Agence nationale de sécurité du médicament et des produits de santé

Report

Heart valves for the new endovascular and transapical approaches

(Aortic and pulmonary transcatheter bioprosthetic valves)

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Introduction

Transcatheter aortic valve bioprostheses and transcatheter pulmonary valve bioprostheses are implantable medical devices that fall under European Council Directive 93/42/EEC. The former are primarily for patients with severe symptomatic aortic stenosis of the aortic heart valve; the second are made to replace the valve of a pulmonary conduit with stenosis or regurgitation and sometimes even bioprostheses that are already in place.

Because the population is ageing, aortic stenosis is the most frequent primary valve disease in industrialised Western countries. In 2013, approximately 300,000 people had this condition around the world, and 1/3 were not eligible for open heart surgery because the surgical risk was too great. In 2014, Tchetche et al. (1) claimed that there were over 120,000 transcatheter aortic valve implantations (TAVI) performed around the world since 2002, and another estimate by Professor Cribier (2) reported 200,000 as of 2015.

According to Cribier, France is forth in terms of number of implants per capita, after Germany, Switzerland, and Austria and ahead of the United States. There had been fewer than 4,000 of these procedures there in 2013, compared to over 5,000 in 2014 (data from the PMSI, 2015, Auffret et al. (3)).

Aortic stenosis is a major healthcare challenge because it is life-threatening in the short- and long-term, giving patients 2-5 more years.

The pulmonary valve is replaced in people with congenital heart disorders, but the prevalence of this procedure remains low.

In accordance with the report submitted to Parliament in September 2012, the ANSM has implemented a programme for increased monitoring of markets for certain medical devices, including heart valves using the new endovascular and transapical approaches. The choice was based on the following criteria:

- -the life-or-death consequences for patients receiving these medical devices
- -the relative newness of heart valves (the first TAVI in France was in 2002 by Professor Cribier, and the first CE marking was granted in 2007)
- -the inherent risk of using them (implanting them in hearts for permanent use)

As part of this specific programme, the following oversight efforts were planned: an assessment to take stock of these transcatheter aortic and pulmonary bioprostheses; a technical and regulatory assessment of instruction leaflets, CE certificates, and any other documents associated with the commercialisation of these devices; an assessment of selected clinical data collected by each manufacturer for all valves; active monitoring of the literature about these medical devices; and an assessment of vigilance data. The available data from French registries has also been studied. Finally, an inspection campaign was conducted for these medical devices.

The monitoring programme began in June 2013. The last data was collected till June 2015. They relate to bioprostheses with CE marking sold in France up through June 2015 and those that manufacturers planned to sell in the short term in June 2013 (though in the end not all of them were marketed during this time frame).

This report does not examine transcatheter aortic valve bioprostheses meant to replace the mitral valve and only mentions the indication for replacing surgical aortic bioprostheses with transcatheter aortic valve bioprostheses (valve in valve implantation or VIV) at the end of the report.

CONTENTS

List of acronyms

- AHA/ACC: American Heart Association / American College of Cardiology
- AOA: Acide Alpha-Amino Oléique
- AVC : Accident Vasculaire Cérébral
- BAV : Bloc Auriculo Ventriculaire
- EOA : Effective Orifice Area : surface valvulaire (cm^2)
- ESC: European Society of Cardiology
- EUROSCORE: European System for Cardiac Operative Risk Evaluation
- GACI : Groupe Athérome coronaire et Cardiologie Interventionnelle
- LPPR : Liste des Prestations et Produits Remboursables
- PMSI : Programme de Médicalisation des Systèmes d'Information
- RAC : Rétrécissement aortique calcifié
- SFC : Société France de Cardiologie
- SFCTCV : Société Française de Chirurgie Thoracique et Cardio-Vasculaire
- Score STS: Society of Thoracic Surgeons
- Score STS-PROM: Society of Thoracic Surgeons-Predicted Risk of Mortality score
- STS: Society of Thoracic Surgeons
- TAVI: Transcatheter Aortic Valve Implantation
- TAVR: Transcatheter Aortic Valve Replacement
- VARC / VARC-2: Valve Academic Research Consortium
- VIV: Valve-in-Valve

Part I. Presentation of heart valves for the new endovascular and transapical approaches

1. Technical characteristics

The structure all these valves share includes 3 valve leaflets of animal origin on a stent-type support structure and a catheter delivery system for guiding and positioning the valve. The valve is designed as a permanent implant while the delivery system is a single-use catheter. In most cases, the valve system was designed for retrograde implanting using a guide following balloon valvuloplasty.

There are various models on the market in France characterised by:

- Whether the 3 leaflets are originally from porcine or bovine sources.
- Whether the support structure is stainless steel, nitinol, or chrome cobalt. In rare cases, it may be made of platinum/iridium or a polymer.
- The type of opening mechanism of the support system during valve implantation: self-expanding support structure, balloon deployment, or filling inflatable channels for one valve in particular.
- Whether the valve is indicated for replacing the aortic or pulmonary valve.
- The approach that is selected for positioning the valve: transfemoral, transapical, subclavian, transcarotid, and transaortic for aortic valves. Transfemoral and jugular approaches for pulmonary valves.

2. Overview of the manufacturers, models of valves, and volumes of sales

We decided to limit the manufacturers identified by only including those whose valves had already a CE marking in June 2013 and whose valves were available in France or who had plans to put their valves on the market in the short term at that time. To date, this number of manufacturers remains relevant, but the number of valve references per manufacturer has increased.

Six manufacturers were identified in late 2013 with 12 transcatheter aortic and pulmonary bioprostheses with CE markings. The various models of transcatheter aortic and pulmonary bioprostheses and their delivery systems with CE markings are detailed in the first table in Appendix 1. This information comes from data collected from June 2013 to December 2015[1]. The second table in Appendix 1 details the bioprostheses that obtained CE markings from December 2013 to December 2015 which were put on the French market during that period or which the manufacturer planned to put on the market in the short term.

[1] This table was updated in December 2015

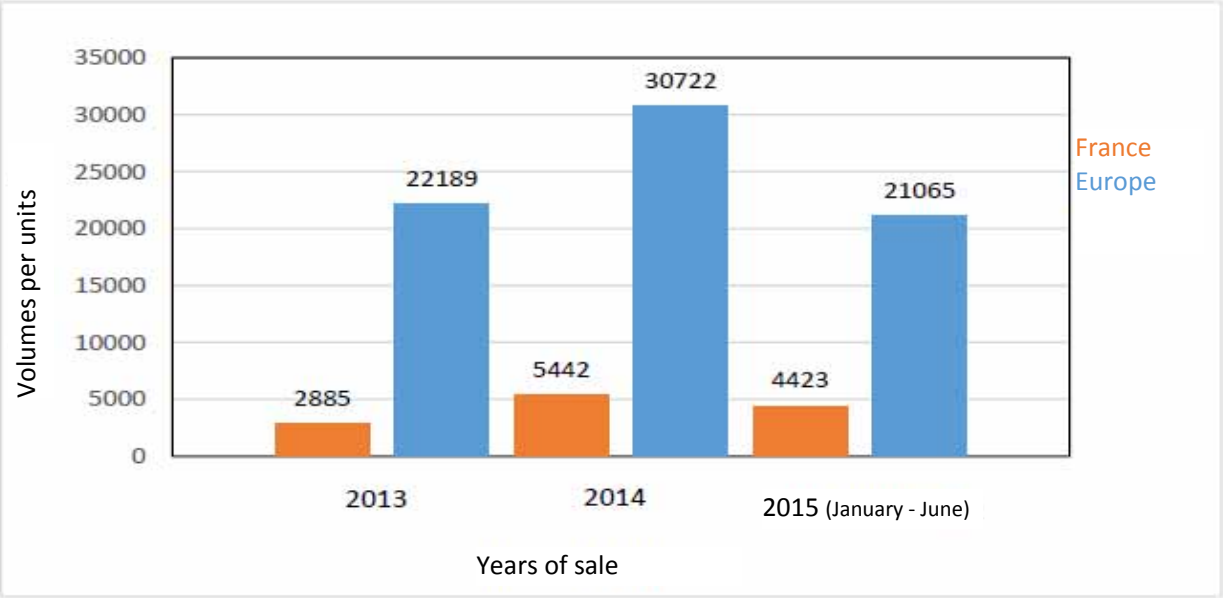

Figure 1: Volume of sales provided by all manufacturers in France and Europe for transcatheter aortic valve bioprostheses - January 2013 - June 2015

The volume of sales of transcatheter aortic valve bioprostheses provided over the period from January 2013 to June 2015 in France is continually increasing (extrapolation of the volume from the first half of 2015 to the second) with a total of 12,750 devices. Moreover, this represents about 13% of sales in Europe in 2013 and 21% for the first half of 2015.

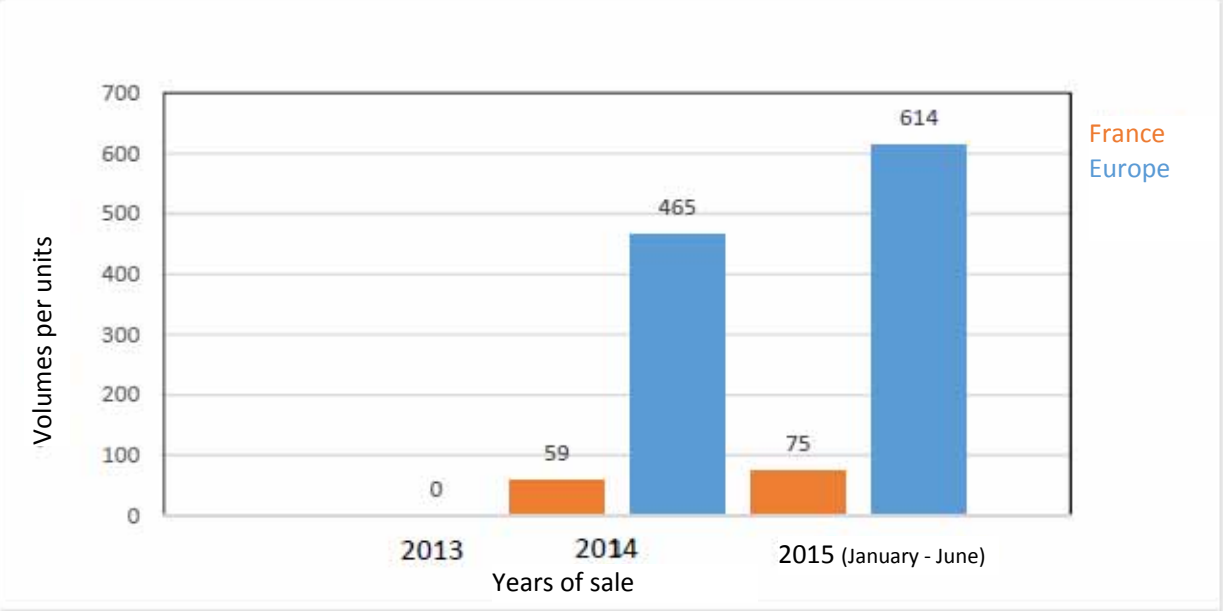

Figure 2: Volume of sales in France and Europe provided by all manufacturers for transcatheter pulmonary bioprostheses - January 2013 - June 2015.

The volume of sales of transcatheter pulmonary valve bioprostheses is also increasing, both in France (with a total of 134 devices) and in Europe (extrapolation from the sales of the first half of 2015 to the second half). However, it only accounts for a small part of the total volume of sales including aortic and pulmonary bioprostheses, namely 1.42% of total sales of cardiac valve bioprostheses in France and 1.92% of total sales of cardiac valve bioprostheses in Europe for the entire period observed.

Moreover, the volume of sales of pulmonary bioprostheses in France is only a relatively small fraction of sales in Europe for this period. It remains stable at about 13% of the European total volume for the three years examined (2013, 2014, and the first half of 2015).

3. Approaches and indications

3.1 Approaches

The placement system or delivery catheter is appropriate for the approach being considered. In France, 80% of these operations involve the transfemoral approach (3), which remains the preferred approach. The rates for procedural success are generally reported in the literature as being above 95%. In the event of too narrow femoral arteries diameters, calcifications, tortuosity or arteries tortuosity, alternative approaches have been developed for aortic bioprostheses. The transapical approach is the second most common approach used for these valves. There are also other approaches that are less common, including the subclavian, transcarotid, and direct transaortic approaches.

