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REVIEW

Management of valvulopathies with acute severe heart failure and cardiogenic shock

Prise en charge des valvulopathies en insuffisance cardiaque aigüe sévère incluant le choc cardiogénique

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Summary Cardiogenic shock is a critical clinical situation, requiring rapid diagnosis, aetiological assessment and immediate initiation of therapy. In industrialized countries, aortic stenosis is the most frequent left-sided valvulopathy, followed by mitral regurgitation, aortic regurgitation and mitral stenosis. Severe valvulopathies leading to cardiogenic shock are not rare conditions, but few data are available on their optimal management. Therapeutic options for such critical conditions include inotropic agents, mechanical support (when feasible) and rapid valvular intervention. Although surgery remains the gold-standard treatment for severe valvular disease, mortality is frequently prohibitive in the setting of cardiogenic shock, necessitating consideration of alternative therapies. Percutaneous management of valvulopathies has emerged as an alternative treatment for patients deemed at high surgical risk in a stable condition. Although few published data are available, catheter-based interventions may be feasible in the cardiogenic shock setting. This review offers an overview of different valvulopathies in the cardiogenic shock setting, and summarizes the different therapeutic options currently available in such critical situations.

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Abbreviations: AR, Aortic Regurgitation; AS, Aortic Stenosis; BAV, Balloon Aortic Valvuloplasty; BMV, Balloon Mitral Valvuloplasty; CS, Cardiogenic Shock; ECMO, Extracorporeal Membrane Oxygenation; LVEF, Left Ventricular Ejection Fraction; MR, Mitral Regurgitation; MS, Mitral Stenosis; SAVR, Surgical Aortic Valve Replacement; TAVR, Transcatheter Aortic Valve Replacement; TMVR, Transcatheter Mitral Valve Replacement.

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MOTS CLÉS

Choc cardiogénique ;
Valvulopathie ;
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percutanées

Résumé Le choc cardiogénique (CC) est une situation clinique critique nécessitant un diagnostic rapide, une évaluation étiologique et la mise en route immédiate du traitement adapté. Dans les pays industrialisés, la sténose aortique est la valvulopathie gauche la plus fréquente, suivie de la régurgitation mitrale, de l'insuffisance aortique et de la sténose mitrale. La survenue d'une valvulopathie sévère conduisant à un état de CC n'est pas rare et peu de données sont disponibles concernant leur prise en charge optimale. La gestion de ces situations critiques comprend le traitement inotrope, le support mécanique lorsque cela est possible et une intervention valvulaire rapide. Bien que la chirurgie reste le traitement de choix pour les valvulopathies sévères, dans le CC, la mortalité est souvent prohibitive, conduisant à envisager des traitements alternatifs. La gestion percutanée des valvulopathies apparaît comme une alternative à la chirurgie chez les patients à risque chirurgical élevé en situation clinique stable. Bien que peu de données soient disponibles dans la littérature, ces traitements percutanés peuvent être transposés en situation de CC. Cependant, le stade de développement de ces techniques est inégal selon la valvulopathie incriminée. Cette revue offre un aperçu des différentes valvulopathies dans un contexte de CC et résume les différentes options thérapeutiques actuellement disponibles dans une situation aussi critique.

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Background

Successful management of cardiogenic shock (CS) depends on rapid diagnosis, aetiological assessment and prompt initiation of therapy. Patients with severe valvulopathies and CS are often excluded from randomized trials, and the role of usual therapies in this specific population remains largely unknown. Management is focused on maintaining blood output and oxygen delivery to vital organs with inotropic agents, and treating the cause [1]. Developments in mechanical support, especially extracorporeal membrane oxygenation (ECMO), but also left ventricular assist devices, including Impella® (Abiomed Inc., Danvers, MA, USA) and Tandem Heart® (TandemLife, Pittsburgh, PA, USA), have allowed stabilization, with the objective of performing interventional treatment when feasible. Urgent surgery remains the gold standard treatment, but may be unsuitable for patients who are haemodynamically unstable, with severe organ dysfunction and a poor prognosis [2]. In these situations, catheter-based therapy may be an acceptable alternative, as a destination therapy or as a bridge to surgery. Few data are available on this topic—mainly case reports [3–10].

