A report for
Universitätsklinikum Schleswig-Holstein/Campus Kiel
on shared decision making
for heart valve replacement

Kleijnen Systematic Reviews Ltd

March 2019

Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York
YO19 6FD
United Kingdom
Telephone: +44 (0)1904 727980
Fax: +44 (0)1904 720429
Email: robert@systematic-reviews.com
Website: www.systematic-reviews.com

Thea Drachen
Steve Ryder
Vanesa Huertas Carrera
Kate Misso
Heike Raatz
Jos Kleijnen
Robert Wolff

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AHA/ACC	American Heart Association/American College of Cardiology
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
COR	Class of recommendation
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
FAQ	Frequently asked question
G-I-N	Guidelines International Network
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HTA	Health technology assessment
INR	International normalised ratio [of blood clotting]
KSR	Kleijnen Systematic Reviews Ltd
LMWH	Low-molecular-weight heparin
LOE	Level of evidence
MA	Meta-analysis
MI	Myocardial infarction
NA	Not applicable
NHP	Nottingham Health Profile
NHS	National Health Service
NOAC	Non-vitamin K antagonist anticoagulation
NOS	Newcastle-Ottawa-Scale
NYHA	New York Heart Association functional class
PICOS	Participants, intervention, comparators, outcomes and study design
PVD	Peripheral vascular disease
QoL	Quality of life
RCT	Randomised controlled trial
RR	Risk ratio
SDM	Shared decision making
SF-12	Short Form Health Survey-12
SF-36	Short Form Health Survey-36
SF-36v2	Short Form Health Survey-36 version 2
SR	Systematic review
TAVR	Transcatheter aortic valve replacement
UFH	Unfractionated heparin
USA	United States of America
VKA	Vitamin K antagonist

1. PROJECT OBJECTIVE

Kleijnen Systematic Reviews Ltd (KSR) has prepared this report to enable patients to elicit their preference between mechanical and bioprosthetic valves for the treatment of heart valve disease.

This is part of the research project “Making SDM a reality” which aims to create interactive websites to inform patients as part of shared decision making (SDM).

2. METHODS

2.1 INCLUSION CRITERIA

The research question underpinning the literature searches for this topic was developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The question was framed in terms of participants, intervention, comparators and outcomes (PICOS), see Table 1.

As detailed below, literature searches were carried out using a stepwise approach to identify relevant studies according to study design. In the first step, searches aimed to identify relevant systematic reviews and guidelines. For this project, no further searches were conducted as relevant results were extracted from the identified literature.

Table 1: Inclusion criteria for searches

PICOS	
Patient population	Patients with indication for heart valve surgery (e.g. severe aortic/mitral stenosis/regurgitation)
Intervention/Comparators	Mechanical valve Bioprosthetic valve. Also called tissue valve (from animal donor)
Outcomes	• Survival/life expectancy • Risk of thromboembolic events: HR stroke and bleeding • Risk of re-operation • Risk of infection • Risk of malfunction • Quality of Life • Impact on daily living
Study design	Systematic reviews (SR)/meta-analyses (MA) of randomised controlled trials (RCTs), or of studies of lower evidence levels (non-randomised/observational studies), if needed. If no SRs/MAs are available, respective primary studies have to systematically searched

In consultation with the commissioner, questions frequently asked by patients in conjunction with outcomes identified in the literature were developed into an evidence table outline.

2.2 FREQUENTLY ASKED QUESTIONS

The following research questions were identified as frequently asked questions (FAQs):

- FAQ 1: What does the treatment involve?
- FAQ 2: How will I benefit from treatment?
    a) Survival/life expectancy
    b) Quality of Life
- FAQ 3: Which side effects or complications might occur?
    a) Risk of thromboembolic events: HR stroke and bleeding
    b) Risk of re-operation
    c) Risk of infection
    d) Risk of malfunction

- FAQ 4: How does the treatment impact my daily living?

2.3 LITERATURE SEARCHES

Literature searches were carried out to identify relevant systematic reviews and guidelines on bio-prosthetic and mechanical heart valves. As relevant reviews and guidelines were retrieved, it was not necessary to conduct additional searches for primary studies.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines to 2014-2018. Where appropriate, searches were limited to remove animal studies. Searches were not limited by language or publication status.

2.4 SEARCH SOURCES

Systematic reviews and guidelines

The following systematic review specific databases were searched from 2014 to present:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 1/ Jan 2019: 2014-2019
- Database of Abstracts of Reviews of Effects (DARE) (CRD): 2014-2015/03/31
- Health Technology Assessment (HTA) database (CRD): 2014-2018/03/31
- KSR Evidence (Internet): 2014-2019/01/15
  https://ksrevidence.com/
- Epistemonikos (Internet): 2014-2019/01/15

The following guidelines resources were searched from 2014 to present:

- Guidelines International Network (G-I-N) (Internet): 2014-2019/01/15
  http://www.g-i-n.net/library/international-guidelines-library
- NHS Evidence (Internet): 01/01/2014-15/01/2019
  www.evidence.nhs.uk/
- ECRI Guidelines Trust (Internet): 2014-2019/01/15
  https://guidelines.ecri.org/

Full details of all search strategies are presented in Appendix 1.

Handling of citations

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

Supplementary searches

In addition, internet searches were performed to add more qualitative patient-related information to inform the more narrative FAQs.

2.5 METHODS OF STUDY SELECTION, QUALITY ASSESSMENT AND DATA EXTRACTION

Literature searches

Literature searches were conducted on 14 and 15 January 2019 to identify evidence to inform questions (frequently asked questions; FAQs) and to answer these FAQs focusing on systematic reviews, meta-analyses and evidence-based guidelines.

For this evidence report, searches for systematic reviews and guidelines were supplemented by targeted web searches to find information for the more narrative FAQs 1 and 4.

Study selection

Two reviewers independently screened the title and abstract of each record identified by the search and determined the potential relevance of each record. For potentially relevant records, the full paper was obtained, independently checked, and inclusion criteria applied. Any disagreements were resolved through discussion.

An evidence hierarchy was used to select the most appropriate study(ies) to populate the evidence tables. Where more than one study could provide evidence, the most relevant studies were selected using the following criteria: recency (most recent preferred), quality (highest quality preferred), representativeness (populations representative of the general target population preferred). Where there were gaps in the evidence (no systematic review or guideline available), as described before, relevant RCTs would have been searched for and extracted, and where no RCTs would have been identified, observational studies would have been employed.

Data extraction

For each study, data were extracted by one reviewer and checked by another. Any disagreements were resolved by consensus.

3. RESULTS

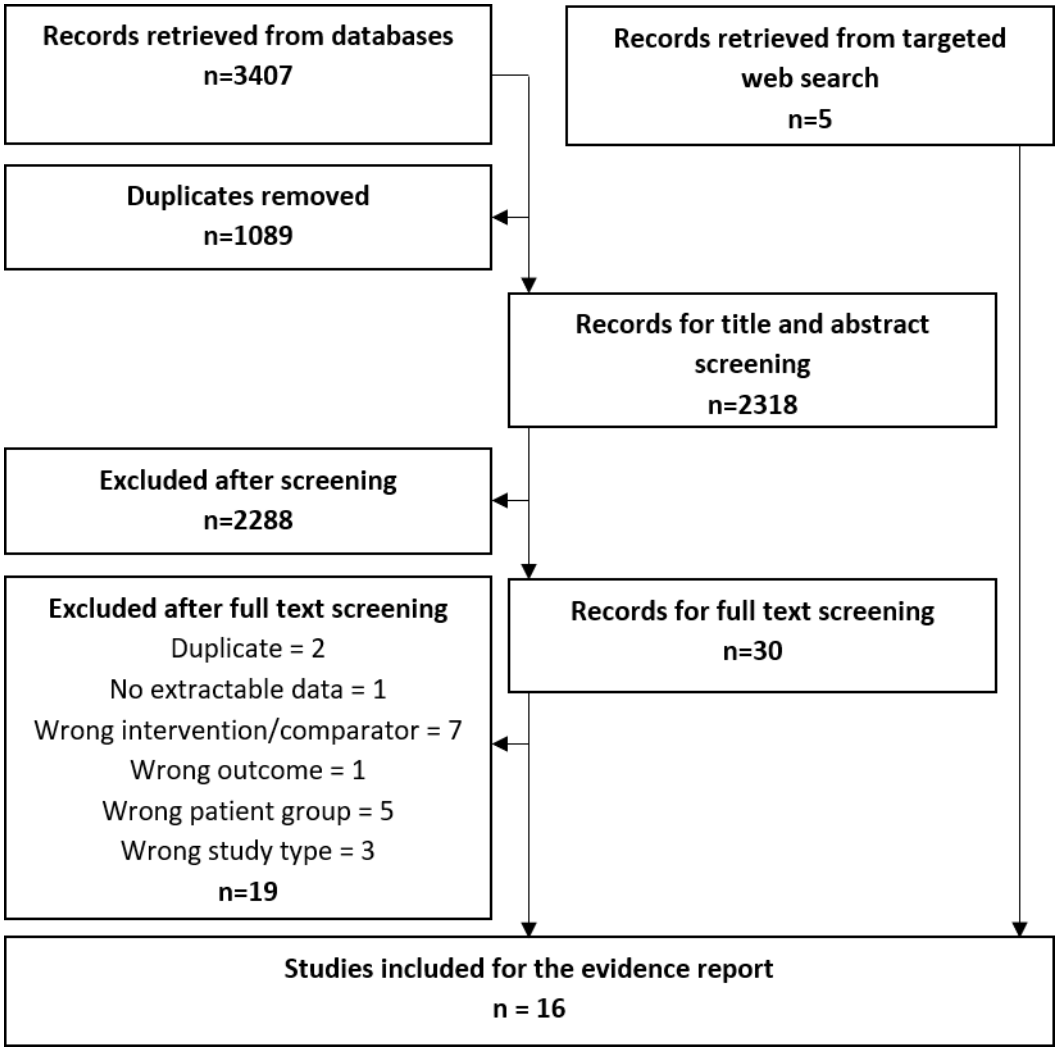
3.1 LITERATURE SEARCH RESULTS AND INCLUSION ASSESSMENT

A total of 3,407 records were retrieved from literature searches. After de-duplication, 2,318 titles and abstracts were screened by two reviewers. Full papers were obtained for 30 records (41 including background). After further review, 19 records were excluded. In addition, internet searches were performed and retrieved five records. Thus 16 records were selected for this report, please see Table 2.

An additional 30 publications were identified and used as reference material, all of which were primary studies used in some of the seven already included papers.

A summary of the study selection process according to a modified PRISMA flow chart is reported in Figure 1.

Figure 1: Study selection process



3.2 OVERVIEW OF THE EVIDENCE

Table 2 summarises the 15 selected studies used to answer the FAQs.

Table 2: Evidence sources

Study ID	What does it involve?	How will I benefit from treatment?	Which side effects/complications?	Will it impact my daily life?
ESC/EACTS 2017 Guideline[1]				✓ antithrombotic
AHA/ACC 2017 focused guideline update[2]				✓ antithrombotic
American Heart Association Inc. 2019[3]	✓			
Bashir 2017[4]		✓	✓	
British Heart Foundation[5]				✓ recovery
Diaz 2018[6]		✓	✓	
Head 2017[7]			✓	
Kiyose 2019[8]		✓	✓	
Koertke 2003[9]				✓ noise
Korteland 2016[10]				✓ noise
Liu 2016[11]		✓	✓	
Magliano 2015[12]		✓	✓	
Nishimura 2014[13]				✓ antithrombotic
Taghadosi 2014[14]				✓ antithrombotic
Tao 2017[15]		✓	✓	
Zhao 2016[16]		✓	✓	

FAQ 1: What does the treatment involve?