3.2 Indications and target populations

Indications for replacing the aortic valve

a) Severe symptomatic aortic stenosis[2]:
This is the first indication for TAVI in patients for whom open heart surgery is not possible or for those with an increased risk of mortality during surgery (the so-called “high-risk surgical patients”). The narrowing that is characteristic of this condition is due to calcification of the cusps which then do not work together to expel blood from the left ventricle to the aorta. This leads to hypertrophy of the left ventricle and a cardiac output not in line with the effort.

b) Replacing a surgical bioprosthesis (VIV):
This technique involves performing a TAVI for a failing surgical bioprosthetic valve (either due to stenosis, regurgitation, or both). Four product lines of transcatheter aortic valve bioprostheses (including all the various sizes for each product line) had CE marking for the VIV indication as of December 2015. The target population for these four lines of products are patients with high or extremely high risk levels associated with surgical interventions.

c) Severe pure aortic regurgitation:
Pure aortic regurgitation occurs when the leaflets of the aortic valve do not close entirely (suboptimal coaptation). The result is that blood that was just expelled from the left ventricle partly flows back into it. Consequently, blood is not distributed correctly to the rest of the body. Severe aortic regurgitation generally leads to heart failure.

[2] Definition of severe aortic valve stenosis (ESC/EACTS, Guidelines, 2012): Valve area < 1 cm^2 (indexed valve area < 0.6 cm^2/m^2 of body surface area; mean transvalvular gradient of > 40 mmHg in patients with a normal cardiac output / transvalvular flow; maximum aortic jet speed of > 4.0 m/s in patients with a normal cardiac output / transvalvular flow).

In 2013, performing a TAVI to treat pure aortic regurgitation remained rare and no collective data had been published on the subject. Since September 2013, only one bioprosthetic received CE marking for this indication and it is meant for patients considered inoperable or high-risk surgical patients. The agency was informed of the placing on the market of this bioprosthesis in France in March 2013.

More information about this indication is available in Part V of this report, specifically Point 3.2.

Indications for replacing the pulmonary valve

Transcatheter pulmonary valve bioprostheses are indicated for patients with congenital heart conditions and those born with a malformation of the pulmonary valve. They are also indicated for patients with a prosthetic pathway (a bioprosthesis implanted previously or a natural pathway with a patch to increase its size) affected by stenosis and/or regurgitation between the right ventricle and the pulmonary artery.

For the first indication, most of these patients have undergone one or more heart surgeries during childhood to restore blood flow to the lungs. These patients often need a second or even third surgery to replace this valve. Placing a transcatheter pulmonary valve bioprosthesis during the first-line treatment helps avoid these later surgeries.

For the second indication, patients have typically undergone a Ross procedure to replace the failing aortic valve with the patient's own pulmonary valve, which is in turn replaced with a bioprosthetic valve.

Two transcatheter pulmonary valve bioprostheses currently have CE marking for this indication.

4. Supervision of the use of these valves in France by the French National Authority for Health

Since 2007, the French National Authority for Health (HAS) has implemented an early assessment of transcatheter aortic valve bioprostheses in order to speed up their availability on the French market. In 2011, it published an assessment report of the first bioprostheses covered by the national health insurance (4). These recommendations also appear in the European Association for Cardio-Thoracic Surgery (EAPCI) 2008 recommendations (5).

The first patients to be covered by the national health insurance for this operation were those with severe symptomatic aortic stenosis for whom surgery was contraindicated. In 2014, this coverage was expanded to include patients classified as having a "high- surgical risk". The decision to classify a patient as "high surgical risk" is taken by a multidisciplinary team including: an interventional cardiologist, a cardiac surgeon, an anaesthesiologist with a specialisation in cardiology, and a radiologist.

A decree from the 3rd of July 2012 limited the authorisation to implant these devices to certain healthcare establishments[3]. The validity of the criteria for this decree was extended by the decree from the 5th of February 2016 (7).

[3] Applying article L1151-1 of the public health code (6)

Summary of Part I:

Monitoring of the market in transcatheter valve bioprostheses began in 2013 and examined 12 medical devices with CE marking that were available in France in 2013 or which the 6 manufacturers questioned planned to put on the market in the short term.
Within this category of devices, we distinguish between aortic and pulmonary bioprostheses.

Transcatheter aortic valve bioprostheses are primarily indicated for patients with severe symptomatic aortic stenosis that is considered inoperable or who are high-risk surgical patients as determined by a multidisciplinary team. Eighty percent of these valves are implanted using the transfemoral approach.
Transcatheter pulmonary valve bioprostheses are indicated for patients with a prosthetic conduit or a valve graft, presenting stenosis and/or regurgitation between the right ventricle and pulmonary artery.

The volume of sales of these two types of valves in France from 2013 to June 2015 is almost 12,900 units with less than 2% of those being pulmonary bioprostheses. The sales figures in France for these two types of valves do not exceed 20% of the sales figures for Europe during the study period (2013 to June 2015).

Implantation of transcatheter aortic valve bioprostheses falls under the decree from the 3rd of July 2012 pursuant to article L.1151-1 of the Public Health Code (6). The validity of the criteria in the decree was extended by the decree on 5 February 2016.

Part II. Control according to regulations

1. CE compliance certificates for Directive 93/42/EEC

All CE certificates confirming compliance with directive 93/42/EEC for the valves involved in this strengthened market surveillance were studied. No specific comment on regulatory matters needs to be made on this point.

2. Instructions for use (IFU)

2.1 Compliance with directive 93/42/EEC

The IFU for each model of valve from each manufacturer were assessed for their compliance with directive 93/42/EEC regarding medical devices. All IFUs examined complied with the directive.

However, certain manufacturers were asked to make a few modifications and some points required justification or development. The list below mentions a few examples:

1) Making the indications for treating pure aortic regurgitation in the promotional material and the IFU consistent.
2) Modifying the indications wording on the French version of the IFU for an aortic bioprosthesis since it restricted the indications to replacing a prosthetic valve, omitting the primary indication of replacing a natural valve.
3) Standardising the IFU with the promotional leaflet for a bioprosthesis on the recommendation of monitoring efforts following patients with significant heart conditions eligible for TAVI.
4) Justifying expanding the target population for a pulmonary valve bioprosthese between the 2006 and 2014 versions of the IFU of this device. The manufacturer indicated having made this modification based on more than 5 years of clinical data and on a risk analysis showing a favourable risk/benefit ratio for the patients newly eligible for the medical device.
5) Clarifying an IFU on the biocompatibility of the valve materials. The manufacturer confirmed the biocompatibility of all the materials and then modified the document.
6) Justifying the lack of explanation, in the IFU of an aortic bioprosthesis, of precautions to follow when implanting this bioprosthesis using the subclavian approach in patients with a pre-existing permeability of the prosthesis of the internal left mammary artery / internal right mammary artery. The manufacturer questioned about this provided elements that show that the risk is under control; moreover, the manufacturer indicated that in addition to the instructional manual, potential users receive specific information during the mandatory training that is provided.

2.2. More in-depth investigations into certain points concerning IFUs

2.2.1 Recommendations of clinical and academic associations for TAVI indications

When the ANSM began monitoring the market for transcatheter aortic and pulmonary valve bioprostheses in 2013, the recommendations from clinical and academic associations that acted as a reference

were the European recommendations published by the ESC/EACTS in 2012 (8) after an initial version was published in 2008 (5).
Like the 2008 version, these recommendations stipulate, in particular, that “TAVI is indicated for patients for whom surgery is contraindicated according to the multidisciplinary team (including a cardiac surgeon, an interventional cardiologist, a radiologist, and an anaesthesiologist/resuscitator) and may be considered for patients who have a high risk associated with surgery even if it is not contraindicated”.
In the latter case, the text highlights the key role of the multidisciplinary team by specifying that the decision to have recourse to TAVI is entirely in the hands of this team which will calculate the risk of the operation for the patient (compared to surgery). This assessment includes examining the patient's clinical state (whether they have comorbidities such as pulmonary or cerebrovascular damages, renal failure, paralysis, etc.) and their anatomy (for example, characteristics that make surgical intervention difficult such as a porcelain aorta or prior radiation therapy for the thorax, among others). The text presents risk scores such as the Euroscore or the STS score as tools for helping with the decision to use or not use TAVI. A Euroscore of ≥ 20% or an STS score of ≥ 10% are suggested as threshold values, “despite their known tendency to overestimate the risk of operating on the patient”. The authors indicate that the STS score could provide a more “realistic” risk assessment.
In 2014, the AHA/ACC also published recommendations on managing patients with heart valve diseases.

The indications on the IFU for each transcatheter aortic valve bioprosthesis listed in Appendix 1 were analysed in light of the European and American recommendations mentioned above.

The discussions concerned:

- Risk scores: During the IFUs analysis, it was noted that the descriptions of the patients for whom the valves are intended vary widely even though they are referring to the same population for all of the valves. There are specifically variations in the risk scores provided (Euroscore, STS, and the procedural operating risk in accordance with the VARC-2 consensus (9)) and the threshold value (depending upon European or American recommendations). The main conclusion drawn following this assessment was that the IFUs generally include the recommendations principles, but the lack of uniformity in the wording for the indications for each valve from one manufacturer to another may be a source of difficulty for users when choosing a valve. Therefore, users need to pay particular attention to the indications for transcatheter valve bioprostheses that are mentioned in the IFUs.

- The mention of a multidisciplinary team: Given the critical role of this team as established in European recommendations in 2012 (8) and then in the American ones in 2014 (10), it should be mentioned by manufacturers as a reminder to users. Of the six manufacturers questioned on this topic, two already mention the role of the team in their valve IFUs, two others are planning to add it into their valve IFUs, and the final two confirm that healthcare professionals using TAVI remind patients of the team’s role.

- The age for patient eligibility for TAVI: unlike the other two criteria presented above, the age at which TAVI is indicated for patients is not mentioned in either the European ESC/EACTS recommendations (5, 8) or the American AHA/ACC recommendations (10).
However, half of the manufacturers specified the age categories for patients to be candidates for TAVI: 1 of the 3 manufacturers mentioned “elderly patients”, another mentioned patients 70 years or older, and the third mentioned patients 80 years or older (a difference that can be explained by the existence of comorbidities for 70-year-old patients, while the 80-years threshold is presented as the only eligibility factor for TAVI by the second manufacturer).
In its world report on ageing and health published in 2015 (11), the WHO suggested dividing old age into two categories: people over 65 are considered elderly and those over 80 are considered very elderly. This formalized the idea of the “elderly patient” with threshold numbers of years. The numbers provided by the 2 manufacturers in their manuals are therefore consistent with the WHO document. For this reason, no comment was made to manufacturers on this specific issue.

Considering the variety in the IFUs for the description of the target patients for transcatheter aortic valve bioprostheses even though the target population is the same, namely “patients with a high risk associated with surgery or for whom surgery is contraindicated”, it would be best to standardise this information. This standardisation effort could be discussed as part of a future European collaboration.

2.2.2 Anti-calcification treatment for certain aortic bioprostheses studied

The formation of calcified lesions on the pericardial tissue from animal sources is a phenomenon that has been documented, but not entirely explained at this stage. It is due in part to the phosphocalcic metabolic activity of the valve receptor sites. One consequence of the presence of calcified lesions on the biological valve leaflets is structural deterioration of the valve, often limiting its lifespan.

With the goal of obtaining non-antigenetic tissue, a tissue that is mechanically strong and with minimal xenogenic degradation (12), the leaflets from animal sources used to design transcatheter valve bioprostheses first undergo various stages of glutaraldehyde treatment.
Anti-calcification treatments may then be applied to these valves, though they are not required. These treatments have been described in the literature for about twenty years.

Most treatments conducted by the manufacturers questioned during this study use alcoholic solutions (ethanol, ispropanol, and 1, 2-octanediol). This process is well described in the literature and limits leaflet calcification by eliminating phospholipids present in the tissue and excess glutaraldehyde and conformationally changing collagen (13, 14).

Half of all of the IFUs examined described using an anti-calcification treatment. When these IFUs included the name of a procedure, the manufacturers were asked about the nature of these procedures.

Additionally, treating porcine pericardium with a specific drug, AOA (a compound derived from oleic acid, a naturally occurring long chain fatty acid), a process used by one 5 of the manufacturers, was the topic of more in-depth research.
Bibliographic articles showing the benefits of this treatment are rare, cover a period from 1994 to 2005, and mainly deal with preclinical results. This manufacturer was therefore asked about elements showing the clinical benefits of the treatment. Preclinical data was provided by the manufacturer, and we have no specific comment on it. Clinical data was also provided. It was not about the manufacturer’s transcatheter aortic valve bioprostheses, but rather two surgical valves they also make. The manufacturer was therefore asked to provide their justification for equivalence between these two valves and the transcatheter aortic valve bioprostheses, especially concerning the nature of the animal tissue used in these valves and the amount of AOA used for each valve.
While the elements brought to the attention of ANSM at this point do not constitute rigorous scientific evidence that treating animal tissue with AOA is better than not treating them this way, there has been no elements that might call into question the safety of medical devices that undergo this process.

2.2.3 Other

One manufacturer was asked to send in elements showing the biocompatibility of an innovative concept of injecting a polymer into the ring of an aortic valve bioprosthesis. The manufacturer provided a complete report assessing its biocompatibility as well as a risk analysis. Analysis of these documents did not lead to any specific comments at this stage.

