Journal of the American Heart Association

ORIGINAL RESEARCH

Outcomes in Patients With Obstructive Hypertrophic Cardiomyopathy and Concomitant Aortic Stenosis Undergoing Surgical Myectomy and Aortic Valve Replacement

Milind Y. Desai, MD, MBA; Alaa Alashi, MD; Zoran B. Popovic, MD, PhD; Per Wierup, MD, PhD; Brian P. Griffin, MD; Maran Thamilarasan, MD; Douglas Johnston, MD; Lars G. Svensson, MD, PhD; Harry M. Lever, MD; Nicholas G. Smedira, MD, MBA

BACKGROUND: Hypertrophic cardiomyopathy (HCM) and aortic stenosis can cause obstruction to the flow of blood out of the left ventricular outflow tract into the aorta, with obstructive HCM resulting in dynamic left ventricular outflow tract obstruction and moderate or severe aortic stenosis causing fixed obstruction caused by calcific degeneration. We sought to report the characteristics and longer-term outcomes of patients with severe obstructive HCM who also had concomitant moderate or severe aortic stenosis requiring surgical myectomy and aortic valve replacement.

METHODS AND RESULTS: We studied 191 consecutive patients (age 67±6 years, 52% men) who underwent myectomy and aortic valve (AV) replacement (90% bioprosthesis) at our center between June 2002 and June 2018. Clinical and echo data including left ventricular outflow tract gradient and indexed AV area were recorded. The primary outcome was death. Prevalence of hypertension (63%) and hyperlipidemia (75%) were high, with a Society of Thoracic Surgeons score of 5±4, and 70% of participants had no HCM-related sudden death risk factors. Basal septal thickness and indexed AV area were 1.9±0.4 cm and 0.72±0.2 cm^2/m^2, respectively, while 100% of patients had dynamic left ventricular outflow tract gradient >50 mm Hg. At 6.5±4 years, 52 (27%) patients died (1.5% in-hospital deaths). One-, 2-, and 5-year survival in the current study sample was 94%, 91%, and 83%, respectively, similar to an age-sex–matched general US population. On multivariate Cox survival analysis, age (hazard ratio [HR], 1.65; 95% CI, 1.24–2.18), chronic kidney disease (HR, 1.58; 95% CI, 1.21–2.32), and right ventricular systolic pressure on preoperative echocardiography (HR, 1.28; 95% CI, 1.05–1.57) were associated with longer-term mortality, but traditional HCM risk factors did not.

CONCLUSIONS: In symptomatic patients with severely obstructive HCM and moderate or severe aortic stenosis undergoing a combined surgical myectomy and AV replacement at our center, the observed postoperative mortality was significantly lower than the expected mortality, and the longer-term survival was similar to a normal age-sex–matched US population.

Key Words: aortic stenosis ■ hypertrophic cardiomyopathy ■ surgery and outcomes

Hypertrophic cardiomyopathy (HCM) and aortic stenosis (AS) are 2 conditions that cause obstruction to blood flow leaving the heart. However, a characteristic distinguishing feature between the 2 is that HCM typically results in dynamic left ventricular (LV) outflow tract (LVOT) obstruction (caused by basal septal hypertrophy and systolic anterior motion of the mitral valve), while severe AS results in

Correspondence to: Milind Desai, MD, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk J1-5, Cleveland, OH 44195. E-mail: desaim2@ccf.org

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- It is important to recognize patients who present with dual left ventricular outflow tract obstructive physiology (caused by severe symptomatic obstructive hypertrophic cardiomyopathy and concomitant moderate or severe aortic stenosis) by careful noninvasive and invasive hemodynamic assessment, as they may benefit from a combination of myectomy and aortic valve replacement.

What Are the Clinical Implications?

- In a group of patients with dual left ventricular outflow tract obstructive physiology treated at an experienced center, the observed postoperative mortality was significantly lower than the expected mortality, and the longer-term survival was similar to a normal age-sex–matched US population.

Nonstandard Abbreviations and Acronyms

ACC/AHA	American College of Cardiology/American Heart Association
AS	aortic stenosis
AV	aortic valve
AVR	aortic valve replacement
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
RVSP	right ventricular systolic pressure
SAM	systolic anterior motion
SCD	sudden cardiac death
STS	Society of Thoracic Surgeons

fixed obstruction as a result of calcific degeneration and consequent narrowing of the aortic valve (AV).[1,2] Simultaneous existence of both conditions in the same patient has been documented, although it is uncommon.[3–5] However, with the increasing sophistication of imaging techniques and changing clinical demographics, there is a greater recognition of the coexistence of these 2 conditions in the same patient. This presence of sequential LVOT obstruction poses particular diagnostic challenges requiring meticulous imaging (especially Doppler echocardiography) to correctly identify the location of LVOT obstruction (Figure 1). Correct identification and quantification of this combined problem is crucial as it may necessitate a more complex invasive approach, which is the only current definitive therapeutic option as there are no large-scale studies demonstrating a clear survival benefit using medical therapy to relieve LVOT obstruction caused by either AS or HCM.

Surgical myectomy provides excellent long-term survival and freedom from recurrent symptoms in patients with obstructive HCM.[6–11] It is currently a class I indication to offer surgical myectomy+/–mitral valve surgery to patients with severe LVOT obstruction, who are intractably symptomatic despite maximally tolerated medical therapy.[1,2] Similarly, surgical AV replacement (AVR) significantly improves survival in patients with severe AS.[12–21] As a result, the current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines designate a class I indication for AVR in patients with severe AS who present with symptoms or those who demonstrate signs of cardiac dysfunction.[22,23] In addition, concomitant AVR is also recommended in patients with moderate AS undergoing cardiac surgery for another indications.[22,23] Over the years, we have recognized the need for performing a combination of surgical myectomy and AVR in multiple patients who present with severe symptomatic obstructive HCM and were incidentally found to have moderate or severe AS. To the best of our knowledge, outcomes data in this intriguing population are unknown. We sought to report the characteristics and longer-term outcomes of such patients.

METHODS

The authors will not make their data, analytic methods, and study materials available to other researchers.

