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THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Management of Mechanical Prosthetic Heart Valve Thrombosis

JACC Review Topic of the Week

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ABSTRACT

Mechanical prosthetic heart valves, though more durable than bioprostheses, are more thrombogenic and require lifelong anticoagulation. Mechanical valve dysfunction can be caused by 4 main phenomena: 1) thrombosis; 2) fibrotic pannus ingrowth; 3) degeneration; and 4) endocarditis. Mechanical valve thrombosis (MVT) is a known complication with clinical presentation ranging from incidental imaging finding to cardiogenic shock. Thus, a high index of suspicion and expedited evaluation are essential. Multimodality imaging, including echocardiography, cine-fluoroscopy, and computed tomography, is commonly used to diagnose MVT and follow treatment response. Although surgery is oftentimes required for obstructive MVT, other guideline-recommended therapies include parenteral anticoagulation and thrombolysis. Transcatheter manipulation of stuck mechanical valve leaflet is another treatment option for those with contraindications to thrombolytic therapy or prohibitive surgical risk or as a bridge to surgery. The optimal strategy depends on degree of valve obstruction and the patient's comorbidities and hemodynamic status on presentation.
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Mechanical heart valves, though more durable than bioprostheses, are more thrombogenic and require lifelong anticoagulation.[1] Mechanical valve (MV) dysfunction can be caused by 4 main phenomena: 1) thrombosis; 2) pannus ingrowth; 3) degeneration; and 4) endocarditis.[2,3] These can occur simultaneously, so identifying the predominant etiology of MV dysfunction is crucial for appropriate management. The clinical presentation of mechanical valve thrombosis (MVT) can range from incidental finding on imaging to cardiogenic shock or thromboembolic events including massive stroke, necessitating a high index of suspicion and expedited diagnostic evaluation. Several imaging modalities can help establish the diagnosis. Although surgery is oftentimes the necessary treatment for obstructive MVT, other modalities including heparin anticoagulation, thrombolysis, and transcatheter interventional techniques are available, with the choice largely influenced by degree of obstruction, valve location, hemodynamic stability, surgical risk, and local expertise. The objectives of this comprehensive review are to delineate the incidence, etiology, clinical presentation, and diagnostic imaging

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ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

ACC = American College of Cardiology

AHA = American Heart Association

AT = acceleration time

CT = computed tomography

EOA = effective orifice area

ET = ejection time

INR = international normalized ratio

LMWH = low-molecular weight heparin

MV = mechanical valve

MVT = mechanical valve thrombosis

TEE = transesophageal echocardiogram

tPA = tissue plasminogen activator

TTE = transthoracic echocardiogram

UFH = unfractionated heparin

modalities, and treatment options for MVT. This is a review of published reports and, therefore, is exempt from ethics board oversight.

INCIDENCE AND ETIOLOGY

The estimated annual rate of MVT ranges from 0.1% to 5.7%, with higher rates seen in specific valve designs, within 3 months from surgical implantation, and for valves in the mitral or tricuspid position compared with the aortic position.[4] This rate is variable and likely underestimated, because routine imaging of MVs is not recommended following a postimplantation transthoracic echocardiogram (TTE). Currently, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend TTE or transesophageal echocardiography (TEE) in patients with prosthetic valves only if clinical symptoms or signs of valve dysfunction are present.[5] Although thrombosis occurs mainly in MVs, cases of surgical or transcatheter bioprosthetic valve thrombosis have been reported.[6] A detailed discussion on bioprosthetic valve thrombosis is outside the scope of this review.

Historically, MVs can be grouped into 3 major designs: caged-ball, tilting disk, and bileaflet valves. Whereas bileaflet designs have become the standard for modern valves, older tilting disk and caged-ball valves can still be encountered in older patients and can confer a higher thrombotic risk. Tilting disk valves are more often associated with catastrophic MVT, in contrast to caged-ball and bileaflet designs.[7]

It is the valve regions of stagnation and blood flow disturbance that can precipitate thrombus formation, tissue overgrowth, and calcification. High shear stress can lead to blood cell damage and platelet activation.[8] Additionally, whereas healthy endothelium actively resists thrombosis, MV surfaces promote clotting through complex processes including protein adsorption; platelet, leukocyte, and red blood cell adhesion; thrombin generation; and complement activation.[9] Common valve designs and hemodynamic properties are discussed in the Supplemental Appendix.

CLINICAL PRESENTATION AND DIAGNOSIS

The presentation of MVT has a wide spectrum of symptomatology that is largely dependent on acuity and degree of resultant valvular obstruction and/or regurgitation. Obstructive MVT often presents with signs and symptoms ranging from decompensated heart failure to cardiogenic shock, especially if diagnosis is delayed. Poor adherence, brief interruption, or subtherapeutic anticoagulation are common.[2] The timing from valve implantation to dysfunction can also aid in elucidating the cause. Early valvular dysfunction (eg, paravalvular leak, patient-prosthesis mismatch, dehiscence, endocarditis) is usually related to technical challenges during surgery or infection. Late valve dysfunction (eg, pannus, thrombosis, and thromboembolism) varies more with the prosthesis type and thrombogenicity, as well as patient-related factors (eg, hypercoagulable states, interrupted anticoagulation). On physical examination, there may be absent clicking associated with valve opening and closing, a new murmur, signs of pulmonary edema and heart failure, and sequelae of pulmonic or systemic thromboembolism.[2] Acute ischemic strokes are the most frequent presentation of embolization from left-sided prostheses.[10] Diagnosis depends heavily on a high index of suspicion and expedited imaging, with each modality having its own benefits and limitations. The **Central Illustration** delineates the proposed evaluation and management of MVT.