Table 3: Description of treatments

Bioprosthetic Valve
This is made from animal-based material, typically porcine or bovine. Bioprosthetic valves can last 10-20 years, and usually do not require the long-term use of medication. For a young person with a tissue valve replacement, the need for additional surgery or another valve replacement later in life is highly likely. For each surgery in which the valve must be replaced, careful considerations should be given to durability and medication options and risks. Well-performed operations have a high probability of success.
Mechanical Valve
This is made from synthetic material. These valves are made of strong durable materials. They are the most long-lasting type of replacement valve, and most of these manufactured valves will last throughout the remainder of the patients' lifetime. Patients who receive a manufactured valve will nearly always require a blood thinning medication throughout the remainder of their lives. The blood thinner will keep clots from forming, which is critical for the person with a mechanical valve because clots can lodge in the valve

flaps or hinges and cause a malfunction. Clots can also break off and form into an embolism (traveling clot), which may move through the bloodstream and lodge into a vessel where it may eventually lead to problems like heart attack or stroke.
From: American Heart Association[3]

FAQ 1: EVIDENCE SUMMARY

What does the treatment involve?

Bioprosthetic Valve

This is made from animal-based material, typically porcine or bovine.

Bioprosthetic valves can last 10-20 years, and usually do not require the long-term use of medication. For a young person with a tissue valve replacement, the need for additional surgery or another valve replacement later in life is highly likely. For each surgery in which the valve must be replaced, careful considerations should be given to durability and medication options and risks. Well-performed operations have a high probability of success.

Mechanical Valve

This is made from synthetic material.

These valves are made of strong durable materials. They are the most long-lasting type of replacement valve, and most of these manufactured valves will last throughout the remainder of the patients' lifetime. Patients who receive a manufactured valve will nearly always require a blood thinning medication throughout the remainder of their lives. The blood thinner will keep clots from forming, which is critical for the person with a mechanical valve because clots can lodge in the valve flaps or hinges and cause a malfunction. Clots can also break off and form into an embolism (traveling clot), which may move through the bloodstream and lodge into a vessel where it may eventually lead to problems like heart attack or stroke.

FAQ 2: How will I benefit from treatment?

a) Survival/life expectancy
b) Quality of Life

FAQ 2a: How does the treatment impact my life expectancy?

Nine different publications were included in this review as of relevance (Nishimura 2014[13]; Head 2017[7]; Zhao 2016[16]; Bashir 2017[4]; Kiyose 2019[8]; Diaz 2018[6]; Liu 2016[11]; Magliano 2015[12] and Tao 2017[15]). Amongst these publications the American Heart Association/American College of Cardiology (AHA/ACC) guidelines were included for issuing recommendations that were based on survival as well as other outcomes.[13] The remaining eight publications were reviews providing results on survival ratios or survival rates.[4, 6-8, 11, 12, 15, 16]

Of the eight included reviews, the review authored by Kiyose 2019[8] was prioritised as a key reference because of its recent publication. Additionally, this review was the only review which excluded observational studies in its selection of the primary evidence.

The eligibility criteria described by Kiyose 2019[8] excluded observational studies as well as studies in children or studies of patients who required tricuspid valve replacement. It included four randomised trials totalling 1,528 participants: Vallejo 1981[17]; Stassano 2009[18]; Veterans 2000[19]; Edinburgh 2003[20]). The mean follow-up for these studies was 2, 8.8, 15 and 20 years respectively.

Through random meta-analysis, Kiyose 2019[8] reported no statistically significant difference for the risk of death between bioprosthetic or mechanical valves, though it is noted how the greatest part of the confidence interval favours mechanical valves (risk ratio (RR) = 1.07; 95% confidence interval (CI) 0.99 to 1.15). These results were confirmed in the subgroup analyses for aortic, mitral or both aortic and mitral valves.[8] These results are available in Table 4.

In terms of quality, though none of the included studies in Kiyose 2019[8] described how the randomisation was made they were all deemed to be at low risk of bias for the remaining domains, albeit blinding was not possible for patients or health professionals. Additionally, the estimated effect was judged of a good precision and absent of serious inconsistency. In contrast, the authors highlight that three of the four included trials were old and employed first generation biological prosthesis and single disk prostheses.[8]

In addition to Kiyose 2019,[8] the review authored by Zhao 2016[16] was selected as highly relevant because of its pragmatic age subgroup analyses. However, notably, this review excluded studies carried out in participants older than 70 years, as well as those that did not specify the age of the patients or were based on an actuarial survival rate.[16] As a result, it included 12 primary studies totalling 8,661 participants (Carrier 2001[21]; Kulik 2006[22]; Prasongsukam 2007[23]; Brown 2008[24]; Stassano 2009[18]; Weber 2012[25]; Chiang 2014[26]; Nishida 2014[27]; McClure 2014[28]; Glaser 2016[29]; Wang 2016[30] and Roumieh 2015[31]). The mean follow-up for these studies ranged from 2.8 ± 2 years[25] to a maximum of 10.9 ± 0.6 years.[27]

Zhao 2016[16] reported a statistically significant difference result for the pooled overall mortality between bioprosthetic and mechanical valves that favoured the latter (hazard ratio (HR) = 1.21; 95% CI 1.02 to 1.43). However, subgroup analyses resulted in no significant difference for the 50-70 years of age (HR = 1.13; 95% CI 0.89 to 1.45) or 60-70 years of age (HR = 0.87; 95% CI 0.66 to 1.15). In contrast, statistically significant results were reported for those participants younger than 65 years of age favouring mechanical valves (HR = 1.47; 95% CI 1.10 to 1.96). Further, two of the included studies were pooled for an estimate of cardiac mortality which resulted in no statistically significant difference for either type of prosthesis (HR = 1.11; 95% CI 0.81 to 1.51).

Critically, amongst the limitations noted by Zhao 2016[16], the authors state that a predominance of participants aged less than 50 years old in the less than 65 years old group could have been decisive in the resulted significant difference between valves for this group. Other limitations highlighted by the authors are that all included studies were observational and hence liable to selection bias. In addition to this, the accuracy of the estimates could have suffered as a result of employing Digitizelt software to extract data from the primary studies. The data of the primary studies was thus interpreted by a software programme rather than a human.

Table 4: Survival with mechanical compared to bioprosthetic heart valve replacement

Studies	Design	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Subgroup	I^2	RR (95% CI)	Quality
4: Edinburgh 2003[20]; Stassano 2009[18]; Veterans Affairs 2000[19]; Vallejo 1981[17]	RCTs	No serious	No serious	Direct	No serious	Unlikely	All Bioprosthetic n=748 Mechanical n=780	22%	1.07 (0.99 to 1.15)	HIGH
3: Edinburgh 2003[20]; Stassano 2009[18]; Veterans Affairs 2000[19]	RCTs	No serious	No serious	Direct	No serious	Unlikely	Aortic valve	51%	1.10 (0.94 to 1.28)	HIGH
3: Edinburgh 2003[20]; Vallejo 1981[17]; Veterans Affairs 2000[19]	RCTs	No serious	No serious	Direct	No serious	Unlikely	Mitral valve	0%	1.01 (0.92 to 1.11)	HIGH
1: Edinburgh 2003[20]	RCT	No serious	No serious	Direct	No serious	Unlikely	Mitral + aortic valve Bioprosthetic n=266 Mechanical n=267	n/a	1.16 (0.91 to 1.49)	HIGH

From Kiyose 2019[8] tables 1 and 3, figure 2 and text
CI = confidence interval; I^2 = Higgins inconsistency test; NA = not applicable; RCT = randomised controlled trial; RR = risk ratio

FAQ 2b: How does the treatment impact my quality of life?

Of the included evidence, only one reported on quality of life (QoL) as an outcome.[7] This systematic review failed to identify any randomised control trials reporting on QoL but did identify six observational studies which reported on QoL experienced by patients undergoing either mechanical or bioprosthetic valve replacement.[32-37] All of these six studies suggest little or no difference in the QoL changes experienced by patients treated with either type of procedure and the key findings are summarised here.

1. Aboud 2009[36] assessed 53 patients with bioprostheses (mean age of 74 years), and 83 patients with mechanical prostheses (mean age of 64 years) who had undergone valve replacement 18-24 months previously. The main QoL instrument was SF-36 and the QoL in patients with mechanical and bioprosthetic valves was similar although physical functioning scores were reported as significantly better in patients undergoing a mechanical prosthesis. However, this difference is likely affected by the difference in mean age between the two valve patient groups. Mean score being 74.8 (12.2 SD) for mechanical and 51.3 (13.6 SD) for bioprosthetic. This being said, it is difficult to substantiate this finding from the evidence presented in the paper and, as no baseline values were assessed, it is not possible to infer relative effectiveness of either treatment.
2. Florath 2005[34] studied QoL after aortic valve replacement in patients older than 65 years. Two hundred and forty-seven patients underwent bioprosthesis and 145 underwent mechanical prosthesis. Follow-up varied between three and 66 months and the main QoL instrument was the Nottingham Health Profile (NHP). In general, the scores between groups were comparable and no significant differences were found between patients receiving stentless bioprosthetic valves and patients receiving mechanical prostheses.
3. Perchinsky 1998[32] compared the QoL in age- and gender-matched patients for those receiving either biological or mechanical prosthetic valves in isolated aortic valve replacement. One hundred of the sampled patients (age range 51 to 65 years) had a mechanical valve inserted and an equal number had porcine bioprostheses. The main QoL tool was SF-12 and results were similar between patients with aortic mechanical and bioprosthetic valve replacement in the studied age group and comparable to the general population of similar age. Although some valve-specific differences existed between the two prosthetic types (e.g. concerns about frequency of medical visits and blood tests ($p < 0.01$), these differences do not appear to affect overall QoL as described by these patients.
4. Sedrakyan 2004[33] involved assessment of change in QoL for 73 patients with tissue valve replacements and 53 patients with mechanical valve replacements performed from April 1998 through to March 1999 at Yale-New Haven Hospital USA. The main QoL instrument was SF-36. After adjusting for baseline QoL, age, and other prognostic factors in an analysis of covariance, improvements in quality of life scores for tissue valve recipients versus mechanical valve recipients were similar after 18 months. The only significant difference between the two groups was for the improvement in role limitations due to physical problems (role physical), which was more favourable in patients with mechanical valve implants ($p = 0.04$).
5. Repack 2016[37] was an assessment in the USA as to whether post-operative QoL differed for composite aortic root replacement patients according to whether it is based on the use of mechanical valves or bioprosthetic valves. The main QoL instrument was SF-36v2 and mean

follow-up time was 32 months. Mean age of patients in the bioprosthetic valve group was 67.5 whereas in the mechanical valve group it was 56.6. Overall, no significant differences were found between the bioprosthetic and mechanical valve groups for any aspects of QoL. This result was contrary to perceptions of QoL in that preconception of a heavy QoL burden for mechanical composite grafts was not born out by the evidence from this study.

6. Ruel 2005[35] was an assessment of long term outcomes of valve replacement in young adults (aged 18 to 50 years) in Canada. The initial operation consisted of aortic valve replacement in 309 patients (mechanical n=171, bioprosthetic n=138), mitral valve replacement in 151 patients (mechanical n=109, bioprosthetic n=42), and dual valve replacement in 40 patients (mechanical n=36, bioprosthetic n=4). The main QoL instrument was SF-12 and median follow-up was 7.1 years. Whilst no significant differences were found for mental component scores and physical component scores irrespective of site of valve, it was noted that the physical component scores were significantly higher in patients with aortic bioprostheses than for those with mechanical aortic valves (by 9.9%; 95% CI: 2.7, 17). This difference was observed irrespective of the use of homografts versus stented bioprostheses.

The clinical evidence is presented in Table 5.

