Heart failure is an inevitable end-stage consequence of significant valvular heart disease (VHD) that is left untreated and increasingly encountered in an ageing society. Recent advances in transcatheter procedures and improved outcomes after valve surgery mean that intervention can (and should) be considered in all patients – even the elderly and those with multiple comorbidities - at earlier stages of the natural history of primary VHD, before the onset of irreversible left ventricular dysfunction (and frequently before the onset of symptoms). All patients with known VHD should be monitored carefully in the setting of a heart valve clinic and those who meet guideline criteria for surgical or transcatheter intervention referred for intervention without delay.

High quality evidence for the use of medical therapy in VHD is limited and achieving target doses in an elderly and comorbid population frequently challenging. Furthermore, determining whether the valve or ventricle is the principal disease driver is crucial (although the distinction is not always binary, and often unclear). Guideline-directed medical therapy remains the mainstay of treatment for secondary mitral regurgitation - although up to 50% of patients may fail to respond and should be considered for cardiac resynchronization, transcatheter or surgical valve intervention. Early and definitive management strategies are essential and should be overseen by a specialist Heart Team that includes a Heart Failure specialist. In this article, we provide an evidence-based summary of approaches to the medical treatment of VHD and clinical guidance for the best management of patients in situations where high quality evidence is lacking.

Graphical Abstract

A schematic diagram summarising key principles of management in patients with heart failure and valvular heart disease.
Introduction

Valvular heart disease (VHD) is estimated to affect 2.5% of the population and 50% of those aged over 65 years.\(^1\)\(^2\) Degenerative disease has eclipsed rheumatic heart disease as the primary aetiology in high-income nations and, in the context of an ageing demographic, the prevalence of moderate-severe VHD in older patients is projected to double by 2046.\(^2\) The burgeoning demographic, the prevalence of moderate-severe VHD in disease has eclipsed rheumatic heart disease as the primary inoperable.\(^3\) Despite vast progress, cohorts with prohibitive burden of disease has spurred advances in transcatheter valve therapies, extending treatment to patients considered surgically inoperable.\(^3\) Despite vast progress, cohorts with prohibitive procedural risk persist, rendering any form of valve intervention unfeasible, whilst other groups remain below the threshold for intervention.\(^4\) In either case, left ventricular systolic dysfunction (LVSD) frequently underpins or accompanies VHD, indicating a role for guideline-directed medical therapy (GDMT). For some valve lesions, GDMT is vital in delaying the emergence of symptoms or need for intervention, whereas in other lesions its place is less well defined. Achieving target doses in an elderly and comorbid population can prove challenging, with notable impacts on quality of life and survival, thereby highlighting the importance of early and definitive management strategies where available.\(^5\)\(^6\) Regardless of aetiology, GDMT remains a cornerstone of heart failure management, although evidence for its use in the setting of VHD and LVSD is frequently lacking (Table 1).\(^7\)\(^-\)\(^18\) This article aims to provide clarity in these situations, with an evidence-based approach to medical treatment of VHD.

Aortic stenosis

Aortic stenosis (AS) affects approximately 12% of individuals aged >75 years.\(^19\) No pharmacological treatments delay its progression and the only available treatment is surgical or transcatheter valve replacement, determined by the severity of AS, symptomatic status and left ventricular (LV) systolic function. Current European Society of Cardiology (ESC) guidelines indicate valve replacement for those patients with severe AS who have symptoms, impaired LV systolic function (ejection fraction <50%) or in whom other cardiac surgery is being performed.\(^20\)

It is currently estimated that 1.2% of patients attending for routine echocardiography have moderate or severe AS with impaired LV systolic function (0.8% moderate AS, 0.4% severe AS).\(^21\) Heart failure in severe AS is multifactorial and reflects myocardial damage secondary to valvulo–arterial impedance and myocardial ischaemia.\(^22\) Four stages of myocardial damage can be observed with incremental impact on mortality [Stage 0: no myocardial damage, 1-year mortality 4.4%; Stage 1: reduced LV systolic function and increased LV filling pressures; Stage 2: additional damage to the left atrium and mitral valve; Stage 3: onset of pulmonary hypertension and tricuspid regurgitation (TR); Stage 4: significant right ventricular dysfunction, 25% 1-year mortality].\(^23\) The prevalence of a LV ejection fraction (LVEF) <50% in patients at greater than intermediate risk for aortic valve replacement is estimated between 30–50%.\(^23\) The impact of myocardial damage on the prognosis of these patients is significant and underscores the importance of regular echocardiographic surveillance and incorporation of additional markers of myocardial injury (Table 2).

