National Institute for Health and Care Excellence

Final

Heart valve disease presenting in adults: investigation and management

[G] Evidence review for monitoring of people with heart valve disease and no current indication for intervention

NICE guideline NG208

Intervention evidence review underpinning recommendation 1.4.1 and research recommendations in the NICE guideline

November 2021

Final

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1.1 Review question: Where there is no current indication for intervention, what is the most clinically and cost-effective type and frequency of test for monitoring in adults with heart valve disease?

1.2 Introduction

Heart valve disease progresses gradually at a slow pace, with only rare unpredictable worsening, abruptly or at a faster pace. Clinical and haemodynamic consequences of heart valve disease usually develop at later stages of the disease. To avoid unnecessary tests but also the late detection of indications for intervention, it is important to determine the most clinically and cost-effective type and frequency of test for monitoring of heart valve disease.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults aged 18 years and over with diagnosed heart valve disease and no current indication for intervention, stratified by the severity of valve disease as follows: • Mild • Moderate • Severe Severity assessed by echo and rated as per The British Society of Echocardiography. Other definitions will be accepted and downgraded for indirectness if appropriate. Exclusion: Children aged less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease. People who have had prior heart valve repair or replacement (transcatheter or surgical).
Interventions	Any of the following assessment strategies used for monitoring purposes, followed by appropriate valve intervention, in the specified population: Biomarkers (alone or in combination with echo): • BNP (B-type natriuretic peptide) • NT-proBNP (N-terminal prohormone brain natriuretic peptide) Imaging: • Echocardiography • CT (alone or in combination with echo)

	• CMR (cardiovascular magnetic resonance; alone or in combination with echo) Patient reported outcome measures (PROMS; alone or in combination with echo), including: • EuroQol • Minnesota Living With Heart Failure Questionnaire (MLHFQ) • Veterans Specific Activity Questionnaire Other methods: • Electrocardiogram (ECG) (alone or in combination with echo) • Clinical review only (no specific tests performed, as defined by the study authors) • Exercise testing (for example Bruce protocol; alone or in combination with echo) Different frequencies of the tests used for monitoring will be considered as separate interventions. Therefore, we will include studies comparing different frequencies of the same or different interventions. Frequency will be categorised into the following groups: • More frequently than once a year (e.g. every 3 or 6 months) • Once a year • Less frequently than once a year (e.g. every 2, 3 or 5 years) Each monitoring test is a different strata and each frequency is a sub-analysis for each test.
Comparisons	Other active comparator listed above No monitoring (for example, tests only performed if new symptoms emerge/symptoms worsen)
Outcomes	Primary outcomes: • All-cause mortality • Cardiac mortality • Health-related quality of life (any validated measure) • Hospitalisation for heart failure or other cardiac reason (e.g., for syncope in severe AS) Secondary outcomes: • New-onset atrial fibrillation If data are available, follow-up will be reported as a first preference at : • 12 months for mild and moderate valve disease • 6 months for severe valve disease. Where multiple time-points are reported within a single study, only the time-point closest to that stated above will be extracted.
Study design	Randomised controlled trials (RCTs) and systematic reviews of RCTs. Published NMAs and IPDs will be considered for inclusion.

If insufficient evidence is found from RCTs, non-randomised studies will be considered for inclusion.

Important confounders NRS must be adjusted for:

- Coronary artery disease
- Aortopathy in aortic valve disease

1.4 Clinical evidence

1.4.1 Included studies

One study was included in the review;[1] this is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below (Table 3).

A search was conducted for randomised trials comparing the effectiveness of various different types and frequencies of monitoring compared to each other or no routine monitoring in patients with heart valve disease and no current indication for intervention. No randomised trials matching the protocol were identified, so observational studies were considered for inclusion as pre-specified in the protocol.

One retrospective cohort study was subsequently included in the review; this study compared a guideline adherent group with a guideline non-adherent group by retrospective review of medical records in those with severe asymptomatic aortic stenosis. However, this study was considered to be indirect compared with the protocol as the frequency of monitoring varied in the guideline adherent group [defined as clinical review with echocardiography and cardiopulmonary physical examination every 12 (±6) months] and there was no description of the monitoring that occurred in the guideline non-adherent group, meaning it could have included those undergoing follow-up more often, less often or using different methods than recommended in the guidelines. However, this study was included due to a lack of other available evidence from comparative studies and downgraded for indirectness.

The protocol specified that any non-randomised studies included should have adjusted outcomes for two key confounders for aortic stenosis: coronary artery disease and aortopathy. The proportion in each group with coronary artery disease was reported to be similar in both groups, but aortopathy was not mentioned and it is unclear whether this may have differed between the groups. For the mortality outcome, a value adjusted for coronary artery disease was provided but only an unadjusted result was available for the heart failure hospitalisation outcome.

Further limitations identified were the fact that the number of patients that received surgical or catheter-based aortic valve replacement during follow-up was higher in the guideline adherent group compared with the guideline non-adherent group, which was taken into account in the risk of bias rating, and the fact that the ideal time-point of 6 months follow-up, as specified in the protocol, could not be obtained for the all-cause mortality outcome and a 1-year time-point was instead obtained.

Further detail about these limitations are discussed in more detail in section 1.7.1.2 below.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E:and GRADE tables in Appendix F.

1.4.2 Excluded studies

See the excluded studies list in Appendix I:.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Ahmed 2017[1] Retrospective review of medical records Medical records reviewed from 25th July 2007 to 6th December 2012 N=300 USA	**Guideline adherent group [clinical review + echocardiography every 12 (±6) months] (n=202):** serial evaluation occurring every 12 (±6) months until aortic valve replacement or death during the follow-up. Appropriate serial evaluations required the following to be performed: comprehensive clinical evaluation that included description of presence or absence of cardiac symptoms, cardiopulmonary physical examination, and 2D and Doppler echocardiogram including assessment of left ventricular function and the haemodynamic severity of aortic stenosis, with documentation of the aortic valve area and either the peak aortic velocity or mean aortic valve gradient **Guideline non-adherent group (n=98):** No definition for guideline non-adherence	Severe asymptomatic aortic stenosis Mean age: 78 (11.6) vs. 79.8 (11.3) years Coronary artery disease, 47.5 vs. 48%	All-cause mortality (median 4.5 years) Heart failure hospitalisation (median 4.5 years)	• Indirectness of interventions compared to the protocol • All-cause mortality adjusted for: age, sex, coronary artery disease, atrial fibrillation, diabetes, peak aortic velocity, mean aortic valve gradient, aortic valve area, prior percutaneous coronary intervention, left ventricular ejection fraction and guideline adherence • Heart failure hospitalisation was not adjusted, but similar at baseline for one of the key confounders listed: coronary artery disease • Aortopathy was not mentioned in the study so unclear if groups were similar at baseline for this factor • Note that the hazard ratios reported in the study were inverted as

Study	Intervention and comparison	Population	Outcomes	Comments
	provided - could include those receiving follow-up with all required components more often than every 12 (±6) months, those receiving follow-up with all required components less often than every 12 (±6) months and also those receiving follow-up within 12 (±6) months but without all of the required components (comprehensive clinical review, cardiopulmonary physical examination and 2D and Doppler echocardiogram, as defined for the other group).			the paper reported the hazard ratios with the guideline adherent group as the control group, whereas we have extracted the guideline non-adherent group as the control group.

See Appendix D: for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

1.4.4.1 Mild heart valve disease

No evidence was identified for this stratum.

1.4.4.2 Moderate heart valve disease

No evidence was identified for this stratum.

1.4.4.3 Severe heart valve disease

Table 3: Clinical evidence summary: Guideline adherent [clinical review + echocardiography every 12 (±6) months] vs. guideline non-adherent group

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with guideline non-adherent group	Risk difference with Guideline adherent group (95% CI)
All-cause mortality - HR (adjusted) 1 year	300 (1 study) 4.5 years	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	HR 0.65 (0.44 to 0.96)[d]	20 per 1000	7 fewer per 1000 (from 1 fewer to 11 fewer)[e]
Cardiac mortality					
Health-related quality of life (any validated measure)					
Heart failure hospitalisation - HR (not adjusted) 6 months	300 (1 study) 4.5 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness	HR 0.6 (0.46 to 0.79)[f]	153 per 1000	58 fewer per 1000 (from 30 fewer to 79 fewer)[g]
New-onset atrial fibrillation					

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with guideline non-adherent group	Risk difference with Guideline adherent group (95% CI)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[b]Downgraded by 1 increment as the interventions and comparisons in this study were indirect compared with the protocol - monitoring in the guideline adherent group may not have been 12 months in all patients and monitoring in the guideline non-adherent group was not defined and could have included various different strategies. There was also no information about aortopathy in the study, one of the confounders listed in the protocol.

[c]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[d]The values reported in the paper (HR 1.54, 95% CI 1.04 to 2.29) were inverted in order to obtain the HR for the guideline adherent group vs. the non-adherent group to achieve the comparison of interest in the protocol

[e]Control group risk at 1 year from survival curve used. A larger benefit (100 fewer per 1000) was observed when the control group risk at 4 years was used; however, this was not included in the report as the 1-year time-point was closest to the time-point of 6 months specified in the protocol

[f]The values reported in the paper (HR 1.66, 95% CI 1.27 to 2.18) were inverted in order to obtain the HR for the guideline adherent group vs. the non-adherent group to achieve the comparison of interest in the protocol

[g]Control group risk at 6 months from survival curve used. A larger benefit (185 fewer per 1000) was observed when the control group risk at 4 years was used; however, this was not included in the report as the time-point specified in the protocol was 6 months

See Appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.5.3 Summary of studies included in the economic evidence review

No economic studies were found

1.5.4 Health economic modelling

This area was not prioritised for new cost-effectiveness analysis.

