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Rapid HTA Report

Sutureless aortic valve replacement for aortic valve stenosis

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Abstract

Background: Aortic stenosis is an important degenerative pathology. Sutureless aortic valve replacement (Su-AVR) is a possible alternative to traditional aortic valve replacement (AVR) and to transcatheter aortic valve implantation (TAVI).

Aim: To assess if Su-AVR used in Italy are effective and cost-effective compared to traditional sutured bioprostheses and TAVI.

Methods: We carried out a rapid HTA report on current use, technical aspect, effectiveness, safety and costs of SuAVR. We carried out a systematic review of the literature about effectiveness safety and economic evaluations and a cost analysis. We collected information from clinical experts and SuAVRs manufacturers.

Results: Two SuAVRs are currently marketed in Italy: Edwards INTUITY Elite and Sorin LivaNova PLC Perceval. The evidence regarding the effectiveness and safety of SuAVR as an alternative to traditional AVR is limited. One randomised trial and three controlled clinical trials were identified and the overall quality of the evidence was moderate. No statistical difference in overall mortality and cause-specific mortality between the two groups were found. Clinical outcomes and safety events were similar between SuAVR and conventional valves using traditional sternotomy approach. We performed a cost analysis based on data from two Italian centers suggesting that the main difference between SuAVR and AVR depends on the cost of the valve. However, there are insufficient data for an economic evaluation on SuAVR compared to traditional valves and TAVI.

Conclusion: Available data show that the efficacy and safety on short term outcomes between SuAVR and traditional valve implantation using sternothomy was substantially similar. However, large randomised controlled trials with long term outcome assessment are needed.

Sintesi in italiano

La stenosi della valvola aortica rappresenta la tipologia più comune tra le patologie cardiache valvolari in Europa [Iung B, 2014]. Il tipo più comune è rappresentato dalla stenosi valvolare aortica degenerativa che è causata da un processo patologico di infiammazione, infiltrazione lipidica dei lembi valvolari aortici che porta ad una progressiva ostruzione della valvola con un processo continuo di calcificazione e rimodellamento della valvola [Otto CM, 1994; Rajamannan NM, 2011].

La prevalenza relativa alla stenosi aortica severa è maggiore nei pazienti anziani anche se sono ad oggi carenti dati epidemiologici sul contesto italiano di prevalenza ed incidenza basati su valutazioni cliniche ed ecocardiografiche. Informazioni indirette basate su fonti amministrative concernenti la sostituzione della valvola aortica indicano che la prevalenza è maggiore nei maschi e che la maggioranza degli interventi è effettuata su pazienti con età superiore a 65 anni.

I pazienti candidati alla sostituzione della valvola sono affetti da stenosi aortica severa. Le valvole aortiche senza suture sono una tecnologia di recente introduzione che consente una rapida sostituzione della valvola nativa con una bioprotesi senza la necessità di suture [Carrel T, 2013] e limitando il periodo ischemico e di perfusione.

Per quanto riguarda la codifica della procedura di sostituzione della valvola aortica senza suture, ad oggi non è previsto un codice specifico ICD9-CM. Il codice analizzato è stato il 35.21 "Sostituzione della valvola aortica con bioprotesi" che include tutte le procedure in cui viene utilizzata una valvola con bioprotesi, standard o senza suture. Il numero stimato totale di dimissioni ospedaliere per AVR-TG nel 2013 in Italia è stato 12.614 di cui l'85% è stato indicato nella SDO (Scheda di Dimissione Ospedaliera) come intervento principale.

In Italia, la maggior parte delle procedure di AVR-TG è concentrata in poche regioni con un numero simile (Emilia, Veneto, Piemonte, Toscana e Lazio) ad eccezione di una (Lombardia).

Il "Flusso consumi" nel 2013 sembra mostrare, eccetto che per la Regione Toscana, un livello moderato di acquisto di valvole aortiche senza suture.

Sebbene il livello di copertura del Flusso Consumi sia migliorato rispetto al 2012, bisogna specificare che i dati in esso contenuti non sono completi per tutto territorio nazionale. Per questa ragione, i dati di acquisto potrebbero indurre a sottovalutare il totale di SU-AVR acquistato.

La tecnologia oggetto del presente report è stata descritta utilizzando le informazioni provenienti dai produttori contattati formalmente e a cui è stato inviato un questionario appositamente sviluppato dal team HTA di Agenas. Inoltre per le informazioni mancanti è stata effettuata una ricerca libera della letteratura e sono stati consultati anche i siti web dei produttori e ulteriori fonti specifiche.

La valvola senza suture è proposta per la stenosi dell'aorta come alternativa sia per la sostituzione della valvola aortica mediante chirurgica convenzionale, sia mediante impianto di valvola transcatetere (TAVI).

La procedura consiste nella sostituzione della valvola nativa con la valvola protesica mediante mini-sternotomia in cui vengono rimosse le calcificazioni aortiche intorno all'anulus all'interno del quale viene inserita la nuova valvola.

I dispositivi ad oggi presenti sul mercato italiano sono due: Edwards INTUITY Elite, model 8300AB prodotto dalla Edwards Lifesciences, Inc. (Struttura in Pericardio bovino su stent in lega di cobalto-nichel (*elgiloy*) ricoperto con poliestere con struttura in acciaio inox); Perceval™ Sutureless Aortic Valve prodotto da Sorin Group (Struttura in Pericardio bovino con telaio in Nitinol). Dal 19 Novembre 2015 Sorin Group è entrata a far parte di LivaNova PLC. Nel presente documento, su richiesta del produttore, LivaNova è citata come produttore del dispositivo Perceval™ Sutureless Aortic Valve.

In Italia le valvole aortiche senza suture sono rimborsate mediante la tariffa del DRG 104 "Interventi sulle valvole cardiache con cateterismo cardiaco" o del DRG 105 "Interventi sulle valvole cardiache senza cateterismo cardiaco". Il rimborso nazionale per i due codici è pari a € 24.675 per il DRG 104 e € 20.487 per il DRG 105 (per ricoveri ordinari con durata di degenza >1 giorno e entro soglia secondo DM 18/12/2012).

L'efficacia clinica e la sicurezza sono state indagate mediante revisione sistematica della letteratura scientifica pubblicata. Sono stati inclusi revisioni sistematiche, studi clinici randomizzati (RCT) e studi clinici controllati che hanno valutato le sostituzioni della valvola aortica senza suture disponibili sul mercato comparate con le procedure tradizionali di sostituzione e le TAVI.

La popolazione è stata inclusa in base ad uno dei seguenti criteri:

a) Velocità di picco > 4.0 m/s (corrispondente ad un gradiente di picco di 64 mm Hg), un gradiente medio >40 mmHg o area valvolare <1.0 cm^2 quando la funzione sistolica ventricolare sinistra è normalmente effettuata mediante ecocardiogramma [Holmes DR, 2012];
b) EuroSCORE logistico superiore del 15% che stima una mortalità del 15% in 30 giorni dopo la procedura [Roques F, 2003] e del 10% in un modello di *score* sviluppato dalla Society for Thoracic Surgeons (STS) [Ferguson TB, 2000].

Gli esiti di efficacia considerati sono stati: mortalità totale, mortalità cardiovascolare; ictus primario, sanguinamento, infarto del miocardio peri procedurale, insufficienza renale acuta, complicanze vascolari maggiori, esiti emodinamici e qualità della vita.

Sono stati inclusi nella revisione sistematica uno studio clinico randomizzato [Borger 2015] e tre studi prospettici comparativi [Muneretto C, 2015; Santarpino G, 2013; Shrestha M, 2013] sintetizzati in maniera qualitativa e quantitativa.

L'analisi quantitativa ha evidenziato che non ci sono differenze statisticamente significative in termini di mortalità complessiva e mortalità specifica tra i due gruppi sperimentali e di controllo.
In termini di sicurezza gli eventi avversi riportati negli studi inclusi sono stati: sanguinamento e necessità di trasfusione (come marcatore di sanguinamento rilevante, aritmia, impianto permanente di pacemaker (come marcatore di aritmia); insufficienza renale.
In linea generale l'incidenza degli eventi avversi tra i due gruppi (sperimentale e di controllo) è risultata simile, anche se le prove sulla sicurezza della valvole aortiche senza suture come alternative alle valvole tradizionali in termini di outcome a lungo termine sono limitate.
La valutazione della dimensione dei costi e degli aspetti economici legati all'utilizzo delle valvole aortiche senza suture è stata effettuata mediante revisione sistematica della letteratura pubblicata in italiano ed inglese riguardante studi economici (tutti) sull'utilizzo delle SuAVR comparate con le valvole tradizionali e le TAVI. Sono stati inoltre riportati i risultati di un *case study* condotto dalla Regione Veneto, che ha rilevato le voci di costo principali legate alla procedura di sostituzione della valvola aortica nativa con valvola senza suture. La valutazione economica seppur parziale ha portato alla definizione di un costo per procedura di sostituzione di valvola aortica nativa con una valvola senza suture.
La ricerca della letteratura scientifica ha portato alla lettura di un solo studio [Pradelli L, 2012], condotto in Italia e finanziato dalla Sorin Group LivaNova PLC, che ha valutato la valvola Perceval S (Sorin Group).
Lo studio italiano incluso nella revisione sistematica ha rilevato il costo sia in caso di procedura isolata che concomitante per 4 paesi (Italia, Germania, Francia e Regno Unito) considerando anche le differenze di approccio chirurgico (sternotomia totale con valvola tradizionale; sternotomia totale con valvola senza suture; mini sternotomia con valvola senza suture).
I valori del costo totale in caso di procedura isolata e di procedura concomitante variano in base alla tipologia di tecnica chirurgica da paese a paese.
Il *case study* condotto dalla Regione Veneto ha riguardato una analisi dei costi rilevando da due centri il costo sia della procedura di impianto di valvola aortica senza sutura che di impianto di valvola tradizionale (la TAVI non è stata considerata). Il costo medio della procedura di impianto della valvola aortica senza sutura è pari a €17.785 mentre il costo medio di un impianto di valvola aortica tradizionale è risultato pari a €13.642. In base ai dati prodotti dal Veneto i costi di procedura vengono coperti ampiamente con il rimborso dei DRG utilizzati (DRG 104 pari a €34.179 e DRG 105 pari a €27.476).
La stenosi aortica è una importante patologia degenerativa che colpisce prevalentemente i maschi. Le SuAVR rappresentano una possibile alternativa alle valvole tradizionali e alle TAVI offrendo pertanto un'alternativa anche in termini di conseguenze della patologia.

In Italia questo tipo di procedure sono principalmente condotte in poche Regioni al nord e al centro del paese. Tuttavia, i dati disponibili mostrano che mentre per gli outcome a breve termini gli eventi sono simili tra il nuovo dispositivo e la valvola tradizionale il potenziale beneficio per gli outcome a lungo termine devono ancora essere definiti in futuri studi. Inoltre, si registra la mancanza di un DRG specifico che consenta l'identificazione e la gestione delle ingenti somme di denaro consumate per la procedura. Ciò è da evidenziare dato che il fattore di costo principale sono i dispositivi stessi.

La base delle prove a nostra disposizione sembrano mostrare un potenziale beneficio dell'uso delle SuAVR in quanto relativamente agli outcome a breve termine i due dispositivi sono risultati simili. Tuttavia, non si possono esprimere raccomandazioni per gli outcome a lungo termine in quanto le evidenze sono limitate a studi che nella maggior parte de casi non sono randomizzati.

La randomizzazione è fondamentale in casi in cui i pazienti e le variabili di contesto giocano un ruolo fondamentale perché consente che siano comparate tutte le situazioni comparabili.

Studi randomizzati multicentrici ben disegnati con valutazioni a lungo termine dovrebbero essere condotti a fianco di valutazioni economiche prospettiche per consentire che la scelta sia basata su prove di buona qualità.

Introduction

This document was developed following the EUnetHTA Core Model (CM) ® application for "Medical and surgical procedures" vers. 2.0. The Core Model is divided into domains representing each a specific area of technology impact that have to be assessed. Each domain contains a series of research questions or Assessment Elements (AEs) identified by a capital letter and number. To test the Model applicability an adapted model by Agenas was elaborated (see Appendix 1 for a full description).

The use of the Core Model is mirrored in the structure of this report, where each chapter corresponds to a Core Model domain and reports the AEs considered for the assessment.

1. Report's objectives: policy and research questions

We developed a rapid HTA report to answer the following questions:

Policy Question: What is the impact of the introduction and use of the sutureless valves for the replacement of the aortic valve in the elderly with aortic valve stenosis?

Research Question: Are sutureless aortic valves safe, effective and cost-effective compared to conventional sutured bioprostheses and transcatheter aortic valve implantation (TAVI) for a patient's cohort with similar clinical indications?

To answer the research question we used the Agenas model and structure (see Appendix 1). For each domain we selected a series of relevant Assessment Elements (AEs) (listed in Appendix 2).

This rapid HTA report developed the following domains:

- Health problem and current use of technology (CUR)
- Description and technical characteristics of technology (TEC)
- Regulatory aspects (REG)
- Clinical effectiveness (EFF)
- Safety (SAF)
- Costs and economic evaluation (ECO)

2. Health problem and current use of technology

Methods

We selected the following AEs:

Assessment Element ID	Research question
A0001a	For which health condition is the technology proposed?
A0001b	Which group of patients represents the target population for the technology?
A0001c	For what purposes is the technology used?
A0018	What are the alternatives to the current management of the health condition?
A0011	What is the diffusion of the technology in Italy?

For the current use assessment during the evaluation we considered not relevant the following AEs (previously selected):

Assessment Element ID	Research question
B0001b	What is(are) the comparator(s)?
B0003b	What is the phase of development of the comparator(s)?
B0004b	Who performs or administers the comparator(s)?
B0005b	In what context and level of care is(are) the comparator(s) used?

We decided not to analyze the information about current use of our comparator derivable from the databases available. In Italy there are no explicit guidelines on ICD9-CM codes (International Classification of Disease – 9th Edition) for our comparator in hospital discharge records. As a consequence, the Italian providers adopt ICD-9-CM codes heterogeneously to identify the procedure.

Health problem was reported in a descriptive summary defined by international and national literature review: in particular, we searched for review articles, epidemiological studies and disease registers. Informal interviews with experts were also carried out to clarify the current management of disease in Italy.

Data and Variables

We decided to use the most recent information contained in the New Health Information System (NSIS) as the official source of the Ministry of Health. Among the broad information contained in NSIS we selected hospital discharges "SDO" and "flusso consumi" database in our investigation.

The source of data for this study was the 2013 national hospital discharges database (SDO 2013). SDO 2013 does not include specific ICD9-CM (International Classification of Diseases - 9th Edition) codes for sutureless aortic valve replacement (SU-AVR). For this reason, the hospital discharges of our interest were identified using ICD9-CM code 35.21 – "open and other replacement of aortic

valve with tissue graft (AVR-TG)". This code identifies all types of prosthetic valve with tissue graft, either standard or sutureless.

We searched discharge records with this code in at least one of variables corresponding to principal and other procedures.

If the above code was present at the same time as DRG 104 and 105 (DRG Version 24), this meant that the procedure was driving to the allocation of the DRG.

The patient record reporting more than one AVR-TG procedure code was considered as a single implantation. Initial exploration showed that 12,614 Italian hospital discharges out of a total 9,843,992 discharges, matched at least one of the above conditions.

In addition, we decided to use 2013 data from "flusso consumi" attested by Veneto Region as compatible with our objectives and our methodological approach [Regione Veneto, 2014] (A0011).

Statistical analysis

Descriptive analyses were used on national and regional estimates on the numbers of AVR-TG e SU-AVR. Data from SDO 2013 were analysed on the hypothesis that each single procedure had been carried out on a single patient, as the available database did not show the patient's code identification. Hospital and demographic characteristics were estimated and tabulated.

Data management and analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

Results

Aortic valve stenosis is the most common type of valvular heart disease in Europe [Iung B, 2014]. It has three main aetiologies: bicuspid, rheumatic and degenerative processes [Roberts W, 2005]. The most common type is degenerative aortic valve stenosis, which is caused by a pathological process based on inflammation, lipid infiltration of the aortic valve leaflets that leads to progressive valve obstruction with an ongoing process of valve remodelling and calcification [Otto CM, 1994; Rajamannan NM, 2011].

