NICE National Institute for Health and Care Excellence

Medical Technologies Advisory Committee (MTAC)

Thursday 17 October 2024

GID-HTE10027 Transcatheter heart valves for transcatheter aortic valve implantation to treat aortic stenosis

This product class was selected for late stage assessment in 2023.

Clinical and economic evidence has been submitted to NICE by the companies in RFIs, and an external assessment group report has been completed by the EAG. Alongside this, a user preference report has been produced by NICE. These were discussed at MTAC (17 July 2024) and draft guidance consulted on between 8 August and 22 August 2024.

This pack presents the information required for the MTAC to make final recommendations on this topic, taking into account draft consultation comments and the EAG's response.

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Papers included in pack:

1. Front sheet
2. Draft Guidance
3. EAG consultation responses
4. EAG Addendum

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HEALTHTECH PROGRAMME

Draft guidance

Transcatheter heart valves for transcatheter aortic valve implantation to treat aortic stenosis: late-stage assessment

Guidance development process

Late-stage assessment (LSA) guidance evaluates categories of technologies that are already in widespread use within the NHS. It assesses whether price variations between technologies in a category are justified by differences in innovation, clinical effectiveness and patient benefits. This will support NHS commissioners, procurement teams, patients and clinicians to choose technologies that maximise clinical effectiveness and value for money.

Find out more on the NICE webpage on late-stage assessment (LSA) for medtech.

This guidance does not replace existing guidance on when to use TAVI to treat aortic stenosis. It only provides information on which valves should be considered once the decision to do TAVI has been made, and on the evidence comparing different types of valve.

The National Institute for Health and Care Excellence (NICE) is producing guidance on using transcatheter heart valves for transcatheter aortic valve implantation to treat aortic stenosis in the NHS in England. The medical technologies advisory committee has considered the evidence and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the

recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence (the external assessment report).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the recommendations may need changing to meet these aims. In particular, please tell us if the recommendations:

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology.
- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have about such effects and how they could be avoided or reduced.

Note that this document is not NICE's final guidance on transcatheter heart valves for transcatheter aortic valve implantation to treat aortic stenosis. The recommendations in section 1 may change after consultation.

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering the comments the committee will prepare its final recommendations. For further

details, see NICE health technology evaluations: the manual and NICE's late-stage assessment interim process and methods statement.

Key dates

Closing date for comments: 2 September 2024

Second medical technologies advisory committee meeting: 17 October 2024

1 Recommendations

1.1 There is not enough evidence to determine whether incremental innovations can justify price variations between different transcatheter heart valves for transcatheter aortic valve implantation (TAVI) in adults with aortic stenosis.

1.2 Use the least expensive option available that is clinically appropriate for TAVI in the person with aortic stenosis.

1.3 NHS trusts should provide access to a range of valves, so that the most clinically appropriate valve is available for everyone with aortic stenosis.

What information is needed

More information is needed to determine whether price variation can be justified between different transcatheter heart valves. Details of all patients should be entered into the UK TAVI registry to enable robust comparisons. Key outcomes and information that should be captured include:

- mortality
- stroke
- paravalvular leak or aortic regurgitation
- permanent pacemaker implantation
- reintervention
- the specific valve used.

All primary studies and analyses of real-world data should adjust for a range of confounding factors including:

- the anatomy of the valve being replaced
- the level and distribution of calcium around the valve
- the person's surgical risk
- the person's age, sex, comorbidities and previous medicine use.

These outcomes and baseline characteristics will also need to be recorded in the UK TAVI registry.

What this means in practice

Procurement and commissioning considerations

- Analyses from the economic evaluation done for NICE's guideline on heart valve disease presenting in adults: investigation and management indicated that a transcatheter heart valve would have to cost £14,800 or less for the procedure to be cost effective for all surgical risks. Most of the transcatheter heart valves currently available in the NHS cost more than £14,800 at their list price.
- 'Added value' agreements between companies and NHS Supply Chain allow for part of the cost of a valve to be returned to an NHS trust based on the number of valves purchased. This can typically only be spent on structural heart-related items or staff within the trust, so will not be resource-releasing for the NHS. Most of the transcatheter heart valves currently available in the NHS cost more than £14,800 even after accounting for 'added value' agreements. The NHS may benefit more from negotiating prices that would be cost-effective across all surgical risk groups than from using those with 'added value' agreements.
- The number of TAVI procedures done annually is rising (NICOR UK TAVI registry 2024 summary report).

Why the committee made these recommendations

Transcatheter heart valves are used to replace a narrowed aortic valve or a failed bioprosthetic valve in people with aortic stenosis. There are many

transcatheter heart valves available, which vary in features and cost. This assessment aims to determine whether the differences in clinical, economic and non-clinical outcomes between the different valves attributed to innovative features or characteristics of the valves could justify price variation.

For most people with aortic stenosis, many of the available valves could be used and are likely to be clinically comparable. For some people a specific valve may be more appropriate. The effectiveness of individual valves is likely to depend both on the features of the valve and the characteristics of the person with aortic stenosis.

Analyses of real-world data from the UK TAVI registry are limited because of unrecorded confounders (factors that may affect the results), missing data and short follow up. There is no high-quality published evidence that is as relevant to the UK population as the TAVI registry. The results from an economic evaluation based on the real-world data analyses are too uncertain to determine whether the differences in cost between valves are justified.

More evidence is needed to show if differences in price between valves can be justified by differences in effectiveness. New valves should be able to show that they work as well as other valves. Evidence needs to be comparative and needs to adjust for baseline characteristics that have a large impact on outcomes. These baseline characteristics will also need to be recorded in the UK TAVI registry. This is to ensure that results reflect the performance of the valve used and not the people it is used in.

2 The technologies

2.1 Transcatheter heart valves are used for a transcatheter aortic valve implantation (TAVI) procedure, when a narrowed native aortic valve or a failed bioprosthetic valve is replaced through a blood vessel in the leg or chest. Transcatheter heart valves consist of a stent frame and animal pericardium tissue leaflets. The valves vary in physical characteristics such as the alloy of the frame, the type of tissue of the leaflets and the available valve sizes. They also vary in technical characteristics such as the expansion mechanism, the presence of locators or anchors and the valve positioning relative to the native aortic valve.

2.2 Transcatheter heart valves are used with a loading and a delivery system. The delivery system can vary in its ability to recapture and reposition the valve, the flexibility of the delivery sheath and the minimum vessel size for access.

2.3 Eleven transcatheter heart valves were available on NHS Supply Chain and included in this assessment. All of them had valid CE certification as class III implantable devices.

ACURATE neo2 (Boston Scientific)

2.4 ACURATE neo2 is a self-expanding transcatheter heart valve made from porcine pericardial tissue. It is positioned supra-annularly and is available in 3 sizes: 23 mm, 25 mm and 27 mm. It is indicated for relief of aortic stenosis in people with symptomatic heart disease due to severe native calcific aortic stenosis when a heart team, including a cardiac surgeon, decides that a transcatheter heart valve replacement is appropriate.

Allegra (Biosensors)

2.5 Allegra is a self-expanding transcatheter heart valve made from bovine pericardial tissue. It is positioned supra-annularly and is available in 3 sizes: 23 mm, 27 mm and 31 mm. It is indicated for

treating severe calcified aortic valve stenosis in people at high surgical risk and for treating severe calcified aortic valve stenosis in people with a symptomatic degeneration of an aortic valve bioprosthesis.

Evolut R, Evolut Pro+ and Evolut FX (Medtronic)

2.6 Evolut R, Evolut Pro+ and Evolut FX are self-expanding transcatheter heart valves made from porcine pericardial tissue. They are positioned supra-annularly and are available in 4 sizes: 23 mm, 26 mm, 29 mm and 34 mm. The valves are indicated for adults presenting with severe native aortic valve stenosis. In severe native bicuspid aortic valve stenosis, the Evolut transcatheter heart valves are indicated for people at intermediate or greater risk for surgical aortic valve replacement (SAVR), or a documented heart team agreement of risk for SAVR because of frailty or comorbidities. Intermediate risk is defined as the Society of Thoracic Surgeons (STS) operative risk score of 4% and above. For people presenting at low risk for SAVR (less than 4%), the systems are indicated for people aged 70 and older with a left ventricular ejection fraction (LVEF) above 30%. Evolut R, Evolut Pro+ and Evolut FX are also indicated for people with a stenosed, insufficient, or combined surgical bioprosthetic valve failure needing valve replacement who are at high or greater risk for SAVR, or there is a documented heart team agreement of risk for SAVR because of frailty or comorbidities. High risk is defined as STS operative risk score of 8% and above. Compared with the Evolut R, the Evolut Pro+ has an additional external pericardial wrap and an updated delivery system. Compared with the Evolut Pro+, the Evolut FX has additional gold markers to visualise implant depth and coronary alignment, and has an updated delivery system.

Hydra (SMT)

2.7 Hydra is a self-expanding transcatheter heart valve made from bovine pericardial tissue. It is positioned supra-annularly and is available in 3 sizes: 22 mm, 26 mm and 30 mm. It is indicated for people with severe degenerative aortic stenosis presenting with a high predictable operative mortality risk for surgical aortic valve replacement. The decision is based on the clinical judgment of the heart team.

Myval Octacor (Meril)

2.8 Myval Octacor is a balloon-expanding transcatheter heart valve made from bovine pericardial tissue. It is positioned intra-annularly and is available in 9 sizes between 20 mm and 32 mm. Myval Octacor is indicated for relief of aortic stenosis in people with symptomatic heart disease because of severe native calcific aortic stenosis as judged by a heart team, including a cardiac surgeon. It is also indicated for people who have a risk for open heart surgery (STS operative risk score of 4% and above risk of mortality at 30 days).

Navitor (Abbott)

2.9 Navitor is a self-expanding transcatheter heart valve made from bovine pericardial tissue. It is the only self-expanding valve with intra-annular leaflets. Navitor is available in 4 sizes: 23 mm, 25 mm, 27 mm and 29 mm. Navitor is indicated for people with symptomatic severe native aortic stenosis who are considered high or extreme risk for SAVR.

Sapien 3 and Sapien 3 Ultra (Edwards)

2.10 Sapien 3 and Sapien 3 Ultra are balloon-expanding transcatheter heart valves made from bovine pericardial tissue. They are positioned intra-annularly and are available in 20 mm, 23 mm and 26 mm sizes. Sapien 3 is also available in a 29 mm size. The

valves are indicated for people with severe, symptomatic, calcific aortic valve stenosis who a heart team considers to be at intermediate or greater risk for open heart surgery. Intermediate or greater risk is defined as a predicted risk of surgical mortality of 3% and above at 30 days, based on the STS risk score and other clinical comorbidities unmeasured by the STS risk calculator. The valves are also indicated for people with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve or a surgical bioprosthetic mitral valve who a heart team, including a cardiac surgeon, considers to be at high or greater risk for open surgical therapy. High or greater risk is defined as a predicted risk of surgical mortality of 8% and above at 30 days, based on the STS risk score and other clinical comorbidities unmeasured by the STS risk calculator. Compared with the Sapien 3, the Sapien 3 Ultra has an augmented outer skirt.

Trilogy (Jenavalve)

2.11 Trilogy is a self-expanding transcatheter heart valve made from porcine pericardial tissue. It is positioned supra-annularly and is available in 3 sizes: 23 mm, 25 mm and 27 mm. Trilogy is indicated for people with native symptomatic, severe aortic regurgitation or symptomatic, severe aortic stenosis who a heart team, including a cardiac surgeon, considers to have high or greater risk for SAVR. High or greater risk is defined as a predicted risk of surgical mortality of 8% and above at 30 days, based on the STS risk score and other clinical comorbidities unmeasured by the STS risk calculator.

3 Committee discussion

The advisory committee considered evidence on 11 transcatheter heart valves for transcatheter aortic valve implantation (TAVI) in people with aortic stenosis from several sources to determine whether price variation between the valves could be justified by differences in their clinical, cost effectiveness or non-clinical outcomes important to users. These included clinical evidence from analyses of real-world UK data by the external assessment group (EAG), a targeted review of the published literature, evidence submitted by the companies and responses from stakeholders. The committee also considered the economic evidence from a review of the published literature, an economic evaluation done by the EAG and a user preference assessment done by NICE.

The condition

3.1 Aortic stenosis occurs when the aortic valve thickens or stiffens and does not open properly. The prevalence among people aged over 55 in the UK is about 1.5% (Strange et al. 2022). Aortic stenosis can lead to heart failure and death if left untreated.

Current practice

Population

3.2 TAVI is primarily used in people who are at high risk for heart surgery or for whom surgery is inappropriate. But it is increasingly considered as a treatment option for people who are at low or intermediate surgical risk following a position statement by NHS England, 2023. In response to this statement, the Society for Cardiothoracic Surgery in Great Britain & Ireland and the Royal College of Surgeons submitted a letter stating that the policy was not clinically appropriate and could increase patient risks if subsequent surgery was needed.

Choice of valve

3.3 Clinical experts advised that the decision about which type of transcatheter heart valve to use is usually made by an interventional cardiologist and largely depends on the clinical characteristics of the person with aortic stenosis. The decision may also be related to the clinician's experience with a particular transcatheter heart valve or the range of valves that are locally available. Most NHS trusts will have access to at least 1 self-expanding and 1 balloon-expanding valve. The clinical experts explained that the anatomy of the valve being replaced, the level and distribution of calcium and the person's surgical risk are particularly important and can be strong predictors of clinical outcomes. The committee heard that most people with aortic stenosis (that is, more than 50%) would not need a specific transcatheter heart valve and a wide range could be used.

3.4 The committee noted that the valves being assessed vary in their indications (see section 2). Clinical experts stated that most people having TAVI are at high surgical risk, with a tricuspid valve anatomy. Also, most TAVI procedures are done to replace a native aortic valve. The committee noted that all the valves in the assessment are indicated for this population. A clinical expert stated that transcatheter heart valves are sometimes used outside of their indication when this is considered clinically appropriate.

Shared decision making

3.5 The committee noted the importance of communication with patients when making decisions about which specific transcatheter heart valve has been chosen. The committee acknowledged that the specific valve is typically chosen by an interventional cardiologist and that there is usually not a meaningful choice to be made by the person with aortic stenosis, because their treatment will not differ based on which valve they have. But a patient expert stated that people having TAVI value having information about the

factors influencing valve choice, so that they can better understand the reasoning. The committee also noted the value of shared decision making and patient involvement across the whole care pathway.

Clinical effectiveness

Availability of clinical evidence to address the decision question

3.6 The committee acknowledged the wealth of evidence on the clinical performance of transcatheter heart valves and the relative treatment effectiveness of TAVI compared with surgery. But, it noted that there was little comparative evidence between different transcatheter heart valves and between companies. The EAG explained that it considered the UK TAVI registry (see section 3.8) the strongest source of clinical evidence. This is because it provided recent data from the UK, and allowed the assessment of multiple valves, while adjusting for recorded confounders. The EAG explained that 4 available network meta-analyses were unreliable because of differences in patient characteristics in the included studies. This can lead to a breach of the assumption of transitivity (that a patient could have been randomised to any of the study arms included in the analysis). The EAG also highlighted that the network meta-analyses included valves that had been withdrawn from market or were no longer available for purchase.

3.7 The committee and companies queried why randomised controlled trial (RCT) data was not considered and noted that it could provide important information, especially about long-term outcomes. The EAG noted that 1 non-inferiority RCT comparing multiple transcatheter heart valves and 4 network meta-analyses (that included RCTs) were included in the evidence summary. But it explained that most RCTs identified during the evidence review included surgery as a comparator, and often included older generation valves or valves no longer available in the NHS. The

EAG explained that because of the recent changes in the populations having TAVI and surgery in the NHS, evidence from an RCT where surgery is a comparator may not reflect current care. The committee queried whether published evidence from countries other than the UK was generalisable to the NHS. An expert adviser said that international evidence is broadly generalisable to the NHS. But a specialist committee member noted that the level of TAVI use in the UK is lower than in many other higher-income countries and that the populations may be different in terms of the proportions of people at different surgical risks.

Quality of UK TAVI registry data

3.8 The UK TAVI registry is a mandatory registry that collects information for all TAVI procedures across England, Wales and Northern Ireland. The UK TAVI registry was created to define the characteristics and clinical outcomes in people having TAVI, regardless of technology or access route, in every centre doing TAVI in the UK. The registry is managed by the National Institute for Cardiovascular Outcomes Research with clinical direction and strategy provided by the British Cardiovascular Interventional Society and the Society for Cardiothoracic Surgeons. The committee agreed that the dataset reflects clinical practice in the NHS, but that it has limitations. The EAG was able to collate data from 7,409 procedures where the TAVI device could be identified. It explained that the registry only contains data on in-hospital outcomes and that the available data only included valves from 4 companies. Clinical experts stated that several clinically important patient characteristics (see section 3.3) are not recorded in the UK TAVI registry, and that it was not designed to make direct valve comparisons. The EAG also highlighted that many fields in the registry were poorly completed.

3.9 To address the lack of long-term data in the UK TAVI registry, the EAG linked the data to Hospital Episode Statistics (HES) based on

the NHS trust, age and sex. The EAG explained that the linked dataset censored 381 procedures from Wales and Northern Ireland and that no match was found for 520 procedures. This resulted in 6,508 matches, of which 6,270 were procedures to replace a native aortic valve. The committee agreed that the linkage was robust. But it noted that the longest follow up within the linked dataset was 31 months, so the results could not be considered to fully represent long-term outcomes. Also, the EAG's decision to only use cases with no missing data markedly reduced the sample size (to 3,917 from 6,270 records in the UK TAVI registry).

Results of UK TAVI registry analyses

3.10 The committee concluded that the UK TAVI registry data did not capture enough detail to provide reliable estimates of relative efficacy between valves. Multivariate analysis of the linked dataset showed statistically significant differences in the odds of experiencing in-hospital stroke, in-hospital aortic regurgitation and in-hospital permanent pacemaker implantation between some of the transcatheter heart valves. These differences were not seen in outcomes after discharge from hospital. The committee noted that the analysis of the linked dataset was limited because it was not possible to adjust for clinically important patient characteristics that are not recorded in the UK TAVI registry or HES (see section 3.3). So, it was not possible to conclude whether the observed outcomes in the analyses were because of features of the valves or the clinical characteristics of the people with aortic stenosis. The EAG explained that the results are also confounded by how much a valve has been used in the NHS during the study period. This leads to higher uncertainty for those valves that have been used less frequently. A specialist committee member explained that the most commonly used valves may be more likely to be used for people who can have a transcatheter heart valve from any company, and who are less likely to experience complications. But it is also possible that cardiologists may prefer to use the transcatheter heart

valve they are most familiar with for people with more complex anatomy who are more likely to experience complications. The committee acknowledged that the differences in how much each valve is used in the NHS can have a significant impact on the validity of the results.

Published evidence

3.11 The committee considered evidence on device-specific short and long-term outcomes from a number of peer-reviewed studies identified by the EAG. This included 4 network meta-analyses comparing multiple valves, 4 studies comparing multiple valves while adjusting for confounders, as well as a number of additional observational, non-randomised, single-arm and retrospective studies. The committee noted that the published evidence assessed by the EAG was not identified by a systematic search. The EAG acknowledged that this approach can lead to bias, but explained that this was a pragmatic choice given the abundance of published evidence, intended to address gaps in the real-world evidence.

Evidence for valves not captured in the UK TAVI registry

3.12 Five transcatheter heart valves (Allegra, Evolut FX, Hydra, Myval Octacor and Trilogy) had no data in the UK TAVI registry because they were new to the NHS Supply Chain framework at the time of assessment. The committee noted that the published evidence identified by the EAG presented the best available evidence for these valves, but it acknowledged that it was sparse and subject to bias and limitations.

Clinical comparability between companies

3.13 It was not clear in the clinical evidence whether there are differences in clinical effectiveness between different companies' transcatheter heart valves due to incremental innovations between the valves. But, the committee acknowledged that clinical

equivalence between companies' valves could not be assumed. The committee recalled that for most people with aortic stenosis, many of the available valves could be used (see section 3.3). So, it is likely that for those people the valves are clinically comparable.

Relative performance between valve generations

3.14 The committee queried whether it is appropriate to assume clinical equivalence between generations of a valve from the same company. Clinical experts commented that it was inappropriate to present results of the registry analysis separately for different generations of valves from the same company, because they considered these largely equivalent. A specialist committee member and company representatives explained that usually newer generations make incremental improvements and that these are often small changes which would not affect outcomes, such as durability. The EAG highlighted that clinical studies between generations typically have short follow up and do not provide long-term data, with the longest follow up being 1 year. It stated that, since differences in clinical outcomes between generations have been seen in the literature, long-term equivalence could not be assumed. A specialist committee member stated that it should not be assumed that a newer valve is non-inferior if the differences between valves are substantial (for example, changes in the leaflet tissue). This was based on the committee member's experience with surgical heart valves. The committee concluded that it is likely that newer generations of valves work as well as previous generations, but that this cannot be assumed.

Economic evaluation

Economic model structure

3.15 The EAG adapted the economic model used in the economic evaluation for NICE's guideline on heart valve disease presenting in adults: investigation and management (from now, NG208), to

allow for direct comparisons of different transcatheter heart valves. The committee considered the structure and assumptions of the EAG's economic model and agreed that it was an appropriate representation of clinical practice in the NHS.

Model clinical inputs

3.16 The committee concluded that the clinical inputs to the economic model had limitations, because they relied on the results of the multivariate analysis of the UK TAVI registry, which were highly uncertain (see section 3.10). The transition probabilities between health states in the model were calculated from the event rates in the linked dataset. The committee recalled the bias and limitations associated with this dataset and agreed that this leads to significant bias in the results of the economic model.

3.17 Expert advisers and the companies suggested that data from RCTs could be used to inform the economic model, especially for long-term outcomes. The EAG explained that using data from different sources for different outcomes is likely to give biased results, because they will not account for all clinically important characteristics. The EAG also noted that although longer-term data is available from RCTs, it is restricted to comparisons of older generation valves, often with surgery as a comparator. The EAG highlighted that simultaneously sourcing all clinical inputs was a significant methodological advantage of using the UK TAVI registry data. It also noted that using different sources for clinical inputs was cited by stakeholders as a limitation of the economic evaluation in NG208.

Model cost inputs

3.18 Some companies have 'added value' arrangements with NHS Supply Chain, in which part of the cost of the valve is returned to be spent on related items or staff, based on the number of valves purchased. The committee concluded that it was appropriate to

account for these ‘added value’ arrangements in the valve cost, but acknowledged that changes in the volume of use could affect the effective price of some valves. It highlighted that the price variation between the valves after the ‘added value’ was accounted for was smaller than the variation between the list prices. It also noted that the resources returned through ‘added value’ agreements can only be spent on structural heart-related products or services at the NHS trust level. The committee heard that analyses from the economic evaluation done for NG208 indicated that a transcatheter heart valve would have to cost £14,800 or less for the procedure to be cost effective for all surgical risks. Most of the transcatheter heart valves currently available in the NHS are above this price at both their list price and after ‘added value’ agreements have been accounted for.

Cost effectiveness

3.19 The committee concluded that the model results were too uncertain to determine whether there were differences in the cost effectiveness of the transcatheter heart valves. The EAG presented the results of the economic evaluation in terms of net monetary benefit including the central value and the 95% confidence interval. The committee noted that although there were differences in the net monetary benefit of the different valves, the confidence intervals overlapped significantly. The committee agreed that it is not possible to establish whether the differences in net monetary benefit were because of differences in valve performance or because of confounding in the clinical data used to inform parameters in the economic model (see section 3.10).

Resource impact

3.20 The committee considered a hypothetical scenario that modelled a conservative estimate of a 10% market shift towards less expensive valves without considering potential clinical differences. It concluded that switching to less expensive valves priced below

the cost-effectiveness threshold that covers all surgical risk groups (see section 3.18) could result in a cost saving for the NHS, which could fund additional TAVI procedures if reinvested into the service.

Justification for price variation

3.21 The committee concluded that it was not possible to determine whether the differences in cost between valves were justified by benefits derived from incremental innovations. The committee considered the combined clinical and economic evidence and recalled its limitations (see sections 3.16, 3.19 and 3.20). It was unable to establish which valve features lead to differences in performance and recalled that the specific transcatheter heart valve chosen often depends on the characteristics of the person with aortic stenosis (see section 3.3). It recalled that clinical equivalence could not be assumed between transcatheter heart valves from different companies or between generations of transcatheter heart valves by the same company, but that it was likely that they were clinically comparable (see sections 3.13 and 3.14). The committee emphasised the importance of having access to a range of valves so that a clinically appropriate valve is always available.

3.22 The committee concluded that most of the reasoning for choosing a specific valve is based on clinical factors and outcomes, so price differences could not be justified by other non-clinical factors. It considered evidence from a user preference assessment that sought to establish specifically which features of a TAVI valve influence a user's decision about which valve to choose. It noted that of the 7 most important criteria identified, 5 (including the top 3) were captured in the EAG's assessment. They accounted for 87% of the weight of users' decision making. The remaining factors were either not possible to account for because they related to characteristics not captured in the clinical data (see section 3.8), or

were technical features that made up only 6% of the overall preference.

Evidence needed to demonstrate additional value

3.23 The committee concluded that more evidence was needed for companies to demonstrate the additional value of a transcatheter heart valve compared with its alternatives. This evidence should be comparative and should adjust for clinically relevant patient characteristics. The committee stated that companies should be able to show clinical superiority to justify a higher price for their valve if it claims to have incremental innovations, or clinical non-inferiority if they are introducing a new valve or a new generation of the technology with minor improvements to the market.

3.24 The committee discussed whether further data collection in the UK TAVI registry could be used to address the uncertainties in the current analyses. Clinical experts explained that this would need additional clinically relevant patient characteristics to be recorded in the registry. The clinical experts also noted that the UK TAVI registry is limited to in-hospital outcomes and that missing data for some fields is prevalent. They stated that additional administrative support would be needed to ensure high-quality registry data collection.

Equality considerations

3.25 The committee concluded that a range of transcatheter heart valves should be available to a clinician to avoid introducing equality issues. Some people may not accept or may have preferences for specific valves because of religious or cultural beliefs, because they contain bovine or porcine leaflets. Transcatheter heart valves are available in different size ranges, which may affect whether they can be used in people with different body sizes (for example, men are more likely to have a large aortic annulus and need a larger valve). Having access to a range of

valves will ensure that a clinically appropriate valve is available that is acceptable to the person with aortic stenosis (see section 3.5).

4 Committee members

This topic was considered by NICE's medical technologies advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE also recruited clinical experts and specialist committee members for this topic.

Specialist committee members

Betsy Evans

Consultant cardiac surgeon, Leeds Teaching Hospitals NHS Foundation Trust

Charles Spencer

Advanced clinical practitioner, South Warwickshire University NHS Foundation Trust

Clare Appleby

Consultant interventional cardiologist, Liverpool Heart and Chest Hospital NHS Foundation Trust

Jon Anderson

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Marjan Jahangiri

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Consultant interventional cardiologist, Sheffield Teaching Hospitals NHS Trust

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Consultant interventional cardiologist, University Hospital Southampton NHS Foundation Trust

Suvitesh Luthra

Consultant cardiac and aortic surgeon, University Hospitals Southampton NHS Foundation Trust

Clinical experts

Dan Blackman

Consultant cardiologist, Leeds Teaching Hospitals NHS Trust

David Hildick-Smith

Consultant cardiologist, University Hospitals Sussex NHS Foundation Trust; President of the British Cardiovascular Intervention Society

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation to treat aortic stenosis

Draft Guidance themed comments

Relevance of NG208

Comment number	Name	Section number	Comment	Response
1	Consultee 1	1.3 What information is needed	We would like to state that the NICE NG208 economic model that was used for the cost-effectiveness of this Late-Stage Assessment was heavily criticised by both clinicians and industry in that consultation and thus the we feel the valve cost of £14,800 stated is not correct for all risk levels. You have not correctly stated the conclusions of NICE NG208 economic analysis for TAVI which are as follows: § TAVI is cost-effective for people at high-risk surgical risk at the current average list price of £17,500. In most scenarios, TAVI is highly cost effective and it becomes dominant when the price of a TAVI valve is reduced to £15,000. § TAVI is not cost effective for people at low or intermediate surgical risk at the current average list price of £17,500. If the price of the valve reaches £15,000, TAVI becomes highly cost effective for people at intermediate risk and at £14,800 it is cost-effective for people at low risk.	

