National Institute for Health and Care Excellence (NICE) guidance on heart valve disease

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ABSTRACT

The National Institute for Health and Care Excellence (NICE) guidelines are evidence-based recommendations for health and care in England. In late 2021, NICE published its first ever guidance on the investigation and management of adults with heart valve disease. This followed on from recent updates to the international societal practice guidelines on heart valve disease produced by the American College of Cardiology and American Heart Association (in 2020) and the European Society of Cardiology and European Association for Cardiothoracic Surgery (in 2021). The purpose of the NICE guidance has significant differences from societal guidelines, as NICE guidance is designed for implementation within the UK's taxpayer-funded National Health Service and thus must account not just for clinical effectiveness of treatments but cost-effectiveness also. This explains some of the differences between recent recommendations from these bodies, most notably in the treatment of patients with symptomatic severe aortic stenosis, in which NICE clearly explains that cost implications influenced their final guidance (which differs from the recently published European and North American guidelines). The aims of this review article are to provide an overview of the scope and recommendations of the NICE guideline and to compare and contrast the guidelines, highlighting reasons for differences between the guidance from professional societies and NICE and discussing the relative strengths and weaknesses of the NICE guideline.

INTRODUCTION

Clinical practice guidelines (CPGs) are now ubiquitous in all fields of clinical medicine. The Institute of Medicine defines guidelines as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances'.[1] Guidelines serve many purposes, but their ultimate aim is to improve patient care. Past studies have shown that adherence to best practice through CPGs improves patient outcomes.[2–4]

CPGs are relatively new in the field of valvular heart disease (VHD). Both the European and North American VHD guidelines are on only their fourth iteration—as illustrated in online supplementary figure 1; the first US guidance was published in 1998 while the first European Society of Cardiology (ESC) document on VHD did not emerge until 2007. The latest iterations of the European[5] and American[6] CPGs on VHD, as well as the first guidance from the UK's National Institute for Health and Care Excellence (NICE) on the investigation and management of adults with heart valve disease,[7] have been published within the past 24 months. Although each guideline was produced by appraisal of the scientific literature, the three documents reach different conclusions regarding certain recommendations. What accounts for these differences? Are current societal guidelines fit for purpose if the same evidence review produces differing conclusions? A recent editorial suggests not—'current cardiovascular society guidelines fall short of best practice. We can and must do better.'[8]

The aims of this review article are first to provide an overview of the NICE guidance, looking at the scope of the guidance and the methods used to derive their recommendations and second, to compare and contrast some key similarities and differences between the NICE and European/North American societal guideline recommendations.

SCOPE AND METHODOLOGY OF NICE GUIDANCE

The NICE guidance published in 2021 relates to diagnosis and management of patients with heart valve disease in adults. As a result, valve conditions usually seen in the congenital heart disease population (eg, pulmonary valve disease) are not covered by this guidance. Indeed, over the past two decades, NICE has separately published many documents related to specific interventional procedures on heart valves (see online supplemental table 1) and several of these are alluded to in the NICE guideline.

NICE publishes its methods document for development of each guideline that it produces. This methods chapter is produced in keeping with the NICE guidelines' manual.[9] The methods document clarifies the review questions for the guideline, the outcomes, the methods (with inclusion and exclusion criteria) for literature searches and data analysis, methods for determining risk of bias in studies and cost-effectiveness thresholds. At the outset of producing the guideline, NICE undertook a scoping exercise to ascertain exactly which questions the guideline should aim to answer. This scoping document[10] eventually led to the final list of 14 questions for the guideline committee to address (table 1).

Broadly speaking, the recommendations in the NICE guideline encompass the diagnosis, assessment, monitoring and treatment of adults with heart valve disease, as illustrated in figure 1. NICE provides recommendations on when to perform echocardiography in adults with suspected valve disease (eg, a heart murmur), specifies timelines if

Table 1 The list of 14 review questions for the NICE guidance to address that was produced following the scoping exercise (adapted from NICE guideline NG208 (2021—Heart Valve Disease Presenting in Adults: Investigation and Management. Available from www.nice.org.uk/guidance/ng208. All rights reserved))

Number	Review questions for the NICE heart valve disease guideline to address
1	In adults with suspected heart valve disease, what symptoms and signs indicate referral (for example, from primary care) for echocardiography?
2	In adults with suspected heart valve disease, what symptoms and signs indicate direct referral (for example, from primary care) to a specialist?
3	In adults who have had echocardiography, what are the indications for referral to a specialist?
4	In adults with heart failure and concomitant heart valve disease, what is the clinical and cost-effectiveness of ACE inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, calcium channel blockers, digoxin, diuretics and nitrates to improve clinical outcome?
5	In adults with heart valve disease without concomitant heart failure, what is the clinical and cost-effectiveness of ACE inhibitors, ARBs, alpha-blockers, beta-blockers, calcium channel blockers, digoxin, diuretics, statins and nitrates to improve clinical outcome?
6	What are the indications that interventions should be offered to adults with asymptomatic, severe heart valve disease?
7	In adults with heart valve disease, what is the prognostic value and cost-effectiveness of stress testing and stress echocardiography to determine the need for intervention?
8	In adults with heart valve disease, what is the prognostic value and cost-effectiveness of cardiac MRI and cardiac CT to determine the need for intervention?
9	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?
10	What is the clinical and cost-effectiveness of transcatheter intervention, surgery (with mechanical or biological valves) and conservative management compared with each other for adults with heart valve disease?
11	What is the clinical and cost-effectiveness of transcatheter or surgical repeat valve intervention for people with biological vales or repaired valves that require reintervention due to failure of the valve?
12	What is the clinical and cost-effectiveness of anticoagulant and/or antiplatelet therapy for adults with transcatheter or surgical biological prosthetic valves or after valve repair?
13	What is the most clinically and cost-effective frequency of echocardiography or clinical review for monitoring in adults with repaired or replaced heart valves?
14	What information and advice are useful and valuable to adults with heart valve disease and their family and carers?

