Optimal treatment for nonsevere coronary artery disease in valve surgeries: Concurrent coronary artery bypass grafting or postoperative medical therapy?

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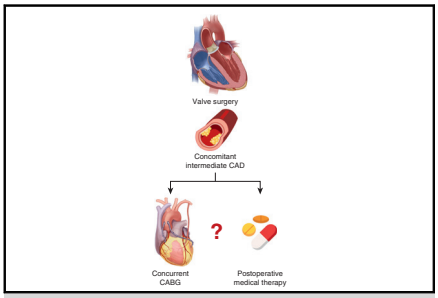
Approximately 30% to 60% of patients with valvular heart disease (VHD) have coexisting coronary artery disease (CAD), particularly those with aortic stenosis (AS).[1,2] However, because of the lack of focus and high-quality randomized trials in this population, current guidelines are too simplistic to address the complex scenarios involving coronary lesions, leading to confusion in clinical practice. The biggest controversy concentrates on the decision-making of concurrent coronary artery bypass grafting (CABG) for patients undergoing valve surgeries with concomitant intermediate CAD and postoperative antithrombotic strategies for these patients with concomitant indications for anticoagulants and antiplatelets simultaneously. Current uncertainties of treatments for this group of patients are summarized in Figure 1.



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CENTRAL MESSAGE

Intermediate CAD complicates surgical decisions and outcomes in VHD. Evidence-based strategies are needed to optimize management.

PERSPECTIVE

This review highlights the need for a paradigm shift in managing intermediate CAD during valve surgeries. Current coronary assessment tools fail to capture the complex ischemic interplay of VHD and CAD, and evidence-based antithrombotic strategies remain lacking. Future research should refine revascularization criteria and antithrombotic protocols for this high-risk population.

REVASCULARIZATION STRATEGY FOR INTERMEDIATE CORONARY ARTERY DISEASE IN VALVE SURGERIES

The 2021 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery and 2020 American College of Cardiology/American Heart Association (AHA) guidelines recommend CABG for patients undergoing valve surgery with significant coronary artery stenosis 70% or more or left main coronary artery stenosis 50% or more (Class IIa, Level C).[3,4] However, based on the concept of complete revascularization during isolated CABG, all coronary arteries more than 1.5 mm in diameter with 70% or more stenosis should be revascularized anatomically, and all functionally ischemic myocardial areas (subtended by coronary arteries with visually assessed ≥50% diameter stenosis) should be grafted.[5,6] Cardiac surgeons currently prefer revascularizing all coronary arteries greater than 1.5 mm in diameter with 50% or more visually assessed stenosis to achieve complete revascularization in practice, largely due to the lack of intraoperative functional assessment.[6] This conceptual contradiction has sparked a debate: Should patients undergoing valve surgery with intermediate (50%-70%) stenosis in non–left main coronary arteries greater than 1.5 mm undergo concurrent revascularization?

When coexisting coronary artery lesions meet the criteria for isolated CAD revascularization, performing complete revascularization during valve surgery is generally accepted. The primary debate, however, lies in patients whose coronary lesions do not meet the

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Abbreviations and Acronyms

AHA = American Heart Association
AS = aortic stenosis
ASA = acetylsalicylic acid
AVR = aortic valve replacement
CABG = coronary artery bypass grafting
CAD = coronary artery disease
ESC = European Society of Cardiology
LAD = left anterior descending
LV = left ventricular
OAC = oral anticoagulant
SAVR = surgical aortic valve replacement
VHD = valvular heart disease
VKA = vitamin K antagonist

recommended criteria, such as non–left main CAD or single- or double-vessel disease not involving the proximal left anterior descending (LAD) artery with intermediate (50%-70%) stenosis. Concurrent CABG may not benefit this group of patients, because the additional procedure could increase mortality and introduce complications related to autologous graft harvesting.[7,8] Previous AHA/American College of Cardiology guidelines considered concurrent CABG reasonable for patients with 50% to 70% stenosis.[9] However, this recommendation was removed in the updated guideline, partly due to randomized trials in patients with isolated CAD showing no advantage of revascularization over medical therapy in nonsevere stable CAD.[6,10] But extrapolating the experience of treating isolated CAD to patients with concomitant diseases is problematic. For instance, given the strong association between AS and CAD progression, the criteria for concurrent revascularization in patients with AS may need to be more aggressive.[11] Additionally, the complexity of antithrombotic strategies may increase the risk of bleeding in patients undergoing valve surgery with concurrent CABG, because additional dual antiplatelet therapy is required to prevent graft restenosis.[12]