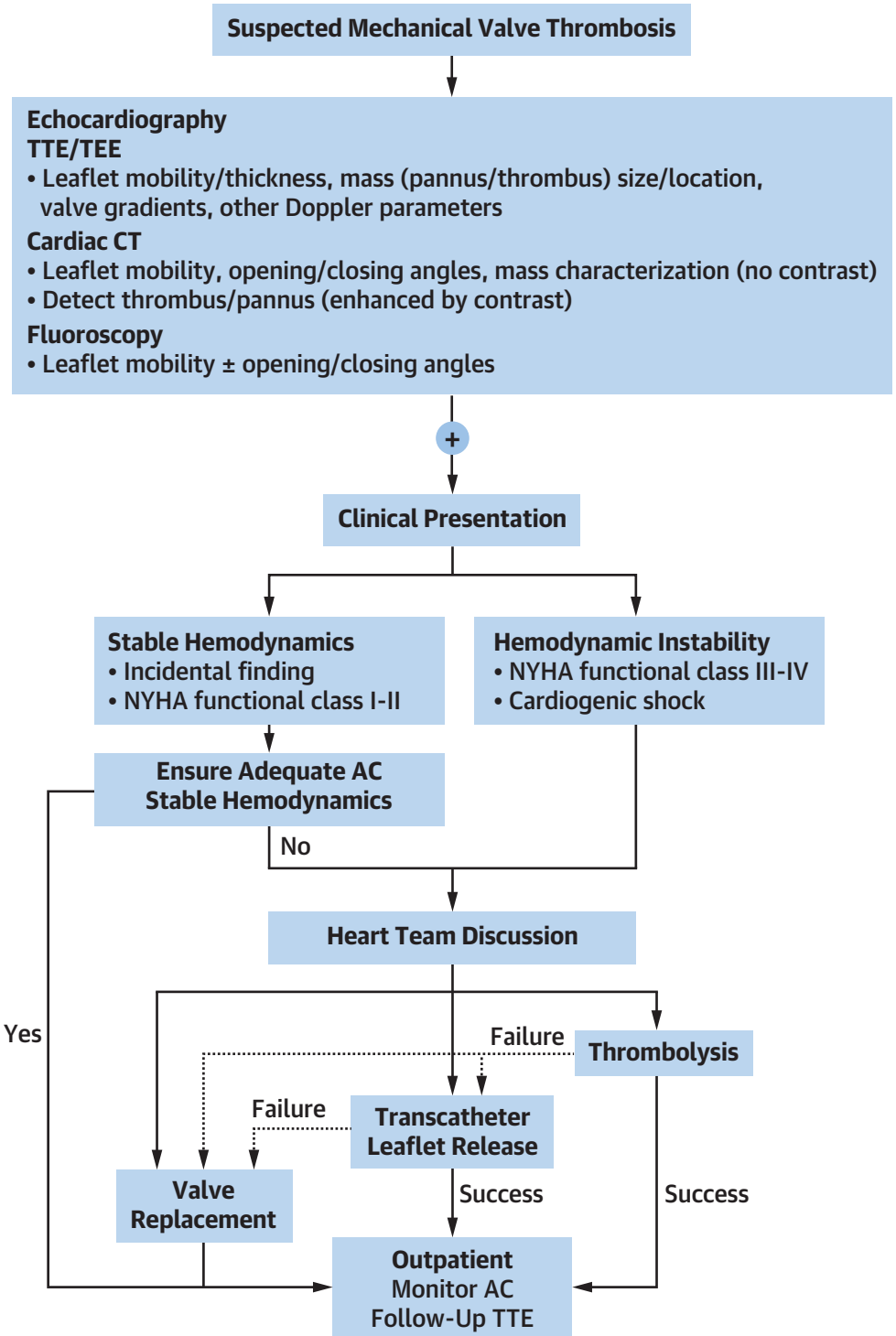
HIGHLIGHTS

- The clinical presentation of mechanical valve thrombosis can range from an incidental finding in an asymptomatic patient to cardiogenic shock.
- Multimodality imaging, including echocardiography, cine-fluoroscopy and CT, is commonly used to establish the diagnosis.
- Guideline-recommended treatments include heparin anticoagulation, thrombolysis, and surgery. Transcatheter manipulation of immobile leaflets can be pursued when thrombolytic or surgical risk is prohibitive or as a bridge to surgery.

MULTIMODALITY IMAGING

There are a variety of imaging modalities that are used to identify the etiology, location, severity, and hemodynamic changes associated with MVT. Increased valvular gradients, impaired mobility, regurgitation, and visualization of thrombus are

CENTRAL ILLUSTRATION **Algorithm for the Evaluation and Management of Mechanical Valve Thrombosis**



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The clinical presentation of mechanical valve thrombosis can vary. Multimodality imaging is critical in establishing the diagnosis, with the optimal treatment strategy largely dependent on the degree of obstruction and hemodynamic status. AC = anticoagulation; CT = computed tomography; NYHA = New York Heart Association; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

particularly relevant findings. Whereas TTE and cinefluoroscopy are more commonly used, other options include TEE and cardiac computed tomography (CT).

ECHOCARDIOGRAPHY. 2D and 3D echocardiography. Initial assessment for MVT using either 2-dimensional (2D) or 3D echocardiography focuses on valve appearance, leaflet mobility, and presence of thrombus. MVs appear as echogenic structures with varying degrees of shadowing artifact, depending on valve position and imaging plane. In normal functioning valves, leaflet motion can be easily appreciated. M-mode echocardiography can be used to increase temporal resolution to better identify characteristic leaflet motion. Thrombus identification depends on size and location, with shadowing artifact being a main limitation, obscuring areas distal to the valve. Each MV has an expected opening and closing angle predetermined by the manufacturer and deviations may be observed.[11] The opening/closing angles of mitral MVs can be correctly identified by TTE in 85% and by TEE in 100% of patients, regardless of valve.[12] However, echocardiography is less accurate for aortic MVs, with TTE and TEE correctly identifying opening angles in patients with single-disk valves in 40% and 77% of cases, respectively, and only in 13% and 35%, respectively, of patients with bileaflet prostheses.[12]

Color Doppler. Valve obstruction can be assessed using color Doppler, manifesting as elevated blood velocity and flow acceleration emanating from the obstruction that is in proportion to the degree of severity. There may be limited or no flow visualization across the valve, an indicator of leaflet restriction and probable thrombosis.[13] With inadequate valve closure, abnormal regurgitation may also be present. This regurgitation can be either transvalvular or paravalvular, the former caused by impaired motion of the valve disks because of vegetations, pannus, or thrombus interfering with complete closure.[5] Paravalvular leak, on the other hand, occurs because of suture line disruption caused by surgical error, suture failure, annular disruption, or endocarditis. Differentiating between the 2 is critical, because it helps establish the potential etiology of valve dysfunction and therapeutic options.[5] TEE may be better in identifying the cause and location of regurgitation, especially in cases of acoustic shadowing, with 3D color Doppler playing a significant role in determining the location and severity.[5]

Spectral Doppler. The transvalvular gradient observed across a prosthetic valve is determined by the size of the effective orifice area (EOA), blood volume, and the increment of time in which the blood is displaced. As such, the presence and severity of obstruction, regurgitant volume, cardiac output, and heart rate all influence the transvalvular gradient. All MVs inherently have transvalvular gradients higher than that of a healthy native valve, and the expected gradient is specific to the valve type and size. Prosthetic valve obstruction is usually defined as a mean transvalvular gradient increase of >50% (or an increase >10 mm Hg across an aortic prosthesis) compared with the postoperative baseline value.[5] Note that elevated gradients can also be observed with pannus formation, valve degeneration, high flow states, or patient-prosthesis mismatch.[5]