NICE, National Institute for Health and Care Excellence.

there is an indication for clinical urgency, recommends whom to refer on to a specialist heart valve clinic and provides some guidance concerning pregnant patients or women of childbearing potential. NICE guidance also outlines the indications for intervention in patients with aortic, mitral and tricuspid regurgitation and aortic and mitral stenosis and makes recommendations on monitoring of patients both before and after valve intervention. NICE also highlights areas in which the current evidence base is suboptimal and lists clinical questions that need to be addressed by future research studies (see online supplemental table 2).

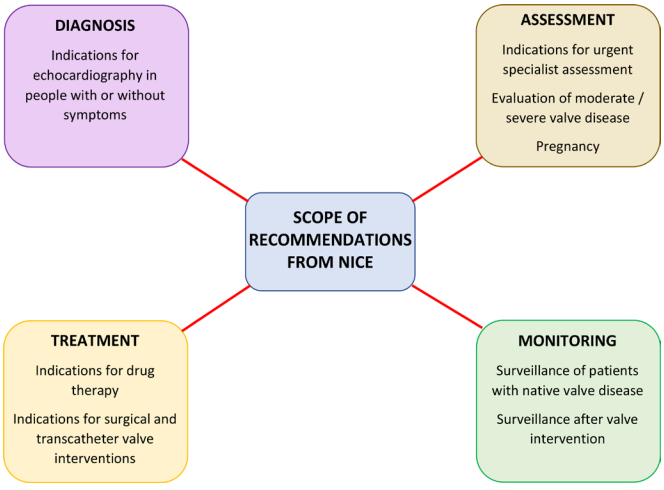

Figure 1 The scope of the topics covered in the NICE guidance can be categorised into those relating to diagnosis, (specialist) assessment, treatment and monitoring of valve disease. NICE, National Institute for Health and Care Excellence.

NICE VERSUS PROFESSIONAL MEDICAL SOCIETIES

As a result of huge variation in healthcare systems around the world and resources available in different countries, it is inevitable that multiple CPGs will exist, as no single guideline could be applied worldwide given current global inequities in healthcare. The ESC, American College of Cardiology (ACC) and American Heart Association (AHA) produce numerous practice guidelines, which are updated every few years. NICE is an independent public body, responsible for providing evidence-based guidelines to help health professionals deliver the best possible care within the financial constraints of the state-funded National Health Service (NHS). NICE guidelines thus take into consideration not just individual but also wider societal needs, aiming to achieve the most benefit for the greatest number of people, with fair distribution of available resources.[11] The NHS has a defined budget and appropriate use of resources is important. NICE methods therefore aim to focus resources on interventions that have been proven to be not just clinically effective but cost-effective also. This is a key difference between NICE guidance documents and the ESC/European Association for Cardiothoracic Surgery (EACTS) and ACC/AHA guidelines. Readers who wish to learn more about the NICE guideline process are directed to a recent review article dedicated to this topic.[11]

THE NICE RECOMMENDATIONS FOR VHD

The first section of the NICE guideline (related to diagnosis of VHD, use of echocardiography and whom to refer on to specialist heart valve clinics) is relevant for general practitioners working in primary care and is summarised in box 1. The next section related to pharmacological therapies in VHD is very brief—the only specific recommendation is to consider beta-adrenoceptor antagonists ('beta-blockers') in patients with moderate-severe mitral stenosis. Previous trials of ACE inhibitors in aortic stenosis and mitral regurgitation (MR), calcium

Box 1 The NICE recommendations related to use of echocardiography for diagnosis and whom to refer on for specialist assessment (adapted from NICE guideline NG208 (2021–Heart Valve Disease Presenting in Adults: Investigation and Management. Available from www.nice.org.uk/guidance/ng208. All rights reserved))

NICE guidance related to diagnosis and specialist assessment for VHD

Echocardiography

1. **Consider** an echocardiogram for adults with a murmur and no other signs or symptoms if valve disease is suspected based on:
⇒ Nature of the murmur.
⇒ Family history.
⇒ Age (especially if >75 years).
⇒ Medical history (eg, AF).
2. **Offer** an echocardiogram to adults with a murmur if valve disease is suspected (based on the nature of the murmur, family history, age or medical history) and they have:
⇒ Symptoms (eg, chest pain, breathlessness).
⇒ Physical signs (eg, peripheral oedema).
⇒ Abnormal ECG.
⇒ Ejection systolic murmur with reduced second heart sound but no other signs/symptoms.