1.5.5 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 4: UK costs of monitoring tests for heart valve disease

Resource	Unit cost	Source
BNP	£22	CHF guideline (NG106)[48]
NT-proBNP	£26	CHF guideline (NG106)[48]
Simple Echocardiogram (a)	£108	NHS reference Costs 2017/18[51]
Complex Echocardiogram (b)	£196	NHS reference Costs 2017/18[51]
Electrocardiogram or stress testing (c)	£58	NHS reference Costs 2017/18[51]
Complex computerised Tomography (CT) (d)	£162	NHS reference Costs 2017/18[51]
Cardiac Magnetic Resonance (CMR) (e)	£399	NHS reference Costs 2017/18[51]

Source: Costs obtained from the CHF guideline[48] and NHS reference cost 2017/18[51], cost codes were agreed by the committee.
Abbreviations: BNP: B-type natriuretic peptide.

(a) Cost code RD51Aoutpatient
(b) Cost code EY50Y outpatient
(c) Cost obtained from the direct access to diagnostic service, cost code EC22Z
(d) Cost code RD28Z
(e) Cost weighted according to units of activity for the outpatient post-contrast only and pre- and post-contrast. Cost code RD09Z + RD10Z

1.6 Evidence statements

1.6.1 Clinical evidence statements

See the summary of evidence in Table 3.

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

Outcomes considered to be critical as listed in the protocol were all-cause mortality, cardiac mortality, health-related quality of life (any validated measure) and hospitalisation for heart failure or any other cardiac reason.

One additional outcome of new-onset atrial fibrillation was included as an important outcome.

It was agreed that the preferred time-points for reporting outcomes would depend on the severity of the valve disease, with 12 months preferable for mild or moderate valve disease and 6-month data preferable for severe valve disease. This reflects how often the respective severities are usually followed up in current practice.

Evidence included in this review was very limited, with only two outcomes from a single study being identified. Outcomes with no evidence were as follows: cardiac mortality, health-related quality of life and new-onset atrial fibrillation.

1.7.1.2 The quality of the evidence

A single, retrospective study, which consisted of a review of medical records, was included in this review and covered the severe valve disease group, consisting of people with severe asymptomatic aortic stenosis. Two outcomes were extracted from the study and both were rated as very low quality evidence, being downgraded for risk of bias, indirectness and imprecision. Indirectness was due to the limitations highlighted below in terms of the definition of monitoring in the non-adherent group.

No relevant studies were identified for the following populations: mild valve disease and moderate valve disease.

This study compared outcomes between a group that adhered to existing guidelines and a group that did not. This study was limited as there was no definition of the level of the monitoring that the non-adherent group actually received and it was unclear whether they were followed up less often, more often or were followed up at the same frequency as the adherent group but the methods used for monitoring did not meet the criteria specified in the guidelines. In addition, in the adherent group the frequency of monitoring varied between participants with 12±6 months being reported for the group.

Further limitations associated with this study concern adjustment for confounders. The protocol specified that any non-randomised studies included should have adjusted outcomes for two key confounders for aortic stenosis: coronary artery disease and aortopathy. Although the proportion in each group with coronary artery disease was reported to be similar in both groups, aortopathy was not mentioned and it is unclear whether this may have differed between the groups. For the all-cause mortality outcome, an adjusted value including coronary artery disease as a covariate was provided. For the heart failure hospitalisation outcome, an adjusted value was not provided, but this outcome was still included in the review as the proportion with coronary artery disease at baseline was similar between the groups and there was no other evidence available. As mentioned, both of these outcomes were not adjusted for aortopathy and it is unclear whether this factor may have differed between the groups. Due to a lack of other available evidence these outcomes were included in the review despite this, but this contributed to the decision to downgrade the outcomes for indirectness.

Additionally, though an absolute effect for the 6 month time-point (as pre-specified for severe valve disease in the protocol) was obtained from the study for the heart failure hospitalisation outcome using the reported hazard ratio and control group risk at 6 months from the survival curve, the same could not be done for the mortality outcome due to there being zero events for this outcome in the control group at 6 months. Therefore, for the all-cause mortality outcome a time-point of 1 year was used. The study reported the control group risk at the 4 year time-point for mortality and this could also be obtained from the survival curve for the heart failure hospitalisation outcome; however, these were not used as this was a much longer follow-up than the 6 month time-point specified in the protocol for severe valve disease.

One factor that was substantially different between the groups during the follow-up was the number of patients in each group that received surgical or catheter-based aortic valve replacement – this was higher in the guideline adherent group compared with the guideline non-adherent group (54 vs. 19.4%) and may have contributed to differences in outcomes. The committee agreed that this may have been the case, as with an enhanced monitoring strategy those requiring intervention could be picked up sooner and intervention performed to improve patient outcomes and prevent deterioration. This was taken into account in the risk of bias assessment for both outcomes and contributed to the overall grading of high or very high risk of bias.

The quality of the evidence identified and the other limitations described in the benefits and harms section below meant that although the included study was taken into account when making the recommendation, the recommendation made was largely based on the clinical experience of the committee and was considered to be in line with current practice. This meant that an offer recommendation was agreed to be appropriate. Although the only evidence identified was in the asymptomatic severe aortic stenosis population, the committee agreed it was appropriate to extrapolate the recommendation to cover any type of asymptomatic severe valve disease.

1.7.1.3 Benefits and harms

The study included in this review compared the outcomes of a guideline adherent group with a guideline non-adherent group in people with asymptomatic severe aortic stenosis by retrospective review of medical records. Of the two outcomes that were reported (all-cause mortality and heart failure hospitalisation), both demonstrated fewer events in the guideline adherent group compared with the guideline non-adherent group based on absolute differences calculated at 6 (heart failure hospitalisation) or 12 months (all-cause mortality), with a clinically important benefit identified for all-cause mortality. Although there was uncertainty in terms of the size of the effect based on the confidence intervals, confidence intervals were quite narrow and were also consistent with reduced events in the guideline adherent group compared with the non-adherent group. No data were available for the following outcomes for the severe asymptomatic aortic stenosis population: cardiac mortality, health-related quality of life and new-onset atrial fibrillation.

The committee agreed that the evidence available was very limited to be able to inform recommendations. They noted the limitations associated with the single study identified, including the lack of definition of the guideline non-adherent group and the fact that monitoring frequency varied between patients in the guideline adherent group. In addition, the committee also highlighted that this study was performed in the USA, where medical insurance is required to cover costs of medical care. They agreed that the requirement for medical insurance means each follow-up appointment represents a further cost to those that are not insured and may affect the premiums of those that claim for these tests on insurance

policies, which may deter people from going if they feel well. The committee highlighted that this makes the study less applicable to the system in the UK.

The committee agreed that despite the limitations, the results of the study made sense, as enhanced monitoring may allow those requiring intervention to be picked up sooner and have intervention to prevent negative outcomes, such as mortality and hospitalisation for heart failure, occurring. However, they noted that there could be an association between being sicker, including having more severe disease or in terms of general health, and being in the guideline non-adherent group, due to the study being non-randomised and not adjusting for such confounders.

In terms of current practice, this was considered to be variable for the asymptomatic severe aortic stenosis population. Currently, frequency of follow-up was considered to be between 6 and 12 months for this group, with this depending on how well the patient was considered to be and also patient preferences. The committee agreed that those that were thought to be particularly unwell may be followed-up more often, every 6 months, whereas most would be followed up every 12 months. The committee explained that the rationale for the current frequency of follow-up in this population was that the rate of progression of the consequences of severe aortic stenosis or the rate at which symptoms develop usually involves a decline over a period of months rather than years, and longer periods between follow-ups would mean negative outcomes occur before the next follow-up in many cases.

Therefore, although the included study did inform the recommendation to a certain extent, it was mostly based on current practice for this population and the committee's experience due to the limitations with the included study. The committee noted that echocardiography had been a required component in the guideline adherent group of the included study and in order to assess possible need for intervention at each follow-up should be performed.

In addition, the committee highlighted that the proposed monitoring strategy for the asymptomatic severe heart valve disease population is relevant to those in whom an intervention may be considered in the future. In those that are too frail for intervention to be considered at all in the future, the committee noted that follow-up may differ for this group.

The committee therefore made a consensus recommendation that people with severe asymptomatic heart valve disease, who may be suitable for future intervention, be followed up every 6-12 months by clinical review and echocardiography. The committee agreed that the exact frequency of monitoring within the 6- to 12-month timeframe should be determined by echocardiography results and shared decision making with the patient. Although the only evidence identified was in the asymptomatic severe aortic stenosis population, the committee agreed it was appropriate to extrapolate the recommendation to cover any type of asymptomatic severe valve disease.

No evidence was identified for any mild or moderate valve disease. Consensus recommendations could not be made for mild or moderate valve disease as there was considered to be more variation in practice for these populations and the recommendation for asymptomatic severe heart valve disease could not be extrapolated to cover these populations as the difference in severity means they are different in terms of the extent of follow-up required. It was therefore agreed that research recommendations would be made to cover these areas, which included asymptomatic mild or moderate valve disease (see Appendix J.1 for details) and symptomatic moderate valve disease (see Appendix J.2.1 for details) , as well as further research recommendations for severe asymptomatic valve disease due to the limitations discussed with the single included study for this population (see Appendix J.3.1 for details).