In line with current guidelines [11], the heart team must be involved in a multidisciplinary discussion to propose the best option for each particular case. The patient and their family have to be clearly informed of the proposals, and must share in the decision making. In some cases, heart transplantation (if feasible) is the most valuable strategy, and these patients should be referred to tertiary centres (so-called "level 3" in the recent Acute Cardiovascular Care Association guidelines [12]).

This review presents the management of each valvular disease in the setting of CS.

Diagnostic difficulties and the importance of aetiology for appropriate management

Accurate valvular evaluation can be very difficult in patients in CS. Experienced physicians and multimodal imaging are often required, especially when multiple valve diseases are combined or in extreme load conditions. For example, in case of aortic stenosis (AS) with severely reduced left ventricular ejection fraction (LVEF) or with concomitant mitral regurgitation (MR), severity can be underestimated, and careful quantification is mandatory. AS with reduced LVEF is highly problematic, because myocardial damage may indeed be an irreversible process, and may govern whether valve replacement is likely to be beneficial or futile. Contractile reserve can help physicians with their decision making, but may be challenging in critical settings (e.g. in a patient in CS on inotropes/vasopressors, arrhythmias, etc.). Absence of contractile reserve is often correlated with a worse prognosis after aortic valve replacement (surgical or transcatheter), but decision making should not rely on this sole variable.

Furthermore, many patients have significant cardiac co-morbid conditions, including coronary artery disease, atrial fibrillation and other valvular lesions, which may compromise a previously stable haemodynamic situation [13]. Consequently, determining whether the valvulopathy is the only factor responsible for a patient's clinical deterioration may be challenging.

Another key point is the underlying aetiology. In acute conditions, the valvular problem is often at the forefront of clinical instability. Complicated endocarditis, mechanical complication of acute myocardial infarction with MR and aortic dissection with massive aortic regurgitation (AR) often result in rapid deterioration of haemodynamic

Table 1 Mechanisms of cardiogenic shock related to valvular diseases, depending on the clinical context, with suggested therapeutic approaches.

Clinical context	Mechanisms	Therapeutic approaches: Heart Team evaluation
Acute setting	Endocarditis with new or worsening mitral/aortic valvulopathy or prosthetic valve failure; aortic dissection with severe AR; papillary muscle rupture with massive MR; acute prosthetic valve thrombosis	First-line surgical repair +++; if suitable anatomy and prohibitive surgical risk, then percutaneous strategy (MitraClip ^{®a}), with or without TCS (IABP, Impella ^{®b}) for acute ischaemic MR; thrombolysis for prosthetic valve thrombosis
Chronic setting	Delayed diagnosis +++; concomitant co-morbid condition (AF/CAD, etc.); combined valvulopathies	Surgical or percutaneous repair (transcatheter strategies preferred if possible), with or without TCS; coronary revascularization, restoration of sinus rhythm, etc.

AF: atrial fibrillation; AR: aortic regurgitation; CAD: coronary artery disease; IABP: intra-aortic balloon pump; MR: mitral regurgitation; TCS: temporary circulatory support.
^a Abbott Vascular Inc., Santa Clara, CA, USA.
^b Abiomed Inc., Danvers, MA, USA.

variables. Urgent surgery, with or without mechanical support, remains for now the treatment of choice in these high-risk situations. Conversely, chronic situations (degenerative, rheumatic, congenital diseases) usually deteriorate as a consequence of a precipitating factor or as a result of a delayed diagnosis. These factors (coronary artery disease, atrial fibrillation) always require clinical insight for prompt management, including coronary revascularization or electrical cardioversion when deemed appropriate (Table 1).

Emergent percutaneous procedures

Transcatheter heart valve interventions have recently changed the landscape of cardiology, and have become a standard of care in the frailest patients, with fewer complications than and similar outcomes to surgery [14–17].

Patients with valvular heart disease who are in CS are a very particular population. Indeed, mechanical correction of a stenosis or a regurgitation could reverse the process, with a complete and durable recovery, allowing favourable long-term outcomes. However, these patients are often at very high surgical risk. In this context, despite the lack of strong evidence, percutaneous strategies seem very attractive, and have been fully integrated into the therapeutic spectrum of heart valve management. A randomized trial for this heterogenous group would be very difficult to conduct, and large registries should be started to provide a global overview of current practices.