In patients with myocardial impairment, discordant echocardiographic markers of AS severity can be observed in up to 50% of patients.\(^24\) ‘Low-gradient AS’ is defined by an aortic valve area (AVA) \(\leq 1\text{cm}^2\) and mean gradient \(<40\text{mmHg}\) and can generate uncertainty concerning the indication for aortic valve intervention.\(^20\) The most common explanation for low-gradient AS is low forward flow (<35 mL/m\(^2\)),\(^24\) which may be observed in the presence of impaired (classical low-flow low-gradient) or preserved LV function (paradoxical low-flow low-gradient AS). Meticulous assessment of AS severity using dobutamine stress echocardiography and/or aortic valve calcium scoring is required in classical low-flow-low-gradient AS. Severe AS is confirmed if the stress mean gradient is \(\geq 40\text{mmHg}\) and AVA \(\leq 1\text{cm}^2\) after administration of intermediate dose dobutamine, and if the aortic valve calcium score is \(\geq 2000\text{Agatston units in men (or \(\geq 1200\text{Agatston units in women) on gated non-contrast computed tomography.}^{20}\)

Pseudo-severe AS is confirmed if these thresholds are not met.

All patients who do not require immediate intervention should maintain regular surveillance in a dedicated heart valve clinic.\(^20\) Here the principal aims are to optimize the timing of intervention by careful symptom assessment, exercise stress testing, serial echocardiography, and management of comorbidities.\(^25\) It is now recognized that moderate AS is not a benign entity. A mean transaortic valve gradient \(\geq 20\text{mmHg}\) carries a greater than 50% 5-year mortality independent of age, gender, systolic and diastolic dysfunction.\(^26\) With studies suggesting a decline in LVEF before the onset of severe AS and accelerated deterioration once the AVA falls below 1.2 cm\(^2\), it is likely that exposure to persistent afterload elevation has a detrimental effect on LV function.\(^27\) Ongoing studies are likely to clarify whether treatment of moderate AS in patients with reduced LVEF reduces all-cause deaths and hospitalizations related to heart failure (TAVR UNLOAD, NCT02661451). While outcomes are awaited, pharmacological therapy to reduce total valvulo–arterial impedance is recommended.

Hypertension is a risk factor for AS and associated with increased rate of progression and reduced survival.\(^28\) It increases LV afterload and thereby LV mass, which is independently associated with mortality—15 g/m\(^2\) increase is associated with a 61% increase in the risk of cardiovascular death. Given that AS-related afterload may only be modified by valve intervention, treatment of hypertension is a valid target. Accordingly, both the ESC and American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend treatment of hypertension in patients with AS, but fail to specify optimal antihypertensive agents or treatment targets.\(^20\)\(^29\) In the absence of clear guidelines, pragmatic goals are a systolic blood pressure of 130–139 mmHg and a diastolic blood pressure of 70–90 mmHg.\(^30\)

There are limited randomized data concerning the treatment of hypertension in AS patients. The Symptomatic Cardiac Obstruction-Pilot Study of Enalapril in Aortic Stenosis (SCOPE-AS) showed that gradual titration of enalapril from 2.5 mg twice daily to 10 mg twice daily was well tolerated in patients with symptomatic severe AS, no syncope or hypotension, and preserved LV systolic function.\(^31\) Similarly, ramipril 10 mg/day was used
Table 1 Inclusion of valvular heart disease in key heart failure trials