Comment number	Name	Section number	Comment	Response
2	Consultee 6 Edwards Lifesciences	Not specified	Throughout the guidance document, there is very little or no justification (or explanation) of why there are major discrepancies between the conclusions of the analyses produced by the EAG, in comparison to the committee considerations and resulting draft guidance recommendations. This has led to the production of a draft guidance document which lacks logic, is confused in its reasoning and in some cases comes to conclusions based on evidence that has not even been presented to the committee. A clear example of this is in the economic modelling conducted by the EAG which bears no resemblance to the "what this means in practice" section of the draft guidance document. The reported NG208 model in the 'what this means in practice' section is not the economic analysis that was used by the committee in its decision making. Furthermore, the NG208 model is constructed using a comparator that was not in the scope of this LSA, devices that are no longer available to the NHS and models mixed valve types, which the EAG expressly said it did not do.	
3	Consultee 6 Edwards Lifesciences	Not specified	Reasons given for not including RCT data included "surgery as a comparator, and often included older generation valves or valves no longer available in the NHS." Please explain why it is considered appropriate to reference the economic model from NG208 which includes surgery as a comparator, includes older generations of valves and valves no longer available in the NHS, whereas RCTs were excluded from the assessment on the same basis	

Comment number	Name	Section number	Comment	Response
4	Consultee 6 Edwards Lifesciences	Not specified	No, the summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence and in the case of cost-effectiveness, the relative NMB findings reported by the EAG are unreported in the draft consultation document. The summary of cost-effectiveness and in particular the references to NG208 highlight clear examples of incomplete and ambiguous reporting and a consequent lack of transparency and fairness. There is a clear discrepancy in the cost-effectiveness presented in the draft guidance. The EAG decided that sAVR was not an appropriate comparator for this LSA and did not include it in their protocol, nor correspondingly in the EAG report. The draft guidance uses the unchanged model from NG208 which was not conducted using the data that was used in the EAG report, used mixed device expansion types and procedural approaches (combining data from transfermoral and transapical), and includes sAVR as a comparator. The committee was not presented with a comparison of TAVI with sAVR. Therefore, any reference to the clinical or the cost effectiveness of TAVi vs sAVR should be removed from this guidance. The EAG protocol clearly states that “Because of differences in indication and outcomes between TAVI device expansion type (balloon or self), the EAG will compare clinical evidence of TAVI devices of the same expansion type.” And in the EAG report that they "did not compare balloon- and self-expanding TAVI devices” This discrepancy between the EAG protocol and the final report conclusion of equivalence across valve types has not been explained.	Heathcote et al. (2023) is included in the EAR; this is a systematic review of economic evaluations of TAVI compared with medical management or SAVR and therefore not relevant to the decision problem. A summary of Senguttuvan et al. (2023) has been included in the Addendum.

Comment number	Name	Section number	Comment	Response
5	Consultee 6 Edwards Lifesciences	1.3 What information is needed	This section (along with all other references to NG208) is highly misleading and should be removed. The analysis presented here is from a completely different dataset to that presented by the EAG. “What This Means in Practice” infers that it is the findings of the committee based on the EAG report that has informed this cost-effectiveness calculation and it is not, it is opinion and commentary based on a completely different dataset. The cost-effectiveness NG208 calculations shown here mixed the device expansion types, did not include the same TAVI registry data used by the EAG to inform its clinical inputs, included data from obsolete technologies, mixed surgical approaches and had sAVR as a comparator. The EAG also states that there is doubt over the relevance of this to the UK NHS population and it is very clear that the listed criteria were not used in their analysis. Irrespective of the flaws and inaccuracies, only two valves are specifically indicated for low-risk patients and as shown, these patients account for less than 10% of the patients treated with TAVI. If the objective is to compare clinical and economic outcomes among the TAVI valves, then high-risk patients should be considered and analysed as a distinct sub-population as this is the only common indications for all TAVI valves. If, despite the inaccuracies and flaws, NICE choses to keep references to NG208, it would be a very misleading omission and not helpful for commissioners to present this biased assessment of it, as the focus is on LR patients. NG208 concludes that TAVI in HR patients is highly cost-effective (the ICER is £7k / QALY) at a valve price of £17,500 and this has not been mentioned anywhere in the guidance.	
6	Consultee 6 Edwards Lifesciences	3.7 Availability of clinical evidence to address the decision question	Please explain why it is considered appropriate to reference the economic model from NG208 which includes surgery as a comparator, includes older generations of valves and valves no longer available in the NHS, whereas RCTs were excluded from the assessment on the same basis .	

Comment number	Name	Section number	Comment	Response
7	Consultee 6 Edwards Lifesciences	3.18 Model cost inputs	Section 3.18 This paragraph is highly misleading, biased and should be removed. All references to the economic model for NG208 should be removed as this uses a different comparator (sAVR) to this LSA EAG analysis, mixes valve types, mixes valve generations and was commented to be not appropriate for the UK NHS TAVI population (all of which were reasons given to reject RCTs). If, however, NICE insists on keeping the reference to NG208, despite the flaws and inconsistencies with other data reviewed and presented by the EAG, only reference to HR patients should be made as this is sole indication common to all valves. For HR patients, TAVI was found to be highly cost-effective with an ICER of £7,014 / QALY (considering a valve cost of £17,500) Considering a £20,000 WTP, most likely a valve at £27,500 would still be cost-effective.	
8	Consultee 7 Boston Scientific	1.3 What information is needed	1. We support the observation that adjustments must be made for confounding factors, and suggest further clarity is provided around the importance of correcting analyses to account for selection bias. 2. We question why the cost effectiveness of TAVI as a whole vs SAVR (from a previous NICE assessment) has been brought into this section, when the Evidence Assessment Group chose not to compare TAVI with SAVR. Further, the quoted cost effective price of £14,800 or less is for all surgical risks; however as discussed during the committee meeting and identified in the Evidence Assessment Report, the vast majority of TAVI procedures performed in the UK are for patients in the high and intermediate surgical risk category. Therefore, if the £14,800 figure is to be quoted, the cost effective prices for the intermediate and high surgical risk categories should also be quoted ahead of £14,800, to better reflect UK clinical practice.	

Comment number	Name	Section number	Comment	Response
9	Consultee 9 Abbott Medical	1.3 What information is needed	Abbott would like to point out that surgery was removed as a comparator during the scoping workshop and therefore are unsure why it has been used as a comparator in the draft guidance.	
10	Consultee 9 Abbott Medical	1.3 What information is needed	Abbott believes that this statement is misleading and does not reflect current TAVI usage in the UK. Abbott would like to point out that intermediate and low risk TAVI is not routinely commissioned in the UK and the mean age of patients undergoing TAVI in the UK remains at 80 years of age. Adding to this, many TAVI valves (including Navitor) are only indicated for use in high risk patients. Due to these reasons, Abbott does not believe that the low risk cost-effectiveness threshold should be stated here. Abbott suggests that one way around this would be to weight the cost-effectiveness threshold using the proportion high vs. low/intermediate risk patients currently being treated within the UK. This weighting would yield a price between £14,800 and £18,000 and would be more reflective of current practice in the UK.	

Comment number	Name	Section number	Comment	Response
11	Consultee 10 Medtronic	1.3 What information is needed	We believe that this section is factually incorrect and misleading and gives the impression that a cost-effective price of £14,800 has been determined by this late-stage assessment. As mentioned in the paragraph this figure of £14,800 came from the NG208, 2021 clinical guideline on heart valve disease. It is inappropriate and misleading to quote this figure here for the following reasons: • The £14,800 price was the cost-effective price in NG208 for **low-risk patients only.** • This late-stage assessment draft guidance states that **TAVI is primarily used in people who are at high risk** for heart surgery or for whom surgery is inappropriate. **The cost-effective price for high-risk patients in NG208 was £18,000** therefore £14,800 is misleading and not representative of the majority of patients being treated. • **In NG208 an average price of £17,500** was used in the base case, and this was found to be **cost effective in high-risk patients at an ICER of £7,014**. • It is also important to note that the model from NG208 was designed to analyse the class effect of TAVI versus SAVR rather than the performance of individual valves versus SAVR. In Medtronic's EAR consultation response, we requested that SAVR be reinstated as a comparator; the EAG responded: ***"The agreed decision problem is based on selection of TAVI (when a clinical decision has been made that TAVI is appropriate); the role of LSA is not to repeat analysis of NG208 to determine cost-effectiveness of TAVI versus SAVR***. Whilst Medtronic still believe SAVR should have been included as a comparator as agreed in the scope, given the significant body of published evidence for TAVI vs. SAVR, it does appear contradictory and inappropriate to first exclude SAVR and then re-include with such a bold and misleading statement without having updated	

Comment number	Name	Section number	Comment	Response
			the model to better align with the decision problem for this current Late-stage assessment • The EAG **did not update the cost or efficacy inputs to account for the significant body of new evidence or changes in costs since the analysis** was done for example, for the Evolut platform, 4-year RCT data is now published from the Evolut low risk trial (only 2-year follow-up was available for NG208). At euroPCR 2024 a cost-effectiveness analysis, based on this data, presented that Evolut TAVI is the only valve to demonstrate cost-effectiveness in low-risk patients in the UK incorporating 4-year outcomes. [redacted] Medtronic agree that TAVI valves should be able to demonstrate cost-effectiveness in all patient populations before widespread access is granted in the NHS and we understand that the committee are keen to provide some quantitative direction for procurement purposes in line with the objectives of the LSA process. However, given the outdated, inaccurate and misleading nature of the current statement we suggest it is re-worded as follows: **"Previous analyses from the economic evaluation done for NICE's 2021 guideline on heart valve disease presenting in adults: investigation and management indicated that TAVI is cost-effective in high-risk patients at a valve price of £17,500 which represents most patients currently treated with TAVI in the NHS. However, the model also indicated that a transcatheter heart valve may need to cost £14,800 or less for the procedure to be cost effective in low-risk patients."**	

Comment number	Name	Section number	Comment	Response
12	Consultee 11 Meril UK	1 Recommendations	• £14,800 was indicated for low risk patients as an optimum price in NG208 high & intermediate risk was prices at higher levels – see below extracts. • NICE NG208 Economic analysis states 2.5.4 Cost of the valve In the base case scenario, the cost of a TAVI valve was assumed to be £17,500, which is the average price across the volume 80% of TAVI valves are purchased in England and Wales under the NHSE High-Cost Tariff Excluded Devices Programme. A second price of £15,000 was tested in the scenario analysis representing a realistic price reduction that may be achieved in the following years. In addition, a threshold analysis on the price of the valve is presented in section 3.3. 3.2.1 High risk In most scenarios, TAVI is highly cost effective and it becomes dominant when the price of a TAVI valve is reduced to £15,000. TAVI becomes not cost-effective when: • Historical and old trials are included in the meta-analysis estimating relative treatment effects • Mild PVLs are assumed to affect mortality • ICU and LOS are not scaled up for higher risk 3.2.2 Intermediate risk In most of the scenarios tested, TAVI is not cost effective compared to surgery. Although, if the price of the valve reaches £15,000, TAVI becomes highly cost effective for people at intermediate risk as well, confirming that the results of the model are extremely sensitivity to the price of the valve. 3.2.3 Low risk As with intermediate risk people, TAVI is not cost effective in most scenarios tested. If the price of a TAVI valve is reduced to £15,000, TAVI is cost effective at a threshold of £30,000 per QALY gained, though not at a threshold of £20,000 3.3 Threshold analysis	

Comment number	Name	Section number	Comment	Response
			The results showed that for intermediate-risk patients, TAVI becomes cost effective at a threshold of £20,000 per QALY gained when the price drops below £15,500. For low-risk patients TAVI becomes cost effective at the same threshold when the price of the valve is reduced to £14,800 3.5 Limitations and interpretation The analysis demonstrated that TAVI is cost effective in patient at high surgical risk but not cost effective in patients at intermediate or low surgical risk compared to surgical aortic valve replacement. The sensitivity analysis shows that the results are extremely sensitive to the price of the TAVI valve. In a scenario where price is reduced to £15,000, TAVI would become cost effective in people at intermediate surgical risk and the same for the low-risk group at a price of £14,800. As discussed and negotiated with NHSE & NHS SC Meril entered the UK market as a cost effective treatment option from the start with Myval Octacor.	

Choice of evidence

Comment number	Name	Section number	Comment	Response
13	Consultee 1	Not specified	• We do not feel all relevant evidence has been taken into account: o The literature screening activity was too narrow and excluded key evidence that could have supported the comparable clinical effectiveness and durability of the valves. o The published clinical evidence seems to have been completely ignored in deference for the UK real world evidence. A better assessment would have been to validate the findings in the real-world data using the published evidence and vice versa. • The assessment did not include the clinical effectiveness comparison of self-expandable valves with balloon expandable valves which may have impacted on the economic evaluation, particularly on the in-hospital budget.	The EAG report describes the literature search strategy and includes a review of the literature in the context of the decision problem within the protocol and EAG report. In addition, a summary of 44 studies not included in the EAG report has been included as an Addendum. For each study this includes a description of the study design, the EAG's interpretation of whether the study was in scope, and key considerations. The EAG report explains the reasons for using UK real-world evidence to populate the economic model of the decision problem, and further expands on these reasons in the Addendum. Both the report and the Addendum set out the strengths and limitations of each approach. The scope of the LSA was to assess the incremental clinical, economic and non-clinical benefits of transcatheter aortic valve implantation (TAVI) devices for people with severe aortic stenosis, to justify price variation and inform procurement decisions. This was not a features-based assessment (for example, the decision problem was not to compare the cost effectiveness of balloon expandable versus self-

Comment number	Name	Section number	Comment	Response
				expanding devices), therefore the EAG reviewed evidence at a device level.
14	Consultee 1	Not specified	Considering that the assessments essentially only considered the real-world evidence and consequentially this supported only 4 of the 8 manufacturers' valves we agree that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence used.	
15	Consultee 6 Edwards Lifesciences	Not specified	Our most serious concern, however, is that NICE has chosen to ignore over 8,000 (eight thousand) publications and yet concludes that "there is not enough evidence to support price variation" when this wealth of evidence, expert opinion, stakeholder advice and new evidence provided by us has been overlooked. The EAG state repeatedly in their report that for reasons of expediency, they did not take a more standard approach of assessing robust randomised controlled trials by conducting systematic literature searches and then using RWE such as the TAVI registry to complement evidence gaps. The EAG stated in response to a stakeholder comment on their report that "it is acknowledged that the evidence included in the report is not the entirety of the evidence available for each device" and that they had quite deliberately "removed the count of the number of papers and number of patients included in them" in order to "not cause confusion." Far from causing confusion, failure to review the full evidence base for each device together with a lack of transparency in reporting what they did review is staggering. It would have added a great deal of clarity for the EAG to report transparently what evidence was reviewed to reveal the small subset of evidence upon which NICE has based its recommendations and the huge volume of data that has been ignored. Any lack of evidence review can only be as a result of the instructions given by NICE to the EAG about the appropriateness of producing an incomplete and expedited report and demonstrates the use of flawed HTA methods as numerous high quality, robust data and analyses were ignored for the sake of expediency.	

Comment number	Name	Section number	Comment	Response
			In a press release issued by NICE on August 9th (which despite assurances that it would be removed is still 'live' on Monday Sept 2nd), under the headline "No evidence to support price variation in heart valves used by the NHS" Prof Jonathan Benger is quoted as saying “We have looked for evidence to determine whether differences in innovation and performance between these valves can justify their range in price, but the information we have seen does not support the current variation in cost.” Prof Benger’s statement overlooks the fact that ‘the information we have seen’ is a small fraction of the available publications and so fails to acknowledge that not assessing the full evidence base has led to the production of wholly unsound recommendations and even more unreliable headlines and commentary.	

Comment number	Name	Section number	Comment	Response
16	Consultee 6 Edwards Lifesciences	Not specified	No, the vast majority of evidence has been ignored. There is a need for NICE to explain the conclusions of the committee of “insufficient evidence” which presumably is reached as a result of only a very small percentage of available TAVI publications being considered. There is an acknowledged flaw in compiling the evidence as there were no systematic literature reviews conducted – if they had done so, the EAG could have reduced limitation and avoided introducing bias. While the EAG claims to have “applied the hierarchy of evidence” they only included a total of 159 clinical studies in the EAG report (42 studies as key evidence being used, 58 studies considered in scope and rejected, a further 59 studies excluded). This compares with 764 references found when the EAG ran scoping searches designed to identify both systematic reviews of clinical effectiveness and systematic reviews of economic evaluations and economic models. A simple MedLine search conducted on 13th August 2024 returned 8,241 publications, 271 meta-analyses and 180 RCTs. There are also 62 published records of TAVI in the international HTA database which could have been drawn upon to support recommendations. Key data has been ignored due to time constraints or lack of understanding of the appropriateness of high-level studies which were recommended by experts as data generalisable to the UK. Edwards has repeatedly supplied published references to aid the decision problem to NICE before and during the official timeline of the TAVI LSA and in the EAG report consultation suggesting ways to incorporate data on thousands of patients distinguishing the various technologies by their indications, valve type and evidence availability. There is no logical explanation in the EAG report or replies to comments as to why much of this data has not been taken into account.	
17	Consultee 6 Edwards Lifesciences	Not specified	No, the recommendations are not sound, nor are they evidence based. The committee has not reviewed all relevant evidence and has been presented with inadequate cost effectiveness analyses to	

Comment number	Name	Section number	Comment	Response
			address the decision problem in this LSA. There is no sound basis upon which ANY recommendations can be made	
18	Consultee 6 Edwards Lifesciences	1.3 What information is needed	This sentence is misleading. It should state that more of the published available evidence for TAVI devices needs to be assessed and analysed before it can be determined whether price variation can be justified, or not justified, between different transcatheter heart valves. The current information reviewed shows that the data chosen by the EAG was not fit to answer the question and / or issue any evidence based guidance. All relevant evidence should have been reviewed.	The EAG has reviewed and provided a summary of additional published evidence submitted by stakeholders see the Addendum. See response to comment 27.
19	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	It is hard to understand why there have been many global assessments of TAVI conducted using available data from RCTs, whereas NICE concludes otherwise. Experts have said that non-UK high-quality evidence is generalisable to the UK. The patients with sSAS are similar to other countries so high-quality published evidence should have been considered in the assessment	The decision problem of the LSA was to assess the incremental clinical, economic and non-clinical benefits of transcatheter aortic valve implantation devices for people with severe aortic stenosis, to justify price variation and inform procurement decisions. In its report, the EAG sets out the limitations of available trial evidence, and real-world evidence, in answering the decision problem. As stated in the Protocol, *"multiple consultation comments were received during the NG208 guideline development that raised concerns that trial participants of the included RCTs were not representative of a UK NHS population (NG208 Consultation Comments and Responses, 2021) and hence may not be relevant to the NHS."* Extrapolation of RCT evidence to real-world setting, and issues in combining RCT evidence due to lack of transitivity across all devices listed in the scope was also discussed in the protocol.

Comment number	Name	Section number	Comment	Response
				Published evidence comparing Sapien 3 and Sapien 3 Ultra was summarised in section 5.2.1 of the original EAG report. Univariate results from the UK TAVI Registry differ between Sapien 3 and Sapien 3 Ultra, due to valve sizes available (larger 29mm valve size is not available for Sapien 3 Ultra). In multivariate analysis (where population differences such as gender and valve size are adjusted for), there was a statistical difference in in-hospital stroke (higher in Sapien 3 compared with Sapien 3 Ultra; OR 3.26 [95% CI 1.23, 8.64]). There was no evidence of a difference in in-hospital death, aortic regurgitation, pacemaker, major bleeding, major vascular complication, TAVI bailout/reintervention before discharge, or death, stroke, pacemaker, aortic reintervention, readmission for heart failure post-discharge between Sapien 3 and Sapien 3 Ultra.
20	Consultee 6 Edwards Lifesciences	2.9 Sapien 3 and Sapien 3 Ultra (Edwards)	Taking the improvements of SAPIEN 3 Ultra as an example , if the assessment were truly looking at incremental innovation, it should provide detail of clinical outcome benefits seen from technology improvements and their associated economic value. This is demonstrated in controlled studies which were provided to the EAG but not reviewed.	The EAG has reviewed and provided a summary of additional published evidence submitted by stakeholders; see the Addendum.
21	Consultee 6 Edwards Lifesciences	3 3 Committee discussion	This statement is misleading as it was to unable assess the cost-effectiveness of the devices not captured in the UK TAVI Registry. The committee therefore could only consider evidence on 6 of the 11 devices. This should be clearly explained.	

Comment number	Name	Section number	Comment	Response
22	Consultee 6 Edwards Lifesciences	3 3 Committee discussion	This statement is also misleading as the targeted review evidence was not used in the assessment as the Registry data only was used. It's important to explain that there was no systematic review of literature for each technology due to time constraints – the EAG acknowledged that it overlooked or ignored an abundance of publications. This is a procedural failure. All relevant evidence should have been identified and reviewed.	As stated in section 4.1.1. of the EAG report: *"It was not feasible for the EAG to systematically search and sift evidence related to all older generations of TAVI devices for each manufacturer listed in the Final Scope. Instead, the EAG took a pragmatic approach, reviewing the published evidence provided by the Companies where more than 2 devices were compared."*. Pragmatic literature searches are permitted in the interim LSA Process and Methods (see section 4.8) which states that the EAG can prioritise the studies or data it considers most valid and relevant to the decision problem presented in the scope (see section 4.9). Therefore, it is factually inaccurate to state that this is a procedural failure. Additional published evidence submitted by stakeholders has been reviewed and summarised by the EAG in the Addendum.
23	Consultee 6 Edwards Lifesciences	3.6 Availability of clinical evidence to address the decision question	The data presented / considered by the EAG overlooks thousands of published studies , including hundreds of meta-analyses. Non-UK data (which the clinical experts indicated is generalisable to a UK setting) including randomized studies such as the PORTICO IDE trial published in the Lancet, the SCOPE I and II trials published in the Lancet and Circulation, and other meta-analyses were supplied during communication / consultation with NICE. All of these studies would have been found if there had been a systematic search. The TAVI registry was not set up to make between-device comparison and its lack of completeness makes it highly unreliable. Linked data was missing on a large percentage of patients and	The EAG identified 4 network meta-analyses and summarised limitations of these (see section 5.1 of EAR). The key limitation was transitivity (section 5.1 of the EAR) which limits the internal validity of the analysis. The EAG has reviewed and provided a summary for additional published evidence submitted by stakeholders; see the Addendum. This includes:

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			there is no data at all on several technologies under review. It is not clear why the data from over 100,000 patients in the network meta-analysis has been dismissed because of heterogeneity (Yang et al. 2023), or why some meta-analyses are missing such Takagi et al. 2019 for example. Yang et al clearly explains that the limitations (differences of aortic valve area, annulus diameter, annulus perimeter, annulus area, aortic angle and the extent of aortic valve calcification among individual patients and surgeon experience) are highlighted to explain moderate amount of heterogeneity in some of the analysis such as permanent pacemaker implantation, major vascular complications and major life threatening bleeding. The reviewer of this meta-analysis has not seen that the heterogeneity does not apply to outcomes such as mortality or stroke which are major cost drivers. In the Yang et al. 2023 meta-analysis, all RCTs and observational studies were assessed by using the Cochrane Collaboration's tool and Newcastle Ottawa Scale. Quality assessments were performed as well as various methodologies (frequentist and Bayesian) to validate the robustness of the findings. It is very difficult to understand why this piece of evidence and others are not seen as being as strong as the UK registry. While some of the TAVI technologies in the Yang et al meta-analyses have been removed, the data is still valid for those that remain and the results, along with other analyses, should be integrated in the assessment. It concludes that "SAPIEN 3 might be the best effective for decreased mortality and stroke" – these are two critical outcomes that should also drive the QALYs found in the EAG analysis and support the EAG NMB findings.	- The study by Makkar et al. 2020 which summarised results from the PORTICO IDE non-inferiority trial compared Portico to other commercially available valves (Sapien, Sapien XT, Sapien 3, CoreValve, Evolut R, Evolut Pro; all combined). This additional study has been considered in the Addendum. - The non-inferiority RCT by Tamburino (2020) which summarises results from the SCOPE II trial, which compared ACURATE neo (older model) with CoreValve Evolut R (older model). The EAG had already included evidence comparing ACURATE neo2 and Evolut R/Pro in the EAG report. This additional study has been considered in the Addendum. - The non-inferiority RCT by Lanz et al. (2019) summarised results from the SCOPE I trial which compared ACURATE neo to Sapien 3. The EAG had included larger studies which compared ACURATE neo2 to Sapien 3 within the EAG report. This additional study has been added to an Addendum. - Takagi et al. 2019 was included in the EAG report (see Table 5 in the EAR). - Yang et al. (2023) includes older devices for some manufacturers,

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				and therefore subject to bias. Timepoints of death and stroke outcomes were short-term but not explicitly defined in Yang et al. Both in-hospital and post-discharge (up to 31 months) of stroke and mortality outcomes were reported from the UK TAVI Registry in the original EAG report and incorporated into multivariable modelling. From multivariable modelling, no statistical difference in in-hospital death, post-discharge death or post-discharge stroke were observed in the UK TAVI Registry data. However, differences in the in-hospital stroke were observed in the multivariable analysis of the UK TAVI Registry data; increased risk for Evolut R, Evolut Pro+, Navitor compared with Sapien 3 Ultra. No statistical difference observed between Sapien 3 Ultra and ACURATE neo2.
24	Consultee 6 Edwards Lifesciences	3.7 Availability of clinical evidence to address the decision question	The limitations expressed about RCT data can also be attributed to the UK TAVI registry, particularly devices that are no longer on the market, or an absence of data for those that are.	The EAG limited analysis to current TAVI device models as listed in the Final Scope, where the valve serial number was verified by the Companies. For TAVI devices with no data in the Registry, the most applicable studies were summarised, and the EAG analysis could be repeated in the future when these valves have data available in the UK TAVI Registry.

Comment number	Name	Section number	Comment	Response
				Senguttuven et al. 2023 compared BE from 1 manufacturer with SE TAVI valves from multiple manufacturers. Different generation devices were also combined. This lacks relevance to the decision problem. The EAG has considered Senguttuven et al. 2023 within the Addendum.
25	Consultee 6 Edwards Lifesciences	3.7 Availability of clinical evidence to address the decision question	Edwards agrees that the RCT data are generalisable to the UK population and should be included in this assessment in order to make accurate comparisons and assessments of cost-effectiveness. Expert comments also reflect the findings from the UK TAVI registry and adds weight to why this assessment should focus on HR only. There are meta-analysis - specifically on HR patients - comparing short-term BEV vs. SEV outcomes that were mentioned many times and were completely overlooked (Senguttuven at al. 2023)	
26	Consultee 6 Edwards Lifesciences	3.7 Quality of UK TAVI registry data	While the sample size remains high, there is clearly an issue in basing guidance when only 53% of the patient outcome data is known. Not only is almost half of the potential data not available, there is unequal distribution among the various TAVI valves which are included. It is unsound of the committee to issue any guidance which is based on inherently biased and uncertain evidence	
27	Consultee 6 Edwards Lifesciences	3.8 Quality of UK TAVI registry data	Comment: Out of the 7,409 procedures, 6,267 (85%) were linked to HES data. And among these 6,267 procedures, 4,710 (75%) were performed using the SAPIEN 3 / SAPIEN 3 Ultra device, 1,092 (17%) with the Evolut (R/Pro+) device but only 295 (5%) and 170 (3%) with Boston and Abbott respectively. This imbalanced sample size brings some important limitations in the ability to compare devices fairly (small sample size leads to wide confidence intervals). This is another reason why RCTs and meta-analyses provided should have been included in the assessment. The experts comment regarding the registry not being designed to make valve comparisons added to the complete imbalance of technologies reviewed and the absence of any data on almost half of the technologies in the LSA make it very difficult to understand why the registry data was felt fit for purpose.	The consultee has challenged the fitness for purpose of the UK registry data in addressing the decision problem. The EAG considers this to be an unbalanced view. In its report, and in the Addendum, the EAG sets out the strengths and limitations of using real world data from a UK setting linked to routine outcome data, versus using data extracted from multiple separate published studies, to populate the economic model. Its conclusion was that neither approach fully addresses the decision problem, without bias or

Comment number	Name	Section number	Comment	Response
				limitation, but that on balance, the linked UK real-world data was more applicable. The EAG did not assert that evidence from the literature was not fit for purpose, and by a similar argument, the consultee's assertion that the UK data is not fit for purpose should not follow. The EAG considered that patient-level real-world evidence from the UK on TAVI devices currently being used in NHS was the most relevant for the decision problem, as this enabled comparison of multiple TAVI devices whilst adjusting for known confounders. The limitation of combining multiple RCTs in network meta-analysis to enable comparison of multiple devices was described in the EAG report (section 5.1).

