Transcutaneous aortic valve implantation by the transfemoral or transapical route

Reassessment report
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The opinion of the working group presented in this report has been validated by each of its members.

Members of the working group were appointed on the basis of suggestions from the relevant associations or learned societies (French Association of Anaesthetists and Resuscitation Specialists, National Professional Cardiology Association, French Society for Thoracic and Cardiovascular Surgery, French Diagnostic and Interventional Cardiac and Vascular Imaging Society) who were contacted with a request for suitable candidates. Some healthcare professionals were also approached directly. In accordance with articles R.161-84 to R.161-86 of the Social Security Code, all members of the group have completed a public declaration of interests, the purpose of which is to inform HAS of any conflict of interest which some members of the group might have with a manufacturer. The public declarations of interest submitted by potential members of the working group were analysed in the light of the “Guide to declarations of interest and conflict management” published in March 2010. The analysis of the working group members’ declarations showed that there were no interests that could give rise to a major conflict. The composition of the working group and the declarations of interest were published on the HAS website (http://www.has-sante.fr) before the group’s first meeting. A reminder of these interests was also given at the start of the group’s meeting and when the working group’s opinion was presented to CNEDiMTS1.

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1 National Committee for the Evaluation of Medical Devices and Health Technologies
3. Summary

3.1. Introduction and background

In 2007, the CNEDiMTS assessed two aortic valve bioprostheses implanted by the transfemoral retrograde route and/or the transapical route (Edwards Sapien 9000 TFX and CoreValve Revalving System) for the treatment of severe aortic stenosis in view of their reimbursement. As the corresponding procedures were not included in the procedures’ reimbursement list, a joint assessment of both the medical devices and the implantation procedures was carried out.

As transcutaneous aortic valve implantation (TAVI) was considered an innovative technology with a significant potential for improving patient management, an early assessment was performed within a specific framework that aims to avoid:

► excessively early access to techniques that have not been sufficiently evaluated and are therefore potentially associated with excessive health and/or economic risks;

► conversely, delaying the access of new, promising techniques to the patients.

In this context, HAS performed early-stage assessment prior to the CE mark granting in order to avoid delaying the access to transcutaneous aortic valve bioprostheses. This early assessment allowed HAS to issue its guidance as soon as the CE mark was obtained. Standard assessment method was applied for this breakthrough innovation. The data available for these bioprostheses at that time were limited and needed to be completed. However, in view of the potential benefit to patients with no therapeutic alternative, it was agreed that greater risks could be accepted within a tightly managed introduction scheme:

► Reimbursement was agreed for an interim period for limited indications until reassessment (end of 2011, Ministerial decision taken on 28 September 2009);

► During this interim period, technology use was restricted to 33 authorised centres with strict implantation conditions (decree of 29 December 2009) by virtue of article L. 1151-1 of the Public Health Code;

► A registry was set up to confirm the clinical benefit of these valves (thorough assessment of the safety and efficacy of the valves in all implanted patients in France - France 2 registry set up by the French Cardiology Society and the French Thoracic and Cardiovascular Surgery Society, and funded by the firms Edwards Lifesciences and Medtronic).

The list of approved centres was fixed for a period of two years, and the reimbursement period of the TAVI expires at the end of 2011. HAS was also asked on 16 March 2011 by the Ministry of Labour, Employment and Health to assess the technology development and evolution opportunities in terms of target population, needs of staff training and technical environment in the context of the overall evolution of cardiac surgery and its alternatives. This assessment report was developed on the basis of a systematic review of the literature and the opinion of a multidisciplinary working group.
3.2. Scope of the assessment

This reassessment concerns aortic valve bioprostheses implanted in France, for which reimbursement decision was taken by the decrees which have been published in the French Official Journal.

3.3. Method

The general method is based on a critical analysis of published scientific literature, data submitted by manufacturers and the opinion of multidisciplinary working group healthcare professionals.

Besides the additional data requested by HAS in 2007, a scientific literature search was conducted by accessing the main medical databases covering the period from 2008 to 2011. Two randomised controlled trials, eight cohort studies, four studies with retrospective analysis and one clinical practice guideline were analysed.