Study Sample

The study sample consisted of 191 consecutive symptomatic patients (aged ≥18 years) with a mixed picture of dynamic LVOT obstruction caused by obstructive HCM and fixed obstruction caused by moderate or severe valvular AS who underwent a combination of surgical relief of LVOT obstruction and surgical AVR at our tertiary care center between June 2002 and September 2018. All patients had a diagnosis of HCM before developing significant valvular AS. Appropriate institutional review board approval with waiver of individual informed consent was obtained. Because of a different pathophysiologic profile, we excluded patients undergoing surgery to remove subaortic membrane (n=63) and those who had amyloidosis on eventual histopathologic analysis of postmyectomy tissue[24] (n=8). By study design, we did not include patients with HCM without concomitant moderate or severe AS (n=7763, which also included 2268 patients who eventually underwent surgical relief of LVOT obstruction). In

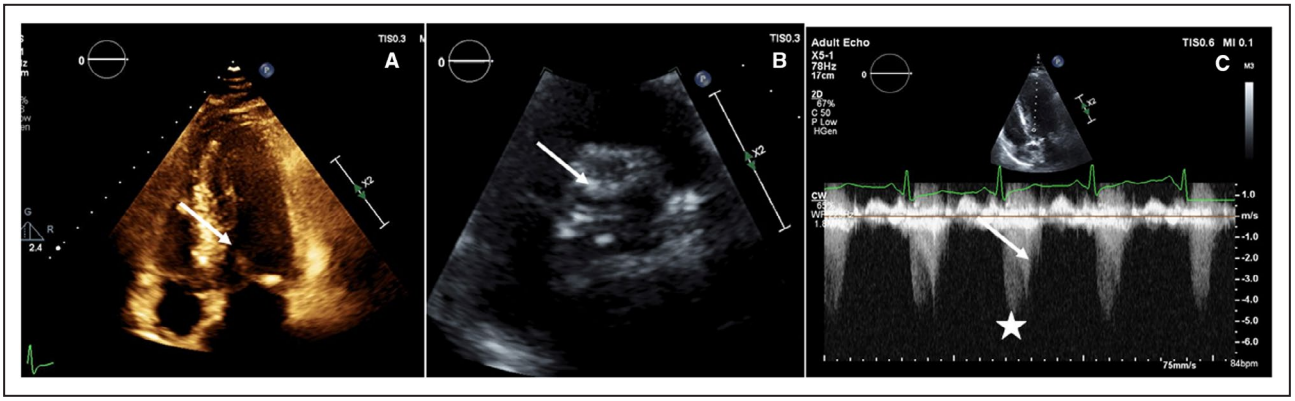

Figure 1. Transthoracic echocardiographic images of a 63-year-old patient with a combination of severe hypertrophic cardiomyopathy (HCM) with dynamic left ventricular outflow tract (LVOT) obstruction and moderately severe aortic stenosis (AS).

A, Severe systolic anterior motion of mitral valve (arrow) in a 4-chamber view. **B**, A heavily calcified trileaflet aortic valve (arrow) consistent with significant AS on a parasternal short-axis view . **C**, Continuous-wave Doppler image across LVOT with 2 signals, with one late-peaking "dagger shaped" (arrow) suggesting severe dynamic LVOT obstruction caused by obstructive HCM (>4 cm/s) and the other throughout the entire systole suggesting fixed obstruction (star) caused by valvular AS (>4 cm/s).

addition, patients undergoing surgical or transcatheter AVR for severe AS requiring a concomitant myectomy or alcohol septal ablation (caused by development of intraprocedural systolic anterior motion [SAM] of the mitral valve and LVOT obstruction) were not included (n=9). The diagnosis of obstructive HCM was made by experienced cardiologists based on typical features, with ventricular myocardial hypertrophy (LV wall thickness ≥15 mm) and presence of SAM and severe (>30 mm Hg) dynamic LVOT obstruction.[1,2] In addition, the diagnosis of concomitant significant AS was made based on the following echocardiographic findings[25,26]: (1) severe AV calcification with significantly reduced leaflet excursion; and (2) planimetry of the AV suggesting AV area <0.85 cm^2/m^2. Continuity equation and stroke volume index were not utilized to ascertain the type and severity of AS.

Baseline clinical data were manually extracted from electronic medical records. Based on the available preoperative data, Society of Thoracic surgeons (STS) score (AVR+coronary bypass grafting) was calculated. Chronic kidney disease (CKD) was defined as glomerular filtration rate <30 mL/min. In addition, standard ACC/AHA HCM sudden cardiac death (SCD) risk factors and 5-year ESC SCD risk score were also calculated.[1,2] History of sudden death was defined as an unexpected sudden collapse occurring <1 hour from symptom onset in otherwise stable patients, followed by successful resuscitation.[27] Because this was a surgical cohort, there were no patients with a prohibitive comorbidity (eg, cancer, advanced neurologic, pulmonary, hepatic, or renal pathologies) at the time that would preclude cardiac surgery. No patient went directly for an operation without being evaluated by a cardiologist (including advanced imaging) at our center and agreement with cardiac surgery. All patients were on maximally tolerated medical therapy at the time of operation.

Follow-up information, including details of AV prosthesis, was collected by manual extraction from electronic medical records and phone calls. Presence of atrial fibrillation was recorded based on history, ECGs, and Holter data. Nonsustained ventricular tachycardia (VT), wide complex tachycardia at ≥120 beats per minute lasting >3 beats but <30 seconds or sustained VT lasting >30 seconds, were recorded based on history and Holter data. Presence of implantable cardioverter-defibrillator and permanent pacemaker were ascertained.

Echocardiography

All patients underwent comprehensive echocardiography using commercially available instruments (Philips, General Electric, and Siemens). Maximal end-diastolic LV wall thickness, LV dimensions, and left atrial area were measured according to guidelines.[28] The degree of resting mitral regurgitation and aortic regurgitation were assessed (none to severe), using multiple criteria.[29] Resting dynamic LVOT peak velocity was measured by continuous-wave Doppler echocardiography, and pressure gradient was estimated using the simplified Bernoulli equation. Care was taken to distinguish the "dagger-shaped" late-peaking LVOT waveform from that of mitral regurgitation jet or the continuous Doppler jet of significant AS (Figure 1). In addition, LVOT diameter was measured and AV assessment, including planimetry, were performed according to guidelines.[26] Because of the mixed picture of LVOT obstruction and AS, the continuity equation and stroke volume index

were not utilized to determine severity and type of AS. In addition, all patients underwent transesophageal echocardiography in the operating room to confirm a mixed obstruction picture of obstructive HCM-related LVOT obstruction and at least moderate AS (calcified valve with restricted leaflet motion and planimetered AV area <0.85 cm^2/m^2) using a similar comprehensive evaluation (including Doppler assessment across AV and LVOT) as described above.[30] While in the operating room, isoprenaline or dobutamine infusion were administered following the completion of myectomy to assess for provocable LVOT gradient.

