007) Fatal ischemic stroke related to nonpermissive peripheral artery access for percutaneous aortic valve replacement. <i>Catheterization & Cardiovascular Interventions</i> 69: 56-63.	n = 1 Follow-up: not reported Transluminal approach	85-year old man who had been refused surgical valve replacement. Procedure was successful but patient had fatal cerebral ischaemic stroke 4 days afterwards.	This patient is reported on in Berry et al 2007 from table 2.
Chandavimol M, McClure SJ, Carere RG et al. (2006) Percutaneous aortic valve implantation: a case report. <i>Canadian Journal of Cardiology</i> 22: 1159-61.	n = 1 Follow-up: not reported Transluminal approach	85-year old man who had been refused surgical valve replacement. Procedure was successful with significant clinical and haemodynamic improvement.	Larger or more recent studies are included in table 2.
Cribier A, Eltchaninoff H, Bash A et al. (2002) Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. <i>Circulation</i> 106: 3006-08.	n = 1 Follow-up: not reported (approximately 4 months) Transluminal approach	Marked haemodynamic improvement immediately after implantation, remaining over 4 months. Patient died 17 weeks after procedure due to noncardiac complications.	More recent study from the same centre included in table 2.
Cribier A, Eltchaninoff H, Tron C et al. (2004) Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. <i>Journal of the</i>	n = 6 Follow-up: not reported Transluminal approach	Technical success: 5/6 Early migration with subsequent death: 1/6 Marked and sustained haemodynamic and clinical improvement was observed after procedure.	More recent study from the same centre included in table 2.

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American College of Cardiology 43: 698-703.		Non-cardiac-related deaths: 3/6 Other patients were alive at 8 weeks with no signs of heart failure.	
Dalby M. (2003) Non-surgical aortic valve replacement. British Journal of Cardiology 10: 450-52.	n = 4 Follow-up: not reported Transluminal approach	Awaiting full article	More recent study from the same centre included in table 2.
Grube E, Laborde JC, Zickmann B et al. (2005) First report on a human percutaneous transluminal implantation of a self-expanding valve prosthesis for interventional treatment of aortic valve stenosis. Catheterization & Cardiovascular Interventions 66: 465-69.	n = 1 Follow-up: 14 days Transluminal approach	Procedure was technically successful Significant immediate reduction in transaortic mean pressure gradient without evidence of aortic or mitral valve insufficiency (improvements remaining at follow-up).	More recent study from the same centre included in table 2.
Grube E, Laborde JC, Gerckens U et al. (2006) Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. Circulation 114: 1616-24.	n = 25 Follow-up: 180 and 365 days in 2 patients Transluminal approach	Technical success: 21/25 (84%) Marked reduction in the aortic valve gradients ($p < 0.0001$). No change in mean aortic regurgitation grade. Major in-hospital cardiovascular and cerebral events: 8/25 patients (32%) including mortality: 5/25 (20%). Among 18 patients with device success surviving to discharge, no adverse events occurred within 30 days after leaving the hospital.	More recent study from the same centre included in table 2.
Lamarche Y, Cartier R, Denault AY et al. (2007) Implantation of the CoreValve percutaneous aortic valve. Annals of Thoracic Surgery 83: 284-87.	n = 1 Follow-up: not reported Transluminal approach	64-year-old woman who was refused aortic valve replacement surgery because of severe pulmonary fibrosis. Immediate haemodynamic improvement of the valvular area and left ventricular ejection fraction and only traces of paravalvular leaks. Patient was easily weaned from ventilation and resumed activity soon after the surgery.	More recent study from the same centre included in table 2.
Lichtenstein S, Cheung A, Ye J et al. (2006) Transapical transcatheter aortic valve implantation. Circulation 114:591-96.	n = 7 Follow-up: 87 ± 56 days Transapical	Outcomes for these patients are reported in Ye et al (2007) in table 2	More recent study from the same centre included in table 2.

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	approach		
Webb JG, Chandavimol M, Thompson CR et al. (2006) Percutaneous aortic valve implantation retrograde from the femoral artery. <i>Circulation</i> 113: 842-50.	n = 18 Follow-up: 75+/-55 days Transluminal approach	Procedural success: 14/18 (78%) Aortic valve area increased from 0.6+/-0.2 to 1.6+/-0.4 cm ² . Iliac arterial injury was seen in first 2 patients and did not recur after improvement in screening and access site management. No intraprocedural deaths. At follow-up, 16 patients (89%) remained alive.	More recent study from the same centre included in table 2.
Wenaweser P, Buellesfeld L, Gerckens U et al. (2007) Percutaneous aortic valve replacement for severe aortic regurgitation in degenerated bioprosthesis: The first valve in valve procedure using the corevalve revalving system. <i>Catheterization & Cardiovascular Interventions</i> 70: 760-64.	n = 1 Follow-up: not reported Transluminal approach	First successful valve in valve procedure in an 80-year-old patient with a severe regurgitation of a degenerated aortic bioprosthesis (prior surgical aortic valve replacement).	More recent study from the same centre included in table 2.
Ye J, Cheung A, Lichtenstein, S et al. (2006) Transapical aortic valve implantation in humans. <i>Journal of Thoracic & Cardiovascular Surgery</i> 131 (5) 1194-1196.	n = 1 Follow-up: approx 2 months Transapical approach	Outcomes for this patient are reported in Ye et al (2007) in table 2	More recent study from the same centre included in table 2.

