

**A COMMISSIONING FRAMEWORK FOR
TRANSCATHETER AORTIC VALVE
IMPLANTATION (TAVI) FOR SEVERE
SYMPTOMATIC AORTIC STENOSIS**

**Dr Su Sethi, Consultant in Public Health Medicine, North West
Specialised Commissioning Group**

**Dr Tim Daniel, Consultant in Public Health Medicine, East Midlands
Specialised Commissioning Group**

**Dr Jonathan Howell, Consultant in Public Health Medicine, West
Midlands Specialised Commissioning Group**

**Dr Carl Griffin, Specialist Trainee in Public Health, West Midlands
Specialised Commissioning Group**

March 2009

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1 INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an emerging technology that offers the potential to treat severe symptomatic aortic stenosis in an elderly population, who for reasons of general frailty and/ or comorbidities are considered unfit for open heart surgery, and it may also represent a cost effective alternative to conventional surgery in a wider group of patients. The evidence base is accumulating but there is a need to align further research and evaluation with generating clinical experience around the UK.

A collaborative approach has been developed between national representative bodies for cardiologists (BCIS) and cardiac surgeons (SCTS) and commissioners with the aim of reducing inequity in access to TAVI, ensuring high standards of clinical delivery and agreeing a national evaluation and research strategy. This collaboration has been supported by both NICE and the DoH.

This commissioning framework sets out the requirements and standards for centre designation, including future roll out of TAVI to new centres. It sets out a managed approach to sustainable delivery of national TAVI capacity that is linked to the collection of high quality data on the clinical and cost effectiveness which will guide future service development.

2 BACKGROUND

Aortic stenosis is the most common acquired valvular heart disease in the western world and its prevalence is increasing with an ageing population. The prevalence of severe symptomatic aortic stenosis (SSAS) is around 3% in those aged over 75 years but this percentage rises steeply with increasing age.

After the onset of symptoms, the prognosis is poor for patients with SSAS and, if untreated, the median survival is only 2 to 3 years. Furthermore, elderly people with SSAS also often have significant associated co-morbidities such as reduced left ventricular function, impaired renal function, pulmonary hypertension, liver cirrhosis and coronary artery disease and therefore the risk of open heart surgery is elevated.

Transcatheter aortic valve implantation (TAVI) (formerly described as percutaneous aortic valve replacement – PAVR) represents an endovascular and less invasive alternative to a conventional open heart procedure that would require sternotomy and cardiopulmonary bypass. To date, interest in transcatheter heart valve treatment has focused on the very high risk or surgically rejected patients with SSAS. The alternative treatment for this group is either conservative medical management, which is essentially palliative as no effective interventions currently exist, or Balloon Aortic Valvuloplasty, which is prone to re-stenosis.

Currently, there are two routes for transcatheter valve replacement for aortic stenosis. These are retrograde via the femoral artery and via transapical access directly through the left ventricle wall. The choice of technique is influenced by calcification and tortuosity of the femoro-iliac access route.

3 THE TECHNOLOGY

There are two manufacturers leading the development of transcatheter aortic bioprosthesis valve implantation technology. These are Edwards Life Sciences (Edwards SAPIEN Transcatheter Heart Valve; second generation) and CoreValve Corporation (CoreValve Percutaneous Revalving System; second generation). These technologies differ in their design, construction and method of implantation. Both the Edwards and the CoreValve systems are currently in use in centres in the UK. Additional commercial manufacturers and improvements in the valve technology are also expected.

A) Edwards Sapien Transcatheter Heart Valve

The first human case was reported in 2002. Since then the first generation valve consisting of equine tissue on a stainless steel frame has been replaced with a second generation bovine tissue valve on a stainless steel frame. Currently the Edwards Sapien valve can be implanted by both a transapical and transfemoral route.