The efficacy criteria adopted were the success of the procedure, survival beyond 30 days, improvement of the symptoms, echocardiographic data and quality of life. The safety criteria were those related to the procedure itself, mortality within 30 days after the procedure, the emergency surgical conversion, bleeding, cerebral complications, other vascular complications, myocardial infarctions, pacemaker implantations, renal insufficiency, aortic valve leaks, endocarditis, valve dysfunctions, reinterventions and repeat hospitalisations.

3.4. Critical analysis of the data

Patient characteristics

The study population comprised elderly patients (over 80 on average) with severe aortic stenosis (effective aortic area of 0.5 to 0.73 cm²) with a high transvalvular gradient (40 to 51 mmHg). In terms of functional status, half the studies included patients in NYHA stage III/IV (85 to 97% of cases), while up to a third of the patients in the other studies were in class I/II. The STS (Society of Thoracic Surgeons) score and logistic Euroscore were not always reported together. The average STS score was between 11.2 and 13, and the logistic Euroscore was between 20.1 and 33.5. In the case of patients with an STS score of < 10 and a logistic Euroscore of < 20, it is not clear whether they had associated comorbidities that were not taken into account in these scores, which would mean that conventional surgery was contraindicated.

Overall analysis of efficacy and safety

The literature describes a learning curve for TAVI by transfemoral or transapical route, but does not clearly define a threshold of activity. Recent data show implantation success rates of around 95% with immediate efficacy results, in particular a reduction in the average transvalvular gradient (8 to 12.7 mmHg post-implantation), an increase in the effective aortic valve area (1.5 to 1.8 cm² post-implantation) and an improvement in patients’ functional status according to the NYHA classification system (more than half of patients in class I/II post-implantation) with no major valve dysfunction. All these results are maintained for up to two years. The real benefit of the technology in terms of patients’ quality of life and general state of health, cannot be assessed due to the only partial results available. Furthermore, the emergency surgical conversion rate varies from 0 to 5.4% depending on the study. The rate of valve-in-valve implantation which reflects failure of a first attempt at implantation
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(specific leak, migration) ranges from 0.5 to 5%. Paravalvular aortic leaks of slight to moderate intensity have also been observed, though the long-term impact of this event is unclear.

All included studies report mortality rates at one month of 1.7 to 18.8%, with 1.7 to 10.4% of cardiovascular origin. The mortality rates at one year range from 21.9 to 50.7%. Most of the trials and registries in which patients are followed-up for up to one month report rates of major or life-threatening bleeding of over 10%, irrespective of the type of valve implanted or the access route used. Bleeding is most common in the first 24 hours after implantation. The frequency of cerebrovascular events at one month ranges from 1.7 to 13.5% (severe in 1.7 to 7% of cases). The studies use varying definitions for vascular complications. Using the harmonised definitions developed on the basis of expert consensus by the VARC (Valve Academic Research Consortium), major vascular complications occur in 6 to 25.9% of cases and minor vascular complications in 7.4 to 28.3% of cases. With regard to cardiac complications, myocardial infarction rates during the first month of follow-up are reported at between 0 and 5.6%. Endocarditis is rare (0 to 1.1%), and the rates of pacemaker implantation vary according to the type of valve implanted. Between 3.4 and 16.3% of patients implanted with an Edwards valve needed to have a pacemaker implanted, as compared to 15.4 to 26.9% of those implanted with a CoreValve device. Finally, stage 3 acute renal insufficiency (within 72 hours of the procedure, using the standardised VARC definitions) was observed in 2.3 to 11.6% of patients.

Comparison with therapeutic alternatives

Two open randomised controlled studies of good methodological quality compared valve implantation by the transfemoral or transapical route (Edwards Sapien valve) to the therapeutic alternatives.

This comparison showed implantation of aortic valves by the transfemoral route to be superior to standard therapy (balloon aortic valvuloplasty in over 60% of cases) for patients for whom aortic valve replacement surgery is contraindicated (predicted probability of 50% or more of either death by 30 days after surgery or a serious irreversible condition) in terms of death from any cause after one year of follow-up (30.7% vs. 49.7%, HR 0.55, 95% CI [0.40 – 0.74], p<0.01).