Epidemiology

Four large population-based studies in Europe and the United States have evaluated the prevalence of aortic valve stenosis and consistently showed an increase in the prevalence of the disease [Lindroos M, 1993; Stewart BF, 1997; Nkomo VT, 2006; Eveborn GW, 2013]. The largest study [Nkomo VT, 2006] was based on various population-based studies by obtaining data from 11,911 randomly selected adults that have prospectively defined echocardiographic valvular analysis. These population-based studies were the Coronary Artery Risk Development in Young Adults (CARDIA) Study [Hughes GH, 1987], the Atherosclerosis Risk in Communities (ARIC) Study [ARIC, 1989], and the Cardiovascular Health Study (CHS) [Fried LP, 1991]. The estimated prevalence of severe aortic valve stenosis was 0.4% in the general population, ≤ 0.2% in subjects aged 65 years or less whereas in subjects between 65 and 74 years it was 1.3% reaching the rate of 2.8% after 75 years. The Tromso study is an ongoing population based prospective study that started in 1973 and randomly included 3,273 patients. The Tromso study researchers performed sequential clinical and echocardiographic evaluations between 1974 and 2008. The study reported greater prevalence of degenerative valvular aortic stenosis especially in older subjects: 3.9% between 70 and 79 years, and 9.8% between 80 and 89 years [Eveborn GW, 2013].

The annual incidence estimates derived from the Tromso study is 4.9 per 1000 [Eveborn GW, 2013] (A0001a, A0001b).

Diagnosis

Echocardiography is mandatory for the diagnosis of aortic stenosis and is also used to assess the presence of valvular aortic stenosis and the degree of valve calcification as well as the size and the wall thickness and function of the left ventricle.

Complementary diagnostic instruments are: computed tomography or magnetic resonance imaging to allow complete assessment of the thoracic aorta, cardiac catheterisation that allows the assessment of transvalvular pressure gradients and haemodynamic conditions and coronary angiography that gives important information about the coronary arteries (A0001a, A0001b).

Clinical course and prognosis

Valvular aortic stenosis is a chronic progressive disease. The natural history of the disease consists of a prolonged latent asymptomatic period that varies widely between individuals. Sudden cardiac death may happen in symptomatic patients [Otto CM, 1997; Pellikka PA, 2005].

Aortic stenosis is considered severe when the valve area is < 1.0 cm^2 but this value need to be indexed to body surface area. Hence, aortic stenosis with an indexed effective opening valve area of less than 0.6 cm^2/m^2 body surface area is considered severe (A0001a, A0001b).

Management of asymptomatic severe aortic stenosis

The management of patients with asymptomatic severe aortic stenosis is controversial and it is still a matter of debate [Kang DH, 2010]. Watchful waiting is a potential safe option but elective surgery might be considered in selected patients with particular conditions (e.g. abnormal exercise test, depressed LV function not due to other causes) (A0001a, A0001b).

Management of symptomatic severe aortic stenosis

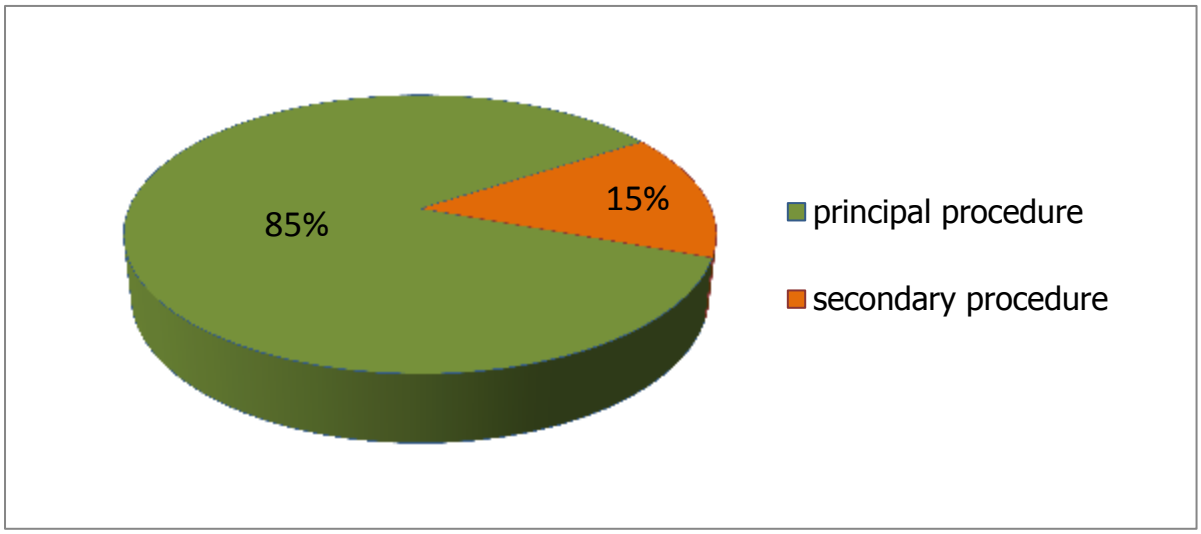
Patients with symptomatic severe aortic stenosis are candidates for early valve replacement. Surgical aortic valve replacement (AVR) is the cornerstone for patients with severe aortic stenosis. The approach has considerably improved survival.

Sutureless aortic valves are a recently introduced technology that allows quick replacement of the native valve with a bioprosthesis without the need to stitch the sewing cuff [Carrel T, 2013]. The rationale for this technology was to facilitate implantation and shorten ischemic and perfusion time period with the aim of reducing the morbidity and mortality, especially in patients who need complex multivalve procedure or patients that require combined valve and coronary interventions (A0001a, A0001b).

Current use

As explained in the methods section, there is no specific ICD9-CM code for AVR with sutureless bioprosthesis. The ICD9-CM code analysed, 35.21 – "open and other replacement of aortic valve with tissue graft (AVR-TG)", includes all the procedures in which a bioprosthetic valve has been used, either standard or sutureless. The estimate total number of AVR-TG in 2013 in Italy was 12,614 and for 85% it was recorded as principal procedure in hospital discharge records (Figure 2.1).

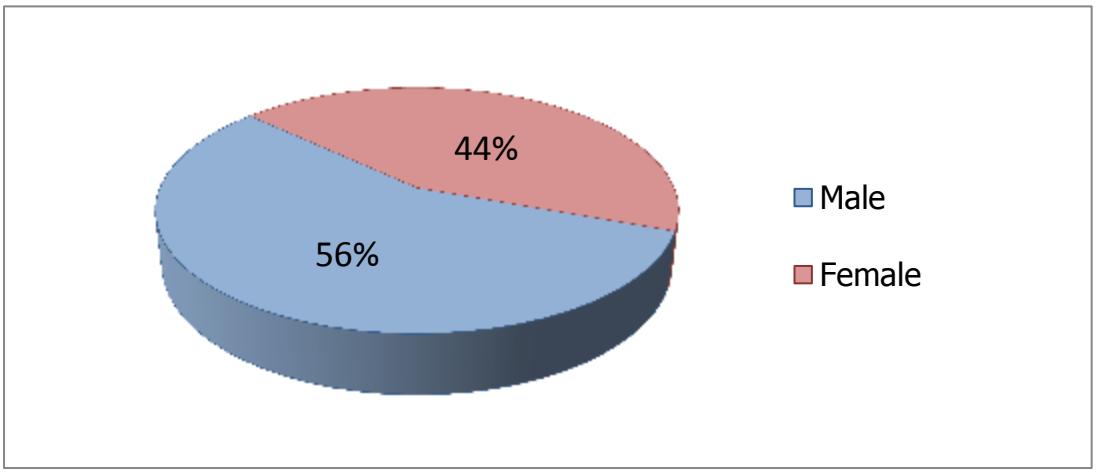
Figure 2.1: AVR-TG performed in 2013 in Italy.



Source: Agenas analysis based on SDO 2013

The data on discharges with *AVR-TG* procedures show that 56% of procedures are performed on males (Figure 2.2) and more than 80% of cases are aged between 65 and 84 years (Table 2.1).

Figure 2.2: Hospital discharges on AVR-TG per gender– SDO 2013 (percentage values)



Source: Agenas analysis based on SDO 2013

Table 2.1: Hospital discharges on AVR-TG by age class – SDO 2013 (absolute and percentage values)

Age class (years)	Absolute values	% values
0-24	40	0.32
25-64	1,629	12.91
65-74	4,571	36.24
75-84	5,708	45.25
85+	666	5.28
Total	12,614	100.00

Source: Age.na.s. analysis based on SDO 2013

Table 2.2 reports AVR-TG total discharge volumes broken down by Region. No case is recorded in two regions (Valle D'Aosta and P.A. Bolzano). Lombardia has the highest volume of AVR-TG (2,500) followed by Emilia Romagna, Veneto, Piemonte, Toscana and Lazio (the volume ranges from 1,430 to 1,067). These regions account for nearly 70% of the total discharges.

Table 2.2: Distribution of AVR-TG total discharge volumes by region - SDO 2013.

Region	Absolute values	% values
PIEMONTE	1,216	9.64
VALLE D'AOSTA	-	-
LOMBARDIA	2,553	20.24
P.A. BOLZANO	-	-
P.A. TRENTO	45	0.36
VENETO	1,282	10.16
FRIULI V. GIULIA	406	3.22
LIGURIA	297	2.35
EMILIA ROMAGNA	1,430	11.34
TOSCANA	1,152	9.13
UMBRIA	197	1.56
MARCHE	193	1.53
LAZIO	1,067	8.46
ABRUZZO	244	1.93
MOLISE	50	0.40
CAMPANIA	481	3.81
PUGLIA	732	5.80
BASILICATA	142	1.13
CALABRIA	257	2.04
SICILIA	611	4.84
SARDEGNA	259	2.05
ITALY	12,614	100.00

Source: Agenas. analysis based on SDO 2013

Hospital discharges in which the 35.21 ICD9-CM procedure code generates the two DRG 104 and 105 are approximately 98% of total AVR-TG. The detailed data, broken down by region and DRG, are reported in Table 2.3.

Table 2.3: Distribution of AVR-TG total discharge volumes by region and DRG- SDO 2013.

Region	DRG (% values)			Total (absolute values)
	104	105	Total	
PIEMONTE	56.8	43.2	100.0	1,195
VALLE D'AOSTA				
LOMBARDIA	66.0	34.0	100.0	2,509
P.A. BOLZANO				
P.A. TRENTO	8.9	91.1	100.0	45
VENETO	18.3	81.7	100.0	1,244
FRIULI V. GIULIA	42.8	57.2	100.0	395
LIGURIA	51.4	48.6	100.0	284
EMILIA ROMAGNA	38.8	61.2	100.0	1,390
TOSCANA	48.4	51.6	100.0	1,117
UMBRIA	31.4	68.6	100.0	191
MARCHE	17.5	82.5	100.0	189
LAZIO	53.0	47.0	100.0	1,039
ABRUZZO	27.8	72.2	100.0	241
MOLISE	50.0	50.0	100.0	46
CAMPANIA	62.6	37.4	100.0	471
PUGLIA	79.1	20.9	100.0	716
BASILICATA	71.9	28.1	100.0	135
CALABRIA	80.2	19.8	100.0	247
SICILIA	61.8	38.2	100.0	602
SARDEGNA	43.7	56.3	100.0	254
ITALY	51.5	48.5	100.0	12,310

Source: Agenas. analysis based on SDO 2013

In 2013, 316 SU-AVRs were purchased nationally (source: "Flusso consumi" run by Ministry of Health - NSIS, year 2013 [Regione Veneto, 2014]). 8 Regions purchased SU-AVR and the detailed data are reported in Table 2.4. Toscana is the region who acquired the greatest amount of SU-AVR (208 devices equal to 66% of national value). In the other regions quantities ranged from a minimum of 4 to a maximum of 27 (A0011).

Table 2.4: SU-AVR purchased in 2013 by Region (year 2013).

Region	Absolute values	% values
LOMBARDIA	27	8.5
VENETO	10	3.2
FRIULI V. GIULIA	24	7.6
EMILIA ROMAGNA	15	4.7
TOSCANA	208	65.8
UMBRIA	4	1.3
LAZIO	24	7.6
CALABRIA	4	1.3
National sub-total	316	100.0

Source: modified from Veneto Region based on national database "Flusso consumi", year 2013.

Conclusions

Prevalence of severe aortic valve stenosis is high in older subjects. However, epidemiological data of incidence and prevalence of the disease based on sequential clinical and echocardiographic evaluations are lacking in Italy. Administrative data on the replacement of aortic valve with tissue graft indicate that the prevalence are higher in males and the majority of the interventions are provided to patients aged 65 or older.

The majority of AVR-TG procedures are performed in few regions that show similar use (Emilia, Veneto, Piemonte, Toscana and Lazio) except for one (Lombardia). The "Flusso consumi" in 2013 seems to show moderate levels of SU-AVR purchasing (except Toscana). The "Flusso consumi" database was created in 2011 with a piloting phase in 2012 and its maintenance became mandatory in 2013. Although the level of data flow coverage has improved compared to 2012, the data are not uniformly complete in the national territory. For this reason, the purchase data may be incomplete, thereby underestimating the total purchased (A0011).

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3. Description and technical characteristics of technology

Methods

The AEs of this domain were:

Assessment Element ID	Research question
B0001	What is this technology?
B0003	What is the phase of development of the technology?
B0004	How is the technology used?
B0005	In which setting and level of care is the technology used?
B0007	Does the technology require additional/special equipment/tools or accomodation?
B0009	What disposables and supplies are needed to use the technology?
F0001a	Is the technology new/innovative?
F0001b	Is the technology a add-on, a replacement or a modification of the standard mode of care?

All AEs were addressed in our assessment.

The manufacturers of the devices identified during the protocol phase (i.e., Edwards Lifesciences and Sorin Group (now LivaNova PLC) were approached by Agenas and invited to contribute to the project by providing information related to all the domains. Specifically, information were requested on: health condition addressed by the device, standard of care for the condition, technical characteristics of the device, current use of technology, regulatory aspects, clinical studies (published or ongoing) and registries available, costs and economic evaluations performed. Information were gathered using a structured form developed by the authors (see Appendix 3). One face-to-face meeting for each of the manufacturers was deemed necessary to present the project and to discuss the information provided by the manufacturers.

Whenever information was not provided by the manufacturers, or believed insufficient/incomplete by the authors, it was integrated with *ad hoc* internet searches and consultation of manufacturers' websites, brochures, instructions for use (IFU), and regulatory bodies' databases.

Results

SuAVR [D'Onofrio A, 2013] for aortic stenosis is proposed as an alternative to both conventional AVR and TAVI, whenever a bioprosthetic aortic valve is indicated. The potential benefits of the procedure are that the diseased valve is removed, combined pathologies of the aortic valve and the coronary arteries can be treated, and the procedure may be quicker because the bioprosthetic valve does not need to be sewn in, reducing cardiopulmonary and aortic cross-clamp times. With the patient under general anaesthesia, access to the heart is usually made through a full- or mini-sternotomy. Once cardiopulmonary bypass and cardioplegia are established, the diseased aortic

valve is removed through an incision in the aorta. Bulky calcifications around the native aortic anulus are removed to achieve a smooth round anulus for the bioprosthetic valve implantation. The bioprosthetic valve, loaded onto a delivery system, is then inserted into the native anulus. Balloon dilatation may be used to maximise the area of contact between the new bioprosthetic valve and the aortic anulus. The position and function of the bioprosthetic valve are assessed intraoperatively by transoesophageal echocardiography [NICE, 2013] (B0001).

A heart team, including among others a clinical cardiologist, an interventional cardiologist, and a cardiac surgeon, should assess patient eligibility for the suitable AVR approach [Vahanian A, 2012]. The SU-AVR is a cardiac surgical procedure and needs to be performed, as any other thoracic surgical procedure, within a proper equipped operating theatre. Inpatient setting within tertiary care facilities represents the proper level of care (B0005). Usually, two surgeons, two nurses, one perfusionist, and one anaesthesiologist are involved in the procedure. Specific training is required for the surgeons and the nurses that will assist in preparing the device (e.g. loading the bioprosthetic valve on the delivery system). Training for the staff may follow different schemes, depending on the manufacturer's policy (B0004).

While disposable items and supplies for SU-AVR are the same as the ones required for standard cardiac valve surgery (B0009), specific tools (e.g., sizers, dilation device) may be required depending on the specific device used.

The two devices available on the Italian market are reported in Table 3.1. A third device, 3f® Enable Aortic Bioprosthesis, model 6000 (Medtronic, Inc.) was identified during the earliest steps of the present project but on 11th May 2015 the manufacturer notified the Italian Ministry of Health the decision to suspend the commercialisation of 3f® Enable Aortic Bioprosthesis, model 6000 [Safety Notification, 2015] (B0001).