Data indicates that over 1000 patients worldwide have received the bioprosthesis. Most have been performed via the femoral route. The initially described antegrade technique via the femoral vein (crossing the septum) has been replaced by the technically easier retrograde technique via the femoral artery. The majority of procedures have now been by the retrograde transfemoral route while only 25% have been by the transapical route.

Edwards Life Sciences have sponsored a randomised controlled trial THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial in the US. This trial started in April 2007 and will run until September 2014. The trial will test the superiority of: Cohort A: the Edwards SAPIEN Transcatheter Heart Valve vs. Other: medical management and/or balloon aortic valvuloplasty for high risk patients and Cohort B: the Edwards SAPIEN Transcatheter Heart Valve vs. Open conventional surgical valve replacement.

B) CoreValve Percutaneous Revalving System

The first human case was reported in 2004. Since then the first generation valve consisting of bovine tissue on a self expanding nitinol frame has been superseded with a second generation porcine tissue valve on a nitinol frame.

The CoreValve system is currently undertaken by the transfemoral route although a transapical approach is in development (five human cases and further efficacy and safety assessments planned). To date, the data indicate that approaching 1800 patients have been treated. A European CoreValve randomised controlled trial is currently being planned but the details of the trial protocol have not yet been published.

4 THE CURRENT EVIDENCE FOR TAVI

NICE Interventional Procedure Guidance (Number 266) was issued in June 2008 allowing the use of TAVI under special arrangements for clinical governance, consent, audit and research.

Current research evidence (published in peer reviewed journals) comprises one registry series and three case-series which are split between the transfemoral and transapical approach. The case series comprise small sized and heterogeneous patient samples characterised by differences in: pre-op Euro score risk, procedure for

patient selection, device type and diameter, general or local anaesthesia, catheter lab or hybrid theatre, recovery room and ICU stay, length of stay.

In these research studies the mean age of patients undergoing TAVI was 82 years, their Euroscore was between 20 and 30 % and NYHA functional class of 3-4. Other risk factors included severe pulmonary and coronary disease, peripheral vascular disease, renal dysfunction, neurological dysfunction, liver cirrhosis, previous cardiac operations, porcelain aorta, diabetes and hypertension. Short term beneficial outcomes following TAVI included high rates of procedural success and significant haemodynamic improvements in: transvalvular gradients, NYHA functional class, LVEF, mitral regurgitation grade, estimated aortic valve area and maintained structural integrity of valve.

There was significant mortality and complications associated with TAVI: 30 day mortality of 12-14% and 16% composite rate of death, stroke or MI. Complications included iliac and aortic artery perforation, vascular infection, haemoperitoneum, cardiac tamponade, multi-organ failure and conversion to open surgery. Technical complications included valve migration after implantation, difficulty of retrograde passage through aortic valves with extensive calcification, inability to pass iliac artery, mal-positioning.

The most up-to-date unpublished data for the Edwards valve is from the Source registry. The 30 day mortality for the transfemoral approach is 6.5% and 10% for the transapical approach. The 30 day mortality for the Corevalve European registry is 6.7%. These data suggest that the 'learning curve effect' is significant but may be tempered by appropriate training and support via proctorship arrangements.

5 A SUMMARY OF THE EVIDENCE ON TAVI

- Although all the studies have demonstrated technical feasibility, the data on TAVI remains observational.
- Benefits: High rates of procedural success and significant haemodynamic improvements in transvalvular gradients, as well as improvements in NYHA functional class, LVEF, mitral regurgitation grade, estimated aortic valve area and structural integrity of valve.
- Risks: Transarterial access and major vascular injury and repair, vascular infection, paravalvular regurgitation, stroke, cardiac tamponade.
- 30 day and longer term mortality rates (data now available up to 2 years) are significant but may be lower than predicted from preoperative surgical risk scores and profile. However there are problems with current risk scoring systems for surgery (such as Euroscore) which have been shown to overestimate the actual observed operative mortality.
- Currently no results from randomised studies either comparing the transfemoral/percutaneous and transapical routes for TAVI against routine palliative care or TAVI against surgical aortic valve replacement. The clear definition of entry criteria for these trials is hindered by the current inaccuracy of risk scores for high risk surgical patients.
- Observational data - short term results, no control groups. This limits assessment of long term device efficacy/durability, true frequency of complications, risk benefit ratio of the procedure for specific patient groups and accurate information for true informed patient consent.
- Cost data have not been systematically collected and hence the cost-effectiveness of TAVI is unknown.
- Feasibility has been tested but results apply only to the high risk/surgically ineligible patient population that was enrolled.