3. Compliance with European regulation 722/2012

Regulation 722/2012 replaced directive 2003/32/EC starting on 29 August 2013. It deals with the risk of transmitting animal-borne spongiform encephalopathy to patients or others through medical devices made using non-viable animal tissue or derivatives rendered non-viable.
This regulation aims to be more stringent than the directive, especially as concerns justifying the use of tissue of animal origin in regards to alternatives that do not contain those tissues. The tissues of animal origin targeted by the regulation come from cows, sheep, and goats as well as various other animals (deer, elk, mink, and cats).

For the manufacturers of transcatheter aortic and pulmonary valve bioprostheses who were polled during this market monitoring effort, 8 models of valves were affected by this text (different sizes per valve model) and are manufactured by 5 of the 6 manufacturers involved in this report.

Compliance with regulation 722/2012 was verified for all valves from these 5 manufacturers.

4. Compliance with international standards NF EN ISO 5840-3 and 14160 applicable

All manufacturers questioned reported complying with ISO 5840-3 and ISO 14160 which are harmonised standards[4].

4.1 NF EN ISO 5840-3 (2013): “Cardiovascular implants - Cardiac valve prostheses - Part 3: Heart valve substitutes implanted by transcatheter techniques”

In several areas, this international standard repeats the provisions in EN ISO 5840 published in 2005 and entitled “Cardiovascular implants - Cardiac valve prostheses” (which was replaced by EN ISO 5840-1 published in November 2015). However, it is deliberately less defined so as not to limit the development and innovation of TAVI. For example, while the minimum number of patients in a clinical trial is defined for sutured surgical valves, it is not defined for TAVI. Similarly, the number of centres performing implants for a clinical trial is defined for surgical biological valves, but not for TAVI.
Standard 5840-3 (2013) is currently being revised.

[4] *A harmonised standard is a European standard developed by a European standardising organisation designated by the European Commission (e.g., CEN, CENELEC or ETSI). Accounting for it (which is not obligatory) presumes compliance of medical devices with European legislation.*

4.2 NF EN ISO 14160 (2011): “Sterilization of health care products - Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives”

All transcatheter aortic and pulmonary valve bioprostheses are sterilized by submerging them in glutaraldehyde, which is a known microbicide that still preserves biological tissue. ISO 14160 specifies the requirements relating to characterising a liquid chemical sterilizing agent and to developing, approving, inspecting, and monitoring the sterilization procedure.

5. Durability data

Implanting tissue of animal origin in humans raises questions about the durability of these tissues with known limiting factors for transcatheter aortic and pulmonary valve bioprostheses including degeneration and calcification.
Chapter 2.2.2 of this report deals with calcification. Degeneration is due to the deterioration of the collagen making up the leaflets and specifically to a morphological alteration of these leaflets as well as structural damage (fragmentation of the elastic collagen fibres during compression of the delivery system). The clinical consequences include the development of regurgitation that is at least stage 3 (major) and/or valvular stenosis. Manufacturers were asked for their available data on the durability of their transcatheter valve bioprostheses product lines. All manufacturers framed their answers with respect to point 7.2.4.1 from ISO 5840-3: 2013 and the related appendix, that is, with respect to in vitro tests. This text requires the valve to function for at least 200 million in vitro test cycles and over 200 million cycles when there is no established clinical history for the materials as valve obturators or leaflets. For the structural support components of the prosthesis if they exist, the standard indicates that it must last at least 400 million cycles.

As for the durability of transcatheter valve bioprostheses implanted in humans, there is little data provided by manufacturers. A bibliographical research effort was therefore necessary.
The VARC-2 consensus (9) suggests measuring post-procedural central and paravalvular aortic regurgitations using Doppler echocardiography as a significant parameter of bioprosthesis malfunctioning. If a malfunction is suspected, the consensus recommends an attentive assessment of the morphology of the valve to check for a structural abnormally. During the bibliographic search, we noticed that most published studies/registries include post-procedural measurements of aortic transvalvular gradients, as the consensus recommends. However, the majority of studies do not offer an in-depth assessment in terms of the structure of the bioprosthesis.
The studies/registries analysed in this bibliographic search document a so-called “long-term” follow-up of about 7 years (15, 16 and 17). At that post-implantation time, the conclusions of studies/registries are relatively uniform with few or no malfunctions of the bioprosthesis. It should, however, be noted that the study conducted by Professor Dvir (at the Saint Paul Hospital in Vancouver) which was presented in May 2016 at the EuroPCR in Paris (18) seems to show signs of degeneration, for the first time, which affects 50% of the transcatheter aortic valve bioprostheses 8 years after implantation. However, these results have yet to be confirmed.

Working from the 3-4 years median survival rate of patients with these implants as reported in these published studies/registries (15, 16, 17), the long-term clinical data available leads to the conclusion that the durability of these bioprostheses is not a limiting factor for using these medical devices at this stage. Nevertheless, this conclusion is only valid when dealing with patients considered inoperable or with a high risk associated with surgery.

More long-term results are expected, especially because placing transcatheter aortic valve bioprostheses in patients with an intermediate risk level (generally younger patients around 60 years old) is becoming more and more common (see Chapter V).

Summary of Part II:

The ANSM inspected the CE certificates and IFUs for the transcatheter aortic and pulmonary valve bioprostheses listed in Appendix 1 in light of directive 93/42/EEC. The results of this examination do not indicate any need to question whether these medical devices meet the essential requirements of the directive specifically relating to these two documents.

Changes to the IFUs were nevertheless carried out by manufacturers at the request of the ANSM in order to provide more complete information, add details, or rectify errors. Moreover, the analysis of indications in the IFU of each transcatheter aortic valve bioprosthesis showed a large variation in the description of the patients for whom the aortic valve bioprostheses are intended, despite the fact that the target population is identical for all these valves (high-risk surgery patients or patients for whom surgery is contraindicated). Since this variation could cause confusion for users choosing valves, users should pay more attention to the indications provided by manufacturers in the IFUs. An effort to standardise this information is desirable and could be discussed as part of a future project for writing a specific guide dedicated to TAVI with the support of the European Commission. The ANSM has positioned itself to participate in this working group.

The Agency's regulatory control also examined whether the transcatheter valve bioprostheses conformed to European regulation 722/2012 concerning risks associated with spongiform encephalopathy. It should be noted that all manufacturers claim their transcatheter bioprostheses comply with this regulation.

Finally, one of the important characteristics of these medical devices is their durability once implanted because they are made of tissue of animal origin. All manufacturers claim to follow ISO 5840-3 (2013) concerning proper functioning after the valve has undergone a set number of test cycles in vitro, but there is little clinical data. A bibliographic search provided relatively detailed data with 7-years post-implantation information and little to no observed degeneration of bioprostheses (provided this is confirmed by the latest work by Professor Dvir (18)). Because there are 7 years of reported durability for these bioprostheses, time may not be a limiting factor for using these medical devices for high-risk surgical patients or those for whom surgery is contraindicated. Nevertheless, more long-term data is necessary because patients with an intermediate surgical are already receiving these medical devices in practice.

Part III. Clinical assessment

Each manufacturer was asked to send in the rates of the main complications linked to these medical devices as part of this surveillanceof the market for transcatheter valve bioprostheses.
Because of the very low numbers of sales of transcatheter pulmonary valve bioprostheses in France, they were excluded from this study, but they could be the subject of later examinations. For informational purposes, the primary complications for pulmonary valves as cited in the literature are: endocarditis, stent fractures, migration of valves once they are implanted, pulmonary thromboembolisation, and pulmonary regurgitation.

Moreover, the work by the ANSM focused on patient safety with TAVI. This report did not examine the performance of these valves, mainly measured using two parameters: decreasing transvalvular gradients and re-establishing an effective valve surface. The results presented in the literature show, for the most part, sure clinical benefits of TAVI for treating severe symptomatic aortic stenosis.

As for aortic bioprostheses, complications were drawn from clinical data from vigilance and clinical trials registered at the Agency. A choice was made to examine the main complications cited in the literature that had a direct impact on mortality or which led to permanent handicap (cerebrovascular accidents, significant to severe paravalvular leaks) and the main complications requiring endovascular or surgical correction or the implantation of a medical device (such as major vascular complications and conduction disorders).

1. Descriptions of complications observed with aortic bioprostheses

The descriptions provided below are deliberately general. To have more detailed descriptions, refer to the VARC and VARC-2 publications (9).

- Cerebrovascular accidents (CVAs): moving the TAVI through arteries and the process of positioning and deploying the device in the calcified aortic annulus may dislodge an obstruction or clot causing a CVA. Most CVAs occur around or after the procedure (within 30 days after implantation), but there are a non-negligible number of late events primarily having thrombogenic causes. CVAs can be ischemic or haemorrhagic.

- Major vascular complications: These complications generally occur within the first month following the procedure and are linked to access or access sites. They are frequent after TAVI, especially when the retrograde transfemoral approach is used. These events are typically iliofemoral dissections, aortic dissections, secondary bleedings, and perforations of the iliac artery, false aneurysms, and distal embolization. All these complications require restorative or endovascular surgery.

- Significant to severe paravalvular leaks: These occur between the natural aortic annulus and the frame of the prosthesis when the prosthesis is not optimally affixed to it, for example when the TAVI is undersized, when there is calcification on the natural aortic annulus, when the prosthesis does not dilate sufficiently, or when the implantation depth of the valve is unsuitable. Paravalvular leaks are known to be a factor for predicting poor clinical results after a TAVI.

- Conduction disorders: The risk posed by the existence of conduction troubles is the onset of left bundle branch blocks and eventually atrioventricular blocks. This risk can be managed preventatively or therapeutically by implanting a pacemaker either during the operation or at a later date. The identified factors for predicting the appearance and continuation of these disorders are: the depth of the valve implantation, the suitability of the prosthesis and aortic annulus, the thickness of the septum, the calcification of non-coronary leaflets, and the presence of a pre-existing right bundle branch block.

2. Rate of complications as calculated using data collected from manufacturers

2.1 Presentation of provided data

The ANSM asked manufacturers to provide the rates for each of the 4 selected complications for each registry/study conducted. The request covered 3 post-implantation periods: 30 days, 1 year, and 2 years. In order to facilitate numeric comparisons and conclusions, we decided to turn the rates provided into number of patients.
All the manufacturers questioned as part of this market surveillance effort sent in their rates for conduction disorders requiring pacemakers to be implanted. Calculations were then performed to obtain the statistics on pacemaker implantation. The ANSM would nevertheless like to emphasize that the VARC-2 consensus began suggesting collecting the conduction disorder rates and pacemaker implantation rates separately in 2012.

2.2 Limits of precision of the data provided and calculations made

Some registries/studies conducted include “different” data that was not able to be excluded from the ANSM’s calculations and therefore remained in the final conclusions. Specifically:

- Including patients with who received an implant using an approach other than the one that was the main focus of the study (femoral or transapical) such as the direct transaortic or subclavian approaches (about 20% of patients).
- Including patients with a lower surgical risk (either intermediate or low) alongside patients with a high risk and those for whom surgery is contraindicated.
- Using different definitions of complication rates based on the period during which the registry/study was conducted: some clinical data provided by manufacturers was collected before the publication of standardised definitions established by the VARC for TAVI complications; others use the VARC system and others use the new VARC-2 version.
- Including different generations of TAVI in the same study/registry without distinguishing between the versions in the numeric results.

The ANSM’s calculations also contain approximations:

- The number of patients for each complication at each period was calculated by multiplying the provided rates of complications by the number of patients “still alive” at each period. The final element was not always available data. When it was not provided, the number of patients “still alive” at each period was replaced by the number of patients initially included in the study/registry (at t = 0).

- It was assumed that the provided rates of complications were “the number of patients with at least one adverse event”. For example: a reported CVA rate of 2% was understood as 2 patients out of 100 having one CVA. Cases of patients with several complications were not able to be examined given the available data.

Moreover, for the calculations made, the following principles were adhered to:

- Rates of complications provided for periods other than the ones requested for this market surveillance, for example 6 months after the operation, were not taken into account.
- Results for feasibility studies were not taken into account because these studies only include a limited number of patients.

Finally, the statistical quality of the studies from which the rate of complications were drawn and provided by manufacturers was not assessed by ANSM as part of the market surveillance efforts (this includes the power of the study, having an appropriate number of patients included, and using appropriate criteria for the main criteria).

2.3 Results

The data provided comes from:

- 14 studies or registries for the transfemoral approach
- 6 studies or registries for the transapical approach

However, the lack of information about complication rates for certain dates of implantation was noted in the studies/registries provided. Figures 3 and 4 below present the number of studies and/or registries for which the rates of each of the 4 clinical complications selected was provided.

