Aortic regurgitation management: a systematic review of clinical practice guidelines and recommendations

Running title: Aortic regurgitation a systematic review of guidelines

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Abstract

Guidelines for the diagnosis and management of aortic regurgitation (AR) contain recommendations which do not always match. We systematically reviewed clinical practice guidelines and summarised similarities and differences in the recommendations as well as gaps in evidence on the management of AR.

We searched MEDLINE and EMBASE (01/01/2011 - 01/09/2021), Google Scholar, and websites of relevant organisations for contemporary guidelines that were rigorously developed as assessed by the Appraisal of Guidelines for Research and Evaluation II tool. Three guidelines met our inclusion criteria. There was consensus on the definition of severe AR and use of echocardiography and of multimodality imaging for diagnosis, with emphasis on comprehensive assessment by the heart valve team to assess suitability and choice of intervention. Surgery is indicated in all symptomatic patients and aortic valve replacement is the cornerstone of treatment. There is consistency in the frequency of follow-up of patients, and safety of non-cardiac surgery in patients without indications for surgery. Discrepancies exist in recommendations for 3-D imaging and the use of global longitudinal strain and biomarkers. Cut-offs for left ventricular ejection fraction and size for recommending surgery in severe asymptomatic AR also vary. There are no specific AR cut-offs for high-risk surgery and the role of percutaneous intervention is yet undefined. Recommendations on the treatment of mixed valvular disease are sparse and lack robust prospective data.

Key words: aortic regurgitation, guidelines, systematic review, valvular heart disease, aortic valve.

Introduction

Aortic regurgitation (AR) is the third most common valvular pathology found in the general population, with a lifetime risk of 13% in men and 8.5% in women. Degeneration of the valve is the most common aetiology of chronic AR, and this process is usually accelerated in the context of a bicuspid aortic valve (BAV) where patients present with severe disease earlier. (1) (2) Severe AR is associated with significant cardiovascular morbidity and mortality. Within ten years of diagnosis of severe AR, 75% of patients die or require aortic valve replacement (AVR). (3) Even in asymptomatic severe AR, mortality can be as high as 19% within 6.6 years of diagnosis. (4)

AR can arise from the intrinsic disease of the aortic valve (AV) leaflets (primary), from distortion and dilatation of the aortic root (secondary) or from mixed pathology (especially in bicuspid AV disease). The El Khoury functional classification (an adaptation of the Carpentier classification originally designed for the mitral valve) can be helpful to appraise the mechanism of AR, guide valve repair technique, and predict recurrence of AR. (5) (6) (7) Volume overload imposed by significant AR leads to increased total stroke volume, resulting in systolic hypertension and afterload mismatch. Compensatory eccentric remodelling initially normalises wall stress, but eventually compensatory mechanisms are overcome. Symptoms then ensue, which usually herald left ventricular (LV) decompensation, and are the strongest indication for intervention. (8) (9) Annual mortality rises to 25% once symptoms occur.

Traditionally, the mainstay of treatment has been AVR, but modern techniques now include surgical repair or transcatheter aortic valve intervention (TAVI). We performed a systematic review of current guidelines and recommendations from professional societies for diagnosis

and management of AR and highlighted areas of agreement, disagreement, and potential gaps in evidence to help clinical decision-making and identify areas requiring further research.

Methods

Data sources and searches

We searched MEDLINE, EMBASE and PUBMED for guidelines published between 1st January 2011 and 1st of September 2021 containing recommendations on the diagnosis and management of AR. We also searched websites of cardiac societies and guideline development organisations (listed in Supplementary Table 1), Google Scholar, the National Library for Health Guidelines Finder, the Canadian Medical Association Clinical Practice Guidelines InfoBase, and the National Guideline Clearinghouse, and the Guidelines International Network International Guideline Library. Only guidelines published in English and containing recommendations for the adult population were included. We planned, conducted, and reported this systematic review under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. (10)

Study selection

Two independent reviewers (VG and CS) reviewed the titles and abstracts in order to identify the relevant articles. Articles were excluded only if both reviewers agreed they were ineligible. Discrepancies were resolved by consensus and involvement of an arbitrator (MYK).

We included only references that met the Institute of Medicine's definition of a guideline. We excluded paediatric guidelines or guidelines that were not produced on behalf of a

professional organisation. If more than one guideline from the same organisation existed, we assessed the most recent one.

Data extraction and quality assessment

We used the 23-item Appraisal of Guidelines for Research and Evaluation (AGREE) II system to determine the rigour of development for each of the guidelines. (11) Two reviewers (VG and BS) independently rated the items, conforming to the instructions of the AGREE II tool. The average rigour scores were calculated by expressing the sum of the individual scores as a percentage of the maximum possible score. Only guidelines with a rigour of agreement ≥50% were included in the data extraction. Editorial independence from the funding body, external funding, and disclosure of relationships with the industry by individual guideline group members were assessed for each of the guidelines.

One reviewer (VG) extracted the data from the final selection of papers. The recommendations were extracted into a table and compared.

Results

We reviewed 1,126 titles of which 27 were potentially eligible after removal of duplicates and title and abstract review. The American College of Cardiology (ACC)/ American Heart Association (AHA), European Society of Cardiology (ESC) and Japanese Circulation Society (JCS) met our selection criteria after full-text analysis and had a rigour score of ≥50% and were retained for analysis. (8) (9) (12) The full selection flow-chart is illustrated in **Figure 1**. **Table 1** summarises the selected guidelines and their recommendations along with conflicts of interest and rigour scores.

Areas of agreement

Diagnostic tests for AR

In all guidelines, echocardiography is the key imaging modality to diagnose AR, define its aetiology and grade its severity. Further imaging with computed tomography (CT) may be appropriate to obtain aortic root dimensions and exclude dissection in the setting of acute AR. Cardiovascular magnetic resonance (CMR) imaging can be considered to assess biventricular volumes and systolic function, aortic size, regurgitant fraction and complements assessment of AR severity where there is diagnostic uncertainty.

Cardiac catheterisation is suggested by two of the guidelines (8) (12) to assess haemodynamics and severity of AR when there is discordance between clinical symptoms and echocardiographic findings.