6 KEY COMMISSIONING CONSIDERATIONS

- This is an emerging procedure which may offer a cost-effective alternative to palliative care or surgical valve replacement in, as yet, undefined patient groups.
- TAVI is still in the phase of clinical development. Further improvements are expected aiming towards a truly percutaneous approach with smaller devices, with the potential of reducing serious adverse events (such as MI, cardiac tamponade, stroke and vascular injury).
- There is a consensus that percutaneous and transapical devices are a clinical reality and TAVI is here to stay.
- Patients are attracted towards percutaneous and transapical, rather than open surgical procedures, because they are less invasive with shorter patient stays.
- We need to work collaboratively with other professional groups to ensure appropriate and controlled roll out of TAVI in the UK. The current devices have only been conditionally approved by the FDA. In the USA their use is confined to feasibility studies in a few selected centres leading up to pivotal RCTs.
- Currently the technique is offered to patients at very high risk for an open surgical approach. Before extending the population to be considered for this technology, TAVI needs to prove its cost effectiveness compared with open surgical aortic valve replacement, which remains the gold standard treatment. The results of RCTs will be pivotal for future decision-making and will be considered alongside UK registry data.
- RCTs need to be performed but these should only take place by, or within, the UK when centres have sufficient experience of the technique. The specific question asked by an individual trial needs careful consideration, especially in the light of ongoing international trials. In the UK, the first step within the clinical governance and research strategy should be carefully collected prospective registry data to give further information on risk profiling.

7 UNRESOLVED COMMISSIONING ISSUES

- How do the outcomes for TAVI compare with conservative management for surgically ineligible patients, or with conventional open heart surgery for a 'high risk' group?
- How do we define the target population for TAVI given this is an elderly vulnerable patient group, many of whom have multiple co-morbidities?
- What is our aim in offering this procedure? Is it compassionate/ palliative and should we be aiming for lesser effectiveness than surgery in this patient group?
- Is it cost effective? What are the current healthcare resources expended on patients not considered appropriate for surgical AVR? How does it impact on HRQOL and how much will it cost?
- Is it appropriate to intervene? What are the views of the patients and their carers?
- What information on the likelihood of improved quality of life can we give to patients so that they can balance this against the risk of the procedure itself?

8 WAY FORWARD

Commissioners will need to develop a commissioning strategy accompanied by commissioning requirements based on the evidence, statements by professional societies, and the need for clinical and research governance assurance.

This will need to address key questions:

- Who should be commissioned to undertake TAVI, where, how and how many patients?
- How should these patients be selected?
- What should be the evaluation and research framework for TAVI?
- How should the UK use the emerging evidence base to aid the organisation of the future roll out of TAVI?

9 COMMISSIONING REQUIREMENTS FOR TAVI

The format for the commissioning requirements is to first present the explanation and rationale for the requirement, followed by a statement of the requirement.

1) Risk Stratification and Patient Selection

Patient selection is critical not least because of the proven efficacy, durability and long term results of conventional aortic valve replacement surgery. Selection for TAVI eligibility is to identify a group where anticipated operative mortality with conventional surgery would be considered prohibitive (top 10% of predicted risk). Operative risk scoring algorithms are currently being used to identify the appropriate high risk patient population.