Table 3.1: Sutureless bioprosthetic aortic valves available on the Italian market. All the devices listed in the table are CE marked and registered within the Italian National Medical Devices Inventory (Repertorio Dispositivi Medici – RDM).

Device name	Manufacturer	RDM registration number
Edwards INTUITY Elite, model 8300AB	Edwards Lifesciences, Inc.	86725–86729
Perceval™ Sutureless Aortic Valve	Sorin Group LivaNova PLC	381674, 1156169, 808829

Source: *Data from RDM database. Devices are listed in alphabetical order by device name.*

Some of the main technical features of the two sutureless bioprosthetic aortic valves identified are presented in Table 3.2. Further information is listed below for each device (in alphabetical order of device name).

Table 3.2: Sutureless bioprosthetic aortic valves available on the Italian market. All the devices listed in the table are CE marked and registered within the Italian National RDM.

Device name	Manufacturer	CE mark	Structure	Number of sutures required	Indication (as reported within IFU)
Edwards INTUITY Elite, model 8300AB	Edwards Lifesciences, Inc.	Oct-2014	Bovine pericardium on Elgiloy stent covered by polyester with a stainless steel frame	3 for valve placement; 3 permanently in place	Indicated for patients whose aortic valvular disease is sufficiently advanced to warrant replacement of their native valve with a prosthetic valve. These devices are also intended for use in patients with a previously implanted aortic valve that requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced with the model 8300AB valve.
Perceval™ Sutureless Aortic Valve	Sorin Group LivaNova PLC	Jan-2011	Bovine pericardium on Nitinol frame	3 for valve placement; 0 permanently in place	Indicated for the replacement of a diseased native or a malfunctioning prosthetic aortic valve via open heart surgery. The prosthesis is indicated in patients who meet the following criteria: - Subjects of age ≥ 75 years; - Subjects with aortic valve stenosis or steno-insufficiency.

Source: *Data provided by the manufacturers and integrated with RDM database and internet searches performed by the authors. Devices are listed in alphabetical order by device name.*

Edwards INTUITY Elite (Edwards Lifesciences)

The Edwards INTUITY Elite, is the second generation sutureless valve produced by Edwards Lifesciences. It is often termed as "rapid deployment valve" as the sutures used for valve placement are supposed to stay in place but it is widely regarded as a "sutureless valve". The previous version (Edwards INTUITY) was launched in 2012 and marketed until 2013. The new generation has a different distribution of the sealing cloth, a fully covered frame, a different holder, a flexible delivery system, and a new balloon design (B0004).

The bioprosthetic valve has a functional component made of bovine pericardium mounted on Elgiloy stent covered by polyester supported by a stainless steel frame, and is available in five sizes (19 mm, 21 mm, 23 mm, 25 mm, 27 mm). Once the proper size has been determined using a set of sizers, the bioprosthetic valve is loaded on a delivery system that include the balloon for the frame deployment. Different from the other bioprosthetic valves of this class, the Edwards' device is not crimped/collapsed on the delivery system. Three sutures need to be placed around the anulus, to guide the proper placement of the bioprosthetic valve. The three sutures need to be tied up and will be not removed. Once the bioprosthetic valve is in place, the frame is expanded by the specific balloon inflation device (B0001).

Edwards Lifesciences provides on-site training by a qualified Edwards product specialist (with no further costs for the centres – other than the device cost). Intraoperative assistance is provided for at least two cases per implanting surgeon. If requested by the implanting surgeons, a proctor (cardiac surgeon) will support the first and/or most complex cases (B0004).

Edwards Lifesciences provides the dedicated tools required for the implantation procedure within the bioprosthetic valve system package/kit (i.e., delivery system and balloon inflation device) (Table 3.3). Valve sizers are not provided within the valve package/kit but since they are specific tools necessary for the implantation, they need to be provided by Edwards (B0007).

Table 3.3: Dedicated tools needed for the implantation of Edwards INTUITY Elite (Edwards Lifesciences).

Item	Description	Use
Delivery system	To insert and release the valve in place	Single use
Balloon inflation device	To expand the valve frame after the positioning	Single use
Sizers kit*	To identify the appropriate valve size	Re-usable

**Sizers are compatible with the ELITE and other prosthetic valves from Edwards Lifesciences.*

Source: *Manufacturer.*

Perceval (Sorin Group LivaNova PLC)

The Perceval Sutureless Aortic valve has been on the market since 2011; although no structural changes have been made to the device, it is now available in four different sizes (B0004).

The bioprosthetic valve has a functional component made of bovine pericardium mounted on a Nitinol super elastic frame and is available in four sizes (Small, Medium, Large, Extra-Large, covering anulus sizes from 19 to 27).. Once the proper size has been determined (using a set of sizers), a dedicated set of devices (collapsing tool and base for the collapsing tool) is needed to load the bioprosthetic valve on the delivery system (holder), before implantation. Three sutures are needed around the anulus to guide the proper placement of the bioprosthetic valve. Three sutures are needed around the annulus to guide the proper placement of the bioprosthetic valve. After the deployment and the postmodeling of the valve by an inflatable system (balloon-catheter and inflation devices) (B0001), the three guiding sutures are removed.

Sorin (now LivaNova) provides a proctorship programme (with no further costs for the centres – other than the device cost). For those centres wishing to perform the implantation procedure by total sternotomy, at least two cases need to be considered as training. Further training sessions need to be arranged if the centre wishes to perform the procedure by mini-invasive approaches (e.g. mini-toracotomy with 5-6 cm incision) (B0004).

LivaNova provides all the dedicated tools required for the implantation procedure. The set is composed by disposable and reusable devices, and is available also with specific items for MICS procedures (Table 3.4) (B0007).

Table 3.4: Dedicated tools needed for the implantation of Perceval (Sorin Group LivaNova PLC).

Item	Description	Use
Dual collapse	To collapse the valve and load it on the delivery system (dual holder)	Single use
Dual collapser base	To support the dual collapse	Re-usable
Sizers kit	To identify the appropriate valve size	Re-usable
Dual holder or Dual MICS holder	To insert and release the valve in place	Single use
Post-dilatation catheter or MICS post-dilatation catheter	To dilate the valve after the positioning	Single use
Inflation device	To inflate the balloon within the post-dilatation catheter	Single use
Smart clip	To lock the dual holder once the valve is loaded	Single use

Key: *MICS = minimally invasive cardiac surgery.*
Source: *Manufacturer.*

Conclusions

SU-AVR are an innovative approach to AVR when a bioprosthesis is indicated. Its advantages over traditional AVR with bioprosthetic valves comes from the reduction of surgical complexity, operation times, and trauma from the improvement of patient's outcomes (F0001a). The SU-AVR will probably replace the traditional AVR with bioprosthetic valve, as there are no differences between the target populations of the two technologies (F0001b). However, the SU-AVR is competing with another innovative approach for similar indications: TAVI. It is possible that in the near future in which reduction of invasiveness is a growing priority, SU-AVR and TAVI will share the market, replacing completely the traditional AVR approach (F0001a).

Two sutureless bioprosthetic aortic valves are currently on the Italian market, Edwards INTUITY Elite and Sorin (now LivaNova) Perceval. The valves have different characteristics and approaches. The Perceval can be defined as a "true sutureless" as none of the three sutures needed for positioning remain after implantation; whereas the INTUITY Elite is implanted without any crimping or collapsing of the frame.

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4. Regulatory aspects

Methods

The AEs of this domain were:

Assessment Element ID	Research question
A0020	What is the marketing authorisation status of the technology?
A0021	What is the reimbursement status of the technology across countries?
I0015	Does the technology require further specific regulations?

All AEs were addressed in our assessment.

Information was collected by direct request to the manufacturers, using a structured form developed by the authors. Methods are described in detail within TEC domain.

Whenever information was not provided by the manufacturers, or believed insufficient/incomplete by the authors, it was integrated by searching regulatory bodies' websites and manufacturers' press releases.

Results

Edwards INTUITY Elite received the CE mark in October 2014, as an update of the previous CE mark for Edwards INTUITY, received in February 2012.

At the time of writing (May 2015), the TRANSFORM study (NCT01700439), initiated in September 2012 to evaluate the Edwards INTUITY valve system, is recruiting participants (950 expected across 35 centres in USA). The TRANSFORM is a single-group assignment study with estimated completion date set for September 2018 (A0020).

Perceval received the CE mark in January 2011. At the time of writing (May 2015), Perceval is used under an Investigational Device Exemption (IDE) framework in the USA. The enrolment of the 300 patients expected was completed and the manufacturer expected to obtain the FDA approval by the end of 2015 or the beginning of 2016 (A0020).

In Italy, the SU-AVR is reimbursed using the DRG 104 – *"Cardiac Valve & Other Major Cardiothoracic procedures w/ cardiac catheterization"* – or DRG 105 – *"Cardiac valve & Other major cardiothoracic procedures w/o cardiac catheterization"* fees. The national fees linked to the two DRG codes are € 24,675 for DRG 104, and € 20,487 for DRG 105, respectively [DM 18/12/2012] (A0021).

Table 4.1: Regional reimbursement fees linked to DRG codes 104 and 105.

Latest update	Region (or Autonomous Province)	DRG 104	DRG 105
2013	ABRUZZO	€ 24,095.33	€ 20,005.17
2013	BASILICATA	€ 24,675.00	€ 20,487.00
2011	BOLZANO AP	€ 25,092.46	€ 18,867.78
2013	CALABRIA	€ 24,675.00	€ 20,487.00
2013	CAMPANIA	€ 24,675.00	€ 20,487.00
2014	EMILIA R.	€ 26,402.45	€ 21,920.66
2009	FRIULI VENEZIA GIULIA	€ 25,492.00	€ 21,551.00
2013	LAZIO	€ 24,675.00	€ 20,487.00
2010	LIGURIA	€ 22,175.74	€ 17,352.40
2015	LOMBARDIA	€ 21,882.00	€ 17,843.00
2014	MARCHE	€ 25,415.25	€ 21,101.61
2013	MOLISE	€ 22,994.87	€ 18,544.39
2013	PIEMONTE	€ 24,675.00	€ 20,487.00
2013	PUGLIA	€ 24,675.00	€ 20,487.00
2009	SARDEGNA	€ 21,183.53	€ 17,043.08
2013	SICILIA	€ 24,675.00	€ 20,487.00
2010	TOSCANA	€ 19,910.00	€ 18,237.00
2011	TRENTO AP	€ 37,685,28	€ 23,345.28
2009	UMBRIA	€ 24,675.00	€ 20,487.00
2013	VALLE D'AOSTA	€ 24,675.00	€ 20,487.00
2011	VENETO	€ 34,179.00	€ 27,476.00

Key: *AP = Autonomous Province; DRG = diagnosis related group.*
Source: *Manufacturer.*

Conclusions

No specific further regulations need to be followed to introduce the SU-AVR (I0015). The two devices assessed in the present report are CE marked for clinical use in Europe.

Bibliography

TUC 2013. Conferenza delle Regioni e delle Province Autonome 13/41/CR05a/C7. Accordo interregionale per la compensazione della mobilità sanitaria (2013). http://www.regioni.it/download/conferenze/297405/

DM 18/12/2012.

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5. Clinical effectiveness

Methods

The AEs belonging to the present domain were:

Assessment Element ID	Research question
D0001	What is the effect of the intervention on all-cause mortality?
D0002	What is the effect on the disease-specific mortality?
D0005a	How does the technology affect symptom frequency of the target condition?
D0005b	How does the technology affect symptom severity of the target condition?
D0005c	How does the technology affect symptom duration of the target condition?
D0012	What is the effect of the technology on generic health-related quality of life?
D0014	What is the effect of the technology on work ability?
D0015	What is the effect of the technology on return to previous living conditions?
D0018	Do differences in acceptability predict the overall uptake of the technology?

All AEs were addressed in our assessment.

Analysis of clinical effectiveness of SU-AVR and its comparators was carried out by systematic review of clinical studies, through systematic searches of literature with appropriate search strategy (Appendix 4).

Types of studies of interest included: systematic reviews, randomised controlled trials (RCT), controlled clinical trials (CCT).

The inclusion criteria for patient population is the presence of at least one of the following:

a) peak velocity > 4.0 m/s (corresponding to a peak gradient of 64 mm Hg), a mean gradient > 40 mmHg, or valve area < 1.0 cm^2 when left ventricular systolic function is normal performed by echocardiogram [Holmes DR, 2012];

b) Logistic EuroSCORE higher than 15%, which estimates a mortality of 15% by 30 days after procedure [Roques F, 2003], and 10% in a score model developed by the Society for Thoracic Surgeons (STS) [Ferguson TB, 2000].

Studies assessing aortic valve replacement using commercially available sutureless valves compared with surgical intervention for aortic valve replacement and TAVI were considered.

The outcomes of interest included: overall mortality, cardiovascular mortality (primary outcomes); major stroke, bleeding complication, peri-procedural myocardial infarction, acute renal injury, major vascular complication, haemodynamic data (peak gradient, prosthetic effective orifice, etc.) and quality of life (secondary outcomes).

Studies of interest were evaluated by researchers independently: a flow chart for the selection of the studies is shown in **Figure 6.1.** A standardized data extraction template was developed and used by two review authors (IA and CR) that independently conducted full data analysis.
Risk of bias using the Cochrane instrument [Higgins JPT, 2011] was used to assess the quality of included articles (items of risk of bias include: sequence generation, allocation concealment, blinding of patients and participants, blinding of outcome assessor, completeness of outcome data, outcome reporting).

Statistical analyses

Where a homogeneous number of studies were identified, a meta-analysis was performed.
Dichotomous outcomes results were expressed as risk ratio (RRs) with 95% confidence intervals (CIs). Where continuous scales of measurement were used to assess the effects of treatment, the mean difference (MD) was used; the standardised mean difference (SMD) was used when different scales had been used.
We performed an analysis according to an intention-to-treat principle.
Heterogeneity was evaluated using a Chi^2 test with n-1 degrees of freedom, with an alpha of 0.10 used for statistical significance and with the I^2 test [Higgins JPT, 2011]. The source of heterogeneity was sought by assessing the participants, the intervention, the comparison group, and the outcomes and by visually assessing the forest plots.
Review Manager software (Revman 5.3) was used for data synthesis. Data were pooled using both the random-effects model and the fixed-effect model to assess robustness of analysis by distribution of observations. A table of findings presented the results of included studies.

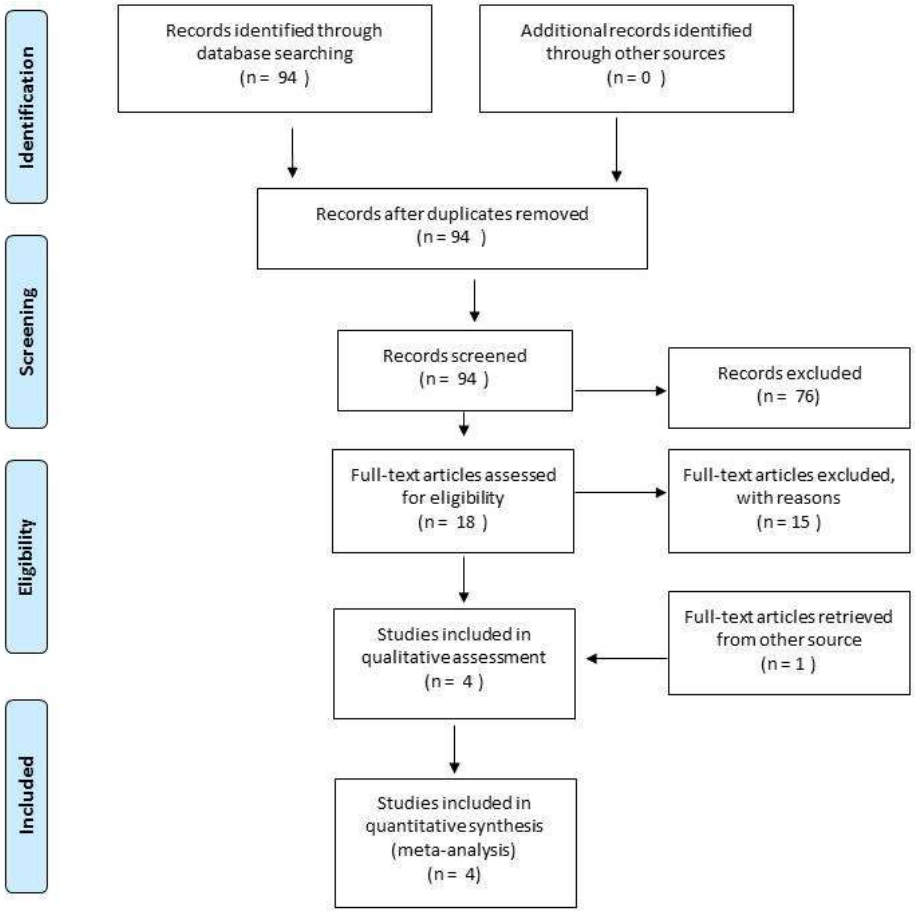
Results

A total of 94 studies were identified from the electronic database searches (Figure 5.1). After exclusion of irrelevant references, 18 potentially relevant articles were retrieved. After detailed evaluation of these articles, one randomised trial [Borger 2015] and three studies [Muneretto C, 2015; Santarpino G, 2013; Shrestha M, 2013] of unclear comparative design remained for assessment.