When compared to conventional surgery, aortic valve implantation via the transfemoral or transapical route in patients at high surgical risk (score STS ≥ 10 and/or predicted risk of post-operative mortality ≥ 15%) was found to be not inferior in respect of death rates (all causes) observed after one year of follow-up (24.2% for the Edwards Sapien valve vs. 26.8% for surgery, non-inferiority p = 0.002; HR 0.83 95% CI [0.60 – 1.15]). However, surgical and transcutaneous aortic valve replacement have their own complications, and patients undergoing these procedures face different risks. Bleeding is more frequent with surgical valve replacement (9.3% vs. 19.5%, p<0.001 after one month), while cerebral (5.5% vs. 2.4%, p=0.04) and vascular complications (17% vs. 3.8%, p<0.001) are observed with transcutaneous valve replacement. Furthermore, in patients monitored for up to one year, the incidence of paravalvular leak is found to be significantly higher following implantation of a prosthetic valve via the transcutaneous route compared to surgical replacement (slight leak: 60.4% vs. 20.1%; moderate to severe leak: 6.8% vs. 1.9%, p<0.001).

Results of French practice

The FRANCE 2 registry describes the efficacy and safety results for all patients included up to 1 March 2011 in the 33 French centres authorised to implant aortic valve bioprostheses by the transarterial (iliofemoral or subclavian) or transapical routes. Four types of valves were
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used (the study started with the Edwards Sapien and CoreValve devices, which were gradually replaced by the next-generation devices Sapien XT and CoreValve Accutrack). Only data at one and six months are suitable for analysis. The results of the registry are in accordance with the data in the literature in terms of efficacy and complications, with a mortality rate (any cause) of 9.9% (95% CI [8.5%-11.4%]) at one month and of 19.1% (95% CI [17%-21.5%]) at six months. An additional analysis of 37 cases in which two valves were used during the same procedure shows a mortality rate (all causes) of 30.5% and 50% at one and six months respectively. 7.1% of the population receiving implants had infections after one month.

Analyses carried out for different types of valves showed a higher incidence of pacemaker implantation with the CoreValve device (any generation; more than 20% of patients). Analyses carried out for different types of valve and different access routes showed that the Sapien XT implanted by the transapical route led to higher mortality (17.9% for the Sapien XT vs. an average rate of 9.9% for the study population) and bleeding (27.1% vs. 16.1%) rates at one month and a lower survival rate with no clinical events (34.1% vs. 46.2%). This latter analysis was conducted on a small population.

Analysis of centres in respect of mortality rates after one month adjusted for the logistic Euroscore and NYHA status showed that centres with a mortality rate of over 13% recruited more patients presenting difficult conditions for aortic clamping, surgical access to the mediastinum or the insertion of catheters. The analysis also showed that 39.7% of patients receiving implants in these centres refused surgery even though there was no documentation of high surgical risk (compared to 4.3 to 15.9% for the other centres). Furthermore, 11.1% of patients had life expectancy of less than a year (compared to 0 to 1.8% for the other centres), and 10.8% had a thrombus, a mass or intracardiac vegetations (compared to 2.9 to 5.5% for the other centres).

A cost study was carried out on the basis of the FRANCE 2 registry data. Various conclusions can be drawn despite the methodological shortcomings of this study: the average costs of the intervention and the hospital stay per patient were estimated at € 22,917 (the price of the valve accounts for 85% of this) and € 32,018 respectively. The average cost of the intervention was higher if an Edwards valve (Sapien or Sapien XT) was used than if a CoreValve was used. The average cost of the hospital stay was higher if an Edwards valve implanted via the transapical route was used than if a CoreValve device was used. This difference was not significant for implantations carried out using an Edwards valve by transarterial route compared to a CoreValve device despite a shorter time spent in hospital and less pacemaker implantation rates. The ratio of the refund paid to the hospital by the health insurance fund and the average cost of the hospital stay was appropriate irrespective of the status of the healthcare centre (private-sector or public-sector). Correlation analyses showed that the logistic Euroscore could not predict the length of the hospital stay or the cost of the intervention or of the stay (probably due to the low dispersion of logistic Euroscore).

Analysis of published clinical practice guidelines

The clinical practice guidelines included in this report were drawn up in 2008, and relate mainly to the patients eligibility criteria for TAVI and the technical environment.