If valve disease is suspected (based on the nature of the murmur, family history, age or medical history):
1. **Offer** urgent (within 2 weeks) specialist assessment that includes echocardiogram (or if not available, an urgent echocardiogram alone) to adults with a systolic murmur and exertional syncope.
2. **Consider** urgent (within 2 weeks) specialist assessment that includes echocardiogram for adults with a murmur and severe symptoms (angina or breathlessness on minimal exertion or at rest) thought to be related to valvular heart disease.

Specialist referral

1. **Offer** referral to a specialist to:
⇒ Adults with moderate or severe valve disease of any type.
⇒ Adults with bicuspid aortic valve disease of any severity (including mild valve disease).
2. **Offer** advice on the implications of treatment choices on any future pregnancy to women who need heart valve intervention.
3. **Offer** advice on family planning to women with severe valve disease, particularly aortic and mitral stenosis.

Refer pregnant women or women who are considering a pregnancy (whether symptomatic or not) 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 (including mild) and associated aortopathy.
⇒ A prosthetic valve.
4. **Consider** seeking specialist advice on the choice of replacement valve if heart valve replacement surgery is being considered for women of childbearing potential.

AF, atrial fibrillation; NICE, National Institute for Health and Care Excellence; VHD, valvular heart disease.

channel antagonists in aortic regurgitation and statins in aortic stenosis were considered outside the scope of the NICE guidance and are thus not discussed.

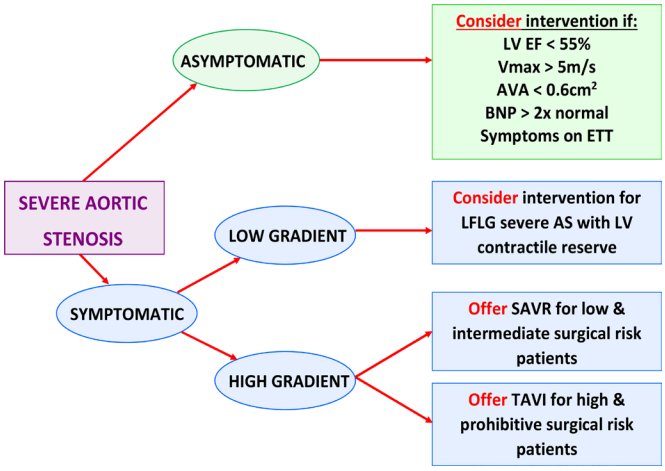

Figure 2 Flow diagram summarising the recommendations from NICE related to patients with severe aortic stenosis (AS). AVA, aortic valve area; BNP, brain natriuretic peptide; ETT, exercise treadmill test; LFLG, low-flow low-gradient; LV EF, left ventricular ejection fraction; NICE, National Institute for Health and Care Excellence; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve intervention; Vmax=maximum aortic valve jet velocity.

The NICE guidance goes on to list indications for intervention, starting off by stating that adults with symptomatic severe VHD should be offered an intervention. For adults with asymptomatic severe disease who are suitable for intervention, but which is not yet required, physicians are advised to offer clinical review every 6–12 months, with an echocardiogram. The guideline also discusses mild valve disease, stating that while mild disease is common and rarely progresses to severe disease, one should consider echocardiographic assessment every 3–5 years for adults with mild aortic or mitral stenosis.

The recommendations relating to aortic stenosis and MR are summarised in figures 2 and 3, respectively. For aortic stenosis, adults with symptomatic severe aortic stenosis should be offered surgery if low or intermediate surgical risk and offered

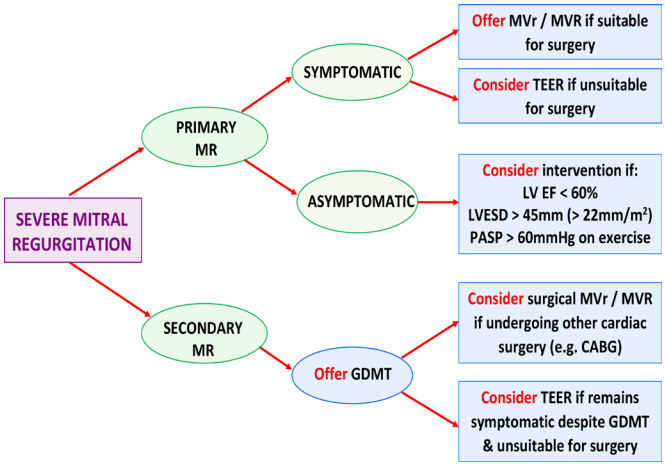

Figure 3 Flow diagram summarising the recommendations from NICE related to patients with severe mitral regurgitation (MR). CABG, coronary artery bypass graft; GDMT, goal-directed medical therapy; LV EF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MVr, mitral valve repair; MVR, mitral valve replacement; NICE, National Institute for Health and Care Excellence; PASP, pulmonary artery systolic pressure; TEER, transcatheter edge-edge repair.