We classified them as controlled clinical trials (CCT). We based this definition on the efforts of the authors to compare like with like in difficult clinical circumstances and their reporting of the demographics between arms.

See Appendix 4 for the effectiveness search strategy and Appendix 5 for the list of the excluded studies.

Figure 5.1: Flow-chart of the studies according to PRISMA (from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.



Description of the included studies

In the randomised trial [Borger 2015] 100 patients with aortic stenosis were allocated to minimally invasive rapid deployment of a novel class of aortic valve prosthesis (n=51 or to full sternotomy using conventional valves (49). Inclusion criteria were 18 years old or older and the presence of low to moderate surgical risk score (logistic EuroSCORE <20) and New York Heart Association (NYHA) class II or greater. At baseline patients characteristics were similar between the two with the exception of hypercholesterolemia and history of smoking, which were higher in the experimental group. The valve used in the experimental group was a stented trileaflet bovine pericardial bioprosthesis with a balloon-expandable (Edwards Intuity) and was deployed after performing an upper hemisternotomy into the third or fourth intercostal space and excision of the aortic valve leaflets. The type of valve used in the control group depended on the choice by the surgeon. Hancock II (Medtronic, n = 3), Mitroflow (Sorin Biomedica Cardia Srl, Italy; n = 3), Trifecta (St. Jude Medical, MN; n = 10), or Perimount Magna Ease (Edwards Lifesciences; n = 32).
The primary endpoints were cross-clamp time and cardiopulmonary bypass (CPB) time. Safety endpoints were cardiac reoperation, thromboembolism, renal failure, paravalvular leak, permanent pacemaker implantation, resternotomy, major bleeding events, endocarditis, myocardial infarction, deep sternal wound infection, cerebrovascular accident or permanent stroke, and respiratory failure. Other secondary endpoints were hemodynamic performance, quality of life outcome measures (EQ-5D), and NYHA classification.
Some trial authors disclosed their financial relationships with Edwards Lifesciences, LLC.
The method of randomisation and the tool used to conceal allocation were not clearly reported. The study was also exposed to performance bias since the participants and the investigators could not be blinded. In addition, no information regarding the blinding of the outcome assessor was reported. However, the study was at low risk of detection of bias since echocardiograms were reviewed by an independent core laboratory and the safety endpoints were reviewed by an independent clinical events committee whose members were independent of both the study sponsor and the investigators as well as the assessment of the aggregate data review.
Relevant outcomes including overall mortality and 30-day mortality were evaluated and reported. The primary analysis was performed on a per-protocol analysis given that in experimental group 2 participants were excluded because of intraoperative screening failure, 3 crossed-over to conventional treatment and were subsequently excluded whereas in the control group 1 participant withdrew from the study before the procedure. A sensitivity analysis was performed using an intention-to-treat analysis and the authors declared that the results remained unchanged.
In the first comparative study, Muneretto et al, prospectively enrolled 163 consecutive patients with severe aortic valve stenosis and an intermediate-to high-risk profile (defined by Society of

Thoracic Surgeons - Predicted Risk Of Mortality [STS-PROM] score >4%). Participants were allocated to Sutureless Aortic Valve Replacement (SuAVR) (n=53), surgical AVR (n=55) or transcatheter aortic valve replacement (n = 55). A multidisciplinary team took decision on the type of intervention based on frailty, anatomy and degree of atherosclerotic disease of the aorta and peripheral vessels of each patient. [Muneretto C, 2015].
All participants allocated in the intervention group received a sutureless prosthesis (Perceval S, Sorin LivaNova PLC, Saluggia, Italy) whereas patients allocated to surgical AVR received either a conventional stented (Perimount Magna Ease, Edwards Lifesciences, Irvine, CA, USA) or a stentless prosthesis (Freedom Solo, Sorin LivaNova PLC, Saluggia, Italy). In this group of patients, the prosthesis was implanted either via conventional midline or ministernotomy (via a J-shaped incision at the third or fourth intercostal space) at the surgeon's discretion. In the third group, a transfemoral route was utilized and a Corevalve (Medtronic, Minneapolis, MN, USA) prosthesis was implanted in all cases.

The mean logistic EuroSCORE was lower in the SuAVR group than the comparison groups albeit not statistically significant (P=0.06). The primary outcomes included early postoperative complications and hospital mortality, 30-day mortality as well as overall survival, survival free from major adverse cardiac and cerebrovascular events (see Table 5.1 for details).

The study was not randomised and was thus vulnerable to selection bias. All subjects were included in analysis. There was no difference among the groups in terms of age, left ventricular ejection fraction, sex, body mass index (BMI), obesity, diabetes and peripheral vascular disease. However, chronic obstructive pulmonary disease was more frequent in TAVR patients ($P < 0.01$), whereas the prevalence of pulmonary hypertension was higher in patients undergoing surgical AVR, either conventional or sutureless. The description of the interventions is also not clear.

The authors declared no conflict of interest but it was unclear whether the study received funding from private companies.

In the second comparative study, Santarpino allocated 50 patients with isolated aortic stenosis to receive SuAVR bioprosthesis (Perceval) and 50 patients to standard AVR [Santarpino G, 2013].
In the experimental group, the surgical intervention was performed through a J-shaped mini sternotomy in the third or fourth intercostal space. The selection of aortic valve prosthesis type was based on the anatomic assessment of native valves, the surgeon's experience, and the patient's preference.

In the control group, participants were allocated when they were not eligible for sutureless implantation on the basis of the following exclusion criteria: age less than 65 years, bicuspid aortic

valve, sinotubular junction to aortic anulus ratio greater than 1.3, and patient preference for a mechanical valve prosthesis. In the control group, a minimally invasive surgery through a J-shaped ministernotomy approach was performed and among the participants, 36 received a stented bioprosthetic valve (15 Sorin Soprano, 21 Sorin Mitroflow), 6 a stentless bioprosthetic valve (Sorin Freedom Solo in all cases), and 8 a mechanical aortic valve (1 Sorin Bicarbon Fitline, 7 Sorin Bicarbon Overline).

The outcomes of interest included (1) in-hospital and 30-day mortality; (2) length of intensive care unit stay (days); (3) amounts of hemoderivatives used (units); (4) duration of orotracheal intubation (hours); (5) respiratory failure; (6) renal impairment; (7) incidence of postoperative arrhythmias; (8) low cardiac output syndrome; and (9) perioperative myocardial infarction.

The two groups showed statistically differences in terms of age (experimental group being older; P=0.001), pre-operative risk based on EuroSCORE (9.9 in the experimental group vs 4.3 in the control group: P=0.001), body surface area (P=0.015), and male/female ratio (males higher in control group; P=0.04).

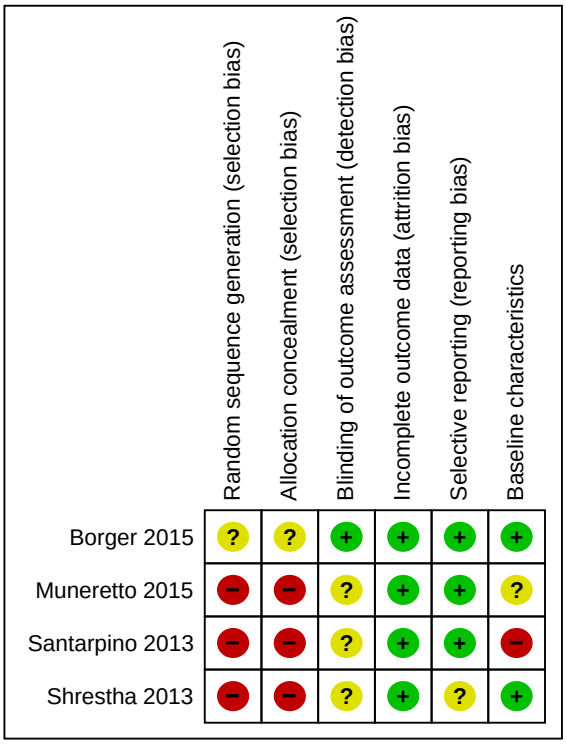
The study was at risk of selection bias because of the absence of randomization. It was unclear whether the outcome assessor was blinded. No relevant issues could be identified in the domains related to incomplete outcome data and selective outcome reporting bias. Baseline differences between the two groups, age, sex and Logistic SCORE, were controlled for in analyses to preclude their bias. Two study authors disclosed conflict of interest with the manufacturer (Sorin LivaNova PLC, Saluggia, Italy) but no statement about funding was reported in the article.

In the last comparative study, Shrestha et al, allocated 50 (47 females, age 79.8 ± 4.5 years) to Perceval S sutureless aortic valve prosthesis and 70 patients (68 females, age 77.4 ± 5.5 years) to SuAVR and 50 patients (47 females) to conventional valves. [Shrestha M, 2013].
The Logistic EuroSCORE was higher in the experimental group with a borderline significance (P = 0.054). No other significant differences were identified in terms of basic prognostic factors. The primary outcomes were cardiopulmonary bypass (CPB) and cross-clamp times though 30-day mortality, including cardiac death, mortality at 1 year and 3 months, endocarditis and re-aortic valve replacement were reported.

Methodologically the study was exposed to selection bias due to the absence of randomization. No information was provided as to whether the outcome assessor was blinded. No apparent exclusion occurred but there were 2.9% and 6.1% of loss to follow-up in the control and experimental group respectively. In addition, the mean time follow-up was significantly less in the group that received SuAVR. There was no significant pre-operative baseline differences. However, no information

related to any arrhythmias were provided (unclear selective reporting bias). The summary of the risk of bias table is provided in Figure 5.2.

Figure. 5.2. Risk of bias

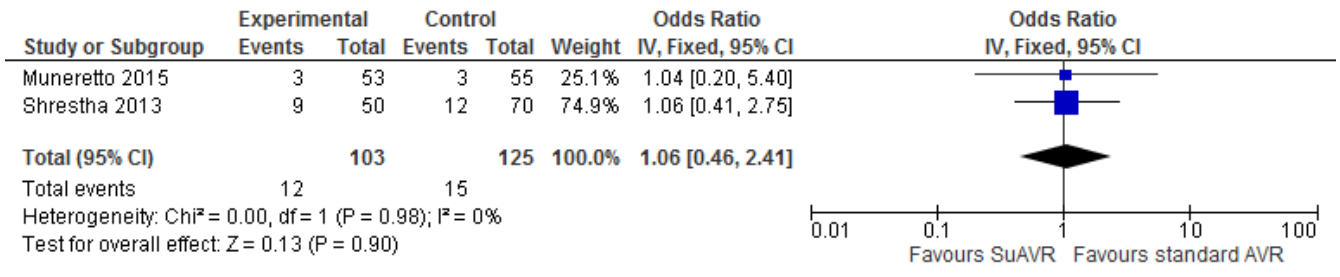


D0001: What is the effect of the intervention on all-cause mortality?

There was no significant difference between the use of SuAVR and standard AVR in each of the studies. A meta-analysis performed using the data from two trials with long follow-up and with no heterogeneity showed no statistically significant difference between the two groups (OR 0.85 [95% CI 0.39 to 1.34]).

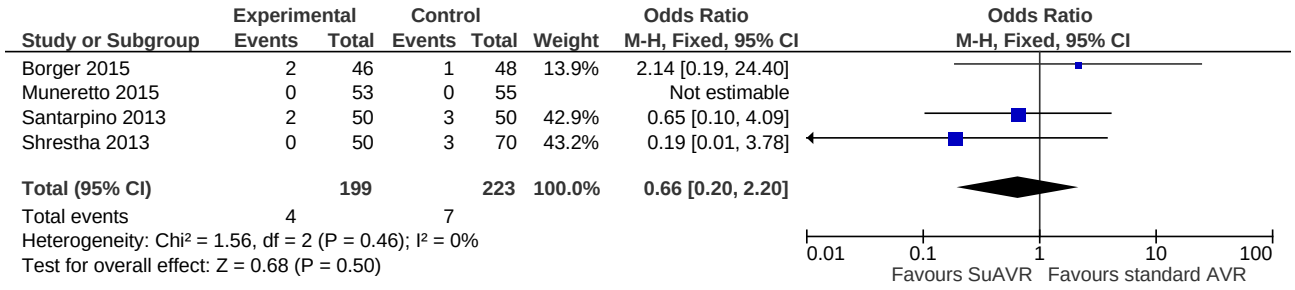
The comparison between SuAVR with TAVR performed on the two trials [Muneretto C, 2015; Shresta M, 2013] did not show significant difference in terms of overall mortality.

Fig.5.3 Overall mortality. SuAVR vs standard AVR



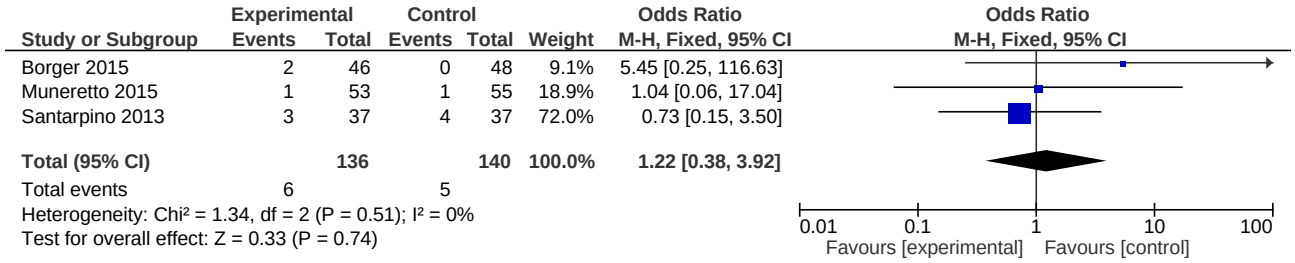
The outcome 30 day-mortality was reported in all the three trials. Combining the data we observed no significant difference between the three groups (Figure 5.4).

Fig. 5.4. 30-day mortality. SuAVR vs standard AVR



Pace-maker implantation was reported in two studies but results were not different (Figure 5.5).

Figure 5.5. Pace-maker implantation. SuAVR vs standard AVR



D0002: What is the effect on the disease-specific mortality?

Only one study [Shresta M] reported data concerning cardiac death. Four events occurred in the control group against one in the experimental group. The difference was not statistically significant (P=0.34). [Shrestha M, 2013].

Muneretto et al compared also SuAVR with TAVR and no significant difference were reported in terms of overall mortality. [Muneretto C, 2014].

No data were available for AE: D0005a, D0005b, D0005c, D0012, D0014, D0015, D0018.

Table 5.1. Summary of findings from the systematic review on clinical effectiveness of sutureless aortic valve replacement for aortic valve stenosis.