Conversely, several observational studies comparing aortic valve replacement (AVR) with and without CABG for intermediate CAD have suggested that concurrent revascularization may reduce ischemic events compared with isolated AVR.[13,14] However, these studies did not specify the postoperative medical therapy, which may have influenced the results. Thalji and colleagues[14] conducted a detailed analysis of long-term survival after isolated AVR versus AVR + CABG in different subgroups, including patients with intermediate (50%-70%) stenosis CAD. They found that long-term survival was superior in patients undergoing AVR with CABG compared with those undergoing isolated AVR, in both moderate and severe CAD. However, they did not exclude patients with proximal LAD disease from this subgroup, who might have been the primary beneficiaries of concurrent CABG. Furthermore, the study suggested that in the subgroup with single-vessel CAD, concurrent CABG did not provide long-term survival benefits in patients with single-vessel left circumflex coronary artery or right CAD. Therefore, it is possible that unless there is more than 50% stenosis involving left main and proximal LAD, concurrent CABG for concomitant intermediate stenosis involving only the right coronary artery or left circumflex coronary artery may not bring more benefit than postoperative medical therapy, particularly intermediate stenosis in their secondary branches (randomized trials needed). Other valve lesions (primary valvular disease) with concomitant CAD have not been studied much. Secondary mitral regurgitation, mostly occurring in patients with severe CAD or post–myocardial infarction, is not included in the topic (primary valve surgeries with intermediate CAD) that we are discussing in this article. Overall, the level of the current evidence is still insufficient to draw definitive conclusions on decision making for concomitant intermediate CAD in valve surgeries.

PATHOPHYSIOLOGY IN CONCOMITANT CORONARY ARTERY DISEASE AND VALVULAR HEART DISEASE

VHD (increased oxygen demand) and CAD (decreased oxygen supply) can each exacerbate myocardial ischemia, and their co-occurrence further compounds the condition. The pathophysiological mechanism of VHD with concomitant CAD is complicated. The increased oxygen consumption due to pressure or volume overload persists throughout the course of VHD. Also, the chronic pathophysiological change of different valve lesions affects myocardial ischemia by different mechanisms. They can be separated into 2 situations according to different mechanisms: pressure load increase and volume load increase. First, in AS, long-term pressure overload promotes concentric hypertrophy of the left ventricle, which is a compensatory mechanism of the heart to maintain cardiac output.[15] The myocardial oxygen demand increases significantly as the left ventricular wall thickens,[16] in which the blood supply may be insufficient when only intermediate or less coronary stenosis is present. In such cases, myocardial ischemia may occur without a significant reduction in coronary functional assessment values. Second, in aortic or mitral regurgitation, long-term volume overload causes the left ventricle undergoing dilation and eccentric hypertrophy to accommodate the increased blood volume.[15] With eccentric hypertrophy, the increased ventricular radius would raise wall stress, which could restrict diastolic myocardial perfusion and increase left ventricular (LV) mass and oxygen demand.[16,17] Diastolic myocardial hypoperfusion would be further aggravated by the decrease of diastolic pressure in aortic