Patients are selected on the basis of the severity of their aortic stenosis, of their symptoms (for symptomatic patients only), of the surgical risk (STS score > 10 and logistic Euroscore > 20 are generally accepted together with a clinical evaluation), and assessment of the feasibility of the technique.
As far as contraindications are concerned, the technique should not be performed on patients with a thrombus, mass or intracardiac vegetations, massive calcifications, unsuitable annulus diameter or a native bicuspid valve. The transfemoral route should not be used for patients with porcelain aorta, tortuosity or bulky atherosclerosis of the ascending aorta. Similarly, the transapical route is contraindicated for any patient with a previous left ventricular surgery with a patch, calcified pericardium, severe respiratory insufficiency or non-reachable left ventricular apex. Finally, the procedure is not recommended for patients with a life expectancy of less than one year, who refuse surgery or who already have a bioprosthesis.

In terms of the technical environment, the guidelines advised restricting the procedure to a limited number of high-volume centres (though no precise threshold was defined) which have both interventional cardiology and cardiac surgery facilities. As patients may need surgical conversion, it is essential that the two types of theatres are close to each other.

Summary

The level of evidence of the studies is greater for the Edwards Sapien valves, on which two randomised controlled studies have been performed. However, limited data are available with regard to the new-generation valves and new access routes in terms of numbers of patients undergoing implantations and length of follow-up.

All the studies report cases of valve-in-valve implantation. The outcome of these patients is not clearly investigated in the studies. Noteworthy, this practice is a contraindication in the CE mark of the two types of valves on sale in France.

The FRANCE 2 registry, which has broad inclusion criteria, shows cases of aortic valve bioprosthesis implantation via the transarterial or transapical route in patients with a life expectancy of less than one year, with intracardiac masses (contraindication in the CE mark) or who refuse conventional aortic valve replacement surgery. Furthermore, there are still questions relating to the activity of the 33 centres, and it would have been useful to have a description of patient characteristics on inclusion in each centre in terms of age, gender, scores, comorbidities and the types of valves implanted. Similarly, it would be helpful to have a full analysis of all factors affecting mortality. Finally, with regard to patients who, on inclusion, had STS and logistic Euroscore figures below the recommended levels, despite the fact that in over 95% of cases decisions were taken by a multidisciplinary team, the data collected did not show whether comorbidities not taken into account in these scores or anatomical contraindications were systematically related.

3.5. Working group opinion

The experts in the working group expressed their opinions in the light of their knowledge of published data and their clinical practice. Not all the proposals were supported by all the participating members.

Indications, non-indications and contraindications

The group unanimously agreed with the following statement:

“Patient with severe, symptomatic aortic stenosis contraindicated for surgery or at high surgical risk. The surgical risk is assessed during a multidisciplinary meeting taking surgical risk scores (logistic Euroscore ≥ 20% or STS ≥ 10%) and comorbidities into account.”
In the light of current clinical data (randomised controlled trials and data obtained from registries for patients contraindicated for surgery or at high surgical risk), TAVI is only recommended in patients with contraindication of surgical aortic valve replacement or high surgical risk.

Despite the higher incidence of pacemaker implantation following implantation of CoreValve devices, the working group did not wish to distinguish indications for CoreValve and Sapien devices.

In the absence of data based on direct comparisons between access routes, preference must be given to the transfemoral route since it is less invasive and a more well-established technique. However, the experts considered that the choice of access route should be left to the discretion of practitioners. The access route should be chosen during the multidisciplinary meeting at which the indication is determined.

Non-indications and contraindications

Instructions for use and contraindications of the CE mark must be respected. Furthermore, based on the results obtained from the FRANCE 2 registry, the experts specified that:

► Aortic valve replacement surgery is the standard treatment for patients at low or moderate surgical risk. If a patient in this category refuses aortic valve replacement surgery, this is a non-indication for TAVI;

► Patients with a life expectancy of less than one year because of extracardiac factors (comorbidities) are not eligible for TAVI (non-indication);

► Patients with a thrombus, intracardiac mass or vegetations must not undergo TAVI (contraindication in the CE mark for the two types of valve available).