Aortic valve obstruction leads to a delay in peak transvalvular velocity generation (ie, prolonged acceleration time [AT]). An AT >100 milliseconds is 86% sensitive and specific for prosthetic aortic valve obstruction.[14] Indexing the AT to total ejection time (ET) (ie, the AT/ET ratio) can be used to further assess for pathologic obstruction; an AT/ET ratio >0.37 provides 96% sensitivity and 82% specificity for stenosis, whereas an AT >128 milliseconds and AT/ET >0.58 is 100% specific for stenosis.[3,14] Other helpful metrics include the Doppler-velocity index, which is the ratio of left ventricular outflow tract velocity-time integral to aortic valve velocity-time integral. A Doppler-velocity index <0.25 is 59% sensitive and 100% specific for stenosis.[14] Comparing the calculated EOA with values reported by the manufacturer is additionally helpful.[3,15] The American Society of Echocardiography guidelines provide tables with normal Doppler echocardiographic parameters that are suggestive of prosthetic valve obstruction for the 4 valve positions (Supplemental Tables 1 to 4).[3] Evaluation of MVs can be challenging in cases with acoustic shadowing, reverberation artifacts, and poor acoustic windows, leading to erroneous measurement of EOA via miscalculation of the left ventricular outflow tract diameter and velocity-time integral. To this end, EOA derived via 3D-TEE has been shown to yield more accurate results.[16]

THROMBUS VS PANNUS. Distinction of thrombus from pannus is essential, because thrombolytic therapy can be used for the former but is contraindicated in the latter. Current guidelines provide no diagnostic strategy to differentiate between thrombus and pannus.[3,5,6,15] One series found that, compared with patients with pannus formation, patients with thrombus had shorter duration of time from valve insertion to malfunction, shorter duration from onset of symptoms to diagnosis, and lower rate of therapeutic anticoagulation (21% vs 89%), whereas pannus

formation was more common in the aortic position (70% vs 21%).[17] TEE detected abnormal prosthetic valve motion in all cases with thrombus compared with 60% of patients with pannus formation. In general, pannus tends to be more circumferential and grows inward from the valve annulus. In contrast, thrombi are large and more asymmetric, with a mass of similar echogenicity to myocardium on the valve in 92% of cases, compared with 29% of cases with pannus formation.[3,17] Ultimately, the gold standard to differentiate thrombus from pannus is by pathological analysis of a surgically explanted valve.

CINE-FLUOROSCOPY. Cine-fluoroscopy is a noninvasive method to assess MV leaflet motion, especially in patients in whom TTE visualization of the valve is suboptimal or inconclusive. For bileaflet MVs, the disks can be directly visualized, opening and closing angles measured in an orthogonal view, then compared to the "normal" angles reported by each valve manufacturer (Supplemental Table 5).[11] Cine-fluoroscopy can also be used sequentially to monitor valve function after intervention. In a study of 82 consecutive patients with suspected MVT evaluated with cine-fluoroscopy, the sensitivity and specificity for diagnosing prosthetic valve obstruction in the mitral or aortic position were 87% and 78%, respectively. Likewise, the positive and negative predictive values were 80% and 91%, respectively.[18] A later study demonstrated that restricted leaflet motion was detected in 100% of all confirmed cases of MVT.[19]

CARDIAC CT AND MAGNETIC RESONANCE. In patients in whom echocardiography or cine-fluoroscopy have been inconclusive, multidetector CT can be useful, because it can measure the degree of leaflet restriction when cine-fluoroscopy is limited by attainable projections by the C-arm in the catheterization laboratory. Studies have shown good concordance between the 2 imaging modalities.[20] Similarly, CT can provide additional information to identify the likely cause of valve obstruction when echocardiography is uncertain.[4] The etiology of valve dysfunction can be discerned by using attenuation values to help differentiate thrombus from pannus. A cutoff point of ≥145 HU more likely represents pannus, with values below this more likely representing thrombus. Complete thrombolysis, defined as complete disappearance of mass on subsequent CT imaging with restoration of valve function, was more commonly achieved for masses with <90 HU compared to those with 90 to 145 HU.[21] Gating can be used to visualize the thrombus because there is excellent temporal resolution even during valve motion; however, the need for retrospective gating to image valve motion results in increased radiation exposure. Additionally, MV artifacts may result in suboptimal image quality for analysis. To this end, adding intravenous contrast can further elucidate etiology.

Whereas there are no contraindications to cardiac magnetic resonance for the evaluation of MVT, significant artifacts often prevent accurate evaluation of structure and function. Currently, cardiac magnetic resonance is not recommended by any of the guidelines.[5,6]

MANAGEMENT

NONOBSTRUCTIVE VS OBSTRUCTIVE THROMBUS. Adequate anticoagulation is critical and associated with few complications and good outcomes in patients with small, nonobstructive thrombi (<5 mm), whereas larger thrombi (>5 mm) have a higher risk of embolization.[22] The European Society of Cardiology guidelines recommend optimization of anticoagulation with interval repeat imaging to monitor for thrombus resolution.[6] Unfractionated or low-molecular weight heparin (LMWH) can be used for anticoagulation until the international normalized ratio (INR) falls in the therapeutic range. With larger thrombi (>10 mm) and evidence of systemic embolization, surgery is recommended.[6]

For obstructive MVT, the management plan should be individualized to the clinical scenario. Therapeutic options include: 1) optimizing anticoagulation; 2) thrombolysis; 3) transcatheter manipulation; and 4) surgery. Currently, the European Society of Cardiology guidelines have a Class I recommendation for surgery to treat obstructive MVT in critically ill patients without serious comorbidities. Thrombolysis should be considered with right-sided MVs or when surgery is prohibitively risky or not available.[6] In comparison, ACC/AHA guidelines give a Class I recommendation for either low-dose, slow thrombolytic therapy or surgery depending on clinical factors including clinical and surgical experience.[5] There are no guidelines for when or how to use transcatheter techniques.