Appendix B: Related NICE guidance for transcatheter aortic valve implantation

Guidance	Recommendation
Interventional procedures	<p>Balloon valvuloplasty for aortic valve stenosis in adults and children. NICE interventional procedures guidance 78 (2004).</p> <p>1.1. Current evidence on the safety and efficacy of balloon valvuloplasty for aortic valve stenosis in adults and children appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance.</p> <p>1.2. In adults, the procedure should only be used to treat patients who are unsuitable for surgery, as the efficacy is usually shortlived.</p> <p>1.3. In infants and children, the procedure should be undertaken in specialist paediatric cardiology units.</p> <p>1.4. The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients into this database (www.ccad.org.uk).</p> <p>Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction. NICE interventional procedures guidance 237 (2007).</p> <p>1.1. The evidence on percutaneous pulmonary valve implantation for right ventricular outflow tract (RVOT) dysfunction is limited to small numbers of patients but shows good short-term efficacy. There is little evidence on long-term efficacy. There are no particular safety concerns in the context of a condition that otherwise requires open cardiac surgery. Clinicians wishing to use this procedure should do so only with special arrangements for clinical governance, consent and for audit or research.</p> <p>1.2. Clinicians should take the following actions:</p> <ul style="list-style-type: none"> • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's long-term efficacy and that there will be a need for repeat procedures or operations. They should provide patients with clear, written information. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is recommended.

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	<p>1.3. The procedure should be performed only in specialist units and with arrangements in place for cardiac surgical support in the event of complications.</p> <p>1.4. Patient selection should be carried out by a multidisciplinary team including a paediatric cardiologist, an interventional cardiologist, a radiologist and a cardiothoracic surgeon with a special interest in congenital heart disease.</p> <p>1.5. This is a technically challenging procedure that should be performed only by clinicians with special training and experience in interventional paediatric cardiology.</p> <p>1.6. The Department of Health runs the UK Central Cardiac Audit Database (UK CCAD) and clinicians should enter details about all patients undergoing percutaneous pulmonary valve implantation for RVOT dysfunction onto this database (www.ccad.org.uk).</p>
Technology appraisals	None
Clinical guidelines	None
Public health	None

Appendix Ca: Literature search for transcatheter aortic valve implantation – transluminal approach

Database	Date searched	Version searched
Cochrane Library	13/11/2007	Issue 4, 2007
CRD databases (DARE & HTA)	13/11/2007	Issue 4, 2007
Embase	13/11/2007	1980 to 2007 Week 45
Medline	13/11/2007	1950 to October Week 5 2007
Premedline	13/11/2007	November 12, 2007
CINAHL	13/11/2007	1982 to November Week 1 2007
British Library Inside Conferences	13/11/2007	-
NRR	13/11/2007	Issue 4, 2007
Controlled Trials Registry	13/11/2007	-

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

1. Heart Valve Diseases/
2. Aortic Valve/
3. exp Aortic Valve Stenosis/
4. or/1-3
5. Heart Valve Prosthesis/
6. Heart Valve Prosthesis Implantation/
7. or/5-6
8. (percutaneou\$ or transcathet\$).tw.
9. 4 and 7 and 8
10. (percutaneou\$ adj3 valve\$ adj3 (replac\$ or implant\$ or prosthe\$)).tw.
11. (transcathet\$ adj3 valve\$ adj3 (replac\$ or implant\$ or prosthe\$)).tw.
12. 10 or 11
13. (percutaneou\$ adj3 (heart adj3 valve\$)).tw.
14. (percutaneou\$ adj3 (aort\$ adj3 valve\$)).tw.
15. (transcathet\$ adj3 (heart adj3 valve\$)).tw.
16. (transcathet\$ adj3 (aort\$ adj3 valve\$)).tw.
17. PAVR.tw.
18. (percutaneou\$ and AVR).tw.
19. (transcathet\$ and AVR).tw.
20. or/13-19
21. 9 or 12 or 20

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Appendix Cb: Literature search for transcatheter aortic valve implantation – transapical approach

Database	Date searched	Version searched
Cochrane Library	10/12/2007	Issue 4, 2007
CRD databases (DARE & HTA)	11/12/2007	November 2007
Embas	12/12/2007	1980 to 2007 Week 49
Medline	12/12/2007	1950 to November Week 2 2007
Premedline	12/12/2007	December 11, 2007
CINAHL	12/12/2007	1982 to December Week 1 2007
British Library Inside Conferences	11/12/2007	-
NRR	10/12/2007	Issue 4, 2007
Controlled Trials Registry	10/12/2007	-

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

1. Heart Valve Diseases/
2. Aortic Valve/
3. exp Aortic Valve Stenosis/
4. or/1-3
5. Heart Valve Prosthesis/
6. Heart Valve Prosthesis Implantation/
7. 5 or 6
8. (transapical or trans-apical or TAVR or transventric\$ or trans-ventric\$).tw.
9. 4 and 7 and 8
10. ((transapical or trans-apical or TAVR) adj3 valve\$ adj3 (replac\$ or implant\$ or prosth\$)).tw.
11. ((transventric\$ or trans-ventric\$) adj3 valve\$ adj3 (replac\$ or implant\$ or prosth\$)).tw.
12. 10 or 11
13. ((transapical or trans-apical or TAVR) adj3 (heart adj3 valve\$)).tw.
14. ((transapical or trans-apical or TAVR) adj3 (aort\$ adj3 valve\$)).tw.
15. ((transventric\$ or trans-ventric\$) adj3 (heart adj3 valve\$)).tw.
16. ((transventric\$ or trans-ventric\$) adj3 (aort\$ adj3 valve\$)).tw.
17. or/13-16
18. 9 or 12 or 17
19. Animals/
20. Humans/
21. 19 not (19 and 20)
22. 18 not 21

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