However between each risk algorithm there can exist differences in variable definitions, actual variables included and their weighting. The STS-PROM initially under predicts but closely approaches the actual observed mortality. In contrast the Euroscore logistic (LES) substantially over predicts preoperative mortality in some surgical procedures by a factor of >3 times (O/E ratio of 0.31%). Also a further shortcoming of models is that some independent risk factors associated with poor outcomes after cardiac surgery are not collected e.g. porcelain aorta.

The U.S PARTNER trial has inclusion criteria of $\geq 15\%$ predicted risk of operative mortality and / or minimum STS score of 10. One hundred percent accuracy cannot be expected for any single risk model however the STS-PROM appears to be the most reliable single risk scoring model of those evaluated for both peri-operative mortality and long term survival. Caution should be exercised when using the LES because overestimation of risk may lead to inclusion of patients for TAVI who could have done well in conventional approaches. There is a need to develop a more robust predictive model that can support decision making around patient selection for operative procedures and TAVI.

Currently, patient selection for TAVI should be based on the simultaneous use of multiple models, to aid concordance in risk assessment. This should include the STS-PROM. Risk factors that are not covered in scores but are seen in practice should be taken into account, e.g. porcelain aorta etc. Currently, there is no robust

surgical risk assessment tool that is consistently used to define cases at high surgical risk. In addition the threshold for offering surgical AVR to patients assessed to be at high risk and willingness to operate varies between surgical centres. Surgical clinical judgement as well as risk scoring will aid the identification of patients best treated with either open heart surgery or TAVI. At the consensus meeting on the 16th December, it was agreed that a small number of UK centres should collect data on ALL patients being referred with SSAS, and those treated medically, surgically or with TAVI would all be tracked. Markers of frailty should be explored and incorporated into future risk models.

The ideal arrangement to achieve the above requirements is a triage and assessment process carried out by a multidisciplinary, multiconsultant-based specialist valve team including interventional cardiologists with the appropriate experience, cardiac surgeons, cardiothoracic anaesthetists, an imaging specialist and nurses. Input from elderly care physicians may be appropriate in individual cases. Some service models have reported the establishment of special valve MDT clinics and a valve disease services coordinator.

Referral of patients with SSAS to a specialist MDT for assessment and definitive treatment will ensure stringent and consistent application of inclusion and exclusion criteria, risk scoring algorithms and proper clinical consideration for surgical AVR given its excellent short-, mid- and long-term outcomes.

Requirement

TAVI should currently be reserved for patients who have been considered by a multidisciplinary team (including two cardiac surgeons, two interventional cardiologists, an imaging specialist, cardiothoracic anaesthetists and experienced nurses) who consider the risk/benefit ratio of open heart surgery and TAVI to favour TAVI. The usual “high risk” patient will have a logistic Euroscore of >20 or an STS score of >10.

2) Patient Eligibility Criteria

Requirement

TAVI should currently be restricted to patients with SSAS, who have been rigorously assessed by the specialist valve MDT to be at high risk for surgery or with absolute contraindications for surgery.

- i) TAVI is not recommended for patients who simply refuse surgery on the basis of personal preference.
- ii) It is currently premature to consider TAVI in patients who are good surgical candidates (moderate/low risk).
- iii) TAVI should not be performed in patients with life expectancy of less than one year.

Patients for TAVI should meet technical anatomical inclusion criteria as per companies' specification i.e. aortic annulus diameter as measured on transthoracic and transoesophageal echocardiography. Currently these are ≥ 20 and ≤ 27 mm for CoreValve and between 18 and 24mm for Edwards Sapien valves. At present there are the only two suppliers of TAVI prostheses. New centres should restrict themselves to one of either device.

3) Delivery systems and routes

Transapical And Transfemoral Approaches

Theoretically, high risk surgical candidates may benefit from TAVI by avoiding partial or complete sternotomy, cardiopulmonary bypass and cardioplegic arrest.

The transapical route overcomes some of the shortcomings of the transfemoral route, i.e. related to small access femoral vessels resulting from the high prevalence of atherosclerosis and peripheral arterial disease in this group.