Aortic stenosis and cardiogenic shock

AS is the most common valve disease leading to surgery or transcatheter intervention in industrialized countries [11,18]. CS related to AS is a dramatic scenario, with a short-term mortality rate of up to 70% without durable intervention [5]. Management of these patients is highly tricky,

as evidence is scarce. Afterload reduction with nitroprusside was investigated in 25 patients with severe AS, LVEF dysfunction and congestive heart failure. Nitroprusside significantly improved the cardiac index (2.52 ± 0.55 L/min), and was safe as a bridge to aortic valve replacement or to oral vasodilator therapy. However, in this trial, patients with hypotension and/or those in whom vasoactive agents were necessary were excluded [19]. Inotropic agents may also be used, but with an increased risk of arrhythmias with dobutamine, and an increase in afterload with vasopressive agents (Table 2).

Surgical reports demonstrated that emergent surgical aortic valve replacement (SAVR) in critically ill patients was feasible, with an overall in-hospital mortality rate of 25–30% [7]. Percutaneous procedures have appeared recently as a promising alternative. Balloon aortic valvuloplasty (BAV) was first introduced by Cribier more than 30 years ago in patients with severe AS [6]. Although initial results were favourable, with an immediate reduction of transvalvular gradients, restenosis occurred frequently (in 70% of cases) at midterm. BAV could be a life-saving strategy in patients in CS, especially when surgical risk seems prohibitive [6,9]. Currently, BAV may be considered in haemodynamically unstable patients, as a bridge to SAVR or to transcatheter aortic valve replacement (TAVR), or as a palliative measure (class IIb recommendation) [11]. Only small observational studies have been published to date—most before the widespread utilization of TAVR [5–7,9]. Two cohorts recently aimed to assess the role of emergent BAV in patients with acute severe heart failure and/or CS. The first study reminded us that emergent BAV makes sense only when followed with a definitive strategy (surgical or transcatheter), with a high in-hospital mortality rate (30%) [20]. The second study [21] enrolled 44 patients with AS, divided into hypotensive and normotensive CS, for whom BAV was performed as a rescue therapy. The 1-month mortality rate was 47%; this was significantly lower in patients with a successful procedure (33% vs 80%; $P=0.04$). The 1-year mortality rate

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Table 2 Drugs, mechanical support and catheter-based therapy for each left-sided valvulopathy.

	Drugs	Mechanical support	Catheter-based therapy
Aortic stenosis	Norepinephrine; inotropic agents ^a ; nitroprusside	IABP; ECMO; LVAD	BAV; TAVR
Aortic regurgitation	Norepinephrine; inotropic agents ^b	–	TAVR
Mitral stenosis	Norepinephrine; inotropic agents ^b	ECMO	BMV; TMVI ^c
Mitral regurgitation	Inotropic agents; nitroprusside; (norepinephrine)	IABP; LVAD; ECMO	MitraClip ^d

BAV: balloon aortic valvuloplasty; BMV: balloon mitral valvuloplasty; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; TAVR: transcatheter aortic valve replacement; TMVI: transcatheter mitral valve implantation.

^a In case of depressed left ventricular ejection fraction.

^b In case of severe right ventricular dysfunction.

^c In case of severe calcified degenerative mitral stenosis.

^d Abbott Vascular Inc., Santa Clara, CA, USA.

was 70%, with a trend towards a better prognosis in non-hypotensive patients in CS. Above all, mortality seems to be related to the duration of shock. Performing BAV before the initiation of vasoactive drugs or within 48 hours after starting them was significantly associated with better survival, as observed previously [5], highlighting the fact that beyond intervention, timing is critical – the earlier that aortic obstruction is relieved in patients in CS, the better the survival. However, BAV does not improve the natural history of the disease, and may even worsen it by inducing myocardial dysfunction or acute AR. For these reasons, direct and definitive left ventricular unloading with a lower risk of post-procedural AR with TAVR could be the optimal strategy. Indeed, improvements in TAVR procedures have allowed new approaches for the frailest or unstable patients. Recent cohorts questioning the superiority of emergent TAVR versus emergent BAV followed by elective TAVR in acute heart failure and/or CS demonstrated a high device success rate, with a short-term mortality rate of around 35% for emergent TAVR [22,23]. Interestingly, despite a higher burden of co-morbidities, emergent/urgent TAVR was not associated with more complications compared with elective procedures. Direct TAVR implantation seems to be a reliable and safe strategy for this high-risk population [24].

