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ORIGINAL INVESTIGATIONS

Hypertrophic Cardiomyopathy With Left Ventricular Apical Aneurysm

Implications for Risk Stratification and Management

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ABSTRACT

BACKGROUND A previously under-recognized subset of hypertrophic cardiomyopathy (HCM) patients with left ventricular (LV) apical aneurysms is being identified with increasing frequency. However, risks associated with this subgroup are unknown.

OBJECTIVES The authors aimed to clarify clinical course and prognosis of a large cohort of HCM patients with LV apical aneurysms over long-term follow-up.

METHODS The authors retrospectively analyzed 1,940 consecutive HCM patients at 2 centers, 93 of which (4.8%) were identified with LV apical aneurysms; mean age was 56 ± 13 years, and 69% were male.

RESULTS Over 4.4 ± 3.2 years, 3 of the 93 patients with LV apical aneurysms (3%) died suddenly or of heart failure, but 22 (24%) survived with contemporary treatment interventions: 18 experienced appropriate implantable cardioverter-defibrillator discharges, 2 underwent heart transplants, and 2 were resuscitated after cardiac arrest. The sudden death event rate was 4.7%/year. Notably, recurrent monomorphic ventricular tachycardia requiring ≥2 implantable cardioverter-defibrillator shocks occurred in 13 patients, including 6 who underwent successful radiofrequency ablation of the arrhythmic focus without ventricular tachycardia recurrence. Five non-anticoagulated patients experienced nonfatal thromboembolic events (1.1%/year), whereas 13 with apical clots and anticoagulation did not incur embolic events. There was no consistent relationship between aneurysm size and adverse HCM-related events. Rate of HCM-related deaths combined with life-saving aborted disease-related events was 6.4%/year, 3-fold greater than the 2.0%/year event rate in 1,847 HCM patients without aneurysms ($p < 0.001$).

CONCLUSIONS HCM patients with LV apical aneurysms are at high risk for arrhythmic sudden death and thromboembolic events. Identification of this phenotype expands risk stratification and can lead to effective treatment interventions for potentially life-threatening complications. (J Am Coll Cardiol 2017;69:761–73)

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

High spatial resolution imaging with cardiovascular magnetic resonance (CMR) has increasingly become part of routine hypertrophic cardiomyopathy (HCM) practice (1–3). CMR has allowed more frequent identification of a subset of patients with thin-walled, left ventricular (LV) apical aneurysms, often associated with regional scarring and muscular mid-cavity obstruction (4).

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance imaging

EF = ejection fraction

ESC = European Society of Cardiology

HCM = hypertrophic cardiomyopathy

HF = heart failure

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

SAM = systolic anterior motion (of the mitral valve)

SD = sudden death

VF = ventricular fibrillation

VT = ventricular tachycardia

Initial reports suggested that this subset experienced increased risk of cardiovascular morbidity and mortality including sudden death (SD), thromboembolic events, and progressive heart failure (HF) symptoms (4-18). However, these descriptions involved small numbers of patients with relatively short follow-up, and management implications for this subgroup of patients remains unclear (1,3). Therefore, we believe it is timely to offer a measure of clarity to understanding the clinical profile, prognosis, and treatment strategies for HCM patients with LV apical aneurysms, by assessing a large cohort of these patients over an extended period of time.

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METHODS

PATIENT SELECTION. We retrospectively analyzed 1,940 HCM patients consecutively enrolled from 1983 to 2014 at 2 HCM centers: Minneapolis Heart Institute Foundation (n = 1,219) and Tufts Medical Center (n = 721). Left ventricular apical aneurysm was identified in 93 patients (4.8%). Initial evaluation was defined as the first clinical assessment during which an echocardiogram diagnostic of HCM was obtained. Most recent clinical assessments were obtained by telephone interview or outpatient clinic visit (n = 84), or by accessing the Social Security Death Index (n = 9) up until January 1, 2015. Follow-up duration from study entry to most recent contact or death was 4.4 ± 3.2 years (range 4 months to 14 years). Outcomes in 1,847 HCM patients from the cohort without apical aneurysm were compared with 93 HCM patients with apical aneurysm.