Definition of severe AR

Key echocardiographic parameters supporting severe AR include vena contracta >0.6 cm, EROA ≥0.3 cm^2, regurgitant volume ≥60 mL/beat, holodiastolic flow reversal in the descending aorta and evidence of LV dilatation (LVESD >50 mm or >25 mm/m^2).

Management of severe AR

Medical therapy

In patients with symptoms and/or LV dysfunction, optimal guideline-directed medical therapy for heart failure and hypertension is useful in patients in whom surgery is not feasible, or in patients who continue to suffer from heart failure or hypertension post-surgery.

(8) (9) The JCS guidelines do not contain any specific medical management recommendations. (12)

Indications for intervention

All three guidelines agree that surgery is indicated in symptomatic severe AR regardless of LV function. In the case of asymptomatic AR, all guidelines agree that intervention is needed when there is LV systolic dysfunction or LV dilatation, however, cut-off values may vary.

Patients undergoing concurrent cardiac surgery

ACC/AHA, ESC and JCS guidelines state that patients with symptomatic and asymptomatic severe AR undergoing CABG, another valve or surgery of the ascending aorta should have surgical intervention of AR at the time of the operation.

Choice of intervention

SAVR (mechanical or bioprosthetic) is the main surgical intervention for severe AR and features in all guidelines.

Defining risk

All three guidelines emphasise the importance of clinical decision making via the multi-disciplinary heart valve team. While assessment of comorbidities, frailty, mobility, and any specific procedure-specific impediments form part of the assessment, the use of specific risk calculators such as STS-PROM and EuroScore II is recommended.

Non-cardiac surgery

The ACC/AHA guidelines suggest an up to date TTE in patients suspected of having moderate to severe AR. (8) All guidelines confirm that in asymptomatic patients with a moderate or greater degree of AR and normal systolic function, undertaking elective non-cardiac surgery is reasonable. (8) (9) (12) If valvular disease falls under the usual recommendations for treatment, AR should be corrected before the elective surgery. When LVEF is <30% (9) (12) and/or PASP ≥50-60mmHg (9), non-cardiac elective surgery should only be performed after optimisation of medical therapy and only if strictly necessary.

Surveillance and follow-up

All guidelines agree that patients with severe asymptomatic AR should undergo 6-12 monthly follow-up. If a fall in LVEF or increase in LV size is observed, repeat imaging should be performed more frequently (3- to 6- month intervals). Mild-moderate AR should be followed up every 1-2 years, and mild AR every 3-5 years.

Areas of disagreement for diagnosis and management of AR

Diagnostic testing of AR

Only the ESC guidelines suggest that 3-D echocardiography and global longitudinal strain (GLS) measurements may be useful in patients with borderline LVEF and may help with the decision for surgery. (9) The JCS guideline recommends exercise stress echocardiography in symptomatic patients to reveal cardiac reserve and subclinical cardiac dysfunction. (12)

ACC/AHA and JCS guidelines also suggest use of CMR or CT for aortic angiography in patients with bicuspid AV when the morphology of the aortic sinuses, sino-tubular junction or ascending aorta cannot be accurately assessed by echo alone. (8) (12)

Definition of severe AR

Two guidelines (8) (12) also mentioned Doppler jet width ≥65% of LVOT diameter while the ESC guidelines generally refer to a 'large' Doppler jet. (9) The same two guidelines suggest that regurgitant fraction ≥50% and angiographic grade 3 to 4 support a diagnosis of severe AR. (8) (12) Two guidelines mention that a pressure halftime of the regurgitant jet of <200m/s indicates severe AR. (9) (12) Although all guidelines mention calculating of the regurgitant fraction using CMR when there is diagnostic uncertainty, only the JCS guidelines mention a cut-off of ≥50% being supportive of severe AR. (12)

Management of severe AR

Medical therapy

Only one guideline refers to acute severe AR separately. They advise medical therapy to reduce LV afterload, but this should not delay urgent surgical intervention.

Indications for intervention

When AR is asymptomatic, surgical intervention is indicated when there is LV systolic dysfunction (LVSD). AHA/ACC guideline suggests a threshold of ≤55% when another cause cannot explain the LVSD, whilst the JCS guideline uses the threshold of <50%. The ESC guideline supports either a resting LVEF of ≤50%, or <55% when surgical risk is low.

Where LV systolic function remains good, LV dilatation is an indication for surgery, but the thresholds vary across guidelines. The AHA/ACC and ESC guidelines agree that LVESD threshold of >50mm or 25mm/m^2 (BSA), or if there is a decline in LVEF or progressive LV dilatation into severe range (LVEDD >65mm). The ESC guideline also supports intervention

when LVESDI is 20mm/m^2 (BSA) when surgical risk is low. JCS state that surgery is reasonable when LVESD is >45mm and may be considered when LVEDD is >60mm or LVESDI >25mm/m^2.

Patients undergoing concurrent cardiac surgery

The AHA/ACC and JCS guidelines propose that AVR is reasonable in patients with moderate AR undergoing other open-heart procedures, however the ESC guidelines rate this as a controversial indication. (9) (13)

Choice of intervention

In specialist centres with the required expertise, aortic valve repair may be considered in anatomically suitable patients when durable results are expected. (9) The AHA/ACC guideline is more specific and mentions that preservation of native aortic valve may be possible in patients undergoing surgical replacement of aortic sinuses and/or ascending aorta. The JCS guideline does not expand upon the choices of surgical intervention for severe AR.

Percutaneous intervention, particularly TAVI, may be feasible for patients who are suitable anatomically and not surgical candidates. (8) (9) ACC/AHA guidelines emphasises that TAVI should not be performed in patients who are surgical candidates.

Defining risk

While all guidelines suggest the use of STS-PROM and EuroScore II for the assessment of risk, there is a specific score that is recommended by the JCS, developed specifically for the population in Japan. Furthermore, while both ACC/AHA and JCS guidelines

recommend specific cut-off values for surgical risk, only ACC/AHA clearly defines what constitutes a prohibitive risk

Mixed valvular disease

Whilst JCS recommends careful assessment to identify the predominant valve pathology when AR is present in the context of AS, ACC/AHA recommend AVR in symptomatic patients when the peak transvalvular velocity is ≥4.0 m/s or mean transvalvular gradient is ≥40 mmHg, or in asymptomatic patients with peak transvalvular velocity is ≥4.0 m/s and LVEF <50%.