Evidence from expert testimony to cover the population of pregnant women or women of childbearing age indicated that monitoring of pregnant women may be different in terms of the frequency and type of monitoring required, which is covered by a recommendation

discussed in evidence review A about referring to a cardiologist with expertise in the care of pregnant women if they have moderate or severe valve disease, bicuspid aortic valve disease of any severity and associated aortopathy, or a mechanical prosthetic valve.

1.7.2 Cost effectiveness and resource use

No health economic evidence was identified for this question.

The committee made a strong consensus recommendation for an enhanced monitoring strategy for the asymptomatic severe heart valve disease group who may be suitable for future intervention. Although the cost effectiveness is uncertain, monitoring of this group is crucial to treatment because it enables identification of those patients for whom surgery is most timely, leading to improved survival and quality of life.

The committee noted that this recommendation was in line with current practice where follow-up was considered every 12 months, where the patient's health is considered stable, or 6 months, where there is concern about the patient's health deteriorating. This means there should not be a resource impact.

1.8 Recommendations supported by this evidence review

This evidence review supports recommendation 1.4.1 and 3 research recommendations on monitoring where there is no current need for intervention.

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Appendices

Appendix A: Review protocols

Table 5: Review protocol: Monitoring of people with heart valve disease and no current indication for intervention

ID	Field	Content
0.	PROSPERO registration number	CRD42020162805
1.	Review title	Clinical protocol for monitoring of people with heart valve disease and no current indication for intervention.
2.	Review question	Where there is no current indication for intervention, what is the most clinically and cost-effective type and frequency of test for monitoring in adults with heart valve disease?
3.	Objective	To establish how often and with what test people with heart valve disease and no current indication for intervention should be assessed to determine the right timing for intervention before they have any major events. Current practice is to use echocardiography for follow-up but the frequency varies. The aim is to determine the optimal frequency of echo and whether any additional tests provide benefit in specific groups.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.

		The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Diagnosed heart valve disease in adults aged 18 years and over: Aortic (including bicuspid) stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation.
6.	Population	Inclusion: Adults aged 18 years and over with diagnosed heart valve disease and no current indication for intervention, stratified by the severity of valve disease as follows: • Mild • Moderate • Severe *Severity assessed by echo and rated as per* The British Society of Echocardiography. Other definitions will be accepted and downgrade for indirectness if appropriate. Exclusion: Children aged less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease. People who have had prior heart valve repair or replacement (transcatheter or surgical).
7.	Intervention/ Test	Any of the following assessment strategies used for monitoring purposes, followed by appropriate valve intervention, in the specified population: Biomarkers (alone or in combination with echo): • BNP (B-type natriuretic peptide) • NT-proBNP (N-terminal prohormone brain natriuretic peptide) Imaging: • Echocardiography • CT (alone or in combination with echo) • CMR (cardiovascular magnetic resonance; alone or in combination with echo) Patient reported outcome measures (PROMS; alone or in combination with echo), including:

		• EuroQol • Minnesota Living With Heart Failure Questionnaire (MLHFQ) • Veterans Specific Activity Questionnaire Other methods: • Electrocardiogram (ECG) (alone or in combination with echo) • Clinical review only (no specific tests performed, as defined by the study authors) • Exercise testing (for example Bruce protocol; alone or in combination with echo) Different frequencies of the tests used for monitoring will be considered as separate interventions. Therefore, we will include studies comparing different frequencies of the same or different interventions. Frequency will be categorised into the following groups: • More frequently than once a year (e.g. every 3 or 6 months) • Once a year • Less frequently than once a year (e.g. every 2, 3 or 5 years) Each monitoring test is a different strata and each frequency is a sub-analysis for each test.
8.	Comparator/Reference standard/Confounding factors	Other active comparator listed above No monitoring (for example, tests only performed if new symptoms emerge/symptoms worsen)
9.	Types of study to be included	Randomised controlled trials (RCTs) and systematic reviews of RCTs. Published NMAs and IPDs will be considered for inclusion. If insufficient[a] evidence is found from RCTs, non-randomised studies will be considered for inclusion. Important confounders NRS must be adjusted for:

[a] This will be assessed for each intervention separately. There is no strict definition, but in discussion with the GC we will consider whether we have enough to form the basis for a recommendation (e.g., one large well-conducted RCT, or more than one small RCTs).

		• Coronary artery disease • Aortopathy in aortic valve disease
10.	Other exclusion criteria	Exclusion criteria: • Non-English language studies • Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
11.	Context	Current practice is to follow people up using echocardiography to monitor whether intervention has become necessary. However, the frequency of follow up is inconsistent across the country and other modalities of follow up are also being variably used.
12.	Primary outcomes (critical outcomes)	• All-cause mortality • Cardiac mortality • Health-related quality of life (any validated measure) • Hospitalisation for heart failure or other cardiac reason (e.g., for syncope in severe AS) If data are available, follow-up will be reported as a first preference at: • 12 months for mild and moderate valve disease • 6 months for severe valve disease. Where multiple time-points are reported within a single study, only the time-point closest to that stated above will be extracted.
13.	Secondary outcomes (important outcomes)	• New-onset atrial fibrillation If data are available, follow-up will be reported as a first preference at: • 12 months for mild and moderate valve disease • 6 months for severe valve disease. Where multiple time-points are reported within a single study, only the time-point closest to that stated above will be extracted.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The

		full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. An in-house developed database, EviBASE, will be used for data extraction and quality assessment of clinical studies. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Checklists used in this intervention review are as follows for different types of study design: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non-randomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and

		95% confidence intervals will be calculated for each outcome. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis. A second reviewer will quality assure 10% of the data analyses. Discrepancies will be identified and resolved through discussion (with a third party where necessary).	
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Type of valve disease: aortic stenosis (bicuspid), aortic stenosis (non-bicuspid/calcific), aortic regurgitation (including bicuspid and non-bicuspid), mitral stenosis, mitral regurgitation, tricuspid regurgitation • Coronary artery disease • Aortopathy in aortic valve disease Studies will be assigned to different subgroups using a threshold of 75%.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic

		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	09/05/2019	
22.	Anticipated completion date	17/06/2021	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☑ / ☑
		Piloting of the study selection process	☑ / ☑
		Formal screening of search results against eligibility criteria	☑ / ☑
		Data extraction	☑ / ☑
		Risk of bias (quality) assessment	☑ / ☑
		Data analysis	☑ / ☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail HVD@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre	
25.	Review team members	From the National Guideline Centre: Sharon Swain [Guideline lead] Eleanor Samarasekera [Senior systematic reviewer] Nicole Downes [Systematic reviewer]	

		George Wood [Systematic reviewer] Robert King [Health economist] Jill Cobb [Information specialist] Katie Broomfield [Project manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10122
29.	Other registration details	None
30.	Reference/URL for published protocol	N/A
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Aortic regurgitation; aortic stenosis; heart valve disease; intervention; mitral regurgitation; mitral

		stenosis; monitoring; monitoring frequency; tricuspid regurgitation	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[49] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.

- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2004 or later that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'.
- Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

Heart valve disease – search strategy 11 - monitoring of people with heart valve disease and no current indication for intervention AND monitoring in people with repaired or replaced heart valves

This literature search strategy was used for the following reviews:

- Where there is no current indication for intervention, what is the most clinically and cost-effective type and frequency of test for monitoring in adults with heart valve disease?
- What is the most clinically and cost-effective frequency of echocardiography or clinical review for monitoring in adults with repaired or replaced heart valves?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[49]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 10 of 12 CENTRAL to 2020 Issue 10 of 12	None

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	Heart Valve Prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp Heart Murmurs/

12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter/
15.	editorial/
16.	news/
17.	exp historical article/
18.	Anecdotes as Topic/
19.	comment/
20.	case report/
21.	(letter or comment*).ti.
22.	or/14-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animals/ not humans/
26.	exp Animals, Laboratory/
27.	exp Animal Experimentation/
28.	exp Models, Animal/
29.	exp Rodentia/
30.	(rat or rats or mouse or mice).ti.
31.	or/24-30
32.	13 not 31
33.	limit 32 to English language
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	exp Natriuretic Peptide, Brain/
37.	Biomarker*.ti,ab.
38.	((brain or b-type) adj2 natriuretic peptide*).ti,ab.
39.	(bnp or nt-probnp or nt-pro bnp or nt-bnp).ti,ab.
40.	exp Echocardiography/
41.	(Echo* or transoesophageal or transesophageal or transthoracic or TOE or TEE or TTE).ti,ab.
42.	exp Electrocardiography/
43.	(electrocardio* or ECG or EKG).ti,ab.
44.	exp Tomography, X-Ray computed/
45.	(comput* adj2 tomograp*).ti,ab.
46.	(CT adj3 (cine or CAT or scan* or x ray* or xray* or imag*)).ti,ab.
47.	exp Magnetic Resonance Imaging/
48.	((magnetic or nuclear) adj2 resonance adj3 imag*).ti,ab.
49.	((cardiac or cardiovascular) adj mr).ti,ab.
50.	(mri* or nmr* or cmr*).ti,ab.
51.	patient reported outcome measures/
52.	("patient reported outcome measures" or PROM*).ti,ab.
53.	(euroqol* or eq5d* or eq 5*).ti,ab.
54.	("minnesota living with heart failure questionnaire" or MLHFQ or MLWHF).ti,ab.