Decisions to implant a primary prevention implantable cardioverter-defibrillator (ICD) in 54 patients was based on assessment of current conventional SD risk markers (3). On a case-by-case basis, the apical aneurysm was judged to confer higher SD risk status, either as an arbitrator to resolve uncertain ICD decisions or alone for primary prevention after implementing a shared decision-making strategy in accord with the desires of the fully informed patient (3,4).

This study was reviewed and approved by institutional review boards of the participating institutions, Allina Health Systems and Tufts Medical Center.

DEFINITIONS. Diagnosis of HCM was based on echocardiographic and/or CMR documentation of a hypertrophied, nondilated LV with wall thickness ≥13 mm, in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy during the patient's clinical course. Apical aneurysm was defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the LV chamber. Obstructive atherosclerotic coronary artery disease was excluded as a cause of LV aneurysm formation in each of the 93 study patients by: 1) absence of significant (≥50%) coronary arterial narrowing of the left anterior descending artery by conventional arteriography or computed tomography angiogram (n = 61); or 2) absent history of chest pain, coronary risk factors, and acute coronary syndrome (n = 32).

HCM-related HF or SD was defined as previously reported (19). Global LV systolic dysfunction (by convention, end-stage HCM) was defined by ejection fraction (EF) <50% at rest (3). Nonfatal adverse disease-related events were heart transplant or listing for heart transplant, appropriate ICD interventions for ventricular tachycardia (VT)/ventricular fibrillation (VF), resuscitated cardiac arrest, or thromboembolic stroke. Arrhythmic events were defined as either SD, successful resuscitation from cardiac arrest, or appropriate ICD interventions triggered by ventricular fibrillation or rapid ventricular tachycardia (rate ≥180 beats/min). The combined endpoint was an aggregate of HCM-related death and nonfatal adverse disease-related events. European Society of Cardiology (ESC) SD risk score was calculated using the clinical variables at the time of study entry for each patient with LV apical aneurysm (20).

IMAGING. Transthoracic echocardiographic studies were performed in a standard fashion. LV wall thickness was the maximum end-diastolic dimension within the chamber. Peak instantaneous LV outflow gradient was estimated by continuous-wave Doppler, and outflow obstruction was defined as a gradient ≥30 mm Hg at rest or with physiological exercise (1). In 16 of the 18 patients with advanced HF symptoms mitral inflow velocity and annular tissue Doppler indices signals were obtained as previously described. Peak pulsed Doppler velocities were assessed to determine early (E) and late (A) diastolic flow across the mitral valve. Tissue Doppler index of the mitral annulus was obtained from the apical 4-chamber view, and peak early tissue Doppler velocities of the septal mitral annulus (e′) were analyzed. Diastolic dysfunction was classified according to previous consensus recommendations (21).

CMR studies were obtained in 57 patients with a 1.5-T clinical scanner (Phillips Gyroscan ACS-NT, Best, the Netherlands and Sonata or Avanto, Siemens

Medical, Erlangen, Germany). Cine sequences were performed in standard views with full LV coverage. Late gadolinium enhancement (LGE) images were acquired 10 to 15 min after intravenous administration of 0.2 mmol/kg gadolinium-DTPA using breath-held segmented inversion-recovery sequence. LGE quantification was performed by manually adjusting grayscale threshold to visually define LGE, expressed as a proportion of total LV myocardium. Aneurysm size was characterized as the maximum transverse dimension measured by CMR (n = 57) or echocardiography (n = 36) in the 4-chamber long-axis view, and characterized as small (<2 cm); medium (2 to 4 cm); or large (>4 cm).

STATISTICAL ANALYSES. Data are displayed as mean ± standard deviation for continuous variables, and as proportions for categorical variables. The Student *t* test assessed the statistical significance of continuous variables, and chi-square or Fisher exact test analyzed categorical variables. Values are $p < 0.05$ were considered significant and were presented 2-sided where appropriate.