In patients with symptomatic AR associated with mitral stenosis (MS), ACC/AHA recommends that percutaneous mitral balloon commissurotomy should be used to treat MS in patients with favourable anatomy, followed by AVR.

The ESC recommends dual valve surgery when AR is co-existent with severe MR (primary or secondary). The JCS recommends treatment guided by the predominant valvular pathology and indicates dual valve surgery for patients who have more than moderate AR but do not clarify the threshold for co-existent MR.

Discussion

We identified three rigorously developed clinical practice guidelines with recommendations for the diagnosis and management of AR. There was consensus on the definition of severe AR, its assessment with echocardiography, CT and CMR. Surgery is indicated in all symptomatic patients and AVR with or without aortic root surgery as the mainstay treatment. There is an emphasis on decision-making by the heart valve team and incorporating a

comprehensive surgical risk assessment, especially as valve-sparing root, or aortic valve repair surgery may be possible. There is consistency in the frequency of follow-up of patients as well as safety of non-cardiac surgery in selected patients without indications for valve intervention. Discrepancies exist in the use of 3-D imaging and GLS to quantify LV function. The cut-off values for LVEF and LVESD/LVEDD that would trigger surgical intervention in severe asymptomatic AR vary. Recommendations on mixed valvular disease vary and are sparse, largely due to a lack of prospective evidence to support recommendations. There is a limited role and recommendation for percutaneous treatment of AR. The central illustration (**Figure 2**) summarises the areas of agreement, disagreement and potential gaps in evidence and/or guidelines that require further development.

Multi-modality assessment of AR

Transthoracic echocardiography (TTE) is the first-line diagnostic tool for diagnosis of AR, allowing accurate quantification of AR severity and determination of the mechanism of valve incompetence. Several echo parameters exist to grade the severity of AR which are used in an integrated manner.(14) Transoesophageal echocardiography (TOE) offers an alternative approach to AR assessment where TTE windows are suboptimal. Multimodality imaging offers complementary information and may provide additional insights to guide management, for example by evaluation of the proximal aorta.

TOE

Identifying the aetiology AR often requires high temporal resolution which can be achieved with TOE and adds incremental diagnostic value over TTE. (15) EROA quantification to grade the severity of AR can be less accurate and poorly reproducible with 2-D TTE, especially where echo windows are suboptimal, and jets are eccentric. (16) Better alignment

and estimation of the PISA can be achieved using axial multiplanar reconstruction by 3-D TOE. With growing expertise in this area, systematic methods of aortic valve and root assessment have been proposed and may facilitate pre-operative planning especially with the growing field of aortic valve sparing surgery. (17) (18)

CMR

CMR is the reference standard for quantifying LV volumes and systolic function and is thus able to measure the impact of significant AR on the left ventricle and its constituent myocardium. It also allows the assessment of structures remote to the heart, including evaluating the aortic arch and descending aorta, which is relevant in excluding coarctation, a known association of bicuspid aortic valve disease.

CMR allows the direct measurement of regurgitant volume (RVol) with 2D phase contrast velocity encoded imaging. While proposed thresholds for quantifying severe AR are variable, RVol by CMR may add useful prognostic information and a regurgitant fraction (RF) >33% (ranging between 33% and 37% depending on the study) was found to be associated with excess risk of adverse outcomes. (19) (20) Furthermore, CMR-detected holo-diastolic flow reversal (HFR), which is non-interpretable in up to 40% of patients in some studies on TTE (21), has been shown to be an accurate marker of severe AR. Emerging techniques, including 4D flow (time-resolved 3D flow acquisition) may add to the diagnostic utility of CMR. AR severity, as determined by TTE, is reclassified by CMR in a significant proportion of patients. (21) Although the availability of CMR is still limited, both HRF and RF are easily measurable, requiring no contrast agent and only a short acquisition time. Evidence on the incremental value on CMR in AR is growing, however, although current guidelines mention CMR as a diagnostic tool when TTE is non-diagnostic (i.e. suboptimal echocardiographic

images, eccentric jet, discordance between clinical assessment and AR grading, multiple valvular lesions), they do not provide clear recommendations about how to define severe AR using CMR.

Biomarkers and GLS

The onset of symptoms related to significant aortic regurgitation can be challenging to detect due to insidious disease progression. Novel biomarkers of LV function such as GLS, and NT-proBNP may be useful for risk stratification. A recent systematic review evaluating GLS in asymptomatic AR suggested that a GLS between -17 and 0% may be associated with worse cardiac outcomes (death or progression to AVR). (22) NT-proBNP may be a useful additional prognostic marker as it correlates well with AR severity and mortality. (23) (24) Closer monitoring of patients at high risk of decompensation may allow early identification of decompensation and referral for intervention before irreversible cardiac damage or adverse events. (22) (25) Further clinical outcome studies are needed to confirm their utility before delivering clinical recommendations.

Indications for intervention

While symptomatic severe AR is an indication for surgery, the LVEF and dilatation thresholds triggering intervention in asymptomatic patients vary. When LVEF is preserved, most guidelines advocate intervention when there is LV dilatation, especially when progressive on serial imaging. Only ESC guidelines suggest considering intervention in patients with LVESDI >20mm/m^2 BSA when surgical risk is low. Evidence has emerged that LV ESDI >20mm/m^2 has been associated with increased mortality, a threshold lower than currently endorsed by most of the guidelines. (26)

Surgical replacement or repair – aortic root dilatation & bicuspid aortic valve

Interventional management of AR can involve surgical replacement, repair or percutaneous intervention. Although AVR remains the first line intervention, a number of repair techniques have emerged with distinct advantages and disadvantages. (27) Furthermore, transcatheter aortic valve implantation (TAVI), although lacking in randomised controlled data, has been successfully used for patients where the surgical risk is prohibitive, showing potential as an alternative for patients in whom the prognosis is poor with conservative treatment alone. (28)

AV-sparing aortic root repair

When AR is driven by aortic root dilatation, aortic root repair with preservation of the aortic valve has been used. Root replacement with expansible aortic ring annuloplasty appears durable and safe. (29) Since the development of this technique, long-term data of valve-sparing root replacement has become available, and this is incorporated into the guidelines.