Pre-operative examination

Rather than listing all the tests which must be carried out during a pre-operative examination prior to TAVI, the working group emphasised the need to record the following items correctly (the tests to assess all these criteria will vary on a case-by-case basis):

► Size and geometry of the annulus;

► Number and symmetry of aortic cusps;

► Sub-aortic geometry;

► Geometry of the aortic root (height of the coronary ostia, depth of the sinuses of Valsalva);

► Ascending aorta: diameter, calcifications, axes (if possible);

► Vascular anatomy: diameters, tortuosity, thrombus, calcifications, identification marks;

► Coronary anatomy;

► Myocardial and valvular function, with assessment of the contractile reserve if necessary.
These assessments are carried out in coordination with a anaesthetic consultation at least 48 hours before the procedure (except in an emergency). The usual tests required in a pre-operative examination of a patient undergoing surgical aortic valve replacement, with biological and bacteriological investigations should be performed.

**Composition of teams and training requirements**

Patients eligible for the procedure must be selected during a multidisciplinary meeting attended by a cardiac surgeon, an interventional cardiologist, a clinical cardiologist and an anaesthetist/resuscitation specialist. The advice of a geriatrician is strongly recommended.

Regarding the composition of the team during the procedure, the working group defined three situations depending on the chosen access route: the transfemoral route, the transapical route and the subclavian route.

- **Transfemoral route**
  The following must be present in the room where the intervention is carried out: an anaesthetist/resuscitation specialist trained in cardiac surgery and two qualified practitioners, at least one of whom must be an interventional cardiologist. The following must be on call: a cardiologist/echographist and a cardiovascular and thoracic surgeon or a vascular surgeon.

- **Transapical route**
  The following must be present in the room where the intervention is carried out: an anaesthetist/resuscitation specialist trained in cardiac surgery and two qualified practitioners, at least one of whom must be a cardiovascular and thoracic surgeon. The following must be on call: a cardiologist/echographist and an interventional cardiologist.

- **Subclavian route**
  The following must be present in the room where the intervention is carried out: an anaesthetist/resuscitation specialist trained in cardiac surgery and two qualified practitioners, at least one of whom must be a cardiovascular and thoracic surgeon or a vascular surgeon. The following must be on call: a cardiologist/echographist and an interventional cardiologist.

It was suggested that irrespective of the access route, a nurse anaesthetist should be present in the room where the intervention is carried out, but this suggestion was not supported by all the members of the working group.

In terms of training, any practitioner working at a centre which is currently authorised or which is likely to be authorised in the near future must:

- Work at a centre which carries out over 200 aortic valve replacements a year;
- Have experience of balloon valvuloplasty and/or closed thoracic aortic endoprosthesis implantation techniques and percutaneous ECMO (extracorporeal membrane oxygenation) techniques;
- Have experience in crossing severe aortic stenosis;
- Have acquired the knowledge needed for this activity during a specific basic training on the use of the devices at the centre where he/she works or at another authorised centre, and have maintained the skills;
- Have undergone practical training in the technique being performed by clinical proctoring.
Technical environment

The essential requirements for the implantation procedure were defined by consensus as follows:

► The technical interventional cardiology and cardiac surgery facilities must be located at the same site and in the same building in case the patient needs an emergency surgical conversion;

► The ideal room would be a hybrid room with the technical properties allowing either cardiac surgery or interventional cardiology procedures to be performed (ECMO available, optimum imaging quality, anaesthesia facilities, air treatment as for an operating room, temperature conditions);

► TAVI by the transapical route can be performed in a cardiac catheterisation room provided that the requirement below is met;

► If the intervention is performed in a cardiac catheterisation room, it must have the same standards and characteristics as a cardiovascular operating room in terms of asepsis, and anaesthesia facilities;

► If the intervention is performed in an operating room, the imaging quality must be as close as possible to that available in a cardiac catheterisation room;

► A continuous monitoring unit, a cardiology intensive care unit or a resuscitation unit must be available to take in charge any eventual complications.

Patient monitoring

The working group recommends that patients be followed-up at one month, six months, one year and once a year thereafter. Monitoring should involve biological tests and an echocardiogram. The follow-up consultation at one year must be carried out at the centre where the implantation procedure took place, and must integrate cardiac and geriatric assessment.

Selection of implantation centres

The working group was asked for its opinion as to whether sufficient implantation centres were available. In the light of their experience, the experts drew attention to some geographical imbalance: some centres had waiting lists, but most were able to meet all local needs.