55.	("Veterans Specific Activity Questionnaire" or VSAQ).ti,ab.
56.	(clinic* adj2 (assess* or general or special* or valve* or monitor* or examin*)).ti,ab.
57.	Exercise tolerance/ or Exercise Test/
58.	((physical* or exercise* or fitness) adj5 (fit* or train* or therap* or activ* or strength or endur* or exert* or capacit* or tolera* or test*)).ti,ab.
59.	(stress test adj2 (cardiac or ECG)).ti,ab.
60.	bruce protocol.ti,ab.
61.	or/36-60
62.	Meta-Analysis/
63.	exp Meta-Analysis as Topic/
64.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
65.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
66.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
67.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
68.	(search* adj4 literature).ab.
69.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
70.	cochrane.jw.
71.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
72.	or/62-71
73.	randomized controlled trial.pt.
74.	controlled clinical trial.pt.
75.	randomi#ed.ti,ab.
76.	placebo.ab.
77.	randomly.ti,ab.
78.	Clinical Trials as topic.sh.
79.	trial.ti.
80.	or/73-79
81.	Epidemiologic studies/
82.	Observational study/
83.	exp Cohort studies/
84.	(cohort adj (study or studies or analys* or data)).ti,ab.
85.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
86.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
87.	Controlled Before-After Studies/
88.	Historically Controlled Study/
89.	Interrupted Time Series Analysis/
90.	(before adj2 after adj2 (study or studies or data)).ti,ab.
91.	or/81-90
92.	35 and 61 and (72 or 80 or 91)

Embase (Ovid) search terms

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	exp brain natriuretic peptide/
35.	Biomarker*.ti,ab.
36.	((brain or b-type) adj2 natriuretic peptide*).ti,ab.
37.	(bnp or nt-probnp or nt-pro bnp or nt-bnp).ti,ab.
38.	exp Echocardiography/
39.	(Echo* or transoesophageal or transesophageal or transthoracic or TOE or TEE or TTE).ti,ab.
40.	exp electrocardiography/

41.	(electrocardio* or ECG or EKG).ti,ab.
42.	exp x-ray computed tomography/
43.	(comput* adj2 tomograp*).ti,ab.
44.	(CT adj3 (cine or CAT or scan* or x ray* or xray* or imag*)).ti,ab.
45.	exp nuclear magnetic resonance imaging/
46.	((magnetic or nuclear) adj2 resonance adj3 imag*).ti,ab.
47.	((cardiac or cardiovascular) adj mr).ti,ab.
48.	(mri* or nmr* or cmr*).ti,ab.
49.	exp patient-reported outcome/
50.	("patient reported outcome measure*" or PROM*).ti,ab.
51.	(euroqol* or eq5d* or eq 5*).ti,ab.
52.	("minnesota living with heart failure questionnaire" or MLHFQ or MLWHF).ti,ab.
53.	("Veterans Specific Activity Questionnaire" or VSAQ).ti,ab.
54.	(clinic* adj2 (assess* or general or special* or valve* or monitor* or examin*)).ti,ab.
55.	Exercise tolerance/ or Exercise Test/
56.	((physical* or exercise* or fitness) adj5 (fit* or train* or therap* or activ* or strength or endur* or exert* or capacit* or tolera* or test*)).ti,ab.
57.	(stress test adj2 (cardiac or ECG)).ti,ab.
58.	bruce protocol.ti,ab.
59.	or/34-58
60.	systematic review/
61.	meta-analysis/
62.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
63.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
64.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
65.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
66.	(search* adj4 literature).ab.
67.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
68.	cochrane.jw.
69.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
70.	or/60-69
71.	random*.ti,ab.
72.	factorial*.ti,ab.
73.	(crossover* or cross over*).ti,ab.
74.	((doubl* or singl*) adj blind*).ti,ab.
75.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
76.	crossover procedure/
77.	single blind procedure/
78.	randomized controlled trial/
79.	double blind procedure/
80.	or/71-79
81.	Clinical study/

82.	Observational study/
83.	family study/
84.	longitudinal study/
85.	retrospective study/
86.	prospective study/
87.	cohort analysis/
88.	follow-up/
89.	cohort*.ti,ab.
90.	88 and 89
91.	(cohort adj (study or studies or analys* or data)).ti,ab.
92.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
93.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
94.	(before adj2 after adj2 (study or studies or data)).ti,ab.
95.	or/81-87,90-94
96.	33 and 59 and (70 or 80 or 95)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Heart Valve Diseases] explode all trees
#2.	MeSH descriptor: [Heart Valves] explode all trees
#3.	((primary or secondary) NEXT valv* disease*):ti,ab
#4.	((valv* or flap* or leaflet*) near/1 (heart or cardiac) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab
#5.	((mitral or aortic or tricuspid or pulmon*) NEXT (valv* or flap* or leaflet*) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab
#6.	((mitral or aortic or tricuspid or pulmon*) NEAR/3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)):ti,ab
#7.	MeSH descriptor: [Heart Valve Prosthesis] explode all trees
#8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) NEXT (valv* or flap* or leaflet*)):ti,ab
#9.	valve-in-valve:ti,ab
#10.	(transcatheter NEAR/2 (valve or valves)):ti,ab
#11.	MeSH descriptor: [Heart Murmurs] explode all trees
#12.	((heart or cardiac) NEXT murmur*):ti,ab
#13.	(or #1-#12)
#14.	MeSH descriptor: [Natriuretic Peptide, Brain] explode all trees
#15.	Biomarker*:ti,ab
#16.	((brain or b-type) near/2 natriuretic peptide*):ti,ab
#17.	(bnp or nt-probnp or nt-pro bnp or nt-bnp):ti,ab
#18.	MeSH descriptor: [Echocardiography] explode all trees
#19.	(electrocardio* or ECG or EKG):ti,ab
#20.	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
#21.	(comput* near/2 tomograp*):ti,ab
#22.	(CT near/3 (cine or CAT or scan* or x ray* or xray* or imag*)):ti,ab

#23.	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#24.	((magnetic or nuclear) near/2 resonance near/3 imag*):ti,ab
#25.	((cardiac or cardiovascular) near/1 mr):ti,ab
#26.	(mri* or nmr* or cmr*):ti,ab
#27.	MeSH descriptor: [Patient Reported Outcome Measures] explode all trees
#28.	("patient reported outcome measures" or PROM).ti,ab
#29.	(euroqol* or eq5d* or eq 5*):ti,ab
#30.	("minnesota living with heart failure questionnaire" or MLHFQ or MLWHF):ti,ab
#31.	("Veterans Specific Activity Questionnaire" or VSAQ).ti,ab
#32.	(clinic* near/2 (assess* or general or special* or valve or monitor* or examin*)):ti,ab
#33.	MeSH descriptor: [Exercise Tolerance] explode all trees
#34.	MeSH descriptor: [Exercise Test] explode all trees
#35.	((physical* or exercise* or fitness) near/5 (fit* or train* or therap* or activ* or strength or endur* or exert* or capacit* or tolera* or test*)):ti,ab
#36.	("stress test" near/2 (cardiac or ECG)):ti,ab
#37.	bruce protocol:ti,ab
#38.	(OR #14-#37)
#39.	#13 and #38

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to heart valve disease population in NHS Economic Evaluation Database (NHS EED) – (this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) – (this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Embase	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.

6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	Heart Valve Prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp Heart Murmurs/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter/
15.	editorial/
16.	news/
17.	exp historical article/
18.	Anecdotes as Topic/
19.	comment/
20.	case report/
21.	(letter or comment*).ti.
22.	or/14-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animals/ not humans/
26.	exp Animals, Laboratory/
27.	exp Animal Experimentation/
28.	exp Models, Animal/
29.	exp Rodentia/
30.	(rat or rats or mouse or mice).ti.
31.	or/24-30
32.	13 not 31
33.	limit 32 to English language
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	Economics/
37.	Value of life/
38.	exp "Costs and Cost Analysis"/
39.	exp Economics, Hospital/
40.	exp Economics, Medical/
41.	Economics, Nursing/
42.	Economics, Pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp Budgets/

45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/36-51
53.	35 and 52

Embase (Ovid) search terms

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.