Comment number	Name	Section number	Comment	Response
28	Consultee 6 Edwards Lifesciences	3.10 Results of UK TAVI registry analyses	The conclusions of the committee underline that making any recommendations based on this data is completely unsound. Additional clinical outcomes - statistically significant - showing difference among TAVI valves (from Table 21 in the EAG report) that should impact the cost-effectiveness and the NMB as well, but do not appear to have been taken into account: • Length of procedure and length of stay • Malposition of the valve • Use of post-implantation balloon dilatation • Major vascular complications • Stroke after discharge • Deaths (unadjusted comparison) • VARC-3 technical success (unadjusted comparison) • Need for bailout TAVI-TAVI (unadjusted comparison) If it is not possible to adjust for clinically important characteristics, then the weight of the missing confounders needs to be determined to explain the results. The EAG also underlines the issue with imbalanced sample size - leading to unfair comparison We do not understand why scenarios never seen in practice or in literature were used in the economic modelling (for example unrealistic predicted event proportions from the multivariate analysis considered for the base case – Table 27 from the EAG report). It is recognised by the EAG that they are “not fully comparable to the results from the published literature.” and could have used RCTs to assess the validity of their model inputs	The EAG considered the following: • Length of stay: clinical experts advised that the numerical differences in length of stay between devices identified from the UK TAVI Registry were not clinically significant, and likely to reflect differences in practice between hospitals (rather than directly relevant to the valve itself). See page 109 of 381 and Table 21 of original EAG report. • Length of procedure: whilst univariate differences were observed between devices, the Clinical Experts advised caution because this outcome may be influenced by differences in characteristics of patients receiving different TAVI devices and may not be directly linked to the TAVI device itself. See page 108/109 of 381 of the original EAG report. Procedure duration was also considered in sensitivity analysis; see Table 33 in the original EAG report. • Malposition: low event rate. See Table 21 of original EAG report. • Use of post-implantation balloon dilatation was included in the economic analysis (additional catheter cost, see Table 33 of original EAG report). • Major vascular complications were included in multivariable analysis (accounting for differences in patient

Comment number	Name	Section number	Comment	Response
				characteristics between devices), however the EAG found no association with device (see Table 23 of the original EAG report). EAG consideration of major vascular complications is described in the original EAG report (see page 150 of 381). • Stroke and death after discharge were both included in multivariable analysis (accounting for differences in patient characteristics between devices) and the EAG found no association with device (see Table 24 of the original EAG report). Both stroke and death were included in the EAG economic model (see section 6.2.1 and model structure illustrated in Figure 11). • VARC-3 technical success is a composite outcome (only up to exit from procedure room). The EAG considered aortic reintervention and readmission for heart failure longitudinally using the UK TAVI Registry in multivariable analysis. After adjusting for population differences between devices, no association between these outcomes and device used was identified; hence not included in economic analysis. See Table 24 of the original EAG report. Scenario analyses were created incorporating feedback from Clinical

Comment number	Name	Section number	Comment	Response
				Experts, see section 6.2.6 of the original EAG report (wider sensitivity analysis also described in section 6.2.5). When interpreting the predicted event proportions (described in Table 27), the EAG commented on the overall uncertainty of the multivariate models (which is reflected in the width of the 95% confidence intervals for probability with the highest NMB). It is unclear what proportions specifically this comment is referring to. However, comparing the crude proportion (without adjusting for covariates) of death at 1 year for the Sapien 3 device was 8.1% (Table 22), compared with the predicted (unadjusted) 1-year rates for death of 11.24% in males and 10.8% in females (Table 27). For stroke at 1 year, the crude proportion was 4.5% (unadjusted, Table 22) and 3.57% in males and 2.79% in females from multivariate analysis (adjusted, Table 27). The results of the multivariable analysis were reviewed by SCMs. The point estimates of the multivariate modelling do not appear unrealistic, however the wide 95% confidence intervals are reflective of the small sample sizes for some devices and also rare events; and therefore reflect the uncertainty associated. Differences between real-world evidence and trial evidence were also highlighted by Deharo et al. 2020 (see

Comment number	Name	Section number	Comment	Response
				Addendum) which stated “Our real-life data showed that mortality was similar to, or slightly higher than, in the initial trials.”

Comment number	Name	Section number	Comment	Response
29	Consultee 6 Edwards Lifesciences	3.11 Published evidence	This is a wholly inappropriate methodology which does not respect the hierarchy of evidence. By not undertaking the correct approach of conducting systematic searches for RCTs and meta-analyses, key evidence has been overlooked, or ignored when supplied to NICE. It also conflicts with the statement that there is “not enough evidence” in the recommendations and conclusions as there is clearly recognition that there is an abundance, most of which has not been considered. RWE should address any gaps in the abundance of published evidence and neither time pressure , nor volume of publications is not an acceptable reason for performing a sub-standard assessment. The method of pragmatic searches was introduced in the interim guidance several months (at the earliest March ’24) after the LSA had commenced and the EAG had conducted its initial searches (Nov ’23). We firmly believe that this pragmatic search method is unsound for the production of national guidance on medical technologies . As has been demonstrated in this LSA, it leads to thousands of publications being ignored. The RWE from the UK TAVI registry is extremely imbalanced with most of the data available coming from one specific category of TAVI devices (balloon-expandable valve in 72% of the UK TAVI registry and 75% once linked with HES data). The remaining evidence from self-expandable devices is also imbalanced, with a majority coming from the Evolut platform (19% and 17%) and only 5% or less are coming from the other 2 self-expandable platform (Boston and Abbott). This paragraph is also misleading as although 4 meta-analyses were considered, only one network meta-analysis was included (Yang et al. 2023)	The EAG considered the patient-level real world evidence from a UK NHS setting the most applicable to the decision problem. Reasons for this are described in Section 5.1 of the EAG report. Real-world evidence (RWE) from the UK TAVI Registry reflects contemporary NHS usage. Four network meta-analyses were described in section 5.1 of the EAG report. One was prioritised due to size and relevance to decision problem. LSAs were launched in October 2023 (see section 1.1. of Interim Process and Methods statement for LSA; where consultation ended 28 March 2024). This TAVI topic was the first and pilot LSA, and as such used to help inform the interim process and methods guidance. The EAG would contest that there are *“thousands of publications being ignored",* as not all publications describing TAVI are relevant to the decision problem. The EAG has considered an additional 44 studies identified by NICE, see the Addendum, and only 2 were considered key evidence, neither of which changed the conclusions of the original EAG report.

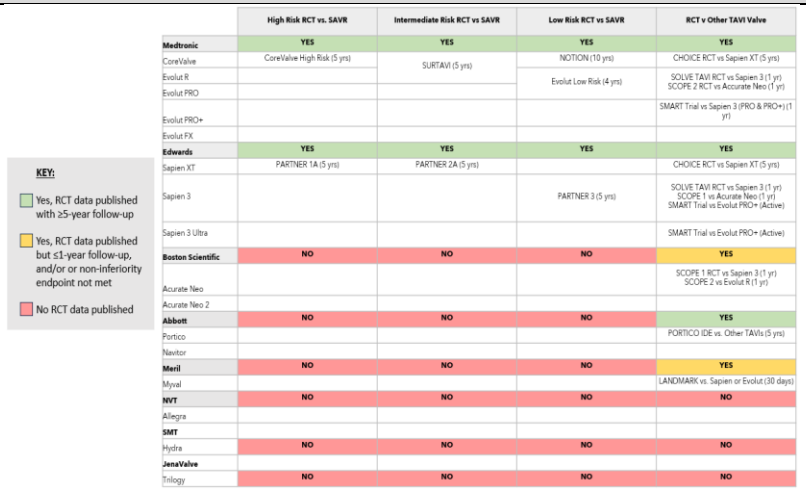
Comment number	Name	Section number	Comment	Response
30	Consultee 6 Edwards Lifesciences	3.17 Model clinical inputs	The EAG needs to validate its assertion that using data from RCTs would give more biased results than the use of data from the TAVI registry and explain why they continued to use parameter inputs which "are not fully comparable to the results from the published literature." If RCTs could be used to inform the economic model (expert advisers) - why wasn't it done? Economic models is that they can cope with uncertainty, which is why DSA, PSA and scenarios analyses are performed. Validating the findings from the EAG with RCTs / meta-analysis and comparing with existing literature (eg Heathcote et al., 2023) would have been the right approach The TAVI registry does not have enough data on all 11 technologies, so to maintain a robust comparison, only SAPIEN / Evolut provide meaningful information.	In the original report, the EAG included 3 RCTs: • Baumbach et al (2024) where the comparator group had mixed valve type and generation. • Herrmann et al (2024) included multiple generations of devices in both intervention and comparator arms, and was conducted in a population with small aortic annulus area only (defined as ≤ 430 mm2); • Thyregod et al (2024) which compared TAVI to SAVR (included for longitudinal evidence for CoreValve up to 10 years). Within the Addendum, the EAG has considered an additional 6 RCTs: • 2 compared TAVI to SAVR (Forrest et al. 2023; Jorgensen et al. 2022); • 3 were non-inferiority trials and had mixed valve type and/or included older generations within arms (Lanz et al. 2019; Tamburino et al. 2020; Makkar et al. 2020a). Noting in Makkar et al. 2020a the valve chosen in the comparator arm (any commercially available valve other than Portico as the intervention arm) was not randomly assigned but was at the discretion of the study site investigator. • 1 was a 2x2 factorial equivalence RCT aiming to compare general

Comment number	Name	Section number	Comment	Response
				anaesthesia with local anaesthesia and conscious sedation, as well as comparing self-expanding with balloon-expanding TAVI devices (Thiele 2020). The study assumed that there was no interaction between randomised comparisons. The study was powered for equivalence of a composite outcome, and only reported outcomes to 30 days. The EAG considered that the identified RCTs were not directly relevant to the decision problem, and therefore did not include their short-term outcomes (between 30 days to 1 year) as a scenario in economic modelling. Other registry studies in TAVI have found differences with trial data, and that without an agreed method for resolution or evidence of process error, explanations of the differences between real-world evidence and trials are conjecture.
31	Consultee 6 Edwards Lifesciences	3.21 Justification for price variation	If the committee is unable to make any determination of the benefits of incremental innovations based on limitations of evidence, please explain what sound evidence is being used to base any guidance to the contrary. Certainly for five of the technologies there is a complete absence of evidence. Please explain how an absence of data, data with high uncertainty and data with significant bias can be used to issue any guidance. Please also explain how any conclusions can be drawn and guidance issued on the five technologies which have no data at all. This section reiterates the flawed logic and false conclusions of sections 3.13 and 3.14 and the lack of evidence based decision making.	

Comment number	Name	Section number	Comment	Response
32	Consultee 6 Edwards Lifesciences	3.23 Evidence needed to demonstrate additional value	The committee drew this conclusion based on a very small percentage of the abundance of evidence that exists for TAVI technologies that was presented to them. Systematic searches and inclusion of relevant publications in the assessment would have presented a fairer picture of the true status of the available clinical evidence. It is a very unfair statement to say that more evidence is needed when there has not been a full assessment of the available evidence. The EAG acknowledges " that the evidence included in the report is not the entirety of the evidence available for each device" – a fair statement here would be to say that that the full evidence base should be assessed to conclude if more evidence is needed.	See response to comment 22.
33	Consultee 6 Edwards Lifesciences	3.24 Evidence needed to demonstrate additional value	Existing data from published literature could and should be used to address uncertainties and to validate / correct the serious flaws in the model data input.	See response to comment 30. The consultee might be expressing an opinion that trial data may be more applicable to the decision problem, but as stated there is an assertion of error, with which the EAG disagrees. There is no evidence presented to support the assertion that the model input data had "serious flaws" (a flaw is defined as a defect). The EAG report presented exploratory data analysis and univariate analysis to check the data, then validated the multivariate analysis against the exploratory data analysis and with SCM oversight.
34	Consultee 7 Boston Scientific	1.1 1 Recommendations	Overall Boston Scientific supports the committee's decision to recognise the multiple challenges, uncertainties, and caveats reported in the Evidence Assessment Report. However, statement 1.1 is not fully reflective of the discussions had, and currently risks misinterpretation. We wish to highlight that there is a wealth of high-quality evidence supporting TAVI. Further, a systematic literature review was not conducted for this assessment, limiting conclusions	See response to comment 22.

Comment number	Name	Section number	Comment	Response
			that can be made about evidence availability. We therefore suggest this first recommendation is reworded to reflect these points.	
35	Consultee 10 Medtronic	Not specified	We are somewhat supportive of the draft recommendations and agree that the committee were not presented with enough evidence by the EAG, to draw solid conclusions on the decision problem as the wealth of published evidence for TAVI was excluded from the EAG analysis. This high volume, high quality, published evidence could have been very informative for the committee in addressing the decision problem and providing more constructive guidance to procurement bodies. Given the delays in this TAVI assessment to date, and time and resource constraints of the LSA process, we are not requesting a reassessment to include the large body of published evidence however we feel that some of the wording in the draft recommendations is misleading. We have made additional comments where we believe there are factual inaccuracies and statements open to misinterpretation that need to be corrected to ensure safe and effective, evidence-based care for patients with aortic stenosis.	

Comment number	Name	Section number	Comment	Response
36	Consultee 10 Medtronic	1.1 1 Recommendations	We agree that the NICE committee were not presented with enough evidence in the EAG report to conclude whether price variations can be justified. However, if standard HTA methods had been applied and a systematic literature review (SLR) conducted by the EAG in line with the scope (i.e. including both alternative TAVI and SAVR as comparators), the committee would have been presented with a wealth of RCT evidence with long-term follow-up across different patient groups for some TAVI valve platforms and a dearth of RCT evidence for other valves – see **appendix 1** for an outline of these RCTs. We feel strongly that, had a different approach been taken, that the committee would have been able to assess the published evidence for each valve platform and draw conclusions regarding the differentiated value. Given that the EAG did not perform SLR, largely excluded all published evidence and instead relied on the UK TAVI registry, we feel that recommendation 1.1 should include the underlined additional wording for clarity as follows: 1.1 There is not enough evidence **from the UK TAVI registry** to determine whether incremental innovations can justify price variations between different transcatheter heart valves for transcatheter aortic valve implantation (TAVI) in adults with aortic stenosis. Appendix 1. Outline of the RCT evidence published for each valve platform.	

Comment number	Name	Section number	Comment	Response
				
37	Consultee 12 Heart Valve Voice	1 Recommendations	Heart Valve Voice, a charity with nearly a decade of experience supporting individuals with heart valve disease, would like to express its deep concerns regarding the recent recommendations from NICE on LSA heart valve treatment options. While we fully support the goal of ensuring the NHS delivers both high-quality and cost-effective care, we believe the current recommendations do not fully reflect the evidence presented which, through many other stakeholders, have provided throughout the consultation process.	
38	Consultee 12 Heart Valve Voice	Not specified	We are particularly troubled by the inconsistency between the recommendations and the evidence presented. The conclusions reached appear to be based on insufficient comparative data between the different Transcatheter Aortic Valve Implantation (TAVI) valves available. Without robust, head-to-head comparisons, it is difficult to confidently make decisions that could affect patient care and outcomes. As we have advocated throughout the process, patient care decisions, especially those involving complex heart valve selection, must be driven by rigorous, high-quality evidence, and any recommendations that oversimplify these decisions risk jeopardising patient safety.	

	High Risk RCT vs. SAVR	Intermediate Risk RCT vs SAVR	Low Risk RCT vs SAVR	RCT v Other TAVI Valve
Medtronic	YES	YES	YES	YES
CoreValve	CoreValve High Risk (5 yrs)	SURTAVI (5 yrs)	NOTION (10 yrs)	CHOICE RCT vs Sapien XT (5 yrs)
Evolut R			Evolut Low Risk (4 yrs)	SOLVE TAVI RCT vs Sapien 3 (1 yr) SCOPE 2 RCT vs Accurate Neo (1 yr)
Evolut PRO				
Evolut PRO+				SMART Trial vs Sapien 3 (PRO & PRO+) (1 yr)
Evolut FX				
Edwards	YES	YES	YES	YES
Sapien XT	PARTNER 1A (5 yrs)	PARTNER 2A (5 yrs)		CHOICE RCT vs Sapien XT (5 yrs)
Sapien 3			PARTNER 3 (5 yrs)	SOLVE TAVI RCT vs Sapien 3 (1 yr) SCOPE 1 vs Acurate Neo (1 yr) SMART Trial vs Evolut PRO+ (Active)
Sapien 3 Ultra				SMART Trial vs Evolut PRO+ (Active)
Boston Scientific	NO	NO	NO	YES
Acurate Neo				SCOPE 1 RCT vs Sapien 3 (1 yr) SCOPE 2 vs Evolut R (1 yr)
Acurate Neo 2				
Abbott	NO	NO	NO	YES
Portico				PORTICO IDE vs. Other TAVIs (5 yrs)
Navitor				
Meril	NO	NO	NO	YES
Myval				LANDMARK vs. Sapien or Evolut (30 days)
NVT	NO	NO	NO	NO
Allegra				
SMT				
Hydra	NO	NO	NO	NO
JenaValve				
Trilogy	NO	NO	NO	NO

Equivalence and comparability

Comment number	Name	Section number	Comment	Response
39	Consultee 6 Edwards Lifesciences	Not specified	Edwards have previously advised that to determine whether price differences between TAVI devices are justified, NICE could and should have created ICERs for each technology. It is clear from the EAG report's conclusions that TAVI devices cannot be assumed to be equivalent, therefore it is wrong and methodologically flawed to cluster them and use an assumption that devices are clinically equivalent to develop cost minimisation recommendations. TAVI devices are clearly not clinically equivalent.	
40	Consultee 6 Edwards Lifesciences	1.2 1 Recommendations	This recommendation has no evidential basis. The absence of evidence of non-equivalence cannot be used to justify an assumption of equivalence. In order to recommend the least expensive option, clinical equivalence between valves needs to be established with a high degree of confidence. The ERG have concluded, and the committee have clearly stated, that clinical equivalence cannot be assumed. That being the case, this recommendation is unreasonable in the light of the evidence. The terms "Least expensive option" and "clinically appropriate" lack any definition to guide clinicians on which valves are clinically appropriate and in which circumstances. At the very least there needs to be a clear explanation of whether this wording means they should use the cheapest device, the TAVI device which is the most cost-effective or the device which leads to the least expensive procedure overall, taking into account all associated costs such as those of adverse events. "Clinically appropriate" should also include the requirement for the device to have regulatory approval and a robust body of evidence to support its use. The EAG summarised that there was an "inability to assess the cost-effectiveness of the devices not captured in the UK TAVI Registry." 5 out of 11 TAVI devices didn't have any data from the UK registry, there were significant imbalance in sample sizes for those that did and some devices had no long-term evidence. This recommendation could be interpreted to mean that any of the 5 should be chosen despite not having any data because it would be the least expensive option. NICE would be putting patients at potentially considerable risk as the least expensive may not be within a licensed	

Comment number	Name	Section number	Comment	Response
			indication and / or may have no long-term data to establish the clinical performance of the technology. It also completely disregards the patients' opinion and doesn't give them fully informed shared decision making opportunities.	
41	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	The document states that clinical equivalence cannot be assumed, so there is flawed logic in the assumption of clinical comparability. The word "likely" is indicative that this is speculative judgement and not an evidence based statement. A wider review of the evidence base would reveal that there are material differences in the clinical performance of TAVI valves	
42	Consultee 6 Edwards Lifesciences	3.13 Clinical comparability between companies	This is a flawed and illogical conclusion. If "clinical equivalence cannot be assumed" then the assertion that the "valves are clinically comparable" is false. The word "likely" is highly ambiguous and unhelpful – this is another example of a non-evidence based statement which is misleading. By definition, if clinical equivalence cannot be assumed, then there is no data upon which to make any recommendation or any comparison between devices in this class of products. Not only can there be no comparison of incremental innovations, there can be no comparison of the economics or of their price. Recommendation 2 is not supported by any data or analysis. Despite the statement in the document "clinical equivalence cannot be assumed" recommendation 2 automatically and incorrectly assumes that there is equivalence between devices, five of which had no data on which to base any assessment.	
43	Consultee 10 Medtronic	1.2 1 Recommendations	We also suggest that an additional recommendation is added to reflect the committee's conclusion that "Clinical equivalence between companies' valves could not be assumed" [Section 3.13] and "companies should be able to show… clinical noninferiority if they are introducing a new valve or a new generation of the technology with minor improvements to the market" [Section 3.23] **1.4 New valves should have evidence to show that they work at least as well as other valves**	

Comment number	Name	Section number	Comment	Response
44	Consultee 10 Medtronic	3.13 Clinical comparability between companies	Section 3.13 reads as follows: "The committee recalled that for most people with aortic stenosis, many of the available valves could be used (see section 3.3). So, it is likely that for those people the valves are clinically comparable" **We recommend that the specialist committee members and/or expert advisors are asked to confirm the accuracy of this statement** since we are surprised that TAVI implanters would agree that the evidence for "many" of the 11 TAVI valves included in this assessment is sufficient to be used in "most people with aortic stenosis". We feel the low volume usage of certain valves in the NHS would indicate otherwise. Also, we feel that the underlined section is more of an assumption than factual statement and appears to contradict other statements from specialist committee members and expert advisors such as: • **"Clinical equivalence between companies' valves could not be assumed" [Section 3.13]** • **"companies should be able to show… clinical noninferiority if they are introducing a new valve or a new generation of the technology with minor improvements to the market" [Section 3.23]** Published RCT evidence also demonstrates that it cannot be assumed that valves are clinically comparable: • Transfemoral transcatheter aortic valve replacement with the self-expanding ACURATE neo did not meet noninferiority compared with the self-expanding CoreValve Evolut in terms of all-cause death or stroke at 1 year. The ACURATE neo was associated with more moderate or severe aortic regurgitation at 30 days and cardiac death at 30 days and 1 year (Tamburino et al., 2020). • TAVI with the self-expanding ACURATE neo did not meet non-inferiority compared to the balloon-expandable SAPIEN 3 device in terms of early safety and clinical efficacy outcomes (Lanz et al., 2019) • Among patients with severe aortic stenosis and a small aortic annulus	If the majority of patients can have any valve, then the information from the UK TAVI Registry should be given more consideration as it represents a comparison of multiple devices in a UK setting, from a single source. See response to comment 50 and 60. Tamburino (2020) and Lanz (2019) have been considered by the EAG – see the Addendum. Herrmann et al. (2024) is already included in the EAG report.

Comment number	Name	Section number	Comment	Response
			who underwent TAVR, a self-expanding supraannular valve was noninferior to a balloon-expandable valve with respect to clinical outcomes and was superior with respect to bioprosthetic-valve dysfunction through 12 months (Herrmann et al., 2024) References: • Tamburino C etal., Comparison of Self-Expanding Bioprostheses for Transcatheter Aortic Valve Replacement in Patients With Symptomatic Severe Aortic Stenosis: SCOPE 2 Randomized Clinical Trial. Circulation. 2020 Dec 22;142(25):2431-2442. doi: 10.1161/CIRCULATIONAHA.120.051547. Epub 2020 Oct 15. PMID: 33054367. • Lanz, Jonas et al., Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial, The Lancet, Volume 394, Issue 10209, 1619 – 1628 • Herrmann HC, Mehran R, Blackman DJ, Bailey S, Möllmann H, Abdel-Wahab M, Ben Ali W, Mahoney PD, Ruge H, Wood DA, Bleiziffer S, Ramlawi B, Gada H, Petronio AS, Resor CD, Merhi W, Garcia Del Blanco B, Attizzani GF, Batchelor WB, Gillam LD, Guerrero M, Rogers T, Rovin JD, Szerlip M, Whisenant B, Deeb GM, Grubb KJ, Padang R, Fan MT, Althouse AD, Tchétché D; SMART Trial Investigators. Self-Expanding or Balloon-Expandable TAVR in Patients with a Small Aortic Annulus. N Engl J Med. 2024 Jun 6;390(21):1959-1971. doi: 10.1056/NEJMoa2312573. Epub 2024 Apr 7. PMID: 38587261.	

Clinical appropriateness

Comment number	Name	Section number	Comment	Response
45	Consultee 6 Edwards Lifesciences	1.3 1 Recommendations	Additionally, criteria need to be developed to allow clinicians and patients to reach an evidence based, informed choice in deciding which valve is clinically appropriate.	
46	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	This is clear recognition that there is uncertainty around clinical performance of newer technology, yet these could fall into the “least expensive” category. Without proof of performance and proper economic evaluation of all valves in the LSA, no guidance should be issued as it’s impossible to judge from the guidance which is or isn’t clinically appropriate . demonstrated by the fact that NICE have not developed any criteria to inform a ‘clinically appropriate’ choice.	
47	Consultee 9 Abbott Medical	1.3 1 Recommendations	Abbott welcomes this recommendation as it is focused on clinical appropriateness.	
48	Consultee 10 Medtronic	1.2 1 Recommendations	Recommendation 1.2 states: “Use the least expensive option available that is clinically appropriate for TAVI in the person with aortic stenosis”. We have received feedback from customers that NICE are suggesting that the cheapest valve should be used and they appear to miss the relevance of “clinically appropriate”. This could be a risk to patients, especially if/when new TAVI valves come to the market without sufficient evidence. To avoid misinterpretation, we suggest recommendation 1.2 is reworded as follows: **1.2 Use the least expensive, clinically appropriate, option for TAVI in the person with aortic stenosis, based on published evidence.**	
49	Consultee 12 Heart Valve Voice	Not specified	Heart valve selection is a nuanced process that requires the expertise of multidisciplinary teams (MDTs), and reducing these decisions to a question of cost-effectiveness alone undermines the individualised care that patients require. We believe that any assessment of heart valve devices must consider the unique clinical needs of each patient, and recommendations should not be made based on incomplete or inadequate data.	

Wording of guidance

Comment number	Name	Section number	Comment	Response
50	Consultee 1	Not specified	Yes, we consider the recommendations sound, and a suitable basis for guidance to the NHS.	
51	Consultee 1	3.24 Evidence needed to demonstrate additional value	We agree the UK TAVI Registry needs to be redesigned to include information that allows for a comparison of valves. However, the collection, analysis, publication, resourcing, responsibility and access also needs to be addressed as these have been a contributory factor to its inadequacy.	
52	Consultee 3 JenaValve Technology GmbH and JenaValve Technology Inc.	1.2 1 Recommendations	Clinician authority and autonomy to apply their subject matter expertise and professional experience is of primary importance in achieving optimal treatment outcomes for UK patients. The Committee's consideration of minority groups, including that of AS pathology, is mindful and inclusive in this discussion and decision process. JenaValve would like to highlight the prognostic importance of device selection and note that there are 7,868 severe, symptomatic AS patients due to native leaflet thickening with minimal calcification (15.4% of severe, symptomatic AS TAVI eligible patients) in the UK right now. We appreciate the Committee for respecting clinician choice to utilize Trilogy as the TAVI of choice of UK clinicians for this severe AS patient minority. References for the numeric values and preference statements above are derived from the following published medical literature: Strange GA, Stewart S, Curzen N, et alUncovering the treatable burden of severe aortic stenosis in the UKOpen Heart 2022;9:e001783. doi: 10.1136/openhrt-2021-001783 Xiong TY, Feng Y, Liao YB, Li YJ, Zhao ZG, Wei X, Xu YN, Wei JF, Peng Y, Piazza N, Mylotte D. Transcatheter aortic valve replacement in	

Comment number	Name	Section number	Comment	Response
			patients with non-calcific aortic stenosis. EuroIntervention. 2018 Feb 2;13(15):e1756-63 Abramowitz, Y., Jilaihawi, H., Pibarot, P., Chakravarty, T., Kashif, M., Kazuno, Y., Maeno, Y., Kawamori, H., Mangat, G., Friedman, J., Cheng, W., & Makkar, R. R. (2017). Severe aortic stenosis with low aortic valve calcification: characteristics and outcome following transcatheter aortic valve implantation. European heart journal. Cardiovascular Imaging, 18(6), 639–647. Claessen BE, Tang GHL, Kini AS, Sharma SK. Considerations for Optimal Device Selection in Transcatheter Aortic Valve Replacement: A Review. JAMA Cardiol. 2021;6(1):102–112. doi:10.1001/jamacardio.2020.3682 Ali N, Blackman DJ. (2019) TAVI: Which valve for which patient? Cardiac Interventions Today. 13(2): 72-78	
53	Consultee 4	1.3 What information is needed	"the person's surgical risk" is incorrect. Surgical risk is commonly used as referring to the risk of surgical AVR, not TAVI. If this phrase is required, it should be changed to "the person's risk for TAVI". The risk for surgical AVR is not relevant to the risk for TAVI.	
54	Consultee 4	3.4 Choice of valve	I think "tricuspid valve anatomy" is better replaced with "trileaflet valve anatomy" - to prevent confusion wth the tricuspid valve	
55	Consultee 5	Not specified	The most cost effective device should be used where appropriate but consideration should be given to Operator experience and Complication rates. We should be aware that inexperienced/training operators may find some devices more challenging to deploy and prefer a particular type, there seems to be little published evidence on this aspect of TAVI. The accepted complication rates are "low" at 1%, predominantly migration/embolisation most requiring Emergent Cardiac Surgery with a high complication rate not to mention vascular access issues. There is some published evidence that some TAVI products migrate more than others, although it is likely that some migration may be linked to	Operator learning curve was acknowledged as a confounder of analysis (see section 5.3.1 of EAG report). The EAG report recommends continued collection of UK data, with additional fields, in part for the purpose of active

Comment number	Name	Section number	Comment	Response
			operator experience (personal observations). There seems to be little published evidence concerning TAVI in general. I suggest that the UK TAVI database is interrogated at intervals to provide the data that we need to recommend TAVI products and this guidance amended appropriately. Perhaps new devices coming to the market should be trialled at a specific UK centre initially. I comment as a Patient voice and from that perspective I regard a 1% serious complication rate as uncomfortable and this should be clearly communicated to a patient at shared decision making. Although patients will be lead by consultant opinion. Surgery should not be marginalised. I would like to think that a cardiologist would be able to use a device that he/she is comfortable and experienced with deploying. [redacted]	surveillance of adverse outcomes.
56	Consultee 6 Edwards Lifesciences	Not specified	This sentence appears to suggest that there is is a separate piece of guidance being created on "using transcatheter heart valves for aortic valve implantation" in addition to the LSA. There is nothing in the current published NICE programme of work that supports this statement. Please provide further details, or clarity, on ongoing additional guidance creation.	