| Pharmacological class | Pharmacological agent | Trial           | VHD patients included | Valve lesions delineated | Reference |
|-----------------------|-----------------------|-----------------|-----------------------|--------------------------|-----------|
| Beta-blockers         | Metoprolol            | MERIT-HF        | Yes                   | No                       | 7         |
| Beta-blockers         | Bisoprolol            | CIBIS-II        | Yes                   | No                       | 8         |
| ACE-inhibitors        | Enalapril             | CONSENSUS       | Yes                   | No                       | 9         |
| ACE-inhibitors        | Enalapril             | SOLVD           | Partial, severe VHD requiring surgery constituted an exclusion criterion | No | 10 |
| ARBs                  | Candesartan           | CHARM-low       | Yes                   | No                       | 11        |
| MRAs                  | Spironolactone        | RALES           | Partial, MR and TR included if responsible for LVSD and symptoms | No | 12 |
| Nitrates and hydralazine | Isosorbide dinitrate and hydralazine | V-HeFT        | Partial, considerable obstructive VHD constituted an exclusion criterion | No | 13 |
| I$_{1}$-channel inhibitors | Ivabradine           | SHIFT           | Yes                   | No                       | 14        |
| Neprilysin inhibitor  | Valvastatin and sacubitril | PARADIGM-HF    | Yes, but not reported as discrete subgroup | Not delineated | 15 |
| SGLT2 inhibitors      | Dapagliflozin         | DAPA-HF         | Partial, Primary VHD constituted an exclusion criterion | Secondary valve disease groups not delineated | 16 |
| SGLT2 inhibitors      | Empagliflozin         | EMPEROR-Reduced | Any severe (obstructive or regurgitant) VHD expected to lead to surgery during the trial period constitutes an exclusion criterion | Not delineated | 17 |
| cGMP-activator        | Vericiguat            | VICTORIA        | Partial, Primary VHD requiring intervention or surgery constituted an exclusion criterion | Not delineated | 18 |

This table demonstrates the inclusion and exclusion of VHD cohorts within major heart failure trials, and whether or not valve lesions were differentiated for subsequent analysis.

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; cGMP, cyclic guanosine monophosphate; I$_{1}$, funny current channel; LVSD, left ventricular systolic dysfunction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium–glucose co-transporter 2; TR, tricuspid regurgitation; VHD, valvular heart disease.

Table 2 Recommended surveillance intervals and considerations for common valve lesions

| Valve lesion          | Classification of severity (quantitative or integrated assessment) | Follow-up interval | Additional considerations |
|-----------------------|---------------------------------------------------------------------|--------------------|--------------------------|
| Aortic stenosis       | $V_{\text{max}} > 4.0$ m/s or EOA < 1.0 cm$^2$                     | 6 months           | Consider annual ETT      |
|                       | $V_{\text{max}} 3.5$–$4.0$ m/s + AV calcium                        | 6 months           | ETT at baseline          |
|                       | $V_{\text{max}} 3.0$–$4.0$ m/s or EOA $1.0$–$1.5$cm$^2$ every year + ETT at baseline | 12 months          | Early surgery if lesion becomes severe |
|                       | $V_{\text{max}} 2.5$–$3.0$ m/s                                   | 36 months          | 3 months if LV dilated   |
| Aortic regurgitation  | Severe                                                              | 6 months           | ETT can be considered    |
|                       | Moderate                                                            | 12–24 months       | Indicated if aortic root dilatation (as per moderate) |
|                       | Mild                                                                | Not indicated      | Annual ETT               |
| Mitral regurgitation  | Severe                                                              | 6 months           |                           |
|                       | Moderate                                                            | 12–24 months       |                           |
|                       | Mild                                                                | Not indicated      |                           |
| Tricuspid regurgitation | Severe                                                            | 6 months           |                           |
|                       | Moderate                                                            | 12–24 months       |                           |

This table summarizes the recommended follow-up for the common valve lesions based on severity and where additional investigations or considerations are required.