Therapeutic interventions in CS related to AS are challenging, because of the paucity of data available to date. Current guidelines are very elusive, and a clear-cut strategy cannot yet be defined. Whereas medical treatment alone is an unreliable option, and surgery is often deemed prohibitive, it is unclear whether direct TAVR or BAV followed by elective TAVR after medical stabilization should be performed. Recent studies have underlined the potential role of emergency TAVR in patients in CS, but their observational nature, with inherent bias, highlights the strong need for a dedicated randomized trial that can shed more light on the issue for optimal clinical decision making in this extremely high-risk population.

Aortic regurgitation and cardiogenic shock

AR is less common than AS in Europe and the USA, with a 0.8% prevalence in series in the USA, and is often less tolerated in an acute setting [18].

Regarding the medical management of AR in the setting of CS, stabilization with airway intubation and haemodynamic support may be required, especially before intervention. Vasopressive agents may be necessary to increase aortic blood pressure and improve vital organ perfusion (Table 2) [13]. Atrial pacing, in order to increase heart rate and thus shorten diastole duration, has been advocated as a helpful option to reduce AR [2].

The key to treatment is therefore urgent valvular intervention. SAVR remains the standard of care for operable patients when experience in catheter-based techniques for AR is limited.

However, TAVR can be considered as an alternative to surgery in patients with a prohibitive surgical risk, after precise anatomical assessment of vascular routes, aortic annulus sizing and dilation of the ascending aorta and valvular calcifications, as the anatomy may be unsuitable for TAVR in case of pure AR. Only one study has assessed the feasibility of rescue TAVR, in five patients with AR and refractory CS among a total population of 686 cases of TAVR [3]. Procedural success was obtained for all patients in the AR with CS group, allowing withdrawal of vasoactive drugs within a few days, and 1-month outcomes were favourable for four patients (80%). These results tend to be more favourable than SAVR in a comparable clinical situation [25], but with a higher mortality than TAVR performed in native AR without CS in patients at high surgical risk [26].

Management of CS in acute AR is a critical situation, without valuable medical or mechanical support options. Few data are available, but SAVR, although considered the standard of care, seems a prohibitive option in a critical setting, allowing TAVR (depending on the underlying process) when anatomically feasible.

Mitral regurgitation and cardiogenic shock

MR is a frequent valvulopathy worldwide, affecting 3% of the general population [27]. Medical options may be indicated in patients with severe MR and CS. Indeed, a combination of inotropic agents, mechanical support with an intra-aortic balloon pump and respiratory support may improve haemodynamic tolerance of MR. Inotropic agents, such as milrinone or dobutamine, may be a better choice than

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vasoconstrictive agents, which may increase afterload and worsen the MR (Table 2). Nitroprusside has been used occasionally to increase cardiac output by reducing afterload and regurgitation volume [28]. In addition, non-invasive ventilation or airway intubation may be useful to decrease left ventricular afterload.

It is essential to distinguish primary from secondary MR before considering interventional management. Indeed, unlike primary MR, where surgery is considered the gold-standard treatment, no evidence of the value of surgery has been demonstrated in secondary MR, associated with evolved ventricular disease in the majority of cases. Valvular intervention in secondary MR may be considered only in case of severe symptoms despite medical therapy [11].

In the particular setting of acute myocardial infarction, MR is frequently related to papillary muscle ischaemia, and may be resolved by early revascularization in the majority of cases. Papillary muscle rupture, occurring in 0.7% of cases of acute myocardial infarction, is associated with severe primary MR and profound CS, requiring urgent surgical repair [29].