Comment number	Name	Section number	Comment	Response
57	Consultee 6 Edwards Lifesciences	Not specified	NICE should also make it clear early in the guidance and the recommendations that five of the eleven technologies have no evidence at all to make a valid comparison. It is our firm belief that these technologies should not form part of the guidance recommendations or have only “in research” recommendations for their use, until such time that they develop an evidence base suitable for HTA. Doing otherwise undermines the work that many other companies do to generate evidence for value assessment.	
58	Consultee 6 Edwards Lifesciences	Not specified	There is a general problem in issuing guidance to use the “least expensive” when there is no clinical evidence for doing so for 5 out of 11 of the technologies. Careless and ill-thought out recommendations, not based in evidence, could introduce risk to the whole TAVI patient population.	
59	Consultee 6 Edwards Lifesciences	Not specified	There are numerous examples where the document has not accurately summarised the views and evidence presented that will be presented in these comments. One instance is that the evidence on 5 out of 11 devices is unknown, which contradicts section 3 of the document which asserts that the committee reviewed evidence and made decisions on price justification on 11 devices.	
60	Consultee 6 Edwards Lifesciences	Not specified	From the EAG analyses and report, one technology, SAPIEN 3, clearly maximises the clinical effectiveness and the value for money (NMB). This is supported by the findings from the literature from both a clinical and economic perspective [Senguttuvan et al , Front Cardiovasc Med. 2023 May 25;10:1130354 and Heathcote et al, Clinicoecon Outcomes Res. 2023; 15: 459–75.- both previously supplied]. Despite the EAG findings, this LSA draft guidance states that “the committee agreed that it is not possible to establish whether the differences in net monetary benefit were because of differences in valve performance or because of confounding in the clinical data used to inform parameters in the economic model.” It therefore follows that there is insufficient evidence to draw any conclusions, as the EAG has only been able to produce an economic model which has “significant bias” and is “highly uncertain.” Please explain how is it possible to make the recommendation to use	

Comment number	Name	Section number	Comment	Response
			the “least expensive option available which is clinically appropriate” when the guidance states that the committee have indicated that it was not possible to establish the reasons for differences in NMB?	
61	Consultee 6 Edwards Lifesciences	1.1 1 Recommendations	Recommendation 1.1 is very misleading as it is unknown whether the lack of evidence to make any determination is due to the inadequate level of data searches and analysis conducted. A more correct statement would be that evidence the EAG chose to assess did not provide enough information to draw any conclusion on the appropriateness of price variations. , It is particularly worrying that guidance recommendations include devices where there was an “inability to assess the cost-effectiveness of the devices not captured in the UK TAVI Registry” - almost half of the technologies in the assessment. Recommendation 1.1 is also not a fair reflection of the conclusion of the committee that “it is not possible to establish whether the differences in net monetary benefit were because of differences in valve performance or because of confounding in the clinical data.” This statement indicates the possibility that differences in NMB could have been due to differences in valve performance. In the summary of the results presented the EAG “does not exclude the possibility that they reflect the true performance of the TAVI devices.” It is not a reasonable conclusion to make a recommendation based on an argument that there isn’t enough evidence. Due to the differences in regulatory indications, the lack of comparison across valve types and committee conclusion that equivalence cannot be assumed between devices there should not be a recommendation issued on variations between device types or on “aortic stenosis” as a blanket indication Consideration should be given to conducting the LSA for high-risk patients by different device type – the overwhelming majority of TAVI procedures - where there is a common ground from a regulatory perspective and an abundance of data.	

Comment number	Name	Section number	Comment	Response
62	Consultee 6 Edwards Lifesciences	1.3 What information is needed	The clinical outcomes listed are captured in the UK TAVI registry. The issue with relying on the TAVI registry for comparative effectiveness evaluation is the number of patients per device in the registry which differs dramatically between devices - making such comparison almost impossible and in 5 of 11 cases unknown	
63	Consultee 6 Edwards Lifesciences	1.3 What information is needed	With all the comorbidities included in the UK TAVI registry, a calculation of the person's surgical risk (EuroScore, STS) should be possible	
64	Consultee 6 Edwards Lifesciences	1.3 What information is needed	These details are all captured in the registry	
65	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	This statement is misleading. The EAG stated the results "were subject to significant uncertainty but did not exclude the possibility that they reflect the true performance of the TAVI devices." Based on the limited evidence reviewed, a more accurate statement would be 'analyses are too uncertain to determine whether or not the differences in cost between valves are justified.' Despite all of the limitations, looking more in depth at the EAG report and the analysis performed in the base case from the economic evaluation, we clearly see an outlier, statistically significant) with the highest NMB - which is SAPIEN 3 for both male and female patients(page 62 of the Committee Papers) There is strong published evidence demonstrating that SAPIEN 3 Ultra is at least as good as SAPIEN 3.	

Comment number	Name	Section number	Comment	Response
66	Consultee 6 Edwards Lifesciences	2.10 Sapien 3 and Sapien 3 Ultra (Edwards)	This is not accurate and LR is missing. Latest IFU (including S3UR) states: 1. The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA transcatheter heart valve system is indicated for use in patients with heart disease due to native calcific aortic stenosis at any or all levels of surgical risk for open heart surgery. 2. The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA transcatheter heart valve system is indicated for patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of an aortic transcatheter bioprosthetic or surgical aortic or mitral bioprosthetic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).	
67	Consultee 6 Edwards Lifesciences	3.19 Cost effectiveness	The confidence intervals for SAPIEN 3 did not overlap. Please change this statement. The differences in NMB are also supported in literature, which has been supplied previously to NICE but has not been considered. It is also important to note that the EAG does not exclude the possibility that these results could “reflect the true performance of the TAVI devices”	
68	Consultee 7 Boston Scientific	1.3 1 Recommendations	We support the recommendation that trusts have access to a range of valves, and that clinicians will continue to have the freedom to choose the most clinically appropriate valve.	
69	Consultee 9 Abbott Medical	1.2 1 Recommendations	Abbott requests that it is made clear whether this "least expensive option" incorporates the value add or not. The least expensive option without the value add may not be the least expensive option when value add is considered.	

Comment number	Name	Section number	Comment	Response
70	Consultee 10 Medtronic	3.14 Relative performance between valve generations	The statement below was made by a Medtronic company representative and we feel that it is important to clarify that she was referring to certain outcomes yet the statement may be interpreted as all outcomes. Therefore we suggest a minor change as follows: “A…. company representatives explained that usually newer generations make incremental improvements and that these are often small changes which would not affect **certain** outcomes, such as durability.”	
71	Consultee 12 Heart Valve Voice	1 Recommendations	NICE is uniquely positioned to champion the collection of comprehensive, long-term data on medical devices, especially given the NHS’s centralised capabilities. Unfortunately, the current systems in place for data collection and clinical audits are underfunded and lack the scope required to generate meaningful, real-world evidence on the long-term performance of heart valves. Heart Valve Voice strongly urges NICE to prioritise the development of more robust data collection processes to ensure that future decisions are grounded in solid, real-world evidence. For this to be effective, the data collection must be clinician-led, adequately funded, and supported by modern, efficient systems. This will not only improve patient safety but also ensure that cost-effectiveness decisions are based on reliable evidence.	

Comment number	Name	Section number	Comment	Response
72	Consultee 12 Heart Valve Voice	Not specified	As the consultation process continues, Heart Valve Voice encourages NICE to take a cautious, evidence-driven approach in refining its recommendations. Decisions based on incomplete or inadequate evidence can place patients at significant risk, compromising the quality of care they receive. We would also call on NICE to collaborate closely with the MHRA and other relevant bodies to improve data collection, enhance monitoring systems, and ensure that the evidence used to inform decisions is both comprehensive and of the highest quality. While we understand the need for cost-effectiveness within the NHS, patient safety and clinical outcomes must always be the priority. In summary, we believe the current recommendations do not reflect the the evidence we and other stakeholders have presented. We hope that as the process moves forward, NICE will carefully reconsider its approach to ensure that patients continue to receive the safest and most effective care possible.	

Indication and regulation

Comment number	Name	Section number	Comment	Response
73	Consultee 6 Edwards Lifesciences	Not specified	Likewise, guidance recommendations should not be issued for technologies outside of their indication for use, especially when they have not generated evidence to gain specific regulatory approval.	
74	Consultee 6 Edwards Lifesciences	1.3 1 Recommendations	This is the only sound recommendation that can be drawn from the evidence presented and clinical expert recommendations. Other evidence has been shown to be highly uncertain yet appears to have been overlooked, whereas this deals well with the recognised uncertainty. It should be clearly noted that not all valves have the licensed indications for all patient categories in this assessment and clinicians should follow Table 2 EAG from a regulatory perspective. Perhaps a form of this table needs to be included in the guidance document.	

Comment number	Name	Section number	Comment	Response
75	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	Valves also vary by licensed indications and level of supporting data This has been completely overlooked in this draft guidance - despite the work done by the EAG on that topic (Page 8 of the Committee papers document)	
76	Consultee 6 Edwards Lifesciences	2.3 2 The technologies	Data was unavailable for 5 out of the 11 TAVI devices. The EAG states their outcomes are unknown, so by definition are not included in the assessment. Also, these valves do not have licensed indications for the entire spectrum being considered. It is unsound to generalise across devices and the recommendations need to be revised accordingly.	
77	Consultee 6 Edwards Lifesciences	3.4 Choice of valve	As there is a large degree of variation in licensed indications, specific recommendations by risk categories should have been considered including the C/E evaluation. All valves are licences for HR patients but not all are licensed in patients with lower risk. TAVI devices are found to be highly cost effective in HR patients with an ICER of £7k / QALY with a device cost at £17.5k and this information should be included in support of the expert observation which is supported by the registry data.	
78	Consultee 6 Edwards Lifesciences	3.4 Choice of valve	The opinion of one clinical expert should not be considered to be authority to use a technology outside of its regulatory approval in this or any other NICE guidance. One opinion is very much at the lowest end of hierarchy of evidence. By inserting this comment by one clinical expert in a guidance document. It also suggests that NICE is endorsing the use of medical devices outside of their indications for use.	
79	Consultee 6 Edwards Lifesciences	3.12 Evidence for valves not captured in the UK TAVI registry	If there is no data for these valves, then no guidance should be issued on them. It is unfair to the companies involved and potentially dangerous for patients to receive recommendations on technologies based on no evidence.	

Previous generations

Comment number	Name	Section number	Comment	Response
80	Consultee 2 British Cardiovascular Intervention Society	Not specified	[redacted] commenting on behalf of the British Cardiovascular Intervention Society (BCIS) With respect to the Draft guidance document, BCIS has the following comments:- 1. The guidance concludes that there was no evidence of a difference between TAVI valves identified by this consultation. It therefore concludes that there is no reason to distinguish between the valves, and therefore the cheapest valve should be used by default. This is an inappropriate conclusion. The LSA process did not look at the appropriate data to assess the 11 different valves. This is why no difference was identified, not because there is no difference. We will expand on this below. 2. The LSA should have looked more broadly at the totality of evidence/data for each valve type. Two of the valve types (Edwards SAPIEN and Medtronic Evolut), have vastly more data to support their safety and efficacy. They have multiple RCTs in many thousands of patients, with follow-up in multiple RCTs up to 5 years. They have registry data including long-term follow-up to 10 years. None of the other valve types has anything like this amount of data. Several have none or almost none from RCTs. 2. The LSA should have considered long-term outcome data with the different valves assessed. Edwards SAPIEN and Medtronic Evolut have RCT data to 5 years, and registry data to 10 years. None of the other valves has 5 year data. 3. The LSA should have considered the totality of global and UK experience with the different valves. Edwards SAPIEN and Medtronic CoreValve/Evolut have been used in the UK for 17	Draft guidance 2: The EAG acknowledged in the key issues of the original EAG report that *"Longitudinal evidence is only available on earlier generation devices where poorer outcomes are expected. Newer device models typically phase out earlier models, however device sizes may vary between models and therefore the populations in which different generations of valves are used cannot be assumed to be exactly equivalent."* The longest available follow-up for the devices listed in the Final Scope, and for the device family where multiple generations of a device were available from a manufacturer, were summarised in Table 37 of the original EAG report. There was a need to be pragmatic in terms of excluding older generations of devices, and also a need to consider the relevance of them to the decision problem. Because the purpose of the LSA is to inform future procurement decisions, evidence relating to older generations of valves will become even less relevant as time goes on. The totality of UK real-world evidence

Comment number	Name	Section number	Comment	Response
			years and in 10s of thousands of patients. None of the other valves has anywhere near this degree of experience globally or in the UK. 4. Considering the above we do not believe it is reasonable to conclude that there is no difference between the TAVI valves, and the cheapest should be used where possible. We believe that those valve types with vastly more data, much longer term follow-up data, and far greater experience globally and in the UK, can be distinguished from the other valve types	for each valve is provided in section 5.3 of the EAG report and has similar relative availability by valve to the clinical evidence. In multivariate analysis, this is reflected in the width of the confidence intervals for the valve-specific covariates for each outcome measure. Lack of RCT evidence for some devices was noted by the EAG in section 5.2. The EAG report recommended continued data collection for all available devices. 3: Please see above response to 2. 4: Please see above response to 2.
81	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	This definition of the assessment is different to the main summary because the only way that "differences in clinical, economic and non-clinical outcomes between the different valves" can be "attributed to innovative features or characteristics of the valves" is by comparing them to previous generations of that valve and not against other valves. It's impossible otherwise to draw any conclusions as to why there are clinical differences. To look at a two-year window of data from the TAVI registry is not going to capture any inter- or intra- valve differences adequately, as shown in the EAG report and in the expert comments. Non-clinical outcomes have been overlooked. From the UK TAVI registry and the EAG report (Table 17), we observe some statistical differences in important outcomes such as the	

Comment number	Name	Section number	Comment	Response
			procedure time and length of stay between the TAVI valves that are not captured in this draft guidance. These are just a few examples of why this guidance is not based on a robust assessment of all relevant evidence	
82	Consultee 6 Edwards Lifesciences	3.14 Relative performance between valve generations	The reported comment by company representatives does not make any sense. There is no reason to make an incremental innovation if it is not intended to improve outcomes. This comment should be removed. The evidence that was asked for by the EAG included the following question: "How does your technology differ from other technologies in the category? Please give details in terms of how the differences affect clinical and non-clinical outcomes." The data supplied in response to this question would show how the improvements in the devices lead to improvements in outcomes. Once again, this guidance is not issued on evidence and “likely” indicates that EAG is basing the relative performance report on anecdote, not on evidence. Until relative performances are assessed based on available robust data, no assumptions should be made.	
83	Consultee 10 Medtronic	3.14 Relative performance between valve generations	We agree with the following statement from section 3.14 and therefore feel it is important that procurement bodies are aware of the similarities between valve iterations as well as the differences: “**it should not be assumed that a newer valve is non-inferior if the differences between valves are substantial (for example, changes in the leaflet tissue)”.** For the Medtronic TAVI valves, there have been no changes made to the valve leaflets themselves and therefore we ask that the following statement is added to the product description for Evolut valves in section 2.6: **“No changes have been made to the valve housing or leaflets as the design has progressed from Evolut R through Evolut FX.”**	

Confounding factors

Comment number	Name	Section number	Comment	Response
84	Consultee 6 Edwards Lifesciences	1.3 What information is needed	While both of these are missing from the RWE in the TAVI registry, the guidance does not explain in what way these factors make a clinical difference, and if so, the magnitude of that difference: Two references that should have been used to inform this conclusion are: • Guimarães et al. International Journal of Cardiology, Volume 306,2020, 20-24 multicenter (n=626): No association between high index calcium score and 30-day mortality and stroke for SAPIEN 3. This study classified high and low scores based on the median value for each sex. • Larroche et al. Int J Cardiovasc Imaging. 2020 Apr;36(4):731-740, single center (n=352): assessing the impact of Aortic valvular calcium score (AVCS) on clinical outcome (Device Success (DS), Major Adverse Cardiac Event (MACE) and PVL) for both BEV and SEV. “the relationship between AVCS and TAVR results seems to be more complex, with a U-shaped curve, where a low calcification rate leads to a risk of embolisation and excessive calcification leads to a risk of misdeployment or para valvular regurgitation. So, there seems to be a middle way to be found and measuring the calcium score when preparing a TAVR could be a simple tool to add to the usual visual assessment. Moreover, the results suggest that a high AVCS particularly affects the DS when it involves auto-expanding valves and when the distribution of valvular calcium is symmetric. These two points could be related to a misdeployment of the prosthesis, in the case of local calcium amalgams, which could lead to the occurrence of leak or obstruction. Indeed, self-expanding valves adhering to existing anatomy while balloon-expandable valves forcing their circular expansion through radial force”. This data suggests that distribution of calcium around the valve is more problematic for self-expandable valves than balloon-expandable valves. This relative effectiveness aspect has not been explored at all in the guidance.	

Comment number	Name	Section number	Comment	Response
85	Consultee 6 Edwards Lifesciences	3.3 Choice of valve	Using the level of calcium as a predictor of outcome for all valves is not supported by literature Guimarães et al 2020, multicenter (n=626): No association between high index calcium score and 30-day mortality and stroke for SAPIEN 3. This study classified high and low scores based on the median value for each sex. Larroche 2020 single center (n=352) - assessing the impact of Aortic valvular calcium score (AVCS) on clinical outcome (Device Success (DS), Major Adverse Cardiac Event (MACE) and PVL) for both BEV and SEV.	
86	Consultee 6 Edwards Lifesciences	3.3 Choice of valve	There is a contradiction in this statement in relation to the evidence assessed. On one hand the EAG states that missing components (anatomy and calcium) might explain the differences observed from the TAVI registry and on the other, they state that the majority (50%+) could actually be treated with any TAVI device. If that's the case then the observed differences in clinical outcomes (focusing on short-term were more reliable) should be considered as valid as they are also aligned with the literature [Senguttuvan et al., meta-analysis for example] and the registry data should serve as a reliable source of evidence	In section 5.3.1 the EAG listed a number of cofounders (as examples) which were listed in the published literature or by Clinical Experts. The EAG has not stated (in their report or otherwise) that the majority of patients can be treated with any device; this comment came from specialist committee members at the MTAC1. The EAG has identified the following excerpt from section 3 of the EAG report: *"The Clinical Experts have advised that there may be occasions where only 1 TAVI device is suitable, Appendix G. The Clinical Experts also advised that while many patients can be treated with any TAVI device, there are some subgroups, such as those with a small annulus, who may be better suited to a particular device for its specific features, such*

Comment number	Name	Section number	Comment	Response
				as expansion type or intra- or supra-annular leaflets (Appendix G; Herrmann et al. 2024).”
87	Consultee 6 Edwards Lifesciences	3.15 Economic model structure	There is no perfect economic model - reason why PSA and DSA were considered. Despite all limitations and uncertainties, some clinical differences are observed from the UK TAVI registry which are aligned with the findings from the literature (RCTs and meta-analysis) - including the Heathcote et al. 2023 publication. From the base case results in the EAG report, we clearly see a device with the highest probability of NMB	No changes required.

Added-value agreements

Comment number	Name	Section number	Comment	Response
88	Consultee 1	1.3 What information is needed	We do not agree with the statement on ‘Added Value’ agreements between companies and NHS Supply Chain. None of these agreements result in cost returning to NHS England, it is retained by the NHS Trust. Only one of these agreements allows for part of the cost of a valve to be returned to an NHS trust to be spent on structural heart-related items. The others are linked to the purchase of other products in the company portfolio and are spent on a variety of items, that may not be structural heart-related. We consider that such agreements, that are volume related, skews the market and are anti-competitive, preventing uptake of newer TAVI valves. This limits choice for the clinicians and patients and runs counter to two of the NICE recommendations. We would like to see TAVI moved from the Specialised Services Devices Programme (SSDP) to the National Tariff. This would allow for wider commissioning of transcatheter mitral technologies and the commissioning of transcatheter tricuspid technologies. This would also negate the need for ‘Added Value’ programmes.	

Comment number	Name	Section number	Comment	Response
89	Consultee 6 Edwards Lifesciences	1.3 What information is needed	This paragraph on added value agreements is not a true or fair assessment of reality. It is also misleading. Without the added value agreements, NHS resources would be further stretched	
90	Consultee 6 Edwards Lifesciences	1.3 What information is needed	This sentence is purely speculative and is not based on anything that has been presented to the committee. It should be removed as it has no basis in any evidence that has been presented to the committee	
91	Consultee 6 Edwards Lifesciences	3.18 Model cost inputs	Edwards does not believe this statement [It also noted that the resources returned through 'added value' agreements can only be spent on structural heart-related products or services at the NHS trust level.] to be true. Please substantiate this comment or remove it.	
92	Consultee 7 Boston Scientific	1.3 What information is needed	3. We question the statement that added value agreements “will not be resource-releasing for the NHS”. The purchases made with the cash released from these agreements are deemed necessary by the hospital, and therefore are likely to have been made/required regardless of the presence of an added value agreement. We request this wording is therefore removed.	
93	Consultee 9 Abbott Medical	1.3 What information is needed	Abbott do not agree with this statement and request that it is removed. Abbott's TAVI Value Model provides Trusts with access to such a broad catalogue of options that it is absolutely possible to achieve ‘resource-releasing’ impact from this 'Added value'.	
94	Consultee 10 Medtronic	1.3 What information is needed	[redacted]	
95	Consultee 11 Meril UK	3.18 Model cost inputs	3.18 above is not compliant in public procurement law	
96	Consultee 11 Meril UK	Not specified	• What is permitted in terms of good and services, to what value vs. volume of TAVI ordered? • Use an RFI to explore what the monies are being used for at each centre.	

Equality issues

Comment number	Name	Section number	Comment	Response
97	Consultee 1	1.3 What information is needed	We would suggest that amongst the recommended confounding factors in the UK TAVI Registry it should include ethnicity as part of both a clinical and a group of equality factors.	
98	Consultee 6 Edwards Lifesciences	Not specified	There is also clear evidence that there is inequity of TAVI availability. Patients of a female gender, black or South Asian ethnicities and high deprivation are associated with significantly reduced odds of receiving AVR in England. Although inequalities are identified in the scope, NICE has not demonstrated any consideration of how this guidance could improve these factors in its recommendations or assessment.	
99	Consultee 6 Edwards Lifesciences	3.25 Equality considerations	There is also clear evidence that there is inequity of TAVI availability. Patients of a female gender, black or South Asian ethnicities and high deprivation are associated with significantly reduced odds of receiving AVR in England. (Rice et al. Open Heart 2023;10:e002373.) Although identified in the scope, NICE has not demonstrated any consideration of these factors in its recommendations or assessment.	
100	Consultee 10 Medtronic	3.25 Equality considerations	Section 3.25 states the following: “Transcatheter heart valves are available in different size ranges, which may affect whether they can be used in people with different body sizes **(for example, men are more likely to have a large aortic annulus and need a larger valve).”** The scoping equality impact assessment for this LSA topic states that women “experience greater 5- year mortality after diagnosis of severe AS” than men. Additionally, the EAR identified evidence that revealed significant differences in timely AVR based on sex (Rice et al. 2023). The NICOR 2024 report for the UK TAVI registry states ‘there may be an under-provision of TAVI treatment to female patients.’ The EAR also stated that “The Clinical Experts also advised that while many patients can be treated with any TAVI device, there are some subgroups, such as those with a small annulus, who may be better suited to a particular device for its specific features, such as expansion type or intra- or supra-annular leaflets”	

Comment number	Name	Section number	Comment	Response
			Given that women are the underserved population regarding sex differences in access to TAVI, we recommend that the statement in section 3.25 is updated as follows: 'Transcatheter heart valves are available with **different design features** and in different size ranges, which may affect whether they can be used in people with different body sizes (**for example, women are more likely to have a small aortic annulus and need a smaller valve)'**	

User preference assessment

Comment number	Name	Section number	Comment	Response
101	Consultee 6 Edwards Lifesciences	3.22 Justification for price variation	User preference analysis was included, but this was based on the opinion of very few clinicians and was not opened to a wider care team input. The limited sample size and narrow field of expertise surveyed indicated that the methods for establishing user preference methods were poor.	
102	Consultee 7 Boston Scientific	3.22 Justification for price variation	When mentioning the User Preference Assessment, it should be clearer that this was a methodology not previously conducted by NICE before, and should be seen as evolving. It had several limitations, including but not limited to, its sample size.	

Resource impact

Comment number	Name	Section number	Comment	Response
103	Consultee 6 Edwards Lifesciences	3.20 Resource impact	It is unclear why the committee were asked to consider this hypothetical, misleading scenario rather than a scenario that is more realistic, supported by literature and within the licensed indications of all technologies concerned Only HR should be considered as this is a common indication across devices and also where there is convergence between the EAG findings and the literature on the better performance of specific devices. What is	

Comment number	Name	Section number	Comment	Response
			more concerning is that the focus is on price and not on value for money – the committee should be asked to consider a scenario where the most cost-effective valves were used in order to achieve the LSA goal to "maximise clinical effectiveness and value for money."	
104	Consultee 7 Boston Scientific	3.20 Resource impact	We require more information around the statement that a 10% shift to less expensive valves could fund additional TAVI procedures if reinvested into the service. A 10% shift could also fund various other non-cardiac initiatives, and indeed could end up plugging inefficiencies in the system elsewhere, with benefits not recognised by TAVI practitioners or heart valve disease patients. If this statement is to be made, we request a commitment to a plan where savings made would be reinvested into alleviating the specific blocks that currently exist in the TAVI pathway, given that the UK is far behind its European neighbours in this area.	

Process

Comment number	Name	Section number	Comment	Response
105	Consultee 4	4 Specialist committee members	Can you explain or otherwise justify the presence of 4 cardiac surgeons in a piece of work on TAVI? Only 3 TAVI cardiologists	
106	Consultee 4	4 Clinical experts	I can see that I have been omitted from this list.	

Comment number	Name	Section number	Comment	Response
107	Consultee 6 Edwards Lifesciences	Not specified	Edwards Lifesciences has participated in and contributed to numerous HTA's both in the UK and globally. We are astounded that NICE has produced guidance using such fundamentally flawed and unfair processes, methods and reasoning, which are clearly evident in this LSA. The choice to repeatedly ignore the majority of stakeholder input and the choice to ignore the overwhelming majority of evidence and information to help to answer the decision problem demonstrates that NICE has not taken an evidence based approach. It is consequently likely to have the opposite of the desired effect of improving quality and value and sets the NHS back many years in its approach to decision making. NICE has exceeded its powers in ignoring the regulatory processes in reaching its unsound conclusions and in not following the standard hierarchy of evidence approach in HTA, going as far as recommending (by default) technologies which are not licensed in a particular indication and/or for which the clinical and economic data are "unknown". Edwards supports the principle behind the introduction of LSA. Throughout this LSA, we have tried our utmost to help NICE produce sound guidance. What NICE could, and should, have done to produce useful guidance is to firstly examine the use of different TAVI devices in high risk (HR) surgical candidates. This is the only indication common to all devices. The analyses for high risk surgical candidates should have then been separated by different expansion types. Low (LR) and intermediate risk (IR) should have been modelled separately where indications for the individual devices permit. This would reflect the output of the regulatory processes for the development of medical technologies.	