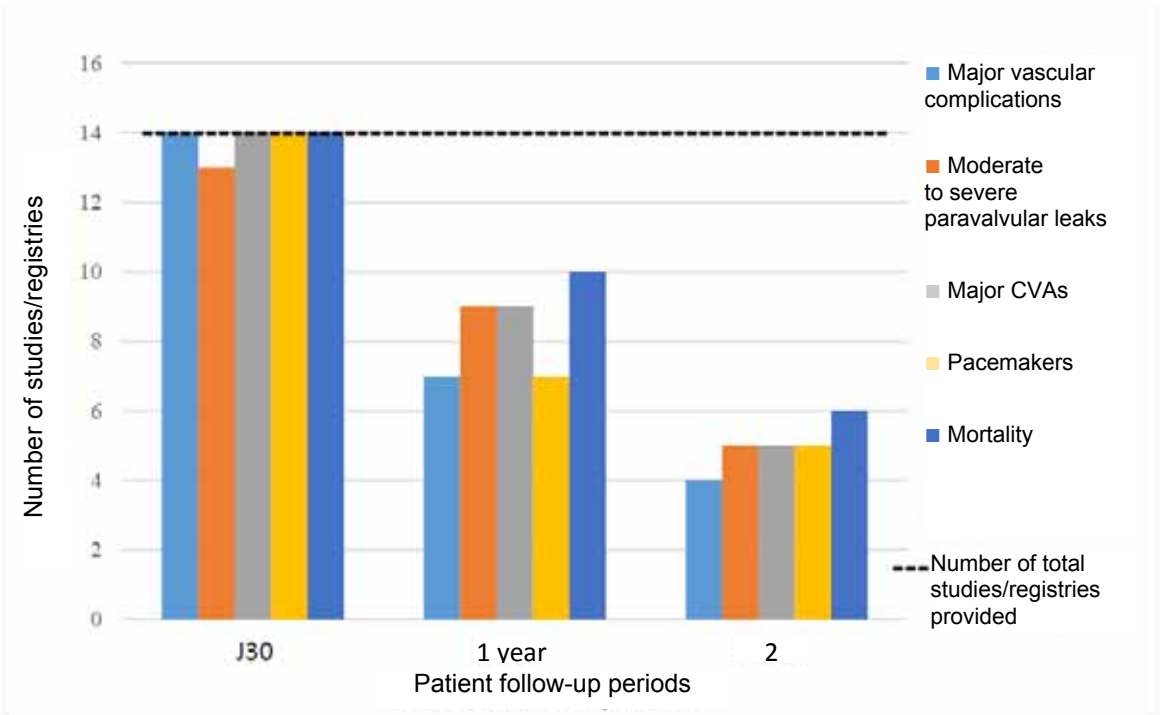

Figure 3: Number of studies/registries by complication and by date of implantation - Transfemoral approach

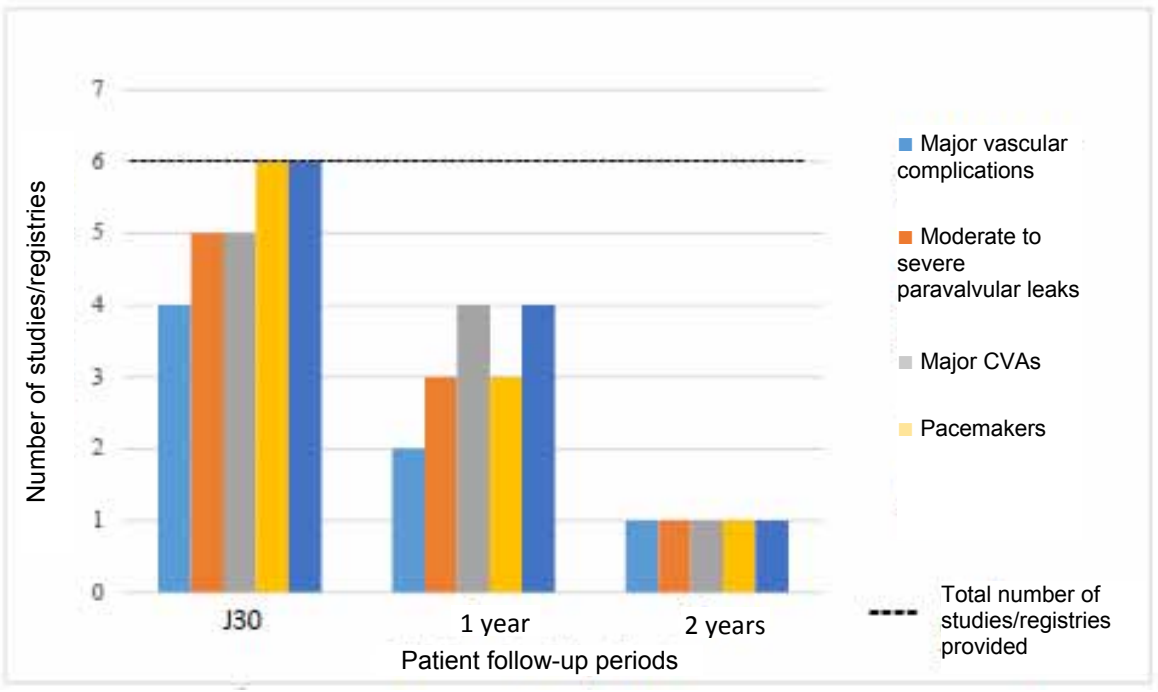

Figure 4: Number of studies/registries by complication and by date of implantation - Transapical approach

The tables presented in Appendix 2 compile the values calculated using data provided by the manufacturers questioned during this market surveillance effort and considering Point 2.2 above.
Figures 5 and 6 below illustrate the numeric results of the tables from Appendix 2:

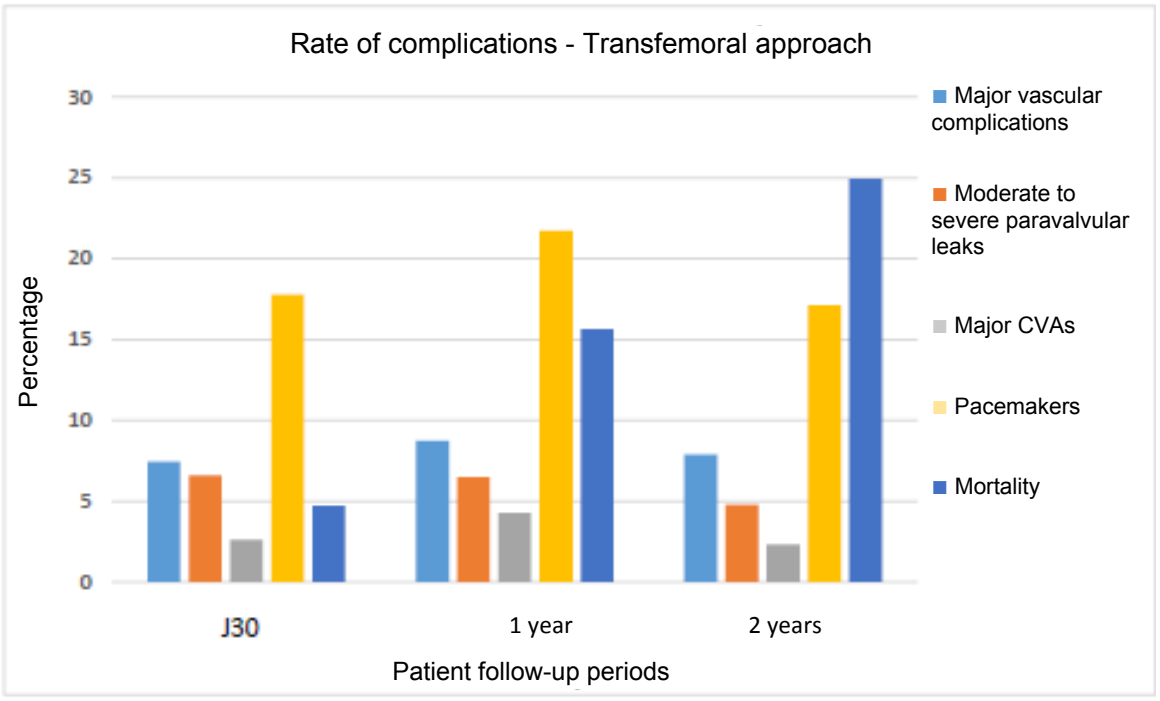

Figure 5: Rate of 4 selected complications and mortality - Transfemoral approach - Data calculated using information provided by manufacturers.

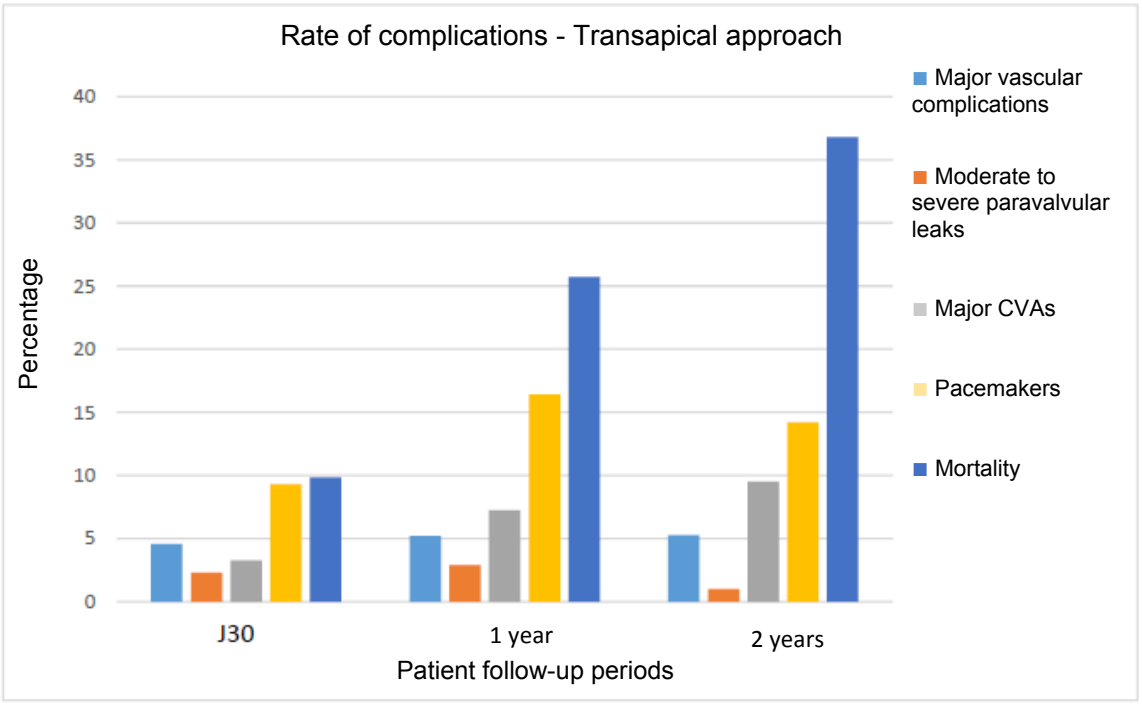

Figure 6: Rate of 4 selected complications and mortality - Transapical approach - Data calculated based on information provided by manufacturers

2.4 Discussion

The first observation to make about Figures 3 and 4 is that the data provided by manufacturers is incomplete. While all the rates of complications after 30 days were sent in by manufacturers for 13 out of the 14 registries/studies conducted for the transfemoral approach for the requested periods, only 4 of the registries/studies sent in all of the rates after 2 years of post-implantation follow-up for this approach. This observation is also true for the registries/studies conducted for the transapical approach with only 1 out of the 6 studies/registries provided at the beginning continuing follow-up for 2 years providing all the requested rates of complications and mortality.
Therefore, it seems manufacturers need to be reminded to pay careful attention to collecting post-implantation data as TAVIs are high-risk medical devices since they are implantable and Class III devices according to directive 93/42/EEC; a two-year follow up period is insufficient for this type of permanent use device.

The second major observation is the percentage of patients who require pacemakers after these valves no matter what approach is used; this is the main “complication” in the data provided by manufacturers.
This observation is well known and has been greatly discussed and reported in the literature.
Research into the potential clinical impact of implanting a permanent pacemaker after TAVI has been conducted. At this stage, the subject has only been examined in a few publications despite the fact that sometimes the percentage of patients requiring pacemakers exceeds 40%. In a 2013 study of 1,556 patients who had a TAVI and then had a pacemaker implanted in the 30-day post-op period, Urena et al. (19) noticed that implanting a pacemaker is not associated with an increased cardiovascular or overall mortality rate or re-hospitalisation due to heart failure with an average post-op follow-up period of 2 years. This view seems to be shared by the scientific community to this day (2016 EuroPCR Conference).