Left-Sided Heart Catheterization

In addition to preoperative coronary angiography, all patients underwent left-sided heart catheterization to confirm the presence of dual obstructive physiology. This was performed using the controlled pullback technique where a guide catheter was positioned across the AV in the left ventricle and the aorta. A 0.035″ support wire was put in place in the LV apex to ensure stability of the catheter. Subsequently, a 0.014″ pressure wire was placed in the left ventricle through the same guide catheter. Pressure wire–enabled recording of LV pressure while controlled pullback of the guide catheter using support wire allowed measurement of pressure at the LV apex, LVOT, and just distal to the AV.

Postoperative Echocardiography

We evaluated postoperative (predischarge) echocardiograms for LV ejection fraction, LVOT gradients, and AV gradients as described above. In addition, we recorded different types of AV prostheses (mechanical and bioprosthesis). We also recorded the effective orifice areas of the prosthetic AV (stroke volume/prosthetic $valve_{velocity\ time\ integral}$) in each patient and indexed it to body surface area.[31]

Surgical Technique

Date and type of surgical procedures performed were recorded. In addition to AVR, the different operative techniques to relieve LVOT obstruction were recorded as follows: myectomy and myectomy+mitral valve repair+/–papillary muscle (resection/reorientation) surgery. Details of surgical techniques by our group have been previously described.[7,10,11,21,32] The basic technique of myectomy involved muscle resection below the membranous septum, removing muscle over both papillary muscles, and often extending to both trigones. We recorded the type of AV prosthesis as mechanical or bioprosthetic. In addition, concomitant coronary bypass grafting, maze, pulmonary vein isolation, and left atrial appendage ligation/excision were also recorded. The final decision regarding the specific operative technique was made by the attending cardiothoracic surgeon. All myectomy specimens were evaluated by dedicated cardiac pathologists and a diagnosis of HCM was made based on a combination of factors including myocyte disarray, myocyte hypertrophy, small coronary arteriole dysplasia, interstitial fibrosis, and endocardial fibroelastosis.[24]

Outcomes Assessment

The duration of follow-up ranged between initial surgery to event/last follow-up. Death notification was confirmed by observation of death certificate or verified with a family member. In addition to outpatient clinic/phone call follow-up and electronic medical record documentation, we searched state and nationally available databases and performed obituary searches. The last search was performed in March 2019. Patients were censored at the time of death or last follow-up. Noncardiac cause of death was also recorded, where feasible. The primary end point was death, and no patients were lost to follow-up. In addition, we included a secondary end point of death (excluding documented noncardiac death caused by cancer, liver failure, primary respiratory, or neurologic issues, censoring at the time of event). Patients with an unknown cause of death were included in the secondary outcome, unless the patient's proximal history, just before death, strongly suggested a noncardiac cause, based on chart review or family discussion.[33] Presence and cause of stroke (transient or permanent) was recorded based on clinical neurologic evaluation and neuroimaging. Arrhythmias, occurring during follow-up (atrial fibrillation, VT, and nonsustained VT) were recorded.

Statistical Analysis

Continuous variables are expressed as mean±SD and/or median (interquartile range) and compared using ANOVA (normal distribution) or Mann-Whitney test (non-normal distribution), as appropriate. Categorical data are expressed as percentage and compared using chi-square test. To assess for the association of various predictors with longer-term deaths, univariate and multivariate Cox proportional hazards analysis was utilized. Hazard ratios (HRs) with 95% CIs were calculated. For univariate analysis, variables that are known to be associated with outcomes in patients with HCM (as well as those undergoing cardiac surgery) were studied. Variables that had a significant ($P<0.05$) association with primary events on univariate analysis were subsequently considered for the multivariate model. No multiplicity adjustment was performed. Additionally, Kaplan-Meier curves were generated to determine the cumulative proportion of patients with events as a function over time, and compared using

log-rank statistic. All events, including those occurring in the immediate postoperative period, were included for survival analysis. In addition, the survival of the study sample was also compared with the survival of an age-sex–matched US population (https://www.cdc.gov/nchs/products/life_tables.htm). Since longer-term secondary events and noncardiac death were competing risks, univariate and multivariate survival analysis was performed by competing risk regression analysis using the Fine-Gray proportional subhazards model, and sub-HRs were calculated, along with 95% CIs.[34,35] Statistical analysis was performed using SPSS version 11.5 (SPSS Inc) and R version 3.4.3 (R Foundation for Statistical Computing). A *P* value <0.05 was considered significant.

RESULTS

The clinical and echocardiographic data of the study sample are shown in Tables 1 and 2. The proportion of patients with standard cardiovascular risk factors such as hypertension (63%), hyperlipidemia (75%), and diabetes (25%) was high, while the proportion of patients with standard HCM risk factors was low (70% had no ACC/AHA HCM SCD risk factors and 79% had ESC 5-year SCD risk score <4%). Mean STS score was 5%±4%; 52% had low (<4%) and 36% had intermediate (4%–8%) STS score. All patients were symptomatic (36% in New York Heart Association class II, 64% in class ≥II, and 19% with concomitant angina) and taking appropriate and maximally tolerated medical therapy. All patients had preserved LV ejection fraction (>55%) and the mean LV mass index was significantly increased at 147±51 g/m^2. All patients had SAM of the mitral valve, a dynamic LVOT gradient ≥50 mm Hg, and indexed AV area ≤0.85 cm^2/m^2, by study design (51% had moderate [indexed AV area between 0.65 and 0.85 cm^2/m^2] and 49% had severe AS [<0.65 cm^2/m^2]). In addition, 26% patients had at least moderate SAM-related mitral regurgitation, while 10% had at least moderate aortic regurgitation. A total of 51 (27%) patients had obstructive coronary artery disease on invasive angiography, and presence of at least moderate AS and severe dynamic LVOT obstruction were confirmed on invasive hemodynamics.

The type of cardiac surgeries were as follows: AVR+isolated myectomy (n=110, 58%), AVR+myectomy plus mitral/subvalvular apparatus surgery (n=59, 31%), AVR+myectomy+coronary artery bypass grafting (n=29, 15%), and AVR+myectomy+coronary artery bypass+mitral/subvalvular apparatus surgery (n=22, 12%). Bioprostheses were implanted at the aortic position in 171 (90%) patients and 20 (10%) had a mechanical prosthesis implanted. In the subgroup of 81 patients with concomitant mitral valve surgery, 22 (11%) underwent mitral valve replacement, while 59 underwent transaortic mitral valve repairs. In addition, 24 (10%) patients had invasive therapies (surgical maze and/or pulmonary vein isolation) for relief of atrial fibrillation, 29 (15%) patients had excision/ligation of left atrial appendage, and 26 (14%) patients had concomitant ascending aortic surgery. The mean time to discharge was 8±5 days. At the time of discharge, the mean LV ejection fraction, resting LVOT gradient, provoked LVOT gradient, mean AV gradient, and indexed effective aortic orifice area were 60%±4%, 10±3 mm Hg (range 0, 18 mm Hg), 19±9 mm Hg (range 0, 28 mm Hg), 14±6 mm Hg (range 8, 20 mm Hg), and 0.94±0.03 cm^2/m^2, respectively. No patients had evidence of patient prosthesis mismatch (indexed effective aortic orifice area <0.85 cm^2/m^2). At 1 year, 69 patients returned for follow-up and the mean LV ejection fraction, maximal LVOT gradient, mean AV gradient, and indexed effective aortic orifice area were 58%±4%, 20±4 mm Hg (range 0, 28 mm Hg), 15±4 mm Hg (range 8, 19 mm Hg), and 0.91±0.04 cm^2/m^2, respectively.