Comment number	Name	Section number	Comment	Response
108	Consultee 6 Edwards Lifesciences	Not specified	In this particular LSA, there has been significant deviation from anything in the NICE procedure manuals and even from either version of the belatedly issued Interim Methods and Process. One example of this (among many others previously communicated to NICE) is that the measurement and criteria for justifying price differences does not exist in any NICE manual – there is no clear description in the methods of what benefits are expected, or threshold of clinical superiority which drive a justifiable price difference. Please explain against what standards were objective measurements of price difference made in this assessment?	
109	Consultee 2 British Cardiovascular Intervention Society	Not specified	[redacted] commenting on behalf of the British Cardiovascular Intervention Society (BCIS) BCIS has major reservations over this document, and the processes which led to its development, which we believe to be highly flawed. With respect to the process, we would highlight the following issues: 1. The process was far too rigid, without application of common sense. This could be attributed to the failure to include appropriate clinical specialists i.e. interventional cardiologists who do TAVI procedures, in the process from the outset. 2. The specialist committee did not include the appropriate specialists. The committee included 5 cardiac surgeons, none of whom does TAVI, and none of whom makes decisions on what TAVI valve to use in a given patient. The specialist committee should have been populated by interventional cardiologists who do TAVI.	

NICE's press release

Comment number	Name	Section number	Comment	Response
110	Consultee 2 British Cardiovascular	Not specified	3. We consider it inappropriate that NICE produced a press release based on draft consultation prior to completion of the consultation phase. Furthermore, the tone and content of the press release did not match the actual guidance.	

Comment number	Name	Section number	Comment	Response
	Intervention Society			
111	Consultee 6 Edwards Lifesciences	Not specified	Given that these are draft recommendations, subject to change, please explain why unequivocal, inaccurate representations - strongly saying that this is the final conclusion - of them have appeared in press releases on August 9th (NICE news) and September 2nd (Health Service Journal)	
112	Consultee 10 Medtronic	Not specified	Press Release 9/8/24: We are very concerned regarding the premature and misleading press release that was issued by NICE on 9th August headlining **"No evidence to support the price variation in heart valves used by the NHS. Draft guidance issued today (9 August) states that the variation in price the NHS is paying for valves used in keyhole heart procedures is not supported by reliable evidence"** The statement **"No evidence to support the price variation in heart valves used by the NHS**" suggests that the committee has **determined that there is no difference between valves**, which is not the case. We believe that this summary is factually inaccurate and misrepresents the committee's conclusions as stated below: **• "It was not clear in the clinical evidence whether there are differences in clinical effectiveness between different companies' transcatheter heart valves due to incremental innovations between the valves" [Section 3.13]** **• "Clinical equivalence between companies' valves could not be assumed. [Section 3.13]** **• "The model results were too uncertain to determine whether there were differences in the cost effectiveness of the transcatheter heart valves" [Section 3.19]** **• "It was not possible to determine whether the differences in cost between valves were justified by benefits derived from incremental innovations".**	

Comment number	Name	Section number	Comment	Response
			We believe that this headline is factually inaccurate in stating that **"there is no evidence to support the price variation....." and "variation in price is not supported by reliable evidence..."** as the EAG did not conduct a systematic review of the substantial body of high-quality published evidence and relied solely on outcomes data from around 30% of patients from the UK TAVI registry for the clinical and economic assessments. This registry data is limited by data availability and completeness and lack of adjustment for confounders and the **committee concluded that the registry data did not capture enough detail to provide reliable estimates of relative efficacy between valves.** The **committee also concluded that the bias and limitations of the clinical inputs to the economic model leads to significant bias in the results of the economic model.** The committee's conclusions clearly show that they were **"unable to determine a difference"** and not that "**there is no evidence to support...**." and we ask that a correction is issued for press statement to reflect that the committee was unable to determine a difference due the exclusion of all of the published evidence from the EAG assessment. We ask NICE to ensure that any subsequent press releases accurately reflect the committee conclusions and the wording in the recommendations.	

Comment number	Name	Section number	Comment	Response
113	Consultee 10 Medtronic	Not specified	Press Release 9/8/24:The quote below from Prof Benger is also factually incorrect and misleading as it states “ We have looked for evidence to determine whether differences in innovation and performance between these valves can justify their range in price, but the i**nformation we have seen does not support the current variation in cost”.** From the very limited “information they had seen”, the committee actually concluded that “th**e registry data did not capture enough detail to provide reliable estimates of relative efficacy between valves**”. The “information that was seen” was limited to TAVI registry data and a systematic literature review of the published evidence was not conducted. **The quote from Prof Benger concludes**: “We hope this **evidence-based guidance** will provide commissioners with the confidence to agree a cost-effective price and allow the NHS to reinvest the money saved to treat more patients as a result”. We believe that this statement is also misleading as the guidance is not based on the evidence and the committee actually concluded “T**he model results were too uncertain to determine whether there were differences in the cost effectiveness of the transcatheter heart valves**” [Section 3.19]	
114	Consultee 10 Medtronic	Not specified	Press Release 9/8/24: We question why a press release was issued at this stage, when the draft guidance is subject to change following consultation.	

Late-stage assessment guidance
GID-HTE10027 Transcatheter heart valves for transcatheter aortic valve implantation (TAVI) in people with aortic stenosis:
Addendum

Produced by	Newcastle External Assessment Group (EAG)
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Responsibility for report:

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
AKI	Acute Kidney Injury
AVA	Aortic Valve Area
BE	Balloon Expanding
CAD	Coronary artery disease
CVA	Cerebrovascular accident
CVT	Clinical valve thrombosis
ECG	Electrocardiogram
GFR	Glomerular Filtration Rate
HALT	Hypo attenuated leaflet thickening
iEOA	indexed effective orifice area
IQR	Interquartile Range
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MDCT	Multi-detector CT
MDT	Multidisciplinary team
MI	Myocardial infarction
N/A	Not applicable
NR	Not reported
NYHA	New York Heart Association
PPI	Permanent pacemaker implantation;
PPMI	Permanent pacemaker implantation
PVL	Paravalvular leak
PVR	Paravalvular regurgitation
RCT	Randomised controlled trial
SE	Self-expanding
SLT	Subclinical leaflet thrombosis
STS	The Society of Thoracic Surgeons
SVD	Structural valve deterioration
TAPSE	Tricuspid annular plane systolic excursion
TAVI	Transcatheter aortic valve implantation
TAVR	Transcatheter aortic valve replacement
TEE	Transoesophageal echocardiogram
THV	Transcatheter Heart Valve

Term	Definition
TIA	Transient ischaemic attack
TTE	Transthoracic echocardiogram
VARC-2	Valve Academic Research Consortium-2
VARC-3	Valve Academic Research Consortium-3

1. Background

In response to comments received on the draft guidance, the aim of this supplementary report is to review and summarise 44 additional pieces of evidence. A total of 43 studies were identified by NICE: original Company Request for Information (N=11), stakeholder consultation responses (N=30) received *prior* to publication of draft guidance, see earlier EAG responses to consultation comments, and public consultation responses (N=2) received *after* publication of draft guidance. 1 additional reference (identified as a reference from 1 of the 43 studies identified by NICE) was also considered by the EAG.

2. Methods

The EAG reviewed full papers for the 44 identified studies and considered relevance to the Final Scope; categorising studies as not in scope, in scope but not key evidence and key evidence. For transparency, study characteristics were tabulated and EAG considerations of generalisability and limitations summarised. Where the EAG considered the study to be out of scope the reason(s) for exclusion were provided. Study results were only extracted for comparative studies comparing outcomes across different TAVI devices in line with the LSA objectives. Direction of results of key evidence were compared with those obtained from analysis of UK TAVI Registry data and evidence already considered within the original EAG report (where statistical comparisons were made to a reference device), to determine general trends.

3. Results

The EAG considered that of the additional 44 studies (Appendix 1), 22 were out of scope (see section 3.3), 20 were in scope but not considered key evidence (see section 3.2) and 2 were in scope and considered key evidence (see section 3.1), neither of which were reported to have received industry funding (Deharo et al. 2020; Thiele et al. 2020).

3.1 Key evidence

The study by Thiele et al. 2020 was an RCT of 2x2 factorial design. The first randomised comparison considered the use of general anaesthesia vs local anaesthesia with conscious sedation. The study's second randomised comparison compared self-expandable (Evolut R) vs balloon-expandable (Sapien 3) valves in 447 patients in Germany. The study was designed to have at least 80% power to detect equivalence in intention to treat analysis for the composite primary endpoint (all-cause mortality, stroke, moderate or severe paravalvular leak, permanent pacemaker) for both randomised comparisons at 30 days. The analyses assumed independence between the 2 randomised comparisons based on clinical plausibility and did not subsequently report any test for interactions between the randomised comparisons. The authors concluded equivalence for both randomised comparisons for the primary outcome. The only secondary endpoint that was not equivalent was permanent pacemaker implantation, compared at 30 days (19.2% for Sapien 3 compared with 23.0% for Evolut R, p=0.06 thus rejecting the equivalence hypothesis), suggesting a possible difference between valves for that outcome. However, the EAG note that the study was not powered to detect differences in individual components of the composite endpoint and no exploration of interactions between the randomised comparisons was reported.

The study by Deharo et al. 2020 was a retrospective cohort from a national hospitalisation database in France (including public and private hospital care) which compared Sapien 3 with Evolut R and reported analysis from a cohort of 10,549 propensity matched pairs (matching based on 38 variables) followed for a median of 232 days (0.6 years). Across all time points for matched pairs (n=10,549) Sapien 3 was associated with statistically lower pacemaker implantation at the time or after the procedure (RR: 0.72 (95%CI 0.69 to 0.76); p<0.0001), lower all-cause mortality at follow-up (OR: 0.88 (95%CI 0.82 to 0.95); p=0.005) and lower rehospitalisation at follow-up (OR: 0.84 (0.78 to 0.90); p<0.001). At 3 years follow-up (n=3,029) lower all-cause mortality was seen with Sapien 3 compared with Evolut R (RR: 0.63 (95%CI 0.52 to 0.78); p<0.0001). No statistically significant differences were observed between arms in all-cause stroke, and negative control outcomes (non-cardiovascular death, cancer, and urinary tract infection). The EAG note that this

analysis was based on routine administrative data, with relatively short term follow up, and lacked clinical detail (such as that obtained from the UK TAVI Registry) including mean aortic valve gradient, valve area, and paravalvular leak; however, the authors did conduct statistical analyses to control for as many confounders as possible using the dataset available to them.

The EAG considered the results of these 2 additional studies when compared with the key evidence and analysis of the UK TAVI Registry data described in the original EAG report, which reported on the TAVI devices listed in the Final Scope. The general trends were as follows:

- Mortality: A statistical difference in procedural mortality between 4 TAVI devices was reported in the retrospective cohort with propensity matching by Rudolph et al. 2024, Table 1. No evidence of a difference in in-hospital mortality was found between devices was observed by the multivariate analysis of the UK TAVI Registry. Equivalence in this outcome was also demonstrated in an RCT (Thiele et al. 2020) with 30 days follow-up. Differences in mortality were reported by 2 cohort studies which incorporated propensity matching (Deharo et al. 2020 up to 3 years; Costa et al. 2022 up to 1 year); both showing higher mortality in Evolut R compared with Sapien 3 valves. No statistical differences in mortality were observed from the EAG's multivariate analysis of UK TAVI Registry data linked to HES data (maximum follow up of 2.6 years).
- Stroke: Differences in in-hospital stroke were observed in multivariate analysis of the UK TAVI Registry data (higher for Evolut R, Evolut Pro+, Navitor and Sapien 3 when compared with Sapien 3 Ultra as the reference which was the most frequently used balloon-expanding valve within the dataset analysed), Table 2. No evidence of a difference in stroke outcomes post-discharge were observed across TAVI devices in multivariate analyses of the UK TAVI Registry (follow-up 2.6 years). There was also no evidence of a difference in stroke outcomes in the Registry data between self-expanding valves (either in-hospital or follow-up to 2.6 years) when compared with Evolut Pro+ (the most frequently used self-expanding valve within the dataset analysed). A total of 5 published studies also reported no difference in stroke outcomes

post-discharge; noting that the devices which were compared varied across studies. Only Costa et al. 2022 reported lower stroke at 1-year with Portico (predecessor to Navitor) when compared with Evolut R.

- Readmission for heart failure: Differences were reported by 2 cohort studies with propensity matching (Deharo et al. 2020 showed Evolut R had more readmissions for heart failure than Sapien 3; Costa et al. 2022 showed more rehospitalisations for heart failure for ACURATE neo compared with Evolut R, and more for ACURATE neo, Evolut Pro and Portico when compared with Sapien 3 and more for ACURATE neo and Portico when compared with Evolut R), Table 3, however the follow-up period was 12 months or shorter. Multivariate analysis of the UK TAVI Registry data did not find a difference in this outcome post-discharge between devices (follow-up to 2.6 years). An additional cohort study with propensity matching did not find evidence of a difference in this outcome at 1 year (Rudolph et al. 2024).
- Reintervention: No differences in reintervention were observed longitudinally in the multivariate analysis of the UK TAVI Registry data or 2 additional retrospective cohort studies which included propensity matching, Table 4.
- Paravalvular leak and aortic regurgitation: Differences in paravalvular leak or aortic regurgitation at discharge were found in the multivariate analysis of the UK TAVI Registry and 1 retrospective cohort with propensity matching (definition of outcome varied, devices compared varied), Table 5. The EAG note that no difference was observed in the moderate or severe prosthesis valve regurgitation at 30 days in the RCT which compared Sapien 3 and Evolut R. The EAG note that statistical differences were observed for this outcome between generations of devices by the same manufacturer: Nazif et al. 2021 and Abdelfattah et al. 2022 comparing Sapien 3 and Sapien 3 Ultra, Gozdek et al. 2023 and Forrest et al. 2020 comparing Evolut R and Evolut Pro. The EAG highlight that technology differences between Evolut Pro+ (generation listed in NICE Final Scope) and Evolut Pro (as reported in these studies) is limited to changes in the profile of the delivery system).
- Permanent pacemaker implantation: 4 studies (including 1 RCT and 2 cohorts with propensity matching, and the multivariate analysis of the UK TAVI Registry) all demonstrated lower pacemaker implantation rate with Sapien 3

and 3 Ultra when compared with Evolut R and Pro+ or Navitor at in-hospital, 30 day and 1 year timepoints, Table 6. Two studies (both cohort studies with propensity matching) also reported lower pacemaker with ACURATE neo at 1 year (Costa et al. 2022, Rudolph et al. 2024) when compared with Evolut R and Portico devices. However, the EAG note that from multivariate analysis of the UK TAVI Registry data, no difference in pacemaker implantation after discharge up to 31 months follow up was found between devices (see Table 24 in original EAG report). No difference was observed in pacemaker outcomes when considering only self-expanding valves from the UK TAVI Registry either (see Table 25 and 26 in the original EAG report).

Table 1: Summary of mortality outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
UK TAVI registry	**Retrospective cohort (multivariate analysis)**	**All-cause mortality**	**In-hospital**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**
Merdler et al. 2023	Retrospective cohort	Mortality	In-hospital	-	-	-	-	-	-	Reference	No statistical difference	-	-	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	All-cause mortality	Procedural	-	No reference; statistical difference between 4 valves reported	-	No reference; statistical difference between 4 valves reported **(ACURATE neo lowest)**	-	No reference; statistical difference between 4 valves	-	-	-	No reference; statistical difference between 4 valves **(Portico highest)**	-
Thiele et al. 2020	RCT (2x2 factorial design comparing anaesthesia and expansion type of device)	All-cause mortality	30 days	-	Reference	-	-	-	No statistical difference	-	-	-	-	-
Nazif et al. 2021	Retrospective cohort (with propensity matching)	All-cause mortality, cardiac death	30 days	-	Reference	No statistical difference	-	-	-	-	-	-	-	-
Gozdek et al. 2023	SR and MA (N=11 observational studies)	All-cause mortality	30 days	-	-	-	-	-	Reference	No statistical difference	-	-	-	-
Forrest et al. 2020	Retrospective cohort	All-cause mortality	30 days	-	-	-	-	-	Reference	No statistical difference (Pro)	-	-	-	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	All-cause mortality	1 year	-	Lower	-	Lower (ACURATE neo)	-	Reference	Lower (Pro)	-	-	No statistical difference (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	All-cause mortality	1 year	-	Reference	-	No statistical difference (ACURATE neo)	-	Higher	No statistical difference (Pro)	-	-	Higher (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	All-cause mortality	1 year	-	No statistical difference	-	Reference (ACURATE neo)	-	Higher	No statistical difference (Pro)	-	-	Higher (Portico)	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	All-cause mortality	30 days and 1 year	-	No reference; no statistical difference	-	No reference; no statistical difference (ACURATE neo)	-	No reference; no statistical difference	-	-	-	No reference; no statistical difference (Portico)	-
UK TAVI registry	**Retrospective cohort (multivariate analysis)**	**All-cause mortality**	**Post-discharge up to 31 months**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**
Deharo et al. 2020	Retrospective cohort (with propensity matching)	All-cause mortality	1 month and 1, 2, 3 years	-	Reference	-	-	-	Higher	-	-	-	-	-
Deharo et al. 2020	Retrospective cohort (with propensity matching)	Cardiovascular mortality	1 month and 1, 2, 3 years	-	Reference	-	-	-	Higher	-	-	-	-	-
Abdelfattah et al. 2022	Meta-analysis (N=7 observational studies)	All-cause mortality	NR	-	Reference	No statistical difference	-	-	-	-	-	-	-	-

Abbreviations: NR, not reported

Table 2: Summary of stroke outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	Stroke	Procedural	-	No reference; no statistical difference	-	No reference; no statistical difference (ACURATE neo)	-	No reference; no statistical difference	-	-	-	No reference; no statistical difference (Portico)	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**Stroke**	**In-hospital**	**-**	**Higher**	**Reference**	**No statistical difference**	**-**	**Higher**	**Higher**	**-**	**-**	**Higher**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**Stroke**	**In-hospital**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**
Thiele et al. 2020	RCT (2x2 factorial design comparing anaesthesia and expansion type of device)	Stroke	30 days	-	Reference	-	-	-	No statistical difference	-	-	-	-	-
Forrest et al. 2020	Retrospective cohort	Stroke	30 days	-	-	-	-	-	Reference	No statistical difference (Pro)	-	-	-	-
Nazif et al. 2021	Retrospective cohort (with propensity matching)	Stroke	Discharge and 30 days	-	Reference	No statistical difference	-	-	-	-	-	-	-	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Stroke	1 year	-	No statistical difference	-	No statistical difference	-	Reference	No statistical difference (Pro)	-	-	Lower (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Stroke	1 year	-	Reference	-	No statistical difference	-	No statistical difference	No statistical difference (Pro)	-	-	No statistical difference	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Stroke	1 year	-	No statistical difference	-	Reference	-	No statistical difference	No statistical difference (Pro)	-	-	No statistical difference	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	Stroke	1 year	-	No reference; no statistical difference	-	No reference; no statistical difference (ACURATE neo)	-	No reference; no statistical difference	-	-	-	No reference; no statistical difference (Portico)	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**Stroke**	**Post-discharge up to 31 months follow-up**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**Stroke**	**Post-discharge up to 31 months follow-up**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**
Abdelfattah et al. 2022	Meta-analysis (N=7 observational studies)	Stroke	NR	-	Reference	No statistical difference	-	-	-	-	-	-	-	-

Abbreviations: NR, not reported

Table 3: Summary of readmission for heart failure outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
Forrest et al. 2020	Retrospective cohort	Valve related readmission	30 days	-	-	-	-	-	Reference	No statistical difference (Pro)	-	-	-	-
Deharo et al. 2020	Retrospective cohort (with propensity matching)	Rehospitalisation for heart failure	Median 0.6 years	-	Reference	-	-	-	Higher	-	-	-	-	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Rehospitalisation for heart failure	1 year	-	No statistical difference	-	Higher (ACURATE neo)	-	Reference	No statistical difference (Pro)	-	-	Higher (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Rehospitalisation for heart failure	1 year	-	Reference	-	Higher (ACURATE neo)	-	No statistical difference	Higher (Pro)	-	-	Higher (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Rehospitalisation for heart failure	1 year	-	Lower	-	Reference (ACURATE neo)	-	Lower	No statistical difference (Pro)	-	-	No statistical difference	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	Further hospitalisation, further hospitalisation due to complication related to the aortic valve intervention	1 year	-	No reference; no statistical difference	-	No reference; no statistical difference (ACURATE neo)	-	No reference; no statistical difference	-	-	-	No reference; no statistical difference (Portico)	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**Readmission for heart failure**	**Post-discharge up to 31 months follow-up**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**Readmission for heart failure**	**Post-discharge up to 31 months follow-up**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**

Table 4: Summary of reintervention outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
Nazif et al. 2021	Retrospective cohort (with propensity matching)	Aortic valve reintervention	Discharge and 30 days	-	Reference	No statistical difference	-	-	-	-	-	-	-	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	Reintervention	1 year	-	No reference; no statistical difference	-	No reference; no statistical difference (ACURATE neo)	-	No reference; no statistical difference	-	-	-	No reference; no statistical difference (Portico)	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**Aortic reintervention (TAVI or SAVR)**	**Post-discharge up to 31 months follow-up**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**

Table 5: Summary of paravalvular leak and aortic regurgitation outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	PVL grade II or III	Discharge	-	No reference; statistical difference between 4 valves reported **(Sapien 3 lowest)**	-	No reference (ACURATE neo); statistical difference between 4 valves reported	-	No reference; statistical difference between 4 valves	-	-	-	No reference; statistical difference between 4 valves **(Portico highest)**	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**Aortic regurgitation**	**In-hospital**	**-**	**No statistical difference**	**Reference**	**Higher**	**-**	**Higher**	**Higher**	**-**	**-**	**Higher**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**Aortic regurgitation**	**In-hospital**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**
Thiele et al. 2020	RCT (2x2 factorial design comparing anaesthesia and expansion type of device)	Moderate or severe prosthetic valve regurgitation	30 days	-	Reference	-	-	-	No statistical difference	-	-	-	-	-
Nazif et al. 2021	Retrospective cohort (with propensity matching)	Paravalvular regurgitation	Discharge and 30 days	-	Reference	Lower	-	-	-	-	-	-	-	-
Merdler et al. 2023	Retrospective cohort	Moderate or severe PVL	In-hospital and 30 days	-	-	-	-	-	-	Reference	No statistical difference	-	-	-
Abdelfattah et al. 2022	Meta-analysis (N=7 observational studies)	Moderate or severe PVL	NR	-	Reference	Lower	-	-	-	-	-	-	-	-
Gozdek et al. 2023	SR and MA (N=11 observational studies)	Moderate to severe PVL	NR	-	-	-	-	-	Reference	Lower (Evolut Pro)	-	-	-	-
Forrest et al. 2020	Retrospective cohort	Moderate to severe aortic regurgitation	NR	-	-	-	-	-	Reference	Lower (Evolut Pro)	-	-	-	-
Abdelfattah et al. 2022	Meta-analysis (N=7 observational studies)	Moderate or severe PVL	NR	-	Reference	Lower	-	-	-	-	-	-	-	-

Abbreviations: NR, not reported; PVL, paravalvular leak

Table 6: Summary of pacemaker implantation outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**PPI**	**In-hospital**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**Higher**	**Higher**	**-**	**-**	**Higher**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**PPI**	**In-hospital**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**
Deharo et al. 2020	Retrospective cohort (with propensity matching)	PPI	At time or after procedure	-	Reference	-	-	-	Higher	-	-	-	-	-
Thiele et al. 2020	RCT	PPI	30 days	-	Reference	-	-	-	Higher	-	-	-	-	-
Nazif et al. 2021	Retrospective cohort (with propensity matching)	PPI	Discharge and 30 days	-	Reference	No statistical difference	-	-	-	-	-	-	-	-
Merdler et al. 2023	Retrospective cohort	PPI	Discharge and 30 days	-	-	-	-	-	-	Reference	No statistical difference	-	-	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	PPI	1 year	-	Reference	-	No statistical difference (ACURATE neo)	-	Higher	Higher (Pro)	-	-	Higher (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	PPI	1 year	-	Lower	-	Lower (ACURATE neo)	-	Reference	No statistical difference (Pro)	-	-	No statistical difference (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	PPI	1 year	-	No statistical difference	-	Reference (ACURATE neo)	-	Higher	Higher (Pro)	-	-	Higher (Portico)	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	New pacemaker or implantable cardiovertor defibrillators	1 year	-	No reference; statistical difference between 4 valves reported	-	No reference; statistical difference between 4 valves reported **(ACURATE neo lowest)**	-	No reference; statistical difference between 4 valves **(Evolut R joint highest: 21.6%)**	-	-	-	No reference; statistical difference between 4 valves **(Portico joint highest: 21.9%)**	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**PPI**	**Post-discharge up to 31 months follow-up**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**PPI**	**Post-discharge up to 31 months follow-up**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**
Abdelfattah et al. 2022	Meta-analysis (N=7 observational studies)	PPI	NR	-	Reference	No statistical difference	-	-	-	-	-	-	-	-
Gozdek et al. 2023	SR and MA (N=11 observational studies)	PPI	NR	-	-	-	-	-	Reference	No statistical difference	-	-	-	-

Abbreviations: MA, meta-anlaysis; NR, not reported. PPI, permanent pacemaker implantation; SR, systematic review

3.2 In-scope but not prioritised

Of the 20 studies considered relevant to the scope but not key evidence, the EAG identified the following limitations (note that multiple limitations may apply):

- 13 studies included older generation devices in the intervention arm or comparator arm or both (Costa et al. 2021; Durand et al. 2021; Gallo et al. 2021; Gozdek et al. 2020; Husser et al. 2019; Kalogeras et al. 2023; Lanz et al. 2019; Mauri et al. 2017; Okuno et al. 2023; Pellegrini et al. 2023; Senguttuvan et al. 2023; Tamburino et al. 2020; Van Belle et al. 2020). The EAG summarised published evidence in the original EAG report which demonstrated differences in outcomes between generations of TAVI devices by the same manufacturer, and therefore did not assume equivalence between generations of devices by the same manufacturer. The EAG also highlight that not all valve sizes are available for device generations by the same manufacturer (for example Sapien 3 is available in 29mm valve size, however the Sapien 3 Ultra is not currently available in the 29mm size). Therefore, the EAG would advise caution in interpreting studies reporting older generation valves as results may not be generalisable. Additional mixed effects modelling could be used to account for similarity (lower variance) between generations by the same manufacturer.
- 4 studies combined TAVI devices from different manufacturers in the comparator arm:
    - Non-inferiority RCT by Makkar et al. 2020a compared Portico (Abbott) with other commercially available devices (Edwards Lifescience: Sapien, Sapien XT, Sapien 3; Medtronic: CoreValve, Evolut R, Evolut R).
    - The systematic review and meta-analysis by Senguttuvan et al. 2023 combined results from 6 RCTs which compared balloon-expanding devices by Edwards Lifesciences (Sapien XT, Sapien 3) with self-expanding device CoreValve, Evolut, Evolut R (Medtronic), ACURATE neo (Boston Scientific), Portico (Abbott), all combined. This included 1 RCT (Thiele et al. 2020) which compared device generations listed in the Final Scope (Sapien 3 compared with Evolut R); which was considered separately by the EAG.