Choice of route will depend on individual clinical features of the patient under consideration. Currently there is no evidence that directly compares the relative efficacy of the two procedures (transapical vs transfemoral).

Requirement

An optimal regional TAVI program should ideally incorporate both transfemoral and transapical procedures. TAVI should be offered by units with the following:

- i. A cardiac surgery department experienced in valve surgery and the management of high risk and complex cases. Currently (based on the experience of the early centres) it is felt that an annual volume of 200 aortic valve replacement operations per year for a unit should ensure a sufficient referral base to generate at least 50 TAVIs a year from GPs, tertiary cardiologists, DGH cardiologists and general physicians. It is accepted that centres might do fewer than this in the early phase of a TAVI programme whilst new referral protocols are being put in place (see 8(iii) below. This level of throughput would guarantee a comprehensive case mix including sufficient high risk surgical caseload and avoid inappropriate selection bias of low and moderate risk cases for TAVI.
- ii. A Cardiology department with expertise in structural heart disease (interventional and echocardiographic) skills including the management of great vessels. More recently the use of catheter-based approaches has been directed to non vascular "structural" heart disease syndromes including adult congenital cardiac abnormalities and valvular heart disease. Structural interventionalists should have specific experience in device closure of defects such as PFO, ASD, VSD closures, percutaneous balloon mitral valvuloplasty, and aortic stenting. This will shorten the learning curve for TAVI.

4) Multidisciplinary Team In Valve Disease

Requirement

- i) An optimal transcatheter programme requires the close collaboration of interventional cardiologists, cardiac surgeons, cardiac imaging specialists, cardiac anaesthetists and cardiac nurses. A team coordinator is recommended (e.g. a nurse manager) as this service needs to link several specialties together.

Interventional cardiologists should be experienced in catheter-based valvular interventions and peripheral access using large devices. Cardiac

surgeons should be experienced in valve surgery and the management of complex cases.

- ii) A synchronised team approach will be extremely important for risk assessment, patient screening, patient selection and pre-op planning, optimal valve positioning, deployment and post- procedure checks; post-operative surveillance, complication management, discharge and planned follow up with monitoring for outcomes. Joint training, close working between all specialists involved is paramount in order to get over the learning curve (technique and device) and to anticipate and mitigate complications that can be potentially disastrous. Team cooperation, collaboration, joint decision making and shared experiences will increase team integration.
- iii) In centres performing TAVI, MDT meetings should be held on a regular basis to discuss treatment indications, procedural techniques, and case outcomes. Hospitals should keep proof of close medico-surgical collaboration and maintain a log of all patients referred for TAVI, regardless of final treatment strategy, to aid evaluation of the programme.

5) Environment For The Procedure

The optimal environment for TAVI should be spacious and i) sterile, ii) have high quality imaging equipment and capacity for emergency open heart surgery.

Catheterization laboratories have good quality imaging but may not be sterile and induce delay in rescue surgery. The overall setting of a hybrid operative theatre is of specific value especially when general anaesthesia, emergency cardiopulmonary bypass or conversion to conventional surgery is required. A hybrid operative theatre combines all aspects of sterility required during conventional surgery, along with emergency back-up measures with the angiographic imaging technology needed in the catheterization laboratory as well as haemodynamic monitoring and recording capabilities.

Requirement

- i) TAVI implantation requires an appropriate, spacious environment with the capacity of a conventional catheter laboratory, with high-grade imaging facilities, and with the capacity to be turned into a cardiac operating theatre. Centres should give due consideration to the development of a well equipped hybrid operative theatre with full operative capabilities and optimal imaging which is the ideal.
- ii) Any hospital wishing to set up a TAVI programme should have the following **minimum** infra-structure available:
 - The ability to set up an MDT
 - Immediate availability of trans-thoracic and transoesophageal echocardiography.
 - Availability of a hybrid theatre or dedicated cardiac catheter lab
 - A theatre with "C" arm screening facilities is not appropriate for TAVI procedures.
 - CT scanning facilities
 - Immediate availability of perfusion services in case of the need for emergency femoro-femoral bypass
 - On-site availability of a surgical recovery area and intensive care with staff experienced in looking after patients following surgical aortic valve replacement.