Regarding percutaneous approaches to the mitral valve, MitraClip® (Abbott Vascular, Santa Clara, CA, USA) is the most established device [14]. Currently, over 25,000 patients have been treated worldwide, with a class IIb level of recommendation for MitraClip® in patients with severe MR who are at high surgical risk [11]. Recently, the device has been studied in secondary MR, with favourable results in terms of mortality and hospitalization for heart failure compared with optimal medical treatment in the COAPT trial, but not in the MITRA-FR trial [17,30].

However, patients in CS or who were haemodynamically unstable were excluded from studies in the absence of robust data supporting the use of the MitraClip® procedure in the acute setting. Thus, the management of acute MR in CS with a MitraClip® implantation is still experimental, but may be an acceptable rescue option, as has been reported in a few cases [10,31]. However, precise anatomical characteristics of the valve should be assessed to evaluate the feasibility of such an approach.

Moreover, with MitraClip®, the risk of afterload mismatch remains possible with a decrease in post-procedural LVEF, and there is an increased risk of major adverse cardiac events and mortality in case of LVEF < 25%. In a recent study including 135 patients implanted with a MitraClip®, twelve patients (8.9%) were in CS, with a $33.4 \pm 22.3\%$ predicted risk of mortality for surgical mitral valve replacement in this CS population. Among patients in CS, two (17%) had secondary MR, four (33%) had primary MR and six (50%) had both. Two patients in CS (17%) had died at 1 month, and six patients (50%) had resolution of shock and were discharged home [32]. These results underline the feasibility of MitraClip® in patients with severe MR and CS, with acceptable results in patients at extremely high surgical risk.

Finally, severe MR in the CS setting is a complex situation requiring optimal medical management, airway intubation and mechanical support in some cases. Percutaneous management is feasible, but remains experimental.

Valvular prosthesis and cardiogenic shock

In recent decades, a shift from mechanical to bioprosthetic valves has been observed, with a consequent risk of valve deterioration and reoperation (required in up to 35% of patients within the first 10 years after mitral valve surgery) [33]. However, reoperative valve surgery is risky, with an excess morbidity and mortality rate of 15% [34]. In case of degenerated prosthetic aortic valve, TAVR has emerged as a promising alternative to surgery, with encouraging results [35]. Only case reports are available in the setting of degenerated aortic valve presenting with CS, showing feasibility [36,37].

Regarding the degenerated mitral valve, catheter-based treatment has been developed, with implantation of percutaneous aortic devices in the mitral position—transcatheter mitral valve replacement (TMVR)—with promising results [38]. Indeed, in the VIVID registry, including 349 patients undergoing TMVR, 30-day survival free from significant MR or left ventricular outflow tract obstruction was 88.8%. The feasibility of TMVR in the CS setting has been demonstrated in case reports and small series via transapical and transseptal access, offering an acceptable and less invasive alternative to surgery [39].

For mechanical prostheses, the most life-threatening complication is valve thrombosis, with an incidence of 0.1–4% per patient per year; this is more common in the mitral position, especially in case of inadequate anticoagulation therapy [40]. In case of obstructive thrombosis, clinical presentation in the setting of CS is frequent, and requires urgent therapy. Mechanical support devices are usually contraindicated because of the decrease in blood flow across the valve, leading to increased thromboembolic risk.

Surgery is the gold-standard treatment, but is associated with a high mortality rate, especially for patients with co-morbidities. In left-sided prosthesis thrombosis, thrombolysis may be considered in patients with a prohibitive surgical risk, despite the risk of thromboembolic and haemorrhagic complications [40]. In the European Society of Cardiology guidelines, surgical valve replacement is indicated as the treatment of choice in patients without serious co-morbidity (class I recommendation, level of evidence C). Thrombolysis should be considered only in critically ill patients with co-morbidities, in institutions without cardiac surgery on-site, and in right-sided prostheses [11].

The success rate of thrombolysis was 82% in a review of 200 cases of left-sided valve thrombosis [41]. Peripheral and cerebral embolism were the most frequent complication (12%), followed by recurrent thrombosis of the valve (11%) and major bleeding (5%).

Management of prosthesis failure in the setting of CS is challenging, with a prohibitive surgical risk in the majority of cases. Thus, catheter-based therapy for a degenerated bioprosthesis and thrombolysis for valve thrombosis may offer an alternative to surgery.