Isolated AR

AR is often due to congenital (e.g. bicuspid) or to acute pathologies (e.g. infective endocarditis) and presents in younger patients. Mechanical valves are therefore used due to their long-term durability, but carry the need for anticoagulation, and risk of thromboembolism. Aortic valve repair is therefore an alternative in selected patients. Although there are no prospective randomised controlled trials comparing AVR and AV repair, a recent meta-analysis of published literature showed that aortic valve repair showed comparable perioperative outcomes, with a higher re-operation rate. (30) However, this is a technically challenging procedure with several different approaches and techniques

depending on the AV pathology at hand. This requires specific expertise and is therefore limited to selected specialist centres. (27)

Bicuspid aortic valve

Congenital bicuspid valve is present in 1-2% of the population and is associated with early valve degeneration and aortopathy. AV repair has been an appealing alternative to AVR in this younger group of patients. Although the approaches have significantly developed and become more standardised, techniques still vary across centres. (31) (32) Data are limited to case series, however, meta-analysis of the data are suggestive of a favourable safety profile and good perioperative outcomes, but with reintervention rates of 20% at 10 years. (33) Despite the systematic reviews covering the area of AV repair, evidence remains heterogenous and registries are underway to try and pool and analyse cohorts of patients undergoing AV repair. (27)

Percutaneous intervention – TAVI

AR is traditionally a contraindication to TAVI as the calcified landing zone is often lacking, (34) removing anatomical landmarks for alignment and potentially leading to malposition. (35) Furthermore, increased movement of valve prosthesis in the regurgitant jet as well as aortic root dilatation may lead to suboptimal prosthesis position and paravalvular leak necessitating a second valve-in-valve prosthesis. (36) Retrievable, repositionable and valves with feelers and clips may facilitate successful implantation in the context of AR. (37) (29) A multicentre observational study demonstrated that more than mild residual AR is associated with doubling of mortality at one year (22% vs 46%).

Pre-operative CT assessment of the aortic annulus is essential to select the correctly sized valve for implantation. Adequate deliberate oversizing leads to a reduction in rates of valve-in-valve procedures; however if excessive, it can cause conduction abnormalities and pacemaker requirement. (35) (38) A recent meta-analysis suggests that newer generation devices have higher success rates due to less frequent mispositioning and paravalvular leak rates. (39) TAVI is an option for patients who are inoperable due to high operative risk.

Mixed valve disease

Valvular lesions coexisting with AR may make the assessment of each individual valvular lesion difficult. (40) One such combination is mixed aortic valve disease (MAVD), when AS coexists with AR. Coexisting pathologies result in increased stroke volumes, higher transaortic peak velocities and mean pressure gradients. (41) Some studies suggest that severe asymptomatic MAVD should be monitored 6-monthly, as half of the patients will become symptomatic and require AVR within one year; this frequency of monitoring is also applicable to asymptomatic severe AV disease. (42)

The natural history of MAVD is yet to be defined but likely differs from that of each of its individual components. In fact, moderate MAVD has a poorer prognosis than moderate AS or AR alone. (43) Current evidence for the need for intervention is extrapolated from data of AS and AR, and the predominant lesion guides the treatment. However, given the combined abnormal preload and afterload, early intervention may play a part in MAVD to avoid irreversible LV remodelling, especially when AR is the predominant lesion. (44) (45) This needs to be formally confirmed in the context of dedicated studies before this is implemented into the guidelines.

Gaps in evidence

There is an increasing need to identify patients in whom valvular heart disease is likely to progress. CMR and biomarkers to predict adverse events are not yet fully incorporated into the recommendations as robust prospective data is still lacking. Development of tools that can predict transition to heart failure could lead to earlier intervention reducing morbidity and mortality.

With the aging population the prevalence of mixed valvular disease is likely to grow. Further evidence is needed to help manage patients with multiple valvular pathologies. Percutaneous interventions are advancing and are now being used in AR. Patient selection is crucial and evidence is required to support its use in patients who are too high risk for surgery. Current risk stratification tools featured in the guidelines are generic, and do not clarify what high- and low-risk means specific to the valvular pathology at hand.

In patients in whom surgery is needed, more evidence and standardisation are required for AV repair techniques. Valve sparing surgery may be advantageous in younger patients, as valve replacement surgery can be done at a later stage. However, the repair techniques are inhomogeneous and are currently limited to certain centres with the required expertise. (27)

Limitations

This systematic review was restricted to guidelines published in the English language, however we used a robust and comprehensive systematic approach using article and guidelines repositories to retrieve all potentially relevant documents. We did not evaluate guidelines focusing solely on the diagnosis of AR for which separate dedicated papers exist.

Moreover, the focus of this review is the analysis of the guidelines which feature the management of chronic AR as opposed to acute AR. Acute AR secondary to infective or structural deformity was therefore not covered in our review.

Conclusions

Current guidelines are convergent on the initial assessment of AR and on the indications for surgical management in patients with symptomatic severe AR. The exact definition and role of CMR and biomarkers in guiding management of patients with AR is lacking, and there is variation in the cut-off values that should trigger intervention in the asymptomatic population. Mixed valve disease raises difficult treatment questions, for which the recommendations are sparse. Nevertheless, there is consensus on the importance of the heart valve MDT in making overall decisions on the management of patients with valvular heart disease.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Data availability statement

The data underlying this article are available in the article and in its online supplementary material. Any additional data will be shared on reasonable request to the corresponding author.