For patients with known survival and event status, the fraction at each follow-up interval was estimated by the Kaplan-Meier method. Differences in survival between groups were assessed using the log-rank test. Survival analysis calculations of nonfatal adverse HCM-related events excluded patients with either resuscitated cardiac arrest or appropriate ICD intervention occurring before initial clinical evaluation at the participating institutions. No adjustments were made to account for clustered observations within families. All statistical calculations and plots were done with Stata version 11.2 (College Station, Texas).

RESULTS

PREVALENCE OF LV APICAL ANEURYSM. LV apical aneurysm was identified in 93 of 1,940 HCM patients (4.8%; 95% confidence interval: 3.8% to 5.7%) (**Table 1**), including in 1 pair of siblings and 1 pair of twins. Selected clinical data from 28 of these patients were part of a previous analysis (4). The proportion of patients with LV apical aneurysms was similar between the 2 centers, Minneapolis Heart Institute (n = 52; 4.3%) and Tufts Medical Center (n = 41; 5.7%; p = 0.19 for difference). LV apical aneurysms could be identified by echocardiography in 50 of the 93 patients (54%), including 32 patients with medium or large aneurysms and 18 patients with smaller aneurysms. Of these 50 patients, identification of the apical aneurysm was enhanced by contrast in 21 (42%), including 11 identified solely by contrast enhancement. LV apical aneurysms were identified by CMR only (n = 39) or computed tomography (n = 4) in 43 (46%) patients, including 3 in whom contrast echocardiography failed to identify a small aneurysm (**Central Illustration**).

LV DIAMETER. Aneurysm size ranged from 1.1 to 5.6 cm (median 1.8 cm; mean 2.1 ± 5.6 cm) (**Figure 1**). Two distinct patterns of LV hypertrophy were identified: 1) segmental wall thickening confined to the distal LV in 47 patients (51%); and 2) diffuse thickening of the septum and free wall, resulting in a "hourglass" configuration with mid-ventricular muscular narrowing creating discrete proximal and distal chambers in 46 patients (49%), 34 of whom had intraventricular mid-cavity pressure gradients of 44 ± 26 mm Hg (range 20 to 150 mm Hg). In 4 other patients without mid-cavity muscular narrowing, LV outflow tract obstruction was due to typical mitral valve systolic anterior motion (SAM) with septal contact (78 ± 15 mm Hg, range 65 to 100 mm Hg) (1). In 57 patients with CMR imaging, the aneurysm rim measured 1.6 ± 0.3 mm (range 1.0 to 2.4 mm).

LATE GADOLINIUM ENHANCEMENT. Each of the 57 study patients imaged by contrast-enhanced CMR had transmural LGE in the aneurysm rim. In addition, high signal intensity LGE was evident in areas of the septum and LV wall contiguous with the aneurysm rim in 30 patients (53%) (**Figure 1 and Central Illustration**). In the 57 patients, LGE occupied 7 ± 7% of LV mass (range 1 to 29), including 7 with extensive/diffuse LGE (≥15% of LV mass).

SERIAL OBSERVATIONS OF ANEURYSM SIZE. There was no consistent relation between aneurysm size and outcome endpoints. Paired imaging studies were available in 25 patients and showed no significant change in aneurysm size for the group over a follow-up of 4.2 ± 3.0 years; maximum transverse dimension width was 2.4 ± 1.0 mm at study entry and 2.6 ± 1.1 mm at follow-up (p = 0.90). While aneurysm size appeared to change little in 24 patients, in 1 patient a significant increase in dimension (2.2 to 4.2 cm, 1.9-fold) was observed over 8 years (**Figure 2**). Over the follow-up period, each aneurysm has remained intact without rupture.

CLINICAL PROFILE. At study entry, the 93 aneurysm patients were 56 ± 13 years of age (range 18 to 86 years of age) (**Table 1**). Maximum LV wall thickness was 19 ± 5 mm (range 13 to 35 mm), and 69% were male. Most patients were asymptomatic or mildly symptomatic (New York Heart Association functional class I/II; n = 87). EF was 60 ± 10%, and in 10 patients

TABLE 1 Demographics, Clinical Features, and Outcomes in 93 HCM Patients With LV Apical Aneurysms