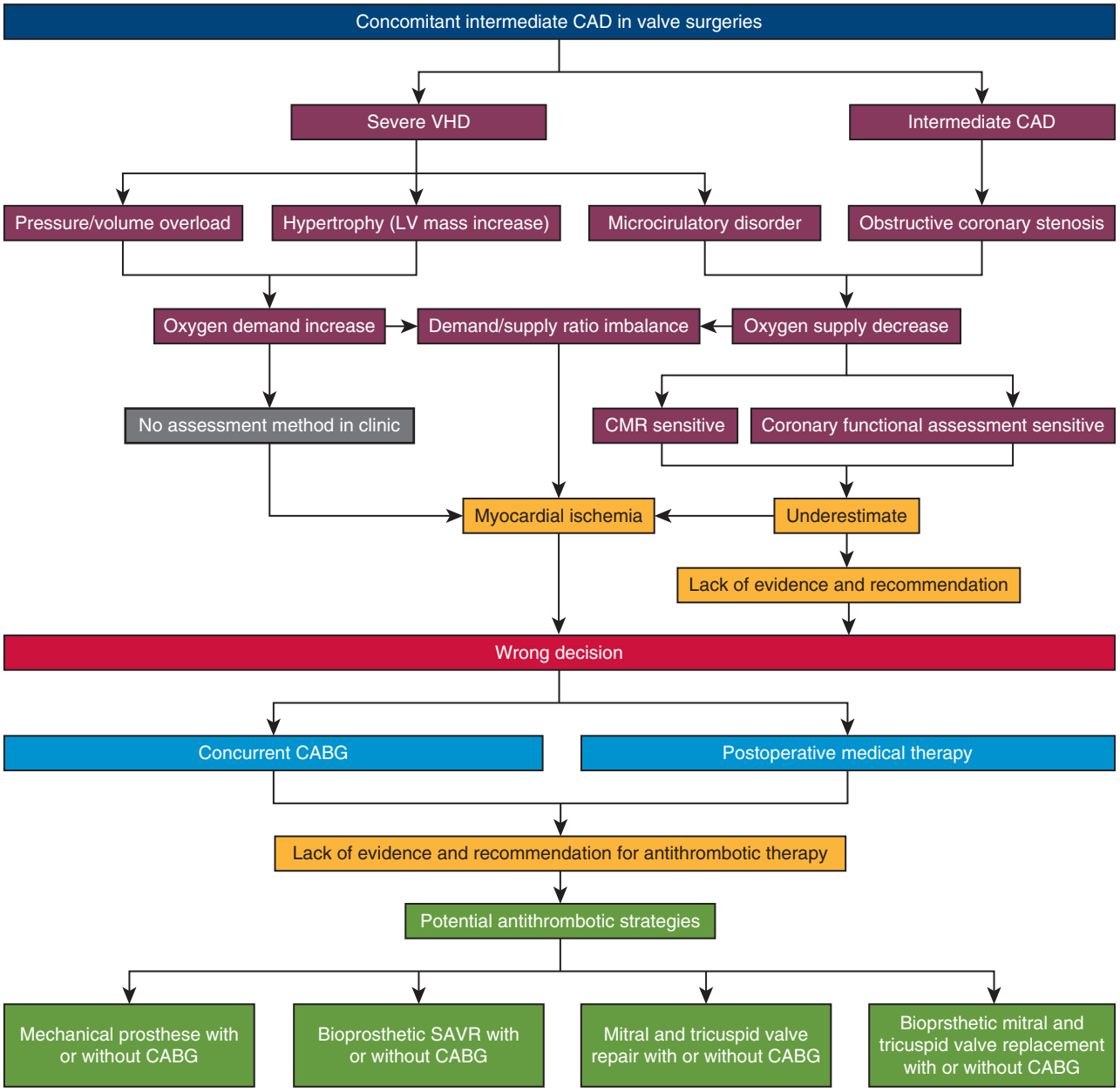

FIGURE 1. Summary of the challenges and uncertainties in managing patients undergoing valve surgery with concurrent CAD, including the limitations of current coronary functional assessment tools in accurately evaluating ischemic burden, and the critical need to explore optimized antithrombotic strategies to mitigate associated risks. *CAD*, Coronary artery disease; *VHD*, valvular heart disease; *LV*, left ventricle; *CMR*, cardiovascular magnetic resonance; *CABG*, coronary artery bypass grafting; *SAVR*, surgical aortic valve replacement.