The breakdown of histopathology of myectomy tissue obtained during surgery was as follows: characteristic HCM (n=157 [82%]) and hypertensive heart disease (n=34 [18%]). The baseline characteristics for these 2 subgroups (histopathologic HCM versus hypertensive heart disease) were similar: age (67±4 versus 68±6, *P*=0.23), sex (51% versus 52%, *P*=0.82), maximal LVOT gradient (83±41 versus 84±42, *P*=0.89), and basal septal thickness (1.9±0.4 versus 1.9±0.3, *P*=0.92). However, the proportion of patients with hypertension was significantly different (55% versus 100%, *P*<0.01).

In addition, during follow-up, there were an additional 9 patients (5%) who underwent implantable defibrillator insertion and 32 patients (17%) with pacemaker implantation, respectively. A total of 31 patients (16%) had evidence of atrial fibrillation during long-term follow-up (excluding immediate postoperative atrial fibrillation within 30 days of surgery) and were treated with medications (89% with amiodarone and the rest using rate control). Nonsustained and sustained VT were noted in 15 (8%) and 2 (1%) patients, respectively. There were no ventricular septal defects in the current study sample.

During a mean follow-up of 6.5±4 years (median, 5.9 years [interquartile range, 3.3–8.7 years]), and 52 (27%) patients died. There were 3 (1.5%) in-hospital deaths (versus an expected mortality based on STS score of 5%) and 2 (1%) strokes following surgery. One-, 2-, and 5-year survival in the current study sample was 94%, 91%, and 83%, respectively, similar to an age-sex–matched general US population (Figure 2). Within the sample, there were 5 patients who had a documented noncardiac cause of death (3 cancers, 1 advanced liver disease, and 1 multiorgan failure). There

Table 1. Baseline Characteristics of the Study Sample

Variable	Total (N=191)
Age, y	67±6
Female sex	100 (52)
Standard cardiovascular comorbidities	
Hypertension	120 (63)
Hyperlipidemia	144 (75)
Diabetes	48 (25)
CKD	11 (6)
Chronic obstructive pulmonary disease	23 (12)
History of stroke	17 (9)
Documented coronary artery disease	119 (11)
History of prior sternotomy	6 (3)
STS score (%)	5±4
STS score category	
Low risk (<4%)	100 (52)
Intermediate risk (4–8%)	68 (36)
High risk (>8%)	23 (12)
HCM-related risk factors	
Family history of hypertrophic cardiomyopathy	10 (5)
Family history of SCD	22 (12)
History SCD	5 (3)
History of nonsustained ventricular tachycardia	22 (12)
Gene positive for HCM (n=61 tested)	20 (33)
History of syncope	42 (22)
History of atrial fibrillation	48 (25)
Implantable defibrillator	6 (3)
Permanent pacemaker	8 (4)
ACC/AHA HCM SCD risk factors	
0	134 (70)
1	46 (24)
≥2	11 (6)
ESC % 5-y HCM SCD risk score	2.9±2
ESC % 5-y HCM SCD risk categories	
Low risk (<4%)	150 (78)
Intermediate (4–6%)	26 (14)
High (>6%)	15 (8)
Cardiac medications	
Aspirin	167 (87)
Statins	137 (72)
β-Blockers	173 (91)
Calcium channel blockers	39 (20)
Disopyramide	8 (4)
Anticoagulation	46 (24)
Symptoms at presentation	
Angina	36 (19)
NYHA class	
II	69 (36)
III	119 (62)
IV	3 (2)

Values are expressed as mean±SD or number (percentage). ACC/AHA indicates American College of Cardiology/American Heart Association; CKD, chronic kidney disease; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; SCD, sudden cardiac death; and STS, Society of Thoracic Surgeons.

were no patients with a documented appropriate implantable cardioverter-defibrillator discharge during follow-up. During follow-up, 3 (1.5%) patients needed a repeat valve replacement procedure (2 in the aortic and 1 in the mitral position).

For the entire study sample, data on univariate and multivariate Cox proportional survival analysis demonstrating data on the association of various relevant

Table 2. Echocardiographic Parameters of the Study Sample

Variable	Total (N=191)
LV ejection fraction, %	64±6
LV mass index, g/m^2	147±51
Indexed LV end-diastolic dimension, cm/m^2	2.3±0.3
Indexed LV end-systolic dimension, cm/m^2	1.2±0.3
Maximal LV thickness, cm	1.9±0.4
Maximal posterior wall thickness, cm	1.2±0.3
Indexed left atrial dimensions, cm/m^2	2.4±0.3
Systolic anterior motion of mitral valve, No. (%)	191 (100)
Dynamic peak resting LVOT gradient, mm Hg	75±43 (range 0–130 mm Hg)
Dynamic peak maximal LVOT gradient, mm Hg	84±41 (range 52–148 mm Hg)
Maximal LVOT gradient ≥50 mm Hg, No. (%)	191 (100)
Moderate to severe resting mitral regurgitation, No. (%)	50 (26)
Bicuspid aortic valve, No. (%)	29 (15)
LVOT diameter	2.0±0.2 cm
Indexed AVA, cm^2/m^2	0.72±0.2
Mean AV gradient, mm Hg*	36±8 mm Hg
Severity of AS, No. (%)	
Moderate (indexed AVA 0.65–0.85 cm^2/m^2)	97 (51)
Severe (indexed AVA <0.65 cm^2/m^2)	94 (49)
Moderate or severe resting aortic regurgitation, No. (%)	19 (10)
Aortic root diameter, cm	3.6±0.6
Ascending aorta ≥4.5 cm, No. (%)	26 (5)
RVSP, mm Hg	34±13
Late gadolinium enhancement on cardiac magnetic resonance (n=65 performed), No. (%)	35 (52)

Values are expressed as mean±SD unless otherwise indicated. AVA indicates aortic valve area; LV, left ventricular; LVOT, left ventricular outflow tract; and RVSP, right ventricular systolic pressure.