    - The network meta-analysis by D'Ascenzo et al. 2021 included 11 RCTs which compared balloon expanding (Sapien, Sapien XT, Sapien 3), self-expanding (CoreValve, Evolut R, Evolut Pro, ACURATE neo) and SAVR. This also included only 1 RCT which compared device generations listed in the Final Scope (Thiele et al. 2020); which was considered separately by the EAG.
    - The network meta-analysis by Ueyama et al. 2021 included 10 RCTs which compared balloon expanding (Sapien, Sapien XT, Sapien 3), self-expanding (CoreValve, Evolut R, Evolut Pro, ACURATE neo) and SAVR.
- 2 studies compared different generation devices from the same manufacturer against each other:
    - Prospective cohort by Tebar et al. 2024 compared ACURATE neo2 with ACURATE neo. Larger studies (for example Kim et al. 2022c, Scotti et al. 2022) and studies with matched baseline characteristics between arms (for example: Buono et al. 2022a) were already included in the original EAG report.
    - Retrospective cohort by Welle et al. 2021 compared Sapien 3 Ultra with Sapien 3. Larger studies (Abdelfattah et al. 2022; Russo et al. 2019 and studies with matched baseline characteristics between arms (for example Nazif et al. 2021; Cannata et al. 2023) were already included in the original EAG report.
- 1 study compared in-hospital outcomes between Myval (it is unclear if this included Myval Octacor which is the latest generation) with Sapien 3 and 3 Ultra (Ubben et al. 2024). However, the EAG had considered published comparative evidence with larger sample size (for example Santos-Martinez et al. 2022) and single arm studies with longer follow-up (for example Moscarella et al. 2024 which reported 2-year follow-up) in the original EAG report.
- 1 reported a meta-analysis of 6 observational studies (Li et al. 2020) comparing Sapien 3 (n=768) and Evolut R (n=896) but reported on procedural or 30-day outcomes only. The EAG note that larger sample sizes and longer

follow-up were included for these devices in the original EAG report (for example: Rudolph et al. 2024).

The EAG note that 4 studies were RCTs, all of which had a non-inferiority design, and were funded by industry (Pellegrini et al. 2023 was a subgroup analysis of Tamburino et al. 2020).

3.3 Not in scope (excluded)

The EAG considered that 22 studies were not in scope. A summary of reasons for exclusion included the following (note that multiple reasons for exclusion may apply):

- 9 studies did not compare outcomes by TAVI device:
    - Attinger-Toller et al. 2021 compared outcomes by age group,
    - Beyersdorf et al. 2021, Forrest et al. 2023 and Jorgensen et al. 2021 compared TAVI with SAVR,
    - Eckel et al. 2022 compared implantation performed in line with the official recommendation of the manufacturer (on-label sizing) or smaller annulus dimensions that were below the official recommendation (off-label sizing);
    - Guerreiro et al. 2020 compared transfemoral and non-transfemoral access routes;
    - Leone et al. 2023 compared outcomes between male and female patients;
    - Moscarella et al. 2023 compared outcomes of aortic valve-in-valve with mitral valve-in-valve;
    - Rheude et al. 2021 combined evidence from multiple TAVI devices to determine the prevalence of subclinical leaflet thrombosis and clinical valve thrombosis following TAVI,
    - Schofer et al. 2022 compared outcomes between different surgical risk categories;
- 2 studies did not explicitly report the TAVI device used (Schofer et al. 2022; Kornyeya et al. 2023 compared self and balloon-expanding devices but did not report which valves in balloon-expanding arm);

- 1 study reported replacement of the mitral valve not aortic valve (Blasco-Turrión et al. 2022);
- 1 study undertaken in a population out of scope (Sanchez-Luna et al. 2023 conducted exclusively in patients with aortic regurgitation).
- 1 was a non-systematic narrative review (Claessen et al. 2021);
- 9 studies were single arm and therefore could not determine incremental benefit of the TAVI device because of a lack of comparator arm (Cuevas et al. 2019; Jagielak et al. 2021; JenaValve Clinical Investigation Report, 2024; Kilic et al. 2024; Malhotra et al. 2024; Moscarella et al. 2023; Rück et al. 2024; Sanchez-Luna et al. 2023; Tarantini et al. 2021);
- 1 additional study was provided academic in confidence [redacted]

4. Conclusions

Following review of 44 studies not included in the original report by the EAG, the EAG consider that 2 additional studies are key evidence in addition to those previously described. The results from the 2 studies are similar to those already included by the EAG and they do not change the conclusion of the original EAG report.

Substantial evidence is available for some manufacturers, including longitudinal analysis and studies on older generations of the valves, which was acknowledged in the original EAG report. However, in the opinion of the EAG, this does not directly support the decision problem of the LSA in assessing the incremental benefit and cost variation of different TAVI devices. Results of the published key evidence were considered similar to the results of the UK TAVI Registry. Additional validation of the multivariate modelling conducted by the EAG (and summarised in the original EAG report) could use patient-level data from trials, in order to replicate RCT inclusion and exclusion criteria, and compared predicted outcomes against those observed in the trials at specified time points. However, this was considered by the EAG as not currently possible because of a lack of clinical information captured in the UK TAVI Registry (for example: STS score or EuroSCORE II to quantify surgical risk, jet velocity, aortic valve calcification, and the valves which could be suitable for

implantation in each patient are not currently recorded) and would need access to participant-level trial data to establish population characteristics.

Throughout the LSA process, the EAG has acknowledged the limitations associated with both the published literature and the UK TAVI Registry analysis. Because the patient-level data from the UK TAVI Registry can be adjusted to account for recorded confounders, the EAG considers that this data remains the most applicable and generalisable source of data to address the LSA decision problem. Further data collection (additional known confounders including documentation of valve choice) and follow-up would strengthen future analyses.

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Appendix: Summary of study characteristics (N=44)

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
1.	Attinger-Toller (JACC Cardiovasc Interv, 2021; 952-960) [SWISS TAVI Registry; NCT01368250] Switzerland (N=15)	Prospective cohort study from Swiss Registry (n=7,097) Follow-up: 1 year Funder: Study grant from the Swiss Heart Foundation and the Swiss Working Group of Interventional Cardiology and Acute Coronary Syndromes and is sponsored by research grants from Medtronic, Edwards Lifesciences, Boston Scientific, and Abbott. The study sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.	Between February 2011 and June 2018	*Inclusion:* Only patients treated with CE marked TAVI devices were considered. Device and access-site selection were at discretion of the TAVI operators, based on clinical and anatomical characteristics. *Exclusion:* NR	Total population (n=7,097) split and analysed by age Group (yrs) • <70 (n=324) • 70–79 (n=1,913) • 80–89 (n=4,353) • ≥90 (n=507) Valves used: CoreValve, Evolut R, Evolut Pro, Sapien/Sapien XT, Sapien 3, Lotus, Lotus Edge, ACURATE / ACURATE neo, Jenavalve, Portico, Direct Flow Medical, Allegra, Engager.	N/A	Not in scope: comparison of outcomes by age group not by valve used.
2.	Beyersdorf (Eur J Cardiothorac Surg, 2021; 1139-1146) Germany (N=92)	Prospective German Registry (n=18,010), including propensity matching based on all baseline characteristics, using nearest neighbour approach (n=3,460) Follow-up: 5 years Funder: Unrestricted grants from medical device companies (Edwards Lifesciences, Medtronic, Abbott, Boston Scientific), the German Center for Cardiovascular Research (DZHK), the German Heart Foundation, the German Ministry of Health and donations from Dr Rolf M. Schwiete Foundation. Funders had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.	Treated in 2011 or 2012 (month NR)	*Inclusion*: The criteria for TAVI implantation in 2011-2012 were based on the position statement of the German Society for Thoracic and Cardiovascular Surgery (DGTHG) and the German Society for Cardiology (DGK). *Exclusion*: first-line indications for TAVI (and who were not eligible for SAVR) such as frailty, re-do procedure, very high risk, prognosis-limiting secondary disease, porcelain aorta and incurable malignancy.	TAVI (n=8,942, including Sapien, Sapien XT, CoreValve, ACURATE TA, JenaValve, Other) compared with SAVR (n=9,068) Propensity score matched cohort included TAVI (n=1,820), SAVR (n=1,820)	N/A	Not in scope: No analysis comparing outcomes by device (main focus on TAVI versus SAVR). Named devices are older generations of those listed in Final Scope, but also includes miscellaneous other where the TAVI valve used was undefined. Comment by Carrel et al. 2020.
3.	Blasco-Turrión (J Clin Med, 2022; 5210) Setting NR (N=5)	Retrospective cohort, registry (n=11) Follow-up: 6 months Funder: Authors report no funding received.	Between 2019 and 2022 (month NR)	*Inclusion*: patients with mitral bioprosthesis degeneration. *Exclusion*: mitral valve-in-ring or valve-in-mitral annular calcification were not included in the registry.	Myval (n=11)	N/A	Not in scope – mitral valve being replaced (not aortic valve).
4.	Claessen (JAMA Cardiol, 2021; 102-112) Setting: NR	Narrative review (not systematic review) Funder: NR	N/A	N/A	Balloon-expandable valves: Sapien, Sapien XT, Sapien 3, Sapien 3 Ultra Self-expanding: CoreValve, CoreValve Evolut R, CoreValve Evolut Pro, CoreValve Evolut Pro+, ACURATE neo, ACURATE	N/A	Not in scope: Not systematic review, narrative review including devices not in scope.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
					neo2, Portico, JenaValve, J-Valve Mechanically-expandable: LOTUS, LOTUS Edge, LOTUS Mantra		
5.	Costa (Cathet Cardio Intervent, 2021; 1167–1176) [OBSERVANT study] Italy (N=93)	Prospective cohort, registry (n=1,440) Clinical outcomes of 2 groups were compared after adjustment using inverse probability of treatment weighting (IPTW) and confirmed by sensitivity analysis with propensity score matching. Variables included in the propensity score were sex, age, body mass index, diabetes, coronary artery disease, severe renal impairment on dialysis, chronic obstructive pulmonary disease, severe frailty (Geriatric Status Scale 2 or 3), severe dyspnea (NYHA classification 3 or 4), pulmonary hypertension, left ventricle ejection fraction, EuroSCORE 2, active malignancy and critical status leading to emergent/urgent TAVI procedure. Follow-up: 5 years Funder: Supported by Italian Ministry of Health and Istituto Superiore di Sanità (Fasc. 1 M30) and partially by a grant from the Finalized Research Project	Between January 2010 and December 2012	*Inclusion*: Consecutive patients with severe aortic stenosis who underwent TAVI through a transfemoral approach *Exclusion*: NR	Medtronic CoreValve (n=830 in IPTW analysis, n=548 in propensity score matched analysis) Sapien (n=610 in IPTW analysis, n=548 in propensity score matched analysis)	*Primary endpoint* All-cause mortality at 5 years – IPTW adjustment: lower for Sapien 52.3%, compared to CoreValve 47.7% (p=0.04). *Secondary endpoints* Stroke, MI, vascular complications, AKI, in-hospital: No difference between arms. Mortality, in-hospital: Higher with CoreValve than Sapien, 4.3% compared with 2.3%, p=0.03. Permanent pacemaker implantation, in-hospital – IPTW adjustment: Higher with CoreValve than Sapien, 22.7% compared with 4.6%, p<0.01. Mean aortic gradient, mean (SD), before discharge – IPTW adjustment: Lower in CoreValve than Sapien, 9.1 (6.1) compared with 10.6 (5.3), p<0.01. Repeat hospitalizations for any cardiac cause, 5 years – IPTW adjustment: Higher for CoreValve 46.9% compared with Sapien 42.1%, p<0.01.	In scope but evidence not considered key evidence: Study reported older generations of valves not in scope, studies of in-scope valves were considered in the original EAG report (e.g. Costa et al. 2022, Rudolph et al. 2024).
6.	Cuevas (EuroIntervention, 2019; 71-73) Spain and Switzerland (N=5)	Prospective, single arm cohort (n=59) Follow-up: 30 days Funder: NR	Between April 2017 and January 2018	*Inclusion*: All patients deemed candidates for TAVI by the local Heart Team and treated with the Allegra valve. *Exclusion*: NR.	Allegra valve (n=59), no comparator	N/A	Not in scope: single-arm cohort making determination of incremental benefit difficult.
7.	D'Ascenzo (Int J Cardiol, 2021; 90-98) [PROSPERO ID CRD42020182407] Setting: NR	Systematic review and network meta-analysis (N=11 RCTs, n=9,752 patients) Follow-up: 2 years Funder: None	NR [Literature search between database inception to April 2020]	*Inclusion*: RCTs enrolling patients with symptomatic severe aortic stenosis and randomized to balloon-expanding TAVI, self-expanding TAVI or surgical aortic valve replacement. *Exclusion*: • enrolling less than 100 patients to avoid limited-sample bias • not published in English • observational, cross-sectional, or other non-RCT design • Boston Lotus valve due to different mechanism of implantation (mechanical expandable).	Balloon-expanding: Sapien, Sapien XT Sapien 3 Self-expanding: CoreValve, CoreValve Evolut R, CoreValve Evolut Pro, ACURATE neo Surgical aortic valve replacement (SAVR) was evaluated in 7 study arms with 4,006 patients, whereas ballon expanding TAVI and self-expanding TAVI respectively in 6 arms with 2,572 patients and 8 arms with 3,174 patients.	Mortality, 1 and 2 years: no statistical difference between balloon- and self-expanding TAVI devices. Stroke, 1 year: no statistical difference between balloon- and self-expanding TAVI devices. Aortic reintervention, 1 year: no statistical difference between balloon- and self-expanding TAVI devices. Pacemaker implantation, 30 days: Lower risk with balloon-expanding than self-expanding TAVI devices; OR 0.51 (95%CI 0.33 to 0.79). Paravalvular leak, 30 days: Lower risk with balloon-expanding than self-	In scope but evidence not considered key evidence: combines TAVI devices from multiple manufacturers together in self-expanding arm, and combines multiple generation devices together (not all in scope). Follow-up of 2 years restricted to mortality outcome only. Authors acknowledge that self-expanding devices are often used in patients with more challenging anatomies such as severe calcified aortic valves and complex arterial access through small ilio-femoral arteries. Trials included in this analysis had exclusion criteria based on valvular and ilio-femoral calcifications, therefore preventing comparison in these specific subsets.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
						expanding TAVI devices; OR 0.31 (95%CI 0.17 to 0.55).	
8.	Deharo (Circulation, 2020; 260-268) France (N=1,546)	Longitudinal retrospective cohort study using national hospitalisation database (n=31,113) with propensity score matching on 38 variables, including baseline characteristics, year of implantation (Sapien 3 available before Evolut R) and hospital procedural volume for TAVI by quartile (n=20,918 after propensity matching). Follow-up: up to 3 years Funder: Authors reported no that no sources of funding were received.	Between 01 January 2014 and 31 Dec 2018 (Sapien 3 available since January 2014, Evolut R available since November 2015)	*Inclusion*: Adults with a single percutaneous procedure for aortic stenosis, treated with Sapien 3 or Evolut R. *Exclusion*: age <18 years, valve-in-valve TAVI procedure, and TAVI via non-percutaneous route.	Sapien 3 (n=10,459 after propensity matching) Evolut R (n=10,459 after propensity matching)	Combined endpoint (cardiovascular death, rehospitalisation for heart failure, all cause stroke) at 3 years: lower for Sapien 3, 53.4% (50.9 to 56.0), than for CoreValve, 58.0% (55.3 to 60.7), RR 0.60 for Sapien 3 vs CoreValve (95% CI 0.48 to 0.76); p<0.0001. All cause death at 3 years: lower for Sapien 3, 37.3% (34.8 to 40.0), than for CoreValve, 39.3% (36.5 to 42.1), RR 0.63 for Sapien 3 vs CoreValve (95% CI 0.52 to 0.78); p<0.0001. Cardiovascular death at 3 years: lower for Sapien 3, 15.4% (13.5 to 17.6), than for CoreValve, 17.5% (15.5 to 19.7), RR 0.80 for Sapien 3 vs CoreValve (95% CI 0.69 to 0.93); p=0.003. Rehospitalisation, up to 2 years: lower in Sapien 3 arm, RR 0.84 (95% CI 0.78 to 0.90); p<0.0001. Pacemaker implantation at time or after the procedure: lower in Sapien 3 than Evolut R arm, RR 0.72 (95% CI 0.69 to 0.76); p<0.0001.	Key evidence: devices in scope, difference in recruitment period between arms however year of implantation included in propensity matched analysis. The authors acknowledge that clinical variables (mean gradient, valve area, calcification, paravalvular leak) were not available in the national database and therefore could not be analysed. The authors also note that "*the CoreValve device has a smaller diameter introducer sheath, so may be used more frequently in patients with complex and small femoral access. We cannot exclude that some biases related to these anatomical considerations exist in our analysis.*"
9.	Durand (Clin Res Cardiol, 2021; 40-49) France (N=48)	Retrospective cohort study using FRANCE TAVI registry (n=5,857) Follow-up: in-hospital (only late discharge outcome compared between devices). Funder: Authors reported that device manufacturers partly funded the registry but had no role in data collection or analysis or in manuscript preparation.	Between 02 January 2013 and 31 December 2015	*Inclusion*: Consecutive patients having TAVI, using transfemoral approach, and discharged directly home. *Exclusion*: Patients who died during the index hospitalisation, transferred to another institution or rehabilitation centre, discharge destination unknown.	Sapien XT or Sapien 3 (n=4,044) CoreValve (n=1,813)	Multivariate analysis shows risk factor for late discharge (>6 days post op) greater in CoreValve group than in in Sapien XT / Sapien 3; HR 1.7 (95% CI 1.5 to 2.0); p<0.001.	In scope but evidence not considered key evidence: Includes older generation devices for both intervention and comparator arms; self-expanding valve group not differentiated for Sapien XT (out of scope) and Sapien 3 (in scope). CoreValve is an earlier generation of valves by Medtronic. EAG had included evidence related to devices in scope in original EAG report (for example: Rudolph et al. 2023). Study evaluates the influence of very early (within 3 days) and early (between 3 and 6 days), and late (>6 days) discharge on long-term outcomes. Valve type not separated for most outcomes.
10.	Eckel (J Clin Med 2022; 5313) [TAVI-SMALL registry] Germany (N=2)	Retrospective cohort analysis from registry (n=654) Follow-up: 30 days Funder: Authors reported no that no external funding were received.	Between June 2012 and December 2021	*Inclusion*: patients with severe native aortic stenosis who underwent transfemoral TAVI with ACURATE neo or ACURATE neo2. *Exclusion*: NR	ACURATE neo (n=464) or ACURATE neo2 (n=191); combined together.	N/A	Not in scope: comparison of the implant performed in line with the official recommendation of the manufacturer (on-label sizing) or below (off-label sizing); no comparison of devices.
11.	Forrest (J Am Coll Cardiol, 2023; 2163-2165) [Evolut Low risk trial; NCT02701283] Australia (N=5), Canada (N=6), France	RCT (n=1,414); reported in research letter. Follow-up: 4 years Funder: Medtronic	Between March 2016 and May 2019	*Inclusion*: aortic valve replacement in low surgical-risk patients with severe aortic stenosis. *Exclusion*: NR	CoreValve / Evolut R / Evolut Pro (n=730; all combined). SAVR (n=684)	N/A	Not in scope: TAVI vs SAVR comparison

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
	(N=3), Japan (N=8), the Netherlands (N=3), New Zealand (N=1), US (N=61)						
12.	Gallo (Circ Cardiovasc Interv, 2021; e010641) [HORSE registry] Canada (N=1), Denmark (N=1), Germany (N=3), Greece (N=1), Ireland (N=1), Italy (N=5), Spain (N=3), Switzerland (N=1)	Retrospective cohort, registry (n=3,862). Inverse probability-weighting (IPW) applied to adjust for baseline differences across 24 covariates considered (age, diabetes, BMI, hypertension, aortic regurgitation ≥ moderate, sex, NYHA III or IV functional class, aortic valve calcification ≥ moderate, left ventricle outflow tract calcification ≥ moderate, low gradient aortic stenosis, atrial fibrillation, COPD, peripheral artery disease, porcelain aorta, previous cardiac surgery, previous MI, previous percutaneous coronary interventions, previous pacemaker/defibrillators, previous stroke, ejection fraction, transcatheter prosthesis size, annulus perimeter size, STS score) Follow-up: procedural Funder: Authors report no funding received.	Between September 2014 and April 2020	*Inclusion*: consecutive patients who underwent transfemoral TAVI for severe aortic stenosis of native aortic valve with either Evolut R/Pro or ACURATE neo devices. *Exclusion*: Patients undergoing TAVI for pure aortic regurgitation, surgical prosthesis degeneration, or from non-transfemoral access. Patients undergoing Evolut R 34mm implantation were also excluded (no comparable vale size for ACURATE neo was available).	Evolut R or Evolut Pro (n=1,959) ACURATE neo (n=1,903)	*Non-horizontal aorta* • Device success, annulus rupture, valve embolization, need for second valve, emergency surgery, coronary obstruction, death, peri-procedural MI, stroke, all in-hospital: no difference between Evolut R/Pro and ACURATE neo devices after IPW adjustment. • Moderate or severe PVL, in-hospital: less likely with Evolut R/Pro than with ACURATE neo: IPW adjusted OR 0.25 (95% CI 0.11 to 0.55), p<0.001 • Permanent pacemaker, in-hospital: increased risk with Evolut R/Pro than ACURATE neo; 1.72 (1.29 to 2.30); p<0.001. • Major vascular complications, in-hospital: decreased risk associated with Evolut R/Pro than ACURATE neo, 0.51 (0.33 to 0.78), p=0.002. *Horizontal aorta*: • Device success, in-hospital: reduced with Evolut R/Pro than with ACURATE neo: OR 0.62 (0.46 to 0.83), p=0.002. • Mortality, procedural: increased risk with Evolut R/Pro than with ACURATE neo: OR 11.41 (1.47 to 88.55); p=0.020. • Permanent pacemaker, in-hospital: Increased risk with Evolut R/Pro compared with ACURATE neo: 2.83 (2.09 to 3.82); p<0.001. • Major vascular complications, in-hospital: decreased risk associated with Evolut R/Pro compared with ACURATE neo: 0.64 (0.42 to 0.98), p=0.0039. • Annulus rupture, valve embolization, need for second valve, emergency surgery, peri-procedural MI, stroke, moderate or sever PVL, in-hospital mortality, all in-hospital: no difference between Evolut R/Pro and ACURATE neo devices after IPW adjustment.	In scope but evidence not considered key evidence: main focus of study is aortic angulation and impact on procedural outcomes. EAG note that selection of device type and size was at the discretion of the attending physician at each centre. Older generation valve used in comparator arm (that is ACURATE neo instead of ACURATE neo2).
13.	Gozdek (J Clin Med, Feb 2020; 397) [**additional information gained from correction published in	Meta-analysis (N=6: including 1 RCT and 5 propensity score matched retrospective cohort studies) (n=2,818 patients).	Between 2012 and 2019, across N=6 studies.	*Inclusion*: • human study • study or study arms comparing directly strategy of transcatheter aortic valve	ACURATE neo (n=1,256) Sapien 3 (n=1,562)	Early safety (composite): no difference between groups. Device success: no difference between groups.	In scope but evidence not considered key evidence: Larger studies with MA comparing Sapien 3 with older generation ACURATE neo already included in the original EAG report (for

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	Gozdek (J Clin Med, Mar 2020; 861) Setting: NR	Follow-up: ranged between 1 month to 12.7 months. Funder: Authors report funding acquisition not available.	[Literature search until October 2019]	replacement with ACURATE neo and Sapien 3 • RCT or propensity score matched observational study. *Exclusion*: • in-vitro study • single arm • adjustment not propensity score or methods not reported • outcomes of interest not reported • sub-studies or overlapping populations. [The EAG note that differing inclusion and exclusion criteria of 6 studies is reported in the Table A3 of the paper]		Major vascular complications, procedural: no difference between groups. AKI, procedural: no difference between groups. MI, periprocedural: no difference between groups. Stroke, timepoint NR: no difference between groups. Serious bleed, procedural: no difference between groups. **Permanent pacemaker implantation, timepoint NR: required less often after ACURATE neo 10.2% compared to SAPIEN 3 14.2% (RR: 0.72 (95%CI 0.58 to 0.89); p=0.002). **Mild PVL, timepoint NR: occurred less frequently in SAPIEN 3 recipients, 27.9% compared to ACURATE neo group, 45.0%; (RR 1.59 (1.39 to 1.83), p<0.00001). **Moderate to severe PVL, timepoint NR: uncommon in the entire series (2.3%); however, significant increase PVL risk with ACURATE neo (7.6%) compared to Sapien 3 (2.3%): (RR 3.06 (2.09 to 4.49); p<0.00001). All-cause mortality, 30 days: 61 (2.2%) patients died within the first 30 days, ACURATE neo (2.9%) and Sapien 3 (1.6%). ACURATE neo associated with 77% higher 30-day mortality risk (RR 1.77 (1.03 to 3.04); p=0.04).	example Yang et al. 2023; the EAG also note that all 6 studies included by Gozdek et al. 2020 were also included in the network meta-analysis by Yang et al. 2023).
14.	Guerreiro (Rev Port Cardiol, (Engl Ed) 2020; 705-717) [The Portuguese National Registry of Transcatheter Aortic Valve Implantation, RNCI-VaP)] Portugal (N=14; including public and private centres, voluntary data entry)	Prospective cohort (n=2,346) Follow-up: 30 day and 1 year Funder: Authors declare there is no specific funding for the registry which has been completely developed, maintained and sponsored by the Portuguese Association of Cardiovascular Intervention	Between January 2007 and December 2018	The decision regarding access route, prosthesis type and size were made according to each centre, taking into consideration the clinical and morphological assessment. *Inclusion*: symptomatic with severe aortic stenosis or prosthetic valve dysfunction for TAVI (discussed by heart team, procedures performed in hospital with on-site cardiac surgery), high risk for traditional SAVR or deemed inoperable. *Exclusion*: life expectancy with TAVI was ≤1 year, patient's quality of life was unlikely to improve with TAVI	Transfemoral access route (n=2,131) Non-transfemoral access route (n=214) The registry collects data on any type of commercial device. At the time of publication, 12 different valves and their iterations were included (CoreValve, Sapien, Portico, ACURATE neo, Lotus Edge, Direct Flow, Allegra, Engager). In analysed cohort: - CoreValve: 52% - Edwards valve: 30.9% - Other valve: 17.1% (assumed all self-expanding).	Study reported that valve type did not influence mortality; however no further detail reported.	Not in scope: focus on access route comparison (transfemoral compared with non-transfemoral); outcomes not differentiated by valve type. Voluntary registry, inclusion of results from private centres (proportion not reported), no audit process, also includes valves not in scope (for example Lotus, Direct Flow Medical); however proportions not reported.

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15.	Husser (JACC Cardiovasc Interv, 2019; 1781-1793) [SELECT RBBB registry] Germany, Switzerland (N=7)	Retrospective cohort from registry (n=296) Included propensity matching (1:1 nearest neighbour) matched on sex, BMI, LVEF <35%, heart rate <60/min, aortic annular area, severe aortic cusps calcification covariates Follow-up: 30 days Funder: NR	Between January 2014 and July 2017	Consecutive patients undergoing TAVI using the ACURATE neo or the Sapien 3 for severe symptomatic aortic stenosis. *Inclusion*: pre-existent complete RBBB, no pacemaker at baseline. *Exclusion*: incomplete mult-islice CT data	ACURATE neo (n=98, and 65 after propensity matching) Sapien 3 (n=198, or 65 after propensity matching)	PPI at 30 days: lower rate with ACURATE neo compared to Sapien 3; OR of 0.37 (95% CI 0.17 to 0.78) in propensity matching (p=0.010), and OR: 0.37 (0.25 to 0.55) in IPTW analysis (p=<0.001). Device success, procedural-related death, annular rupture, cardiac tamponade, multiple valves, conversion to sternotomy, life-threatening bleeding, major vascular complications, stroke, AKI stage 2 or 3, MI, hospital stay, death, in-hospital: No statistical difference between arms. Mortality, 30 days: No statistical difference between arms.	In scope but evidence not considered key evidence: Larger studies with MA comparing Sapien 3 with older generation ACURATE neo already included in the original EAG report (for example Yang et al. 2023). Studies comparing newer generations (Sapien 3 Ultra and ACURATE neo2) previously considered in EAG report (for example Pellegrini et al. 2023).
16.	Jagielak (Cardiol J, 2021; 384-390) [NAUTILUS study] Brazil, Poland, Switzerland (N=8)	Prospective, single arm cohort (n=27) Follow-up: 30 days Funder: NR	NR	Consecutive patients with severe, symptomatic aortic stenosis at high surgical risk treated with Allegra. *Inclusion*: • age ≥75 years • symptomatic (New York Heart Association [NYHA] class II or greater), • severe degenerative native AS (mean transvalvular pressure gradient >40 mmHg and / /or aortic jet velocity >4.0 m/s and/or aortic valve area of <1.0 cm² [or aortic valve area index ≤0.6 cm2/m2]) • high risk for surgical aortic valve replacement with a logistic EuroSCORE ≥20% • documented agreement of the Heart Team that the patient is at high risk for surgery due to frailty and / or coexisting comorbidities. *Exclusion*: (among others in study protocol; no trial registration identified by the EAG) • unicuspid or bicuspid valve disease • non-calcified aortic valve disease • mixed valve disease with predominant aortic regurgitation greater than 3+ or with associated severe (greater than 3+) mitral regurgitation • aortic annulus size <19 mm or >29 mm • type of femoral access, or any other anatomical conditions that prevented safe placement of an 18 French introducer sheath and manipulation of the TAVI system (e.g. severe femoral-iliac obstructive calcification or tortuosity).	Allegra valve (n=27) using transfemoral approach (1 excluded as converted to balloon aortic valvuloplasty, 1 valve dislodged and converted to open heart surgery). No comparator.	N/A	Not in scope: single-arm cohort making determination of incremental benefit difficult. Study reported short-term follow-up; studies with larger sample size and with longer follow-up were considered in the original EAG report.
17.	JenaValve (Clinical Investigation Report, 2024) provided AiC [ALIGN-AS; NCT02732691] [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not in scope: [redacted] The ALIGN-AS study was included in the original EAG report. Results from n=68 patients are available on the trial registration (NCT02732691); 30-day all-cause mortality 2.9%.