Anticoagulation. Anticoagulation for MVs remains limited to oral anticoagulation with warfarin and parenteral heparinoid agents. Subtherapeutic anticoagulation is the most important factor involved in the pathogenesis of MVT.[10] Treatment with unfractionated heparin (UFH) plus warfarin has been successful, with at least partial thrombus resolution in patients with asymptomatic, small (<10 mm), left-sided MVT.[23] A meta-analysis of patients with mitral or aortic MVT reported that compared to patients

with a mean target INR <3.0, a target >3.0 reduced the incidence of thromboembolism.[24] Current ACC/AHA guidelines give a Class 1 recommendation for a target INR of 2.5 for aortic MVs in the absence of thromboembolic risk factors (eg, older-generation valves, atrial fibrillation, previous thromboembolism, hypercoagulable states, and left ventricular systolic dysfunction).[5] An INR target of 3.0 is recommended for aortic MVs in the presence of these risk factors, as well as for all mitral MVs irrespective of risk factors. For patients with an indication for antiplatelet therapy (eg, stroke or other thromboembolic event), it is reasonable to add low-dose aspirin after assessing bleeding risk.[5]

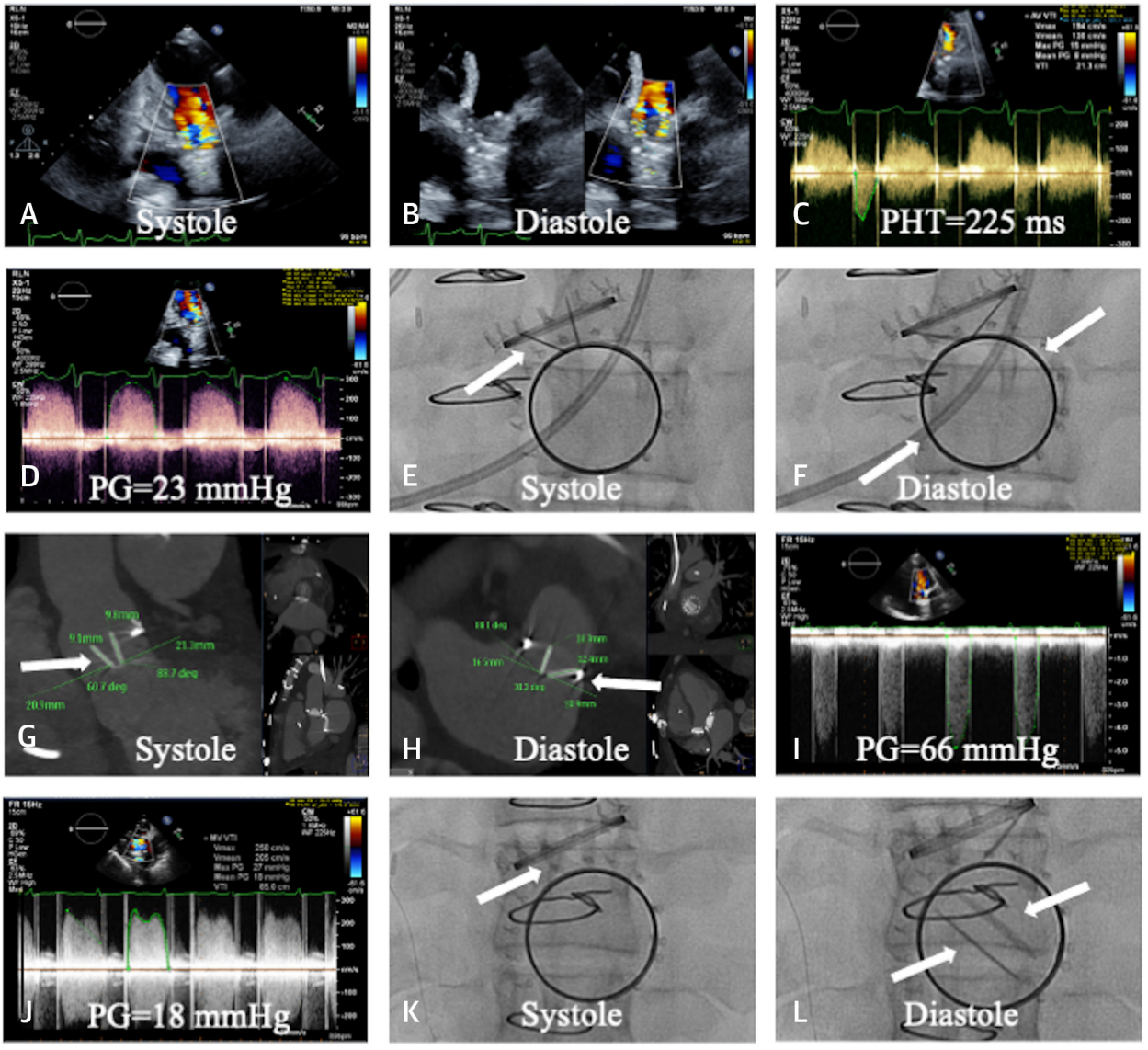
Anticoagulation with LMWH, in comparison with UFH, is generally associated with less thrombocytopenia, lower bleeding risk, more predictable pharmacokinetics, the potential for self-administration, and a lower hospital length of stay.[25] In a comparative, nonrandomized study of 208 consecutive patients who underwent single or double MV replacement, patients were first anticoagulated with UFH, then switched to LMWH until treatment with oral anticoagulation reached therapeutic range. Compared with patients treated with UFH only, no thromboembolic events were reported in the LMWH treatment group, concluding that LMWH is relatively safe and inexpensive.[26] Nevertheless, reports of thrombosed MVs and maternal and fetal deaths have been reported with the use of LMWH.[27-29] For these reasons, the ACC/AHA guidelines recommend shared decision making in choosing an anticoagulation strategy during pregnancy and switching to LMWH at least 1 week before delivery. Similarly, for pregnant women who require >5 mg/d of warfarin to achieve a therapeutic INR, switching to LMWH for the first trimester is also reasonable given the risk of teratogenicity.[5]

Direct oral anticoagulants are attractive agents because of their ease of administration without need for dietary modification, frequent blood draws, and dose adjustment, but they are presently contraindicated for use with MVs. Dabigatran is the most-studied direct oral anticoagulant in MVs, and although initial in vitro and animal model studies were promising, a phase II multicenter randomized controlled trial evaluating its use in MVs was stopped prematurely because there were higher rates of thrombotic and bleeding events in the dabigatran group.[30] A later study suggested that a dose of roughly 620 mg twice daily, far exceeding the 150 mg twice daily studied in the randomized controlled trial, would be required to achieve adequate anticoagulation prophylaxis, likely significantly increasing bleeding risk.[31] Nevertheless, a recent pilot study of 10 patients considered to be at low risk for elective MV replacement and treated with rivaroxaban showed no death or thromboembolic or bleeding events during 6-month follow-up.[32] These results highlight the need for larger studies investigating the use of direct oral anticoagulants in patients with MVs.