Box 2 The NICE recommendations related to aortic regurgitation, tricuspid regurgitation and mitral stenosis (adapted from NICE guideline NG208 (2021–Heart Valve Disease Presenting in Adults: Investigation and Management. Available from www.nice.org.uk/guidance/ng208. All rights reserved))

NICE guidance related to aortic and tricuspid regurgitation and mitral stenosis

Aortic regurgitation

1. **Offer** surgery, if suitable (by median sternotomy or minimally invasive surgery), as first-line intervention for adults with severe aortic regurgitation (or mixed aortic valve disease) and an indication for surgery who are at low or intermediate surgical risk.
2. **Consider** referring adults with asymptomatic severe aortic regurgitation for intervention, if suitable, if they have either of:
   - ⇒ Left ventricular ejection fraction <55%.
   - ⇒ End-systolic diameter >50 mm/end-systolic diameter index >24 mm/m^2.

Tricuspid regurgitation

1. **Consider** surgical tricuspid valve repair at the time of mitral valve surgery when tricuspid regurgitation is moderate or severe.
2. **Consider** surgical tricuspid valve repair at the time of aortic valve surgery when tricuspid regurgitation is severe.

Mitral stenosis

1. **Consider** transcatheter valvotomy for adults with rheumatic severe mitral stenosis, if the valve is suitable for this procedure.
2. **Offer** surgical mitral valve replacement to adults with rheumatic severe mitral stenosis, if transcatheter valvotomy is unsuitable.

NICE, National Institute for Health and Care Excellence.

transcatheter aortic valve intervention (TAVI) if they are a high or prohibitive risk for cardiac surgery. For MR, surgical mitral valve repair is preferred to replacement for primary degenerative MR. For patients with either primary or secondary MR, a transcatheter edge-edge repair (TEER) *can* be considered in symptomatic patients if clinically appropriate. Indications for intervention, as recommended by NICE, for patients with aortic regurgitation, mitral stenosis and tricuspid regurgitation are listed in box 2.

THE SIMILARITIES AND THE DIFFERENCES

While it may be in our professional nature to focus on the differences between guidelines, there are also similarities that merit consideration. All three guidelines provide general comments and recommendations regarding diagnosis, use of echocardiography as the front-line investigation, follow-up schedules for patients not requiring intervention and the potential added value of other imaging modalities in specific situations.

The three guidelines are largely aligned on the treatment of primary and secondary MR, as illustrated in online supplemental tables 3 and 4. For patients in whom intervention is required for primary MR, all three guidelines consider surgery as the treatment of choice (repair preferable to replacement), although they all also support consideration of TEER in patients at high or prohibitive surgical risk in whom valve anatomy is suitable

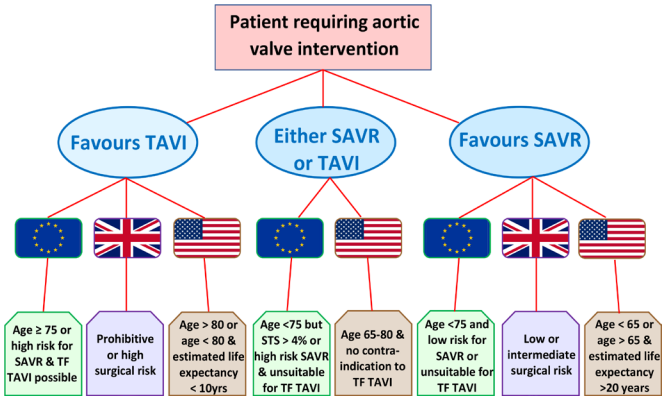

Figure 4 Recommendations for the treatment of patients with aortic stenosis that require intervention as per the European, American and NICE guidelines. NICE, National Institute for Health and Care Excellence; SAVR, surgical aortic valve replacement; STS, Society for Thoracic Surgery; TAVI, transcatheter aortic valve intervention; TF, transfemoral.

for a transcatheter procedure. For secondary MR, the picture is slightly more complex. This is first due to the lack of long-term data from surgical randomised trials demonstrating a survival benefit and, second, the conflicting results of the COAPT[12] and MITRA-FR[13] trials. However, the guidelines all permit either surgery or TEER if patients remain symptomatic with severe secondary MR despite optimal medical therapy.

An important difference between NICE and the ESC/EACTS and ACC/AHA guidelines concerns the management of patients with symptomatic severe aortic stenosis (see figure 4 and table 2). Both European and North American documents initially appear to stratify guidance around patient age (rather than estimated surgical risk, as in the NICE guidance). However, there is more nuance than might first be apparent and the accompanying explanatory texts detail this. The ACC/AHA guidance states 'A key factor in decision-making is the ratio of patient life expectancy to known valve durability, with patient age often used as a surrogate for life expectancy'.[6] After listing the predicted life expectancies for 60-year-old, 70-year-old and 80-year-old men and women in the USA, the guidance explains that these data informed the age cut-offs chosen and should serve as 'a starting point for shared-decision making, not as absolute values for chronological age'.[6] The novelty of the 2020 ACC/AHA and 2021 ESC/EACTS guidelines has thus been to introduce indications for TAVI regardless of consideration of surgical risk, following the results of randomised trials in low-risk patients. Age thresholds are justified, nonetheless, by uncertainties about the long-term results of TAVI, in contrast to surgery. Thus, age is used primarily as a surrogate for life expectancy rather than for surgical risk.