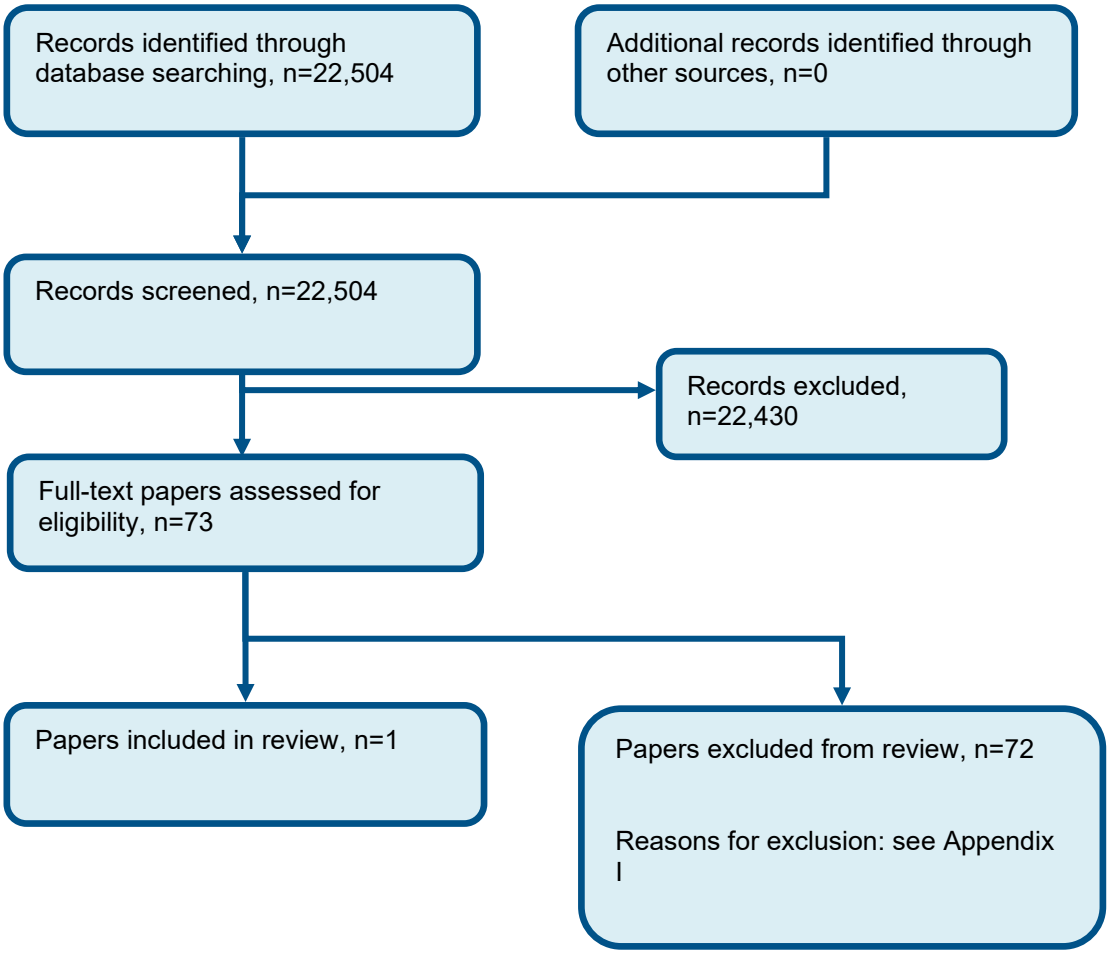
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Heart Valve Diseases EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Heart Valves EXPLODE ALL TREES
#3.	(((primary or secondary) adj Valv* adj disease*))
#4.	(((valv* or flap* or leaflet*) adj (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#5.	((heart or cardiac) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*))
#6.	(((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#7.	(((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)))
#8.	MeSH DESCRIPTOR Heart Valve Prosthesis EXPLODE ALL TREES
#9.	(((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)))
#10.	(valve-in-valve)
#11.	((transcatheter adj2 (valve or valves)))
#12.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of monitoring of people with heart valve disease and no current indication for intervention



Appendix D: Clinical evidence tables

Study	**Ahmed 2017[1]**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=300)
Countries and setting	Conducted in USA; Setting: Mixed - retrospective review of medical records
Line of therapy	Not applicable
Duration of study	Other: Medical records reviewed from 25th July 2007 to 6th December 2012
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed according to current practice guidelines
Stratum	Severe: All have severe asymptomatic aortic stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥18 years; severe aortic stenosis according to current practice guidelines; asymptomatic status, defined as absence of dyspnoea, angina, presyncope and syncope; no prior catheter or surgical aortic valve intervention; no indication for cardiac surgery; and clinical evaluation before 31st December 2012 to enable adequate follow-up duration.
Exclusion criteria	Not reported.
Recruitment/selection of patients	Retrospective review of medical records between 25th July 2007 and 6th December 2012

Age, gender and ethnicity	Age - Mean (SD): Guidelines adherent, 78 (11.6) years; guidelines non-adherent, 79.8 (11.3) years. Gender (M:F): Guidelines adherent, 100/102; guidelines non-adherent, 43/55. Ethnicity: White, 98%; African American, 1.3%; Unknown, 0.7%
Further population details	1. Aortopathy in aortic valve disease: Not stated / Unclear (Not reported). 2. Coronary artery disease: Not stated / Unclear (Mixed - 47.7% with coronary artery disease in the population). 3. Type of valve disease: aortic stenosis (non-bicuspid/calcific) (Note no mention of any with bicuspid/congenital disease but does not state they were excluded either. Based on mean age have classified as non-bicuspid as calcific more commonly affects older people).
Extra comments	Note following factors are written as guideline adherent vs. non-adherent group. Hypertension, 87.6 vs. 84.7%; hyperlipidaemia, 59.4 vs. 48%; diabetes, 27.7 vs. 21.4%; chronic obstructive pulmonary disease, 15.4 vs. 15.3%; malignant neoplasm, 9.9 vs. 8.2%; coronary artery disease, 47.5 vs. 48%; peripheral vascular disease, 14.4 vs. 15.3%; sleep apnoea, 14.9 vs. 15.3%; previous stroke/TIA, 10.4 vs. 8.2%; previous percutaneous coronary intervention, 23.8 vs. 23.5%; previous myocardial infarction, 6.4 vs. 9.2%; previous coronary artery bypass grafting, 22.3 vs. 13.3%; previous sternotomy, 7.4 vs. 10.2%; implantable cardioverter defibrillator, 5.5 vs. 4.1%; permanent pacemaker, 9.4 vs. 13.3%; moderate aortic regurgitation, 16.5 vs. 11%; severe aortic regurgitation, 0.5 vs. 0%; moderate mitral regurgitation, 21.8 vs. 17.7%; severe mitral regurgitation, 2.5% vs. 5.2%%; moderate tricuspid regurgitation, 10.3 vs. 18.8%; severe tricuspid regurgitation, 6.7 vs. 9.4%; median (IQR) creatinine level, 1.06 (0.45) vs. 1.02 (0.41) mg/dL; mean (SD) LVEF, 60 (10) vs. 60 (15)%; mean (SD) STS Mortality Risk score, 3.2 (3.3) vs. 3.3 (2.8); mean (SD) STS Mortality or Morbidity Risk score, 18.8 (10.5) vs. 18.3 (8.4); mean (SD) end-diastolic dimension, 4.5 (1) vs. 4.3 (1) cm; mean (SD) end-systolic dimension, 3 (1.1) vs. 2.9 (1.2) cm; mean (SD) septal wall thickness, 1.3 (0.3) vs. 1.3 (0.5) cm; mean (SD) posterior wall thickness, 1.2 (0.3) vs. 1.2 (0.3) cm; mean (SD) peak aortic velocity, 4 (0.9) vs. 3.9 (1) m/s; mean (SD) integral-derived aortic valve area, 0.78 (0.2) vs. 0.80 (0.29) cm^2; mean (SD) dimensionless index, 0.23 (0.06) vs. 0.22 (0.1); mean (SD) aortic gradient, 37.5 (15.3) vs. 36.1 (16.4) mmHg; mean (SD) cardiac output, 4.9 (17) vs. 4.5 (2) L/min; mean (SD) left atrial volume, 43 (23.5) vs. 43 (27.2) ml; mean (SD) left atrial dimension, 43 (9) vs. 41 (10) mm.
Indirectness of population	No indirectness
Interventions	(n=202) Intervention 1: Imaging - Echocardiography every 12 months. Guideline adherence - defined as serial evaluation occurring every 12 (±6) months until aortic valve replacement or death during the follow-up. Appropriate serial evaluations required the following to be performed: comprehensive clinical evaluation that included description of presence or absence of cardiac symptoms; cardiopulmonary physical examination; and 2D and Doppler echocardiogram including assessment of left ventricular function and the haemodynamic severity of aortic stenosis, with

	documentation of the aortic valve area and either the peak aortic velocity or mean aortic valve gradient. Duration NA. Concurrent medication/care: Not reported. Indirectness: Serious indirectness; Indirectness comment: Monitoring every 12 (+/- 6) months - may not be every 12 months in all cases (n=98) Intervention 2: Imaging - Echocardiography less often than every 12 months. No definition for guideline non-adherence provided - could include those receiving follow-up with all required components more often than every 12 (±6) months, those receiving follow-up with all required components less often than every 12 (±6) months and also those receiving follow-up within 12 (±6) months but without all of the required components (comprehensive clinical review, cardiopulmonary physical examination and 2D and Doppler echocardiogram, as defined for the other group). Duration NA. Concurrent medication/care: Not reported. Indirectness: Serious indirectness; Indirectness comment: No definition of this group in terms of how/when monitoring was performed. Could include follow-up performed more/less often than required by guidelines and also those where follow-up methods (clinical review, echocardiography and cardiopulmonary physical examination) inadequate but within guideline time frame
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUIDELINE ADHERENT GROUP - CLINICAL REVIEW + ECHOCARDIOGRAPHY EVERY 12 (+/- 6) MONTHS] versus GUIDELINE NON-ADHERENT GROUP - NO DETAILS OF MONITORING IN THIS GROUP

Protocol outcome 1: All-cause mortality at 12 months
- Actual outcome for Severe: All-cause mortality at Median (IQR) follow-up duration: 4.5 (2.8-6.5) years; Group 1: n=202 ; Group 2: n=98; HR 0.65; Lower CI 0.44 to Upper CI 0.96. The values reported in the paper (HR 1.54, 95% CI 1.04 to 2.29) were inverted in order to obtain the HR for the guideline adherent group vs. the non-adherent group; Test statistic: 0.03; Follow up details: Median (IQR) follow-up duration: 4.5 (2.8-6.5) years
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding/performance: care received during follow-up period not specified and could have differed between the groups - valve interventions differed substantially between the groups - 54 vs. 19.4%. ; Indirectness of outcome: Serious indirectness, Comments: Adjusted for various factors - including coronary artery disease but not including aortopathy. Unclear whether aortopathy was present within the population as no details provided; Baseline details: Comparable for most of listed factors, but larger differences for some (hyperlipidaemia, AF, previous CABG, moderate tricuspid regurgitation). One of pre-specified confounders adjusted for (coronary artery disease), but other (aortopathy) not mentioned in the study; Key confounders: Coronary artery disease, aortopathy; Group 1 Number missing: no dropouts/missing data reported; Group 2 Number missing: no dropouts/missing data reported.