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Table 1. Recommendations for aortic regurgitation diagnosis and management

Organization responsible for guideline development	American College of Cardiology / American Heart Association (ACC/AHA) [6]	European Society of Cardiology (ESC) [7]	JCS/JSCS/JATS/JSVS [13]
Country where applied	USA	Europe	Japan
Year of publication	2020	2021	2020
AGREE II rigor Score %	93%	89%	50%
Conflicts of interest	EI, SCI a,b	EI, SCI a	EI, SCI a
Methods used to evaluate evidence	Systematic review	Systematic review	Systematic review
Methods used to formulate recommendations	Formal consensus	Formal consensus	Formal consensus
Consideration of Costs	Information from studies on cost considered where available	Not reported	Cost considered
Screening	• In first degree relatives of patients with known BAV a screening TTE might be considered to look for BAV or asymptomatic dilatation of the aortic sinuses and ascending aorta (**IIbB-NR**)	• In first degree relatives of patients with known BAV a screening TTE might be considered	• Not reported
Key diagnostic imaging	**Acute AR** • **TTE** or **TOE** is indispensable in confirming the presence, severity, and aetiology of acute AR **Chronic AR** • **TTE** preferred for assessment of cause and severity of AR (**IB-NR**)	• **TTE** or **TOE** are key investigations for confirming the presence, severity, and aetiology of acute AR, as well as feasibility of valve-sparing aortic surgery or valve repair	• **TTE (I)**

Table 1. Recommendations for aortic regurgitation diagnosis and management

Additional tests	**Acute AR** • **CT** imaging to look for aortic dissection • **TOE** may be helpful when CT imaging is unavailable or during intra-operative assessment • **Angiogram** only considered when differential diagnosis includes ACS **Chronic AR** • **TOE/CMR/Cardiac catheterisation** should be considered for assessment of LV systolic function, systolic and diastolic volumes, aortic size, and AR severity, if there is discrepancy between clinical and TTE findings (**IB-NR**) • **Aortic MR angiography or CT angiography** is indicated for patients with bicuspid AV when morphology of the aortic sinuses, sinotubular junction or ascending aorta cannot be assessed accurately or fully by TTE (**IB-NR**)	**TOE** • Preoperatively • Intraoperative evaluation of surgical result undergoing AV preservation or repair **3-D echo and GLS** • May be useful in patients with borderline LV EF where they may help in decision for surgery **CMR** • Should be used to quantify the regurgitant fraction when echo measurements are equivocal or discordant with clinical findings **CCT** • If aortic dilatation, to measure max aortic diameter at four levels	**TOE** • If TTE imaging is suboptimal for assessment of aetiology and severity (**IB**) **Stress echocardiography** • To assess cardiac reserve and reveal subclinical cardiac dysfunction in asymptomatic patients **CMR** • Reasonable to assess haemodynamic and severity of regurgitation if TTE images are suboptimal or there is discrepancy between symptoms and echo findings (**IIaB**) **CCT** • Reasonable for patients undergoing aortic valve repair to evaluate leaflets and aortic root (**IIaC**) **Aortic MR angiography or CT angiography** • Is indicated for patients with bicuspid AV when morphology of the aortic sinuses, sinotubular junction or ascending aorta cannot be assessed accurately or fully by TTE **Cardiac catheterization** • Reasonable to assess haemodynamics and severity of AR if TTE images are suboptimal and/or there is discrepancy between symptoms and echo findings (**IIaC**)

Table 1. Recommendations for aortic regurgitation diagnosis and management

CAD assessment prior to valve intervention	**Invasive coronary angiography** • In patients with symptoms of angina, objective evidence of ischaemia, decreased LV systolic function, hx of CAD or coronary risk factors (including men >40 years of age and postmenopausal women) (**IC-LD**) **CT coronary angiogram** • Is reasonable in patients with low to intermediate pretest probability of CAD to exclude the presence of significant CAD (**IIaB-NR**)	**Invasive coronary angiography** • Recommended in patients with history of cardiovascular disease, suspected ischemia, LV systolic dysfunction, men >40 years of age and postmenopausal women or ≥ 1 cardiovascular risk factors (**IC**) **CT coronary angiogram** • Can be performed if risk of coronary disease is low, technically not feasible or associated with a high risk (**IIaC**)	**Invasive coronary angiography** • Recommended in patients with history of CAD, suspected ischemia, LV systolic dysfunction, men >40 years of age and postmenopausal women or ≥ 1 cardiovascular risk factors (**IC**)
Surveillance of AR	**Mild AR**, progressive (Stage B) • Every 3-5 years **Moderate AR**, progressive (Stage B) • Every 1-2 years **Severe asymptomatic** (Stage C1) • Every 6-12 months • If an apparent significant fall in EF or increase in LV size is observed, repeat imaging typically is performed at 3- to 6-month intervals unless there is clinical deterioration	**Mild to moderate AR** • Yearly follow up, with echo every 2 years **Severe asymptomatic AR** with **normal** LV function • Yearly follow up **Severe asymptomatic AR** with LVEF/diameter showing significant changes or approaching thresholds for surgery • Every 3-6 months	**Mild AR** • Every 3-5 years **Moderate AR** • Every 1-2 years **Severe AR** • Every 6-12 months* *Dilating LV – more frequent monitoring may be required
Markers of severe AR	• Vena contracta >0.6 cm	• Vena contracta >0.6 cm	• Vena contracta ≥ 0.6 cm
	• Holodiastolic flow reversal in the proximal abdominal aorta	• Holodiastolic flow reversal in the descending aorta (end-diastolic velocity >20cm/s)	• Holodiastolic flow reversal in the descending aorta
	• Regurgitant volume ≥60 mL/ beat	• Regurgitant volume ≥60 mL/ beat	• Regurgitant volume ≥ 60 mL/beat
	• EROA ≥0.3 cm^2	• EROA ≥0.3 cm^2	• EROA ≥ 0.3 cm^2
	• Evidence of LV dilation	• Evidence of LV dilation	• Evidence of LV dilatation
	• Doppler jet width ≥65% of LVOT	• Large Doppler jet in central jets	• Jet width ≥ 65% of LVOT