- Robust arrangements for immediate renal support if necessary.
- Immediate on site access to vascular surgeons and interventional radiologists to deal with major peripheral vascular complications.

6) Imaging

Excellent imaging is central to ensuring exact valve positioning and deployment and thus optimal patient outcome. It is important that TAVI centres and teams have expertise, experience and established competences in all of the advanced imaging modalities needed for pre-procedural assessment and planning ie of the patient's iliofemoral system, aorta and stenotic valve. The evaluations are important for patient selection and also for pre-procedural morphology assessment of the LVOT, aortic root, aortic annulus, planning of access approach, valve sizing, positioning and placement of the device implant and checks post procedure, at discharge and at follow-up.

Requirement

TAVI implantation requires high quality imaging equipment, technical and interpretational expertise on operating sites including aortography, coronary angiography, fluoroscopy, transthoracic and transoesophageal echocardiography, and multislice CT.

7) Training And Education

Tertiary cardiovascular care is rapidly moving toward catheter based techniques. Cardiac surgeons to date are the most experienced clinicians presently offering definitive treatment for aortic valve disease. Yet endovascular skills, catheter skills and techniques are not currently part of the training programme curriculum for cardiac surgeons.

The field of teaching, training and certification for catheter-based technologies such as TAVI needs to be developed to include both surgeons and interventional cardiologists presently training and proctorship is being offered by the companies concerned.

TAVI is a complex procedure and in the setting of severe aortic stenosis and elderly high risk patients, errors are not well tolerated. Early studies have demonstrated the existence of a learning curve.

Webb reported a 30 day mortality of 16% and procedural success rates of 76% in the first 25 patients, these improved to 8% and 96% respectively in the next 25 patients. Better understanding with experience of the requirements of accurate positioning and improvements in imaging led to a decrease in malposition rates (8% -0 %). Periprocedural mortality also fell from 4% - 0%. Improvements were also seen in major arterial complications. Survival rates at 0, 1 and 6 months improved from 96%, 84%, 70% (initial cohort) to 100%, 92% and 88% (later cohort). Webb further demonstrated the achievement of a 30 day mortality of 10% implant success rate of 90% and a major stroke rate of 2% after his Centre's first 90 pts.

Walther using the transapical approach also reported more deaths in the first 25 patients and better overall survival figures in the second 25 patients at 30 days (88% vs 96%), 6 months (68% vs 80%) and one year (64% vs 80%).

A case series of 10 patients using Corevalve was associated with a 30 day mortality of 20% and vascular complications in 5 patients, 2 patients required reoperation. Three month mortality was 30%.

The learning curve was attributable to;

- i) Incremental improvements in equipment and technique.
- ii) Better understanding with experience of the requirements of patient selection, accurate positioning and improvements in imaging.

The learning curve required to master this technology should not be underestimated and should be reflected in the training requirements.