*Aortic valve (AV) gradient was not utilized to determine severity of aortic stenosis (AS).

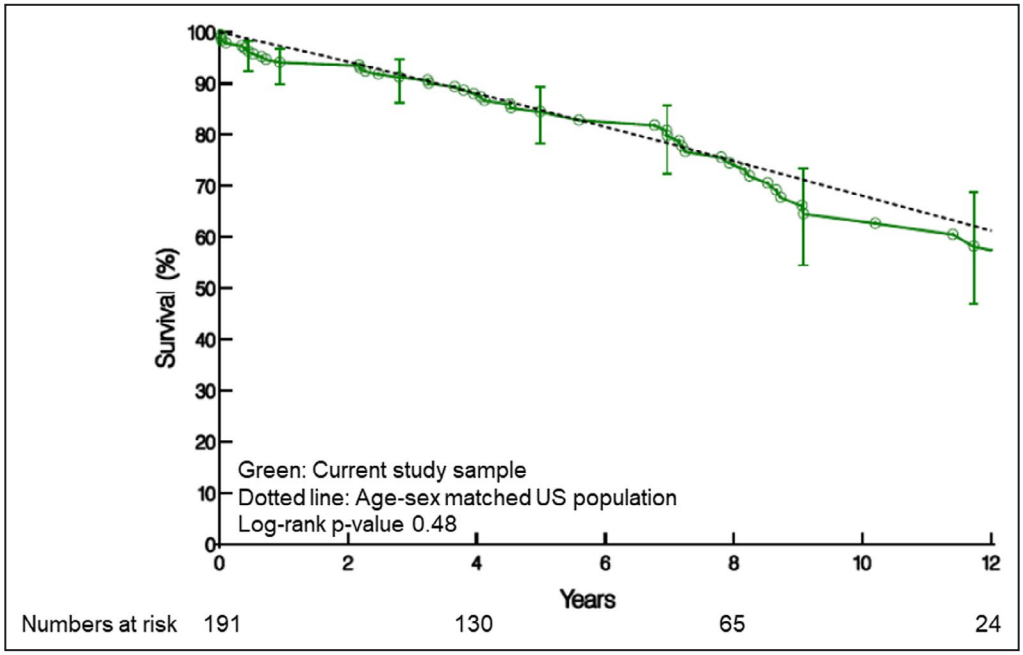

Figure 2. Kaplan-Meier survival curve demonstrating long-term survival of the entire study sample compared with an age-sex–matched US population.

predictors with longer-term mortality are shown in Table 3. We demonstrate that standard cardiovascular risk factors such as age (HR, 1.65), CKD (HR, 1.58), and right ventricular systolic pressure (RVSP) on resting preoperative echocardiography (HR, 1.28) were associated with longer-term mortality, but traditional risk factors associated with outcomes in HCM were not. Histopathologic diagnosis of HCM versus hypertensive heart disease was also not associated with longer-term mortality. The type of AV prosthesis was also not associated with longer-term survival. The findings were similar if STS score (a composite of various relevant cardiovascular risk factors associated with mortality) was included in survival analysis instead of its constituent predictors (HR, 1.10).

The findings of multivariate survival analysis for the primary outcome of death in the subgroup excluding patients with documented obstructive coronary artery disease were similar as follows (total n=140, number of deaths=36): age (for every 10-year increase: HR, 1.61; 95% CI, 1.32–1.79 [*P*<0.001]), CKD (HR, 1.43; 95% CI, 1.21–1.93 [*P*<0.001]), and resting RVSP (HR, 1.21; 95% CI, 1.09–1.97 [*P*=0.02]) were associated with mortality.

Similarly, the findings of multivariate survival analysis for the primary outcome of death in the subgroup of patients with histopathologic diagnosis of HCM were similar as follows (total n=157, number of deaths=43): age (for every 10-year increase: HR, 1.58; 95% CI, 1.27–1.83 [*P*<0.001]), CKD (HR, 1.37; 95% CI, 1.17–2.04 [*P*<0.001]), and resting RVSP (HR, 1.22; 95% CI, 1.07–1.91 [*P*=0.03]) were associated with mortality.

For the entire study sample, the results of multivariate survival analysis using competing risk assumption for the secondary end point (excluding documented noncardiac deaths, n=47) had similar results: age (for every 10-year increase: sub-HR, 1.58; 95% CI, 1.26–1.82 [*P*<0.001]), CKD (sub-HR, 1.51; 95% CI, 1.27–1.83 [*P*<0.001]), and resting RVSP (sub-HR, 1.23; 95% CI, 1.09–1.61 [*P*=0.01]) were associated with the secondary end point.

DISCUSSION

The current study describes characteristics and outcomes of patients presenting with a combination of symptomatic severely obstructive HCM and moderate or severe AS undergoing surgical relief of LVOT obstruction and AVR at our tertiary care center. These patients were significantly older than patients with standard HCM[1,2] with an equal proportion of men and women. There was a high incidence of standard cardiovascular risk factors. On the other hand, the majority of the patients had no ACC/AHA SCD risk factors and the ESC HCM 5-year SCD risk score was low. This was different than the patients with standard obstructive HCM undergoing surgery at our institution, as would be expected.[36] All patients had significant sequential LVOT obstruction, including severe dynamic LVOT obstruction and at least moderate fixed obstruction caused

Table 3. Univariate and Multivariate Cox Proportional Hazard Analysis for Longer-Term Mortality