regurgitation. Moreover, valvular disease–induced hypertrophy can result in myocardial fibrosis due to chronic ischemia caused by an imbalance in the oxygen supply/demand ratio.[18,19] This process may be accelerated when accompanied by obstructive CAD. Myocardial fibrosis can significantly increase the risk of mortality.[20,21] Therefore, in patients with hypertrophy due to valvular disease and concomitant moderate coronary stenosis, a more aggressive approach to concurrent CABG may be warranted. Given the complex mechanisms of ischemia in patients with VHD and CAD, current coronary functional assessment methods are insufficient to evaluate myocardial ischemia in those with concomitant conditions.

LIMITATION OF CORONARY FUNCTIONAL ASSESSMENT IN VALVULAR HEART DISEASE WITH INTERMEDIATE CORONARY ARTERY DISEASE

The latest guideline seems to still place hope on using coronary functional assessments, such as instantaneous

wave-free ratio or fractional flow reserve, to guide decision-making for patients with VHD and concomitant intermediate CAD in the future.[22] A randomized trial comparing quantitative flow ratio–guided revascularization with coronary angiography–guided revascularization for patients undergoing primary valve surgery with combined CAD is currently recruiting (ClinicalTrials.gov ID: NCT03977129). The application of coronary functional assessment in guiding decision-making for VHD with concomitant CAD remains controversial because of the distinct pathophysiological differences between concomitant CAD and isolated CAD. However, the cardiovascular community continues to focus on determining which method of coronary functional assessment is most appropriate for patients with VHD and concomitant CAD, although all current methods may underestimate the degree of ischemia in these patients.

Myocardial ischemia is determined by both coronary blood supply and myocardial oxygen demand—the supply/demand ratio. Myocardial ischemia occurs when coronary blood flow fails to meet the oxygen demand of the myocardium. In patients with VHD and CAD, myocardial oxygen demand increases significantly due to the progressive rise in preload and afterload, followed by ventricular remodeling (hypertrophy), while simultaneously, blood supply decreases due to obstructive coronary lesions. Hypertrophy may cause a 2- to 3-fold increase in LV mass. Resting myocardial oxygen consumption is normally 8 to 13 mL 100 g^{-1} min^{-1}. At rest, it is linearly related to LV mass,[15,16,23] as shown in Figure 2. This is a critical reason that patients with AS-caused ventricular hypertrophy have the symptom of angina pectoris.[16,24] Resting LV myocardial oxygen consumption (mL.min^{-1}) is also linearly related to peak meridional wall stress (kdynes.cm^{-2}). Doubling wall tension approximately doubles LV oxygen consumption.[16] In such cases, coronary functional assessments would underestimate the degree of myocardial ischemia (not to be confused with the degree of obstruction) due to the increased oxygen demand of the myocardium. Coronary flow reserve is reduced in isolated AS, contributing to ischemia to some extent. However, no significant difference in flow reserve has been observed between patients with AS with or without angina.[24] Thus, a reduction in flow reserve alone at normal resting heart rates does not fully explain the symptoms.[25] Whether using hyperemic methods (fractional flow reserve) or nonhyperemic methods (instantaneous wave-free ratio) for functional assessment, these tests only provide information about coronary artery supply, not the critical supply/demand ratio, which is the true determinant of myocardial ischemia. Additionally, coronary functional assessments have clear limitations in evaluating microcirculatory dysfunctions, a common pathophysiological change in VHD.[26] Thus, assessing myocardial ischemia in patients with VHD and concomitant CAD using only coronary functional assessments (focused on blood supply) is inadequate, because these tests overlook both myocardial oxygen demand and microcirculatory dysfunctions. Although stress cardiovascular magnetic resonance can better diagnose hypoperfusion caused by microcirculatory dysfunction compared with coronary functional assessments, it still does not provide direct evidence of myocardial ischemia. Coronary functional assessments can be applied successfully in patients with isolated CAD, because this group does not face the issue of increased oxygen demand. Therefore, current methods of coronary functional assessment are not applicable to patients with VHD and concomitant CAD, unless they are calibrated in different clinical scenarios. Accurate assessment of myocardial ischemia and informed decision-making regarding concurrent CABG can be achieved only by incorporating both oxygen demand and supply into the evaluation. However, measuring oxygen demand remains challenging; therefore, assessing ischemia through direct indicators, such as local oxygen saturation and metabolites (eg, lactate, nicotinamide adenine dinucleotide), may offer a more accurate method for evaluating ischemia in the future.