THROMBOLYSIS. Several trials have explored thrombolytic therapy, with varying results. In the PRO-TEE (Prosthetic Valve Thrombolysis—Role of Transesophageal Echocardiography) registry, thrombus area and prior stroke were strongly related to an increased risk of complications from thrombolysis. Compared to patients with thrombus size <0.8 cm^2, an incremental increase in thrombus area of 1 cm^2 by TEE measurement was associated with a 2.4-fold increased complication risk, and a history of prior stroke was associated with a 4.5-fold increase in complication rate. Conversely, a thrombus area of <0.8 cm^2 identified patients with low complication risk (6%), compared to a thrombus area 0.8 cm^2 to 1.6 cm^2 (29%) and >1.6 cm^2 (47%).[33] In the TROIA (Comparison of Different Transesophageal Echocardiography Guided Thrombolytic Regimens for Prosthetic Valve Thrombosis) trial, which included the largest patient cohort with MVT, a low-dose (25 mg) and slow (6 hours) infusion of tissue plasminogen activator (tPA) without bolus was implemented. The study showed no difference in mortality when compared to higher doses or faster infusions; however, there were fewer nonfatal major complications with a low-dose, slow-infusion regimen.[34] A subgroup analysis showed a 100% success rate in 24 pregnant women.[35] This study was followed by the PROMETEE (Prosthetic Mechanical Valve Thrombosis and the Predictors of Outcome) trial, which used a low-dose (25 mg), ultra-slow (25 hours) tPA infusion. The study showed a 90% success rate with low complications (<2% each for mortality, bleeding, and major embolus).[36] In each of these trials, anticoagulation was maintained using UFH and paused during thrombolytic infusion, with interval echocardiographic imaging done to assess need for repeat dosing until resolution was achieved. Important contraindications to thrombolysis included left atrial thrombus, ischemic stroke within 3 weeks of presentation, history of hemorrhagic stroke, or a bleeding diathesis (generally an INR >3).

Thrombolysis has also been proven safe for patients with left-sided MVs presenting with a high INR. An observational study of 30 such patients showed that thrombolysis can be considered, with a 24- to 48-hour delay in initiation of thrombolytics resulting in a lower bleeding risk without increasing mortality. A low-dose infusion was also associated with a lower

FIGURE 1 **Aortic and Mitral Mechanical Valve Thromboses Treated With Low-Dose tPA**



A woman with St Jude 25-mm mechanical mitral and 21-mm mechanical aortic valves (Abbott Laboratories) presented with decompensated heart failure. Transthoracic echocardiogram showed turbulent flows and aliasing of color Doppler of the aortic **(A)** and mitral **(B)** valves, maximum transaortic velocity of 4.9 m/s, dimensionless index of 0.11, and regurgitation with pressure half-time (PHT) of 225 milliseconds **(C)**. Transmitral pressure gradient was elevated **(D)**, with leaflet restriction confirmed on fluoroscopy **(E, F)** (**arrows** indicate restricted leaflets). Low-dose, ultra-slow tissue plasminogen activator (tPA) infusion was initiated. Subsequent computed tomography imaging showed improved leaflet motion **(G, H)** (**arrows** indicate leaflets). Aortic **(I)** and mitral **(J)** pressure gradients improved before discharge home. Outpatient fluoroscopy showed mobile valve leaflets **(K, L)** (**arrows** indicate leaflets).

incidence of ischemic stroke and a trend toward less bleeding.[37] **Figure 1** illustrates a patient who presented with decompensated heart failure caused by dual aortic and mitral MVTs and was successfully treated with thrombolytic therapy.

Studies have included mostly patients with left-sided MVs, leaving a paucity of data on the efficacy of thrombolysis for right-sided MVT. However, a small study of 16 patients who underwent thrombolysis of tricuspid or pulmonary MVs achieved thrombus resolution in 100% and 75%, respectively, without major complications.[38] The most important complications of thrombolytic therapy are pulmonary or systemic thromboembolic events and hemorrhage.

TABLE 1 Case Reports of Transcatheter Manipulation of Stuck MV Leaflets

First Author	Year	N	Valve Position	Valve Type	Initial Mean Gradient (mm Hg)	Intervention	Final Mean Gradient (mm Hg)	Complications
Jabbour et al[39]	1996	1	Aortic	21-mm MH tilting disk	NA	Transcatheter manipulation using multipurpose guide catheter to restore partial leaflet motion and hemodynamic stability, followed by immediate redo surgery	Reported insignificant prosthetic gradient on aortic pullback	None
Vihinen et al[40]	2011	1	Mitral	NA	8	Transcatheter manipulation using deflectable ablation catheter via transseptal puncture	5	None
Hariram[41]	2014	5		23-mm ATS	25	Transcatheter manipulation using guiding catheter via transseptal puncture	7	None
			Mitral	23-mm ATS	30		6	
				25-mm ATS	28		10	
				25-mm St Jude	17		5	
				31-mm St Jude	26		6	
Chen et al[42]	2020	1	Mitral	29-mm Carbomedics	24	Transcatheter manipulation using stiff guidewire followed by sequential inflations of coronary balloons	NA	None

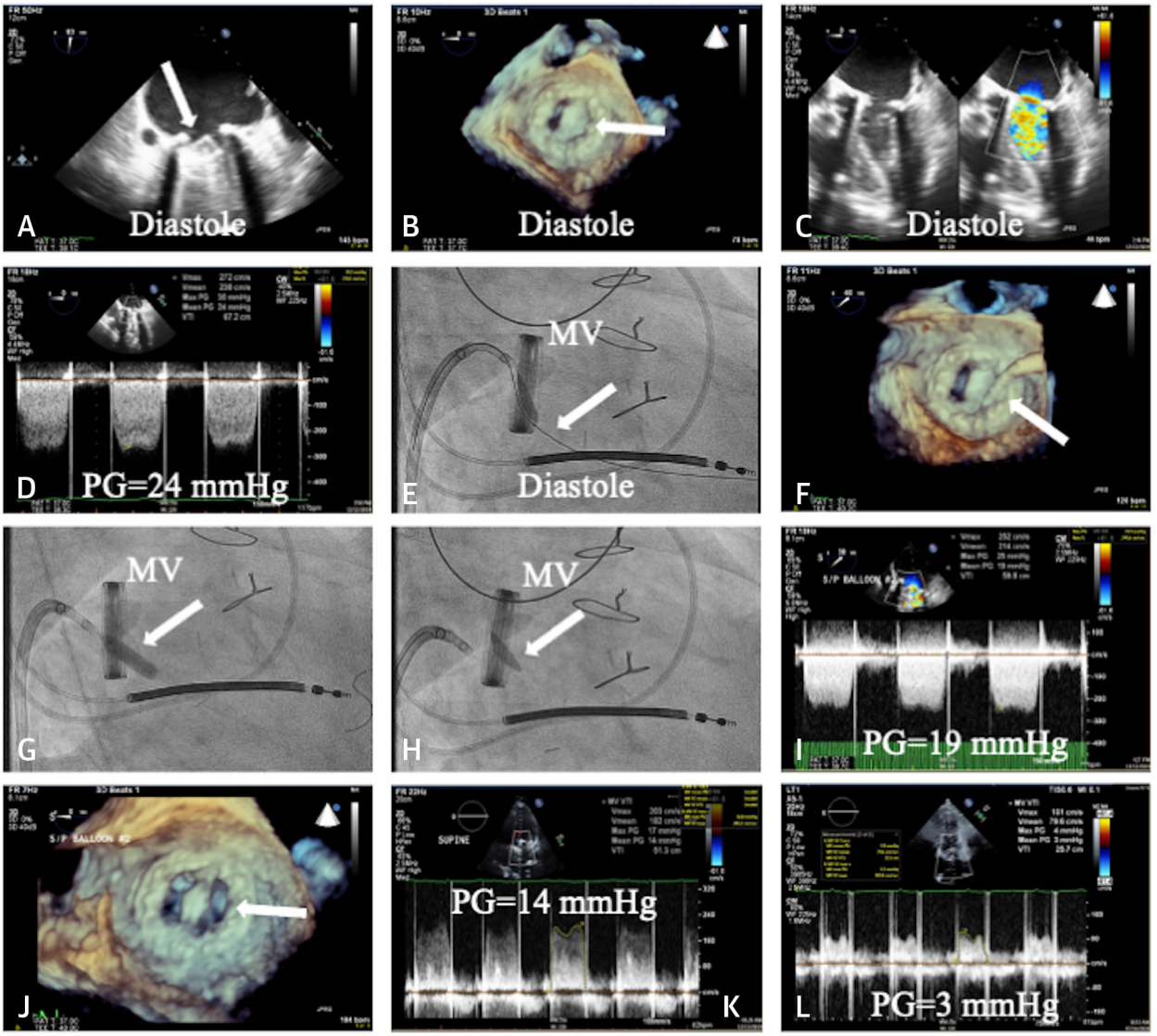
MH = Medtronic-Hall; MV = mechanical valve; NA = not available.