Table 1. Recommendations for aortic regurgitation diagnosis and management

		• Regurgitant fraction ≥50%	• Not reported	• Regurgitant fraction ≥ 50%
		• Not reported	• Pressure halftime of regurgitant jet <200 m/s	• Pressure halftime of regurgitation jet <200 m/s
		• Angiography grade 3 to 4	• Not reported	• Angiography grade 3 to 4
Medical therapy for <u>chronic</u> AR		• **Asymptomatic** patients with chronic AR (Stages B and C), hypertension (systolic blood pressure >140 mm Hg) treatment is recommended (**IB-NR**) • In patients with **symptoms** and/or **LV systolic dysfunction** (Stages C2 and D) but prohibitive surgical risk, GDMT for reduced LVEF with ACE-I, ARBs and/or sacubitril/valsartan is recommended (**IB-NR**)	• Medical therapy (ACE-I or dihydropiridines) may provide symptomatic improvement in patients with severe AR in whom surgery is not feasible • In patients who undergo surgery but continue to suffer from heart failure or hypertension, ACE-I, ARBs and beta-blockers are useful	• Not reported
Therapy for <u>acute</u> severe AR		• Medical therapy to reduce LV afterload may be given for stabilization but surgery should not be delayed especially if there is hypotension, pulmonary oedema or evidence of low flow • Intra-aortic balloon counterpulsation is contraindicated	• Not reported	• Not reported
Intervention in symptomatic patients		**Symptomatic** severe AR (Stage D) • AVR is indicated regardless of LV systolic function (**IB-NR**)	**Symptomatic** severe AR • Surgery is indicated regardless of LV systolic function (**IB**)	**Symptomatic** severe AR **(IB)** • Surgery is indicated regardless of LV systolic function as surgical risk is not prohibitive
Surgical intervention in asymptomatic patients	**Impaired LV systolic function**	**Asymptomatic** patients with severe AR and LV systolic dysfunction (LVEF ≤55%) (Stage C2) • AVR is indicated if no other cause for LV systolic dysfunction is identified (**IB-NR**)	**Asymptomatic** patients with severe AR and resting LVEF ≤50% - surgery is indicated (**IB**) **Asymptomatic** patients with resting LVEF <55% if low-risk surgery (**IIbC**)	**Asymptomatic** severe AR and LVEF <50% (**IB**)

Table 1. Recommendations for aortic regurgitation diagnosis and management

	Preserved LV systolic function	**Asymptomatic** patients with severe AR and normal LV systolic function (LVEF >55%) • AVR is reasonable when LV severely enlarged (LVESDI >50 mm or indexed LVESDI >25 mm/m2) (Stage C2) (**IIaB-NR**) Asymptomatic patients with severe AR and normal LV systolic function at rest (LVEF >55%; Stage C1) and low surgical risk AVR may be considered on the basis of progressive decline in LV EF on at least 3 serial studies or a progressive increase in LV dilatation into the severe range (LV end-diastolic dimension [LVEDD] >65 mm) (**IIbB-NR**)	**Asymptomatic** patients with severe AR and: • LVESD >50mm (**IB**) OR • LVESDI >25mm/m^2 BSA (**IB**) OR • LVESDI >20mm/m^2 BSA if low-risk surgery (**IIbC**) Progressive enlargement of the LV, or progressive decrease in its function in asymptomatic patients not reaching the thresholds for surgery but significant LV dilatation (LVEDD >65 mm), may be an appropriate indicator	**Asymptomatic** severe AR with LV EF ≥50% and: • Reasonable if LVESD >45 mm (**IIaB**) • May be considered if LVEDD >60 mm (**IIbC**) • May be considered after careful follow-up if indexed LVESDI >25 mm/m^2 (**IIbC**)
Other considerations when aortic root is dilated		• In patients with BAV and indications for AVR, replacement of the aortic sinuses and/or ascending aorta is reasonable if surgery is performed at a comprehensive valve centre when aortic dimension is ≥45 mm (**IIaB-NR**) • In patients with BAV who meet criteria for replacement of aortic sinuses, valve-sparing surgery may be considered if performed at a comprehensive valve centre (**IIbC-LD**)	• If surgery is indicated for severe AR, replacement or aortic root or tubular ascending aorta should be considered when ≥45 mm (**IIaC**)	• If surgery is indicated for severe AR, replacement or aortic root or tubular ascending aorta should be considered when: o ≥45mm and BAV (**IIaC**) or Marfan syndrome (**IC**) o ≥50mm when tricuspid AV (**IIaC**)
Surgical intervention of AR in the context of concurrent cardiac surgery		Patients undergoing cardiac surgery for other indications with: • **Severe AR** (Stage C or D) - AVR is indicated (**IC-EO**) • **Moderate AR** (Stage B) - AVR is reasonable (**IIaC-EO**)	• Patients with **severe AR** (symptomatic and asymptomatic) undergoing CABG or surgery of the ascending aorta or another valve (**IC**)	• **Recommended** for patients with **severe AR** undergoing CABG or surgery of the ascending aorta or other heart valves (**IC**) • **Reasonable** for patients with **moderate AR** undergoing CABG or surgery of the ascending aorta or other heart valves (**IIaC**)
Choice of surgical procedure		• AVR (mechanical or bioprosthetic valve) • Preservation of native aortic valve may be possible	• AVR • Aortic valve repair may be considered in	• None specifically mentioned

Table 1. Recommendations for aortic regurgitation diagnosis and management

	in patients with favourable valve anatomy who are undergoing surgical replacement of aortic sinuses and/or ascending aorta	selected patients at experienced centres when durable results are expected (**IIbC**)	
Percutaneous therapy	• TAVI should not be performed in patients with isolated severe AR who have indications for SAVR and are surgical candidates (**IIIB-NR**)	• TAVI may be considered in experienced centres for selected patients ineligible for SAVR	• None specifically mentioned
Defining risk	<u>High risk SAVR:</u> • Society of Thoracic Surgeons (STS) predicted risk of death >8% <u>OR</u> • Frailty - ≥2 indices (moderate to severe) <u>OR</u> • 1 to 2 organ system compromise not to be improve postoperatively <u>OR</u> • Procedure-specific impediment <u>Prohibitive risk SAVR:</u> • STS predicted risk of death or major comorbidity (all-cause) >50% at 1-year <u>OR</u> • Frailty ≥2 indices (moderate to severe) <u>OR</u> • ≥3 organ system compromise not to be improve postoperatively <u>OR</u> • Severe procedure-specific impediment	• Medical comorbidities • Frailty • Poor mobility • EuroSCORE II and the Society of Thoracic Surgeons (STS) score	• Medical comorbidities • Frailty • Cognitive function • JapanScore 2 • EuroSCORE II • Society of Thoracic Surgeons (STS) predicted risk of mortality (PROM) score
Mixed valvular disease	• In symptomatic patients with combined **AS** and **AR** and a peak transvalvular jet velocity of ≥4.0 m/s or mean transvalvular gradient of ≥ 40 mmHg, **AVR** is recommended (**IB-NR**) • In asymptomatic patients with combined **AS** and **AR** who have a jet velocity of ≥4.0 m/s with an LV EF <50%, **AVR** is recommended (**IC-EO**) • In symptomatic patients with combined **MS** and **AR** despite diuretic therapy, intervention with valve surgery should be sought o If MV anatomy is favourable, **PMBC** to treat MS, followed by **AVR/SAVR** and **open commissurotomy** in order to reduce risks of double valve replacement would be reasonable	• If **AR** requiring surgery is associated with severe **MR** (primary or secondary), both should be addressed during the same operation • If **MV** requiring surgery is associated with moderate **AR,** decision to treat the AV is controversial	**AS** and **AR** • Requires careful assessment to work out the predominant valve pathology **MR** and **AR** • Surgical indications determined by the predominant valve lesion • Dual valve surgery is recommended for >moderate AR if surgical intervention is indicated for severe MR