Variable	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (for every 10-y increase)	1.49 (1.22–1.82)	<0.001	1.65 (1.24–2.18)	<0.001
Female sex	1.07 (0.61–1.88)	0.82		
History of hypertension	1.65 (0.90–3.00)	0.12		
History of dyslipidemia	1.35 (0.75–2.43)	0.31		
History of diabetes	1.04 (0.55–1.97)	0.90		
History of CKD	1.96 (1.39–2.74)	<0.001	1.58 (1.21–2.32)	<0.001
History of obstructive coronary artery disease	1.02 (0.56–1.86)	0.96		
History of chronic pulmonary disease	1.34 (0.92–2.35)	0.42		
History of atrial fibrillation	1.45 (1.76–1.75)	0.24		
Syncope	1.45 (0.79–2.64)	0.41		
NYHA class II vs ≥III	1.08 (0.59–1.97)	0.79		
Family history of SCD	1.01 (0.39–1.57)	0.99		
Family history of hypertrophic cardiomyopathy	1.63 (0.39–6.89)	0.50		
Medical therapy for hypertrophic cardiomyopathy	0.71 (0.27–1.86)	0.48		
History of nonsustained ventricular tachycardia	1.17 (0.52–1.66)	0.70		
STS score*	1.10 (1.04–1.15)	<0.001		
ESC risk score	1.05 (0.93–1.19)	0.43		
ACC/AHA risk factors (0 vs ≥1)	1.13 (0.67–1.89)	0.65		
LV ejection fraction	1.03 (0.98–1.07)	0.26		
Maximal LV thickness	1.17 (0.56–2.46)	0.67		
Indexed left atrial size	1.03 (0.89–1.33)	0.54		
Moderate or severe mitral regurgitation vs less	1.06 (0.56–2.01)	0.99		
Moderate or severe aortic regurgitation vs less	1.03 (0.63–1.89)	0.76		
Maximal LVOT gradient (for every 10-mm Hg increase)	1.02 (0.96–1.08)	0.59		
Indexed LV mass (for every 10-g/m^2 increase)	1.04 (0.98–1.11)	0.16		
Indexed LV end-systolic diameter	1.01 (0.96–1.04)	0.83		
RVSP (for every 10-mm Hg increase)	1.22 (1.02–1.46)	0.01	1.28 (1.05–1.57)	0.01
Indexed AVA (for every 0.1-cm^2/m^2 decrease)	1.03 (0.97–1.06)	0.52		
AVR+myectomy	Reference			
AVR+myectomy+CABG	1.21 (0.83–1.59)	0.46		
AVR+myectomy+CABG+mitral valve surgery	1.37 (0.83–1.42)	0.31		
Concomitant ascending aortic replacement	1.14 (0.79–1.49)	0.62		
Aortic valve mechanical vs bioprosthesis	1.15 (0.73–1.78)	0.53		
Indexed prosthetic effective aortic valve orifice area	1.01 (0.98–1.03)	0.78		
Maximal postoperative LVOT gradient	0.99 (0.98–1.01)	0.62		
Mean postoperative aortic prosthetic gradient	1.00 (0.99–1.01)	0.69		
Histopathologic diagnosis of HCM vs hypertensive heart disease	1.24 (0.82–2.41)	0.62		
Postoperative pacemaker implantation	1.12 (0.64–1.51)	0.73		

ACC/AHA indicates American Heart Association/American College of Cardiology; AVA, aortic valve area; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; ESC, European Society of Cardiology; HR, hazard ratio; LV, left ventricular; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure; and SCD, sudden cardiac death.

*When Society of Thoracic Surgeons (STS) score (a composite of established cardiovascular risk factors) was substituted for age and kidney disease, the findings on multivariate analysis were similar.

by AS (15% also had concomitant bicuspid AV). All patients underwent a combination of surgical myectomy and AVR (42% had additional operations including mitral valve repair/replacement, ascending aortic replacement, or coronary bypass grafting) with an observed in-hospital mortality of 1.5% (significantly lower than the expected mortality of 5%, based on STS score). Unlike a previous report, female sex was not associated with a higher longer-term event rate.[37] The pacemaker rate was high, as would be expected from this

older group of patients undergoing myectomy (which itself results in left bundle branch block in all cases) and AVR. Interestingly, on histopathologic analysis of the myectomy specimens in the current study, while 18% had a diagnosis of hypertensive heart disease, the majority (82%) had features that were characteristic of HCM,[24] with similar baseline characteristics and long-term outcomes. As demonstrated in the current study, longer-term survival is associated with standard cardiovascular risk factors such as increasing age, CKD, and higher RVSP, likely caused by dual obstructive physiology and not by pure HCM-related risk factors. Hence, it appears that despite having histopathologic features suggestive of HCM, the pathophysiologic impact of sequential LVOT obstruction (dynamic caused by HCM and fixed caused by AS) is potentially greater than what is seen in a patient with standard obstructive HCM. While purely speculative, it could be that in such patients, afterload mismatch, commonly seen in AS, in addition to excessive hypertrophy, might predispose this patient population to subendocardial ischemia with its downstream ramifications. The findings were similar even in the subgroup where concomitant coronary artery disease was excluded. An important observation is that the longer-term survival of patients was similar to a normal age-sex–matched US population. Hence, it is crucial to recognize concomitant significant AS in such patients, because the natural history of significant AS without AVR is dismal.[25]

In the context of blood ejecting from LVOT into the aorta, multiple pathophysiologic conditions that result in fixed or dynamic obstruction need to be recognized. While AS (valvular narrowing) and subaortic membrane (narrow LVOT) result in a fixed profile of obstruction, obstructive HCM (as a result of SAM of mitral valve and dynamic LVOT obstruction) can occur as a result of a complex interplay of basal septal hypertrophy, narrow LVOT, mitral valve/papillary muscle abnormalities, and a steeper LV inflow to outflow (aorto-LVOT) angle.[38,39] While it is not common to observe both AS and HCM simultaneously in the same patient, there are patients in whom these conditions coexist.[3,4] This presence of sequential LVOT obstruction poses particular diagnostic challenges requiring meticulous imaging (especially Doppler echocardiography [Figure 1]) to correctly identify the location (valvular or subvalvular) and type of LVOT obstruction (fixed or dynamic). In many cases, invasive hemodynamics may need to be considered for a complete elucidation of the dual problem.

Correct identification of this dual obstructive physiology is also crucial for accurate diagnosis, as it might have implications on family screening, follow-up recommendations, and therapeutic options. The current study demonstrates that an experienced setup in terms of expertise in clinical management, advanced imaging invasive hemodynamic assessment, and cardiac surgery is required. In symptomatic patients who require advanced therapies, it necessitates an altered and a more complex (in the majority of cases, an invasive) approach. A previous study has reported 2% mortality in 47 patients with severe AS (of 3523 patients) who underwent AVR and concomitant myectomy for the primary indication of severe AS.[5] This is unlike the current study where the primary cause was HCM. While there are small studies on disopyramide[40] and emerging data on novel therapeutic agents that can modulate dynamic LVOT obstruction,[41] there are currently no large-scale studies demonstrating that medical therapy is associated with a survival benefit in patients with obstructive HCM and, particularly, severe AS. AVR and surgical myectomy are considered class 1 indications and definitive therapies to relieve fixed and dynamic obstruction in symptomatic patients with severe AS and obstructive HCM, respectively, with excellent longer-term survival.[1,2,22,23] The current study demonstrates that in a carefully selected group of symptomatic patients with concomitant fixed and dynamic LVOT obstruction a combination of myectomy and AVR had excellent surgical results and longer-term survival similar to an age-sex–matched normal US population. However, any suggestion of performing such a complex combined operation has to be balanced against procedural risk and overall experience of the center (including imaging and surgical expertise) at managing these complex patients. The current study also highlights the importance of high volume and experience in invasive management of AS and HCM in patients with severe LVOT obstruction.[10,11,16,21] In recent years, the paradigm of invasive management of AS is rapidly shifting towards transcatheter AVR.[42–45] With increasing sophistication of percutaneous procedures, it is conceivable that many such patients (especially those with higher STS score *and* appropriate septal arterial perforator/LVOT anatomy) could be treated using a combination of alcohol septal ablation and transcatheter AVR. However, in such patients, a surgical approach has advantages over a percutaneous approach because of its ability to address multiple problems simultaneously, including dynamic LVOT obstruction (using myectomy or mitral/papillary muscle-based procedures), significant AS, and concomitant coronary artery disease. The results of the current study could serve as a benchmark for future comparison of myectomy+surgical AVR versus transcatheter AVR+alcohol septal ablation strategies. However, this requires further investigation.