Protocol outcome 2: Hospitalisation for heart failure or other cardiac reason at 12 months
- Actual outcome for Severe: Hospitalisation for heart failure at Median (IQR) follow-up duration: 4.5 (2.8-6.5) years; Group 1: n=202 ; Group 2: n=98; HR

0.6; Lower CI 0.46 to Upper CI 0.79. The values reported in the paper (HR 1.66, 95% CI 1.27 to 2.18) were inverted in order to obtain the HR for the guideline adherent group vs. the non-adherent group; Test statistic: <0.001; Follow up details: Median (IQR) follow-up duration: 4.5 (2.8-6.5) years Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding/performance: care received during follow-up period not specified and could have differed between the groups. Valve interventions differed substantially between the groups - 54 vs. 19.4%. Measurement: retrospective review of medical records and no definition of outcome - could have been recorded differently for different patients in the database.; Indirectness of outcome: Serious indirectness, Comments: Outcome not adjusted for any baseline variables, though proportion with coronary artery disease at baseline was similar between groups. Aortopathy presence in the population not mentioned.; Baseline details: Comparable for most of listed factors, but larger differences for some (hyperlipidaemia, AF, previous CABG, moderate tricuspid regurgitation). One of pre-specified confounders (coronary artery disease) similar at baseline, but other (aortopathy) not mentioned in the study; Key confounders: Coronary artery disease, aortopathy; Group 1 Number missing: no dropouts/missing data reported; Group 2 Number missing: no dropouts/missing data reported.	
Protocol outcomes not reported by the study	All-cause mortality at 6 months; Cardiac mortality at 12 months; Cardiac mortality at 6 months; Quality of life at 6 months; Quality of life at 12 months; New-onset atrial fibrillation at 12 months; New-onset atrial fibrillation at 6 months

Appendix E: Forest plots

E.1 Mild heart valve disease

No evidence was identified for this stratum.

E.2 Moderate heart valve disease

No evidence was identified for this stratum.

E.3 Severe heart valve disease

E.3.1 Guideline adherent [clinical review + echocardiography every 12 (±6) months] vs. guideline non-adherent group

Figure 2: All-cause mortality – HR (adjusted)

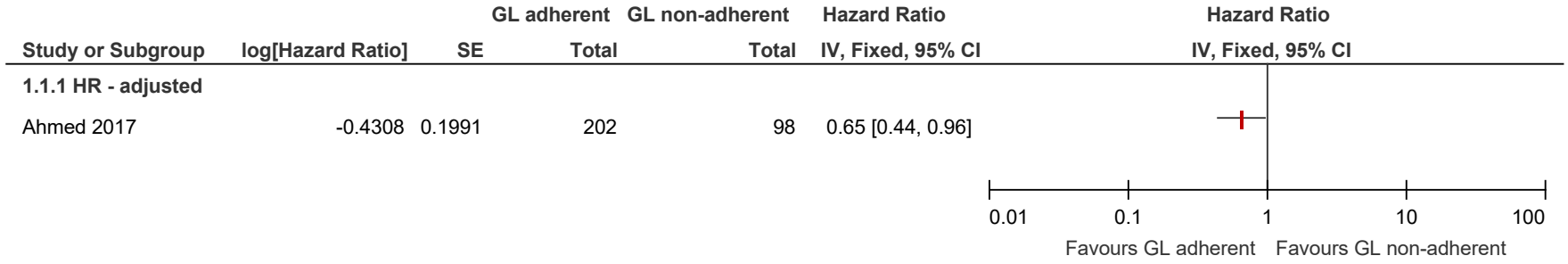
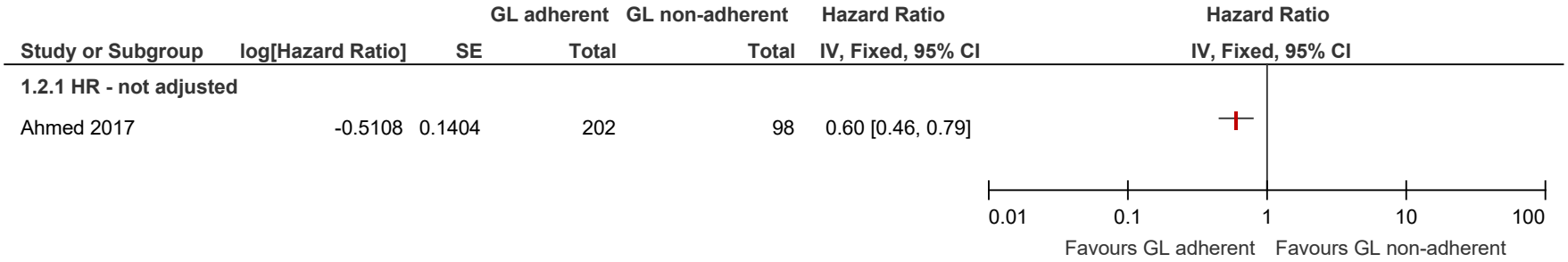


Figure 3: Hospitalisation for heart failure – HR (not adjusted)



Appendix F: GRADE tables

F.1 Mild heart valve disease

No evidence was identified for this stratum.

F.2 Moderate heart valve disease

No evidence was identified for this stratum.

F.3 Severe heart valve disease

Table 9: Clinical evidence profile: Guideline adherent [clinical review + echocardiography every 12 (±6) months] vs. guideline non-adherent group

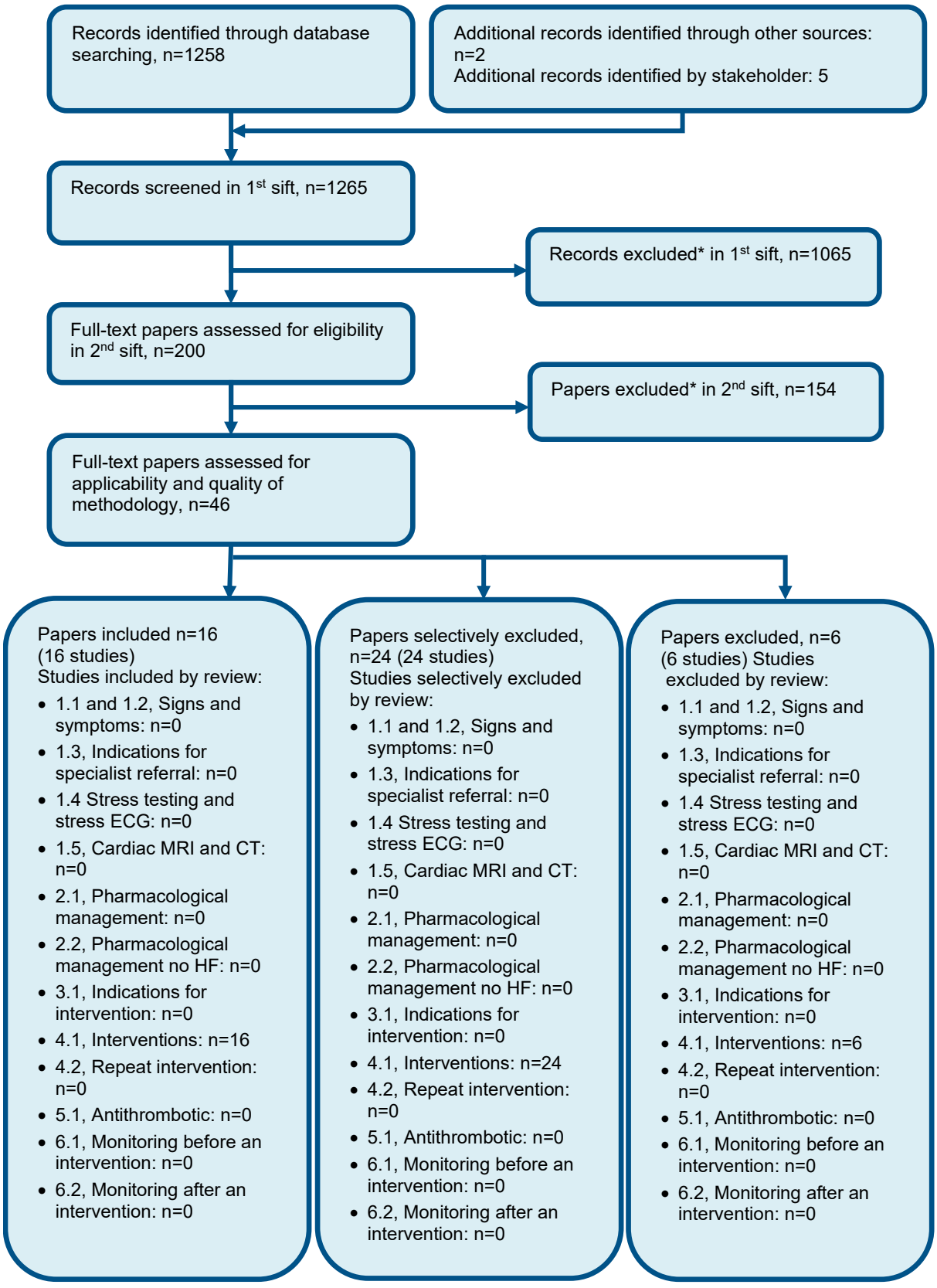
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guideline adherent group	guideline non-adherent group	Relative (95% CI)	Absolute		
All-cause mortality - HR (adjusted) 1 year (follow-up median 4.5 years)												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	2/202 (0.99%)	2/98 (2%)	HR 0.65 (0.44 to 0.96)[4]	7 fewer per 1000 (from 1 fewer to 11 fewer)[5]	⊕OOO VERY LOW	CRITICAL