In the literature, however, there are mentions of the negative effect of having a pacemaker on left ventricular function over time (19, 20). In June 2016, Bourantas et al. (21) reported discordant results on the impact of conduction anomalies on mortality in patients who had undergone TAVI. The authors cite three studies that show no link and one that shows increased mortality in patients who developed a blocked left atrial appendage during the procedure. Without getting into the direct link between these two parameters as mentioned previously in this report, the potential that conduction malfunctions have a negative impact on the systolic function of the left ventricle and the functional state of the patient cannot be excluded.
Therefore, while this study has no specific comments about the high rate of patients requiring pacemakers, the potential influence of a pacemaker on left ventricular function should be the subject of more in-depth research.

The third remark concerns the non-negligible rates of major vascular complications for cases using the transfemoral approach. One of the development approaches implemented by TAVI manufacturers to reduce these rates is decreasing the diameter of catheters for inserting these devices. The diameters have gone from 18 Fr (French) to 14 Fr in just a few years. The results presented in Figures 5 and 6 came from studies of all generations of valves including the very first versions; this may have affected the rates.
Considering the observed prevalence of the transfemoral approach (used for around 80% of TAVI patients according to the literature), reducing this rate should remain one of the future points of development for TAVI.

Moreover, it has been noted that all the rates of complication for the transfemoral approach, with the exception of mortality, are higher 1 year after implantation than for 2 years after implantation (conditional on the statistical significance of the differences found). This is also the case for paravalvular leaks and pacemakers for the transapical approach. This observation could be explained by the lack of data 2 years after implantation.

At last, mortality rate observed after 2 years of follow-up (around 25% for the transfemoral approach and slightly below 40% for the transapical approach) are below the rates referenced in the literature for high-risk patients with severe aortic stenosis who are treated with drugs, namely 50% mortality after 2 years and 80% mortality after 5 years (3). The mortality rates calculated after 1 year of follow up for the transfemoral and transapical approaches in the data provided by manufacturers (approximately 15% and 25%, respectively) are similar to those of high-risk surgical patient treated using surgery (around 25%) (4, 22). The risk/benefit ratio for these techniques therefore remains favourable according to the numbers.

3. Data from the registries about the 4 selected complications

The data from registries were examined for the four complications selected for this report, namely major vascular complications, moderate to severe paravalvular leaks, major CVAs, and pacemaker implantation rates. The mortality rate was also examined.

3.1 France 2 record

As part of the strengthened surveillance of TAVI, the intermediary report from December 2014 on the France 2 registry was sent to ANSM (23). This registry was started by the Ministry for Health upon the recommendation of HAS in order to collect clinical data on these devices. It was conducted under the aegis of the clinical and academic cardiology and thoracic surgery and cardiovascular society (SFCTCV). It is a prospective, observational registry covering 34 centres authorised to conduct TAVIs. Between 4,100 and 4,200 patients with degenerative severe symptomatic aortic stenosis were included between 1 January 2010 and 31 January 2012.

The main objective of the registry was to monitor the 1-month and 6-month survival rates and have follow up every year for a period of 5 years. The secondary objectives were to record the event-free survival and the onset of malfunctions of the mitral valve or aortic valve bioprostheses.
It should be noted that the registry concerned both valves and they were from the first generation of devices.
This report focused on the rates of the 4 selected clinical complications (CVA, major vascular complications, pacemakers, and moderate to severe paravascular leaks) presented in the registry. The numbers provided in Appendix 3 were calculated using data from Tables 309 to 338 of the intermediary report from the France 2 registry (22). Figures 7 and 8 illustrate these results.

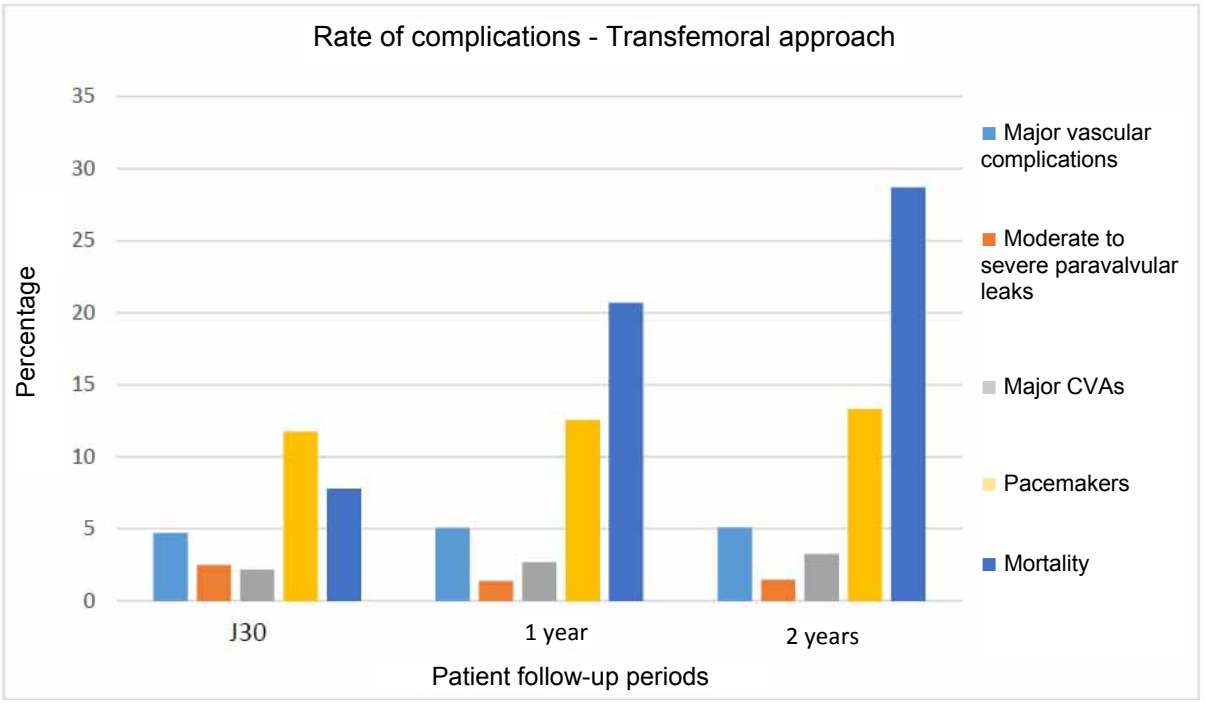

Figure 7: Rate of 4 selected complications and mortality - transfemoral approach - Data from France 2 registry

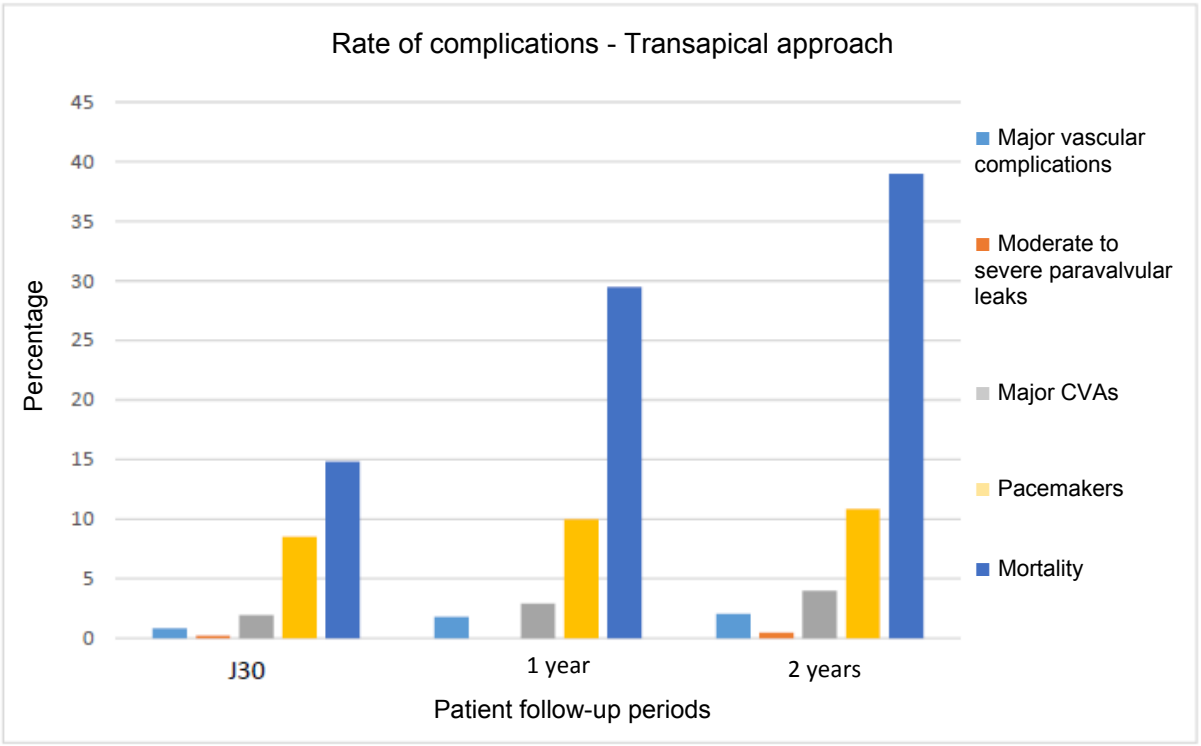

Figure 8: Rate of 4 selected complications and mortality - transapical approach - Data from France 2 registry

Discussion of results in Figures 7 and 8:
The France 2 registry has the advantage of having a very high follow-up rate. Therefore, contrary to the data provided by all the manufacturers for this strengthened surveillance, the data for the four selected complications is available here for 30 days, 1 year, and 2 years after the implant was placed. As in the results from data provided by manufacturers, of the 4 selected complications, implantation of cardiac pacemakers is the most frequent for both the transfemoral and transapical approaches. Major vascular complications also remain the second most frequent complication observed for the transfemoral approach.
The proportion of patients operated on using the transfemoral approach (73%) and the transapical approach (18%) is also similar to the numbers observed in data provided by manufacturers and in the literature more generally.

Moreover, it was noted in the registry reports that 3.5% of all patients included had a TAVI after they refused surgery. According to a univariate analysis by the authors of the report, the mortality rate one month after the TAVI was in part affected by these patients. It should be noted that HAS published an opinion in October 2015 regarding the reassessment of eligibility criteria for centres, in which they noted that a patient refusing surgery did not constitute an indication for TAVI and that communication with practitioners responsible for implantations needed to be strengthened as concerns indications eligible for coverage on the list of refundable products and services.

Comparison of results from Figures 5 and 6 (from manufacturer data) and Figures 7 and 8 (from France 2 registry):

Keeping the limits referenced in point 2.2 in mind as well as the lack of assessment of the quality of statistics from various studies/registries provided by manufacturers, the comparison here remains qualitative in content.

Overall higher mortality rates were observed in the France 2 registry (transfemoral approach: 7.8% at D30, 20.7% at 1 year and 28.7% at 2 years - Transapical approach: 14.8% at D30, 29.5% at 1 year and 38.9% at 2 years) compared to the results calculated using manufacturer data (transfemoral approach: 4.7 % at D30, 15.6 % at 1 year and 24.9 % at 2 years - Transapical approach: 9.8% at D30, 25.7% at 1 year and 36.8% at 2 years). These differences are more pronounced for the transfemoral than for the transapical approach. The procedural risk of surgery for the patient is one factor that could be an explanation for this phenomenon: 34.9% of patients in the France 2 registry had intermediate or low risk levels, but the authors of the report indicate that most had a concomitant condition contraindicating surgery and the others had a technical contraindication for extracorporeal circulation. In the studies/registries provided, it is probable that a non-negligible proportion of patients with an intermediate risk were included without having a concomitant condition contraindicating surgery, which could have directly influence the observed mortality rates.

On the other hand, most of the rates of complications were higher in the data provided by manufacturers compared to the data in France 2 registry: for the transapical approach, all rates were slightly higher while for the transfemoral approach, there was an even more noticeable difference for the rate of pacemakers implanted, major vascular complications, and paravalvular leaks.
One explanation could be the heterogeneity of sources for the data provided by manufacturers in terms of type of study (clinical studies, but also registries, retrospectives, prospectives, etc.), the origin of the data (different countries with multiple centres that perform implants), and clinical practices in various centres performing implants.

Results after 3 years follow up in the registry

In October 2016, the authors of the record published the results with an average of 3.8 years of follow-up (24) and which included 90% of initial patients, namely 3,781 patients. The authors report a mortality rate from all causes of 42% and a lack of new operation or intervention due to structural degradation of the valve. The data presented was not sufficient to determine the rates of the 4 complications selected in this report after 3 years.

One of the 4 complications is cited by the authors as one of the factors for predicting mortality from any cause after 3 years: receiving a pacemaker. As a matter of fact, the authors indicate that the 3-year mortality rate was 41.4% for patients without a pacemaker following a TAVI and 45.4% for patients with a pacemaker ($p < 0.02$). The authors conclude that longer-term data needs to be collected through studies specifically centred on the potential link between these two parameters. The rates presented are still below those described in the literature for patients with a high risk associated with surgery who are treated with drugs, namely 50% after 2 years and 80% after 5 years according to Auffret et al. (3), and they are at the same level as rates in the PARTNER I study for patients with a high risk associated with surgery who undergo surgery (3-year mortality of 44.8% for patients who undergo surgery).