NICE guidance on treatment of severe aortic stenosis states that for patients at high or prohibitive surgical risk, TAVI is recommended whereas for patients at low or intermediate risk, surgical aortic valve replacement is recommended (figure 2). NICE stated that TAVI was not cost-effective for the NHS in low or intermediate-risk patients. This was largely attributed to the current list price for TAVI valves (in excess of £20 000 per valve in the UK). This helps to explain why the NICE guidance for TAVI is more restrictive in relation to ACC/AHA and ESC/EACTS guidelines. In its TAVI implementation strategy, NHS England and Improvement stated that they were 'aware that transcatheter aortic valve implantation (TAVI) is clinically effective but not currently cost effective for patients defined as intermediate

Table 2 ACC/AHA, ESC/EACTS and NICE recommendations on management of patients with severe aortic stenosis (AS), differentiated by symptom status and class of recommendation

ACC/AHA	ESC/EACTS	NICE
Symptomatic	**Symptomatic**	**Symptomatic**
Class I indications	**Class I indications**	**'Offer' intervention**
Severe high-gradient AS with symptoms (**1 A**)	Severe high-gradient AS with symptoms (**1 B**)	Severe high-gradient AS with symptoms
Severe low-gradient AS with symptoms and reduced LV EF (**1 B-NR**)	Severe low-gradient AS with symptoms, reduced LV EF and contractile reserve (**1 B**)	
Severe low-gradient AS with symptoms and preserved LV EF (**1 B-NR**)		
	Class II indications	**'Consider' intervention**
	Severe low-gradient AS with symptoms and preserved LV EF (**IIa C**)	Severe low-gradient AS with symptoms, reduced LV EF and contractile reserve
	Severe low-gradient AS with symptoms, reduced LV EF and no contractile reserve (**IIa C**)	
Asymptomatic	**Asymptomatic**	**Asymptomatic**
Class I indications	**Class I indications**	
Severe AS with LV EF <50%(**1 B-NR**)	Severe AS with LV EF <50% (**1 B**)	
Severe AS in patients undergoing cardiac surgery for other reasons (**1 B-NR**)	Severe AS with symptoms on exercise testing (**1 C**)	
Class II indications	**Class II indications**	**'Consider' intervention**
Severe AS and low surgical risk if exercise test demonstrates decreased exercise tolerance or fall in systolic BP of ≥10 mm Hg on exercise (**2a B-NR**)	Severe AS with LV EF <55% without another obvious cause (**IIa B**)	Severe AS with LV EF <55% without another obvious cause
Very severe AS (Vmax >5 m/s) and low surgical risk (**2a B-NR**)	Severe AS and exercise test demonstrates fall in systolic BP of ≥20 mm Hg on exercise (**IIa C**)	Severe AS with symptoms on exercise testing
Severe AS at low surgical risk with serum BNP >3× normal (**2a B-NR**)	Severe AS at low surgical risk with serum BNP >3× normal (**IIa B**)	Severe AS with serum BNP >2× normal
Severe AS at low surgical risk with serial testing showing increase in Vmax >0.3 m/s per year (**2a B-NR**)	Very severe AS (Vmax >5 m/s or mean gradient >60 mm Hg) and low surgical risk (**IIa B**)	Very severe AS (Vmax >5 m/s or aortic valve area <0.6 cm^2)
Severe AS at low surgical risk with fall in LV EF on ≥3 serial studies to <60% (**2a B-NR**)	Severe AS at low surgical risk with serial testing showing increase in Vmax >0.3 m/s per year (**IIa B**)	

All three guidelines recommend intervention for symptomatic severe high-gradient AS. Severe low-gradient AS has class I recommendations for intervention in the ACC/AHA and ESC/EACTS guidance, but a weaker 'consider' recommendation in the NICE guideline. Indications for considering intervention in patients with asymptomatic severe stenosis are similar among all three guidelines.
ACC, American College of Cardiology; AHA, American Heart Association; BNP, brain natriuretic peptide; BP, blood pressure; EACTS, European Association for Cardiothoracic Surgery; ESC, European Society of Cardiology; LV EF, left ventricular ejection fraction; NICE, National Institute for Health and Care Excellence; Vmax, maximum aortic valve jet velocity.

or low risk for cardiac surgery for aortic valve disease. NHS England Specialised Commissioning are currently working with their commissioning partner NHS Supply Chain in the development of a procurement strategy to explore cost-effective solutions with suppliers within this area. If a cost-effective solution is found then NICE will update the recommendations in this guideline.'[14] There is a clear inference, therefore, that the recommendation might change in the future if the costs of the TAVI valves were significantly lower.

IS THE NICE APPROACH THE RIGHT APPROACH?

The NICE process for developing guidelines has many positive aspects. These include the open publication of the methodologies used including cost-effectiveness analyses, the ability for interested stakeholders (including healthcare professionals, professional societies, patients and industry) to receive a draft copy of the guideline and to make comments (which receive individual point-by-point responses) and an expert selection process that aims to minimise bias with strict policies regarding competing interests. A multidisciplinary team including experts in literature review, health informatics and health economics assist clinicians and patient representatives with production of guidelines.