TRANSCATHETER INTERVENTIONS. Percutaneous transcatheter manipulation of stuck MV leaflets has emerged as a viable option in patients who fail thrombolysis, present with cardiogenic shock, or whose risk for redo surgery is unacceptably high. Transcatheter intervention may not be a definitive treatment but may offer a bridge to redo surgery in patients who are too sick on presentation. Only a few case reports exist on percutaneous manipulation of thrombosed MVs. **Table 1** summarizes these case reports, in which restricted MV leaflets were successfully mobilized using different wires, catheters, and balloons, resulting in clinical improvement without major complications.[39-42] **Figure 2** describes a patient who presented with cardiogenic shock caused by obstructive mitral MVT. Due to her supratherapeutic INR and prohibitively high surgical risk, she ultimately underwent transcatheter manipulation of the stuck mechanical valve leaflets using sequentially larger noncompliant balloons without major complications. Though a percutaneous approach is not part of the guidelines for management of obstructive MVT, the procedure has been proven to be safe and effective in a small number of patients and should be considered for those who fail or have a contraindication to thrombolysis, decline redo surgery, have unacceptably high surgical risk, and as a bridge to redo surgery through the acute phase of cardiogenic shock.

REDO SURGERY. Several trials have explored surgical outcomes for MVT. A lower functional class on presentation carries higher surgical risk, with 1 study demonstrating that patients with New York Heart Association functional class IV heart failure had a 17.5% risk of perioperative mortality compared to 4.7% for patients with functional classes I-III.[2] An advantage of surgery is that it allows for replacement of older, more thrombogenic valves with newer designs and allows for definitive diagnosis and treatment in cases of unclear etiology.

The clinical outcomes of patients with MVT treated with thrombolysis vs surgery have been previously reported. In a meta-analysis of 7 observational studies, there was no difference in complete restoration of valve function or death between the 2 treatment strategies. However, urgent surgery was associated with a significant reduction in thromboembolism, major bleeding, and recurrent MVT. This meta-analysis, however, included studies that did not implement the low-dose, slow infusion used in more recent studies.[43] A subsequent meta-analysis of 48 observational studies did find a significant reduction in mortality with thrombolysis (6.6%) over surgery (18.1%), but given that none of these studies were randomized, the results are only hypothesis-generating.[44] To this end, the recent HATTUSHA (Thrombolysis or Surgery in Patients With Obstructive Mechanical Valve Thrombosis) trial,[45] a multicenter observational prospective study of 158 patients with MVT undergoing a slow and/or ultra-slow infusion of low-dose tPA or surgery, found similar outcomes. It showed a success rate (defined as Doppler documentation of complete improvement in valve hemodynamics, a reduction in major diameter and/or area

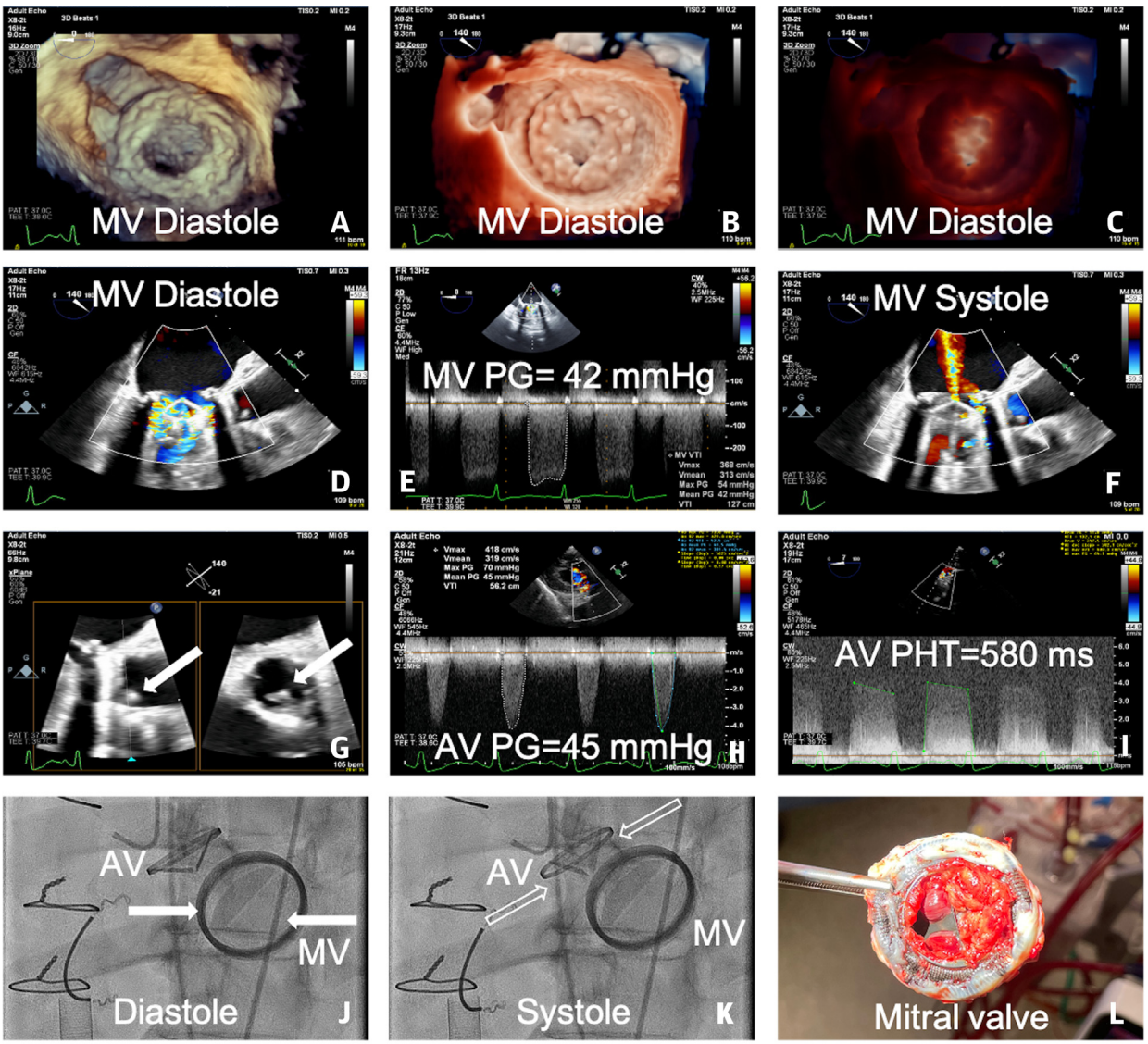
FIGURE 2 **Mechanical MV Thrombosis Successfully Treated With Transcatheter Manipulation**