Table 5: Quality of life after bioprosthetic compared to mechanical heart valve replacement

No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of effects	Quality
SF-12							
1[a]	Very Serious[1,2]	No Serious	Serious[1]	No Serious	Site of surgery not considered as confounder. Recruitment period was 10-year period (1986-1996). No consideration as to whether or not this was important. Technologies may not be reflective of current practice.	Using the SF-12 form, authors were unable to find any significant difference between the study patients in the bioprostheses (n=84) and mechanical (n=94) groups with respect to their mental or physical scores.	VERY LOW
1[b]	Very Serious[1,3,4]	Serious[3]	Serious[1]	No Serious	Authors acknowledge that analysis was restricted to technologies available at time of writing (2005). Accordingly they may not be reflective of current practice.	No differences except for physical component scores which were significantly higher in patients with aortic bioprostheses than in those with mechanical aortic valves (by 9.9%; 95% CI: 2.7, 17.1). This difference was observed irrespectively of the use of homografts versus stented bioprostheses. This difference was only observed for patients undergoing aortic valve replacement (n=309) and not for those undergoing either mitral valve replacement (n=151) or dual valve replacement (n=40)	VERY LOW

No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of effects	Quality
SF-36							
1[c]	Serious[4]	No Serious	No Serious	No Serious	Technologies may not be reflective of current practice.	After adjusting for preoperative QoL scores, age, gender, history of MI, PVD, NYHA class, aortic stenosis, and procedure type, improvements in mean QoL scores for the tissue (n=73) and mechanical implant groups (n=53) were similar. The only exception was for the Role Physical domain, in which improvement was more favourable in the mechanical implant group (by mean difference 17.0; 95% CI: -33.8, -0.34)	MODERATE
1[d]	Very Serious[1,3]	Serious[3]	Serious[1]	No Serious	Recruitment period was Jan 2010 - April 2014 so technologies may be reflective of current practice.	There was no statistically significant difference between the average scores for each QoL domain of SF-36v2 for patients with bioprosthetic (n = 51) or a mechanical aortic valve (n = 95)	LOW
1[e]	Very Serious[1,3,4]	Serious[3]	Serious[1]	Serious[5]	Recruitment period was Jan 2001 - December 2002 so technologies may not be reflective of current practice.	The quality of life in patients with mechanical (n=83) and bioprosthetic (n=53) valves was similar at 2 years postoperatively	VERY LOW
Nottingham Health Profile							
1[f]	Very Serious[1,2,4]	No Serious	Serious[1]	No Serious	Recruitment period was 1996 and 2001, so technologies may not be reflective of current practice.	No significant differences were found between patients receiving stentless bioprosthetic valves (n=247) and patients receiving mechanical prostheses (n=145).	LOW

No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of effects	Quality
a Perchinsky 1998[32]; b Ruel 2005[35]; c Sedrakyan 2004[33]; d Repack 2016[37]; e Aboud 2009[36]; f Florath 2005[34] 1 Baseline QoL not evaluated; 2 No evidence on time varying confounders; 3 Sub groups varied considerably in terms of e.g. age/sex/functional class (confounders not assessed); 4 Confounding for patient selection cannot be ruled out; 5 Reporting inconsistencies CI = confidence intervals; MI = myocardial infarction; NYHA = New York Heart Association functional class; PVD = peripheral vascular disease; QoL = quality of life; SF-12 = Short Form Health Survey-12; SF-36 = Short Form Health Survey-36; SF-36v2 = Short Form Health Survey-36 version 2							

FAQ 2: EVIDENCE SUMMARY

How will I benefit from treatment?

The benefits of heart valve replacement can be expressed in terms of:

Survival (life expectancy)

In overall terms, no significant difference in life expectancy has been observed between implant of a bioprosthetic or mechanical valve. The most reliable evidence was found in a review, published in 2019, which combined analysis from four high quality randomised controlled trials. Analysis based on these four studies suggested similarity in life expectancy associated with either type of valve implant. This finding was largely consistent with the finding in an earlier review of observational studies which suggested that an overall advantage observed in favour of mechanical valves might partly be explained by the age of patients undergoing the procedure. This study did find that younger patients (aged less than 65) might anticipate a longer life following implantation of a mechanical valve, however the authors suggest that the quality of underlying evidence was at risk of bias and findings might be unreliable.

Quality of life

Six studies (albeit of relatively low quality) reported little or no difference in the quality of life changes experienced by patients treated with either type of procedure. Quality of life was measured in a variety of different ways. Two studies used an index, based on 12 items, and found no difference in quality of life related to procedure except that bioprosthetic heart valves were associated with improved physical functioning. Three studies used a more detailed index based on 36 items and confirmed the overall finding that quality of life was not impacted by choice of procedure. However, in these studies, mechanical valves were associated with greater improvement in one element of quality of life described as "physical role". The final study was judged to be of very low quality but, once again, failed to detect any significant difference between bioprosthetic and mechanical heart valve replacement.

FAQ 3: Which side effects and complications might occur?

a) Risk of thromboembolic events
b) Risk of re-operation
c) Risk of infection
d) Risk of malfunction

FAQ 3a: How does the treatment impact my risk of thromboembolic events?

The risk of thromboembolic events (specifically, bleeding events and systemic arterial embolism) associated with different forms of heart valve was assessed by Kiyose 2019[8] drawing from RCT-based evidence from Edinburgh 2003[20], Vallejo 1981[17], Veterans Affairs 2000[19] and Stassano 2009.[18]

Kiyose 2019[8] examined the risk of bleeding for sub groups (see Table 6) and found that it was lower in patients treated with biological prostheses than in those treated with mechanical prostheses (RR=0.64; 95% CI 0.52-0.78; I2 = 0%). Evidence used to assess risk of bleeding was assessed to be of high quality according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system as assessed by Kiyose 2019.[8] However, it should be noted that definitions of bleeding varied from study to study. Furthermore, primary studies reported by Kiyose 2019[8] failed to

report the number of patients who had a bleeding event after heart valve replacement and no reliable method was found to impute these numbers. Edinburgh 2003[20] included all major (65%) and minor bleeding, Veterans Affairs 2000[19] included "clinically important bleeding", Vallejo 1981[17] only considered bleeds which required hospitalisation or resulted in death and Stassano 2009[18] made no reference to the magnitude of bleeding.

Head 2017[7] has suggested that recent developments in non-vitamin K antagonist anticoagulation (NOAC) agents may mean that bleeding-related complications might be easier to manage in the future thereby reducing some of the risks associated with heart valve replacement (possibly reducing the differential impact on bleeding observed between procedure types).

Kiyose 2019[8] found there were no significant differences in the risk of systemic arterial embolism (blocked arteries) (RR=0.93, 95% CI 0.66-1.31; I2=31%) between the group that received bioprostheses and the group that received mechanical prostheses (see Table 7) based on evidence from Edinburgh 2003[20], Vallejo 1981[17], Veterans Affairs 2000[19] and Stassano 2009.[18] Evidence used to assess risk of embolism was assessed to be of medium quality according to the GRADE system as assessed by Kiyose 2019.[8] Once again, patient numbers were not reported in primary studies.

Liu 2016[11] examined the link between thrombosis and different forms of heart valve replacement based on observational rather than trial data.[38,39,40] Whilst the review does suggest that mechanical valves are associated with higher risk of thrombosis, the risk of selection bias in studies cannot be ruled out and the limited number of studies that permit analysis of thromboembolism means that interpretation should be treated with caution, particularly as follow-up periods varied considerably both within and between studies Follow up patient years for bioprosthetic versus mechanical valves were: 1210 vs. 1433 in Kaplan 2002[38], 226 vs. 299 in Filsoufu 2005[39] and 567 vs. 829 in Chang 2006[40], respectively. Results are set out in Table 8.

The clinical evidence is summarised in Table 9.

Table 6: Risk of bleeding after heart valve replacement

Bleeding				
Aortic valve	**Weight**	**RR**	**Lower 95% CI**	**Upper 95% CI**
Edinburgh 2003[20]	11.4%	0.69	0.38	1.28
Stassano 2009[18]	6.8%	0.49	0.22	1.08
Veterans Affairs 2000[19]	46.2%	0.59	0.43	0.8
Subtotal (95% CI)	**64.4%**	**0.59**	**0.46**	**0.77**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.48, df = 2 (p = 0.79); I^2 = 0%. Test for overall effect: Z = 3.98 (p < 0.0001)				
Mitral valve	**Weight**	**RR**	**Lower 95% CI**	**Upper 95% CI**
Edinburgh 2003[20]	10.1%	0.70	0.37	1.34
Vallejo 1981[17]	1.6%	0.95	0.18	4.94
Veterans Affairs 2000[19]	20.1%	0.58	0.37	0.93
Subtotal (95% CI)	**31.8%**	**0.63**	**0.44**	**0.91**
Heterogeneity: Tau^2 = 0.00; Chi2 = 0.44, df = 2 (p = 0.80); I^2 = 0%. Test for overall effect: Z = 2.44 (p = 0.01)				
Mitral + aortic valve	**Weight**	**RR**	**Lower 95% CI**	**Upper 95% CI**
Edinburgh 2003[20]	3.8%	2.01	0.70	5.8
Subtotal (95% CI)	**3.8%**	**2.01**	**0.70**	**5.8**

Bleeding				
Heterogeneity: Not applicable. Test for overall effect: Z = 1.29 (p = 0.20)				
Total (95% CI)	**100.0%**	**0.64**	**0.52**	**0.78**
Heterogeneity: Tau^2 = 0.00; Chi2 = 5.74, df = 6 (p = 0.45); I^2 = 0%. Test for overall effect: Z = 4.32 (p < 0.0001). Test for subgroup differences: Chi^2 = 4.82, df = 2 (p = 0.09); I^2 = 58.5%				
Ref: Kiyose 2019[8] CI = confidence interval; I^2 = Higgins inconsistency test; RR = relative risk				

Table 7: Risk of systemic arterial embolism after heart valve replacement

Systemic arterial embolism				
Aortic valve	**Weight**	**RR**	**Lower 95% CI**	**Upper 95% CI**
Edinburgh 2003[20]	16.7%	1.63	0.84	3.19
Stassano 2009[18]	6.4%	0.44	0.13	1.54
Veterans Affairs 2000[19]	18.6%	1.00	0.54	1.85
Subtotal (95% CI)	**41.7%**	**1.05**	**0.58**	**1.91**
Heterogeneity: Tau^2 = 0.12; Chi^2 = 3.46, df = 2 (p = 0.18); I^2 = 42%. Test for overall effect: Z = 0.16 (p =0.87)				
Mitral valve	**Weight**	**RR**	**Lower 95% CI**	**Upper 95% CI**
Edinburgh 2003[20]	26.3%	0.60	0.38	0.94
Vallejo 1981[17]	11.3%	0.87	0.36	2.12
Veterans Affairs 2000[19]	15.7%	1.22	0.60	2.47
Subtotal (95% CI)	**53.2%**	**0.80**	**0.51**	**1.25**
Heterogeneity: Tau^2 = 0.05; Chi^2 = 2.94, df = 2 (p = 0.23); I^2 = 32%. Test for overall effect: Z = 0.99 (p = 0.32)				
Mitral + aortic valve	**Weight**	**RR**	**Lower 95% CI**	**Upper 95% CI**
Edinburgh 2003[20]	5.1%	1.41	0.34	5.80
Subtotal (95% CI)	**5.1%**	**1.41**	**0.34**	**5.80**
Heterogeneity: Not applicable. Test for overall effect: Z = 0.47 (p = 0.64)				
Total (95% CI)	**100.0%**	**0.93**	**0.66**	**1.31**
Heterogeneity: Tau^2 = 0.06; Chi^2 = 8.69, df = 6 (p = 0.19); I^2 = 31%; Test for overall effect: Z = 0.41 (p = 0.68); Test for subgroup differences: Chi^2 = 0.92, df = 2 (p = 0.63); I^2 = 0%				
Ref: Kiyose 2019[8] CI = confidence interval; I^2 = Higgins inconsistency test; RR = relative risk				