Study ID	Year	Country	Study Design	Procedure	Patients	Groups (number of patients)	Device assessed (Manufacturer)	Comparator	Outcomes reported	Funding	Conflict of interest
Borger	2015	Germany	Randomised controlled trial	Minimally Invasive Rapid Deployment	100 patients with aortic stenosis	were allocated to minimally invasive rapid deployment of a novel class of aortic valve prosthesis (n=51 or to full sternotomy using conventional valves (49)	stented trileaflet bovine pericardial bioprosthesis with a balloon-expandable (Edwards Intuity)	Traditional valves: Hancock II (Medtronic, n = 3), Mitroflow (Sorin Biomedica Cardia Srl, Italy; n = 3), Trifecta (St. Jude Medical, MN; n = 10), or Perimount Magna Ease (Edwards Lifesciences; n = 32).	Primary outcomes: 1. cross-clamp time 2. cardiopulmonary bypass time. Safety endpoints: cardiac reoperation, thromboembolism, renal failure, paravalvular leak, permanent pacemaker implantation, resternotomy, major bleeding events, endocarditis, myocardial infarction, deep sternal wound infection, cerebrovascular accident or permanent stroke, and respiratory failure. Other secondary endpoints: hemodynamic performance, quality of life outcome measures (EQ-5D), and NYHA classification.	Edwards Lifesciences, LLC.	Some trial authors disclosed their financial relationships with Edwards Lifesciences, LLC.
Muneretto, 2015	2005	Italy	Prospective comparative study		163 consecutive patients with severe aortic valve stenosis and an intermediate- to high-risk profile	Surgical implantation of a sutureless valve (n = 53); standard aortic valve replacement (n = 55); TAVR (n = 55)	Unclear description	(a) Conventional stented (Perimount Magna Ease, Edwards Lifesciences, Irvine, CA, USA) or stentless prosthesis (Freedom Solo, Sorin LivaNova PLC, Saluggia, Italy) implanted using surgical AVR using either; (b) Corevalve (Medtronic, Minneapolis, MN, USA) implanted using TAVI c) Sutureless valve	Bleeding requiring any surgery; Anaemia requiring at least 2 units of RBCs; Acute renal failure; Atrial fibrillation; Stroke; Postoperative AMI; IABP; Tamponade; Sternal complications; Left bundle branch block; AVB/PM implantation; Peripheral vascular complications; Hospital mortality (30 days); Postoperative haemodynamics; Postoperative haemodynamics; Overall mortality; Cardiac death; Late myocardial infarction; Major haemorrhagic events; Cerebrovascular accidents	Not reported	Declared no conflict of interest
Santarpino, 2013	2013	Germany	Prospective comparative study	Minimally invasive isolated aortic valve replacement.	100 patients underwent minimally invasive isolated aortic valve replacement. Of these, 50 patients received a Perceval Sorin	50 patients received a Perceval (Sorin Group LivaNova PLC, Saluggia, Italy) bioprosthesis	Perceval (Sorin Group LivaNova PLC, Saluggia, Italy)	36 received a stented bioprost hetic valve (15 Sorin Soprano, 21 Sorin Mitroflow), 6 a stentless bioprosthetic valve (Sorin	Cross-clamp time, Cardiopulmonary bypass time, Implant failure, Prosthesis size, Conversion to full sternotomy. Follow up data: Thirty-day mortality, Intensive care unit stay, Hospital stay, Blood transfusion, Orotracheal intubation time, Respiratory	Not reported	Not reported

					Group LivaNova PLC, Saluggia, Italy) bioprosthesis (group P) and 50 patients received a non- Perceval valve (group NP).	(group P) and 50 patients received a non- Perceval valve (group NP).		Freedom Solo in all cases), and 8 a mechanical aortic valve (1 Sorin Bicarbon Fitline, 7 Sorin Bicarbon Overline).	insufficiency Renal insufficiency, Arrhythmias, Low cardiac output syndrome Perioperative myocardial infarction Pacemaker implantation		
Shrestha, 2013	2013	Germany	Prospective comparative study	Aortic valve replacement (AVR) and sutureless valves compared with conventional biological valves.	120 geriatric patients with small anulus:	70 patients (68 females, age 77.4 ± 5.5 years),conventional valves AND in 50 patients (47 females, age 79.8 ± 4.5 years), SuAVR	Perceval (Sorin LivaNova PLC)	conventional biological valves: Sorin Mitroflow, Carpentier Edwards Perimount, St. Judes Epic Supra, Medtronic Mosaic Cinch	CPB and cross-clamp times; mean operation time; Thirty-day mortality; The mean gradient and the EOA of the valve prosthesis at discharge; The ICU and hospital stays; left ventricular ejection fraction; mean follow-up time; Mortality at 1 year; Mortality at 3 years; Endocarditis;Re-AVR (n) .	The institution received an unrestricted research grant from Sorin LivaNova PLC for the conduct of the study.	Declared no conflict of interest

Conclusions

In the present assessment the evidence regarding the effectiveness of SuAVR as an alternative to AVR derived from 4 studies comprising 422 participants. These studies were one randomised trial and three non-randomised comparative trials and the overall quality of the evidence was moderate. Clinical outcomes and safety events were similar between SuAVR and conventional valves using traditional sternotomy approach. No evidence regarding long term outcomes were reported. Well designed and adequately powered randomised trials that evaluate long term outcomes are needed.

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6. Safety

Methods

The AE belonging to the present domain was:

Assessment Element ID	Research question
C0001	What harms are associated with the use of the technology?

The AE was addressed in our assessment.

Types of studies of interest were systematic reviews, randomised controlled trials (RCT), and controlled clinical trials (CCT). (C0001).

The inclusion criteria for patient population is the presence of at least one of the following:

a) peak velocity > 4.0 m/s (corresponding to a peak gradient of 64 mm Hg), a mean gradient > 40 mmHg, or valve area < 1.0 cm^2 when left ventricular systolic function is normal performed by echocardiogram [Holmes DR, 2012];

b) Logistic EuroSCORE higher than 15%, which estimates a mortality of 15% by 30 days after procedure [Roques F, 2003], and 10% in a score model developed by the Society for Thoracic Surgeons (STS) [Ferguson TB, 2000].

Studies assessing aortic valve replacement using commercially available sutureless valves compared with surgical intervention for aortic valve replacement and TAVI were considered.

Risk of bias using the Cochrane instrument [Higgins JPT, 2011] was used to assess the quality of included articles (items of risk of bias include: sequence generation, allocation concealment, blinding of patients and participants, blinding of outcome assessor, incomplete outcome data and selective outcome reporting).

Statistical analyses

Where homogeneous studies were identified, a meta-analysis was performed.

Dichotomous outcomes results were expressed as risk ratio (RRs) with 95% confidence intervals (CIs). Where continuous scales of measurement were used to assess the effects of treatment, the mean difference (MD) were used; the standardised mean difference (SMD) was used when different scales were reported..

Heterogeneity was evaluated using a Chi^2 test with N-1 degrees of freedom, with an alpha of 0.10 used for statistical significance and with the I^2 test [Higgins JPT, 2011]. The source of heterogeneity was sought by assessing the participants, the intervention, the comparison group, and resultant outcomes and by visually assessing the forest plots.

Review Manager software (Revman 5.3) was used for data synthesis. Data were pooled using both the random-effects model and the fixed-effect model to assess robustness of analysis by distribution of observations.

Results

The study screening process is shown in Figure 5.1. one randomised trial [Borger 2015] and three controlled clinical trials [Muneretto C, 2015; Santarpino G, 2013; Shrestha M, 2013] remained for assessment.

The adverse events reported by the included studies were the following: bleeding and (units of) blood transfusion as a marker of important bleeding, arrhythmias, permanent pacemaker implantation as a marker of important arrhythmias, and renal insufficiency.

Bleeding and transfusion requirement

Borger et al reported similar rates for major bleeding between the groups (6.5% in the sutureless group and 8.3% in the control group; P = 0.74) [Borger MA, 2015].

Muneretto C et al. reported bleeding requiring surgery was similar across the three groups: 6 in the SuAVR group, 4 in the AVR group and none in the TAVR group (P = 0.51) Anemia requiring at least 2 units of red blood cells (RBCs) was lower in the SuAVR group (22.6%) than in AVR (47%) and TAVI group (42%) [Muneretto C, 2015].

Santarpino G and collegues did not report any bleeding event but reported a higher number of RBCs transfused in the control group (2.3 +/- 2.8) than in the experimental group (1.1 +/- 1.1) (P = 0.007). [Santarpino G, 2013].

In the study of Shrestha M. and collegues, two thoracotomy re-interventions in each group were performed due to postoperative bleeding. [Shrestha M, 2013].

Arrhythmias and permanent pacemaker implantation

In Borger, two patients in the experimental group received a pacemaker implantation but no pacemaker was implanted in none of the control group population. The difference was not statistically significant [Borger MA, 2015].

In Muneretto C, the incidence of advanced atrioventricular block requiring pacemaker implantation was higher in the TAVR group (26%) than in the AVR and SuAVR groups (2% in both groups; P <0.001) as well as the incidence of left bundle branch block (TAVR 60%; AVR 3.6% and SuAVR 7.6%; P <0.001). Conversely, patients undergoing TAVR were less likely to develop atrial fibrillation (TAVR 11%, AVR 47%, SuAVR 31 58%; P < 0.001) [Muneretto C, 2013].

In the study by Sartarpino G et al., authors did not report the type of arrhythmias that occurred. The incidence of arrhythmias cases was 7 (14%) and 10 (20%) in the experimental and control

group respectively. Of these, 3 and 4 required pacemaker implantation in the respective groups. No statistical difference was identified. [Santarpino G, 2013].

Renal insufficiency

The incidence of acute renal failure was reported in three of the four studies [Borger 2015; Muneretto 2013; Santarpino 2013]. The incidence were between 2%, 4% and 8% in the intervention groups and 0%, 6% and 13% in the control group without detecting any statistical difference. [Muneretto C, 2015; Santarpino G, 2013].

The last study did not clearly report the incidence of acute renal failure but acknowledged the cause of 2 deaths (1 in each group) related to renal impairment. [Shreshta M, 2013].

Conclusions

The incidence of several safety outcomes was similar between the two comparison groups.

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7. Costs and economic evaluation

Methods

The AEs we selected for this domain were 7 (see below):

Assessment Element ID	Research question
E0001	Can you identify what types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?
E0002	Can you quantify what amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?
E0009	What were the measured and/or estimated unit costs of the resources used by the assessed technology and its comparator(s)?
E0005	What is/are the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?
E0006	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?
E0010	What are the uncertainties surrounding the inputs and economic evaluation(s) of the technology and its comparator(s)?
G0007	What are the likely budget impacts of implementing the technologies being compared?

To answer those AEs we carried out:

1. a systematic review of the economic evaluation studies about SU-AVR;
2. a cost analysis based on 1 Italian Region (Veneto);
3. clinical experts' and manufacturers' information gathering.

We thus could estimate the cost of a single replacement. The estimate included cost-related information (e.g. operating theatres, preoperative and postoperative examination, staff time, material cost, length of hospital stay etc.).

Systematic review

For the systematic review we carried out a search on Medline, EmBase, NHS Economic Evaluation Database (NHS EED) and cost-Effectiveness Analysis (CEA) Registry. We included economic evaluations with different designs (cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA); cost-consequences analysis (CCA); cost-minimisation analysis (CMA)) comparing SU-AVR versus TAVI and/or standard bioprostheses (stented and/or stentless valves) from 2005 to April 2015. We used EndNote X7.2 (Thomson Reuters) to manage retrieved studies. Extractions were performed in double by two researchers, results compared and disagreements were solved through discussion. Methodological quality was assessed using the checklist for economic evaluations of health programmes [Drummond M, 1997]. Studies were analysed and synthetized using a layout based on the extraction sheets.

We described the included studies in terms of:

1. Types of resources used (E0001)
2. Amounts of the resources used (E0002)

3. Estimated unit costs of the resources used (E0009)
4. Estimate health related outcomes (E0005)
5. Difference (estimate) in costs and outcomes between the technology and comparator (E0006)
6. Uncertainties surrounding the inputs (E0010)

Cost analysis

For the case study we reported a cost analysis based on data provided by the Veneto Region which participated in the production of this report. The analysis reported the costs of two centers using a structured form organised by Veneto Region (values at 2014). The analysis considered only direct costs and included general costs (estimated in 15% of the total direct costs by Veneto Region).

The costs were detected for both traditional and sutureless valve and were categorised as:

- Preoperative examination
- Operating room
- Health personnel
- Materials
- Hospital stay
- Intraoperative and post-operative examinations

Experts' and manufacturers' information

Clinical experts' information were collected during meetings and working groups and manufacturers' and distributors' information about costs collected via a structured questionnaire (see Appendix 3).

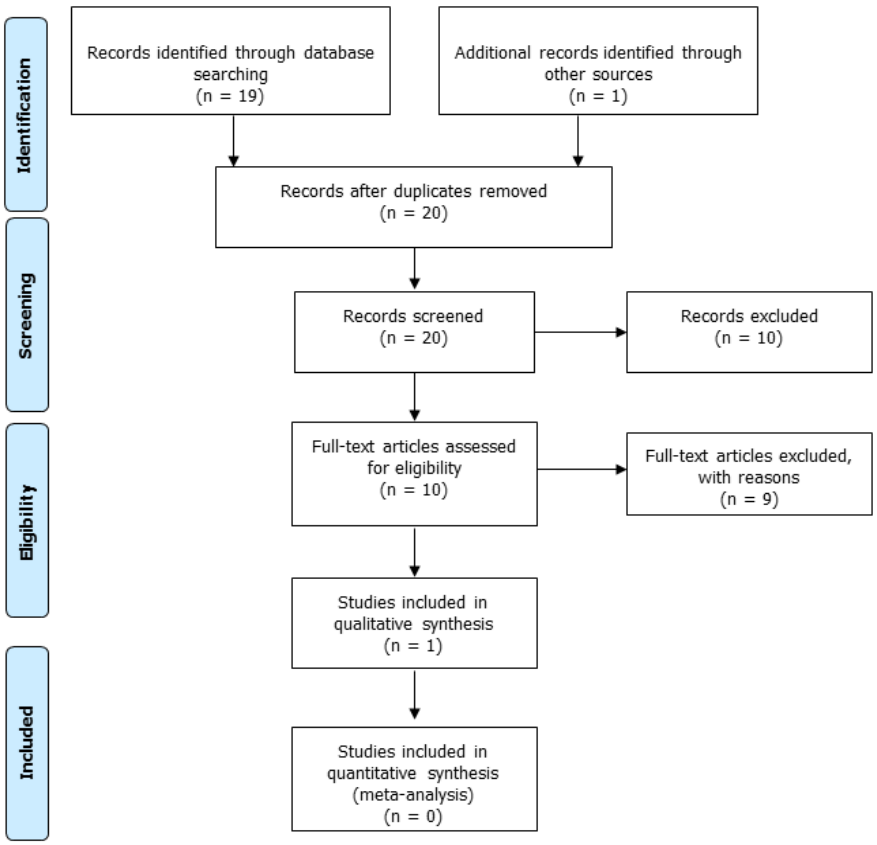
Results

All AEs were addressed in our assessment.

Systematic review of economic evaluations

The search strategy identified 19 studies. An additional study was identified through other sources, therefore a total of 20 records was screened. After first screening (by title and abstract) we excluded 10 items. According to our inclusion criteria we assessed 10 articles for eligibility and we excluded 9 of them. We eventually included one study [Pradelli L, 2012]. Figure 7.1 shows the PRISMA flow diagram describing the inclusion process of the economic studies. Search strategy and excluded records along with the reason for exclusion are reported in Appendix 6 and Appendix 7 respectively. The only study included is not strictly an economic evaluation (CEA, CUA, BUA) so we described it only for the cost analysis section.

Figure 7.1: Flow-chart of the studies according to PRISMA (from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097



Description of included study [Pradelli L, 2012]

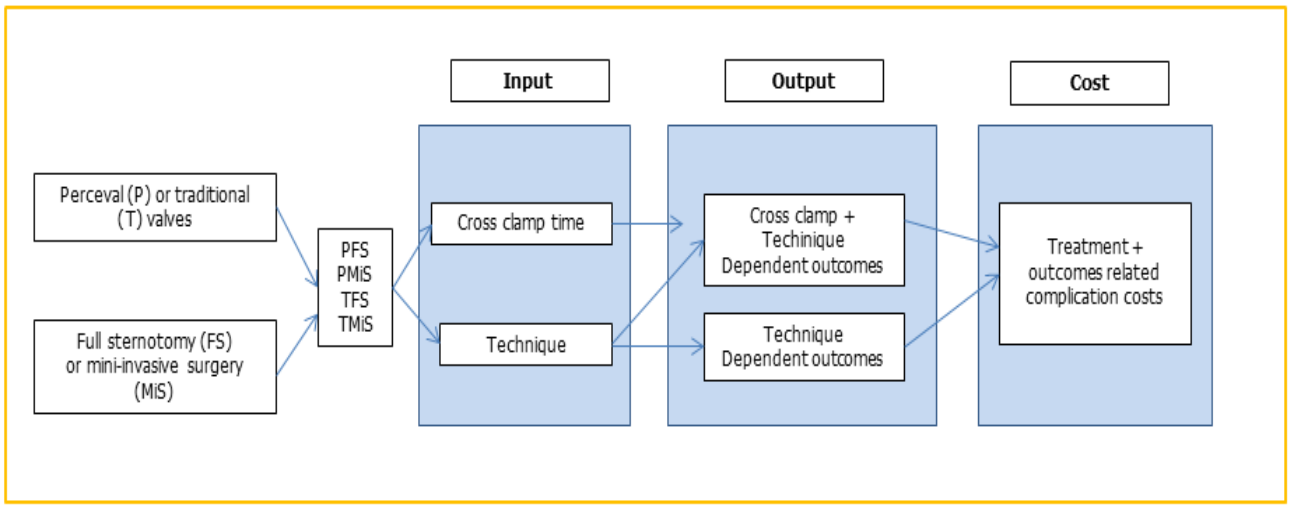
Pradelli et al. proposed a cost analysis model to evaluate the cost of the main surgical alternatives for AVR (TAVI was excluded) in medium to high-risk patients. The study was based on the hypothesis that a reduction in CCT during surgical replacement may reduce the total cost of the procedure. The valve assessed was the Perceval S (Sorin Group LivaNova PLC) and the study was conducted in Italy and funded by Sorin Group LivaNova PLC. Table 7.1 reports the general description of the included study.