3.2 Other registries

For informational purposes, a second French registry was started in February 2013. It is the France TAVI registry, established under the aegis of the French Cardiology Society (SFC) and the French Society for Thoracic and Cardiovascular Surgery (SFCTCV). The goals of this registry are to study whether indications for placing TAVIs are followed in practice as they are defined by the LPPR, to observe whether a multidisciplinary meeting is held, and to record the type of valve implanted as well as the approach.
In September 2016, the France TAVI registry included over 16,200 patients in 50 centres. The first results from this record were not published at the time this report was written.

On a European level, many registries have also been started examining transcatheter aortic valve bioprostheses. Table 1 succinctly presents these registries and Table 2 shows the rates of the 4 selected complications.

The data come from a meta-analysis published by Zeinah et al. in 2015 (25).

Table 1: Presentation of the European TAVI registries

Registries	Period	Number of patients included	Number of centres performing implants
Belgian Registry	2007-2010	328	15
France 2 Registry	2010-2011	3,150	34
Germany Registry	2009-2010	1,310	22
Italy Registry	2008-2012	774	21
Spain Registry	2010-2011	1,416	44
Switzerland Registry	2011-2013	556	8
England Registry	2007-2010	1,593	30

It should be noted that the France 2 registry is the largest to date in Europe in terms of patients included and centres performing implants (excluding the on-going France TAVI Registry).

Table 2: Rate of 4 selected complications at D30 for all registries combined

Registries	*% major vascular complications*	*% pacemakers*	*% CVA*	*% paravalvular leaks*	*% mortality at D30*
All	/	7%	3%	7%	8%

The authors noted a clear heterogeneity of results between member states. They explain this in part by the differences in practices selecting patients and the risk profile of patients. This observation led them to highlight the urgency of defining standardised criteria for selection patients who receive TAVIs. They also indicate the Euroscore's ineffectiveness in creating predictions for everyday clinical practice of the30-day mortality and consider that developing a TAVI risk score to help selecting patients is important.

Comparison with the France 2 results at day after the procedure:
The rates of the 4 selected complications as well as the 30-day mortality rates from the France 2 registry and the rest of the European registries compiled by Zeinah et al. are consistent.

4. Other data from the literature

Beyond the 4 selected complications previously discussed in this report, ANSM also examined the literature for other safety issues relating to transcatheter aortic valve bioprostheses.

The literature monitoring between June 2013 and December 2015 on EMBASE (keyword: TAVI) revealed other complications relating to the TAVI procedure, but they were relatively rare. Specifically, there were coronary obstructions, valve embolization, atrial fibrillation, and myocardial infarctions.

Of the most recent meta-analyses, the one by Garguilo et al. (26) was retained because it covered a relatively long period for the TAVI procedure, specifically 14 years (from April 2002 to April 2016) and included a total of 16,638 patients. The authors conducted this analysis following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) protocol. Five randomised studies (including the major American studies PARTNER, PARTNER 2A, and US Corevalve) and 31 observational studies were selected. No safety issues other than the ones mentioned in this report were brought up.

In May 2016, the English Medicines and Healthcare Products Regulatory Agency (MHRA) wrote a report (27) presenting the strengths and limitations of transcatheter aortic valve bioprostheses as well as an overall view of these medical devices. A bibliographic search for the keywords “TAVI” and “complications” for international articles published between January 2015 and April 2016 helped select 72 publications including several meta-analyses and systematic reviews on the subject.
The MHRA cited the 4 complications selected in this report as the most serious complications following a TAVI. In addition, the observations by the MHRA on known complications of the TAVI procedure are similar to those in this report with, perhaps, one additional recommendation for vascular complications. MHRA highlights the need to conduct complementary studies on the potential influence of these complications on 30-day mortality rates post-TAVI.
Like Garguilo et al. in their meta-analysis, the MHRA found no safety concern other than the ones mentioned in this report for these medical devices.

Moreover, the bibliography for the MHRA report includes the publication of the results of the Transcatheter Valve Therapy (TVT) record by Holmes et al. (28). This record is important because it was started and monitored by the two major American clinical and academic associations in the field: the Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC). It includes results from 348 centres in the United States for 26,414 patients who underwent a TAVI procedure between 2012 and 2014 and is a reference for the FDA. This record does not broach any safety issues other than the ones in this report.

Finally, the authors of the France 2 Registry found 8 other factors predictive of patient mortality in addition to having a pacemaker. This includes 6 pre-procedural comorbidity factors (being male, BMI, atrial fibrillation, being on dialysis, functional classification of patient, Euroscore), 1 post-procedural factor (moderate to severe aortic regurgitation) and 1 procedural factor (use of transapical or subclavian approach). The authors highlight that the observation of a link between the 3-year mortality rate and the use of the subclavian approach for the TAVI procedure is a new one, with a higher mortality rate for this approach. Consequently, they restate that the transfemoral approach remains the preference for implanting a transcatheter aortic valve prosthesis. To the best knowledge of the authors of this report, this point has not been the subject of other published studies.

Summary of Part III:

The study of clinical data on transcatheter aortic bioprostheses was centred on 4 complications selected because of their prevalence and/or clinical impact. They are: CVAs, major vascular complications, moderate to severe paravalvular leaks, and conduction disorders (replaced by the number of pacemakers given to patients).

One of the first observations was the very large amount of clinical data collected and available for these medical devices. However, in spite of this observation, there was also a lack of complete data provided by manufacturers involved in this surveillance of the market (information on the 4 complications gathered for three defined follow-up periods for this market surveillance). Given the high level of risk associated with TAVIs (a Class III permanent, implantable medical device), a more rigorous and organised follow-up is expected. Manufacturers must pay particular attention to collecting data after sales as part of their post market surveillance.

In terms of data analysis, it was also noted that inserting a pacemaker after a TAVI is the most frequent complication of the four analysed. Major vascular complications are the second most frequent source of complications for patients who received a transfemoral TAVI.
While the data collected up to this point concerning the rates of these two complications has not yet indicated a justification for taking any measures, it should attract the attention of manufacturers and users regarding their daily habits.
Additionally, these specific studies could be useful for examining the potential influence of implanting a pacemaker on patient mortality given the results recorded after 3 years of follow up in the France 2 registry. More specifically, the impact of a conduction disorder and the implantation of a pacemaker on the systolic functioning of the left ventricle should be explored.
Similarly, data on the rates of conduction disorders pre- or post-TAVI should be collected and made available, as recommended in the VARC-2 document.
Mastering the rate of major vascular complications should also remain one of the key elements to develop in the future with TAVIs and complementary studies would help shed light on the link that may exist between this complication and the post-TAVI mortality rate.
The effect of the subclavian approach on mortality could also be something to examine.

Finally, no safety concern for transcatheter aortic valve bioprostheses other than the ones mentioned in this report were discovered through bibliographic searches such as the ones conducted as part of the market surveillance efforts.

PART IV. Analysis of medical device vigilance data from 2010 to 2015

Medical device vigilance system involves monitoring and analysing reports of serious incidents or the risk of serious incidents (defined in article *L.5212-2* of the public health code) that raise questions about medical devices after they have been placed on the market.

Declaring these events helps determine frequency incidents or unexpected typology incidents and detect any alarm signals. It is therefore necessary to systematically inform ANSM of any serious incident or the risk of a serious incident and provide any information available concerning the safety of medical devices to facilitate the detection of anything alarm signals.

An analysis of signals of the medical device vigilance system with aortic and pulmonary TAVI was conducted for a six-year period from early 2010 to late 2015.

Between 1 January 2010 and 31 December 2015, 78% of reports of incidents with TAVIs came from manufacturers and 22% from healthcare establishments or professionals.
This trend is the opposite of the 2014 activity assessment report from ANSM. The latter showed that out of 13,817 signals from medical device vigilance system reports that year excluding breast implants, 54% were reported by healthcare establishments, 37% by manufacturers, and 9% by other actors such as healthcare professionals outside of hospitals or patient associations.
The reason behind this difference for TAVI incidents is unknown. One possible explanation could be that it is a recent, sensitive technology, which could lead industry actors to collect as much market follow-up data as possible. Nevertheless, that can introduce another filter: ANSM may not be informed of an incident or the risk of a serious incident if the manufacturer considers it as not reportable while the agency might have a different interpretation.

1. Annual changes in the number of incidents

From 1 January 2010 to 31 December 2015, 176 alerts concerning aortic or pulmonary TAVI were recorded by the ANSM, including 13 corrective safety actions and 163 incidents.

Figure 9: Changes from 2010 to 2015 in the annual number incidents or safety actions reported to ANSM

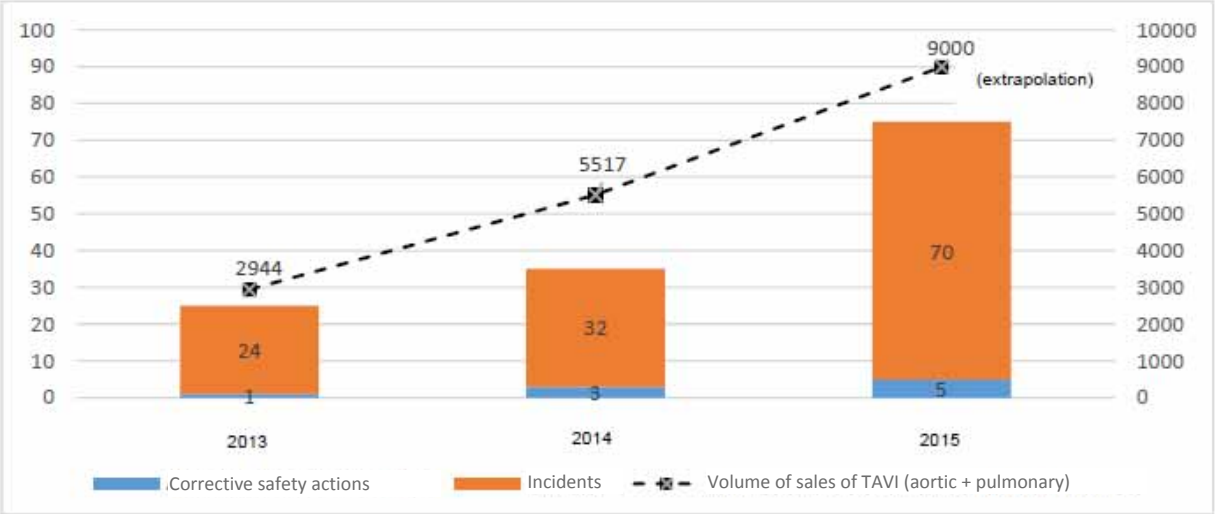

Figure 10: Progression in the volume of sales of transcatheter aortic bioprostheses and the number of incidents in France from 2013 to 2015. The 2015 sales volume was extrapolated from the sales data for the first 6 months of the year.

Figure 9 above shows the changes in the number of alerts for the study period for all types of TAVI. The number of alerts has progressively increased from 2010 to 2014, going from 1 in 2010 to 32 in 2014. In 2015, the number of alerts more or less doubled compared to the previous year.

This increase can be explained by two factors:
-On the one hand, the increasing number of implants in France as the technique has gained momentum as described in Chapter 2 of Part I (see page 4). The increased number of alerts seems moreover to correspond to the increase in sales volumes for TAVIs in France, as shown in Figure 10.

-On the other hand, the recent diversity of transcatheter aortic valve bioprostheses on the market. In fact from 2010 to 2013, almost all alerts concerned the 2 historic models of bioprostheses or their delivery systems. Beginning in 2014, the more recent models of bioprostheses also became the subjects of medical device vigilance system reports. The variety of models represented in medical device vigilance report is more pronounced in 2015.

This trend is likely to continue in the coming years.

2. Main safety alerts

2.1 The delivery system for the Boston Scientific Lotus Valve

The Lotus valves and their delivery system obtained CE markings in October 2013. Following several alerts of the valve unexpectedly detaching from its delivery system during the procedure, Boston Scientific sent out safety information to users in August 2014 informing them of the risks associated with this problem and methods to minimize the risk of this occurring.
Following its investigations, the manufacturer then modified the design of the delivery system to correct this problem; then, in November 2014, it recalled the uncorrected delivery systems.

2.2 St Jude Medical Portico Valves

The Portico valves obtained CE marking in November 2012 (for the 23 mm diameter version) and December 2013 (for the 25 mm version). In September 2014, St. Jude Medical decided to temporarily suspend use of these devices around the world following several alerts of reduced mobility of valve leaflets detected by a 4D scanner.

Following its investigations, the manufacturer estimated that the overall analysis of the risk/benefit ratio for the Portico valve was not changed by this anomaly and decided to lift its suspension.