Table 8: Risk of thrombosis after heart valve replacement

Thrombosis						
Aortic valve	**Log (HR)**	**SE**	**Weight**	**RR**	**Lower 95% CI**	**Upper 95% CI**
Kaplan 2002[38]	1.24	1.03	26.0%	3.46	0.46	26.02
Filsoufu 2005[39]	1.52	1.25	17.7%	4.57	0.39	52.98
Chang 2006[40]	1.35	0.7	56.3%	3.86	0.98	15.21
Total (95% CI)			**100.0%**	**3.86**	**1.38**	**10.82**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.03, df = 2 (p = 0.99); I^2 = 0%; Test for overall effect: Z = 2.57 (p = 0.01)						
Ref: Liu 2016[11] CI = confidence interval; I^2 = Higgins inconsistency test; RR = relative risk						

Table 9: Risk of bleeding, embolism and thrombosis after heart valve replacement

No of studies	Considerations	Summary of effects	Quality of Evidence (GRADE)
Bleeding			
4: Edinburgh 2003[20], Stassano 2009[18], Veterans Affairs 2000[19], Vallejo 1981[17]	Definitions of bleeding varied from review to review. If patients are predisposed to bleeding then bioprosthetic valves may offer clinical advantage over mechanical valves. Recent developments in managing of bleeds may lead to a less clear advantage of bioprosthetic valves over mechanical valves in the future.	Favours bioprosthetic. Meta-analysis risk ratio 0.64 (0.52,0.78)	HIGH[a]
Systemic arterial embolism			
4: Edinburgh 2003[20], Stassano 2009[18], Veterans Affairs 2000[19], Vallejo 1981[17]	No difference was observed for any sub group except for Edinburgh 2003[20] mitral valve where bioprosthetic was associated with a more favourable outcome.	No difference. Meta-analysis risk ratio 0.93 (0.66,1.31)	MEDIUM[b]
Thrombosis			
3: Kaplan 2002[38], Filsoufu 2005[39], Chang 2006[40]	Limited observational data might be subject to selection bias. Variation within and between studies in terms of follow up years, limits comparability.	Favours bioprosthetic. Meta-analysis hazard ratio 3.86 (1.38,10.82)	LOW (OBSERVATIONAL STUDIES)

From Kiyose 2019[8] and Liu 2016[11]
a) There was no evidence of serious study limitations, serious inconsistency, indirectness, imprecision or publication bias
b) There was no evidence of serious study limitations, serious inconsistency, indirectness or publication bias. Some imprecision was detected as the effect size was compatible with either substantial benefit or harm.

FAQ 3b: How does the treatment impact my need for a reoperation?

Several systematic reviews gave information on risk of reoperation, but the most recent (Kiyose 2019[8]) was prioritised as the only systematic review based solely on RCTs. The other six were either inconclusive[4] or backing up the findings[6, 11, 12, 15, 16] of the prioritised study. Risk of reoperation is already a known factor, and this outcome favours mechanical over bioprosthetic heart valve replacement regardless of location (aortic or mitral). See details in Table 10.

Table 10: Need for reoperation after heart valve replacement

Studies	Design	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Subgroup	I^2	Relative Effect (95% CI)	Quality
Aortic or mitral valve. Follow-up 2 – 20 years (study means)										
4: Edinburgh 2003[20]; Stassano 2009[18]; Veterans Affairs 2000[19]; Vallejo 1981[17]	RCTs	No serious	No serious	Direct	No serious	Unlikely	Bioprosthetic (n=748) Mechanical (n=780)	42%	Risk ratio 3.60 (2.44 to 5.32), favouring mechanical, P = 0.00001	HIGH
Aortic valve. Follow-up 8 - 20 years (study means)										
3: Edinburgh 2003[20]; Stassano 2009[18]; Veterans Affairs 2000[19]	RCTs	No serious	No serious	Direct	No serious	Unlikely		35%	Risk ratio 4.17 (2.41 to 7.21), favouring mechanical, P<0.00001	HIGH
Mitral valve. Follow-up 2 - 20 years (study means)										
3: Edinburgh 2003[20]; Vallejo 1981[17]; Veterans Affairs 2000[19]	RCTs	No serious	No serious	Direct	No serious	Unlikely		70%	Risk ratio 3.21 (1.30 to 7.92), favouring mechanical, P=0.01	HIGH
Aortic + mitral valve. Follow-up 20 years (study mean)										
1: Edinburgh 2003[20]	RCTs	No serious	No serious	Direct	No serious	Unlikely	Bioprosthetic (n=421) Mechanical (n=422)	NA	Risk ratio 2.93 (1.26 to 6.80), favouring mechanical, P=0.01	HIGH

From Kiyose 2019[8] Tables 1 and 3, Figure 3 and text
CI = confidence intervals; I^2 = Higgins inconsistency test; NA = not applicable

FAQ 3c: How does the treatment impact my risk of infection?

For the outcome risk of infection, only one systematic review, Kiyose 2019[8], contained data specifically comparing risk of endocarditis between bioprosthetic and mechanical valve replacement from randomised control trials. The data suggest no particular difference between intervention types. The authors note that results in the trials with modern and old prostheses were similar. See details in Table 11.

FAQ 3d: How does the treatment impact my risk of malfunction?

The only systematic reviews giving information on risk of malfunction were Zhao 2016[16] and Liu 2016[11]. For Zhao 2016[16], a pooled effect was not estimable and the reported estimated hazard ratios were interpreted with caution. The low-quality evidence based on two observational studies suggested that there was a lower risk of prosthetic valve failure associated with mechanical valve replacement. However, not only was this risk not statistically significant but it is worth noting it is largely based on a study using data from 1975 to 1992. Results are presented below in Table 12.

Table 11: Risk of endocarditis after heart valve replacement

Studies	Design	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	I^2	Relative Effect (95% CI)	Quality
Aortic valve.									
3: Edinburgh 2003[20]; Stassano 2009[18]; Veterans Affairs 2000[19]	RCTs	No serious	No serious	Direct	No serious	Unlikely	55%	Risk ratio 1.11 (0.46 to 2.67), favouring mechanical, p=0.81	HIGH
Mitral valve.									
3: Edinburgh 2003[20]; Vallejo 1981[17]; Veterans Affairs 2000[19]	RCTs	No serious	No serious	Direct	No serious	Unlikely	0%	Risk ratio 1.42 (0.67 to 3.01), favouring mechanical, P=0.59	HIGH
Aortic + mitral valve.									
1: Edinburgh 2003[20]	RCTs	No serious	No serious	Direct	No serious	Unlikely	NA	Risk ratio 2.12(0.3 to 14.94), favouring mechanical, P=0.45	HIGH

Table 12: Risk of malfunction after heart valve replacement

No of studies	Design	Prosthetic valve failure / number of patients	I^2	Relative Effect (95% CI)	Quality
Follow-up 3.7-4.8 years (study means)					
2: Filsoufi 2005[39], Munro 1995[46]	observational, retrospective studies	Bioprosthetic (3/117) Mechanical (0/61)	0%*	Hazard ratio 0.35 (0.06 to 2.01), no significant difference, P = 0.24	23[39] and 19[46] out of 34 possible**

From Liu 2016[11] Figure 3, Tables 1 and 3 and text

*There was minimal heterogeneity between studies, but heterogeneity of the patients included in the summarized studies

**Quality scores of included papers were based on the STROBE quality score systems. 34 items relevant to the quality appraisal were used for assessment in the meta-analysis.[11] Scores ranged from 0 (lowest) to 34 (highest). Information taken from Liu 2016[11],no further information available.

CI = confidence intervals; I^2 = Index of Inconsistency

FAQ 3: EVIDENCE SUMMARY

What are the side effects of treatment?

Risk of thromboembolic events - bleeding

High quality evidence suggests bioprosthetic valves are preferred to mechanical heart valves, with a 36% lower risk of bleeding. Bioprosthetic valves replacement carries a lower risk of bleeding regardless if it is an aortal or a mitral valve replacement.

Risk of thromboembolic events - systemic arterial embolism

Medium quality evidence suggests no significant difference in risk of a systemic arterial embolism between bioprosthetic and mechanical heart valve replacement. This is regardless of valve replacement location (mitral or aortal).

Risk of thromboembolic events - thrombosis

Low quality evidence suggests bioprosthetic valves are preferred to mechanical heart valves.

Risk of reoperation

High quality evidence suggests that risk of re-operation is at least three times higher with Bioprosthetic compared to mechanical heart valve replacement, regardless of valve location (aortic or mitral).

Risk of infection (specifically endocarditis)

Low quality evidence suggests that there was a 75% higher risk of endocarditis associated with bioprosthetic compared to mechanical valve replacement. However, the authors remark that that patients in the bioprosthetic valve group were of inferior physical condition compared to those in the mechanical valve group, which would presumably leave the bioprosthetic group more vulnerable to endocarditis. Thus, the suggestion of a higher risk with bioprosthetic valve must be taken very sceptically.

Risk of malfunction

Low quality evidence suggests that there was a lower risk of prosthetic valve failure associated with mechanical valve replacement compared to bioprosthetic. However, not only was this risk not statistically significant but it is worth noting it is largely based on a study using data from 1975 to 1992.

FAQ 4: How does the treatment impact my daily living?

A different impact on daily living is to be expected as a result of either type of heart valve. This is due to the need of antithrombotic therapy (blood thinners), noise from the valve, the different length of the recovery phase, and religious beliefs.

Antithrombotic therapy

The European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) and the American Heart Association/American College of Cardiology (AHA/ACC) provide specific guidelines on the recommendations for antithrombotic therapy in patients with heart valve disease. The strength of each recommendation is based on the magnitude and certainty of benefit against risk and it is indicated by the Class of Recommendation (COR). The quality of the scientific evidence is indicated by the Level of Evidence (LOE). How these are judged is described in Table 13-16.

Table 13: ESC/EACTS Class of recommendation description

COR	Description
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

From ESC/EACTS 2017 guideline[1]
COR = class of recommendation; EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology

Table 14: AHA/ACC Class of recommendation description

COR	Description
Class I (Strong)	Benefit >>> Risk
Class IIa (Moderate)	Benefit >> Risk
Class IIb (Weak)	Benefit ≥ Risk
Class III: No benefit (Moderate)	Benefit = Risk
Class III: Harm (Strong)	Risk > Benefit

From AHA/ACC 2017 focused guideline update[2]
AHA/ACC = American Heart Association/American College of Cardiology; COR = class of recommendation

Table 15: ESC/EACTS Level of evidence description

LOE	Description
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

From ESC/EACTS 2017 guideline[1]
EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology; LOE = level of evidence

Table 16: AHA/ACC Level of evidence description

LOE	Description
Level A	High-quality evidence from more than 1 RCT Meta-analyses of high-quality RCTs

LOE	Description
	One or more RCTs corroborated by high-quality registry studies
Level B-R	Moderate-quality evidence from 1 or more RCTs Meta-analyses of moderate-quality RCTs
Level B-NR	Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies or registry studies Meta-analyses of such studies
Level C-LD	Randomized or nonrandomized observational or registry studies with limitations of design or execution Meta-analyses of such studies Physiological or mechanistic studies in human subjects
Level C-EO	Consensus of expert opinion based on clinical experience
From AHA/ACC 2017 focused guideline update[2] AHA/ACC = American Heart Association/American College of Cardiology; LOE = level of evidence; RCT = randomised controlled trial	

According to the ESC/EACTS guideline[1] and the AHA/ACC guideline update[2,13], mechanical valves are not recommended for patients for whom antithrombotic therapy is contraindicated. The summary of recommendations state that *'A bioprosthesis is recommended in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired.'* The COR given is Class and the LOE awarded is Level C. This must be interpreted as a benefit that overweighs all risks and that is based on expert opinion, case studies or standard of care.[14] It is necessary to note that this recommendation includes patient's desire in the decision-making process as consequent changes in lifestyle many need to be made, namely pregnancy, sport and work activity.