Requirements

- i) The presence of a learning curve requires careful and controlled replication of early experience and reproducibility of results, for both the technique itself and across all stages of the patient pathway. Optimal training requires:
 - a. Theoretical didactic lecture-based training.
 - b. Ideally, simulator training.
 - c. The observation of 2-5 cases at an experienced centre.
 - d. Performance of cases with a proctor at the home institution until the proctor considers the operators competent. The numbers will vary but it is likely that, following cases where the proctor is the first operator with the training team assisting, 5-10 cases will be needed where the local team is performing the case assisted by the proctor. It is possible that a greater number may be required. The proctor should provide a certificate of approval at the appropriate stage.
- ii) Ideally, a centre should undertake a training programme that encompasses both the transfemoral and the transapical routes. If a centre chooses to use only the transfemoral approach (e.g. with a current Corevalve programme), then their MDT should include surgeons with experience of the transapical approach, and they should refer patients for whom the transapical approach is deemed the optimal treatment to another centre with the appropriate experience.
- iii) Established centres should further define training needs and competencies and assist in the development of training and accreditation programmes in catheter based therapies. This will be in order to train other new centres and in due course to offer access to training programmes for cardiac surgery and cardiology SpRs. These should be developed for the NHS by the collaboration of the first wave of centres and in liaison with BCIS and SCTS.
- iv) An integrated team approach (for subspecialists in valve disease) is required for training. Operator and team experience are both important for successful outcomes.

8) Centre Selection

The full and longer term implications of this technology in terms of clinical efficacy, complications and valve durability are still not known. In America the procedure is still being considered investigational by the FDA and requiring initial feasibility studies leading up to pivotal RCTs. The latter stage has been reached for the Edwards valve but not yet started for Corevalve. Trials and registries of new technologies from other companies will also be required.

Requirement

- i) Regional Centres of expertise will be desirable at the current stage of managed introduction, clinical development and evaluation of a new and complex procedure that is to be performed on an elderly, multiply co-morbid and high risk patient group. There are challenges inherent in both the procedure and the patient group. Hence early favourable experience with TAVI in the initial centres of excellence will need to be cautiously replicated in the next wave of new centres by a careful process of proctorship and phased roll out supervised by the first wave lead centres, and as part of a designation process. SCGs are advised to introduce one centre at a time. A strategy of exposing several small centres, each with its own small caseload and learning curve, to this development at the same time may worsen overall outcomes and may not be sustainable in the longer term.
- ii) Centre selection and roll out should be based on estimated population need, the commissioning requirements and the professional recommendations contained within the joint EACTS, ESC and EAPC consensus statement and the joint position statement of the British Cardiovascular Intervention Society (BCIS) and the Society of Cardiothoracic Surgeons (SCTS). There is currently a lack of epidemiological data to determine population need, but at the consensus meeting it was suggested an estimate of commissioning need for a population was around 16 per million (around 800 TAVI procedures per year for England). There was a consensus that TAVI should not be done in all interventional cardiology units currently and that a programme should be developed only in a surgical centre. Within individual regions, there are often multiple interventional centres with on-site surgery, and it was agreed that simultaneous start-up of multiple centres was not appropriate. Each regional SCG should determine their own population needs for access to treatment after discussions with the local clinical network. Another consideration may be to select centres with the best cardiac structural clinical skills, experience, surgical volume, infrastructure and clinical and research governance track record to potentially maximise outcomes in readiness for them to develop into future pivotal trial centres.
- iii) Currently, there is no evidence to suggest an actual minimum number of procedures needed to maintain skills and optimise outcomes. It is likely that a minimum of 25 procedures in the first year of activity would be performed with a view to building up a regional referral pattern. Optimum number of procedures in the future will depend on the accumulating evidence for this procedure but it is recommended that only centres that are undertaking at least 50 procedures per year should be considered for clinical trials. A smaller number of units who are doing more procedures is likely to provide a better service than a large number of units each delivering a small number of cases.

9) **Governance, Evaluation and Clinical Research**

Current evidence suggests that TAVI offers immediate symptomatic relief and improvement in functional status to elderly patients with SSAS in whom surgery is either contraindicated or considered to carry a prohibitive operative risk. The benefits appear to be sustained in the short term but long-term follow-up data are not yet available. There are also no data regarding the impact of TAVI, compared with conventional management, on survival, event-free survival, quality of life and costs

The strength of the current evidence is limited, being derived only from single- and multi-centre case series and registries. Interpretation of the data is complicated by the heterogeneity of the groups studied, with variation in patient selection procedures, baseline operative risk, valve design, sheath size, route and mode of access, haemodynamic support, anaesthesia, use of catheter laboratory or hybrid theatre, place of recovery and ICU stay, duration of hospital stay etc.