AV, aortic valve; EOA, estimated orifice area; ETT, exercise tolerance test; LV, left ventricle; $V_{\text{max}}$, aortic maximum velocity.

to effectively reduce blood pressure and LV mass at 12 months in patients with moderate-severe asymptomatic AS compared to placebo. Further studies also suggest a protective effect of angiotensin-converting enzyme (ACE) inhibition and angiotensin receptor blockers (ARBs), which reduce progression of aortic valve calcification, all-cause mortality (−24%) and cardiovascular events (−23%). Along with ACE inhibitors and ARBs, beta-blockers are used extensively in the management of heart failure. Metoprolol reduces valve gradients and myocardial oxygen consumption in asymptomatic moderate-severe AS, whilst patients already receiving beta-blockers at baseline in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study demonstrated reduced cardiovascular [hazard ratio (HR) 0.4, 95% confidence interval (CI) 0.2–0.7]
and all-cause mortality (HR 0.5, 95% CI 0.3–0.7).\textsuperscript{33,34} Although evidence is insufficient to justify the universal recommendation of beta-blockers in AS, cautious use in patients with prior myocardial infarction, angina, heart failure and cardiac arrhythmias is reasonable.

Calcium channel blockers (CCBs) and alpha-blockers should be avoided where possible in patients with AS and hypertension. In a retrospective study of 314 patients with moderate-severe AS, use of CCBs was associated with a sevenfold increase in mortality, independent of age, gender, diabetes, LVEF and AVA (although the study failed to differentiate between dihydropyridine and non-dihydropyridine agents).\textsuperscript{35} In the SEAS cohort, alpha-blockers were the only antihypertensive agents associated with increased cardiovascular events.\textsuperscript{36}

A study investigating 804 subjects undergoing transcatheter aortic valve implantation identified loop diuretic administration in 48% of patients pre-procedure (with 22% having an ejection fraction <40%).\textsuperscript{37} Diuretic usage signalled a more comorbid, frail group of patients at greatest risk of poor outcomes. Loop diuretics should be used cautiously in patients with severe AS, LV hypertrophy and small ventricular cavities where abrupt changes in intravascular volume may result in significant hypotension. Mineralocorticoid receptor antagonists (MRAs) are likely to be well tolerated in patients with AS but have not been shown to delay onset of LVSD or reduction in LV mass.\textsuperscript{38} Nitrates reduce LV end-diastolic pressure and acute administration of sodium nitroprusside can reduce vascular resistance, thereby improving valvulo–arterial impedance and reducing LV work. Enhanced perfusion and augmented cardiac indices have been observed with administration of nitroprusside in patients with severe AS, reduced LV function and congestive cardiac failure.\textsuperscript{39} A retrospective evaluation of AS patients with acute pulmonary oedema failed to show any association between nitrate administration and the development of clinically relevant hypotension.\textsuperscript{40} Despite some reassurance from this evidence, no large studies have evaluated the impact of nitrates on the myocardial response to AS or clinical outcomes. Their role in AS therefore remains unclear, although ill-effects are probably theoretical.

**Targeting aortic stenosis progression**

Common pathways underpin the pathological mechanisms of AS and atherosclerosis prompting research to evaluate translational benefit.\textsuperscript{41} Statins have faced the greatest scrutiny with observational studies demonstrating reduced valvular calcification and haemodynamic deterioration. Despite early enthusiasm, subsequent randomized trials have failed to exhibit consistent improvement in survival.\textsuperscript{42} Lipoprotein(a) (LPA) polymorphisms are associated with valvular calcification and therapies which lower LPA levels [such as niacin and proprotein convertase subtilisin/kexin type 9 (PCSK9)] are currently being investigated.\textsuperscript{43,44} Drugs modulating calcium homeostasis and conventionally used in osteoporosis are now being investigated by comparison of valvular calcification in patients receiving alendronic acid (a bisphosphonate) or denosumab (a monoclonal antibody RANKL-activator) (SALTIRE II, NCT02132026). However, to date no agents have demonstrated the ability to arrest the progression of disease or development of heart failure and further work is required to establish clinical utility.