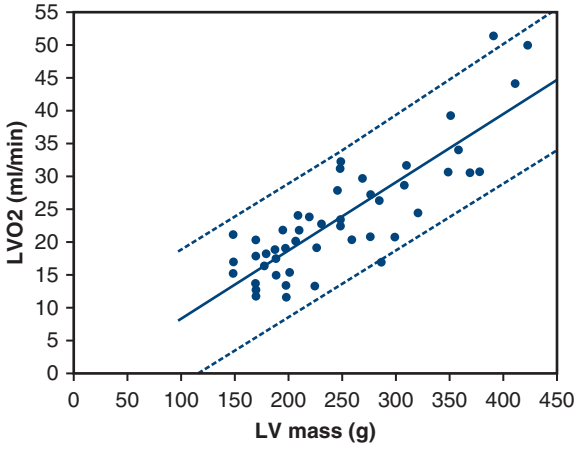

FIGURE 2. Relation of resting left ventricular myocardial oxygen consumption (*LVO2*) to LV mass.[15,16]

ANTITHROMBOTIC STRATEGIES FOR VALVE SURGERY WITH CONCOMITANT CORONARY ARTERY DISEASE

Evidence regarding antithrombotic strategies for patients undergoing valve surgery with concomitant CAD, whether or not they undergo concurrent CABG, remains limited and the issue is highly complex. We propose several potential strategies for various clinical scenarios, based on existing evidence and inferences from related studies, as summarized in Figure 3. We believe these insights could be valuable for future studies focusing on this patient population. With or without concurrent CABG may lead to different