One aspect of the NICE process that can have drawbacks is the relative lack of room for professional expert opinion. On the one hand, this appears understandable, as clinician recommendations may have an underlying bias, but also professional society guidelines are themselves often criticised for over-reliance on 'expert opinion'. However, there are instances when such clinician advice is crucial. In that regard, the draft consultation process with option for feedback from stakeholders can be vital. The draft guidance of the NICE VHD guidance originally suggested that, in adults with symptomatic severe aortic stenosis, TAVI should be offered only to those deemed inoperable due to prohibitive surgical risk—that is, patients at high surgical risk would not have been offered TAVI. Similarly, mitral TEER was initially not considered an option in patients with symptomatic severe secondary MR, despite the results of the COAPT trial. Through detailed feedback from multiple stakeholders, who pointed out that these recommendations were not consistent with current clinical practice, the guidance was amended so that the final version did allow for TAVI in high surgical risk patients and TEER in selected patients with severe secondary MR. This was not a victory for 'lobbying', as such, but a victory for patients who now had more choice and more treatment options.

This issue is crucial to recognise as, in an ideal world, physicians would have high-quality unbiased randomised trial data to guide all important clinical decisions. However, this is not the case and especially so in VHD, which still has very few guideline recommendations assigned the highest level of evidence (A).[15 16] As a result, there will always be a need for *some* degree of professional judgement and clinical experience to help inform CPGs.

CONFLICTS OF INTEREST IN CPGS

There are many different types of conflict of interest (CoI)—financial, occupational, intellectual, academic, political and institutional. Some, but not all, can be managed to a degree. Financial CoIs are the easiest to identify and are widespread—a recent analysis of several ESC clinical guidelines found relevant

financial CoIs (mostly direct personal payments) among a majority of guideline authors and reviewers.[17] This is relevant because loss of trust among physicians in professional guidelines is a grave development with potential for patient care to be adversely impacted.[18]

The most obvious CoI, yet impossible to eliminate, is that of occupation. Surgeons like to perform surgery. Interventional cardiologists like to perform structural interventions. These immovable truisms inevitably influence the lens through which data are interpreted. This was elegantly highlighted recently in simultaneously published opinion pieces regarding the ESC/EACTS VHD guideline recommendations on the role of TAVI in treatment of aortic stenosis—the piece authored by interventional cardiologists felt the guidance was too restrictive with TAVI,[19] while the piece authored by surgeons felt the guidance went too far.[20]

The guidelines take different approaches to management of CoIs. NICE has the most stringent policies, excluding anyone with a financial CoI with relevant industry—irrespective of level of expertise—and also aims to manage intellectual and societal CoIs as well. As an example, the NICE Topic Advisor for the heart valve disease guideline had to stand down from the Council of the British Heart Valve Society to take up their role with NICE.

If we accept that many types of CoI can never be completely eliminated, then what are the optimal 'ground rules' for constructing CPGs? The current approach taken by the American College of Physicians, in classifying a CoI as low, moderate or high and managing involvement in CPG production accordingly, is a promising starting point.[21]

CONCLUSION

There is broad agreement on many topics among the European (ESC/EACTS), North American (ACC/AHA) and British (NICE) clinical guidelines on VHD. The recent guidance from NICE has some important differences, but these are in part related to the need for NICE guidance to account for cost and cost-effectiveness of therapies. NICE guidelines have different purposes to professional societal guidelines, as they are used to help inform healthcare policy across the state-funded UK NHS. This is not a concern for the ACC/AHA and ESC/EACTS guidelines. Differences between the NICE and the ACC/AHA and ESC/EACTS guidelines on VHD should be interpreted accordingly. The NICE guidance provides clear benchmarking national standards for diagnosis and initial specialist assessment of patients with heart valve diseases and also recommendations for intervention—either surgical or transcatheter—and monitoring of patients after valve intervention. NICE also highlights areas in which the current evidence base is inadequate and thus suggests topics that should be the subject of future research studies.

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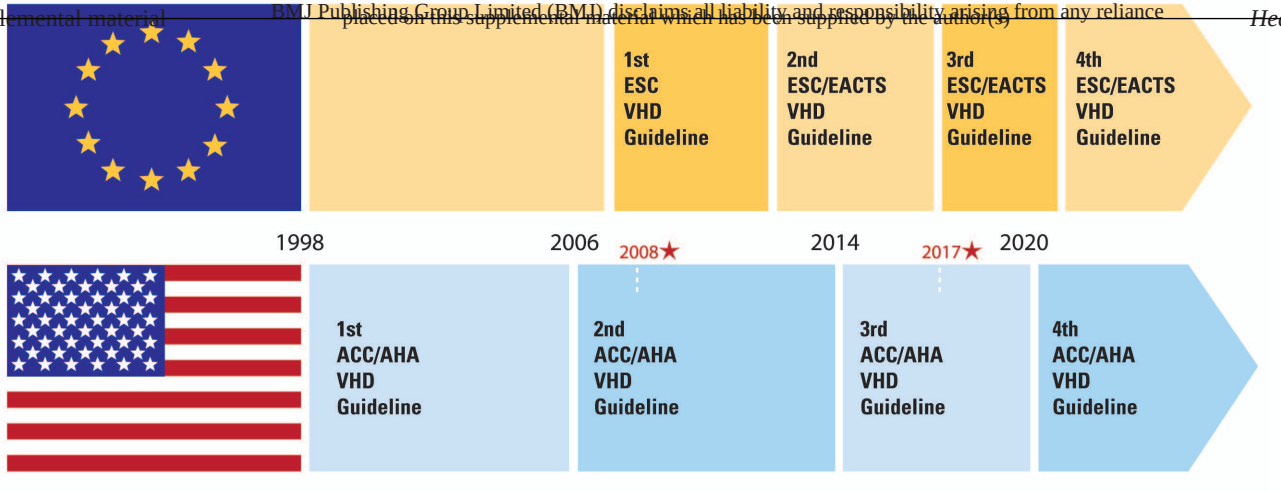
1st ESC VHD Guideline
2nd ESC/EACTS VHD Guideline
3rd ESC/EACTS VHD Guideline
4th ESC/EACTS VHD Guideline
1998
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1st ACC/AHA VHD Guideline
2nd ACC/AHA VHD Guideline
3rd ACC/AHA VHD Guideline
4th ACC/AHA VHD Guideline