Consequently, several research teams around the world have shown that the issue of reduced leaflet mobility was not confined to Portico valves, but rather affected all biological, surgical, and transcatheter valves available on the market.

After analysing the available data on this anomaly, ANSM has concluded that it does not justify taking any action at this stage.
In fact, the reduced leaflet mobility does not seem to have repercussions for valve function and has no known clinical consequences for the patients. Moreover, this phenomenon seems to be sensitive to a modification of the typical anti-coagulant treatment. ANSM is continuing to monitor available data on this topic, particularly on-going studies aiming to optimise anticoagulant therapies associated with biological valve prostheses, which could help limit this phenomenon.

2.3 Edwards Commander delivery system for the Sapien 3 valve

The Edwards Commander delivery systems obtained CE marking in January 2014. In February 2015, Edwards sent out safety information after they detected a deviation in the number of alerts about defects with an internal mechanism in the Commander system that could complicate using it. At the same time, the manufacturer implemented solutions to correct this defect.

Following investigations by ANSM and discussions with Edwards, the latter took complementary actions to guarantee the safety of its patients. Consequently, the manufacturer sent out a new information in June 2015 explaining to users that the corrected Commander systems were available on the market and committed to recalling all uncorrected and unused Commander systems as soon as logistically possible. This recall took place in August 2015.

3. Main incidents reported

The 176 safety alerts and incidents reported to ANSM can be grouped into 4 large categories:

- -clinical complications
- -technical or mechanical problems relating to using the delivery systems or accessories
- -functional problems with the valve
- -quality defects

It is important to note that the data presented here are not directly comparable to those from clinical trials or the registries in Chapter 3.
As a matter of fact, they are primarily serious incidents or risks of serious incidents implicating the transcatheter aortic valve bioprostheses that were reported as part of the medical device vigilance system; the clinical studies and registries, meanwhile, aim account for all serious clinical complications whether or not they are linked to a possible defect with the devices.

Table 3 below shows examples of the main types[5] of incidents reported by category.

Table 3: Main types of incidents reported from 2010 to 2015

Categories of incidents	Number of alerts received from 2010 to 2015	The main types of incidents
Clinical complications	77	Conduction disorders Death CVA Thrombosis Aortic dissection
Technical or mechanical problems related to the delivery systems or accessories	86	Non-optimum position of the valve, Problems deploying or delivering the valve Fluid leaks via the delivery system Rupture of the balloon carrying the valve (for those models that are deployed using a balloon)
Functional problems with valves	8	Early degeneration of biological valve leaflets Valve leaks
Quality defects	5	Labelling or packing issues

Unlike quality defects which generally have a clear cause (a problem during production or distribution), the other categories of incidents cannot always be attributed to a specific cause.

This is because these incidents generally result from a combination of several factors, the most frequently reported of which are:
- the patient's anatomical constraints (tortuous aorta, major angulation between the aorta and femoral artery, etc.)
- the presence of vascular obstacles on the path to the original valve can make the procedure complex (for example, stenosis or calcifications)
- possible underlying conditions
- defects or failures of the devices used during implantation

Summary of Part IV

To date, vigilance data from 2010 to 2015 has not revealed any specific new issues with transcatheter aortic bioprostheses that justify any action.

The number of incidents reported involving TAVIs has increased since 2010, but this seems to track with the increased volume of sales of these devices in France.

ANSM is continuing to monitor incidents involving these devices.

[5]*Definition of the type of incident: name for the malfunction or complication reported to ANSM as part of its vigilance system (for example: thrombosis, valve fails to deploy, etc.)*

PART V: Current and future developments

1. Rapid changes in designs of models being placed on the market

Models of transcatheter aortic valve bioprostheses are constantly changing to meet the needs and expectations of healthcare professions and to try to mitigate the most frequent complications. These changes include:

- Reducing moderate to severe paravalvular leaks by changing the architecture of prostheses (adding the external sealing skirt to limit the space between the prosthesis and the aortic annulus), the measurement of the aortic root, and how the bioprosthesis deploys
- Reducing the risk of coronary occlusion (using the anatomical position of the valve) and of the aortic annulus rupturing
- Reducing the rate of vascular complications by, in particular, decreasing the diameter of the positioning catheters
- Limiting the rate of conduction disorders by placing the valve in an optimal position. Certain second-generation bioprostheses can be repositioned and recaptured.

In this respect, the data provided by manufacturers brings about the release of a modified version of an existing valve approximately every 3-4 years. This rapid replacement raises the question of a sufficient time for the clinical data collection to obtain CE marking.
Many clinical studies are ongoing concerning transcatheter aortic valve bioprostheses and their changes, including several for which clinical trial authorisations were requested from ANSM.
It should be noted that all transcatheter aortic bioprostheses studied in this report obtained CE markings using 30-day post-procedural clinical data (these studies are for the most part being continued by manufacturers after they have obtained CE markings, for periods ranging from 2 to 5 years). This length of time was justified for the first generations of bioprostheses after it was shown that the 1-year mortality rate was lower for TAVI patients than for patients who were treated with drugs; this turned the situation into an opportunity for patients for whom surgery was contraindicated. However, ANSM believes that the CE marking for later versions should be supported by more long-term clinical data that what is currently being observed. This point was discussed with the relevant European authorities as part of the revision work on the MEDDEV 2.7.1 application guide dedicated to clinical development and intended for manufacturers and notified bodies. The new version of this guide was adopted and published in June 2016 (29) and stipulates (in Appendix 8 dedicated to devices to cover unsatisfied demand in the medical field) that in order to market medical devices after an initial innovative medical device, manufacturers must include clinical proof collected using the first device.

An upcoming European effort should write a specific guide for manufacturers of transcatheter aortic bioprostheses. This work, which began in 2016, could match the new European medical devices regulation on this specific point. ANSM has joined the European group in charge of writing this guide.

2. Increasing target population for treating severe aortic stenosis

2.1 Defining a patient's surgical risk based on risk scores

Risk scores such as Euroscore, STS, and more recently Euroscore II and STS-PROM remain indicators that help estimate a patient's surgical risk. However, these scores are not useful for predicting the long-term clinical consequences and the procedural complications of a TAVI. They were developed and approved in populations deemed to have a "standard" surgical risk and help predict short-term mortality (at the hospital or within 30 days after implantation) after an operation to replace the aortic valve (Zeinah et al. (25)). They are indicated as being very insufficient when it comes to estimating the risk for a population as heterogeneous as the one of patients eligible for TAVI.
On this note, there are on-going discussions within the scientific community about how to adapt these risk scores to TAVI. The questions debated are:

1) how to improve distinguishing between low surgical risk and high surgical risk
2) how to identify patients who should be steered towards a TAVI
3) how to predict procedural risks and clinical consequences for TAVI candidates Similarly, certain authors suggest a pragmatic stratification of risk for patients with severe aortic stenosis using patient age as the main criterion (or patient life expectancy) and the existence of risk factors.

At this stage, it is important to remember the fact that the role played by the multidisciplinary team (which is alone responsible for assessing the patient's surgical risk) is absolutely essential in the decision to have recourse to TAVI, as we mentioned in point 2.2 of Part II of this report. Standardised criteria for selecting patients should be established, as Zeinah et al. highlighted (25).

2.2 Changes in the level of surgical risk

In 2012, ESC recommendations indicated that TAVI should not be performed for patients with an intermediate surgical risk and that studies were necessary for this population. In 2014, the American recommendations reiterated this message.

In clinical practice from 2011 to 2016, however, there was a shift to include more intermediate or even low surgical risk patients. According to the data in the France 2 registry, the Euroscore of patients undergoing TAVI in France has progressively decreased from 2010-2011 and went from 21.9 in 2011 to 18.8 in 2014. According to Popma (30), intermediate-risk patients could make up 40-50% of the current population of patients receiving aortic valve replacements using surgery.
This phenomenon is not limited to France. The same situation can be seen in other European countries in the last few years. In a monocentric study of 420 patients led by the German Heart Centre Munich, STS scores went from 7.1± 5.4% to 4.8 ± 2.6% (Lange et al. (31)). In a prospective monocentric study of 389 patients in Switzerland, 65.3% of patients were intermediate-risk patients and 10.5% were low-risk patients (Wenaweser et al. (32)). In a retrospective monocentric study in Italy, the average STS score was 4.5% for 182 patients (Latib et al. (33)).

In order to obtain appropriate clinical data, clinical trials were or are being conducted for intermediate risk patients, comparing their results to patients who receive surgery. The primary criteria examined in these studies are the mortality rate (including all causes of death) and the rate of CVAs causing handicaps after 2 years of follow-up. One such study is the PARTNER II (cohort A) study; one of its conclusions was that TAVI was not inferior to surgery for the two main criteria defined (the results were published in April 2016 by Leon et al. (34)). Another such study is the NOTION (Nordic Aortic Valve Intervention) study which came to similar conclusions based on its 1 year post-implantation results. There is also the SURTAVI (surgical replacement and transcatheter aortic valve implantation) study which is currently recruiting patients and whose objective is to include 2,500 patients. Some of these studies submitted clinical trial authorisation requests to ANSM.

At the time this report was written, performing TAVI on intermediate-risk patients was still being debated within the scientific community in terms of the risk/benefit ratio of this procedure compared to surgery.
One idea from these debates is that while studies of CVA and mortality rates are essential, improving results in terms of reducing paravalvular leaks, vascular complications, and pacemaker implantation is necessary to generalise TAVIs to intermediary-risk surgical patients.

Additionally, one of the main subjects debated concerns the durability of transcatheter aortic bioprostheses once implanted in a person. This issue, which is raised for high-risk surgical patients, is all the more relevant for intermediate-risk patients whose life expectancy is longer. Long-term durability data is therefore necessary to extend current TAVI indications to other populations.

3. Indications for VIV and treating severe pure aortic regurgitations

3.1 Valve in valve

Ye et al. (35) was the first team to perform a transapical VIV implant in a patient whose surgical prosthesis was failing. From April 2007 to December 2013, 459 patients were included in the VIVID (Valve in Valve International Data) registry which was started in 2010 led by Professor Dvir's team (18). This record is the largest to date in terms of the number of patients monitored for having had this technique performed on them. Recruitment took place in 55 international centres.
The monitoring results of these patients as published by Ye et al. (36) show a 2-year survival rate of 82.8%, a 5-year survival rate of 40.1%, and a perceptible improvement in their health (NYHA score). The authors of the article then suggested that mid-term results were encouraging for patients deemed high-risk surgery patients and that VIV could be an acceptable alternative therapy when an aortic surgical prosthesis needed to be replaced. The article does note, however, that particular attention must be paid to defining the type of population that VIV would truly benefit.
The VIV technique has not been the subject of in-depth investigations as part of this strengthened surveillance programme for transcatheter cardiac valve bioprostheses. ANSM does not have statistics indicating the number of VIV procedures that have been performed in France. An HAS report from 2011 nevertheless indicates that VIV procedures represent 0.5 to 5% of the number of TAVIs described in the studies. VIV is discussed in more detail in Part V Point 3.1. To date, 2 manufacturers have obtained CE markings for indicating VIV with some of their bioprostheses.

3.2 Treating pure aortic regurgitation

The anatomy of patients with severe pure aortic regurgitation is complex. Typically, the aortic root is dilated as is the ascending aorta, and often the aortic annulus is elliptical. The reference treatment for these patients, who are typically young, remains surgery. It is preferred due to the implication of the descending aorta in many patients. In this case, TAVI would concern patients excluded from surgery. The main challenge with TAVI treating this aortic valve condition relates to anchoring it in a non calcified aortic annulus.

The indication for treating severe pure regurgitation with TAVI is described in Part I of this report in Point 3.2c.

It should be noted that the literature primarily cites cases of performing TAVI with a transcatheter aortic valve bioprosthesis that does not have CE marking for this indication. The publication by Roy et al. (37) in 2013 presents a prospective and retrospective collection of cases of 43 patients excluded from surgery who therefore received a TAVI due to that indication (mainly through the femoral approach) in 14 centres in Europe (in England, Germany, France, Belgium, Italy, Spain, and Poland). While the results are deemed acceptable (including rate of CVAs 30 days after implantation and mortality rate for all causes after 1 year), the authors highlight the non-negligible rate of patients who required a second valve implant during the first implant procedure (18.6%) and the very high rate of patients still with aortic regurgitation after implantation, though the latter was also of low intensity (79.1%).

They insist that particular attention needs to be paid to selecting patients and emphasize that surgery remains the reference treatment.
Similarly, the clinical study conducted by Testa et al. (38) included 1,583 patients, of whom 26 had pure aortic regurgitation; these patients had received transcatheter aortic bioprostheses without CE markings for this indication. The authors also highlight here the need to carefully select patients who at this stage are still patients that cannot have surgery.