When a mechanical valve has been implanted, antithrombotic therapy is strongly recommended.[1,2,13] This is supported by the highest LOE (Level A). Hence, lifetime anticoagulation with a vitamin K antagonist (VKA), and subsequent International Normalised Ratio [of Blood Clotting] (INR) monitoring needs to be considered by patients and/or carers. The results or adverse effects of this type of therapy vary depending on the specific drug, absorption, various foods, alcohol, other medications and changes in liver function.

It must also be noted that a bioprosthetic valve implantation is not necessarily fully exempt from pharmacological management, especially in the early days after the interventions. Additionally, antithrombotic agents other than anticoagulants may also need to be employed.[13] Table 17-18 reflect some of the key recommendations regarding antithrombotic therapy for these interventions.

Table 17: ESC/EACTS recommendations

COR	LOE	ESC/EACTS Recommendation
I	B	Oral anticoagulation using a VKA is recommended lifelong for all patients
I	C	Bridging using therapeutic doses of UFH or LMWH is recommended when VKA treatment should be interrupted in patients with mechanical prostheses.
I	B	INR self-management is recommended for patients with mechanical prostheses, provided appropriate training and quality control are performed.
III	B	The use of NOACs is contraindicated for patients with mechanical prostheses.
I	C	Oral anticoagulation is recommended lifelong for patients with surgical or transcatheter implanted bioprostheses who have other indications for anticoagulation.
From ESC/EACTS 2017 guideline[1]		

COR	LOE	ESC/EACTS Recommendation
COR = class of recommendation; EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology; INR = International Normalised Ratio [of Blood Clotting]; LOE = level of evidence; NOAC = non-vitamin K antagonist oral anticoagulant; TAVR = Transcatheter Aortic Valve Replacement; VKA = Vitamin K antagonist		

Table 18: AHA/ACC recommendations

COR	LOE	AHA/ACC Recommendation
I	A	Anticoagulation with a VKA and INR monitoring is recommended in patients with a mechanical prosthetic valve.
I	A	Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis.
IIa	B	Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve.
IIb	C	Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily.
From AHA/ACC 2017 focused guideline update[2] AHA/ACC = American Heart Association/American College of Cardiology; COR = class of recommendation; INR = International Normalised Ratio [of Blood Clotting]; LOE = level of evidence; TAVR = Transcatheter Aortic Valve Replacement; VKA = Vitamin K antagonist		

A qualitative study reported by Taghadosi 2014[14] has provided valuable results in understanding the impact on daily living that these recommendations might have. This study is based on 22 interviews of 13 participants.[14]

As reported by Taghadosi 2014, patients may struggle with the inconveniences and economic disbursement associated to antithrombotic therapy. However, the selection of the participants for this study was not randomised and the article does not report enough details on how the interviews were carried out. Therefore, the study cannot be judged at a low risk of bias. Moreover, as this study was undertaken in Iran, the external validity of this study needs to be taken into account.

The guidelines provide further recommendations for patients with mechanical valves undergoing other diagnostic or surgical procedures. In these instances, the pharmacological management needs to factor in the type of procedure, bleeding risk, patient's own risk factors as well as the type, location and number of heart valve prostheses.[2] Tables 19-20 present recommendations for bridging therapy.

Patients' feeling regarding issues resulting from contraindications to other drugs or interventions were also observed in the interviews carried by Taghadosi 2014.[14]

Table 19: ESC/EACTS recommendations for bridging therapy

COR	LOE	Recommendation
I	C	Bridging using therapeutic doses of UFH or LMWH is recommended when VKA treatment should be interrupted.
From ESC/EACTS 2017 guideline[1] COR = class of recommendation; ESC = European Society of Cardiology; EACTS = European Association for Cardio-Thoracic Surgery; LMWH = low-molecular-weight heparin; LOE = level of evidence; UFH = unfractionated heparin; VKA = Vitamin K antagonist		

Table 20: AHA/ACC recommendations for bridging therapy

COR	LOE	Recommendation

COR	LOE	Recommendation
I	C	Continuation of VKA anticoagulation with a therapeutic INR is recommended in patients with mechanical heart valves undergoing minor procedures (such as dental extractions or cataract removal) where bleeding is easily controlled.
I	C	Temporary interruption of VKA anticoagulation, without bridging agents while the INR is subtherapeutic, is recommended in patients with a bileaflet mechanical AVR and no other risk factors for thrombosis who are undergoing invasive or surgical procedures.

From AHA/ACC 2017 focused guideline update[2]
AHA/ACC = American Heart Association/American College of Cardiology; COR = class of recommendation; INR = International Normalised Ratio [of Blood Clotting]; LOE = level of evidence; VKA = Vitamin K antagonist

Noise

There is some evidence that clicking associated with implant of mechanical valves has a deleterious impact on daily living. A cross-sectional single-centre survey undertaken by revealed that valve sound was either found to be occasionally, frequently or always bothersome in 44% of cases with mechanical valves (n=190) whereas the comparative figure for Bioprosthetic valves was 12%.[10] However, a study undertaken by Koertke in 2003[9] of 566 patients who received a mechanical valve prosthesis between 1994 and 1998 found that 94.2% of patients had no "persistent complaints about the valve noise". They concluded that it remained unclear whether noise disturbance was either a reason or consequence of lower quality of life. The same study suggested that specific demographic factors might play a role in noise perception with people aged 60 years or less having an 8.2% additional risk of heightened noise perception; being female had an independent 11% risk but being female and younger than 60 years resulted in a risk factor of 17.1%.[9] Whether patients become accustomed or not to the sounds associated with valves is an area which may require further research.

Recovery phase

A patient's recovery phase is likely to be determined by factors other than the type of valve implanted. Patients can usually expect to sit out of bed the day after the procedure and although discomfort might be expected, pain relief can be administered to reduce its impact. On average, it can take about one week to be discharged post-operatively and between two to three months to fully recover from the procedure.[5]

Religious and ethical considerations

The choice of the type of valve may also be impacted by the personal beliefs of religious affiliations of the patient. For example, Muslim patients may decline bioprosthetic valves of porcine origin and some Jewish patients may be conflicted in accepting a bioprosthetic valve that is not kosher.

FAQ 4: EVIDENCE SUMMARY

What will be the impact on my daily living?

Researchers have looked into how the different types of heart valve might affect the patients' daily living and the potential resulting burden.

A key difference exists in the medication that the patient needs to take for each type of valve. Mechanical valves require long-term blood thinners. This type of medication may limit the regular daily activities, prospective elective surgery, concomitant medications or other life choices. In addition, this type of medication may require burdensome monitoring.

The level of clicking noise perceived by patients who have been implanted a mechanical valve is understood to be higher than by patients with bioprosthetic valves. This noise may be critical in the overall comfort and rest achieved by the patient.

Whilst the recovery time from the intervention may be a key element in the patient's own decision-making this cannot be established or projected without an individual discussion between the patient and his consultant.

In parallel to all clinical and personal considerations, patient's beliefs may need to be observed in individual cases.

Table 21: Overview of clinical studies populating the evidence table

Study ID	Participants	Interventions	Outcomes	Study Design	Follow-up
AHA/ACC 2017 focused guideline update[2]	Unrestricted (adults)	n/a	n/a	Guidelines	n/a
Bashir 2017[4]	Composite aortic root replacement	Mechanical versus bioprosthetic valves	In-hospital mortality; post-operative bleeding; renal failure; stroke; re-operation; and 1-year mortality	Systematic review of cohorts	Up to 10 years
Diaz 2018[6]	Between 50 and 70 years of age	Mechanical versus bioprosthetic valves	Long-term survival	Systematic review of RCTs and propensity score matched observational studies	Minimum of 5 years
ESC/EACTS 2017 guideline[1]	Unrestricted (adults)	n/a	n/a	Guidelines	n/a
Head 2017[7]	Aortic valve replacement	Mechanical versus bioprosthetic valves	Risks and benefits	Literature review	Unrestricted
Kiyose 2019[8]	Tricuspid valve replacement (and children) were excluded	Mechanical versus bioprosthetic valves	Total mortality; embolic events; bleeding events; new surgery; and infectious endocarditis	Systematic review of RCTs	Between 2 and 20 years
Koertke 2003[9]	Unrestricted (adults).	Mechanical valves	Disturbance by noise perception	Cross-sectional	n/a
Korteland 2016[10]	Aortic valve replacement. Between 18 and 60 years of age	Mechanical versus bioprosthetic valves	Quality of life (SF-36)	Cross-sectional	n/a (Between 1 and 10 years after intervention)
Liu 2016[11]	Tricuspid valve replacement	Mechanical versus bioprosthetic valves	Long term survival; reoperation; thromboembolism and anticoagulant related bleeding; valve failure; and pacemaker implantation	Meta-analysis	14,694 patient-years

Study ID	Participants	Interventions	Outcomes	Study Design	Follow-up
Magliano 2015[12]	Unrestricted (adults).	Carpentier-Edwards pericardial prostheses	Operative mortality rate; overall mortality; and reoperation rate	Systematic review of RCTs and observational studies	Minimum of 5 years
Nishimura 2014[13]	Unrestricted (adults)	n/a	n/a	Guidelines	n/a
Taghadosi 2014[14]	Unrestricted (adults).	Unrestricted (mechanical and bioprosthetic valves)	Perception and experiences after the intervention	Cross-sectional qualitative study	n/a
Tao 2017[15]	Infective endocarditis	Mechanical versus bioprosthetic valves	Mortality; In-hospital death or 30-day mortality; embolic events; reoperation; and recurrence of infective endocarditis	Meta-analysis	Up to 5 years
Zhao 2016[16]	Aortic valve replacement. Younger than 70 years of age	Mechanical versus bioprosthetic valves	Long-term mortality; major adverse event prosthesis related events; anticoagulant related events; major bleeding; reoperation; structural valve degeneration	Systematic review of RCTs and observational studies	Mostly up to 15 years

4. DISCUSSION

4.1 STRENGTHS, LIMITATIONS AND UNCERTAINTIES

This review has employed a systematic yet pragmatic approach hence the searches and selection of the studies have been carried out purposefully to provide relevant evidence to enable the patient's decision-making.

The report focuses on evidence from systematic reviews and guidelines, including a number of systematic reviews with meta-analyses. Much of the evidence may relate to technologies and procedures that have improved over time. With this in mind, only the most current reviews were prioritised so that the validity of the findings could be interpreted in today's setting. It is worth noting that even the most recent reviews e.g. Kiyose 2019[8] relied on evidence from trials which were old and used first generation biological prostheses and single-disk mechanical prostheses. These technologies are unlikely to be reflective of current practices and greater durability of biological prostheses. A lack of contemporary trial evidence was acknowledged in a review undertaken by Head et al.[7] who also looked at recent observational studies. This review of 19 such studies (dating from 1995 to 2016) found no significant improvement in survival associated with either mechanical or bioprosthetic valves. It was noted that studies that included younger patients found a significant benefit of mechanical over bioprosthetic valves but overall *"there does not seem to be sufficient evidence to support lowering the age cut-off for implanting bioprosthetic valves below the age of 60 years to improve long-term survival".*[7]Amongst the limitations of this review we must acknowledge the scarce number of publications that form the bases of the outcomes here explored. Further, the publication authored by Kiyose 2019[8] has been given a prominent role in this review that could be judged to be disproportionate to the provided level of evidence. More critically, though this review has reported the quality of the primary studies, as described in the selected reviews; it has not assessed the methodological quality of the reviews. Similarly, no assessment has been carried out ~~f~~or the included guidelines (Nishimura 2014[13]).