Table 7.1 General information of included study (Pradelli L, 2012)

Study objective	Country	Population	Intervention	Comparator
Evaluate the cost of the main surgical alternatives for AVR in medium-to-high risk patients. To this aim, a simulation model was built to estimate the effects of using different valves and surgical techniques on clinical outcomes, possible complications and related treatment costs.	Italy	Medium-to-high risk patients with symptomatic, calcific aortic stenosis.	Perceval S (Sorin Group LivaNova PLC)	The main surgical options available for patients that need AVR and are at medium to- high surgical risk can be defined by the type of prosthesis implanted (sutureless vs sutured) and the surgical approach to the ostium (full sternotomy [FS] vs mini-invasive [MiS] techniques).

Pradelli and colleagues built a simulation model to estimate the effect of using different valves and surgical techniques on clinical outcomes, complication and treatment costs (see Figure 7.2).

Figure 7.2 Representation of the model structure (from Pradelli L, 2012)



PFS= Perceval; PMiS= Perceval mini-invasive surgery: TFS= traditional full sternotomy; TMiS= traditional mini-invasive surgery

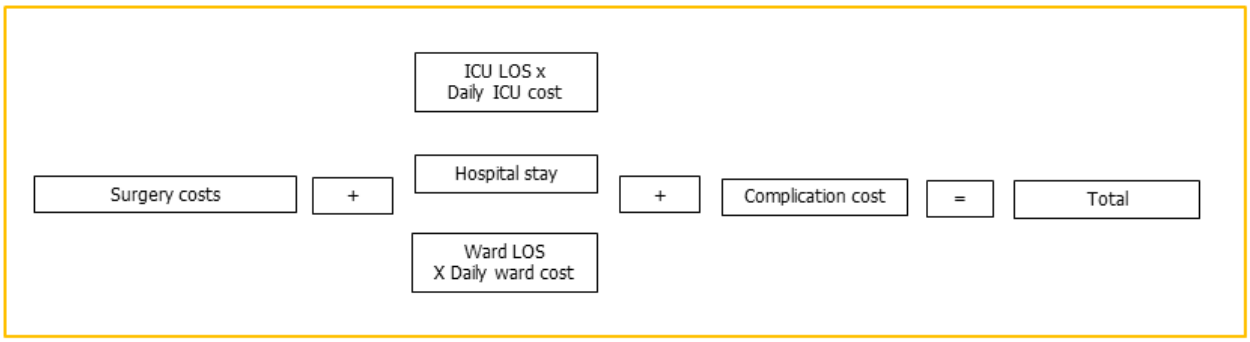
The model represents the two surgical techniques combined with the two type of valves (sutureless and traditional) for a total of 5 strategies, resulting in a combination of technique and type of valve. Cost analysis was based on data from four European countries: Italy, Germany,

France and United Kindom (UK). The study considered only direct costs of replacement and complications occurred during index hospitalization. Past costs were updated to 2011 (2012 for Italian costs) values using official inflation indices.

Types and amounts of the resources used (E0002 and E0001)

The cost model used in the study was reported in Figure 7.3. It comprises: surgery costs, hospital stay costs and complication costs.

Figure 7.3. Illustration of the costs structure (from Pradelli L, 2012)



Surgery costs comprise:

- Operating room (130 min)
- CCT specific for each procedure
- 90 min for room preparation/asepsis
- 2 surgeons
- 1 anaesthesiologist
- 1 assistant anaesthesiologist
- 1 instrumentalist
- 1 perfusionist
- 1 nurse
- 1 health operator (for asepsis)
- Single red blood cell transfusion

Hospital stay includes the ward stay and ICU day. The resource consumption was not reported.

Complication costs include:

- Sepsis episode
- Dialysis Hospital day
- Ventilation associated pneumonia (VAP) episode
- Rehabilitation day

Estimated unit costs of the resources used (E0009)

Table 7.2 summarizes costs for surgery, hospital stay and complications of the procedures excluding the valve's cost (sutured or sutureless) for each countries considered (Italy, France, Germany, UK). Authors used secondary sources to collect information on costs, thus they were not directly observed [see Pradelli L, 2012 for details on the sources used].

Table 7.2. Unit costs of procedure

Item	Italy (€)	France (€)	Germany (€)	UK (£)
Surgery unit costs				
Minute of OR	23.5	23.50	23.50	21.28
Health personnel costs (per minute)				
2 surgeon	1.28	2.29	0.96	1.38
Anaesthesiologist	1.28	2.65	0.96	1.38
Assistant	1.28	2.65	0.96	1.38
Instrumentalist	0.44	0.68	0.61	0.78
Perfusionist	1.28	2.65	0.96	0.95
Nurse	0.44	0.68	0.61	0.78
Health operator	0.32	0.50	0.27	0.13
Transfusion				
Red blood cell unit	153	183.84	105.53	172.76
Hospital stay costs				
Ward day	411.71	444.59	448.44	371.62
Intensive Care Unit day	1,109.57	1,328.31	1,141.86	1,703.72
Complication				
Sepsis episode	2,060.86	3,723.43	3,264.30	7,768.83
Dialysis H day	311.31	154.20	74.29	68.42
VAP episode	8,095.63	12,818	4,664.32	6,686.35
Rehabilitation day	261.41	261.78	290.29	292.95

The total costs (mean) for isolated or concomitant AVR procedures was obtained with 20,000 iterations of the model. Table 7.3 and Table 7.4 show the total amount for isolated and concomitant procedures. For isolated procedures the model shows that the total cost are low when the valve is implanted using mini-invasive technique. The potential cost saving comes from the absence of suturing and using a less invasive surgical technique, as reflected in all the parameters considered (ward stay, surgery, rehabilitation, ICU and complications costs). All costs considered exclude the cost of the valve.

The uncertainties surrounding the inputs (E0010) were measured by the probabilistic sensitivity analysis using tornado diagram (not tabular form). The diagram shows which parameter influenced the analysis and the model. For isolated procedures the main parameters of influence, including costs of the procedures are:

- surgery cost/minute and hospital stay using sutureless valve in mini invasive technique;
- surgery cost/minute and rehabilitation rate/cost using sutureless valve in isolated full sternotomy;
- cross clamp time and surgery cost/minute in case of traditional valve in isolated full sternotomy.

For concomitant procedures the use of sutureless valve in full sternotomy are sensitive to surgery cost/minute and rehabilitation rate/cost while the traditional valve in full sternotomy are sensitive to cross clam time and surgery cost/minute.

Table 7.3. Total costs for isolated procedure

Country	Valve/ Surgery technique	Surgery	Ward stay	Rehabilisation	Intensive Care Unit	Complications	Total (€)	Difference Δ
Italy (€)	TFS	7,201	4,937	3,925	3,365	352.8	**19,780**	-
	PFS	5,855	3,723	3,925	2,362	280.3	**16,150**	3,602
	PMiS	5,891	3,298	2,326	2,057	238.8	**13,810**	5,970
France (€)	TFS	8,589	5,331	3,93	4,029	426.4	**22,310**	-
	PFS	6,956	4,021	3,93	2,828	368.9	**18,100**	4,164
	PMiS	7,002	3,561	2,329	2,462	288.4	**15,640**	6,663
Germany (€)	TFS	6,932	5,377	4,359	3,463	259.7	**20,390**	-
	PFS	5,641	4,056	4,359	2,431	229.1	**16,720**	3,641
	PMiS	5,676	3,592	2,583	2,116	166.7	**14,130**	6,257
UK (£)	TFS	6,813	4,456	4,398	5,167	483.9	**21,320**	-
	PFS	5,533	3,361	4,398	3,627	441.1	**17,360**	3,915
	PMiS	5,568	2,976	2,607	3,158	299	**14,610**	6,711

Key: TFS: Traditional full sternotomy; PFS: Perceval full sternotomy; PMiS: Perceval mini-invasive surgery.

Table 7.4. Total costs for concomitant procedure

Country	Valve	Surgery	Ward stay	Rehabilisation	Intensive Care Unit	Complications	Total	Difference Δ
Italy (€)	T	8,011	6,072	3,925	4,365	430.5	**22,800**	6,063
	P	6,294	3,816	3,925	2,42	284.8	**16,740**	
France (€)	T	9,572	6,557	3,930	5,226	492.6	**25,780**	6,968
	P	7,490	4,121	3,930	2,897	371.7	**18,810**	
Germany (€)	T	7,709	6,614	4,359	4,492	295.4	**23,470**	6,169
	P	6,063	4,156	4,359	2,491	230.5	**17,300**	
UK (£)	T	7,584	5,481	4,398	6,703	535.5	**24,700**	6,748
	P	4,951	3,444	4,398	3,716	442.9	**17,950**	

Key: T: traditional; P: Perceval

Case study results (data from Veneto Region) (G0007)

Types amounts and unit costs of the resources used (E0002, E0001, E0009)

Estimating the financial consequences of the introduction of a technology is important for a health care system. In Italy there is no formal validated framework or methodology to carry out a budget impact analysis (BIA).

However we can consider the case study of Veneto region and the cost results reported in this domain as a part of a BIA.

Types of resources used (E0002), their amounts (E0001) and unit costs (E0009) were reported in table 7.4 and table 7.5 for both traditional and sutureless valve for each center.

Based on data reported by Veneto the estimated total costs using traditional valve is €13,642 calculated as mean of the total costs for the two centers involved in the analysis. For sutureless valves the mean value of total costs is €17,785. Table 7.6 and table 7.7 show the total costs for traditional and sutureless valve replacement.

Table 7.4: Type, amount and unit costs of resources used for traditional valve replacement.

	Centre 1			Centre 2		
Preoperative examination	**Number**	**Time (hour)**	**Cost (€)**	**Number**	**Time (hour)**	**Cost (€)**
Electrocardiography	1		13	1		13
Transthoracic Echocardiography	1		56	1		56
Heart catheterization plus Coronary angiography	1		1,369	1		1,369
Spirometry	1		25	1		25
Echoi dpplerof the supra-aortic trunks	1		48	1		48
Chest X-ray	1		25	1		25
Laboratory tests	28		97	28		97
Operating Room						
Ammortization, services, common costs		6	480		6	570
Health Personnel	**Number**			**Number**		
Surgeon	2	4	576	2	4	576
Anesthetist	1	5	360	1	5	360
Perfusionist	1	3	84	1	3	79
Nurse	2	6	336	2	6	317
Nurse assistant	1	1	20	1	1	20
Materials						
Traditional Valve	1		2,600	1		2,606
2/0 Tycron sutures with pledgets (2 aortic valve kits with 3x7 and 3x3 pledgets)			320	1		300
Arterial cannula	1		16	1		16
Cavo-atrial cannula	1		16	1		16
Cardioplegia Catheter	1		25	1		25
Infusion double needle (cannula)	1		12	1		12
Left heart vent catheter	1		26	1		26
Oxygenator	1		332	1		332
Blood cardioplegic solution	1		66	1		85
Cardioplegic kit	1		94	1		62
Extracorporeal circulation (EC) kit	1		289	1		214
General material			970	20		1,153
Hospital stay	**Days**					
Coronary care unit	7		1,448	8		2,525
Intensice Care Unit (post operative)	1		820	1		1,183
Intraoperative and post operative examinations						
Transthoracic Echocardiography	3		168	3		168
Transesophageal echocardiography	1		84	1		84
Electrocardiography	2		25	2		25
Chest X-ray	3		75	3		75
Laboratory tests	4		192	4		196

Tab 7.5 Type, amount and unit costs **(€)** of resources used for sutureless valve replacement.

	Centre 1			Centre 2		
Preoperative examination	**Number**	**Time (hour)**	**Cost (€)**	**N**	**Time (hour)**	**Cost (€)**
Electrocardiography	1		13	1		13
Transthoracic Echocardiography	1		56	1		56
Heart catheterization plus Coronary angiography	1		1,369	1		1,369
Spirometry	1		25	1		25
Echoi dpplerof the supra-aortic trunks	1		48	1		48
Chest X-ray	1		25	1		25
Laboratory tests	28		97	28		97
Operating Room						
Ammortization, services, common costs		6	480		6	570
Health Personnel	**Number**			**Number**		
Surgeon	2	3.5	504	2	3,5	504
Anesthetist	1	4.5	324	1	4,5	324
Perfusionist	1	2.5	70	1	2,5	66
Nurse	2	5.5	308	2	5,5	291
Nurse assistant	1	1	20	1	1	20
Materials						
Sutureless Valve	1		6,690	1		6,690
Arterial cannula	1		16	1		16
Cavo-atrial cannula	1		16	1		16
Cardioplegia Catheter	1		25	1		25
Infusion double needle (cannula)	1		12	1		12
Left heart vent catheter	1		26	1		26
Oxygenator	1		332	1		332
Blood cardioplegic solution	1		66	1		34
Cardioplegic kit	1		94	1		62
Extracorporeal circulation (EC) kit	1		289	1		214
General material			970	20		1,153
Hospital stay	**Days**					
Coronary care unit	7		1,448	8		2,525
Intensice Care Unit (post operative)	1		820	1		1,183
Intraoperative and post operative examinations						
Transthoracic Echocardiography	3		168	3		168
Transesophageal echocardiography	1		84	1		84
Electrocardiography	2		25	2		25
Chest X-ray	3		75	3		75
Laboratory tests	4		192	4		196

Table 7.6: Total costs (€) for traditional valve replacement.

	Centre 1	Centre 2
Preoperative examinations	1,633	1,633
Operating room	480	570
Health Personnel	1,376	1,352
Materials (comprised cost of valve)	4,766	4,847
Hospital stay	2,268	3,708
Intraoperative and postoperative examination	544	548
Total direct costs (€)	**11,067**	**12,658**
General costs (15%) (€)	**1,660**	**1,899**
Total for traditional valve (€)	**12,727**	**14,557**

Table 7.7: Total costs **(€)** for sutureless valve replacement.

	Centre 1	Centre 2
Preoperative examinations	1,633	1,633
Operating room	480	570
Health Personnel	1,226	1,204
Materials (comprised cost of valve)	8,536	8,580
Hospital stay	2,268	3,708
Intraoperative and postoperative examination	544	548
Total direct costs (€)	**14,687**	**16,243**
General costs (15%) (€)	**2,203**	**2,437**
Total for sutureless valve (€)	**16,890**	**18,680**

The cost difference between the two centers is mainly due to the cost of hospitalizations. This is due both to the different number of hospital stays and to the different cost evaluation of hospital stay (Veneto region Report, 2014).

The cost of sutureless aortic valve device accounts for approximately 65% of the total cost of intervention (operating room, personnel, materials), while the estimated value for the traditional valve is 39%. The difference between the two replacements (traditional vs sutureless) is due to time consumption of resources during replacement (5 hours vs 4.5 hours respectively) and to the use of personnel and the absence of suture for the new technology.

Conclusions

This domain assessed all economic data available on the use of sutureless valves compared to TAVI and traditional valves based on a systematic review and a case study based on data from Veneto Region.

Cost analysis using data from the two centres seems to reveal that the main difference between SuAVR and traditional valve replacement depends on valve's cost.

Nonetheless a more comprehensive economic evaluation of SuAVR should include TAVI as a comparator and be based on more information about costs and consequences to be collected in a larger number of NHS Italian centres. In addition, the correlation between SuAVR costs and surgical options available for patients (especially mini-invasive techniques) should be investigated.

As today, there are insufficient data on economic evaluation on SuAVR compared to traditional valves and TAVI. Studies to gather further information on costs of SuAVR are needed.