Patients	93 (5)
Age, yrs	56 ± 13
Male	64 (69)
NYHA functional class (study entry)	
I	61 (66)
II	26 (28)
III	6 (6)
IV	0 (0)
Max LV thickness, mm	19 ± 5
LV wall thickness ≥30 mm	6 (6)
LVOT gradient at rest ≥30 mm Hg	4 (4)
Mid-cavity muscular obstruction	34 (37)
LA dimension, mm	43 ± 8
Mitral regurgitation, moderate or severe	14 (15)
LVED, mm	48 ± 6
LVEF, %	60 ± 10
LV apical aneurysm identified on echo	50 (54)
CMR performed	57 (61)
LGE present	57 (100)
% LGE of LV	7 ± 7
% LGE ≥15% LV myocardium	7/57 (12)
LV morphology	
Hourglass shape	46 (49)
Distal hypertrophy	47 (51)
LV aneurysm size	
Small (<2 cm)	53 (57)
Medium (2–4 cm)	30 (32)
Large (>4 cm)	10 (11)
Syncope	18 (19)
NSVT (ambulatory 24–48-h Holter)	33 (35)
Family history of HCM-related SD	11 (12)
No. of conventional risk factors	0.8 ± 0.7
≥1 Risk factor	56 (60)
End-stage HCM; EF <50%	10 (11)
Septal myectomy	2 (2)
Alcohol septal ablation	0
ICD	56 (60)
Radiofrequency VT ablation	7 (8)
Family history of HCM	24 (26)
Sarcomere genes identified	9/29 (31)
Myosin binding protein-C	2 (7)
Beta-myosin heavy chain	4 (14)
Troponin T	1 (3)
Troponin I	1 (3)
Alpha-tropomyosin	1 (3)
Medications	
Beta-blocker	80 (86)
Calcium-channel blocker	36 (39)
Disopyramide	2 (2)
Amiodarone	18 (19)
Sotalol	7 (8)
ACE/ARB	34 (37)
Diuretic	29 (31)
Coumadin	39 (42)
Aspirin	61 (66)
Novel anticoagulation	7 (8)
Duration of follow up, yrs	4.4 ± 3.2
HCM events	
Progression to NYHA functional class III/IV	12 (13)
Received or listed for heart transplantation	3 (3)
Resuscitated cardiac arrest	2 (2)
Appropriate ICD interventions	18* (19)
Apical thrombus identified	13 (14)
Nonfatal thromboembolic event	5 (5)
Mortality	13 (14)
Non-HCM-related	10 (11)
HCM-related	
Sudden death	1 (1)
Heart failure	2 (2)
Thromboembolic	0

Values are n (%) or mean ± SD. *Includes 13 patients with ≥2 appropriate ICD interventions and 4 patients with ≥4 appropriate ICD interventions.

ACE/ARB = angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CMR = cardiovascular magnetic resonance; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricular; LVED = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; Max = maximum; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; SD = sudden death; VT = ventricular tachycardia.

was <50%. Of these 10 patients, EF was decreased in 5 predominantly due to the presence of a medium or large sized akinetic/dyskinetic aneurysm; in the other 5 patients systolic dysfunction extended beyond the aneurysm, involving the entire LV chamber.