Table 22: Summary of evidence

Evidence	Favours Bioprosthetic	Favours Mechanical	Notes
How will I benefit from treatment?			
Risk of dying		✓	No statistically significant difference was observed between bioprosthetic and mechanical heart valve replacement was observed.
How does the treatment impact my quality of life?			
Quality of life based on 12 domains (SF-12)	✓		Low quality evidence (GRADE) based on two studies failed to observe a statistically significant difference between bioprosthetic and mechanical heart valve replacement. Bioprosthetic heart valves were associated with improved QoL on one sub scale, namely physical functioning.
Quality of life based on 36 domains (SF-36)		✓	Mixed quality evidence (GRADE) based on three reviews failed to observe a statistically significant difference between bioprosthetic and mechanical heart valve replacement. Mechanical heart valves were associated with improved QoL on one sub scale, namely the physical role domain.
Quality of life (Nottingham Health profile	-	-	Very low-quality evidence (GRADE) based on a single study failed to observe any significant difference between bioprosthetic and mechanical heart valve replacement.
Which side effects and complications might occur?			
Risk of bleeding	✓		High quality evidence (GRADE) based on meta-analysis of four trials suggests bioprosthetic valves are preferred to mechanical heart valves, with 36% less risk of bleeding.
Risk of systemic arterial embolism	-	-	Medium quality evidence (GRADE) based on meta-analysis of four trials suggests no significant difference between bioprosthetic and mechanical heart valve replacement
Risk of thrombosis	✓		Low quality evidence (GRADE) based on meta-analysis based on three observational studies suggests bioprosthetic valves are preferred to mechanical heart valves.

Evidence	Favours Bioprosthetic	Favours Mechanical	Notes
Risk of re-operation		✓	High quality evidence from one systematic review suggests that risk of re-operation is at least three times higher with Bioprosthetic valve replacement compared to mechanical valve replacement.
Risk of infection (endocarditis)	-	-	High quality evidence (GRADE) based on meta-analysis of three trials suggests no observable difference in risk of endocarditis for patients with mechanical valve replacement compared to mechanical valve replacement.
Risk of malfunction		✓	Low quality evidence based on two observational studies suggested that there was a lower risk of prosthetic valve failure associated with mechanical valve replacement. However, not only was this risk not statistically significant but it is worth noting it is largely based on a study using data from 1975 to 1992.
How does the treatment impact my daily living?			
Patients needing anti–thrombotic therapy	✓		Mechanical valves are not recommended for patients for whom antithrombotic therapy is contraindicated.
Patients with religious and ethical considerations		✓	Muslim patients may decline bioprosthetic valves of porcine origin and some Jewish may be conflicted in accepting a bioprosthetic valve that is not kosher
Noise factors	✓		There is low quality evidence that clicking associated with implant of mechanical valves has a more deleterious impact on daily living than any noise associated with Bioprosthetic valves
Recovery phase	-	-	A patient's recovery phase is likely to be determined by factors other than they type of valve implanted

KEY	
-	No noticeable difference
✓	Noticeably better but not statistically significant (or subject to probable bias)
✓	Statistically significantly better or guideline recommendation

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; QoL = quality of life

5. REFERENCES

[1] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38(36):2739-2791.

[2] 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *American Heart Association* 2014.

[3] American Heart Association Inc. Types of replacement heart valves [Internet]. AHA, 2019 [accessed 12.3.19]. Available from: https://www.heart.org/en/health-topics/heart-valve-problems-and-disease/understanding-your-heart-valve-treatment-options/types-of-replacement-heart-valves

[4] Bashir M, Harky A, Froghi S, Adams B, Garner M, Gupta P, et al. A systematic review and meta-analysis of mechanical vs biological composite aortic root replacement, early and 1-year results. *Gen Thorac Cardiovasc Surg* 2019;67(1):70-76.

[5] British Heart Foundation. Heart valve surgery [Internet]. London: BHF, n.d. [accessed 13.3.19]. Available from: https://www.bhf.org.uk/informationsupport/treatments/valve-heart-surgery

[6] Diaz R, Hernandez-Vaquero D, Alvarez-Cabo R, Avanzas P, Silva J, Moris C, et al. Long-term outcomes of mechanical versus biological aortic valve prosthesis: systematic review and meta-analysis. *J Thorac Cardiovasc Surg* 2018.

[7] Head SJ, Celik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. *Eur Heart J* 2017;38(28):2183-2191.

[8] Kiyose AT, Suzumura EA, Laranjeira L, Buehler AM, Santo JAE, Berwanger O, et al. Comparison of biological and mechanical prostheses for heart valve surgery: a systematic review of randomized controlled trials. *Arq Bras Cardiol* 2019.

[9] Koertke H, Hoffmann-Koch A, Boethig D, Minami K, Breymann T, El-Arousy M, et al. Does the noise of mechanical heart valve prostheses affect quality of life as measured by the SF-36 questionnaire? *Eur J Cardiothorac Surg* 2003;24(1):52-7; discussion 57-8.

[10] Korteland NM, Top D, Borsboom GJ, Roos-Hesselink JW, Bogers AJ, Takkenberg JJ. Quality of life and prosthetic aortic valve selection in non-elderly adult patients. *Interact Cardiovasc Thorac Surg* 2016;22(6):723-8.

[11] Liu P, Qiao W-H, Sun F-Q, Ruan X-L, Al Shirbini M, Hu D, et al. Should a mechanical or biological prosthesis be used for a tricuspid valve replacement? A meta-analysis. *J Card Surg* 2016;31(5):294-302.

[12] Magliano CA, Saraiva RM, Azevedo VM, Innocenzi AM, Tura BR, Santos M. Efficacy of Carpentier-Edwards pericardial prostheses: a systematic review and meta-analysis. *Int J Technol Assess Health Care* 2015;31(1-2):19-26.

[13] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(23):e521-643.

[14] Taghadosi M, Memarian R, Ahmadi F. The experiences of "difficult life" in heart valve replaced patients. *Iran Red Crescent Med J* 2014;16(8):e19147.

[15] Tao E, Wan L, Wang W, Luo Y, Zeng J, Wu X. The prognosis of infective endocarditis treated with biological valves versus mechanical valves: a meta-analysis. *PLoS One* 2017;12(4):e0174519.

[16] Zhao DF, Seco M, Wu JJ, Edelman JB, Wilson MK, Vallely MP, et al. Mechanical versus bioprosthetic aortic valve replacement in middle-aged adults: a systematic review and meta-analysis. *Ann Thorac Surg* 2016;102(1):315-27.

[17] Vallejo JL. [Randomized, prospective, clinical study comparing the Bjork-Shiley, Lillehei-Kaster and Angell-Shiley prostheses in the mitral position]. *Rev Esp Cardiol* 1981;34(6):457-63.

[18] Stassano P, Di Tommaso L, Monaco M, Iorio F, Pepino P, Spampinato N, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. *J Am Coll Cardiol* 2009;54(20):1862-8.

[19] Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol* 2000;36(4):1152-8.

[20] Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ, et al. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *Heart* 2003;89(7):715-21.

[21] Carrier M, Pellerin M, Perrault LP, Page P, Hebert Y, Cartier R, et al. Aortic valve replacement with mechanical and biologic prosthesis in middle-aged patients. *Ann Thorac Surg* 2001;71(5 Suppl):S253-6.

[22] Kulik A, Bedard P, Lam BK, Rubens FD, Hendry PJ, Masters RG, et al. Mechanical versus bioprosthetic valve replacement in middle-aged patients. *Eur J Cardiothorac Surg* 2006;30(3):485-91.

[23] Prasongsukarn K, Jamieson WR, Germann E, Chan F, Lichtenstein SV. Aortic and mitral prosthetic valve replacement in age groups 61-65 & 66-70 years. *Asian Cardiovasc Thorac Ann* 2007;15(2):127-33.

[24] Brown ML, Schaff HV, Lahr BD, Mullany CJ, Sundt TM, Dearani JA, et al. Aortic valve replacement in patients aged 50 to 70 years: improved outcome with mechanical versus biologic prostheses. *J Thorac Cardiovasc Surg* 2008;135(4):878-84; discussion 884.

[25] Weber A, Noureddine H, Englberger L, Dick F, Gahl B, Aymard T, et al. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. *J Thorac Cardiovasc Surg* 2012;144(5):1075-83.

[26] Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA* 2014;312(13):1323-9.

[27] Nishida T, Sonoda H, Oishi Y, Tatewaki H, Tanoue Y, Shiokawa Y, et al. Long-term results of aortic valve replacement with mechanical prosthesis or carpentier-edwards perimount bioprosthesis in Japanese patients according to age. *Circ J* 2014;78(11):2688-95.

[28] McClure RS, McGurk S, Cevasco M, Maloney A, Gosev I, Wiegerinck EM, et al. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: a propensity-matched analysis. *J Thorac Cardiovasc Surg* 2014;148(5):1931-9.

[29] Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. *Eur Heart J* 2016;37(34):2658-67.

[30] Wang Y, Chen S, Shi J, Li G, Dong N. Mid- to long-term outcome comparison of the Medtronic Hancock II and bi-leaflet mechanical aortic valve replacement in patients younger than 60 years of age: a propensity-matched analysis. *Interact Cardiovasc Thorac Surg* 2016;22(3):280-6.

[31] Roumieh M, Ius F, Tudorache I, Ismail I, Fleissner F, Haverich A, et al. Comparison between biological and mechanical aortic valve prostheses in middle-aged patients matched through propensity score analysis: long-term results. *Eur J Cardiothorac Surg* 2015;48(1):129-36.

[32] Perchinsky M, Henderson C, Jamieson W, Anderson WJ, Lamy A, Lowe N, et al. Quality of life in patients with bioprostheses and mechanical prostheses. Evaluation of cohorts of patients aged 51 to 65 years at implantation. *Circulation* 1998;98(19 Suppl):II81-6; discussion II86-7.

[33] Sedrakyan A, Hebert P, Vaccarino V, Paltiel AD, Elefteriades JA, Mattera J, et al. Quality of life after aortic valve replacement with tissue and mechanical implants. *J Thorac Cardiovasc Surg* 2004;128(2):266-72.

[34] Florath I, Albert A, Rosendahl U, Alexander T, Ennker IC, Ennker J. Mid term outcome and quality of life after aortic valve replacement in elderly people: mechanical versus stentless biological valves. *Heart* 2005;91(8):1023-9.

[35] Ruel M, Kulik A, Lam BK, Rubens FD, Hendry PJ, Masters RG, et al. Long-term outcomes of valve replacement with modern prostheses in young adults. *Eur J Cardiothorac Surg* 2005;27(3):425-33; discussion 433.

[36] Aboud A, Breuer M, Bossert T, Gummert JF. Quality of life after mechanical vs. biological aortic valve replacement. *Asian Cardiovasc Thorac Ann* 2009;17(1):35-38.

[37] Repack A, Ziganshin BA, Elefteriades JA, Mukherjee SK. Comparison of quality of life perceived by patients with bioprosthetic versus mechanical valves after composite aortic root replacement. *Cardiology* 2016;133(1):3-9.

[38] Kaplan M, Kut MS, Demirtas MM, Cimen S, Ozler A. Prosthetic replacement of tricuspid valve: bioprosthetic or mechanical. *Ann Thorac Surg* 2002;73(2):467-73.

[39] Filsoufi F, Anyanwu AC, Salzberg SP, Frankel T, Cohn LH, Adams DH. Long-term outcomes of tricuspid valve replacement in the current era. *Ann Thorac Surg* 2005;80(3):845-50.

[40] Chang BC, Lim SH, Yi G, Hong YS, Lee S, Yoo KJ, et al. Long-term clinical results of tricuspid valve replacement. *Ann Thorac Surg* 2006;81(4):1317-23, discussion 1323-4.

[41] Kim JB, Ejiofor JI, Yammine M, Camuso JM, Walsh CW, Ando M, et al. Are homografts superior to conventional prosthetic valves in the setting of infective endocarditis involving the aortic valve? *J Thorac Cardiovasc Surg* 2016;151(5):1239-46, 1248 e1-2.