IPG Code	Interventional Procedures Guidance Title	Year
IPG 731	Transcatheter tricuspid valve leaflet repair for tricuspid regurgitation	2022
IPG 730	Transcatheter tricuspid valve annuloplasty for tricuspid regurgitation	2022
IPG 707	Transapical transcatheter mitral valve-in-ring implantation after failed annuloplasty for mitral valve repair	2021
IPG 706	Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis	2021
IPG 700	Percutaneous insertion of a closure device to repair a paravalvular leak around a replaced mitral or aortic valve	2021
IPG 653	Valve-in-valve TAVI for aortic bioprosthetic valve dysfunction	2019
IPG 649	Percutaneous mitral valve leaflet repair for mitral regurgitation	2019
IPG 624	Sutureless aortic valve replacement for aortic stenosis	2018
IPG 604	Aortic valve reconstruction with processed bovine pericardium	2018
IPG 586	Transcatheter aortic valve implantation for aortic stenosis	2017
IPG 436	Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction*	2013
IPG 352	Percutaneous mitral valve annuloplasty	2010
IPG 245	Thoracoscopically assisted mitral valve surgery	2007
IPG 78	Balloon valvuloplasty for aortic valve stenosis in adults and children*	2004
IPG 67	Balloon dilatation of pulmonary valve stenosis*	2004

Legend: A list of previously published guidance documents regarding interventional procedures – related to heart valve disease – evaluated by NICE. Some of these documents are referred to in the NICE clinical guideline on heart valve disease (* indicates guidance partly or fully related to heart valve disease in children).

Category of Research Question	Recommended Questions for Future Research Studies
Information and advice	What are the information and advice needs of all adult age groups with heart valve disease of all severities and stages?
Pharmacological management for adults with heart valve disease	What is the clinical and cost effectiveness of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers and diuretics for adults with severe aortic stenosis? What is the clinical and cost effectiveness of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers and calcium channel blockers, including compared with placebo, for adults with aortic regurgitation? What is the clinical and cost effectiveness of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers and diuretics for adults with primary severe mitral regurgitation? What is the clinical and cost effectiveness of beta-blockers for adults over 75 years with non-rheumatic/calcific mitral stenosis, in both sinus rhythm and atrial fibrillation? What is the clinical and cost effectiveness of pharmacological management of heart failure for adults with heart failure and severe aortic stenosis, severe aortic regurgitation or severe mitral regurgitation?
Monitoring when there is no current need for intervention	What is the most clinically and cost-effective monitoring strategy (type and frequency of test) for adults with asymptomatic severe heart valve disease (aortic regurgitation, mitral stenosis, mitral regurgitation or tricuspid regurgitation) and no current indication for intervention? What is the most clinically and cost-effective monitoring (type and frequency of test) for adults with asymptomatic mild or moderate heart valve disease (AS, AR, MS, MR, TR) and no current need for intervention?
Indications for interventions – stress testing or echocardiography	What is the prognostic value of severe mitral regurgitation unmasked on exercise echocardiography in adults with symptomatic non-severe mitral regurgitation at rest? What is the prognostic value of parameters observed on exercise stress testing and exercise stress echocardiography in asymptomatic severe aortic regurgitation?
Indications for interventions – CT or MRI	In adults with aortic or primary mitral regurgitation in whom the need for intervention is unclear after echocardiography, what is the prognostic value and cost effectiveness of cardiac MRI to assess the severity of valvular regurgitation? In adults with aortic or mitral regurgitation in whom the need for intervention is unclear after echocardiography, what is the prognostic value and cost effectiveness of left ventricular ejection fraction (LVEF) measured on cardiac MRI to assess the need for intervention? In adults with asymptomatic severe aortic stenosis what is the prognostic value and cost effectiveness of LVEF measured