**Aortic regurgitation**

Chronic aortic regurgitation (AR) affects 0.5% of the population.\textsuperscript{1} Symptoms attributed to valve dysfunction, LV dilatation and systolic dysfunction are indications for valve replacement.\textsuperscript{40,41} The natural history of chronic AR is characterized by progressive LV pressure and volume overload. In the early stages, myocardial compliance and reactive LV hypertrophy ensure that stroke volume is maintained with normal end-diastolic pressures.\textsuperscript{45} During this period, patients are frequently asymptomatic. As valvular insufficiency advances, the left ventricle dilates and compensatory mechanisms are overcome with subsequent development of LV dysfunction. The aims of medical management are to control systemic hypertension, reduce regurgitant volume and minimize adverse remodelling.\textsuperscript{29}

Calcium channel antagonists have a vasodilatory effect and their putative benefit in chronic AR lies in their ability to reduce LV afterload and attenuate declining ejection fraction. In an investigation of 143 asymptomatic patients with AR, nifedipine reduced or delayed the need for surgery, a finding supported by a subsequent smaller study.\textsuperscript{46,47} On the basis of this evidence, nifedipine may reduce the risk of LVSD in asymptomatic patients, but its impact on survival remains unclear.

The vasodilatory effects of ACE inhibitors/ARBs reduce preload and diminish regurgitant volume whilst increasing effective stroke volume. However, these theoretical benefits are yet to be translated consistently into clinical endpoints. Administration of quinapril resulted in reduced LV mass and increased LVEF in chronic AR, whereas enalapril only improved LV end-diastolic diameter in another study.\textsuperscript{48,49} Similarly, Evangelista et al. reported no delay or reduction in aortic valve surgery in patients with severe AR and preserved LV function treated with either enalapril or nifedipine.\textsuperscript{50} The greatest benefit has been noted in comorbid patients at prohibitive surgical risk. Thus, in a cohort study of 2266 patients with AR (45% of whom had LV systolic dysfunction), ACE/ARB reduced the composite endpoint of death or hospitalization due to heart failure.\textsuperscript{51}

Beta-blockers reduce afterload and aortic wall stress but may increase regurgitant volume due to a prolonged diastolic interval. In one small randomized study, metoprolol was associated with no change in LV dimensions in patients with AR over a 6-month interval compared with placebo, suggesting that concerns of harmful effects are unfounded.\textsuperscript{52} Indeed, a retrospective cohort study of 756 patients with AR reported increased survival in those receiving beta-blockers, although there was an associated increase in valve surgery.\textsuperscript{53} Beta-blockers may have a specific role in Marfan’s syndrome, with one randomized trial reporting reduced risk of aortic root dilatation, although this result is yet to be extrapolated to other groups.\textsuperscript{54}

Pharmacological management may play an important role in selected AR patients with hypertension or those unfit for surgery. However, it should be emphasized that GDMT is not a substitute for aortic valve replacement (and root surgery where indicated).
when guideline criteria are met, and should not be used as a temporising measure to delay referral for surgery.

**Mitral regurgitation**

Mitral regurgitation (MR) is among the most common valve conditions in high income countries with an estimated prevalence of 22.1% (2.3% moderate-severe) in patients aged >65 years that is set to increase significantly over the next decades as a consequence of the ageing population.1,2 MR can be sub-classified into primary MR, which occurs predominantly due to leaflet dysfunction, and secondary MR caused by multifactorial left atrio-ventricular dysfunction and adverse remodelling.

**Primary mitral regurgitation**

There is no evidence to support the use of vasodilators (including ACE inhibitors) in asymptomatic primary MR with normal LV systolic function. Afterload is typically normal in the early phases of compensated chronic MR but increased in chronic AR,35 potentially explaining the contrasting effects of vasodilatation in the two valvular lesions.36 The confounding effect of the favourable loading conditions created by a double outlet chamber in MR can result in maintained LV ejection performance and mask the insidious onset of LV contractile impairment.57 As such, patients with severe chronic primary MR meeting guideline thresholds should be referred for surgical or transcatheter intervention depending on anatomical and clinical suitability for treatment.20