[42] Fedoruk LM, Jamieson WR, Ling H, Macnab JS, Germann E, Karim SS, et al. Predictors of recurrence and reoperation for prosthetic valve endocarditis after valve replacement surgery for native valve endocarditis. *J Thorac Cardiovasc Surg* 2009;137(2):326-33.

[43] Moon MR, Miller DC, Moore KA, Oyer PE, Mitchell RS, Robbins RC, et al. Treatment of endocarditis with valve replacement: the question of tissue versus mechanical prosthesis. *Ann Thorac Surg* 2001;71(4):1164-71.

[44] Reul GJ, Sweeney MS. Bioprosthetic versus mechanical valve replacement in patients with infective endocarditis. *J Card Surg* 1989;4(4):348-51.

[45] Wos S, Jasinski M, Bachowski R, Piekarski M, Ceglarek W, Domaradzki W, et al. Results of mechanical prosthetic valve replacement in active valvular endocarditis. *J Cardiovasc Surg (Torino)* 1996;37(6 Suppl 1):29-32.

[46] Munro AI, Jamieson WR, Tyers GF, Germann E. Tricuspid valve replacement: porcine bioprostheses and mechanical prostheses. *Ann Thorac Surg* 1995;60(2 Suppl):S470-3; discussion S473-4.

APPENDIX 1: SEARCH STRATEGIES

Database	Dates	Results
CDSR	2014 - Issue 1/12 January 2019	18
DARE (CRD)	2014 - Issue 2 of 4, April 2015	64
HTA (CRD)	2014 - 2014-31/3/2018	42
Epistemonikos	2014 - 2019/01/15	1231
ECRI Guidelines	up to 2019/01/15	101
NHS Evidence	01/01/2014 - 15/01/2019	653
KSR Evidence	2014-2019/01/15	1290
GIN	2014-2019/01/15	8
Total		**3407**
Total after de-duplication		**2318**

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 1/12 January 2019
Limited 2014-2019
Searched 14.1.19

#1 MeSH descriptor: [Heart Valve Prosthesis] this term only510
#2 MeSH descriptor: [Heart Valve Prosthesis Implantation] explode all trees691
#3 (artificial* near/3 valv*):ti,ab,kw 77
#4 ((percutaneous* or sternotom* or thoracotom*) near/3 (implant* or replacement* or valv* or prosthe*)):ti,ab,kw 401
#5 ((heart or cardiac* or aort* or pericardi* or bicuspid* or tricuspid* or atrioventricular or mitral* or pulmonary or av) near/3 (prosthe* or valv* or heterograft* or hetero-graft* or implant*)):ti,ab,kw 6443
#6 (lung near/2 arter* near/3 (prosthe* or valv*)):ti,ab,kw 4
#7 (("Transcatheter Aortic Valve" adj2 Replac*) or TAVR):ti,ab 327
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7 6610
#9 ((Mechnical* or metallic* or manufactur* or synthetic*) near/3 valv*):ti,ab,kw 9
#10 MHV:ti,ab 21
#11 ((stent* near/2 framed) near/3 (replac* or valv* or implant* or prosthe*)):ti,ab,kw 0
#12 ("caged ball" or "ball and cage" or "tilting disk" or "bi-leaflet" or "tri-leaflet or bileaflet or trileaflet"):ti,ab,kw 25
#13 ("starr-edward*" or "smeloff-cutter" or Hufnagel or bjork-shiley or Bjoerk-shiley or CarboMedics or cryovalve* or cryo-valve*):ti,ab,kw 57
#14 (ATS near/3 (valv* or "open pivot" or prosthes*)):ti,ab,kw 5
#15 ((SJM or "St jude Medical") near/3 (valv* or mechanical* or prosthe* or regent or bileaflet* or bi-leaflet*)):ti,ab,kw 56
#16 ("3f Enable" or "3f-Enable" or "Aortech Aspire" or Elan or Evolut or "Freedom Solo" or INTUITY or Mitroflow or "PERCEVAL S" or "Prima Plus" or "Soprano Armonia" or "Sorin Pericarbon Freedom" or "Toronto SPV" or "Trifecta valve*"):ti,ab,kw 95
#17 ((Quattro or tiara or bicarbon or mira or "ON-X") near/3 (valv* or prosthe* or implant*)):ti,ab,kw 113
#18 ((disk* or disc*) near/3 valv*):ti,ab,kw 61
#19 (Aortech Ultracor or Duromedics or Medtronic Hall or Omnicarbon or TEKNA or CardiAQ):ti,ab,kw 19
#20 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19382
#21 ((bio-prosthe* or biologic* prosthe* or bioprosthe*) near/3 valv*):ti,ab,kw 1334
#22 (Tissue* near/3 valv*):ti,ab 35

#23 (Tissue* near/3 (heart valv* or cardiac valv*)):ti,ab,kw 653
#24 (biologic* near/3 valv*):ti,ab,kw35
#25 (biologic* near/3 valv*):ti,ab,kw35
#26 (Cardiac Biological near/3 (valv* or prosthe*)):ti,ab,kw 7
#27 ((freestyle or mosaic or liotta or Supra-G) near/3 (valv* or implant* or prosthe*)):ti,ab,kw 23
#28 (perimount magna near/3 (ease or mitral or valv* or implant* or prosthe*)):ti,ab,kw 5
#29 (Epic near/2 Stent* near/3 valv*):ti,ab,kw 0
#30 ("carpentier edwards" near/3 (valv* or implant* or prosthe* or bioprosthe* or pericardi* or perimount or porcine or supraannular or supra-annular)):ti,ab,kw 29
#31 (Hancock near/3 (valv* or implant* or prosthe*)):ti,ab,kw 12
#32 ("Acurate TA" or "Acurate TF" or Centera or "CoreValve ReValving" or "Cribier Edwards valve" or "DirectFlow" or "Edwards SAPIEN valve" or Engager or "Inovare Valve*" or JenaValve or "Lotus Valve*" or "Portico valve*" or Biocor):ti,ab,kw 102
#33 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 2049
#34 MeSH descriptor: [Heterografts] explode all trees 0
#35 (Donor* near/3 valv*):ti,ab,kw 2
#36 ((porcine* or pig or pigs* or cow or cows or bovine*) near/3 (valv* or prosthe* or bioprosthe*)):ti,ab,kw 81
#37 (Ross near/2 procedure*):ti,ab,kw 17
#38 (pulmonary near/3 (autograft* or auto-graft*)):ti,ab,kw 11
#39 (valv* near/3 (Homograft* or Homo-graft* or xenograft* or xeno-graft* or allograft* or allo-graft* or allotransplant* or allo-transplant* or isograft* or iso-graft*)):ti,ab,kw 27
#40 ((allogeneic or homostatic* or homo-static*) near/3 valv*):ti,ab,kw 0
#41 #34 or #35 or #36 or #37 or #38 or #39 or #40 123
#42 MeSH descriptor: [Heart] explode all trees 6652
#43 (heart or cardiac* or aort* or pericardi* or bicuspid* or tricuspid* or atrioventricular or mitral* or pulmonary or av or coronary or aortocoron* or myocard* or valv*):ti,ab,kw 180453
#44 #42 or #43 180474
#45 (Homograft* or Homo-graft* or xenograft* or xeno-graft* or allograft* or allo-graft* or allotransplant* or allo-transplant* or isograft* or iso-graft*):ti,ab,kw 4341
#46 (Donor* near/3 graft*):ti,ab,kw 757
#47 ((allogeneic or homostatic* or homo-static*) near/3 graft*):ti,ab,kw 86
#48 #45 or #46 or #47 5060
#49 #44 and #48 552
#50 #33 or #41 or #49 2579
#51 #20 and #50 182
#52 #8 or #51 with Cochrane Library publication date Between Jan 2014 and Jan 2019 4249

CDSR search retrieved 18 records.

Database of Abstracts of Reviews of Effects (DARE) (CRD): Issue 2 of 4, April 2015
Health Technology Assessment Database (HTA) (CRD): 2014-31/3/2018
Limited 2014-2018
Searched 14.1.19
1 MeSH DESCRIPTOR Heart Valve Prosthesis Implantation EXPLODE ALL TREES IN DARE,HTA 110
2 MeSH DESCRIPTOR Heart Valves IN DARE,HTA 7
3 ((artificial* NEAR valv*))4

4 (((percutaneous* or sternotom* or thoracotom*) NEAR (implant* or replacement* or valv* or prosthe*))) 84
5 (((heart or cardiac* or aort* or pericardi* or bicuspid* or tricuspid* or atrioventricular or mitral* or pulmonary or av) NEAR (prosthe* or valv* or heterograft* or hetero-graft* or implant*))) 673
6 ((lung NEAR arter* NEAR (prosthe* or valv*))) 0
7 ((("Transcatheter Aortic Valve" adj2 Replac*) or TAVR)) 24
8 (#1 or #2 or #3 or #4 or #5 or #6 or #7) 711
9 (((Mechnical* or metallic* or manufactur* or synthetic*) NEAR valv*)) 4
10 (MHV) 0
11 (((stent* NEAR framed) NEAR (replac* or valv* or implant* or prosthe*))) 0
12 (((caged ball) or (ball and cage) or (tilting disk) or bi-leaflet or tri-leaflet or bileaflet or trileaflet)) 4
13 ((starr-edward* or smeloff-cutter or Hufnagel or bjork-shiley or Bjoerk-shiley or CarboMedics or cryovalve* or cryo-valve*)) 0
14 ((ATS NEAR (valv* or open pivot or prosthes*))) 1
15 (((SJM or (St jude Medical)) NEAR (valv* or mechanical* or prosthe* or regent or bileaflet* or bi-leaflet*))) 0
16 ((3f Enable or 3f-Enable or (Aortech Aspire) or Elan or Evolut or (Freedom Solo) or INTUITY or Mitroflow or PERCEVAL-S or (Prima Plus) or (Soprano Armonia) or (Sorin Pericarbon Freedom) or Toronto-SPV or Trifecta valve*)) 10
17 (((Quattro or tiara or bicarbon or mira or ON-X) NEAR (valv* or prosthe* or implant*))) 1
18 (((disk* or disc*) NEAR valv*)) 0
19 ((Aortech Ultracor or Duromedics or Medtronic Hall or Omnicarbon or TEKNA or CardiAQ)) 0
20 (#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19) 19
21 (((bio-prosthe* or biologic* prosthe* or bioprosthe*) NEAR valv*)) 23
22 ((Tissue* NEAR valv*)) 8
23 ((Tissue* NEAR (heart valv* or cardiac valv*))) 2
24 ((biologic* NEAR valv*)) 2
25 ((Cardiac Biological NEAR (valv* or prosthe*))) 0
26 (((freestyle or mosaic or liotta or Supra-G) NEAR (valv* or implant* or prosthe*))) 0
27 ((perimount magna NEAR (ease or mitral or valv* or implant* or prosthe*))) 0
28 ((Epic NEAR Stent* NEAR valv*))0
29 ((carpentier edwards NEAR (valv* or implant* or prosthe* or bioprosthe* or pericardi* or perimount or porcine or supraannular or supra-annular))) 0
30 ((Hancock NEAR (valv* or implant* or prosthe*))) 0
31 ((Acurate TA or Acurate TF or Centera or CoreValve ReValving or Cribier Edwards valve or DirectFlow or Edwards SAPIEN valve or Engager or Inovare Valve* or JenaValve or Lotus Valve* or Portico valve* or Biocor)) 2
32 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31) 32
33 MeSH DESCRIPTOR Heterografts IN DARE,HTA 0
34 ((Donor* NEAR valv*)) 0
35 (((porcine* or pig or pigs* or cow or cows or bovine*) NEAR (valv* or prosthe* or bioprosthe*))) 2
36 ((Ross NEAR procedure*)) 4
37 ((pulmonary NEAR (autograft* or auto-graft*))) 1
38 ((valv* NEAR (Homograft* or Homo-graft* or xenograft* or xeno-graft* or allograft* or allo-graft* or allotransplant* or allo-transplant* or isograft* or iso-graft*))) 2
39 (((allogeneic or homostatic* or homo-static*) NEAR valv*)) 0
40 (#33 or #34 or #35 or #36 or #37 or #38 or #39) 7

41 MeSH DESCRIPTOR Heart EXPLODE ALL TREES IN DARE,HTA 289
42 ((heart or cardiac* or aort* or pericardi* or bicuspid* or tricuspid* or atrioventricular or mitral* or pulmonary or av or coronary or aortocoron* or myocard* or valv*)) 11461
43 (#41 or #42) 11469
44 ((Homograft* or Homo-graft* or xenograft* or xeno-graft* or allograft* or allo-graft* or allotransplant* or allo-transplant* or isograft* or iso-graft*)) 197
45 ((Donor* NEAR graft*)) 21
46 (((allogeneic or homostatic* or homo-static*) NEAR graft*)) 7
47 (#44 or #45 or #46) 223
48 (#43 and #47) 39
49 (#20 or #32 or #48) 81
50 (#20 and #49) 19
51 (#8 or #50) 719
52 (#8 or #50) IN DARE, HTA 539
53 (#8 or #50) IN DARE, HTA FROM 2014 TO 2019 106
54 (#8 or #50) IN HTA FROM 2014 TO 201942
55 (#8 or #50) IN DARE FROM 2014 TO 2019 64

DARE search retrieved 64 records.
HTA search retrieved 42 records.