A woman with a 29-mm Carbomedics mitral mechanical prosthesis (Corcym) presented in cardiogenic shock. Three-dimensional transesophageal echocardiogram revealed a restricted leaflet **(A, B)** (**arrows** indicate leaflet), turbulent flows **(C),** elevated pressure gradient (PG) **(D),** and maximum transvalvular velocity of 2.7 m/s. Given her prohibitive surgical risk and supratherapeutic international normalized ratio, transcatheter leaflet release was attempted. Using fluoroscopy, the valve was crossed with a 0.014-inch guidewire via transseptal approach **(E, F)** (**arrows** indicate catheter crossing valve). Progressively larger noncompliant coronary balloons were inflated **(G)** (**arrow** indicates inflated balloon), which released the leaflet **(H)** (**arrow** indicates mobile leaflet), decreased the mitral PG **(I),** and mobilized the restricted leaflet **(J).** Mitral PG **(K, L)** improved before discharge. MV = mitral valve.

of the thrombus by 75%, and symptomatic improvement) of 90.4% with the use of thrombolytic therapy. Most notably, patients treated with thrombolytic therapy, compared with surgery, had a lower rate of major (6% vs 41.3%) and minor (8.4% vs 38.7%) complications and a lower 3-month mortality (2.4% vs 18.7%). Redo surgery may still be required in cases during which thrombolytic therapy does not achieve hemodynamic stability. Moreover, fresh thrombus is more likely to respond to thrombolytics or transcatheter release, whereas mature, organized thrombus is more likely to require surgery.

FIGURE 3 Redo Surgery for Dual Mechanical Valve Thromboses Following Failed Thrombolytics