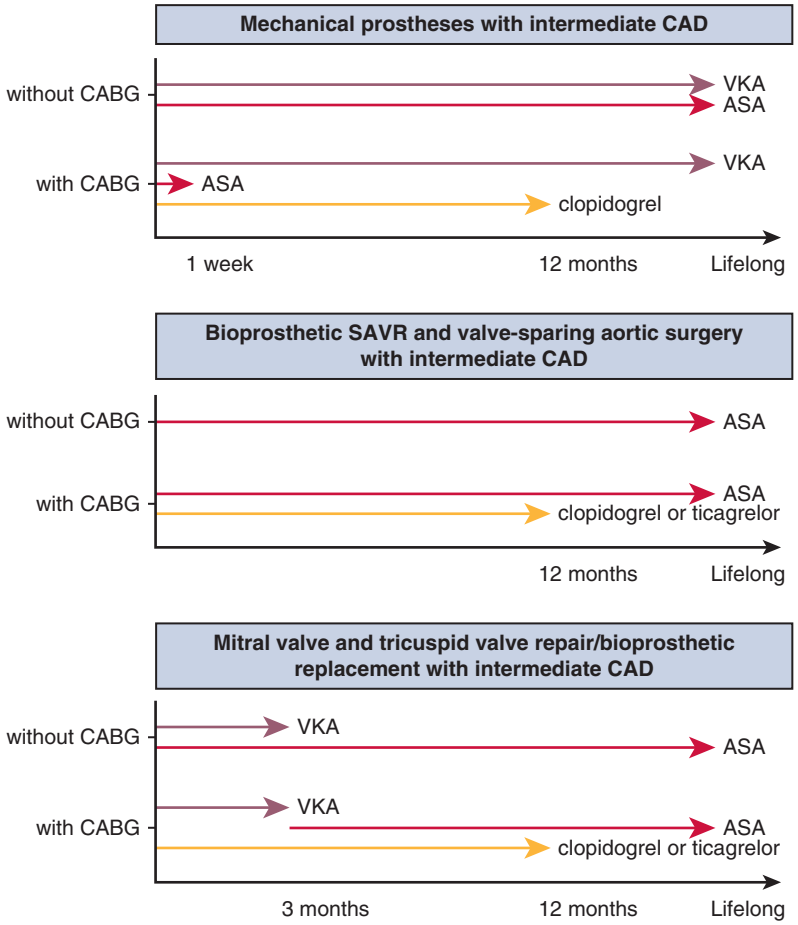

FIGURE 3. Antithrombotic strategies for the patients undergoing different valve surgeries with concomitant intermediate CAD (further randomized trials needed). *CAD*, Coronary artery disease; *CABG*, coronary artery bypass grafting; *VKA*, vitamin K antagonist; *ASA*, acetylsalicylic acid.

antithrombotic strategies, which should be taken into consideration of decision-making before surgeries. We think that would be helpful for later studies focusing on this population.

Mechanical Prostheses With Intermediate Coronary Artery Disease

For patients with mechanical prostheses and untreated intermediate CAD, current guidelines recommend lifelong vitamin K antagonists (VKAs) combined with lifelong low-dose acetylsalicylic acid (ASA) to prevent adverse ischemic events, although high-quality evidence supporting this recommendation is lacking (Class IIb, Level C).[3,27] For the patients who accept mechanical prostheses and concurrent CABG, there was no clear recommendation in the guidelines. The latest studies on antiplatelet strategy after isolated CABG suggested that clopidogrel/ticagrelor plus ASA therapy is better than single ASA therapy.[12,28-30] However, triple therapy with oral anticoagulants (OACs) and dual antiplatelet therapy after valve surgeries and concurrent CABG carry an extremely high risk of bleeding. Therefore, guidelines recommend early cessation (<1 week) of ASA, continuation of OAC and a P2Y12 inhibitor, and discontinuation of antiplatelet therapy after 12 months in patients treated with OACs, based on studies involving patients who received anticoagulation after percutaneous coronary intervention.[3,31-37] The AFIRE trial concluded that monotherapy with OACs was noninferior to combination therapy with OAC plus single antiplatelet therapy for efficacy and superior for safety in patients with atrial fibrillation and stable CAD.[37] Thus, discontinuing antiplatelet therapy after 1 year for patients with mechanical prostheses and concurrent CABG is reasonable. Given these randomized studies, along with guideline recommendations for those requiring concomitant antiplatelet therapy, patients with mechanical prostheses undergoing CABG may benefit more from the strategy with lifelong VKA plus short-term ASA (<1 week) and 1 year of clopidogrel or ticagrelor.

Bioprosthetic Surgical Aortic Valve Replacement and Valve-Sparing Aortic Surgery With Intermediate Coronary Artery Disease

Current evidence supports that ASA therapy for 3 months after isolated bioprosthetic surgical aortic valve replacement (SAVR) might be an alternative compared with OAC therapy.[38,39] Thus, ASA has been recommended to the patients undergoing bioprosthetic SAVR and valve-sparing aortic surgery in the current guideline (Class IIa, Level B).[3,27] Given the need for lifelong ASA therapy to prevent adverse ischemic events, the optimal antithrombotic strategy for patients undergoing bioprosthetic SAVR or valve-sparing aortic surgery with untreated intermediate CAD would be lifelong ASA alone, which serves a dual purpose. Whereas for patients undergoing bioprosthetic SAVR or valve-sparing aortic surgery with concurrent CABG, dual antiplatelet therapy with clopidogrel/ticagrelor plus ASA for 1 year and then lifelong ASA is a reasonable choice (based on the consideration of improving patency of grafts after CABG).[12,28-30]

Mitral Valve and Tricuspid Valve Repair With Intermediate Coronary Artery Disease