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8. Discussion

Aortic stenosis is an important degenerative pathology mainly affecting males. SU-AVR is a possible alternative to traditional valve replacement and TAVI offering comparable clinical outcomes and safety profile. All have the potential to alter the course of the stenosis. In Italy, these procedures are mainly carried out in a few large regions in the North and Centre. However, current data on the potential comparative benefits are inconclusive with major trials still underway and lack of a dedicated DRG code to enable identification and administration of the considerable sums of money involved in the procedure. It should be emphasised that the major cost driver are the devices themselves. Available data show that the potential benefits are limited to short-term outcomes and further research concerning long-term outcomes based on well-designed randomised trials is needed. Given the lack of good quality data on the clinical performance of SU-AVR, we were only able to identify a cost analysis based on secondary data.

9. Recommendations

The evidence base is too narrow for us to recommend a specific device or procedure over the alternatives. There are no randomised trials comparing SuAVR with TAVI or sutured valves. Randomisation is essential to enable like being compared with like in a field in which many patients and contextual variables play such a large part. Large multicentre well designed randomised trials should be conducted alongside prospective economic evaluations to allow choice to be based on good evidence.

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11. Competing interests declaration

Authors, Clinical expert and External Reviewers declare that they do not receive benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

Glossary

AE – Assessment Element

AVR - Aortic Valve Replacement

ICD9-CM - International Classification of Disease – 9th Edition

NSIS - New Health Information System

SU-AVR - Sutureless Aortic Valve Replacement

TAVI - Transcatheter Aortic Valve Implantation

Appendix 1 – The Agenas adaptation of the EUnetHTA Core Model ®

Health Technology Assessment (HTA) is the multidisciplinary evaluation of one or more health interventions in their context of use. Since 2006 Agenas has been involved in the EU HTA network EUnetHTA (http://www.eunethta.eu/contactus/all/356/all). EUnetHTA's main aim is to increase collaboration and avoid inefficiencies and duplications by using shared, standardised and agreed methods. These in a continuous development cycle. One of the methods produced and used is the HTA Core Model ® (http://meka.thl.fi/htacore/BrowseModel.aspx). The idea behind the Model is the provision of a standard method for HTA evidence synthesis, structuring and presenting in a standard format to facilitate its use by network agencies and others.

The Core Model is divided into domains which represent the various aspects of the assessment of health technologies' research. Each domain contains a series of research questions or Assessment Elements (AEs). Ver 2.0 of the EUnetHTA Core Model is divided into domains:

1. Health problem and current use of technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Safety (SAF)
4. Clinical effectiveness (EFF)
5. Costs and economic evaluation (ECO)
6. Ethical analysis (ETH)
7. Organisational aspects (ORG)
8. Social aspects (SOC)
9. Legal aspects (LEG)

While using the Core Model in both Joint Actions 1 and 2 with the European Commission, Agenas identified some recurring common problems with the Core Model requiring further development work if the Model were to be used in the production of Health Technology Assessment reports in Italy.

The problems are mainly AE repetition, partial or complete overlap of AE content and likely answers, as well as lack of definition and clarity.

As a consequence Agenas undertook its own review of the Model to streamline its use and increase its relevance to everyday work of both HTA doers and HTA users. The Model basis for the review was version 2.0, medical and surgical intervention application.

The review process included a visual inspection of the 104 AEs with linked clarifications to identify any likely overlaps. The second phase consisted in grouping all AEs related to a unique concept (such as informed consent, technology and comparator(s) descriptions, regulatory information, mortality as a burden of illness measure, mortality as an outcome measure) into the likeliest domain of relevance. Agenas also attempted to link some of the text of each AE's clarification note more closely with the AE and corrected any English syntax problems. In addition a single AE containing multiple questions was divided into sub questions. All original AE identifiers were

maintained to denote the origin of the AE. To make identification of the information quicker and unpack some domains, Agenas also introduced two new domains REG or Regulatory Information and HAZ or Environmental Hazard for the assessment of possible harms not directly caused to the technology's recipient.

Agenas started using its Core Model adaptation for the 2014-2015 crop of Agenas HTA reports. Although some Agenas HTA reports are adaptations to Italy of up to date reports produced elsewhere or updates of previous Agenas work. In these cases the Agenas Core Model adaption use will be partial. Agenas plans to evaluate and develop the Model further.

Appendix 2 – List of selected Assessment Elements (AEs)

Domain: Health problem and current use of technology (CUR)

A0001a: For which health condition is the technology proposed?

Clarification: All relevant conditions and populations for which the technology is proposed should be included. This question is especially relevant when there are multiple potential target conditions and populations for which the technology is used, and multiple intended uses, both indicated and other.

A0001b: Which group of patients represents the target population for the technology?

Clarification: Describe the specific group(s) of patients on which the technology is used within the present assessment.

A0001c: For what purposes is the technology used?

Clarification: Describe the aims of the technology (in terms of benefits to the target population).

A0018: What are the alternatives to the current management of the health condition?

Clarification: Provide a brief overview of all the treatment alternatives. Refer to the latest guidelines and/or medical handbooks for a more detailed description.

A0011: What is the diffusion of the technology across the European countries?

Clarification: Provide national data (or estimates) of trend and current utilisation rates of the technology under assessment. Variations in utilisation reflect market access, sales figures, actual usage in hospital level and adherence to the use of the technology by both professionals and patients. Data on current and previous utilisation reflect the phase of the technology (experimental, emerging, established or obsolete). This also has implications for the availability of evidence and the level of uncertainties.

B0001b What is(are) the comparator(s)?

Clarification: This is relevant in all assessments. Use the descriptions of the comparator(s) defined in the scope of the project and elaborate them here in more detail. The term "comparator(s)" may include a single device, or a sequence of devices and procedures. The assessment should address all the competitor devices within a certain level. Describe in detail each of the devices identified in terms of type of device, mechanism of action.

B0003b What is the phase of development of the comparator(s)?

Clarification: Most technologies are introduced at approximately the same time in several countries. This information is relevant for the assessment while the evidence base may change rapidly for technologies that are at an earlier stage in their development. It is also important to establish whether new versions of the technology with substantial improvements are expected in the near future.

B0004b Who performs or administers the comparator(s)?

Clarification: Describe the following aspects:

- Which professionals (nurses, doctors, and other professionals) use the comparator(s)? Describe the staff involved in terms of skills and number of units.
- Do the patients themselves, or their carers, administer the comparator(s)?
- Which professionals select the patients, make referrals, decide to initiate the use of the comparator(s), or interpret the outcome?

B0005b In what context and level of care is(are) the comparator(s) used?

Clarification: Describe the level of care in which the comparator(s) is(are) used: self-care, primary care, secondary or tertiary care. If secondary or tertiary care, describe whether it is intended to be used in the outpatient or inpatient setting.

Domain: Description and technical characteristics of technology (TEC)

B0001: What is this technology?

Clarification: This is relevant in all assessments. Use the descriptions of the technology defined in the scope of the project and elaborate them here in more detail. The term "technology" may include a single device, or a sequence of devices and procedures. The assessment should address all the competitor devices within a certain level. Describe in detail each of the devices identified in terms of type of device, mechanism of action. Describe briefly how the devices differ from their predecessors.

B0003: What is the phase of development of the technology?

Clarification: Most technologies will be introduced at approximately the same time in several countries. This information is relevant for the assessment while the evidence base may change rapidly for technologies that are at an earlier stage in their development. Report when the technology has been introduced across the European countries and if new versions with substantial improvements are expected in the near future (6 months).

B0004: How is the technology used?

Clarification: Describe the following aspects:

- Which professionals (nurses, doctors, and other professionals) use the technology? Describe the staff involved in terms of skills and number of units.
- Do the patients themselves, or their carers, administer the technology?
- Which professionals select the patients, make referrals, decide to initiate the use of the technology, or interpret the outcome?

B0005: In which setting and level of care is the technology used?

Clarification: Describe the level of care in which the technology is used: self-care, primary care, secondary or tertiary care. If secondary or tertiary care, describe whether it is intended to be used in the outpatient or inpatient setting.

B0007: Does the technology require additional/special equipment/tools or accomodation?

Clarification: List those parts of the technology (devices, equipment, software, etc.) that need to be purchased (and often installed) by an organisation in order to use the technology. Includes need for back-up investment to cover for breakdowns in use.This may include a building programme.

B0009: What disposables and supplies are needed to use the technology?

Clarification: Describe all required disposable items necessary for using the technology, such as: syringes, needles, pharmaceuticals and contrast agents, fluids, bandages and tests to identify patients eligible for treatment.

F0001a: Is the technology new/innovative?

Clarification: Explain how the possible use/non-use of the technology would affect the current treatment process and practices. How substantial is the change to current practices? Notice that the technology may be in a different phase of utilisation for different health conditions or purposes of use.

F0001b: Is the technology a add-on, a replacement or a modification of the standard mode of care?

Clarification: Describe the role of the technology in the management pathway as: i) substitution technology; ii) additive or complementary.

Domain: Regulatory aspects (REG)

A0020: What is the marketing authorisation status of the technology?

Clarification: There are both international and national market authorisation systems. An overview of the status with regard to key processes, e.g. CE marking, EMA/FDA approval is recommended. Also information on national data and an analysis of possible discrepancies can be highly useful.

A0021: What is the reimbursement status of the technology across countries?

Clarification: Information on national reimbursement status from different countries for the technology. Notice that reimbursement status may differ for different purposes: e.g. treatment vs. prevention. Information on full coverage, co-payments, coverage under special circumstances/conditional coverage is useful.

I0015: Does the technology require further specific regulations?

Clarification: Report if the technology needs to follow a special regulatory pathway due to its nature (e.g., borderline medical device).

Domain: Safety (SAF)

C0001: What harms are associated with the use of the technology?

Clarification: Here one should identify and describe the direct harms of the use and he administration of the technology. User dependent harms are described in C0007, and comparative harms in C0008. Harms are identified in placebo-controlled trials, observational studies, vigilance and in registries. It is important to refer to the source and report separately harms identified in spontaneous reporting databases. Harms should be reported per indication or target population. The identified harms shoud be categorised according to their severity and frequency. The seriousness of harm is typically graded based on events that pose a threat to a patient's life or functioning. Frequency of occurrence for each harm is usually presented in comparison with placebo or no treatment, as percentages or risk ratios. Finally, the harms should be grouped by their severity and frequency and ordered so that the severe and/or frequent harms are presented first. If there are many different harms reported in the literature, concentrate on reporting the most serious and the most frequent harms.

Domain: Clinical effectiveness (EFF)

D0001: What is the effect of the intervention on all-cause mortality?

Mortality is the preferred, objective endpoint for assessments of life- threatening conditions. All-cause mortality is expressed either as mortality rates (incidence in given population, at given time point and usually risk standardised), or survival (number of people alive for a given period after an intervention). Several methods are used to adjust mortality rates and survival curves, e.g. relative survival (observed versus expected survival), which can be quite misleading; and hazard ratio (derived from a statistical method comparing the median survivals in the two groups). Note that progression-free survival is not a mortality endpoint; it describes the time from the beginning of an intervention until a patient shows signs of disease progression. Consider separately absolute mortality (compared to placebo or waiting list) and mortality relative to the comparator. See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf.

D0002: What is the effect on the disease-specific mortality?

Clarification: Disease-specific mortality is a proportion of the all-cause mortality. Even if a given treatment reduces one type of death, it could increase the risk of dying from another cause, to an equal or greater extent. Disease-specific mortality is typically presented as rates and as age- and risk- adjusted measures such as hazard ratio.

D0005a: How does the technology affect symptom frequency of the target condition?

Clarification: Describe the efficacy and effectiveness of the technology on frequency of relevant disease outcomes and other changes in physical and psychological conditions. Report changes in frequency of symptoms, both in absolute terms and relative to the comparator.

D0005b: How does the technology affect symptom severity of the target condition?

Clarification: Describe the efficacy and effectiveness of the technology on the severity of relevant disease outcomes. Outcomes such as function, quality of life and patient satisfaction are reported in other assessment elements of this domain. Report changes in severity of symptoms and findings, both in absolute terms and relative to the comparator.

D0005c: How does the technology affect symptom duration of the target condition?

Describe the efficacy and effectiveness of the technology on the duration of relevant disease outcomes. Outcomes such as function, quality of life and patient satisfaction are reported in other assessment elements of this domain. Report changes in duration of symptoms and findings, both in absolute terms and relative to the comparator.

D0012: What is the effect of the technology on generic health-related quality of life?

Clarification: Health related quality of life (HRQL) is typically measured with self- or interviewer-administered questionnaires to measure cross-sectional differences in quality of life between patients at a point in time (discriminative instruments) or longitudinal changes in HRQL within patients during a period of time (evaluative instruments). Two basic approaches to quality-of-life measurement are available: generic instruments that provide a summary of HRQL; and

specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Generic instruments include health profiles and instruments that generate health utilities. Each approach has its strengths and weaknesses and may be suitable for different circumstances. See also Methodological guideline for REA of pharmaceuticals: Health-related quality of life and utility measures.

http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf. If disease specific data are available, these can be reported separately.

D0014: What is the effect of the technology on work ability?

Clarification: Describe the effects of the intervention on sick leave, absenteeism from work or place of production return-to-work, retirement and other relevant outcomes describing working capacity.

D0015: What is the effect of the technology on return to previous living conditions?

Clarification: Re integration of a dischargee or patientto the living conditions in which patients lived before intervention is one of the most important intervention goals particularly for elderly patients.

D0018: Do differences in acceptability predict the overall uptake of the technology?

Clarification: Differences in acceptability may predict the overall uptake of the technology and would impact on the overall effectiveness.

Domain: Costs and economic evaluation (ECO)

E0001: Can you identify what types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?

Clarification: Report the resource items taken into account in the analysis of the assessed technology and its comparator(s), the reasons for their inclusion as well as the sources of information used when identifying these. It must be included the resources related to the use of the technology and/or resources due to the use of technology. It is relevant the analysis perspective for the identification of resources. Providing the results in tabular form is recommended. (e.g. length of stay in hospital).

E0002: Can you quantify what amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?

Report the quantity of resource required to estimate overall costs (e.g. 5 days of stay in hospital(E0009). Include the appropriate values, ranges, probability distributions as well as all references used. Providing the results in tabular form is recommended. Report the methods and data source(s) used to measure resource use associated with the technologies.

E0009: What were the measured and/or estimated unit costs of the resources used by the assessed technology and its comparator(s)?

For each technology report mean values of estimated costs and, where possible, information concerning distributions surrounding these estimates. Cost estimates from different viewpoints can be reported here (e.g., patient, hospital, societal). In addition, reporting disease-stage-specific cost estimates and costs estimated using varied discount rates. Providing the results in tabular form is recommended.

E0005: What is(are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?

For each technology report mean values of estimated effects and, where possible, information concerning distributions surrounding these estimates. It is suggested that estimates are expressed both in natural units, whenever possible, and in alternative forms, such as QALYs. Report the methods and data source(s) used to estimate the outcomes associated with the technologies.

E0006: What are the estimated differences in costs and outcomes between the technology and its comparator(s)?

There are numerous ways of calculating or comparing the differences in the costs and effects of the assessed technology and its comparator(s); typically, one or more of the following approaches are used when reporting the results of health-economic evaluations: - listing the costs and outcomes of each technology in tabular form - an incremental cost-effectiveness ratio (ICER) - an incremental cost effectiveness plane or efficiency frontier - the net monetary benefit (NMB) and/or net health benefit (NHB).

E0010: What are the uncertainties surrounding the inputs and economic evaluation(s) of the technology and its comparator(s)?

The effects of uncertainty should be reported separately for parameter values, assumptions and analytical methods used in the analysis, whenever possible. For example: - deterministic sensitivity analysis in tabular form or using a Tornado diagram - probabilistic sensitivity analysis, e.g., in the form of a CEAC - value-of-information analysis. The methods used in the sensitivity analysis should be reported in detail here.

G0007: What are the likely budget impacts of implementing the technologies being compared?

Whenever a technology is introduced, there will be an impact on health care budgets. Budget impact analysis attempts to examine the likely impact of introducing a technology on financial outlays from, e.g., the perspective of different payers. Different payers include: government-level institutions; regions; municipalities; employers; insurance companies and patients/participants. The relevant perspective from which to estimate budget impact may change during different phases of the management process Budget impact analysis provides data to inform an assessment of the affordability of a technology. It also provides a service planning tool to inform decisions about taking the technology into use.