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				[redacted]			
18.	Jørgensen (Eur Heart J, 2021; 2912-2919) [NOTION NCT01057173] Study protocol published in Thyregod (Trials, 2013; 11) Denmark (N=2), Sweden (N=1)	RCT (n=280) Follow-up: up to 8 years Funder: Authors declared funding by the Danish Heart Foundation and Medtronic	Between 2010 and 2013 (month NR)	*Inclusion*: • Patients aged ≥70 years • severe symptomatic degenerative aortic valve stenosis. • Asymptomatic patients could be included if they had left ventricular posterior wall thickness ≥17 mm, decreasing left ventricular ejection fraction, or new-onset AF. • Expected to survive for more than 1 year • Able to provide consent. *Exclusion:* • Isolated AV insufficiency • Other significant cardiac valve or septal diseases • Coronary artery comorbidity requiring revascularisation (PCI or CABG) • Intracardiac lesion (thrombus, tumour, vegetation) • Previous open cardiac surgery • Myocardial infarction or PCI within the last year • Stroke or transient ischemic attack within the last 30 days • Renal insufficiency requiring haemodialysis • Pulmonary insufficiency (FEV1 or diffusion capacity <40% of expected) • Active infectious disease requiring antibiotics • Emergency intervention (within 24 hours after the indication for intervention has been made) • Unstable pre-interventional condition requiring inotropic support or mechanical cardiac assistance • A known hypersensitivity or contraindication to nitinol, heparin, clopidogrel, acetyl salicylic acid, or contrast material • Currently participating in an investigational drug or another device study.	CoreValve (n=145) SAVR (n=135)	N/A	Not in scope: Comparison of TAVI vs SAVR; only 1 device used in TAVI arm, treated as single arms study. The authors acknowledge that the TAVI arm was restricted to use of CoreValve and that newer generations are available with sealing skirts, reduced profile of the delivery catheters, and positionability of the valve. The EAG note that 10-year results from NOTION was included in the original EAG report (Thyregod et al. 2024; including 145 patients treated with CoreValve.
19.	Kalogeras (J Am Heart Assoc, 2023; e028038) [Athens-London-Aortic-Stenosis, ATLAS registry] Greece, UK (N=2)	Retrospective cohort, registry (n=1,673) including propensity score matched analysis (n=278) based on age, mitral regurgitation, extensive calcification of the aorta, previous balloon aortic valvuloplasty, access site, with	Between August 2017 and February 2021	*Inclusion:* All patients with severe symptomatic aortic valve stenosis, final decision on appropriateness for TAVI, device selection and access route was determined by the Heart Team. Patients treated with Sapien 3 or Ultra valve ≤23mm or Evolut Pro/Pro+ ≤26mm were included in the “small cohort”.	Self-expanding (n=917): Evolut Pro, Pro+ and R (patients with large anatomies, annulus perimeter >81.7mm were treated with 34mm device only available for Evolut R during	Mortality: When adjusting for age, sex, baseline LV function, baseline degree of MR, epicardial coronary artery disease, extensive calcification of the aorta, no difference in mortality when comparing balloon-expandable with self-expanding, HR: 1.23 (95%CI	In scope but evidence not considered key evidence: Despite propensity score matching, differences in pre-operative heart rhythm were observed between matched groups.

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		1:1 nearest neighbour matching with caliper of 0.1 Follow-up: median 15 months Funder: None			study period); n=139 after propensity matching Balloon-expanding (n=756): Sapien 3, Sapien 3 Ultra; n=139 after propensity matching	0.8 to 1.9); p=0.349. However, in propensity matched small cohort group higher survival in self-expanding group at 1 year (97% compared with 92.3%) and 3 years (91.8% compared with 78.7%), p=0.096. Peak aortic valve gradient, mmHg, at predischarge: In propensity matched 'small cohort' lower in self-expanding arm, 18 (8.3) compared with 25.2 (8.8); p<0.001. Mean aortic valve gradient, mmHg, at predischarge: In propensity matched 'small cohort' lower in self-expanding arm, 9.7 (4.6) compared with 13.5 (5.3); p<0.001. Residual moderate or severe paravalvular regurgitation, at discharge: In propensity matched 'small cohort' lower in self-expanding arm 4.4% compared with 2.2%; p<0.001. Valve malposition, bailout valve-in-valve, tamponade, conversion to full sternotomy, new pacemaker implantation, MI, bail out PCI, cerebrovascular accident, AKI (stage 3), life-threatening or major bleeding, major vascular complications, death, at discharge: No statistical difference in each complication between arms.	Authors acknowledge that the balloon-expanding valves were introduced later and therefore have shorter follow-up times.
20.	Kilic (Arch Med Sci, 2024; 410-419) Turkey, Italy, Greece (N=4)	Prospective cohort (n=207) Follow-up: 2 years Funder: NR	Between 2019 and -2021 (months not reported)	*Inclusion:* Consecutive patients presenting with degenerative severe aortic stenosis, treated with Myval, with 2 years follow-up. Patients were advised to undergo TAVI only if there were at high or intermediate risk for SAVR. *Exclusion:* NR	Myval	N/A	Not in scope: single-arm cohort making determination of incremental benefit difficult. Longitudinal follow-up at 2 years for Myval device was included in the original EAG report (for example: Moscarella et al. 2024).
21.	Kornyeva (Front Cardiovasc Med, 2023; 1175246) Germany (N=1)	Retrospective cohort, database (n=507), with propensity score matching (n=384). Authors report that since most variables where already balanced before matching, only the annulus perimeter, annulus area, and body surface area were entered into the logistic model to calculate the propensity score. Funder: NR	Between September 2014 and June 2020	*Inclusion:* Patients with small aortic annulus (CT-derived annular perimeter <72mm, or aortic annulus area <400mm2), who underwent TAVI with contemporary self-expanding or balloon-expanding valves identified by a database. *Exclusion:* Patients with a valve-in-valve procedures.	Self-expanding: Evolut R/Pro, Portico, ACURATE neo2, Balloon-expanding: NR	N/A	Not in scope: All self-expanding devices aggregated together, balloon-expanding valves not explicitly reported.
22.	Lanz (Lancet, 2019; 1619-1628) [SCOPE I trial: NCT03011346]	RCT, non-inferiority (n=739) Powered based on composite VARC-2 derived primary end point at 30 days (early safety and	Between 08 February 2018 and 02 February 2019	Patients aged 75 years or older with symptomatic, severe aortic stenosis who were deemed to be at increased surgical risk by the heart team constituted the target population and were screened for eligibility.	ACURATE neo (n=372) compared with Sapien 3 (n=367)	Primary endpoint at 30 days higher with ACURATE neo, 24% compared with 16%, p=0.42 non-inferiority. Secondary analysis of primary endpoint, p=0.0156.	In scope but evidence not considered key evidence: Includes comparison of device in scope with older generation device. Short-term outcomes.

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	Germany, the Netherlands, Switzerland, UK (N=20 centres; including 1 from UK)	clinical efficacy: all-cause death, any stroke, life-threatening or disabling bleeding, major vascular complications, coronary artery obstruction requiring intervention, AKI stage 2 or higher, rehospitalisation for valve-related symptoms or congestive heart failure, valve-related dysfunction requiring repeat procedure, and valve-related dysfunction determined by echocardiography) predicted as 22% and assumed non-inferiority margin of 7.7%. Funder: Boston Scientific		*Inclusion:* • ≥75 years of age • Severe aortic stenosis was defined by an aortic valve area less than 1.0 cm2 or less than 0.6 cm2/m2 if indexed to body surface area. • Symptomatic (NYHA functional class>I, angina or syncope). • At increased risk for mortality if undergoing SAVR as determined by: - the heart team, or - an STS-PROM score >10%, or - a Logistics EuroSCORE>20%. • Heart team agrees on eligibility for participation. • Aortic annulus perimeter 66-85mm and area 338-573 mm2 based on multi-slice CT. • Minimum diameter of arterial aorto-iliac-femoral axis on 1 side ≥5.5mm. • Patient understand the purpose, potential risks and benefits of the trial, is able to provide written informed content [sic] and willing to participate in all parts of the follow-up. *Exclusion:* • Non-valvular, congenital or non-calcific acquired aortic stenosis, uni- or bicuspid aortic valve. • Anatomy not appropriate for transfemoral TAVR due to degree or eccentricity of calcification or tortuosity of aorto-iliac-femoral arteries. • Pre-existing prosthetic heart valve in aortic or mitral position. • Emergency procedures, cardiogenic shock (vasopressor dependence, mechanical hemodynamic support) or severely reduced left ventricular ejection fraction (<20%). • Concomitant planned procedure except for percutaneous coronary intervention. • Stroke or myocardial infarction (except type 2) in prior 30 days. • Planned non-cardiac surgery within 30 days after TAVR. • Severe coagulation conditions, inability to tolerate anticoagulation/antiplatelet therapy. • Evidence of intra-cardiac mass, thrombus or vegetation. • Active bacterial endocarditis or other active infection. • Hypertrophic cardiomyopathy with or without obstruction. • Contraindication to contrast media or allergy to nitinol. • Participation in another trial leading to deviations in the preparation and conduction of the intervention or the post-implantation management.		Implantation of multiple valves at time of procedure higher in ACURATE neo, 3% compared with 1%, p=0.0119. All-cause death at 30 days: no statistical difference between arms, 2% ACURATE neo compared with 1% Sapien 3; p=0.09. Stroke at 30 days: no statistical difference between arms, 2% in ACURATE neo and 3% with Sapien 3, p=0.33. AKI stage 2 or 3 at 30 days: higher in ACURATE neo arm, 3% compared with 1%, p=0.0340. Moderate or severe AR at 30 days: higher in ACURATE neo arm, 9.4% compared with 2.8%; p<0.0001.	Authors acknowledge that the trial was not powered for differences in individual clinical endpoints, secondary analysis did not account for multiple hypothesis testing, and results at risk of selection bias.
23.	Leone (Int J Cardiol, 2023; 16-23) [TAVI-SMALL 2 registry] International (N=16, high-volume centres)	Retrospective cohort, registry (n=1,378) Propensity score matching (including age, BMI, body surface area, hypertension, COPD, coronary artery disease, prior MI, peripheral vascular disease,	Between June 2011 and April 2020	*Inclusion:* Patients with severe native aortic valve stenosis and small artic annuli (annular area < 400mm2 and/or annular perimeter <72mm on CT) treated with transfemoral implantation of current-generation self-expanding (Evolut R, Evolut Pro, ACURATE neo, Portico) and balloon-expandable (Sapien 3). Local multidisciplinary heart teams	NR	N/A	Not in scope: all TAVI devices aggregated together, main analysis reports differences in outcomes between males and females; no analysis of results by TAVI device.

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		previous percutaneous transluminal angioplasty, prior CABG, previous pacemaker, or implantable cardiovertor-defibrillator, NYHA functional class III or IV, STS score, aortic annular perimeter). Funder: None		evaluated all patients and confirmed the indications for TAVI. *Exclusion:* valve-in-valve procedures, TAVI for pure aortic regurgitation, lack of pre-procedural CT.			
24.	Li (Ann Palliat Med, 2020; 700-708) Israel (N=2), Germany (N=2), Spain (N=1), US (N=1)	Meta-analysis (N=6 observational studies, n=1,664) Follow-up: 30 days Funder: Science and Technology Support Plan of Sichuan Province (2016FZ0078, 2018SZ0172); Science and Technology Innovative Research Groups Program of Sichuan Province (2017TD0004); "13th Five-Year" National key Research and Development Program of China (2016YFC1102204, 2017YFC1104204); 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University.	NR [Literature search between 2008 and 2018]	*Inclusion:* • Studies reporting outcomes of Sapien 3 versus Evolut R. • Randomized clinical trial, prospective or retrospective cohort observational studies. *Exclusion*: • Studies published in form of letter, review, editorial comment or a case report. • Un-extractable data for statistical analysis. • If duplicate data source occurred, 1 with the largest sample size was included to avoid duplicate publication.	Sapien 3 (n=768) vs Evolut R (n=896)	*Primary outcomes* • Procedural success: No statistical difference between arms, 94.1% in Sapien 3, 95.7% in Evolut R; OR 1.15 (95%CI 0.70 to 1.91) • 30-day all-cause mortality: No statistical difference between Sapien 3 and Evolut R; 1.6% and 2.1% respectively; OR 0.72 (0.33 to 1.57). *Secondary outcomes* • AKI post-procedure: Sapien 3 associated with higher risk, 4.1% vs. 2.0%; OR 2.34 (1.26 to 4.34) • Stroke at 30-days: No statistical difference between arms; 2.0% in both arms; OR 1.07 (0.51 to 2.25), • Bleeding (major and life-threating) post-procedure: No statistical difference between arms, 3.0% vs. 2.4%; OR 1.08 (0.56 to 2.08) • Major vascular complications, post-procedure: No statistical difference between arms, 4.3% vs. 3.4, OR 1.24 (0.71 to 2.17) • New permanent pacemaker implantation: Sapien 3 lower risk, 11.5% vs.17.0%; OR 0.69 (0.51 to 0.93). • Peak aortic valve gradient post-procedure: No statistical difference between groups [Standard Mean difference, SMD,1.14 (0.97 to 1.31). • Mean aortic valve gradient post-procedure: Sapien 3 higher mean aortic valve gradient [SMD: 1.24 (1.10 to1.39). • Mean LVEF post-procedure: higher in SAPIEN S3 group [SMD: 1.19 (1.04 to 1.33). • Moderate and severe PVL at 30 days: no statistical difference between valves, 1.6% vs.2.4%, OR 0.74 (0.25 to 2.15).	In scope but evidence not considered key evidence: Authors acknowledge that only 1 study reported long-term outcomes, that recapture and depth of implantation was not reported which may influenced results, that there was substantial heterogeneity between studies regarding pre-dilation and PVL. Publication bias was not assessed as there were less than ten studies included in the meta-analysis.
25.	Makkar (Lancet, 2020a; 669-683) [PORTICO IDE trial; NCT02000115] Australia and US (N=52)	RCT, non-inferiority (n=750) Powered based on 30.8% composite primary safety endpoint (all-cause death, disabling stroke, life threatening bleed requiring blood transfusion,	Between 30 May 2014 and 12 September 2014, and 21 August 2015 and 10 October 2017; paused for 11	Patients with symptomatic, severe aortic stenosis, considered high or extreme surgical risk by MDT. *Inclusion:* • IC1-Subjects must have co-morbidities such that the surgeon and cardiologist Co-Investigators concur that the predicted risk of operative mortality is ≥15% or a minimum STS	Portico (n=381) compared with any commercially available, FDA approved valve (Sapien, Sapien XT, Sapien 3, CoreValve, Evolut R, Evolut Pro) all combined (n=369)	Primary safety endpoint at 30 days was higher in Portico arm (13.8% compared with 9.6%, p=0.034 for non-inferiority, indicating non-inferiority criterion met in the intention to treat (ITT) population).	In scope but evidence not considered key evidence: Selection of the valve in the comparator arm was not randomly assigned but left to the discretion of the study site investigator. Comparator arm combination of valves from multiple manufacturers, therefore difficult to determine incremental benefit.

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		AKI requiring dialysis, major vascular complication at 30 days), and 25.0% composite primary efficacy endpoint (all-cause mortality or disabling stroke at 1 year), 80% power and 5% significance level to show non-inferiority. Funder: Abbott	months by funder.	score of 8%. A candidate who does not meet the STS score criteria of ≥ 8% can be included in the study if a peer review by at least 2 surgeons concludes and documents that the patient's predicted risk of operative mortality is ≥15%. The surgeon's assessment of operative comorbidities not captured by the STS score must be documented in the study case report form as well as in the patient medical record. • IC2-Subject is 21 years of age or older at the time of consent. • IC3-Subject has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or Doppler Velocity Index <0.25 and an initial aortic valve area (AVA) of ≤ 1.0 cm2 (indexed EOA ≤ 0.6 cm2/m2). (Qualifying AVA baseline measurement must be within 60 days prior to informed consent). • IC4-Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of II, III, or IV. • IC5-The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site. • IC6-The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits. • IC7-Subject's aortic annulus is 19-27mm diameter as measured by CT conducted within 12 months prior to informed consent. Note: if CT is contraindicated and/or not possible to be obtained for certain subjects, a 3D echo and non-contrast CT of chest and abdomen/pelvis may be accepted if approved by the subject selection committee. *For a subject to be considered an Extreme Risk candidate they must meet IC2, 3, 4, 5, 6, 7 of the above criteria, and IC8.* • IC8-The subject, after formal consults by a cardiologist and 2 cardiovascular surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout *Exclusion:* • EC1-Evidence of an acute myocardial infarction (defined as: ST Segment Elevation as evidenced on 12 Lead ECG) within 30 days prior to index procedure. • EC2-Aortic valve is a congenital unicuspid or congenital bicuspid valve,or is non-calcified as verified by echocardiography.		<u>Primary efficacy endpoint at 1 year</u> were similar between groups (14.8% Portico, compared with 13.4% in commercial valve group., p=0.0058 for non-inferiority indicating non-inferiority criterion met in the intention to treat (ITT) population). <u>Moderate/severe aortic regurgitation at 1 year</u> showed non-inferiority was not met (7.8% Portico compared with 1.5% commercially available valves, p=0.571). <u>Death at 2 years</u> in ITT population (22.3% Portico and 20.2% commercially available valves; p=0.40) was similar between groups. <u>Disabling stroke at 2 years</u> in ITT population (3.1% Portico compared with 5.0% commercial valves; p=0.23) was similar between groups.	Authors acknowledge that the valves used in the comparator arm had undergone multiple iterations since the initiation of the trial, which may have contributed to improved outcomes in comparator arm. The authors acknowledge that the comparator arm included both balloon-expandable, and supra-annular self-expandable valves combined which may have confounded results; the study was not powered for post-hoc analyses comparing individual valve types.

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				• EC3-Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+). • EC4-Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to index procedure. • EC5-pre-existing prosthetic heart valve or other implant in any valve position, prosthetic ring, severe circumferential mitral annular calcification (MAC) which is continuous with calcium in the LVOT, severe (greater than 3+) mitral insufficiency, or severe mitral stenosis with pulmonary compromise. Subjects with pre-existing surgical bioprosthetic aortic heart valve should be considered for the Valve-in-Valve registry. • EC6-Blood dyscrasias as defined: leukopenia (WBC<3000 mm3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count <50,000 cells/mm³). • EC7-History of bleeding diathesis or coagulopathy. • EC8-Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support. • EC9-Untreated clinically significant coronary artery disease requiring revascularization. • EC10-Hemodynamic instability requiring inotropic support or mechanical heart assistance. • EC11-Need for emergency surgery for any reason. • EC12-Hypertrophic cardiomyopathy with or without obstruction (HOCM). • EC13-Severe ventricular dysfunction with LVEF <20% as measured by resting echocardiogram. • EC14-Echocardiographic evidence of intracardiac mass, thrombus or vegetation. • EC15-Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure. • EC16-A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media which cannot be adequately premedicated. • EC17-Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA). • EC18-Renal insufficiency (creatinine > 3.0 mg/dL) and/or end stage renal disease requiring chronic dialysis. • EC19-Life expectancy <12 months from the time of informed consent due to non-cardiac comorbid conditions. • EC20-Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe			

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				"unfolding" and tortuosity of the thoracic aorta (applicable for transfemoral patients only). • EC21-Native aortic annulus size <19 mm or >27 mm per the baseline diagnostic imaging. • EC22-Aortic root angulation >70° (applicable for transfemoral patients only). • EC23-Currently participating in an investigational drug or device study. • EC24-Active bacterial endocarditis within 6 months prior to the index procedure. • EC25-Bulky calcified aortic valve leaflets in close proximity to coronary ostia. • EC26-Non-calcified aortic annulus • EC27-Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath such as severe obstructive calcification, or severe tortuosity (applicable for transfemoral patients only). Additional Exclusion Criteria (Transcatheter Access-Related) For selection of an appropriate alternative access delivery method, subjects were screened using the following access specific exclusion criteria: *Transaortic Subject Cohort Specific Exclusion Criteria* • EC1-Subject has pre-existing patent RIMA graft that would preclude access. • EC2-Subject has a hostile chest or other condition that complicates transaortic access. • EC3-Subject has a porcelain aorta, defined as an extensive circumferential calcification of the ascending aorta that would complicate TAo access. *Subclavian/Axillary Subject Cohort Specific Exclusion Criteria* • EC1-Subject's access vessel (subclavian/axillary) diameter will not allow for introduction of the applicable 18 Fr or 19 Fr delivery system. • EC2-Subject's subclavian/axillary arteries have severe calcification and/or tortuosity. • EC3-Subject's aortic root angulation is: Left Subclavian/Left Axillary: >70◦ Right Subclavian/Right Axillary: >30◦ • EC4-Subject has a history of patent LIMA/RIMA graft that would preclude access EC 5.			
26.	Malhotra (Heart Lung Circ, 2024; 324-331) Australia (N=1)	Single arm retrospective observational cohort study (n=60) Follow-up: 30 days Funder: No company funding	From 2021 until September 2022 (starting month not specified)	Consecutive patients treated with Navitor outside of a company-sponsored clinical trial. Specific inclusion and exclusion criteria not explicitly reported.	Navitor	*N/A*	Not in scope: single-arm cohort making determination of incremental benefit difficult. Study reported short-term follow-up; studies with larger sample size with longer follow-up were considered in the original EAG report. Furthermore, the cohort included 3 patients (5%) with bicuspid aortic valve disease, and in 21.67% patients the indication for TAVI was failed or degenerated SAVR, which may limit generalisability of results.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
27.	Mauri (Circ Cardiovasc Interv, 2017; e005013) Germany (N=5)	Retrospective cohort with 1:1 propensity score matching (n=246, with 92 matched pairs) Propensity score was modelled with multivariate logistic regression model based on baseline characteristics: sex, age, left ventricular ejection fraction, annulus diameter, body surface area, and logistic EuroSCORE. A rigorous 1:1 nearest neighbour matching algorithm without replacement was used with a 0.2 caliper setting Funder: NR	Between February 2014 to August 2016	*Inclusion:* • Severe aortic stenosis (confirmed by echocardiography) • Small annular dimension (defined as an annulus area <400 mm2) • Transfemoral TAVR with either a Symetis ACURATE neo THV size small (Symetis SA, Ecublens, Switzerland) or an Edwards SAPIEN 3 THV size 23 mm (Edwards Lifesciences, Irvine, CA). • Eligibility for TAVI decided within local institutional heart team. *Exclusion:* NR	Self-expanding (ACURATE neo; older generation) vs balloon-expanding (Sapien 3)	• Death: No statistical difference between ACURATE neo and Sapien 3 arms at 30 days (p=1.00) and 1 year (p=0.23). • Stroke, procedural: No statistical difference between arms; p=1.00. • Vascular complications, procedural: No statistical difference between arms; p=0.152. • Bleeding, procedural: No statistical difference between arms, p=0.832. • PPI, procedural: No statistical difference between arms; p=0.678. • Paravalvular regurgitation: No statistical difference between arms at discharge (p=0.208) of 1 year (p=0.527). • Mean (SD) transvalvular gradients: statistically lower in ACURATE neo post-procedure, 9.3 (3.9) mmHg compared with 14.5 (5.5) mmHg in Sapien 3 group, p<0.001). Sustained at 1 year, 6.6 (2.7) in ACURATE neo and 17.5 (6.5) mmHg with Sapien 3; p=0.008. • Indexed effective orifice area, post-procedure: Statistically larger in ACURATE neo 0.96 (0.3) cm2/m2 compared with 0.80 (0.2) cm2/m2 with Sapien 3; p=0.003. Sustained at 1 year, 1.01 (0.3) cm2/m2 in ACURATE neo and 0.74 (0.2) cm2/m2 with Sapien 3; p=0.031. • Severe patient-prosthesis mismatch, 1 year: Lower rates with ACURATE neo, 3% compared with 22%, p=0.004.	In scope but evidence not considered key evidence: Includes older generation device for 1 manufacturer. Results restricted to patients with small annulus area. Authors acknowledge that propensity matching could not account for unknown or unmeasured confounders, centre effects were observed in 1 centre in Sapien 3 arm.
28.	Moscarella (Int J Cardiol, 2023; 35-45) International (N=17)	Prospective registry (n=97) Follow-up: 1 year Funder: NR	Between April 2019 to January 2022	*Inclusion:* Consecutive patients with severe symptomatic aortic bioprosthetic heart valve failure and mitral bioprosthetic heart valve or annuloplasty ring failure undergoing transcatheter aortic valve in valve and mitral valve in valve or valve-in-ring implantation with Myval. Symptomatic patients with a significant increase in trans-prosthetic gradient or severe regurgitation, who were deemed to be too high-risk for surgical valve replacement based on Heart Team decision, were considered as potential candidates for transcatheter valve-in-valve or valve-in-ring implantation.	Myval (n=97; aortic valve-in-valve 33, mitral valve-in-valve or valve-in-ring 64)	N/A	Not in scope: main analysis compares aortic valve-in-valve with mitral valve-in-valve (incorrect population). Single-arm cohort (all treated with Myval) making determination of incremental benefit difficult. Longer follow-up for single arm was included in the original EAG report (for example Moscarella et al. 2024). However, this study does present evidence of Myval in valve-in-valve procedures (not explicitly contraindicated in this population, but not explicitly indicated either).
29.	Okuno (JACC Cardiovasc Inter, 2023; 429-440) [Swiss TAVI Registry, NCT01368250] Switzerland (N=1)	Prospective cohort (n=723); with propensity score matching (n=342) calculated using multivariable logistic regression model based on 33 variables that may affect valve-type selection). Given potentially difference in outcome by generation of device, 83 patients treated with older generation devices were matched independently from the overall cohort, using 1:1 greedy nearest neighbour with caliper of 0.02.	Between January 2012 and June 2021.	*Inclusion:* Consecutive patients with severe aortic stenosis, with aortic valve annulus area (<430 mm2) undergoing TAVI with CoreValve Evolut or Sapien. *Exclusion:* Patients who underwent TAVI for degenerated surgical or transcatheter aortic bioprosthesis, TAVI for pure native aortic valve regurgitation.	Balloon-expanding (Sapien XT, Sapien 3, Sapien 3 Ultra) Self-expanding (CoreValve, Evolut R, Evolut Pro, Evolut Pro+)	Technical success, composite outcome, discharge: No statistical difference between arms. New permanent pacemaker implantation, 30 days: higher in self-expanding arm (20.6% compared with 8.3%, HR: 2.68 (1.46 to 4.93), p=0.002). Disabling stroke: no difference in arms at 30 days, but lower in balloon expanding at 1 year (0.6% compared	In scope but evidence not considered key evidence: Mixed old and new generation in both arms; although majority new generation (93.6%). Difference in post-dilation reported between groups: 32.2% in self-expanding group compared with 19.9% in balloon-expandable group. Authors acknowledged potential bias caused by unmeasured or unrecognised confounding; limitation of all observational studies.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
		Follow-up: 5 years Funder: NR				with 5.4%, HR 9.07 (1.12 to 73.23), p0.038), and 5 years (0.6% compared with 6.6%, HR 10.01 (1.25 to 80.01), p=0.030) <u>All-cause mortality, life-threatening or major bleeding, NYHA functional class III or IV</u>: no difference in each outcome between arms at 30 days, 1 year, 5 years <u>MI, structural valve deterioration, unplanned repeat aortic valve intervention (including valve-in-series, surgical revision, and aortic valve treatment):</u> no difference in each outcome between arms at 1 or 5 years.	
30.	Pellegrini (EuroIntervention, 2023; e1077-e1087) [SCOPE II subanalysis; overlap with Tamburino et al. 2020 – see later in addendum] Europe (N=23)	Subgroup analysis of as-treated population from an non-inferiority RCT (n=796) Subgroup 1: patients with no previous pacemaker were analysed for PPI at 30 days (n=648) Subgroup 2: patients without previous left bundle branch block (LBBB) were analysed for LBBB at 30 days (n=426) Follow-up: up to 1 year Funder: Sponsored by CERIC (Center for European Research Initiatives in Cardiovascular Medicine) with support from a dedicated research grant from Symetis SA (Ecublens, Switzerland) [EAG note that Boston Scientific acquired Symetis]	NR (assumed the same as reported by Tamburino between April 2017 and April 2019)	*Inclusion:* As-treated population from SCOPE II trial (considering treatment actually received by the participants, regardless of adherence to randomisation assignment), only patients who survived to 30 days or with known pacemaker status at 30 days were included. *Exclusion*: Subgroup 1: patients with prior pacemaker. Subgroup 2: patients with missing or uninterpretable ECG at baseline, discharge or 30 days, and prior LBBB.	Subgroup 1: ACURATE neo (n=333) and CoreValve Evolut (n=315) Subgroup 2: ACURATE neo (n=217) and CoreValve Evolut (n=209)	<u>Permanent pacemaker implantation, 30 days</u>: Lower for ACURATE neo, 12.3% compared with 21.0%, p=0.004. Multivariable analysis reported lower risk with ACURATE neo, OR 0.50 (95%CI 0.31 to 0.81). p=0.005 (when valve used, RBBB, left bundle branch block, moderate to severe aortic calcification, moderate to severe LVOT calcification, pre-dilatation were included in the logistic regression model). <u>LBBB, 30 days</u>: lower for ACURATE neo, 5.5% compared with 13.4%, p=0.007. No multivariable analysis reported.	<u>In scope but evidence not considered key evidence</u>: Subanalysis of Tamburino et al. 2020 (reported in addendum), older generations of devices in comparator arm. Differences in baseline characteristics between TAVI devices across subgroups. In subgroup 1 (PPI at 30 days) differences in baseline first degree atrio-ventricular block, aortic annulus perimeter, pre-dilatation and post-dilatation reported (adjusted for in multivariable analysis). In subgroup 2 (LBBB at 30 days) differences in baseline first degree atrio-ventricular block, aortic annulus area, aortic annulus perimeter, pre-dilatation and post-dilatation reported.
31.	Rheude (Am J Cardiol, 2021; 92-99) Setting: NR	Meta-analysis (N=20 studies, which included 5 RCT and 15 observational studies; n=12,128 patients) Funder: NR	Between 2007 and 2018 [Literature search between January 2010 to December 2019]	*Inclusion:* • Reports of bioprosthetic valve thrombosis in patients treated with TAVI, • Availability of data for at least 1 outcome of interest: subclinical leaflet thrombosis, clinical valve thrombosis. • Publication as full-length manuscript. *Exclusion:* • Duplicated publication data; • Outcomes of interest not clearly reported or impossibility to extract or calculate them from the published results.	Mixture of TAVI devices including self and balloon expanding, including Biovalve, Centera, CoreValve, Evolut, Evolut R, Direct Flow, JenaValve, Lotus, Portico, Sapien, Sapien XT, Sapien 3, Symetis, Symetis ACURATE.	N/A	<u>Not in scope</u>: All TAVI devices aggregated together, no device comparison.
32.	Rück (EuroIntervention, 2024, e781-e782) Sweden (N=1)	Cohort (n=452)	Between October 2015 and	*Inclusion:* Consecutive patients who underwent TAVI with first generation ACURATE neo. *Exclusion:* NR	ACURATE neo (n=452)	N/A	<u>Not in scope:</u> single-arm cohort making determination of incremental benefit difficult. Follow-up up to 7 years was reported in