Antithrombotic therapy remains controversial for patients undergoing mitral valve repair. Observational data suggest a comparable risk of thromboembolism with ASA or VKAs after mitral valve repair,[40] but randomized data are lacking. Thus, the guideline still recommends patients undergoing mitral valve repair to receive OACs with VKA for 3 months.[3,27] In such cases, patients undergoing mitral or tricuspid valve repair with untreated intermediate CAD ideally should receive dual therapy with VKA and ASA for 3 months, followed by lifelong ASA. Patients undergoing mitral or tricuspid valve repair with concurrent CABG ideally should receive dual therapy with VKA and clopidogrel for 3 months (based on inferences from studies on atrial fibrillation with concomitant percutaneous coronary intervention), followed by dual antiplatelet therapy with clopidogrel or ticagrelor and ASA for 9 months (evidence from studies on post-CABG antiplatelet strategies) and then lifelong ASA.[12,28-34] If future randomized trials confirm a comparable risk of thromboembolism with ASA or VKA after mitral valve repair, the antithrombotic strategy for this patient group could be as straightforward as for those undergoing bioprosthetic SAVR.

Bioprosthetic Mitral and Tricuspid Valve Replacement With Intermediate Coronary Artery Disease

VKA for 3 months should be considered in all patients with a bioprosthetic mitral or tricuspid replacement, according to the recommendation of ESC 2021 VHD guidelines.[3] However, the AHA 2020 guideline for VHD recommends ASA as the alternative antithrombotic therapy in the same position as bioprosthetic SAVR (Class IIa, Level B),[27] of which evidence comes from limited evidence.[41,42] Given the controversy, a 3-month course of VKA appears more prudent for patients undergoing bioprosthetic mitral and tricuspid valve replacement at this time. Thus, antithrombotic therapy for patients undergoing bioprosthetic mitral or tricuspid valve replacement with concomitant intermediate CAD should be the same as for patients undergoing mitral or tricuspid valve repair with intermediate CAD.

The strategies proposed are based on limited direct evidence and further inferences from related studies. Thery all should be validated in the future randomized trials. Given the complexity of antithrombotic therapies and the high bleeding risk in patients with mechanical prostheses and concomitant CAD, bioprostheses (single antiplatelet therapy) may have expanded applicability in patients with concomitant CAD in the future.

MULTIDISCIPLINARY HEART TEAM

In the current era of Heart Team–based decision-making, the role of shared decision-making and multidisciplinary discussions is increasingly recognized, particularly for patients with complicated situations, as well as in cases of uncertainty or lack of strong evidence.[43,44] ESC and AHA guidelines for VHD and CAD have emphasized the key role of a multidisciplinary Heart Team for patients when the optimal treatment strategy is unclear: A Heart Team approach that includes representatives from interventional cardiology, cardiac surgery, and clinical cardiology is recommended to improve patient outcomes (Class I, Level C).[3,22,27] Regarding the situation we discussed, the specific approach to these patients remaining controversial due to the lack of robust evidence, engaging patients, referring cardiologists, and surgeons in shared decision-making can help balance the risks and benefits of concurrent revascularization versus medical management.

CONCLUSIONS

In patients with VHD and intermediate CAD, determining the necessity of concurrent CABG during valve surgery remains a significant clinical challenge. Current guidelines offer limited guidance, particularly regarding intermediate stenosis and its influence on patient outcomes Our review highlights the limitations of coronary functional assessments in this population, because these assessments frequently fail to account for increased myocardial oxygen demand and microcirculatory dysfunction caused by left ventricular hypertrophy. The complexities of antithrombotic management further complicate clinical decision-making. Looking ahead, there is an urgent need for targeted clinical trials to investigate optimal revascularization strategies for this subgroup, particularly

in cases involving non–left main artery and nonproximal LAD artery disease. Establishing evidence-based protocols will be essential in resolving ongoing controversies and enhancing outcomes for these high-risk patients.

Conflict of Interest Statement

The author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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