The working group was unanimously of the opinion that a minimum threshold of activity should be defined for the centres in order to maintain their level of expertise. A threshold of two implantations per month was suggested, but this is an arbitrary proposal which was not supported by all the experts in the working group.

Antibiotic prophylaxis, anticoagulant and anti-platelet treatments

Antibiotic prophylaxis to prevent infectious endocarditis in accordance with the French Society for Anaesthesia and Resuscitation guidelines, and anticoagulant treatment in accordance with the local protocol are given to all patients.
Platelet anti-aggregant treatment is essential following TAVI. However, the working group did not wish to give formal recommendations regarding which medicinal products should be used, or any dose or treatment duration specifications, since these parameters must be left to the practitioner’s discretion in accordance with local protocol.

Lacking data

The working group emphasised the need to continue with the FRANCE 2 registry in order to obtain longer-term data on the safety and efficacy of the various types of valves implanted. The experts recommend that results from at least three years follow-up, including quality of life data, should be collected. Furthermore, data on patient characteristics on inclusion, efficacy, safety, and the trend in implantation volumes over time for each centre should also be collected.

The experts observed in the light of clinical data and their own experience that there was a learning curve for the technique. However, this has not been described in detail and it is impossible to determine the threshold beyond which a practitioner can be said to have mastered the technique.

Perspectives

The working group considered three possible ways in which the technique might evolve.

1- It is possible in the future that cardiac surgery and interventional cardiology facilities would no more be required to be on the same site. However, the risk of surgical conversion and vascular complications mean that this is not feasible at present.

2- Valve-in-valve implantation (contraindication in the CE mark) covers two clinical situations:

- Implanting two aortic valve bioprostheses in the same procedure because of complications encountered when implanting the first valve. Under these circumstances the working group is of the opinion that implanting a second valve is essential to save the patient’s life.

- Implanting a transcutaneous aortic valve bioprosthesis into an existing degenerated bioprosthesis. For the group, clinical data from comparative studies are needed before TAVI can be considered in this clinical situation.

It is essential that the CE mark is obtained for these indications before the valve-in-valve procedure can be envisaged.

3- Regarding the possibility of an extension of indication for TAVI to all patients having surgical indication, the working group was unanimously of the opinion that a randomised, controlled study investigating efficiency, using valve replacement surgery as the comparator, was essential.

If new valves are licensed in the future, the working group considers that it is essential to require clinical data (standardised safety and efficacy criteria) from a registry with a one-year follow-up period.
4. HAS conclusions

In the current state of the art, HAS recommends to limit TAVI to patients with contraindication of surgical valve replacement following assessment in a multidisciplinary meeting and who meet the eligibility criteria of the authorised centres. HAS also emphasises the need to give patients written information on the uncertainties related to the mid- and long-term efficacy of the technique and its complications.

HAS notes that data from the FRANCE 2 registry show that some implantations are performed in situations not covered by the recommended indications. HAS also reminds practitioners of the need to comply with all the contraindications listed in the CE marks of the devices, and that this technique must not be used on compassionate grounds in patients with a life expectancy of less than one year with regard to the associated comorbidities, or in patients who are eligible for surgery but refuse it. **HAS also points out that surgical aortic valve replacement remains the standard treatment irrespective of the surgical risk.**

Authorised centres must respect the following requirements:

► Authorised centres must comply with the indications and the conditions for prescription and use recommended in HAS guidance (in particular, the need for interventional cardiology and cardiac surgery facilities to be located in the same building);
► A centre must perform at least two transarterial or transapical aortic valve bioprosthesis implantations per month;
► Centres must regularly send clinical data to the national FRANCE 2 registry, set up in accordance with a protocol that complies with HAS guidance;
► The overall analysis of data from the registry, and the results of additional clinical studies, must be sent to HAS once the one-year results for all patients on the FRANCE 2 registry are available.

HAS will reassess this technology in 2014 and requests that the following information be submitted:

► Efficacy and safety data for the various types of valves and access routes for each centre performing implantations under the FRANCE 2 registry;
► Annual record of each centre's volume of activity;
► Data comparing the efficacy and safety of the various types of valves in the validated indications.

Finally, HAS is of the opinion that any extension of indication to patients for whom surgery is not contraindicated must be subject to a demonstration of efficacy, safety and efficiency versus surgical aortic valve replacement.