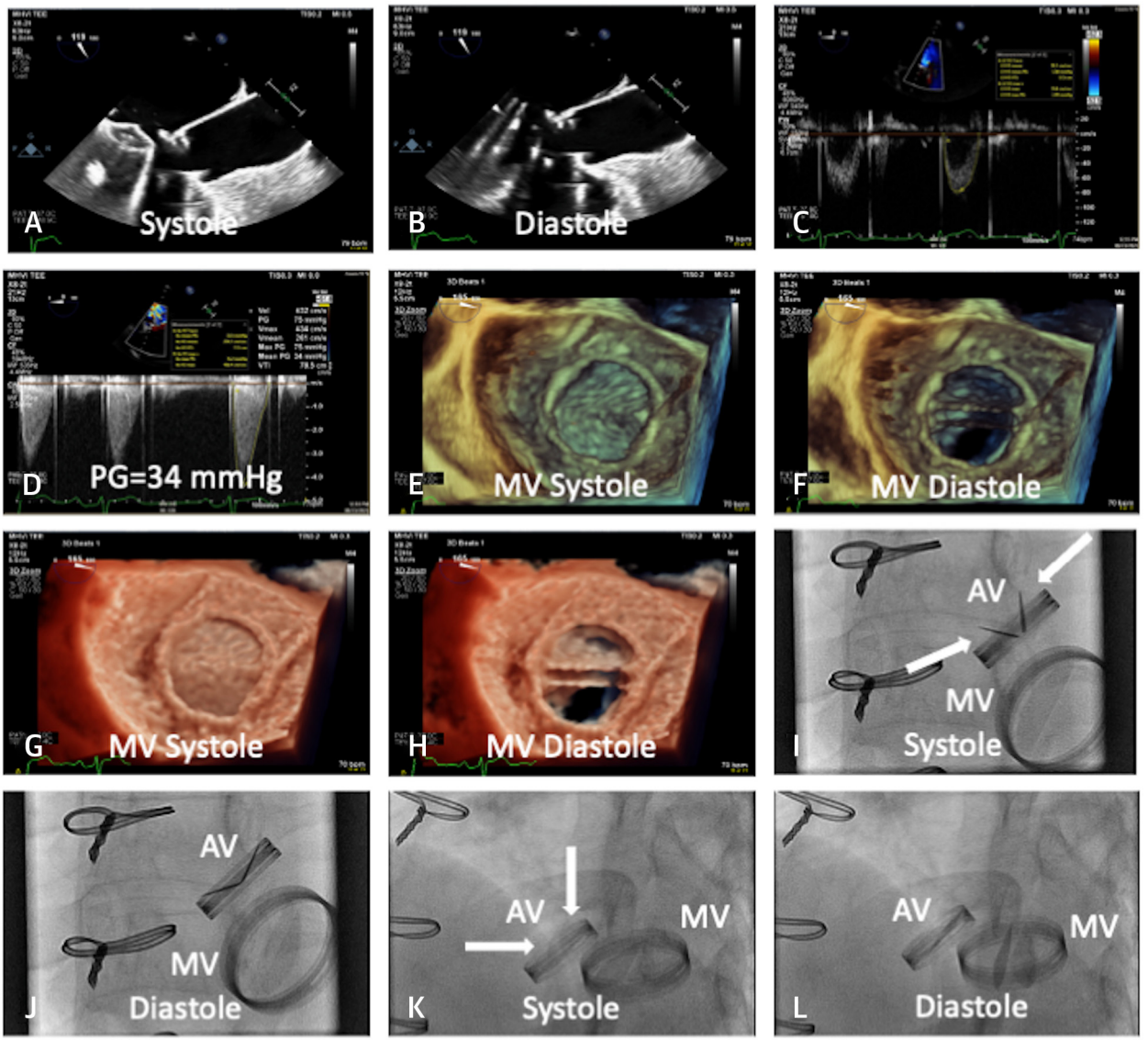


A woman with a 31-mm Carbomedics mechanical mitral valve (Corcym) and 21-mm St Jude mechanical aortic valve (Abbott Laboratories) presented in cardiogenic shock. Echocardiography revealed immobile mitral leaflets **(A to C),** flow turbulence, elevated PG **(D, E)**, and regurgitation **(F).** There was thrombus at the right coronary cusp **(G)** (**arrows** indicate thrombus), elevated aortic PG **(H)** (dimensionless index: 0.19; acceleration time [AT]: 80 milliseconds; ejection time [ET]: 170 milliseconds; AT/ET: 0.47), and regurgitation **(I).** Fluoroscopy confirmed valve restriction **(J, K)** (**solid and dashed arrows** indicate immobile mitral and aortic leaflets, respectively). She underwent replacement (**L** shows explanted mitral prosthesis) with 19-mm Inspiris aortic bioprosthetic (Edwards Lifesciences) and 27-mm Epic mitral bioprosthetic (Abbott) valves. AV = aortic valve; other abbreviations as in Figures 1 and 2.

Figure 3 describes a patient who, after prior thrombolytic therapy for aortic and mitral MVTs, returned in cardiogenic shock caused by recurrence of MVTs and ultimately underwent surgical replacement with dual bioprostheses.

Valve thrombosis is a separate process from pannus removal, which is ingrowth of tissue. If there is pannus, it is aggressively removed while maintaining adequate viable annulus for valve implantation. When redo surgery is pursued for MVT, the valve

FIGURE 4 **Aortic Mechanical Valve Thrombosis Treated With Bioprosthetic Valve Replacement**



A woman with a mechanical MV (model unknown) and a Hancock mechanical AV (Medtronic, unknown size) who was asymptomatic, was incidentally found to have restricted AV leaflets on transthoracic echocardiogram. Transesophageal echocardiogram confirmed aortic leaflet restriction **(A, B)**, and elevated PG **(C, D)** (dimensionless index: 0.23). There was normal MV function **(E to K)**. Fluoroscopy showed restricted AV leaflets with opening angle of 55° **(I, J)** (normal >85°; **arrows** indicate restricted AV leaflets), and normal mechanical MV leaflets **(K, L)** (**arrows** indicate normal leaflet motion). Given the findings, she underwent replacement with a 21-mm On-X aortic mechanical valve (CryoLife). Postdischarge transthoracic echocardiogram showed a normal AV dimensionless index. Abbreviations as in Figures 1 to 3.

must be replaced and not simply declotted. Risk of rethrombosis is multifactorial and very dependent on the etiology of the initial thrombotic event. If thrombosis occurs with guideline INR goals, a hematology consultation can help assess for hypercoagulable states before deciding on future INR goal, antiplatelet therapy, and potential use of a bioprosthetic valve. Following valve replacement, ideal follow-up consists of a postdischarge TTE, followed by repeat TTE imaging at 3 months and

annually thereafter. The decision between replacement with a bioprosthesis vs another MV is largely determined by age, comorbidities, ability/willingness to take anticoagulation, and feasibility of future valve-in-valve if a bioprosthesis is selected. Conundrums such as this support the need for the multidisciplinary team approach in helping patients make informed choices about their treatment options. Notably, the newer-generation On-X MV (CryoLife) has improved hemocompatibility and requires a lower anticoagulation target in patients with low thromboembolic risk. An initial INR target of 2.5 to 3.0 and low-dose aspirin for the first 3 months after surgery is recommended, after which the INR target can be reduced to 1.5 to 2.0 with simultaneous low-dose aspirin use. Patients with high thromboembolic risk should remain on the higher INR target.[5] Current guidelines recommend an INR of 2.5 to 3.5 for mitral MVs. The recently published PROACT (Prospective Randomized On-X Anticoagulation Clinical Trial) Mitral, a randomized controlled noninferiority study, assessed the safety and efficacy of warfarin at doses lower than currently recommended in patients with an On-X mitral MV. The trial randomized 401 patients to low-dose warfarin (target INR: 2.0-2.5) or standard-dose warfarin (target INR: 2.5-3.5) and followed them for a mean of 4.1 years. The study failed to demonstrate noninferiority for the composite outcome of thromboembolism, valve thrombosis, and bleeding events.[46] **Figure 4** highlights a case of a patient with aortic MVT who ultimately underwent redo surgical replacement with an On-X aortic MV. Concerns remained regarding thrombosis despite a therapeutic INR. To this end, the PROACT Xa trial, a randomized, multicenter, open-label study, will compare the efficacy between apixaban and warfarin for anticoagulation in 1,000 patients implanted with the newer-generation On-X MV.[47]

CONCLUSIONS

Prosthetic valve thrombosis is a known MV complication. Whereas the clinical presentation can vary, clinicians must keep a high index of suspicion for MVT in patients who present with signs and symptoms of heart failure or cardiogenic shock. Multimodality imaging with echocardiography, cinefluoroscopy, and CT is critical for prompt diagnosis and to guide management. The optimal strategy—anticoagulation, thrombolysis, transcatheter intervention, or redo surgery—depends on the degree of obstruction and the patient's hemodynamic status on presentation.

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Dr Waksman has served on advisory boards of Abbott Vascular, Boston Scientific, Medtronic, Philips IGT, and Pi-Cardia Ltd; has been a consultant for Abbott Vascular, Biotronik, Boston Scientific, Cordis, Medtronic, Philips IGT, Pi-Cardia Ltd, Swiss Interventional Systems/SIS Medical AG, Transmural Systems, and Venous MedTech; has received institutional grant support from Amgen, Biotronik, Boston Scientific, Chiesi, Medtronic, and Philips IGT; and is an investor in MedAlliance and Transmural Systems. Dr Rogers has been a consultant and physician proctor for Medtronic, Edwards Lifesciences, and Boston Scientific; has served on advisory boards of Medtronic and Boston Scientific; and holds equity interest in Transmural Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS diagnosis, imaging, mechanical valve, surgery, thrombosis, transcatheter

APPENDIX For supplemental methods, references, and tables, please see the online version of this paper.