Cardiac mortality												
0	No evidence available											CRITICAL
Health-related quality of life (any validated measure)												
0	No evidence available											CRITICAL
Heart failure hospitalisation - HR (not adjusted) 6 months (follow-up median 4.5 years)												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	9/202 (4.5%)	15/98 (15.3%)	HR 0.6 (0.46 to 0.79)[6]	58 fewer per 1000 (from 30 fewer to 79 fewer)[7]	⊕OOO VERY LOW	CRITICAL
New-onset atrial fibrillation												
0	No evidence available											IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment as the interventions and comparisons in this study were indirect compared with the protocol - monitoring in the guideline adherent group may not have been 12 months in all patients and monitoring in the guideline nonadherent group was not defined and could have included various different strategies. There was also no information about aortopathy in the study, one of the confounders listed in the protocol.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] The values reported in the paper (HR 1.54, 95% CI 1.04 to 2.29) were inverted in order to obtain the HR for the guideline adherent group vs. the non-adherent group to achieve the comparison of interest in the protocol
[5] Control group risk at 1 year from survival curve used. A larger benefit (100 fewer per 1000) was observed when the control group risk at 4 years was used; however, this was not included in the report as the 1-year time-point was closest to the time-point of 6 months specified in the protocol

[6] The values reported in the paper (HR 1.66, 95% CI 1.27 to 2.18) were inverted in order to obtain the HR for the guideline adherent group vs. the non-adherent group to achieve the comparison of interest in the protocol
[7] Control group risk at 6 months from survival curve used, A larger benefit (185 fewer per 1000) was observed when the control group risk at 4 years was used; however, this was not included in the report as the 1-year time-point was closest to the time-point of 6 months specified in the protocol

Appendix G: Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Alharthi 2008[2]	Incorrect study design: narrative review
Attizzani 2015[3]	Not review population
Avierinos 2002[4]	Inappropriate comparison. Incorrect interventions
Badoz 2016[5]	Inappropriate comparison. Incorrect interventions. No suitable outcomes
Bergler-Klein 2014[6]	Incorrect study design: narrative review
Bhavnani 2018[7]	Not guideline condition. Not review population
Binder 2013[8]	Not review population. Incorrect interventions
Bing 2019[9]	Incorrect study design : narrative review
Carreras 1988[10]	Not review population. Inappropriate comparison. Incorrect interventions
Casas-Rojo 2016[11]	Inappropriate comparison. Incorrect interventions
Cawley 2009[12]	Incorrect study design: narrative review
Chan 2015[13]	No suitable outcomes
Chieffo 2015[14]	Not review population. Inappropriate comparison. Incorrect interventions
Chodor 2017[15]	Not review population. Incorrect interventions
Cieslikowski 2007[16]	Incorrect interventions. Inappropriate comparison
Condado 2016[17]	Not review population. Incorrect interventions
Cornily 2010[18]	Not review population. Incorrect interventions
Cujec 1992[19]	Not review population. Incorrect interventions. Inappropriate comparison
Cupps 2003[20]	Inappropriate comparison. Incorrect interventions
Das 2003[21]	Incorrect study design: narrative review
Devereux 1989[23]	Incorrect study design: narrative review
Devereux 1994[22]	Incorrect study design: narrative review
Emerson 2015[24]	Not review population. Incorrect interventions
Eroglu 2006[25]	Not review population. Inappropriate comparison. Incorrect interventions
Ersboll 2015[26]	Inappropriate comparison. Incorrect interventions
Faletra 1996[27]	Inappropriate comparison. Incorrect interventions
Felmly 2017[28]	Not review population. Incorrect interventions
Finegold 2013[29]	Inappropriate comparison. Incorrect interventions
Frankis 1999[30]	Incorrect study design: narrative review
Gallo 2020[31]	Incorrect study design: narrative review
Genereux 2016[32]	Inappropriate comparison. Incorrect interventions
Goodman 2016[33]	Inappropriate comparison. Incorrect interventions

Study	Exclusion reason
Greve 2014[34]	Inappropriate comparison. Incorrect interventions
Harris 2017[35]	Inappropriate comparison. No suitable outcomes
Henri 2014[37]	Incorrect study design: narrative review
Henri 2016[36]	Inappropriate comparison. Incorrect interventions
Henry 1980[38]	Not review population. Inappropriate comparison. Incorrect interventions
Jansen 2013[39]	Inappropriate comparison. Incorrect interventions
Johl 2017[40]	Inappropriate comparison. Incorrect interventions
Kochanowski 2012[41]	Inappropriate comparison. Incorrect interventions
Krieger 2016[42]	No suitable outcomes
Lee 2007[44]	Incorrect study design: narrative review
Lee 2018[43]	No suitable outcomes
Lee 2018[45]	Not review population. Incorrect interventions
Magne 2014[46]	Incorrect study design: narrative review
Mutnuru 2016[47]	Incorrect interventions. Inappropriate comparison
Nchimi 2018[50]	Inappropriate comparison. Incorrect interventions
Oury 2018[52]	Incorrect study design: narrative review
Owen 2011[53]	Incorrect study design: narrative review
Oxorn 1996[54]	Incorrect study design: narrative review
Picano 2009[55]	Incorrect study design: narrative review
Prabhu 2009[56]	Incorrect study design: narrative review
Prior 2000[57]	No suitable outcomes
Quinones 1998[58]	Incorrect study design: narrative review
Redfors 2017[59]	Systematic review is not relevant to review question or unclear PICO
Shavelle 2007[60]	Incorrect study design: narrative review
Sherifi 2018[61]	Not review population. Inappropriate comparison. Incorrect interventions
Shub 1990[62]	Inappropriate comparison. Incorrect interventions
Stewart 2009[63]	Incorrect study design: narrative review
Suri 2011[64]	Inappropriate comparison. Incorrect interventions
Taggu 2009[65]	Inappropriate comparison. Incorrect interventions
Tang 2015[66]	Incorrect interventions. Inappropriate comparison
Tanguturi 2017[67]	Inappropriate comparison. Incorrect interventions
Tani 2000[68]	Not review population. Incorrect interventions. Inappropriate comparison
Tastet 2017[69]	Incorrect study design: narrative review
Trinh 2017[70]	Inappropriate comparison. Incorrect interventions
Trochu 2014[71]	Incorrect study design: narrative review
Velu 2019[72]	Not review population. Incorrect interventions. Inappropriate comparison
Wystub 2019[73]	Not review population. Inappropriate comparison. Incorrect interventions
Zaidi 2012[74]	Inappropriate comparison. No suitable outcomes. Incorrect interventions

Study	Exclusion reason
Zilberszac 2017[76]	Not review population. Incorrect interventions. Inappropriate comparison
Zilberszac 2018[75]	Incorrect interventions. Inappropriate comparison

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix J: Research recommendations

J.1 Asymptomatic mild or moderate heart valve disease

J.1.1 Research recommendation

What is the most clinically and cost-effective monitoring (type and frequency of test) for adults with asymptomatic mild or moderate heart valve disease (aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation) and no current need for intervention?

J.1.2 Why this is important

We do not have good data on how people with mild or moderate valve disease progress over time. Because we are unable to identify who is likely to progress, and over what time frame, many patients are followed up routinely every 12 months, in order to 'capture' those that progress more quickly and need closer monitoring. For some this may be too frequent (especially those with mild disease, for whom some may not need follow-u at all). For others, this may not be frequent enough. If we had good data on optimal monitoring periods for patients with mild and moderate valve disease, we could be much more efficient with follow-up approaches, targeting patients who need this most, while avoiding frequent follow-up in those who do not need it or need it less often.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	If we could determine how frequently patients need to be followed up, we could reduce the frequency of follow up for some patients, while maintaining an appropriate frequency of follow up to avoid missing important changes in others. In addition, if we could understand the best type of follow-up required - clinical review, echocardiography, blood tests or a combination - that would greatly facilitate optimal follow-up.
Relevance to NICE guidance	No evidence was found on people with mild to moderate heart valve disease. Research would support recommendations to be made on the type and frequency of monitoring.
Relevance to the NHS	Research in this area would inform NICE recommendations on the frequency and type of follow-up required for patients. If reduced follow-up frequency for some patients was shown to be as effective as more frequent follow-up, this would provide major advantages in resource use for the NHS (for example 2 yearly instead of annual follow up would halve the number of follow-up appointments needed). This would also free up resources for those who

	needed urgent assessment or more frequent follow-up.
National priorities	None known
Current evidence base	No relevant studies were identified mild valve disease and moderate valve disease. Monitoring of this group is crucial to treatment because it enables identification of those patients for whom surgery is most timely, leading to improved survival and quality of life.
Equality considerations	The frequency of follow-up impacts particularly on those who are working (generally younger ages, <65 years), and those with reduced mobility or poor access to transport, in whom less frequent follow-up is especially advantageous. In addition, for older patients if regular follow-up was shown to make no difference to outcomes (as they were unlikely to progress within their lifetime), this could result in no follow-up (discharge from clinic) for selected patients.