Limitations

This was an observational study from a single tertiary center, which could have potential selection bias. The findings of this study should not be extrapolated to

patients with severe AS and a narrow LVOT caused by basal septal hypertrophy who need a concomitant myectomy to expand the LVOT. The results of all testing were available to all clinicians at the time of decision-making, introducing further bias. Multimodality imaging was not routinely performed and, hence, data were available in all patients. In addition, given the overall expertise involved with both imaging and invasive management of LVOT obstruction, our results might not be generalizable to other lesser experienced centers. We did not include patients needing emergent ASA during TAVR, as this was only performed as a bailout procedure attributable to unexpected development of intraprocedural SAM and LVOT obstruction. We report all-cause mortality, which is more objective than trying to ascertain a specific cause of death.[46] However, the findings were similar when patients with documented noncardiac causes of death were excluded. Finally, the current study only tested associations, not causality.

CONCLUSIONS

In a large HCM and valve practice, it is not uncommon to encounter patients who have symptoms from dual obstructive physiology (significant obstructive HCM and AS). It is crucial to identify the presence of sequential obstruction to the flow of blood from the left ventricle to the aorta by careful imaging and hemodynamic assessment. In patients presenting with a combination of severe symptomatic obstructive HCM and moderate or severe AS undergoing a combined surgical myectomy and AVR at our tertiary care center, the observed postoperative mortality was significantly lower than the expected mortality, and longer-term survival was similar to a normal age-sex–matched US population. These findings need additional validation.

ARTICLE INFORMATION

Received September 17, 2020; accepted December 10, 2020.

Affiliation

Hypertrophic Cardiomyopathy and Valve Center, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH.

Sources of Funding

None.

Disclosures

Dr Desai is supported by the Haslam Family Endowed Chair in Cardiovascular Medicine. The remaining authors have no disclosures to report.

REFERENCES

1. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:e783–e831. doi: 10.1161/CIR.0b013e318223e2bd
2. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733–2779. doi: 10.1093/eurheartj/ehu284
3. Vanichsarn C, Siegel RJ. Fool me once, fool me twice: hypertrophic cardiomyopathy with aortic stenosis. *Am J Med*. 2015;128:1076–1079. doi: 10.1016/j.amjmed.2015.05.003
4. Cui H, Schaff HV, Abel MD, Helder MRK, Frye RL, Ommen SR, Nishimura RA. Left ventricular ejection hemodynamics before and after relief of outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy and valvular aortic stenosis. *J Thorac Cardiovasc Surg*. 2020;159:844–852.e1. doi: 10.1016/j.jtcvs.2019.03.071
5. Kayalar N, Schaff HV, Daly RC, Dearani JA, Park SJ. Concomitant septal myectomy at the time of aortic valve replacement for severe aortic stenosis. *Ann Thorac Surg*. 2010;89:459–464. doi: 10.1016/j.athoracsur.2009.10.065
6. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;46:470–476. doi: 10.1016/j.jacc.2005.02.090
7. Smedira NG, Lytle BW, Lever HM, Rajeswaran J, Krishnaswamy G, Kaple RK, Dolney DO, Blackstone EH. Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. *Ann Thorac Surg*. 2008;85:127–133. doi: 10.1016/j.athoracsur.2007.07.063
8. Woo A, Williams WG, Choi R, Wigle ED, Rozenblyum E, Fedwick K, Siu S, Ralph-Edwards A, Rakowski H. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. *Circulation*. 2005;111:2033–2041. doi: 10.1161/01.CIR.0000162460.36735.71
9. Ball W, Ivanov J, Rakowski H, Wigle ED, Linghorne M, Ralph-Edwards A, Williams WG, Schwartz L, Guttman A, Woo A. Long-term survival in patients with resting obstructive hypertrophic cardiomyopathy comparison of conservative versus invasive treatment. *J Am Coll Cardiol*. 2011;58:2313–2321. doi: 10.1016/j.jacc.2011.08.040
10. Desai MY, Bhonsale A, Smedira NG, Naji P, Thamilarasan M, Lytle BW, Lever HM. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. *Circulation*. 2013;128:209–216. doi: 10.1161/CIRCULATIONAHA.112.000849
11. Hodges K, Rivas CG, Aguilera J, Borden R, Alashi A, Blackstone EH, Desai MY, Smedira NG. Surgical management of left ventricular outflow tract obstruction in a specialized hypertrophic obstructive cardiomyopathy center. *J Thorac Cardiovasc Surg*. 2019;157:2289–2299. doi: 10.1016/j.jtcvs.2018.11.148
12. Connolly HM, Oh JK, Orszulak TA, Osborn SL, Roger VL, Hodge DO, Bailey KR, Seward JB, Tajik AJ. Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction. Prognostic indicators. *Circulation*. 1997;95:2395–2400. doi: 10.1161/01.CIR.95.10.2395
13. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol*. 2000;35:747–756. doi: 10.1016/S0735-1097(99)00584-7
14. Brogan WC III, Grayburn PA, Lange RA, Hillis LD. Prognosis after valve replacement in patients with severe aortic stenosis and a low transvalvular pressure gradient. *J Am Coll Cardiol*. 1993;21:1657–1660. doi: 10.1016/0735-1097(93)90383-C
15. Pereira JJ, Lauer MS, Bashir M, Afridi I, Blackstone EH, Stewart WJ, McCarthy PM, Thomas JD, Asher CR. Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. *J Am Coll Cardiol*. 2002;39:1356–1363. doi: 10.1016/S0735-1097(02)01759-X
16. Mihaljevic T, Nowicki ER, Rajeswaran J, Blackstone EH, Lagazzi L, Thomas J, Lytle BW, Cosgrove DM. Survival after valve replacement for aortic stenosis: implications for decision making. *J Thorac Cardiovasc Surg*. 2008;135:1270–1278; discussion 1278–1279. doi: 10.1016/j.jtcvs.2007.12.042