Table 1. Recommendations for aortic regurgitation diagnosis and management

Non-cardiac surgery	• In patients with suspected moderate-severe regurgitation an up-to-date preoperative TTE recommended
	• VHD that fall under standard recommendations for intervention should be corrected before non-cardiac surgery (depending on urgency of surgery) **(IC-EO)**
	• In **asymptomatic patients** with moderate of greater degree of AR and **normal LV systolic function** it is reasonable to perform elective noncardiac surgery
		• Can be performed **safely** in **asymptomatic severe AR** patients with preserved LV function
		  • Presence of symptoms or LV dysfunction should prompt consideration of valvular surgery, but this is seldom needed before non-cardiac surgery
		  • If severe AR and LVEF <30% and/or SPAP is 50-60 mmHg, non-cardiac surgery should only be performed if strictly necessary after optimization of medical therapy for heart failure
			• Noncardiac surgery can be performed **safely** in **asymptomatic** severe AR when LV function is maintained
			• Valve surgery prior to noncardiac surgery may be considered for symptomatic patients or patients with reduced cardiac function
			• If heart failure is medically managed, valve surgery prior to noncardiac surgery is rarely required
			• When LVEF <30% non-cardiac surgery should only be performed after optimal medical therapy and only when it is absolutely necessary

ACEi, angiotensin-converting enzyme inhibitors; **AR,** aortic regurgitation; **ARB**, Angiotensin receptor blockers; **AS**, aortic stenosis; **AVR**, aortic valve replacement; **BAV**, bicuspid aortic valve; **BSA**, body surface area; **CABG**, coronary artery bypass grafting; **CAD**, coronary artery disease; **CCT**, cardiac computer tomography; **CMR**, cardiovascular magnetic resonance; **EDD**, end-diastolic diameter; **EDDI**, end-diastolic diameter index; **EF**, ejection fraction; **ERO**, effective regurgitant orifice; **ESD**, end-systolic diameter; **EDV**, end diastolic volume; **ESVI**, end-systolic dimension index; **GDMT**, guideline-directed medical therapy; **LV**, left ventricle; **LVOT**, left ventricular outflow tract; **MR**, mitral regurgitation; **MS**, mitral stenosis; **MV**, mitral valve; **PMBC**, percutaneous mitral balloon commissurotomy; **SAVR**, surgical aortic valve replacement; **SPAP**, systolic pulmonary artery pressure; **TAVI**, transcatheter aortic valve implantation; **TTE**, transthoracic echocardiogram; **TOE**, transoesophageal echocardiogram; **VHD**, valvular heart disease.

EI, editorial independence declared; SCI, statement about conflicts of interest of group members present

a - Relationship with industry is reported by any group member;
b - A group member is reported recused when a relevant area is under discussion;
c - Conflicts of interest only available upon request.

Level of evidence: A = Data derived from multiple randomized clinical trials or meta-analysis. B = Data derived from a single randomized trial or nonrandomized studies. C = Only consensus opinion of experts, case studies or standard of care.
Recommendation class: Class I = benefit >>> risk. Class IIa = benefit >> risk. IIb benefit ≥ risk. Class III = risk > benefit

The application of class of recommendation and level of evidence characterization of STS clinical practice guidelines is according to those recommended by ACCF/AHA: Level of Evidence (LoE) A, B, C.
Class of recommendations: I, conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective; Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment; IIa, weight of evidence/opinion is in favor of usefulness/efficacy; IIb, usefulness/efficacy is less well established by evidence/opinion; III, conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