In 2016, just as in 2013, only one transcatheter aortic bioprosthesis had obtained CE marking to treat pure aortic regurgitation of the original aortic valve. Aside from one feasibility study which only examined a small number of patients, one study was published by Seiffert et al. in 2014 and examined 30 patients (39). In this series, only 3.3% of patients required a second valve during the procedure and 10% had slight regurgitation after the procedure. The authors indicate that the 6-month results show the valve is appropriate for the condition, but underscore that there was a significant number of non-cardiac early deaths linked to the extreme surgical risk for the selected patients. Once again as in other publications, the importance of patient selection is clear.

The conclusions of the authors of the few existing articles on treating pure aortic regurgitation using TAVI describe non negligible 30-day mortality rates. They emphasize the poor prognosis of patients treated with drugs for this condition and the benefits of TAVI, but also underscore the importance of selecting patients eligible for this technique.

Summary of Part V:

The data manufacturers provided to ANSM reveal that a modified version of an existing valve appears on the market approximately every 3 to 4 years. The modifications made primarily aim to:

- **decrease paravalvular leaks by optimising the device through filling in the gap between the arterial wall of the aortic annulus and the bioprosthesis**
- **reduce the rate of major vascular complications by designing delivery catheters with smaller and smaller diameters**
- **limit conduction disorders with the ability to recapture and reposition a bioprosthesis before definitively placing it**

Placing on the market of consecutive versions of bioprostheses in rapid succession raises the question of whether there is enough clinical experience with each version. Currently, this experience is generally just 30 days after implantation. However, a longer period is preferable. This is why this issue should be discussed as part of the European work that began in late 2015 on writing a specific guide for manufacturers of these devices; ANSM is a part of these efforts. In addition to technical and/or clinical prescriptions, this guide could address questions relating to establishing standardised criteria for selecting patients eligible for TAVI and adapting risk scores to the TAVI technique.

The subject of TAVI for intermediate-risk patients could also be discussed in this guide. In fact, while French national health insurance currently only covers this procedure for high-risk surgical patients or those for whom surgery is contraindicated, providing TAVI for intermediate-risk patients seems to have been widespread for several years. Nevertheless, the subject is still being debated within the scientific community, especially the risk/benefit ratio of this procedure compared to surgery. These debates have suggested that even though studies of CVA and mortality rates are essential, improving results by reducing paravalvular leaks, vascular complications, and pacemaker implantations will be necessary to extend TAVI to intermediate-risk surgical patients.
One of the interesting points in these debates is the lack of long-term clinical data for these medical devices. This is all the more important because intermediate-risk patients are generally younger than high-risk surgical patients or those for whom surgery is contraindicated.

Finally, it should be noted that to date, 2 manufacturers have obtained CE marking for the VIV indication for some of their bioprostheses and that treating severe pure aortic regurgitation with TAVI does not seem to have to become a major indication at this stage.

Synopsis

Transcatheter aortic and pulmonary valve bioprostheses are one of the 5 categories of medical devices included in the strengthened surveillance plan defined by law no. 2011-2012 from 29 December 2011. They were chosen because of their life-or-death importance for the patients receiving them and their relative newness (with the 1st TAVI performed in France in 2002) and because of the inherent risk of using them (implanting them in the heart for permanent use).

ANSM questioned six manufacturers of transcatheter aortic and pulmonary valve bioprostheses with CE markings available on the French market in 2013 (when this market surveillance began) or who planned in the short term to put one on the market. The goal was to create an overview of these medical devices. The overview was then extended to late December 2015. Twelve lines of medical device total were included in this market surveillance effort. ANSM assessed the documents accompanying these devices when they were placed on the market (including CE certificates and instructions for use) as well as some clinical data. Given the low number of transcatheter pulmonary valve bioprostheses available in France compared to the number of aortic bioprostheses (less than 2% in 2014), the assessment of clinical data was not conducted for the pulmonary valves.

For the period including 2013, 2014, and the first half of 2015, almost 12,900 transcatheter aortic and pulmonary bioprostheses were available on the French market, including 11 different product lines (1 line was still not on the market in June 2015) according to data provided by the manufacturers. This number accounts for approximately 17% of the volume of transcatheter bioprostheses in the European market.

The ANSM's analysis of the CE certificates did not lead to any specific comments. As for the assessment of IFUs, it did not show a failure to comply with directive 93/42/EEC, but still led to discussions with the manufacturers and requests for changes. Among the different points discussed was the lack of uniformity of the descriptions of the target population for whom aortic bioprostheses are intended even though the valves are dedicated to the exact same group (patient with severe aortic stenosis contra indicated to surgery or at high surgical risk). Since this lack of uniformity may cause difficulties for users choosing valves, particular attention needs to be paid to this issue.
The other key point made following this analysis of IFUs related to the central role of the multidisciplinary team in choosing whether or not to perform a TAVI. ANSM ensured that this information be mentioned in the IFUs or at least in the user training programme.

Finally, the third important point made after this examination regarded the durability of transcatheter aortic valve bioprostheses. Clinical follow-up data beyond 2 years after the implantation remain rare, or at least incomplete. The literature provides follow-up of about 7 years for high-risk surgical patients or those for whom surgery is contraindicated which generally shows little to no degeneration of the bioprostheses. More long-term data is necessary.

The analysis of the clinical data provided by manufacturers also concentrated on the four complications selected because of their prevalence and/or clinical impact: CVAs, major vascular complications, moderate to severe paravalvular leaks, and conduction troubles (replaced with pacemakers being implanted). For this analysis as well, the lack of complete data provided for the 2-year follow-up, as requested for each study, was noted. This also raises some question of the quality of post-market surveillance carried out for these medical devices.

Analysis of the provided data also showed that getting a pacemaker and presenting vascular complications were the two most frequent complications after at TAVI, though at this stage they are not so common as to justify any corrective measures.
However, manufacturers must continue their efforts to decrease the impact of the delivery system on the patient's vascular system and specific studies of the potential effects of a pacemaker on the systolic function of the left ventricle and on patient mortality could prove necessary. The effect of the subclavian approach on mortality could also be something to examine.
Data on the rates of conduction disorders pre- or post-TAVI should be collected and made available, as recommended in the VARC-2 document.

Analysis of vigilance data from 2010 to 2015, with the exception of safety alerts described in Point 2 of Chapter IV which are already identified and monitored, has not shown any issue with TAVI that would justify taking action. The number of incident alerts for TAVI has increased since 2010, but this seems to track with the increased sales volumes of these medical devices in France. ANSM is nonetheless continuing to monitor incidents involving them.

Finally, rapid changes in transcatheter aortic valve bioprostheses were observed, including in terms of valve design (external skirt, repositioning and recapture capacity), indication (valve-in-valve, pure aortic regurgitation), and target population (intermediate-risk patients). The short intervals between when consecutive versions of the bioprostheses are placed on the market raises the question of whether that is enough time for clinical experience with each version. Currently, this experience is generally just 30 days after implantation. However, a longer period is preferable. These changes must draw specific attention from notified bodies, especially in terms of the amount of time for collecting clinical data to receive CE marking.

A discussion regarding writing a specific guide intended for manufacturers and notified bodies about transcatheter aortic valve bioprostheses began in December 2015 driven by the European Commission. The goal is to detail the information expected as part of a demonstration of the safety and performance of these medical devices as required by directive 93/42/EEC and by medical device regulations. ANSM participated in the first working group meeting led by the relevant English authority. The different points of improvement discussed in this report could be examined during the efforts to write this guide.

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⇨ Appendix 1: Transcatheter aortic and pulmonary valve bioprostheses and their delivery systems with CE marking

Table 1: Data obtained in late 2013

Manufacturers	Valve references	Type of leaflet	Delivery system (approach)	Date of 1st CE marking
Boston Scientific	Lotus Valve System	Bovine pericardium	Lotus Valve system	October 2013
Direct Flow Medical	Direct Flow Medical	Bovine pericardium	DirectTrack	January 2013
Edwards	Sapien Pulmonic	Bovine pericardium	Retroflex 3 (venous approach)	May 2010
	Sapien XT	Bovine pericardium	Novaflex (transfemoral)	March 2010 (23, 26 mm) April 2012 (29 mm)
			Ascendra (transapical) (1) Ascendra 2 (transapical) (1)	July 2010 (23, 26 mm) February 2011 (29 mm)
			Ascendra + (transapical and transaortic)	May 2012 (23, 26, 29 mm)
Jenavalve	Jenavalve	Valve with porcine aortic root	Cathlete and Cathlete+ (transapical)	September 2011
Medtronic	Melody (pulmonary valve)	Bovine jugular valve	All	November 2006
	Corevalve system	Porcine pericardium	Accutrak(1)	November 2006 (26, 29, 31 mm)
	Corevalve Evolut System	Porcine pericardium	Accutrak	November 2006 (23 mm)
	Engager	Bovine pericardium	Engager delivery system (transapical)	February 2013
Saint Jude Medical	Portico	Bovine and porcine pericardia	Portico (transfemoral)	November 2012 (23mm) December 2013 (25 mm)

(1) manufacturer stopped marketing these references in September 2015

Table 2: Additions - December 2015

Manufacturers	Valve references	Type of leaflet	Delivery system (approach)	Date of 1st CE marking
Edwards	Sapien 3	Bovine pericardium	Commander (transfemoral)	January 2014
			Certitude (transapical and transaortic)	2014
Medtronic	Corevalve Evolut R System	Porcine pericardium	EnVeo R	January 2015 (23, 26, 29 mm)

⇨ Appendix 2: Table of the rates of the 4 complications calculated based on data provided by the manufacturers

Table 1 - Major vascular complications - Transfemoral and transapical approaches

Approach	Femoral			Transapical		
Follow-up periods	D30	1 year	2 years	D30	1 year	2 years
Number of studies/registries	14	7	4	4	2	1
Total number of patients	5860	3861	3561	1164	1019	894
Number of patients with the complication	437	337	281	53	53	47
Percentage	7.45%	8.72%	7.89%	4.55%	5.20%	5.25%

Table 2 – Moderate to severe paravalvular leaks - Transfemoral and transapical approaches

Approach	Femoral			Transapical		
Follow-up periods	D30	1 year	2 years	D30	1 year	2 years
Number of studies/registries	13	9	5	5	3	1
Total number of patients	5823	4395	3561	1347	1104	894
Number of patients with the complication	384	285	170	31	32	9
Percentage	6.59%	6.48%	4.77%	2.30%	2.89%	1.00%

Table 3: Major CVAs - Transfemoral and transapical approaches

Approach	Femoral			Transapical		
Follow-up periods	D30	1 year	2 years	D30	1 year	2 years
Number of studies/registries	14	9	5	5	4	1
Total number of patients	5860	4377	3661	1314	1229	894
Number of patients with the complication	153	187	85	43	89	85
Percentage	2.61%	4.27%	2.32%	3.27%	7.24%	9.5%

Table 4: Implanting new pacemakers - Transfemoral and transapical approaches

Approach	Femoral			Transapical		
Follow-up periods	D30	1 year	2 years	D30	1 year	2 years
Number of studies/registries	14	7	5	6	3	1
Total number of patients	5860	2546	3681	1374	335	894
Number of patients with the complication	1042	553	630	128	55	127
Percentage	17.78%	21.72%	17.11%	9.31%	16.41%	14.20%

Table 5: Mortality rate - Transfemoral and transapical approach

Approach	Femoral			Transapical		
Follow-up periods	D30	1 year	2 years	D30	1 year	2 years
Number of studies/registries	14	10	6	6	4	1
Total number of patients	5860	4515	3681	1374	1229	894
Number of patients with the complication	275	705	918	135	316	329
Percentage	4.69%	15.61%	24.93%	9.82%	25.71%	36.80%

⇨ Appendix 3: Table of rates of the 4 complications selected in the France 2 registries

Table 1 - Transfemoral approach. Total number of patients = 3,003

	Major vascular complications	Moderate to severe paravalvular leaks	Major CVAs	Placing new pacemakers	Mortality
	D30				
Number of patients	142	50	65	353	234
%	4.72	2.5	2.16	11.75	7.79
	1 year(1)				
Number of patients	152	48	81	377	622
%	5.06	1.38	2.69	12.55	20.71
	2 years(2)				
Number of patients	153	37	98	400	862
%	5.09	1.46	3.26	13.32	28.70

Table 2 - Transapical approach. Total number of patients = 729

	Major vascular complications	Moderate to severe paravalvular leaks	Major CVAs	Placing new pacemakers	Mortality
	D30				
Number of patients	6	1	14	62	108
%	0.82	0.22	1.92	8.5	14.81
	1 year(1)				
Number of patients	13	0	21	73	215
%	1.78	0	2.88	10.01	29.49
	2 years(2)				
Number of patients	15	1	29	79	284
%	2.05	0.45	3.97	10.83	38.95

(1) Calculations by adding values presented in the 30-day report between 1 month and 6 months and between 6 months and 1 year.
(2) Calculations by adding values presented in the 30-day report between 1 month and 6 months, between 6 months and 1 year, and between 1 year and 2 years.