17. Kang DH, Park SJ, Rim JH, Yun SC, Kim DH, Song JM, Choo SJ, Park SW, Song JK, Lee JW, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. *Circulation*. 2010;121:1502–1509. doi: 10.1161/CIRCULATIONAHA.109.909903
18. Ashikhmina EA, Schaff HV, Dearani JA, Sundt TM III, Suri RM, Park SJ, Burkhart HM, Li Z, Daly RC. Aortic valve replacement in the elderly: determinants of late outcome. *Circulation*. 2011;124:1070–1078. doi: 10.1161/CIRCULATIONAHA.110.987560
19. Malouf J, Le Tourneau T, Pellikka P, Sundt TM, Scott C, Schaff HV, Enriquez-Sarano M. Aortic valve stenosis in community medical practice: determinants of outcome and implications for aortic valve replacement. *J Thorac Cardiovasc Surg*. 2012;144:1421–1427. doi: 10.1016/j.jtcvs.2011.09.075
20. Malaisrie SC, McCarthy PM, McGee EC, Lee R, Rigolin VH, Davidson CJ, Beohar N, Lapin B, Subacius H, Bonow RO. Contemporary perioperative results of isolated aortic valve replacement for aortic stenosis. *Ann Thorac Surg*. 2010;89:751–756. doi: 10.1016/j.athoracsur.2009.11.024
21. Parikh R, Goodman AL, Barr T, Sabik JF, Svensson LG, Rodriguez LL, Lytle BW, Grimm RA, Griffin BP, Desai MY. Outcomes of surgical aortic valve replacement for severe aortic stenosis: incorporation of left ventricular systolic function and stroke volume index. *J Thorac Cardiovasc Surg*. 2015;149:1558–1566.e1. doi: 10.1016/j.jtcvs.2015.03.008
22. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg*. 2012;42:S1–S44. doi: 10.1093/ejcts/ezs455.
23. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2438–2488. doi: 10.1016/j.jacc.2014.02.537
24. Alashi A, Desai RM, Khullar T, Hodges K, Rodriguez ER, Tan C, Popovic ZB, Thamilarasan M, Wierup P, Lever HM, et al. Different histopathologic diagnoses in patients with clinically diagnosed hypertrophic cardiomyopathy after surgical myectomy. *Circulation*. 2019;140:344–346. doi: 10.1161/CIRCULATIONAHA.119.040129
25. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;70:252–289. doi: 10.1016/j.jacc.2017.03.011
26. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, Lancellotti P, LeFevre M, Miller F Jr, Otto CM. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30:372–392. doi: 10.1016/j.echo.2017.02.009
27. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, Graham KJ, Burton DA, Cecchi F. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation*. 2000;102:858–864. doi: 10.1161/01.CIR.102.8.858
28. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463. doi: 10.1016/j.echo.2005.10.005
29. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777–802. doi: 10.1016/S0894-7317(03)00335-3
30. Reeves ST, Finley AC, Skubas NJ, Swaminathan M, Whitley WS, Glas KE, Hahn RT, Shanewise JS, Adams MS, Shernan SK. Basic perioperative transesophageal echocardiography examination: a consensus statement of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. *J Am Soc Echocardiogr*. 2013;26:443–456. doi: 10.1016/j.echo.2013.02.015
31. Zoghbi WA, Chambers JB, Dumesnil JG, Foster E, Gottdiener JS, Grayburn PA, Khandheria BK, Levine RA, Marx GR, Miller FA Jr, et al. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2009;22:975–1014; quiz 1082–1084. doi: 10.1016/j.echo.2009.07.013.
32. Kwon DH, Smedira NG, Thamilarasan M, Lytle BW, Lever H, Desai MY. Characteristics and surgical outcomes of symptomatic patients with hypertrophic cardiomyopathy with abnormal papillary muscle morphology undergoing papillary muscle reorientation. *J Thorac Cardiovasc Surg*. 2010;140:317–324. doi: 10.1016/j.jtcvs.2009.10.045
33. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Circulation*. 2015;132:302–361. doi: 10.1161/CIR.0000000000000156
34. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509. doi: 10.1080/01621459.1999.10474144
35. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone Marrow Transplant*. 2007;40:381–387. doi: 10.1038/sj.bmt.1705727
36. Alashi A, Smedira NG, Hodges K, Popovic Z, Thamilarasan M, Wierup P, Lever H, Desai MY. Outcomes in guideline-based class I indication versus earlier referral for surgical myectomy in hypertrophic obstructive cardiomyopathy. *J Am Heart Assoc*. 2021;10:e016210. doi: 10.1161/JAHA.120.016210
37. Geske JB, Ong KC, Siontis KC, Hebl VB, Ackerman MJ, Hodge DO, Miller VM, Nishimura RA, Oh JK, Schaff HV, et al. Women with hypertrophic cardiomyopathy have worse survival. *Eur Heart J*. 2017;38:3434–3440. doi: 10.1093/eurheartj/ehx527
38. Patel P, Dhillon A, Popovic ZB, Smedira NG, Rizzo J, Thamilarasan M, Agler D, Lytle BW, Lever HM, Desai MY, et al. Left ventricular outflow tract obstruction in hypertrophic cardiomyopathy patients without severe septal hypertrophy: implications of mitral valve and papillary muscle abnormalities assessed using cardiac magnetic resonance and echocardiography. *Circ Cardiovasc Imaging*. 2015;8:e003132. doi: 10.1161/CIRCIMAGING.115.003132
39. Kwon DH, Smedira NG, Popovic ZB, Lytle BW, Setser RM, Thamilarasan M, Schoenhagen P, Flamm SD, Lever HM, Desai MY. Steep left ventricle to aortic root angle and hypertrophic obstructive cardiomyopathy: study of a novel association using three-dimensional multimodality imaging. *Heart*. 2009;95:1784–1791. doi: 10.1136/hrt.2009.166777
40. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, Casey S, Maron BJ. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;45:1251–1258. doi: 10.1016/j.jacc.2005.01.012
41. Heitner SB, Jacoby D, Lester SJ, Owens A, Wang A, Zhang D, Lambing J, Lee J, Semigran M, Sehnert AJ. Mavacamten treatment for obstructive hypertrophic cardiomyopathy: a clinical trial. *Ann Intern Med*. 2019;170:741–748. doi: 10.7326/M18-3016
42. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk

patients. *N Engl J Med*. 2019;380:1695–1705. doi: 10.1056/NEJMoa1814052
43. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–2484. doi: 10.1016/S0140-6736(15)60308-7
44. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620. doi: 10.1056/NEJMoa1514616
45. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–1607. doi: 10.1056/NEJMoa1008232
46. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol*. 1999;34:618–620. doi: 10.1016/S0735-1097(99)00250-8