J.1.4 Modified PICO table

Population	Inclusion Adults aged 18 years and over with mild to moderate diagnosed heart valve disease and no current indication for intervention Severity assessed by echo and rated as per The British Society of Echocardiography Exclusion • Children aged less than 18 years. • Adults with congenital heart disease (apart from bicuspid aortic valves, which are included). • Tricuspid stenosis and pulmonary valve disease. • People who have had prior heart valve repair or replacement (transcatheter or surgical).
Intervention	Any of the following assessment strategies used for monitoring purposes, followed by appropriate valve intervention, in the specified population: Biomarkers (alone or in combination with echo): • BNP (B-type natriuretic peptide) • NT-proBNP (N-terminal prohormone brain natriuretic peptide) Imaging: • Echocardiography • CT (alone or in combination with echo)

	• CMR (cardiovascular magnetic resonance; alone or in combination with echo) Patient reported outcome measures (PROMS; alone or in combination with echo), including: • EuroQol • Minnesota Living With Heart Failure Questionnaire (MLHFQ) • Veterans Specific Activity Questionnaire Other methods: • Electrocardiogram (ECG) (alone or in combination with echo) • Clinical review only (no specific tests performed, as defined by the study authors) • Exercise testing (for example Bruce protocol; alone or in combination with echo)
Comparator	Other active comparator listed above No monitoring (for example, tests only performed if new symptoms emerge/symptoms worsen)
Outcome	Primary outcomes All-cause mortality; Cardiac mortality; Health-related quality of life (any validated measure) and Hospitalisation for heart failure or other cardiac reason (e.g., for syncope in severe AS) Secondary outcomes New-onset atrial fibrillation
Study design	Adequately powered randomised controlled trial (ideally)
Timeframe	Long term
Additional information	None

J.2 Symptomatic moderate heart valve disease

J.2.1 Research recommendation

What is the most clinically and cost-effective monitoring strategy (type and frequency of test) for adults with symptomatic moderate heart valve disease (aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation) and no current indication for intervention?

J.2.2 Why this is important

Currently, it is not widely considered that moderate heart valve disease is able to cause symptoms, as the heart usually copes adequately with moderate valve disease. It is usually

only severe heart valve disease that can cause symptoms such as breathlessness, when the heart is no longer able to compensate for the degree of valve disease. However, some patients with moderate valve disease have symptoms such as breathlessness, and it is not known whether this is due to the valve disease or other conditions. It is also not known whether this group of patients progresses to severe disease more quickly than patients with moderate valve disease but without symptoms. Understanding more about this group of patients, and in particular what frequency and form of assessment and follow-up results in better outcomes, would be important for aiding clinical management decisions.

J.2.3 Rationale for research recommendation

Importance to 'patients' or the population	If we could determine the optimal frequency and type of follow-up, and whether this should differ from asymptomatic patients with moderate heart valve disease, these patients could avoid unnecessary investigations or treatments, or may require more frequent follow-up to identify any decompensation early and avoid irreversible cardiac damage.
Relevance to NICE guidance	No evidence was found on people with mild or moderate heart valve disease. Research would support recommendations to be made on the type and frequency of monitoring, and whether this should differ from asymptomatic patients with moderate heart valve disease.
Relevance to the NHS	Research in this area would inform NICE recommendations on the frequency and type of follow-up required for patients. If more frequent or a different type of follow-up was shown to reduce the number of people presenting with late decompensated heart failure, this could improve the long term outcome for patients, by avoid irreversible cardiac damage. If patients with moderate heart valve disease and symptoms were shown to be no different from patients with asymptomatic moderate heart valve disease, the two groups of patients could be managed similarly.
National priorities	None known
Current evidence base	No relevant studies were identified on people who are symptomatic and have moderate heart valve disease with no current need for intervention, including aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation? Monitoring of this group is crucial to treatment because it enables identification of those patients for whom surgery is most timely, leading to improved survival and quality of life.
Equality considerations	None known

J.2.4 Modified PICO table

Population	Inclusion Adults aged 18 years and over who are symptomatic with moderate diagnosed heart valve disease and no current indication for intervention Severity assessed by echo and rated as per The British Society of Echocardiography Exclusion • Children aged less than 18 years. • Adults with congenital heart disease (excluding bicuspid aortic valves). • Tricuspid stenosis and pulmonary valve disease. • People who have had prior heart valve repair or replacement (transcatheter or surgical).
Intervention	Any of the following assessment strategies used for monitoring purposes, followed by appropriate valve intervention, in the specified population: Biomarkers (alone or in combination with echo): • BNP (B-type natriuretic peptide) • NT-proBNP (N-terminal prohormone brain natriuretic peptide) Imaging: • Echocardiography • CT (alone or in combination with echo) • CMR (cardiovascular magnetic resonance; alone or in combination with echo) Patient reported outcome measures (PROMS; alone or in combination with echo), including: • EuroQol • Minnesota Living With Heart Failure Questionnaire (MLHFQ) • Veterans Specific Activity Questionnaire Other methods: • Electrocardiogram (ECG) (alone or in combination with echo) • Clinical review only (no specific tests performed, as defined by the study authors) • Exercise testing (for example Bruce protocol; alone or in combination with echo)
Comparator	Other active comparator listed above No monitoring (for example, tests only performed if new symptoms emerge/symptoms worsen)

Outcome	Primary outcomes All-cause mortality; Cardiac mortality; Health-related quality of life (any validated measure) and Hospitalisation for heart failure or other cardiac reason (e.g., for syncope in severe AS) Secondary outcomes New-onset atrial fibrillation
Study design	Adequately powered randomised controlled trial (ideally)
Timeframe	Long term
Additional information	None

J.3 Asymptomatic severe heart valve disease

J.3.1 Research recommendation

What is the most clinically and cost-effective monitoring strategy (type and frequency of test) for adults with asymptomatic severe heart valve disease (aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation or tricuspid regurgitation) and no current indication for intervention?

J.3.2 Why this is important

Asymptomatic severe disease can progress to become symptomatic, or for reduced cardiac function to develop, indicating decompensation from the previously stable situation. This is associated with reduced prognosis, and these would be indications for surgery. There is divided opinion on how frequently and what type of monitoring would best capture patients soon after decompensation occurs, in order to avoid patients presenting late after decompensation (which can result in irreversible cardiac damage), while also avoiding inappropriately frequent follow-up.

J.3.3 Rationale for research recommendation

Importance to 'patients' or the population	If the optimal frequency and type of follow-up could be determined, this could result in timely surgery/intervention and would potentially avoid some patients developing irreversible cardiac dysfunction, while also avoiding unnecessarily frequent follow-up.
Relevance to NICE guidance	The evidence available was very limited to be able to inform recommendations. The committee noted the limitations associated with the single study identified, including the lack of definition of the guideline non-adherent group and the fact that monitoring frequency varied between patients in the guideline adherent group. In addition, the committee also highlighted that this

	study was performed in the USA, where medical insurance is required to cover costs of medical care. Evidence is needed on people with asymptomatic severe aortic regurgitation, mitral stenosis, mitral regurgitation or tricuspid regurgitation, as well as further evidence for the asymptomatic severe aortic stenosis population, and no current indication for intervention in order that stronger recommendations can be made.
Relevance to the NHS	Research in this area would inform NICE recommendations on the frequency and type of follow-up required for patients. If more frequent or a different type of follow-up was shown to reduce the number of people presenting with late decompensated heart failure, this could improve the long term outcome for patients, by avoid irreversible cardiac damage. If reduced follow-up frequency for some patients was shown to be as effective as more frequent follow-up, this would provide major advantages in resource use for the NHS. This would also free up resources for those who needed urgent assessment or more frequent follow-up.
National priorities	None known
Current evidence base	A single, retrospective study, which consisted of a review of medical records, was included in this review and covered the severe valve disease group, consisting of people with severe asymptomatic aortic stenosis. This study compared outcomes between a group that adhered to existing guidelines and a group that did not. This study was limited as there was no definition of the level of the monitoring that the non-adherent group actually received and it was unclear whether they were followed up less often, more often or were followed up at the same frequency as the adherent group but the methods used for monitoring did not meet the criteria specified in the guidelines. Further research is needed to determine the most clinically and cost effective type and frequency of monitoring.
Equality considerations	None known

J.3.4 Modified PICO table

Population	Inclusion Adults aged 18 years and over with diagnosed heart valve disease and no current indication for intervention with asymptomatic severe aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation or tricuspid regurgitation

	Severity assessed by echo and rated as per The British Society of Echocardiography Exclusion • Children aged less than 18 years. • Adults with congenital heart disease (excluding bicuspid aortic valves). • Tricuspid stenosis and pulmonary valve disease. • People who have had prior heart valve repair or replacement (transcatheter or surgical).
Intervention	Any of the following assessment strategies used for monitoring purposes, followed by appropriate valve intervention, in the specified population: Biomarkers (alone or in combination with echo): • BNP (B-type natriuretic peptide) • NT-proBNP (N-terminal prohormone brain natriuretic peptide) Imaging: • Echocardiography • CT (alone or in combination with echo) • CMR (cardiovascular magnetic resonance; alone or in combination with echo) Patient reported outcome measures (PROMS; alone or in combination with echo), including: • EuroQol • Minnesota Living With Heart Failure Questionnaire (MLHFQ) • Veterans Specific Activity Questionnaire Other methods: • Electrocardiogram (ECG) (alone or in combination with echo) • Clinical review only (no specific tests performed, as defined by the study authors) • Exercise testing (for example Bruce protocol; alone or in combination with echo)
Comparator	Other active comparator listed above No monitoring (for example, tests only performed if new symptoms emerge/symptoms worsen)
Outcome	Primary outcomes All-cause mortality; Cardiac mortality; Health-related quality of life (any validated measure) and Hospitalisation for heart failure or other cardiac reason (e.g., for syncope in severe AS) Secondary outcomes New-onset atrial fibrillation

Study design	Adequately powered randomised controlled trial (ideally)
Timeframe	Long term
Additional information	None