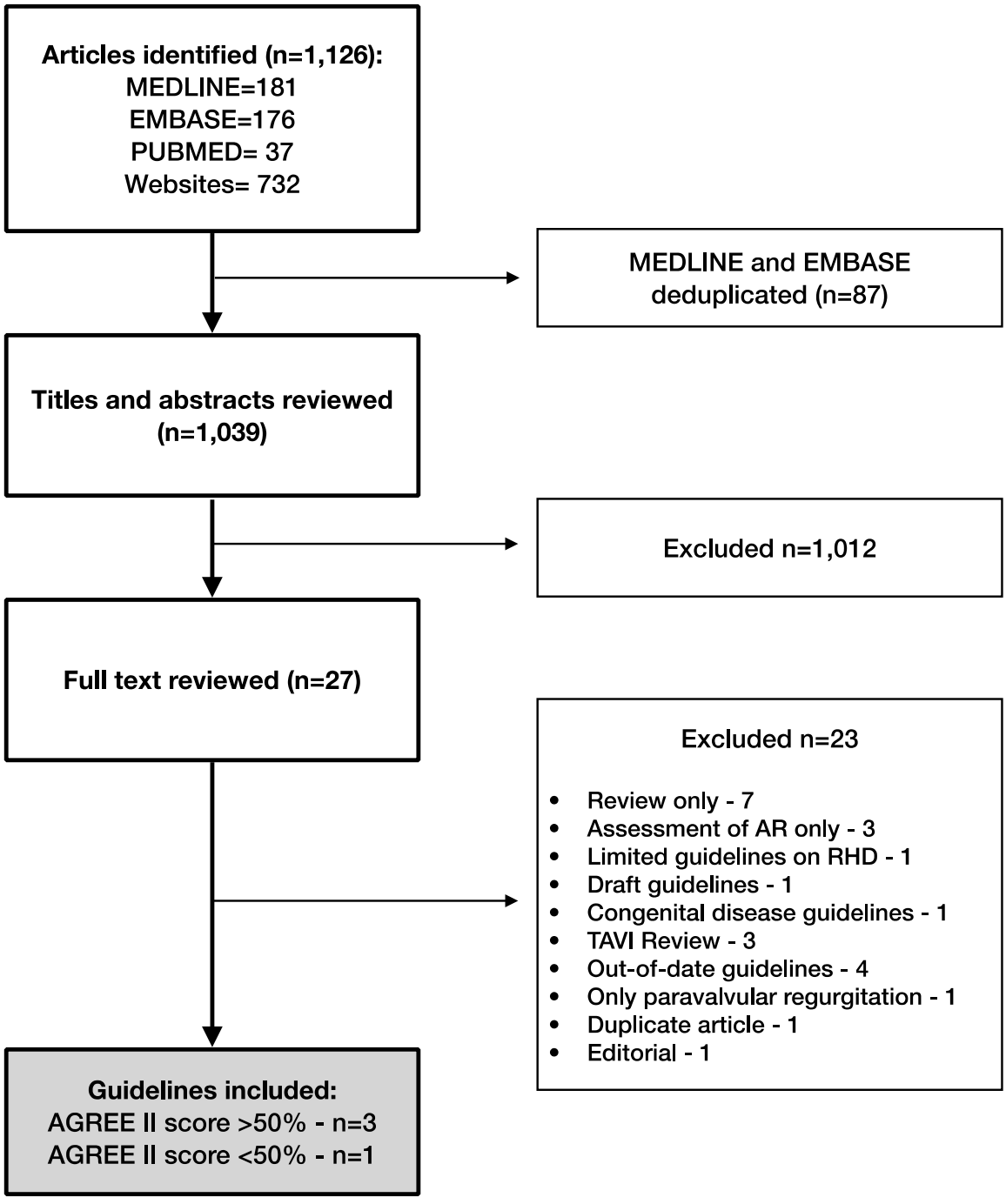

Figure 1 - Summary of the guideline search and review process

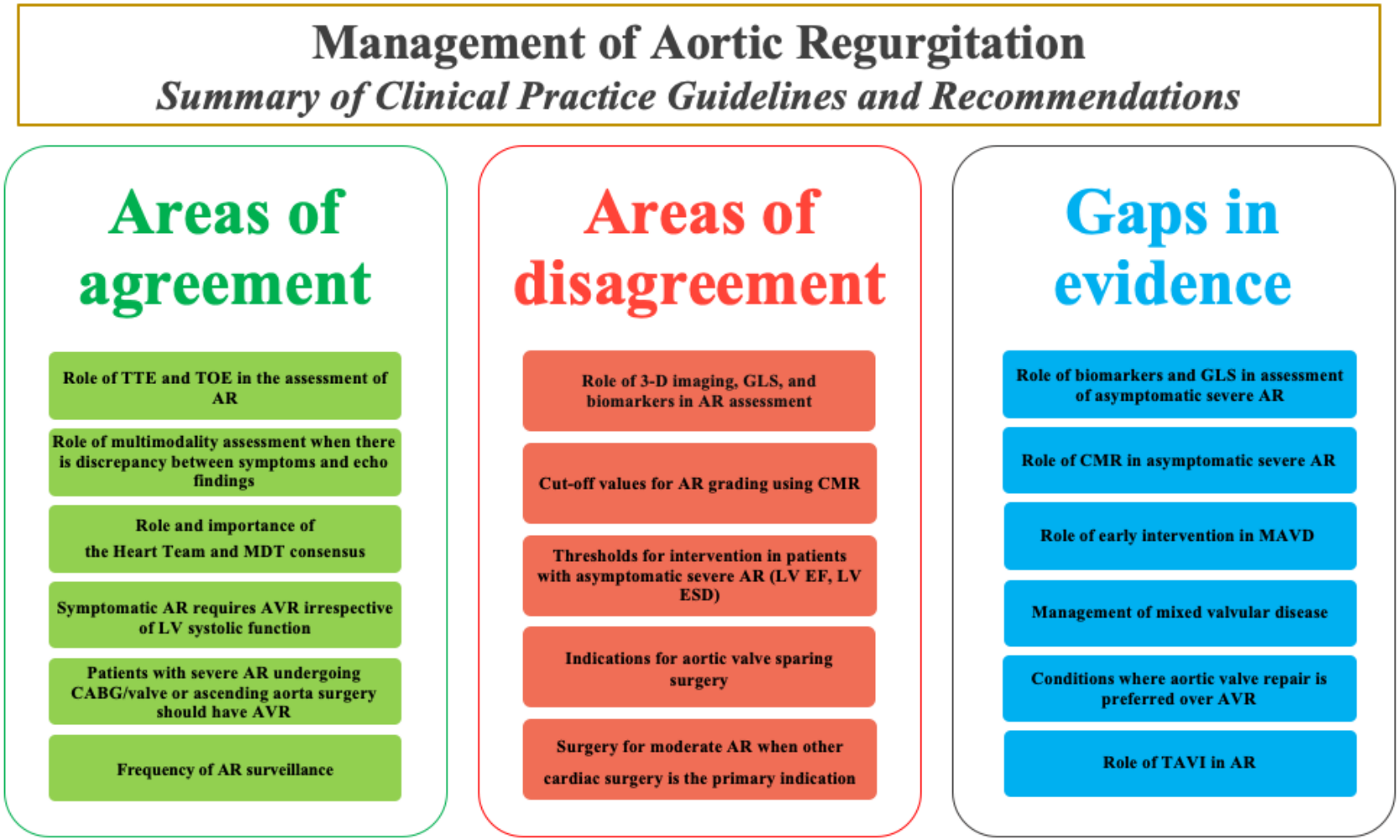

Figure 2 - Central illustration