KSR Evidence (Internet): 2014-2019/01/15
Limited 2014-2019
Searched 15.1.19
1 (artificial* AND valv*) in All text 32
2 (percutaneous* or sternotom* or thoracotom*) AND (implant* or replacement* or valv* or prosthe*) in All text 234
3 (heart or cardiac* or aort* or pericardi* or bicuspid* or tricuspid* or atrioventricular or mitral* or pulmonary or av) AND (prosthe* or valv* or heterograft* or hetero-graft* or implant*) in All text 1057
4 lung arter* AND (prosthe* or valv*) in All text 20
5 "Transcatheter Aortic Valve" AND Replac* in All text 185
6 TAVR in All text 99
7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 1140
8 (Mechnical* or metallic* or manufactur* or synthetic*) AND valv* in All text 2
9 MHV in All text 2
10 "stent framed" AND (replac* or valv* or implant* or prosthe*) in All text -
11 "caged ball" or "ball and cage" or "tilting disk" or "bi-leaflet" or "tri-leaflet or bileaflet or trileaflet" in All text -
12 "starr-edward*" or "smeloff-cutter" or Hufnagel or bjork-shiley or Bjoerk-shiley or CarboMedics or cryovalve* or cryo-valve* in All text 1
13 ATS AND (valv* or "open pivot" or prosthes*) in All text -
14 (SJM or "St jude Medical") AND (valv* or mechanical* or prosthe* or regent or bileaflet* or bi-leaflet*) in All text 3
15 "3f Enable" or "3f-Enable" or "Aortech Aspire" or Elan or Evolut or "Freedom Solo" or INTUITY or Mitroflow or "PERCEVAL S" or "Prima Plus" or "Soprano Armonia" or "Sorin Pericarbon Freedom" or "Toronto SPV" or "Trifecta valve" in All text 7
16 (Quattro or tiara or bicarbon or mira or "ON-X") AND (valv* or prosthe* or implant*) in All text 6
17 (disk* or disc*) AND valv* in All text 46

18 Aortech Ultracor or Duromedics or Medtronic Hall or Omnicarbon or TEKNA or CardiAQ in All text -
19 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 65
20 (bio-prosthe* or biologic* prosthe* or bioprosthe*) AND valv* in All text 48
21 Tissue* AND valv* in All text 23
22 Tissue* AND (heart valv* or cardiac valv*) in All text 17
23 biologic* AND valv* in All text 16
24 "Cardiac Biological" AND (valv* or prosthe*) in All text -
25 (freestyle or mosaic or liotta or Supra-G) AND (valv* or implant* or prosthe*) in All text 1
26 perimount magna AND (ease or mitral or valv* or implant* or prosthe*) in All text 1
27 (Epic Stent* AND valv*) in All text -
28 "carpentier edwards" AND (valv* or implant* or prosthe* or bioprosthe* or pericardi* or perimount or porcine or supraannular or supra-annular) in All text 1
29 Hancock AND (valv* or implant* or prosthe*) in All text -
30 "Acurate TA" or "Acurate TF" or Centera or "CoreValve ReValving" or "Cribier Edwards valve" or "DirectFlow" or "Edwards SAPIEN valve" or Engager or "Inovare Valve*" or JenaValve or "Lotus Valve" or "Portico valve" or Biocor in All text 2
31 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 82
32 "Donor valve" OR "donor valves" OR "Ross procedure" in All text 4
33 (porcine* or pig or pigs* or cow or cows or bovine*) AND (valv* or prosthe* or bioprosthe*) in All text 8
34 pulmonary AND (autograft* or auto-graft*) in All text 2
35 valv* AND (Homograft* or Homo-graft* or xenograft* or xeno-graft* or allograft* or allo-graft* or allotransplant* or allo-transplant* or isograft* or iso-graft*) in All text 8
36 (allogeneic or homostatic* or homo-static*) AND valv* in All text 1
37 #32 OR #33 OR #34 OR #35 OR #36 19
38 heart or cardiac* or aort* or pericardi* or bicuspid* or tricuspid* or atrioventricular or mitral* or pulmonary or av or coronary or aortocoron* or myocard* or valv* in All text 10742
39 (Homograft* or Homo-graft* or xenograft* or xeno-graft* or allograft* or allo-graft* or allotransplant* or allo-transplant* or isograft* or iso-graft*) in All text 315
40 Donor* AND grafts* in All text 41
41 (allogeneic or homostatic* or homo-static*) AND graft* in All text 40
42 #39 OR #40 OR #41 371
43 38 AND 42 in All text 183
44 #31 OR #37 OR #43 274
45 #19 AND 44 in All text 176
46 #7 OR #45 1315
Limited 2014-2019 = 1290

Database last updated 15 Jan 2019, 11:18 a.m.

International Guideline Library (GIN) (Internet): 2014-2019/01/15
Limited 2014-2019
Searched 15.1.19
https://www.g-i-n.net/library/international-guidelines-library/international-guidelines-library/

Search term	Hits
heart valve	15
bioprosthesis	0
bioprosthetic	0
valve	16

valves	2
heterograft	0
"Transcatheter Aortic Valve"	3
TAVR	0
MHV	0
"caged ball"	0
"ball and cage"	0
"tilting disk"	0
"bi-leaflet"	0
"bileaflet"	0
trileaflet	0
tri-leaflet	0
"starr-edward"	0
"smeloff-cutter"	0
Hufnagel	0
bjork-shiley	0
Bjoerk-shiley	0
CarboMedics	0
cryovalve	0
"St jude Medical"	0
"Cardiac Biological"	0
"carpentier edwards"	0
autograft	0
auto*graft	0
xenograft	0
xeno-graft	0
Total including duplicates	**36**
Total without duplicates – all years	**15**
Total without duplicates – 2014-2017	**8**

Epistemonikos (Internet): 2014-2019/01/15
Searched 15.1.19
https://www.epistemonikos.org/en/

Limited 2014-2019.
Limited to systematic reviews, Cochrane SRs omitted.

(title:((artificial* AND valv*)) OR abstract:((artificial* AND valv*))) OR (title:(((percutaneous* OR sternotom* OR thoracotom*) AND (implant* OR replacement* OR valv* OR prosthe*))) OR abstract:(((percutaneous* OR sternotom* OR thoracotom*) AND (implant* OR replacement* OR valv* OR prosthe*)))) OR (title:(((heart OR cardiac* OR aort* OR pericardi* OR bicuspid* OR tricuspid* OR atrioventricular OR mitral* OR pulmonary OR av) AND (prosthe* OR valv* OR heterograft* OR hetero-graft* OR implant*))) OR abstract:(((heart OR cardiac* OR aort* OR pericardi* OR bicuspid* OR tricuspid* OR atrioventricular OR mitral* OR pulmonary OR av) AND (prosthe* OR valv* OR heterograft* OR hetero-graft* OR implant*)))) OR (title:("lung artery" AND (prosthe* OR valv*)) OR abstract:("lung artery" AND (prosthe* OR valv*))) OR (title:("Transcatheter Aortic Valve" AND Replac*) OR abstract:("Transcatheter Aortic Valve" AND Replac*)) OR (title:(TAVR AND MHV) OR abstract:(TAVR AND MHV)) OR (title:(((Mechnical* OR metallic* OR manufactur* OR synthetic*) AND valv*)) OR abstract:(((Mechnical* OR metallic* OR manufactur* OR synthetic*) AND valv*))) OR (title:("stent framed" AND (replac* OR valv* OR implant* OR prosthe*)) OR

abstract:("stent framed" AND (replac* OR valv* OR implant* OR prosthe*))) OR (title:("caged ball" OR "ball AND cage" OR "tilting disk" OR "bi-leaflet" OR tri-leaflet OR bileaflet OR trileaflet OR "starr-edward*" OR "smeloff-cutter" OR Hufnagel OR bjork-shiley OR Bjoerk-shiley OR CarboMedics OR cryovalve* OR cryo-valve*) OR abstract:("caged ball" OR "ball AND cage" OR "tilting disk" OR "bi-leaflet" OR tri-leaflet OR bileaflet OR trileaflet OR "starr-edward*" OR "smeloff-cutter" OR Hufnagel OR bjork-shiley OR Bjoerk-shiley OR CarboMedics OR cryovalve* OR cryo-valve*)) OR (title:(ATS AND (valv* OR "open pivot" OR prosthes*)) OR abstract:(ATS AND (valv* OR "open pivot" OR prosthes*))) OR (title:((Tissue* AND valv*)) OR abstract:((Tissue* AND valv*))) OR (title:((biologic* AND valv*)) OR abstract:((biologic* AND valv*))) OR (title:(Cardiac Biological AND (valv* OR prosthe*)) OR abstract:(Cardiac Biological AND (valv* OR prosthe*))) OR (title:((Donor* AND valv*)) OR abstract:((Donor* AND valv*))) OR (title:((porcine* OR pig OR pigs* OR cow OR cows OR bovine*) AND (valv* OR prosthe* OR bioprosthe*)) OR abstract:((porcine* OR pig OR pigs* OR cow OR cows OR bovine*) AND (valv* OR prosthe* OR bioprosthe*))) OR (title:((valv* AND (Homograft* OR Homo-graft* OR xenograft* OR xeno-graft* OR allograft* OR allo-graft* OR allotransplant* OR allo-transplant* OR isograft* OR iso-graft*))) OR abstract:((valv* AND (Homograft* OR Homo-graft* OR xenograft* OR xeno-graft* OR allograft* OR allo-graft* OR allotransplant* OR allo-transplant* OR isograft* OR iso-graft*)))) OR (title:((heart OR cardiac* OR aort* OR pericardi* OR bicuspid* OR tricuspid* OR atrioventricular OR mitral* OR pulmonary OR av OR coronary OR aortocoron* OR myocard*) AND valv*) OR abstract:((heart OR cardiac* OR aort* OR pericardi* OR bicuspid* OR tricuspid* OR atrioventricular OR mitral* OR pulmonary OR av OR coronary OR aortocoron* OR myocard*) AND valv*))

Retrieved 1231 records.

ECRI Guidelines Trust (Internet): up to 2019/01/15
Searched 15.1.19
https://guidelines.ecri.org/

Searched for Valve, limited to Clinical Area: Cardiology

101 results, saved to Word file.

NHS Evidence search (Internet): limited 01/01/2014-15/01/2019
Searched 15.1.19
https://www.evidence.nhs.uk/

Searched for: Heart valve
Limited by date: **01/01/2014-15/01/2019**
Limited to Guidance and Secondary Evidence.

653 results.