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
		Follow-up: echocardiographic median 39 months (3.25 years) up to 69 months (5.75 years) Funder: Boston Scientific	December 2018				original EAG report (for example: Siqueira et al. 2021).
33.	Sanchez-Luna (EuroIntervention, 2023; 580-588) Europe, US and Asia-Pacific region (N=17)	Retrospective cohort (n=113) Follow-up: 1 year Funder: NR	From January 2019 (end date NR)	*Inclusion:* Consecutive patients with symptomatic severe non-calcified aortic regurgitation, with comorbidities that would preclude SAVR according to Heart Team at each centre. undergoing TAVI with Myval. *Exclusion:* Patients with aortic stenosis (peak aortic jet velocity on continuous-wave Doppler >2.5 m/s).	Myval (n=113)	N/A	Not in scope: incorrect population (regurgitation), single-arm cohort making determination of incremental benefit difficult
34.	Schofer (Clin Res Cardiol, 2022; 934-943) Germany (N=NR)	Retrospective non-randomised cohort from German administrative claims database (n=21,430) Funder: Open Access funding enabled and organized by Projekt DEAL.	Between January 2017 and December 2019	*Inclusion:* Patients aged 20 years or older, insured by the Allegemeine Ortskrankenkasse (provides healthcare insurance for 30% of German population), who received endovascular TAVI. *Exclusion:* Primary diagnosis of endocarditis, aortic valve insufficiency or received other valve interventions.	Balloon-expandable and self-expanding (devices used not reported).	N/A	Not in scope: main analysis was 30 day outcomes for different risk categories, no analysis comparing devices reported. EAG note that expansion type was only available for 14,777 patients (69%) from 2018 and 2019; no additional information on devices used reported.
35.	Senguttuvan (Front Cardiovasc Med, 2023; 1130354) [CRD42020181190] Setting: NR	Systematic review and meta-analysis (N=6 RCTs, n=2,935 patients) Primary endpoint varied across studies and included device success, post-procedural aortic regurgitation assessed by MRI, primary composite safety and efficacy outcome, haemodynamics, composite efficacy outcome only. Included 1 RCT with post-hoc analysis. Funder: No commercial funding reported	Across 6 studies patients recruited between earliest of March 2012 and latest February 2019.	High-risk patients with severe native aortic stenosis undergoing transfemoral TAVI. *Inclusion:* • Randomized controlled trials (RCTs) in patients with severe native AS undergoing TAVI. • RCTs or post hoc analysis of RCTs comparing valve platforms into BE vs. SE or an RCT with pre-specified analysis by valve platforms. If a trial included MEV platform in either study arm (SEV or BEV), then it had to be <5% for inclusion in the current study. • Study should report all-cause mortality at 30 days as either primary or secondary outcome. *Exclusion:* NR	• Abdel-Wahab (2014): Sapien XT compared with CoreValve. • Kooistra (2020): Sapien 3 compared with CoreValve. • Lanz (2019): Sapien 3 compared with ACURATE neo. • Linke et al. (2017): Sapien XT, Sapien 3 compared with CoreValve, Evolut (other non-balloon expanding valves were used in 5 patients). • Makkar (2020b); Sapien 3 compared with Evolut R, Evolut Pro, Portico. • Thiele (2020); Sapien 3 compared with Evolut R.	All-cause mortality balloon expanding associated with lower risk, RR: 0.51, 95%CI 0.31 to 0.82; p<0.006, compared to self-expanding. Implantation of more than 1 device balloon expanding associated with lower risk when compared to self-expanding, RR: 0.15, 95%CI 0.07 to 0.31; p<0.00001. Moderate/severe aortic regurgitation or paravalvular leak balloon expanding associated with lower risk compared to self-expanding, RR: 0.29, 0.17 to 0.48; p<0.00001.	In scope but evidence not considered key evidence: Study included older generation of devices (for example: Sapien XT, CoreValve, ACURATE neo); technology changes between these and those listed in the Final Scope (see Table 3 of the EAR) therefore cannot assume equivalence. Comparator arm included SEV from multiple manufacturers and some devices were recapturable; this makes determination of the incremental benefit difficult. SR included mechanically expandable valve (MEV) in; acknowledging MEV had to be <5% for inclusion in SR. SR restricted to RCTs reporting all-cause mortality at 30 days as a primary or secondary outcome. Authors acknowledge that “Some studies also excluded patients with heavy calcification in the aortic annulus, left ventricular outflow tract (LVOT) or sinotabular junction, limiting the interpretation of these findings to those subgroups”. Authors assessed risk of bias using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2); 4 were considered to have low risk of bias, 1 some concern, and 1 high risk of bias.
36.	Tamburino (Circulation, 2020; 2431-2442) [SCOPE II trial; NCT03192813] Denmark, France, Germany, Italy, Spain, UK (N=23 centres, including 2 from UK)	RCT, non-inferiority (n=796). Powered based on composite primary end point (all-cause death, any stroke at 1 year) predicted as 12% in comparator arm and assumed non-inferiority margin of 6%.	Between April 2017 and April 2019	Symptomatic patients aged ≥75 years, with severe aortic stenosis with an indication of transfemoral TAVI. *Inclusion:* • Patient with severe symptomatic aortic stenosis defined by a mean aortic gradient > 40 mmHg or peak jet velocity > 4.0 m/s or an aortic valve area (AVA) < 1cm2 or AVA	Comparison of ACURATE neo (n=398) with CoreValve Evolut R and Pro (n=398)	Primary composite endpoint at 1 year was 15.8% in ACURATE neo arm and 13.9% in CoreValve Evolut arm; p=0.0549 for non-inferiority. Inconsistent results between ITT and per-protocol analyses, therefore the authors stated that non-inferiority of ACURATE neo was not established for the primary end point.	In scope but evidence not considered key evidence: Older generations of devices in comparator arm. Authors acknowledge that centres contributing to the trial had different levels of experience with the devices, and the proportion where Evolut Pro was used (which included an external pericardial wrap) was not recorded.

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		Follow-up: 1 year Funder: This trial was sponsored by the Center for European Research Initiatives in Cardiovascular Medicine with support by a dedicated research grant from Symetis SA (Ecublens, Switzerland). [The EAG note that Symetis was acquired by Boston Scientific]		indexed to body surface area (BSA) of <0.6 cm2/m2 • Patient is symptomatic (NYHA functional class > I, angina or syncope) • Patients are considered at high risk for mortality with conventional surgical aortic valve replacement as assessed by a Heart Team consisting of a cardiologist and surgeon or as confirmed by a logistic EuroSCORE I >20% and / or STS score >10%. • Aortic annulus dimensions suitable for both valve types (diameter range: 21-26 mm and perimeter rage from 66 – 81.7 mm), based on ECG-gated multi-slice computed tomographic measurements. • Findings of transthoracic echocardiography (TTE), Transesophageal echocardiography (TEE) and conventional aortography should be integrated in the anatomic assessment. • Arterial aorto-iliac-femoral axis suitable for transfemoral access as assessed by conventional angiography and/or multidetector computed tomographic angiography (access vessel diameter ≥ 6mm). • Patient understands the purpose, the potential risks as well as benefits of the trial and is willing to participate in all parts of the follow-up. • Patient age 75 years or older. • Patient has given written consent to participate in the trial. *Exclusion:* • Severely reduced left ventricular (LV) function (ejection fraction <20%). • Pre-existing prosthetic heart valve in aortic and/or mitral position. • Participation in another trial, which would lead to deviations in the preparation or performance of the intervention or the post-implantation management from this protocol. • Severe coagulation conditions. • Inability to tolerate anticoagulation therapy. • Contraindication to contrast media or allergy to nitinol. • Active infection, including endocarditis. • Congenital aortic stenosis or unicuspid or bicuspid aortic valve. • Non-valvular aortic stenosis. • Hypertrophic obstructive cardiomyopathy. • New or untreated echocardiographic evidence of intracardiac mass, thrombus, or vegetation. • Non-calcific acquired aortic stenosis. • Severe eccentricity of calcification. • Anatomy not appropriate for transfemoral implant due to size, disease and degree of calcification or tortuosity of the aorta or iliofemoral arteries. • Severe mitral regurgitation.		<u>New permanent pacemaker at 30 days</u> occurred in 10.5% in ACURATE neo and 18.0% in CoreValve Evolut; p=0.0027. <u>Cardiac death at 30 days</u> occurred in 2.8% in ACURATE neo and 0.8% in CoreValve Evolut; p=0.03. <u>Cardiac death at 1 year</u> occurred in 8.4% in ACURATE neo and 3.9% in CoreValve Evolut; p=0.01.	

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37.	Tamm (pre-publication) [AIC] [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not in scope: [redacted]
38.	Tarantini (Catheter Cardiovasc Interv, 2021; 876-884) SOURCE 3 10 European countries (N=80)	Prospective post-market registry (n=1,694) Follow-up: 4 years Funder: Edwards Lifesciences	Between July 2014 and October 2015.	*Inclusion:* Patients with severe, symptomatic, calcific AS who were at high risk for surgery in real-world practice for 5 years, receiving the Sapien 3 valve (23, 26, 29 mm) via transfemoral route, in line with Sapien 3 indications for us. *Exclusion:* NR	Sapien 3 (n=1,694)	N/A	Not in scope: single-arm cohort making determination of incremental benefit difficult. Focus of analysis was comparison of outcomes between males and females.
39.	Tebar (Catheter Cardiovasc Interv, 2024; 1015-1022) PRECISA [NCT03846557] Spain (number of centres not known: study narratively reports 5 medical centres, 7 medical centres, and trial registry reports 10 centres)	Prospective cohort (n=296) Follow-up: 1 year. Funder: NR	Between January 2019 and September 2021 (ACURATE neo used between January 2019 to September 2020; ACURATE neo2 from October 2020 to September 2021)	*Inclusion:* Consecutive adult (aged 18 years or older) with severe aortic stenosis, requiring aortic valve prosthesis implantation. Both tricuspid and non-tricuspid anatomies, and various access routes were considered for inclusion). *Exclusion:* None.	ACURATE neo2 (n=118) ACURATE neo (n=178)	*Primary outcome* Device success (absence of procedural mortality, accurate positioning of single prosthetic valve, absence of prosthesis-patient mismatch, mean aortic gradient <20mmHg, absence of moderate or severe prosthetic valve regurgitation), at discharge: Higher in ACURATE neo than ACURATE neo2: 18% compared with 9.3%, p=0.04 (p=0.01 from propensity score analysis adjusting for predictor variables) Moderate or severe paravalvular aortic regurgitation: Higher in ACURATE neo arm at discharge (9.8% compared with 5%, p=0.03) at 30 days (4% compared with 2.5%, p=0.04) and 1 year (21.9% compared with 13.6%, p=0.047). Mean aortic valve gradient ≥20 mmHg: no difference between arms at discharge, higher in ACURATE neo at 30 days (4% compared with 2.5%; p=0.04) and no difference at 1 year. Cardiac tamponade, at time of valve implantation: higher in ACURATE neo2, 3.4% compared with 0% for ACURATE neo; p=0.02.	In scope but evidence not considered key evidence: Larger cohort included in original EAG report (for example: Kim et al. 2022c). Historical comparator group. No statistical differences in baseline characteristics reported, however difference in post-dilation were reported: 47.2% with ACURATE neo and 12.7% in ACURATE neo2 group; p<0.0001, and differences in post-dilation balloon diameter, 22.9 (2.0) in ACURATE neo compared with 24.0 (0.9) in the ACURATE neo2 group, p=0.02. Propensity score analysis not reported for all outcomes, predictor variables used in this analysis not reported. Short term outcomes. Confusion over reporting of primary outcome reported in methods section as device success, but values reported in Table 4 and breakdown of the primary outcome appear device failure. Authors acknowledge the tendency to use ACURATE neo2 valve predominantly in women with small aortic annulus, that differences in post-dilation between arms, and differences in access approach may have influenced outcomes.
40.	Thiele (Eur Heart J, 2020a; 1890-1899)[SOLVE-TAVI trial; NCT02737150] [Additional detail regarding study design reported in Thiele (Circulation, 2020b; 1437-1447)] Germany (N=7)	RCT; 2x2 factorial (n=447) Comparison of general anaesthesia and local anaesthesia with conscious sedation, and also comparison of self-expandable with balloon-expandable. Powered for equivalence in primary endpoint (all-cause mortality, stroke, moderate or severe PVL, and permanent pacemaker implantation at 30-day follow-up) Follow-up: 30 days	Between April 2016 and April 2018	*Inclusion:* Patients with symptomatic aortic valve stenosis, age ≥75 years, at high risk for conventional SAVR (logistic EuroSCORE ≥20%, or STS ≥10%, or other high risk criteria as deemed by heart team consensus), a native aortic valve annulus size (between 18 and 29 mm) appropriate for the available valve sizes, suitable for transfemoral vascular access. *Exclusion:* Contraindication for specific valve type, cardiogenic shock or haemodynamic instability, history of or active endocarditis, active infection requiring antibiotic treatment, life expectancy <12 months, active peptic ulcer or upper GI bleeding <3 months, hypersensitivity or contraindication to aspirin, heparin or clopidogrel, participation in another trial.	Evolut R (n=225) compared with Sapien 3 (n=222)	*Primary endpoint* Composite (all-cause mortality, stroke, moderate or severe PVL, permanent pacemaker) at 30 days: equivalent between groups 28.4% in Evolut R compared with 25.9% Sapien 3; p=0.04 for equivalence. All-cause mortality, 30 days: similar between Evolut R and Sapien 3, 3.2% and 2.3% respectively, p<0.0001 for equivalence. Stroke, 30 days: similar between Evolut R and Sapien 3, 0.5% and 4.7% respectively, p=0.003 for equivalence.	Key evidence 2x2 factorial design, but no interactions was assumed to be clinically plausible but no exploration of this was reported. Statistical difference in the contrast agent used between TAVI device arms (higher with Evolut R, p<0.001). In self-expanding TAVI arm, 2 participants electively crossed over to balloon-expanding, and other valves were used in 2 additional participants. In the balloon-expanding device arm, 1 participant electively crossed over to the self-expanding arm. A per protocol analysis was conducted that adjusted for this and had similar findings to the intention to treat analysis.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
		Funder: German Heart Research Foundation and the Leipzig Heart Institute Germany		The EAG note that additional exclusion criteria were listed in Thiele et al. 2020b, including: mode of anaesthesia or for TAVI procedure, clear patient-specific clinical reasons to prefer 1 form of anaesthesia over the other.		Moderate to severe PVL, 30 days: similar between Evolut R and Sapien 3, 3.4% and 1.5% respectively, p=0.0001 for equivalence. Permanent pacemaker, 30 days: significantly higher for Evolut R than Sapien 3, 23.0% and 19.2% respectively, p=0.06 for equivalence.	Authors acknowledge that the RCT was powered to show equivalence in treatment groups on composite clinical endpoint only; not component endpoints, and that "valve choice should take into account individual factors in which a specific valve type might be favoured (for example severe calcification, bicuspid anatomy, horizontal aorta, or the requirement of uncomplicated coronary access).
41.	Ubben (J Clin Med, 2024; 3163) Germany (N=6)	Retrospective cohort (n=402) Follow-up: until discharge Funder: Meril Life Sciences via research grant for investigator-sponsored trials.	Between 01 March and 31 August 2020.	*Inclusion:* Consecutive patients who underwent TAVI for severe symptomatic aortic valve stenosis with Myval or Sapien 3 or Sapien 3 Ultra. *Exclusion:* pre-existing prosthetic heart valves in aortic position and patients who underwent an emergent TAVI or TAVI with mechanical circulatory support.	Myval (n=134) Sapien 3/3 Ultra (n=268)	Major vascular complication, at discharge: higher in Myval (9%) compared with Sapien 3/3 Ultra (5%), p=0.02 All-cause mortality, cardiac mortality, stroke, disabling stroke, new pacemaker implantation, annular rupture, new onset AF, cerebrovascular events, AKI, bleeding (type 3), endocarditis, MI, minor vascular complications, at discharge: No difference between arms.	In scope but evidence not considered key evidence: Short term outcomes, studies with longer follow-up for Myval were included in original EAG report (for example: Baumbach et al. 2024) Unclear whether the intervention included both Myval and Myval Octacor (latest iteration). Reported baseline characteristics of cohorts not statistically different but no formal matching of patient characteristics reported. Authors acknowledge that the analysis includes learning curve of the Myval device.
42.	Ueyama (Am J Cardiol, 2021; 104-111) Setting: NR	Network meta-analysis (N=10 RCTs, n=9,388) [Note N=3 studies directly compared balloon expanding and self-expanding TAVI devices, 4 compared self-expanding TAVI with SAVR and 3 compared balloon-expanding TAVI with SAVR] Follow-up: up to 5 years Funder: NR	NR (Literature search between database inception to 06 February 2021)	*Inclusion:* RCTs comparing TAVI and SAVR or balloon-expanding and self-expanding in patients with severe aortic stenosis, reporting at least 1 of the pre-specified outcomes (structural valve deterioration, moderate to severe aortic regurgitation, aortic valve reintervention at the longest available follow-up), study reported outcome at follow-up of at least 1 or more years, published in peer-reviewed journal or presented in international academic conferences. *Exclusion:* None.	Balloon-expandable included Sapien, Sapien XT, Sapien 3 (all combined, n=2,562). Self-expanding included: CoreValve, Evolut R, Evolut Pro, ACURATE neo (all combined, n=2,863) SAVR (n=3,963)	Structural valve deterioration, 5 years: Self-expanding valves lower risk than balloon-expanding; HR 0.14 (0.07 to 0.27) Moderate to severe aortic regurgitation, 5 years: Self-expanding valves associated with high risk than balloon; HR 1.78 (95% CI 1.03 to 3.07). Aortic valve re-intervention, 5 years: No statistical difference between balloon and self-expanding valves. Mean gradient, mmHg, 5 years: Lower with self-expanding versus balloon-expanding, mean difference: -5.13 (95%CI -6.21 to -4.04); p<0.001. EOA, cm2, 5 years: higher with self-expanding compared with balloon-expanding, mean difference: 0.25 (0.15 to 0.35), p<0.001.	In scope but evidence not considered key evidence: Different device manufacturers and models combined to directly/indirectly compare self-expanding with balloon expanding; unable to determine incremental benefit of devices. EAG note that it is unclear whether all RCTs were statistically powered to detect differences in the outcomes extracted. Authors acknowledge that definition of outcomes was not consistent across studies, and that there was heterogeneity in surgical risk and device generation in studies included.
43.	Van Belle (Circulation, 2020; 243-259) [NCT01777828] France (N=48)	Prospectively cohort, registry, FRANCE-TAVI (n=12,141). Includes both propensity score matching on 25 clinical and anatomical variables (n=7,820 after matching) and inverse probability of treatment weighting (n=12,141). Follow-up: 30 days, up to 2 years.	Between 02 January 2013 and 31 December 2015. (Sapien XT used between January 2013 to last quarter 2014, Sapien 3 used from	*Inclusion:* All patients included in the FRANCE-TAVI registry. *Exclusion:* Patients with previous SAVR (including those referred for valve-in-valve procedures), those treated with different valve design (Lotus, Boston Scientific, Direct Flow, JenaValve).	CoreValve (n=4,103; n=3,910 after matching) compared with Sapien XT/3 (n=8,038; n=3,910 after matching)	Mortality, in-hospital: Higher in CoreValve than Sapien XT/3, confirmed by propensity matching (5.6% compared with 4.2%, p=0.01) and IPTW cohorts (5.6% compared with 3.8%, p=0.001). Moderate or severe paravalvular leak, at discharge: Higher in CoreValve than Sapien XT/3, confirmed by propensity matching (15.5% compared with 8.3%; p<0.0001) and	In scope but evidence not considered key evidence: Older generation devices in both intervention and comparator arm; no longer available in NHS. EAG note that 4 sizes were available for each device, but different sizing (CoreValve: 23, 26, 29, 31mm; Sapien 3: 20, 23, 26, 29mm). Combination of generations in the Sapien (balloon expanding) arm; which may influence results.

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		Funder: The registry was established by the French Society of Cardiology and French Working Group of Interventional Cardiology with the participation of the French Society of Thoracic and Cardiovascular Surgery and with support from Edwards Lifesciences and Medtronic.	last quarter 2014 to December 2015).			IPTW cohorts (15.6% compared with 7.5%; p<0.0001). Second valve used, at discharge: higher with CoreValve than Sapien XT/3, confirmed by propensity matching (3.7% compared with 1.0%, p<0.0001) and IPTW cohorts (3.7% compared with 0.8%, p<0.0001). Permanent pacemaker, at discharge: higher with CoreValve than Sapien XT/3, 22.3% compared with 11.0%, p<0.0001. Mean gradient, post-procedure: lower with CoreValve than Sapien XT/3, confirmed by propensity matching (mean difference: -0.21 (-0.24 to -0.19); p<0.0001) and IPTW cohorts (mean difference: -0.23 (-0.25 to -0.21), p<0.001). Hospitalisation for acute cardiac event (including acute coronary syndrome or heart failure), 2 years: Increased risk associated with self-expanding compared to balloon-expanding in propensity matched cohort (HR 1.26 (1.06 to 1.48); p=0.001) and with IPTW cohort (HR: 1.28 (1.10 to 1.54); p=0.0001). Aortic valve re-intervention, 2 years: No statistical difference between arms confirmed by propensity matched and IPTW cohorts. Stroke, 2 years: No statistical difference between arms confirmed by propensity matched and IPTW cohorts. All-cause mortality, 2 years: higher for CoreValve than Sapien XT/3 confirmed by propensity matched (HR 1.17 (1.06 to 1.28); p=0.002) and IPTW cohorts (HR: 1.18 (1.08 to 1.29); p<0.0001). Proportional hazard assumption was not satisfied because excess mortality risk of CoreValve compared to Sapien XT/3 only observed for the first 3-month period (HR: 1.37, (1.16 to 1.60), p=0.0001.	
44.	Welle (Catheter Cardiovasc Interv, 2021; 895-902) US (N=1)	Retrospective cohort identified from registry (n=260) Follow-up: 30 days. Funder: NR	Between July 2018 and July 2019 Sapien 3 Ultra available option from	*Inclusion:* Consecutive patients undergoing TAVI for severe aortic stenosis. Valve selection was collaboratively chosen by Heart Team. *Exclusion:* off-label TAVI, conversion to SAVR strategy prior to TAVI, those receiving self-expanding TAVI, aortic valve-in-valve procedure, died prior to discharge of index hospitalisation.	Sapien 3 Ultra (n=101) Sapien 3 (n=159)	PVL, 30 days: Proportion with mild PVL less in Sapien 3 Ultra arm compared with Sapien 3, 10.8% compared with 36.5%; p<0.0001. Proportion with moderate also less in Sapien 3 Ultra arm, 0% compared with 5.8% (p=NR). Univariate analysis showed TAVI device was associated	In scope but evidence not considered key evidence: No adjustment for population differences between arms; statistical differences in male sex, annular area, perimeter and diameter, aortic valve calcium score, proximal left anterior descending stenosis, valve size, access site observed and not adjusted for. Valve size of 29mm not

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			February 2019 onwards.			with mild PVL, but TAVI device not associated with moderate PVL. LVEF and aortic valve mean gradient, 30 days: No difference between arms.	available in Sapien 3 Ultra. Comparator arm also includes historical comparator group (July 2018 to February 2019 Sapien 3 Ultra was not available). Larger studies with matching between Sapien 3 and Sapien 3 Ultra already included in EAG report (e.g. Nazif et al. 2021, Cannata et al. 2023).

Abbreviations: AKI, Acute Kidney Injury; AVA, Aortic Valve Area; BE, Balloon Expanding; CAD, Coronary artery disease; CVA, Cerebrovascular accident; CVT, Clinical valve thrombosis; ECG, Electrocardiogram; GFR, Glomerular Filtration Rate; HALT, Hypo attenuated leaflet thickening; iEOA, indexed effective orifice area; IPTW, inverse probability of treatment weighting; IQR, Interquartile Range; LBBB, left bundle branch block; LV, Left ventricular; LVEF, Left ventricular ejection fraction; LVOT, Left ventricular outflow tract; MA, meta-analysis; MDCT, Multi-detector CT; MDT, Multidisciplinary team; MI, Myocardial infarction; N/A, Not applicable; NR, Not reported; NYHA, New York Heart Association; PPI, Permanent pacemaker implantation; ; PPMI, Permanent pacemaker implantation; PVL, Paravalvular leak; PVR, Paravalvular regurgitation; RCT, Randomised controlled trial; SE, Self-expanding expansion type; SLT, Subclinical leaflet thrombosis; STS, The Society of Thoracic Surgeons; SUCRA, Surface Under the Cumulative Ranking; SVD, Structural valve deterioration; TAPSE, Tricuspid annular plane systolic excursion; TAVI, Transcatheter aortic valve implantation; TAVR, Transcatheter aortic valve replacement; TEE, Transoesophageal echocardiogram; THV, Transcatheter Heart Valve; TIA, Transient ischaemic attack; TTE, Transthoracic echocardiogram; VARC-2, Valve Academic Research Consortium-2; VARC-3, Valve Academic Research Consortium-3;