The onset of LVSD is a clear indication for intervention. Whilst standard heart failure medical therapy (beta-blockers, ACE inhibitors and aldosterone antagonists) may provide symptomatic and prognostic benefits, instigation of such treatment should not delay referral for intervention, irrespective of symptom status.20,29 Similarly, those with concomitant systemic hypertension should be treated as per international guidelines to reduce cardiovascular risk and lower LV systolic pressure (thereby reducing MR severity).20,29

**Secondary mitral regurgitation**

Secondary MR is the most common form of MR, occurring in 12% of patients immediately after myocardial infarction and 24% of patients with chronic systolic heart failure (of any aetiology). Furthermore, secondary MR is haemodynamically significant in ≈30%38−40 and an independent driver of prognosis, particularly in patients with an intermediate heart failure phenotype.51 Even mild secondary MR is associated with a twofold increase in the risk of all-cause/cardiatic mortality and hospitalization for heart failure.62

Left ventricular dilatation is a critical determinant of secondary MR and GDMT for heart failure is the recommended first-line treatment to reduce LV end-diastolic volume, hospitalization and mortality.63 In the double-blind randomized PRIME (Pharmacological Reduction of Functional Ischemic Mitral Regurgitation) study, angiotensin receptor–neprilysin inhibition (ARNI) resulted in a greater reduction in effective regurgitant orifice area, regurgitant volume and LV end-diastolic volume index compared with valsartan at 1-year follow-up.15 Beta-blockade is also beneficial, with studies of metoprolol and carvedilol demonstrating reduction in LV end-diastolic volume and severity of secondary MR in 40% of patients.64−66 Furthermore, up-titration of isosorbide dinitrate and lisinopril led to reduction in LV end-diastolic volume and MR grade at 1-year follow-up in 42% of patients with severe secondary MR.67 Although there is relatively little substantial evidence demonstrating that ivabradine reduces chronic MR,68 several reports describe its use in patients presenting with acute decompen-sated MR when beta-blockers are relatively contraindicated.69 There is greater evidence supporting its use in patients with mitral stenosis who remain in sinus rhythm. Indeed, several studies have confirmed reduced heart rate and improved symptoms with similar efficacy (and improved tolerance) compared to metoprool, suggesting a potential role in the setting of beta-blocker intolerance.70

In a prospective study of 163 patients with heart failure and reduced ejection fraction (31% of whom had moderate or severe secondary MR), GDMT (including diuretics) was associated with reduction in MR severity (Grade <3) in 38% of patients over 4-year follow-up. Left bundle branch block was the principal predictor of a negative response to treatment.71

**Cardiac resynchronization therapy**

Left bundle branch block is a key mechanism of disproportionately secondary MR, whereby LV residual volume is greater than would be expected relative to end-diastolic volume. Cardiac resynchronization therapy (CRT) restores synchronous LV contraction, and reduces leaflet tethering and closing forces on the mitral valve apparatus, thereby improving leaflet coaptation. In addition to favourable LV remodelling, studies have shown that CRT results in a sustained reduction in the severity of secondary MR in roughly 50% of patients.72−75 Positive predictors of MR reduction include an LV end-systolic dimension index <29mm/m², absence of scar at the point of papillary muscle insertion, and anterosetal to posterior wall radial strain dysynchrony >200 ms.76 CRT therefore plays an important role alongside GDMT in carefully selected patients with secondary MR prior to consideration of transcatheter or surgical intervention.

**Transcatheter edge-to-edge repair**

The COAPT (Cardiovascular Outcomes Assessment of the Mitra-Clip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial resulted in a 36-month primary outcome of death/heart failure hospitalization of 58.8% vs. 88% in the GDMT cohort with a number needed to treat (NNT) of 3.2.77 Conversely, the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trial failed to demonstrate any benefit in favour of transcatheter edge-to-edge repair.78 The contrasting findings were largely (but not solely) attributed to the selection of patients with disproportionately severe MR relative to their heart failure phenotype in the case of the COAPT trial, and a more advanced heart failure phenotype in MITRA-FR.63 Up-titration of

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GDRT in secondary MR may be limited by factors including renal function and patient tolerance, and such patients need to be identified early. Furthermore, it is important that GDRT optimization is less sequential and that early referral for structural intervention is considered prior to reaching the stage of advanced LV remodelling. With GDRT as a prerequisite, the two randomized trials emphasize that timely referral of carefully selected patients to the Heart Team for consideration of transcatheter or surgical mitral valve intervention can yield significant incremental prognostic benefit.