Mitral stenosis and cardiogenic shock

Mitral stenosis (MS), mainly resulting from rheumatic infection, is still highly prevalent worldwide. Heart failure is the most frequent clinical presentation, often associated with

atrial fibrillation, and the mortality rate reaches 15–20% in pregnant women with severe heart failure [4,8]. Medical management is relatively limited in patients with MS in CS.

Surgery is challenging in this acute setting, especially in pregnancy, as the haemodynamic changes during cardiopulmonary bypass are critical.

Balloon mitral valvuloplasty (BMV) was the first catheter-based valvular treatment, described in 1982 [42]. When subvalvular and valvular anatomies are favourable, particularly in terms of calcifications, BMV is the cornerstone of treatment for severe MS [42]. Two studies have reported results for BMV in the treatment of MS in a CS setting. The most recent study included 96 patients undergoing BMV for MS during pregnancy, with 16 patients (17%) in CS. Procedural success was achieved in 80% of patients. In five cases, acute severe MR occurred. In the overall cohort, 11 patients died, six (31%) in the “failure group” and five (6%) in the “success group” [4]. The second study included 40 patients with MR in CS, with a 35% rate of mortality after emergent BMV [8].

In severe calcified degenerative MS, limited data have suggested transcatheter mitral valve intervention as an alternative treatment in patients at high surgical risk; this may be feasible in the acute setting [43].

MS with CS is not a rare situation worldwide, and affects younger patients more than the other valvular heart diseases. Urgent BMV appears feasible in critically ill patients, even pregnant patients, and may be considered as the first-line therapy.

Right-sided valvulopathies presenting in a cardiogenic shock setting

CS in patients with isolated right-sided valvular disease is extremely rare, as these diseases are well tolerated haemodynamically for a long time [2]. In fact, the haemodynamic failure is related to right heart failure, leading to hepatic and renal failure. Inotropic agents may be useful in this situation. Surgery remains the first-line therapy, but may be contraindicated because of co-morbidities and evolved right heart failure. Surgical management should be performed before organ dysfunction [44]. In case of severe tricuspid regurgitation with right heart failure, percutaneous strategies may be discussed, but remain experimental [44].

The place of mechanical circulatory support

Mechanical circulatory devices could be life saving for selected patients in CS with critical impairment of tissue perfusion. To date, no randomized data support their use in contemporary practice. However, percutaneous assist devices overcome the limitations of medical therapies, improve haemodynamics and could prevent irreversible organ dysfunction. Each of these devices has specific characteristics, with different haemodynamic profiles and indications.

Aortic valvulopathies are usually contraindications for transvalvular pumps, but the latter have been proven to be

feasible and safe, especially in selected high-risk patients with AS [45]. Left ventricle-to-aorta devices, by offloading the left ventricle and decreasing retrograde mitral flow, are able to prevent end-organ injury in patients with severe MR, permitting stabilization before valve replacement [46].

ECMO can be inserted quickly, and rapidly restores tissue perfusion; however, it increases afterload, and should only be considered as a salvation measure. In case of prosthetic valve failure, transvalvular pumps are contraindicated (especially aortic valves), and ECMO use is associated with a very high risk of valve thrombosis (especially for mitral valves).

After all, circulatory support must always be regarded as a bridge to a durable therapy: surgical or transcatheter repair, long-term assist device or heart transplantation.

Conclusion

Treatment of valvular heart diseases in acute situations remains challenging, especially in the CS setting. Strong evidence in support of any intervention is limited. Optimal management requires multidisciplinary expertise, involving cardiologists, anaesthesiologists and cardiac surgeons. Inotropes, vasopressors and mechanical support can be used as stabilization measures, providing a bridge to valve intervention. Urgent surgical repair or replacement of the failed valve may be considered as first-line therapy, especially in young patients. Catheter-based valvular procedures have emerged recently, offering an acceptable alternative to surgery in these critical situations. Finally, one of the common considerations in all the various clinical settings is the possible indication for urgent cardiac transplantation in patients admitted for CS resulting from severe valvular heart disease, who therefore require a consultation in a specific centre with a high level of expertise and a heart transplantation programme.

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Disclosure of interest

The authors declare that they have no competing interest.

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