Appendix 3 – Questions for the manufacturer/distributor

Dear manufacturer/distributor, we are sending you this request to integrate the information and data available to us to produce our Health Technology Assessment report for the Ministry of Health (MoH). This will be a public document, so we ask you not release any information which you would not like to see in print. Please also be aware that the aim of the HTA document is to conduct a factual assessment of the performance of this class of devices. We are interested in the factual accuracy of the document but the interpretation of those facts is our role. Thank you for your help. Your help will be acknowledged is you so wish after the public consultation phase on the MoH website.

Manufacturer/Distributor:

Contact Person:

Health problem and current use of technology

1. Which group of patients represents the target population for your technology?
2. Are there similar devices that can be considered as "competitors" of your sutureless aortic valve? (please specify device names and manufacturers)
3. Which other devices or therapies can be considered as the main comparators of the sutureless aortic valve?
4. Are there specific ICD9-CM codes that identify the procedure of implantation of sutureless aortic valve (and comparators) in the hospital discharge database?
5. Are there registers of the implantations of the technology?

Description and technical characteristics of technology

6. What is the phase of development of the model currently on the market?
7. How many versions/evolutions of the device have been launched between 2005 and 2015?
8. Which professionals decide on the use of the technology?
9. Which professionals (nurses, doctors, and other professionals) use the technology? Describe the staff involved in terms of skills and number of units.
10. Does the technology require specific equipment/tools?
11. What disposables and supplies are needed to use the technology?
12. Does the technology require specific equipment/tools? If yes, please provide descriptions and CND codes for all of them.

Regulatory aspects

13. Has your device obtained the CE mark? If yes, When? (please report month and year)
14. Has your device been approved by the FDA?
    14.a If yes, When? (Please report month and year)
    14.b If not, please report details on the FDA approval status (if any).
15. When was your device launched in Italy?
16. What is the reimbursement status of the technology in Italy?
17. Does the technology require further specific regulations?

Clinical Effectiveness and Safety

18. Are there comparative clinical studies (on humans) published/ongoing aimed to compare your device versus other treatments? (if yes, please report full references)
19. Are there non-comparative clinical studies (on humans) published/ongoing aimed to report on effectiveness and safety of your device? (if yes, please report full references)
20. Is there any register for data collection and patient's follow-up? If yes, who runs it? (please specify web-link and/or key-person name and e-mail address)
21. Can you specify the ID number(s) of the ongoing trial?

Costs and economic evaluation

22. What is the list price of your sutureless aortic valve? (please, indicate the price, VAT excluded, for all the equipment needed for the implantation procedure)
23. Please fill the table below with all the relevant items for a single implantation procedure:

Item	Number of units	Price per unit (VAT excluded)

24. Are there economic evaluation studies published/ongoing reporting on your sutureless aortic valve? (if yes, please report full references)

Other questions:

25. Is a specific training provided to the staff?
    25.a If yes, who provide it?
    25.b How much this training costs and who fund it?
26. Do you have any report about the learning curve of the implantation procedure? (please report full reference).
27. How does the implantation procedure of your device differ from the conventional one in terms of additional/special equipment/tool or surgical complexity?
28. At today, how many of your sutureless aortic valves have been implanted in Italy? How many around the world?
29. At today, how many Italian hospitals implanted your sutureless aortic valve? (Please specify if private or public providers).

Appendix 4 – Search strategy effectiveness domain.

MEDLINE

MESH descriptor: Aortic valve stenosis" OR "aortic valve replacement" OR AVR OR aortic valve* stenosis OR "aortic stenosis" OR aortic surgery; OR cardiac surgery; OR "aortic valve replacement*" OR " aortic disease*" OR aortic calcification* OR valve calcification* OR MESH descriptor: "Heart Valve Prosthesis" OR MESH descriptor: "aortic valve/surgery" OR TAVI	AND	"sutureless aortic valves" OR ("Sutureless prostheses" AND "aortic valve") OR "3f Enable prosthesis" OR Perceval "	AND	MESH descriptor: Safety OR Safety OR Effectiveness OR MESH descriptor: Comparative Effectiveness Research OR MESH descriptor: "quality of life" OR MESH descriptor: "Return to work" OR MESH descriptor: "Patient Satisfaction" OR MESH descriptor: "Hospitalization OR MESH descriptor:"Patient discharge" Ricerca in [Title/Abstract] per OR "return-to-work" OR "Back-to-Work" OR Acceptability OR "Acceptability of Health Care" OR "Patient Acceptance" OR Complications OR pain MESH descriptor: Survival Rate OR MESH descriptor:	AND	MESH descriptor: Aged OR Elderly OR "over 70" OR "over 80"

				Treatment Outcome OR MESH descriptor: "Postoperative Complications/epidemiology" "Adverse events" OR "side effects" OR "renal failure" OR " neurological events" OR endocarditis OR "structural valve deterioration"		

EMBASE

'aortic valve'/exp OR 'aortic valve disease'/exp OR 'heart valve stenosis'/exp OR 'heart valve prosthesis'/exp OR 'heart valve bioprosthesis'/exp OR 'valvular heart disease'/exp OR 'aortic valve replacement'/exp OR TAVI	AND	(sutureless AND aortic AND valves) OR (sutureless AND ('prostheses'/exp OR prostheses)) OR sutureless OR "3f Enable prosthesis" OR Perceval	AND	EMTREE TERM: 'quality of life'/exp OR EMTREE TERM: work capacity/exp OR EMTREE TERM: 'life satisfaction'/exp OR EMTREE TERM: 'patient satisfaction'/exp OR EMTREE TERM: 'patient information'/exp OR "quality of life" OR QoL OR satisfaction OR "working staus" OR (Patients AND (satisfaction OR "working status" OR OR "return-to-work" OR "Back-to-Work" OR Acceptability OR "Acceptability of Health Care" OR "Patient Acceptance" OR Complications OR pain OR 'risk assessment'/exp OR 'device safety'/exp OR 'device failure analysis'/exp OR 'clinical effectiveness'/exp OR 'comparative effectiveness'/exp OR 'program effectiveness'/exp OR 'program evaluation'/exp OR 'program	AND	'aged'/exp OR 'very elderly'/exp OR "over 70" OR "over 80"

				acceptability'/exp OR Safety/exp OR Effectiveness OR Comparative Effectiveness Research Survival Rate OR Treatment Outcome OR "Postoperative Complications" "Adverse events" OR "side effects" OR "renal failure" OR "neurological events" OR endocarditis OR "structural valve deterioration"		

CLINICALTRIALS.GOV

Aortic Aortic Valve aortic valve replacement Aortic Valve Stenosis Stenosis Aortic Valve Stenosis ValveAortic aortic valve replacement	AND	Sutureless OR (minimally AND invasive) OR Perceval OR 3f

Appendix 5 – Effectiveness domain. List of excluded studies

Study ID	Reason for exclusion	Reference
Concistre 2013	Both comparisons received sutureless - AVR	Concistre G, Santarpino G, Pfeiffer S *et al*. Two alternative sutureless strategies for aortic valve replacement: a two-center experience. Innovations (Phila) 2013
D'Onofrio A 2012	propensity-matched, multicenter study (retrospective analysis of data registry)	D'Onofrio A, Messina A, Lorusso R *et al*. Sutureless aortic valve replacement as an alternative treatment for patients belonging to the "gray zone" between transcatheter aortic valve implantation and conventional surgery: a propensity-matched, multicenter analysis. J Thorac Cardiovasc Surg 2012; 144(5):1010-6
D'Onofrio A 2012	propensity-matched, retrospective analysis	D'Onofrio A, Rizzoli G, Messina A *et al*. Conventional surgery, sutureless valves, and transapical aortic valve replacement: what is the best option for patients with aortic valve stenosis? A multicenter, propensity-matched analysis. J Thorac Cardiovasc Surg 2013; 146(5):1065-70;
Doss 2012	Article not found	Doss M, Buhr E, Moritz A, Martens S. Sutureless aortic valve replacement: catheter-based transapical versus direct transaortic implantation. J Heart Valve Dis 2012; 21(6):758-63.
Grubitzsch 2005	Comparison between older stentless and newer generation stentless pericardial valves	Grubitzsch H., Linneweber J., Kossagk C., Sanli E., Beholz S., Konertz W.F. Aortic valve replacement with new-generation stentless pericardial valves: Short-term clinical and hemodynamic results. J. Heart Valve Dis. 2005; 14(5):623-9.
Karimov 2013	Article not found	Karimov JH, Massiello AL, Fukamachi K. Overview of current sutureless and transcatheter mitral valve replacement technology. Expert Rev Med Devices 2013; 10(1):73-83
Konig 2014	Article not found	Konig KC, Wahlers T, Scherner M, Wippermann J. Sutureless Perceval aortic valve in comparison with the stented Carpentier-Edwards Perimount aortic valve. J Heart Valve Dis 2014;
Pollari 2012	propensity-matched, retrospective study	Pollari F, Santarpino G, Dell'Aquila AM *et al*. Better short-term outcome by using sutureless valves: a propensity-matched score analysis. Ann Thorac Surg 2014; 98(2):611-6; discussion 616-7
Pope 2014	Narrative review	Pope NH, Ailawadi G. Minimally invasive valve surgery. J Cardiovasc Transl Res 2014; 7(4):387-94.
Raja 2013	Narrative review	Raja SG. Sutureless aortic valve replacement using perceval s valve. Recent Pat Cardiovasc Drug Discov 2013; 8(2):75-80.
Santarpino 2014	propensity-matched, retrospective study	Sutureless replacement versus transcatheter valve implantation in aortic valve stenosis: A propensity-matched analysis of 2 strategies in high-risk patients. J. Thorac. Cardiovasc. Surg. 2014
Sepehripour 2012	Narrative review	Sepehripour AH, Harling L, Athanasiou T. What are the current results of sutureless valves in high-risk aortic valve disease patients? Interact Cardiovasc Thorac Surg

		2012
Wendt 2009	Narrative review	Wendt D, Thielmann M, Pizanis N, Janosi RA, Kamler M, Jakob H. Sutureless aortic valves over the last 45 years. Minim Invasive Ther Allied Technol 2009; 18(3):122-30
Yang 2013	Comparison between stented pericardial valve in a Valsalva graft (Gen1) and with the stentless 3f valve (Gen2); retrospective cohort study	Yang J.A., Neely R.C., Stewart A.S. Modified bentall procedure with composite biologic grafts. J. Card. Surg. 2013; 28(6):731-5.
Zannis 2012	All pts received sutureless - AVR	Zannis K, Folliguet T, Laborde F. New sutureless aortic valve prosthesis: another tool in less invasive aortic valve replacement. Curr Opin Cardiol 2012; 27(2):125-9.

Appendix 6 – Search strategy economic domain

RICERCA MEDLINE

	AND		AND		AND	
MESH descriptor: Aortic valve stenosis" OR "aortic valve replacement" OR AVR OR aortic valve* stenosis OR "aortic stenosis" OR aortic surgery; OR cardiac surgery; OR "aortic valve replacement*" OR " aortic disease*" OR aortic calcification* OR valve calcification* OR MESH descriptor: "Heart Valve Prosthesis" OR MESH descriptor: "aortic valve/surgery" OR TAVI		"sutureless aortic valves" OR ("Sutureless prostheses" AND "aortic valve") OR "3f Enable prosthesis" OR Perceval "		Mesh descriptor ""Costs and Cost Analysis" OR Mesh descriptor "Economics" OR Mesh descriptor "Cost Allocation" OR Mesh descriptor "Cost-Benefit Analysis" OR Mesh descriptor "Cost of Illness" OR Mesh descriptor "Cost Control" OR Mesh descriptor "Cost Savings" OR Mesh descriptor "Health Care Costs" OR Mesh descriptor "Direct Service Costs" OR Mesh descriptor "Hospital Costs" OR Mesh descriptor "Efficiency, Organizational/economics Cost-effectiveness [Title/Abstract] OR Cost-utility [Title/Abstract] OR Cost – effectiveness [Title/Abstract] OR Cost – utility [Title/Abstract] OR "resource used" [Title/Abstract] OR		MESH descriptor: Aged OR Elderly OR "over 70" OR "over 80"

				"Cost effectiveness analysis" *[Title/Abstract] OR CMA (title/abstract) OR "cost effectiveness" (title/abstract) OR CEA (title/abstract) OR "cost utility" (title/abstract) OR CUA (title/abstract) OR CEA [Title/Abstract] "Cost utility analysis " [Title/Abstract] OR "Cost benefit analysis" [Title/Abstract] OR "Cost consequences analysis "*[Title/Abstract] OR " Cost minimization analysis" *[Title/Abstract] OR (economic AND (evaluation OR analysis OR aspect OR assessment)) [Title/Abstract] OR "Budget Impact Analysis" [title/abstract]		

RICERCA EMBASE 14

'aorta valve'/exp OR 'aorta valve disease'/exp OR 'heart valve stenosis'/exp OR 'heart valve prosthesis'/exp OR 'heart valve bioprosthesis'/exp OR 'valvular heart disease'/exp OR 'aorta valve replacement'/exp OR TAVI	AND	(sutureless AND aortic AND valves) OR (sutureless AND ('prostheses'/exp OR prostheses)) OR sutureless OR "3f Enable prosthesis" OR Perceval	AND	"Economic aspect"/exp OR 'cost analysis'/exp OR 'cost of illness'/exp OR " economic evaluation"/exp OR 'cost minimization analysis'/exp OR CMA:ab,ti 'cost effectiveness analysis'/exp OR CEA:ab,ti OR OR 'cost benefit analysis'/exp OR 'cost utility':ab,ti OR CUA:ab,ti OR 'hospitalization cost'/exp 'health care cost'/exp OR (economic AND ('evaluation'/exp OR 'analysis'/exp OR aspect OR assessment)) OR ('budget impact analysis':ab,ti OR BIA:ab,ti)" OR Cost Analysis/:ab,ti OR "Economics"/:ab,ti OR "Cost Allocation"/:ab,ti OR "Cost-Benefit/:ab,ti OR "Cost Control"/exp OR "Cost Saving"/:ab,ti	AND	'aged'/exp OR 'very elderly'/exp OR "over 70" OR "over 80"

				OR "Cost-effectiveness"/:ab,ti OR "Cost-utility"/:ab,ti		

Ricerca econlit

Aortic Aortic Valve aortic valve replacement Aortic Valve Stenosis Stenosis Aortic Valve Stenosis ValveAortic aortic valve replacement	AND	Sutureless OR (minimally AND invasive) OR Perceval OR 3f

Appendix 7 – Economic domain. List of excluded studies

Posters and abstracts

Meuris B., Verbrugghe P., Sainte S., De Praetere H., Rega F. Sutureless aortic valves save hospital costs when compared to traditional valves. Interact. Cardiovasc. Thorac. Surg. 2014; 19:S6.

Pollari F., Santarpino G., Dell'Aquila A.M. et al. Cost reduction and improve outcome by using sutureless prosthesis. Thorac. Cardiovasc. Surg. 2014; 62.

Pradelli L., Giardina S., Ranucci M. Lifetime cost-effectiveness of concomitant aortic valve replacements in France and the United Kingdom. Value Health 2013; 16(7):A531.

Pradelli L., Giardina S., Ranucci M. Lifetime cost-effectiveness of isolated and concomitant aortic valve replacements in Germany. Value Health 2013; 16(7):A531.

Pradelli L., Giardina S., Ranucci M. Lifetime cost-effectiveness of isolated aortic valve replacements associated with the mini-inva sive implantation of a new sutureless and collapsed valve in France and United Kingdom. Value Health 2013; 16(7):A530.

Pradelli L., Zaniolo O., Giardina S., Ranucci M. Outcomes and costs of concomitant aortic valve replacements associated with a new sutureless and collapsed valve in Italy, france, Germany, and the UK. Value Health 2012; 15(7):A281..

Pradelli L., Zaniolo O., Giardina S., Ranucci M. Outcomes and costs of isolated aortic valve replacements associated with the mini-invasive implantation of a new sutureless and collapsed valve in Italy, France, Germany, and UK. Value Health 2012; 15(7):A350.

Santarpino G., Giardina S., Pollari F., Vogt F., Pfeiffer S., Fischlein T. Cost saving after sutureless replacement in aortic valve stenosis: Results from a propensity-matched score analysis in Germany. Value Health 2013; 16(7):A520.

Not presenting costs data

Pollari F, Santarpino G, Dell'Aquila AM et al. Better short-term outcome by using sutureless valves: a propensity-matched score analysis. Ann Thorac Surg 2014; 98(2):611-6; discussion 616-7.