**Tertiary mitral regurgitation**

The mitral annular area reduces by approximately 25% during systole in sinus rhythm owing to anteroposterior shortening that maintains the integrity of mitral leaflet coaptation. This anular contraction is lost in the setting of atrial tachyarrhythmias with resulting MR. Chronic atrial arrhythmias are associated with progressive left atrial and annular dilatation—this so-called ‘atrial’ or ‘tertiary’ MR affects 3–15% of chronic atrial fibrillation patients and is associated with adverse clinical outcomes.79 Where possible, restoration of sinus rhythm should be attempted using either pharmacological measures or radiofrequency ablation. This may lessen the severity of MR and avert the need for valve surgery. Assessment of the severity of MR in patients for whom this strategy is inappropriate or unsuccessful should only be undertaken when adequate rate control has been successfully achieved. Elevated ventricular rates may worsen annular dysfunction and mitral leaflet coaptation.79,80

Overall therefore, whilst there is clearly a strong theoretical and clinical evidence base enshrining GDRT (including CRT) as the cornerstone of secondary MR treatment, it is worth noting that studies to date have consistently demonstrated that only up to 50% of patients respond favourably in terms of reducing MR severity.81 Regular clinical assessment and echocardiographic quantification of LV and regurgitant volume are therefore essential to identify non-responders. Patients who remain symptomatic and refractory or intolerant of GDRT should be referred to dedicated heart valve specialists for consideration of transcatheter or surgical mitral valve interventions.

**Tricuspid regurgitation**

Significant TR affects 2.7% of patients attending for routine transthoracic echocardiography with an increased prevalence amongst females and the elderly.2,82 Regardless of aetiology, TR is frequently associated with right ventricular injury, functional impairment and poor outcomes (1-year all-cause mortality: moderate TR 29.5%, severe TR 45.6%).83 Despite poor prognosis, TR is undertreated. In a study of 534 patients with severe TR and congestive heart failure, only 10% underwent surgery (despite at least one indication for intervention in 30%) with demonstrable survival benefit (HR 0.44, 95% CI 0.27–0.71).84 Whilst management of pulmonary hypertension and loop diuretics may reduce volume overload and improve symptoms, no medical treatment strategies have proven efficacy in preventing the development of right heart failure. Given the meagre outlook without intervention, TR is best managed in a dedicated heart valve clinic in conjunction with heart failure clinicians.

**Conclusions**

Heart failure in the context of significant VHD is an increasingly encountered clinical phenomenon in an ageing society. Whilst the distinction is not always binary and often unclear, discriminating between the valve or ventricle as the principal disease driver in certain valve lesions is crucial in determining the correct therapeutic strategy (summarized in the Graphical Abstract). Patients with severe AS, AR or primary MR who meet guideline criteria for surgical or transcatheter intervention should be referred without delay. In those with secondary MR, GDRT remains the mainstay of treatment although up to 50% of patients may fail to respond and should be considered for cardiac resynchronization, transcatheter or surgical valve intervention as appropriate. The relative lack of high quality evidence for the use of GDRT in the setting of VHD with LVSD supports early involvement of a specialist heart valve team to guide management and ensure timely valve intervention.

**Key messages**

- The prevalence of valvular heart disease is increasing and patients frequently present with concurrent left ventricular systolic dysfunction.
- Medical therapy plays an important role in secondary mitral regurgitation by delaying or reducing the need for intervention—its role in other valve lesions is limited.
- Valve intervention is frequently necessary and transcatheter techniques are creating treatment options for patients previously considered inoperable.
- Management is frequently complex and optimum care should be delivered by a dedicated multidisciplinary Heart Team.

**Conflict of interest**

None declared.

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