	on cardiac MRI to assess the need for intervention? In adults with asymptomatic severe tricuspid regurgitation what is the prognostic value and cost effectiveness of cardiac MRI for assessment of the right ventricle to assess the need for intervention?
Indications for interventions – global longitudinal strain	In adults with severe heart valve disease what is the prognostic value and cost effectiveness of global longitudinal strain to assess the need for intervention? In adults with asymptomatic, severe aortic regurgitation or mitral regurgitation what is the prognostic value and cost effectiveness of B-type natriuretic peptide (BNP) to assess the need for intervention?
Interventions for a failed valve	What is the clinical and cost effectiveness of transcatheter intervention compared with surgical redo intervention for adults with failing biological prosthetic tricuspid valves or failing repaired native tricuspid valves when either procedure is suitable?
Monitoring after an intervention	What is the most clinically and cost-effective timing, nature and frequency of follow up for different types of valve interventions, including repair and replacement with tissue or mechanical valves?
Antithrombotic therapy after intervention	What is the clinical and cost effectiveness of single or dual antiplatelet therapies or anticoagulants compared with placebo after transcatheter or surgical valve replacement (implantation) with biological prosthesis and after valve repair? In adults with biological valve replacement, what effect does anticoagulation or antiplatelet therapy have on long-term valve function and outcomes?
Repeat Interventions	What is the clinical and cost effectiveness of transcatheter intervention compared with surgical redo intervention for adults with failing biological prosthetic aortic valves when either procedure is suitable? What is the clinical and cost effectiveness of transcatheter intervention compared with surgical redo intervention for adults with failing biological prosthetic mitral valves when either procedure is suitable?

Table T2: Recommended questions for future clinical research studies to aim to answer, that currently have an insufficient evidence base, were suggested by the NICE committee [Adapted from NICE Guideline NG208 [2021 – Heart Valve Disease Presenting in Adults: Investigation and Management. Available from www.nice.org.uk/guidance/ng208. All rights reserved]

ACC / AHA	ESC / EACTS	NICE
SYMPTOMATIC	***SYMPTOMATIC***	***SYMPTOMATIC***
Class I Indications	**Class I Indications**	**'*Offer*' Intervention**
Severe primary MR irrespective of LV function **[1 B-NR]**	Severe primary MR who are operable and not high risk **[1 B]**	Offer surgical MV repair for severe primary MR; offer surgical MV replacement where repair is not feasible
Class II Indications	**Class II Indications**	**'*Consider*' intervention**
Consider TEER for severe primary MR deemed unsuitable for surgery, who are technically feasible & patient life expectancy > 1 year **[2a B-NR]**	Consider TEER for severe primary MR deemed unsuitable for surgery, who are technically feasible & procedure not deemed futile **[IIb B]**	Consider TEER if severe primary MR and not suitable for surgery
ASYMPTOMATIC	***ASYMPTOMATIC***	***ASYMPTOMATIC***
Class I Indications	**Class I Indications**	**'*Offer*' Intervention**
Severe primary MR with LV dysfunction (EF < 60% or LVESD >40mm) [**1 B-NR]**	Severe primary MR with LV dysfunction (EF < 60% or LVESD >40mm) **[I B]**	
Class II Indications	**Class II Indications**	**'*Consider*' intervention**
Severe primary MR with preserved LV function where MV repair can be performed with high likelihood (>95%) of success with expected mortality <1% in a valve centre of excellence **[2a B-NR]**	Severe primary MR with preserved LV function but AF or pulmonary hypertension (PASP >50mmHg at rest) **[IIa B]**	Severe primary MR with LV EF <60%
Severe primary MR with preserved LV function but with progressive rise in LV dimensions or fall in LV EF on 3 serial imaging studies **[2b B-NR]**	Severe primary MR with preserved LV function but LA dilatation (LAVI >60ml/m^2 or diameter >55mm) **[IIa B]**	Severe primary MR with LVESD >45mm or LVESDi > 22mm/m^2
		Severe primary MR with increase in PASP > 60mmHg on exercise testing

ACC / AHA	ESC / EACTS	NICE
Class I Indications	**Class I Indications**	**'*Offer*' Intervention**
	Severe secondary MR and undergoing CABG or other cardiac surgery **[I B]**	
Class II Indications	**Class II Indications**	**'*Consider*' intervention**
Consider TEER for severe secondary MR with persistent symptoms despite GDMT if LV EF 20-50%, LVEDD < 70mm & PASP <70mmHg **[2a B-R]**	Consider TEER for severe secondary MR in patients deemed unsuitable for surgery & who are technically feasible **[IIa B]**	Consider TEER for severe secondary MR with HF symptoms despite GDMT
Severe secondary MR and undergoing CABG or other cardiac surgery **[2a B-NR]**	Consider MV surgery for severe secondary MR as judged appropriate by the heart team **[IIb C]**	Severe secondary MR and patient having cardiac surgery for another indication (surgical MV repair or replacement)
Consider MV surgery for severe secondary MR from atrial annular dilatation with LV EF >50% **[2b B-NR]**	Consider TEER or other transcatheter MV therapy if unsuitable for surgery & not thought high likelihood of success for TEER, after careful heart team assessment **[IIb C]**	
Consider MV surgery for severe secondary MR from LV dysfunction (EF < 50%) with persistent HF symptoms despite GDMT **[2b B-NR]**		
Consider chordal-sparing mitral valve replacement over downsized annuloplasty in symptomatic patients despite GDMT with CAD and severe secondary MR due to LV systolic dysfunction **[2b B-R]**		