Requirement

There is an urgent need to collect high-quality data to define the appropriate place of TAVI in the clinical management of patients with SSAS. The data collection process will include three complementary elements: a registry, a prospective cohort study and a randomised controlled trial. An application for funding of the research costs of the integrated evaluative process will be submitted to the NIHR HTA programme.

i) TAVI registry:

Mandatory collection of key data will be required from all UK centres in which the procedure is undertaken, in the form of a registry. The registry will include all new patients undergoing the procedure, as well as those who have already received it.

SCTS and BCIS have agreed a TAVI dataset, which will allow collection of data using the existing Central Cardiac Audit Database (CCAD). The collection of complete and accurate data will require active project management and a project co-ordinator will be appointed under the National Institute for Clinical Outcomes Research (NICOR) supervisory infrastructure.

Safety and efficacy endpoints must be clearly defined to include mortality (30 day, in-hospital and 1 year), major adverse cardiovascular events, vascular complications, conversion to conventional surgery, other predicted or unpredicted adverse events, quality of life metrics (including PROMs and subjective assessment) before and after the procedure, and procedural data on valve deployment and function (e.g. haemodynamics, valve migration, paravalvular leaks). The duration of follow-up to assess safety and efficacy should be at least 5 years.

In view of the vulnerable case mix of patients (elderly with multiple co-morbidities), it is important that evaluation should incorporate short and longer term change in quality of life including the reporting of subjective outcomes.

Continued funding of TAVI centres will be dependent on compliance with data collection and submission. The registry team will liaise with the NICE Interventional Procedures Committee to ensure that the data collected meet the needs of any future appraisal by NICE.

ii) Prospective cohort study:

There are some patients with SSAS for whom TAVI may be inappropriate (e.g. those requiring surgical coronary revascularisation) and others for whom surgery is not technically feasible (e.g. porcelain aorta). There are also those for whom neither intervention is appropriate (e.g. due to frailty or comorbidities with a dominant influence on prognosis or symptoms). In order to better understand the natural history of SSAS and the influence of various interventions on outcomes, including those patients for whom a randomised comparison of treatment alternatives is not feasible, a prospective cohort study is proposed. This will include all patients referred for consideration of intervention for SSAS in five or six large centres that offer all treatment options. A prospective cohort study of this type will provide valuable insights into the assessment of procedural risks and benefits and inform decision making in patient selection for TAVI or surgery.

iii) Randomised controlled trial:

An RCT is required to compare the efficacy, safety and cost-utility of TAVI with conventional surgical valve replacement in patients at high operative risk. The trial population will comprise patients for whom both conventional surgery and TAVI are technically feasible. A trial in this high-risk group is an essential pre-requisite before considering any extension of TAVI to patients at lower surgical risk, where conventional aortic valve surgery remains the gold standard treatment. A Trial Development Group will be established to ensure that the trial design addresses the key clinical questions and to ensure it complements other ongoing and planned trials. An RCT should be conducted before widespread dissemination of TAVI into a population who would be considered at moderate/low risk for conventional surgery.

Participation in a clinical trial will be limited to centres that have passed through the learning curve and have established experience with TAVI (e.g. at least 50 procedures; see Section 8 re: Centre Selection). A centre will also need to be fully compliant with data collection and submission requirements for the TAVI Registry.

iv) Predictive modelling of operative risk with conventional surgery:

The currently available risk scoring systems for the estimation of surgical risk are known to be inadequate and, as an initial step, it is proposed to use the current SCTS database to attempt to develop a better predictive model for operative risk with conventional surgery. This work has been agreed between commissioners, SCTS and BCIS. The retrospective risk-modelling analysis will be led by Professor Nick Freemantle, University of Birmingham, with the work being conducted under the NICOR supervisory infrastructure.