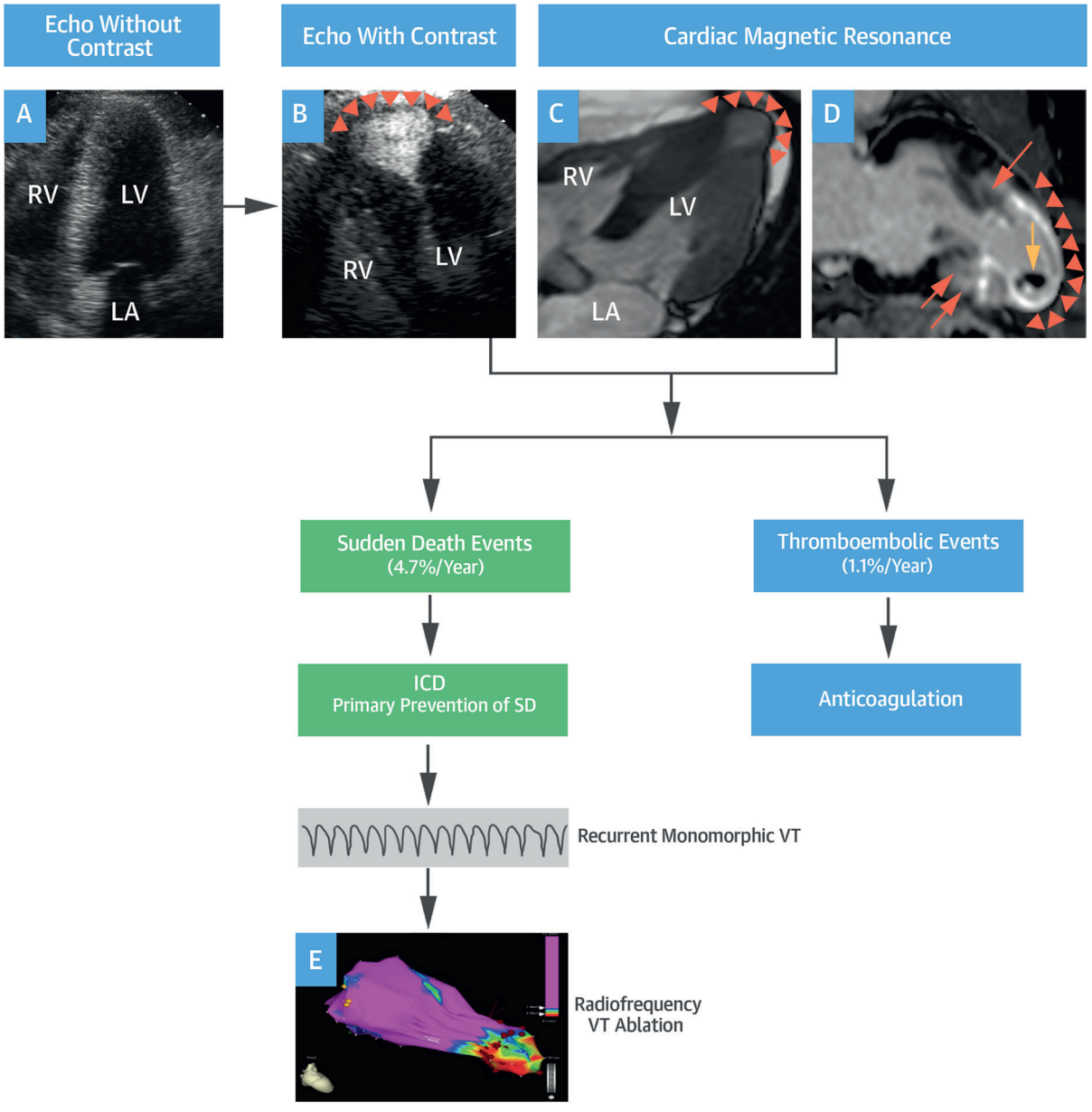
Of 54 patients who underwent ICD placement for primary prevention, the apical aneurysm was specifically considered in this decision in 33, including 19 in whom the aneurysm alone was judged to be high-risk, and 14 in whom the aneurysm acted as an arbitrator of risk in patients with 1 established or ambiguous risk factor. ICD was placed for secondary prevention in 2 additional patients after successful resuscitation from out-of-hospital cardiac arrest. Of the 93 aneurysm patients, 28 (30%) had a family history of HCM and/or a disease-causing sarcomere mutation (Table 1).

MORTALITY. Over the follow up period, 80 of the 93 study patients (86%) survived and 13 (14%) died (Figure 3); all-cause mortality rate was 3.4%/year.

HCM-RELATED MORTALITY. In 3 patients (3.2%; 0.8%/year) (Table 2), death was attributable to HCM at 42 ± 2 years of age (range 39 to 44 years). One patient died suddenly with a small apical aneurysm but without conventional high-risk markers. Two other nonobstructive patients died of advanced HF in the end-stage (EF <50%).

NON-HCM MORTALITY. Ten patients died of causes unrelated to HCM at 70 ± 17 years (range 37 to 89 years): 4 due to cancer, 3 from advanced pulmonary disease, 2 of liver failure, and 1 at aortic valve

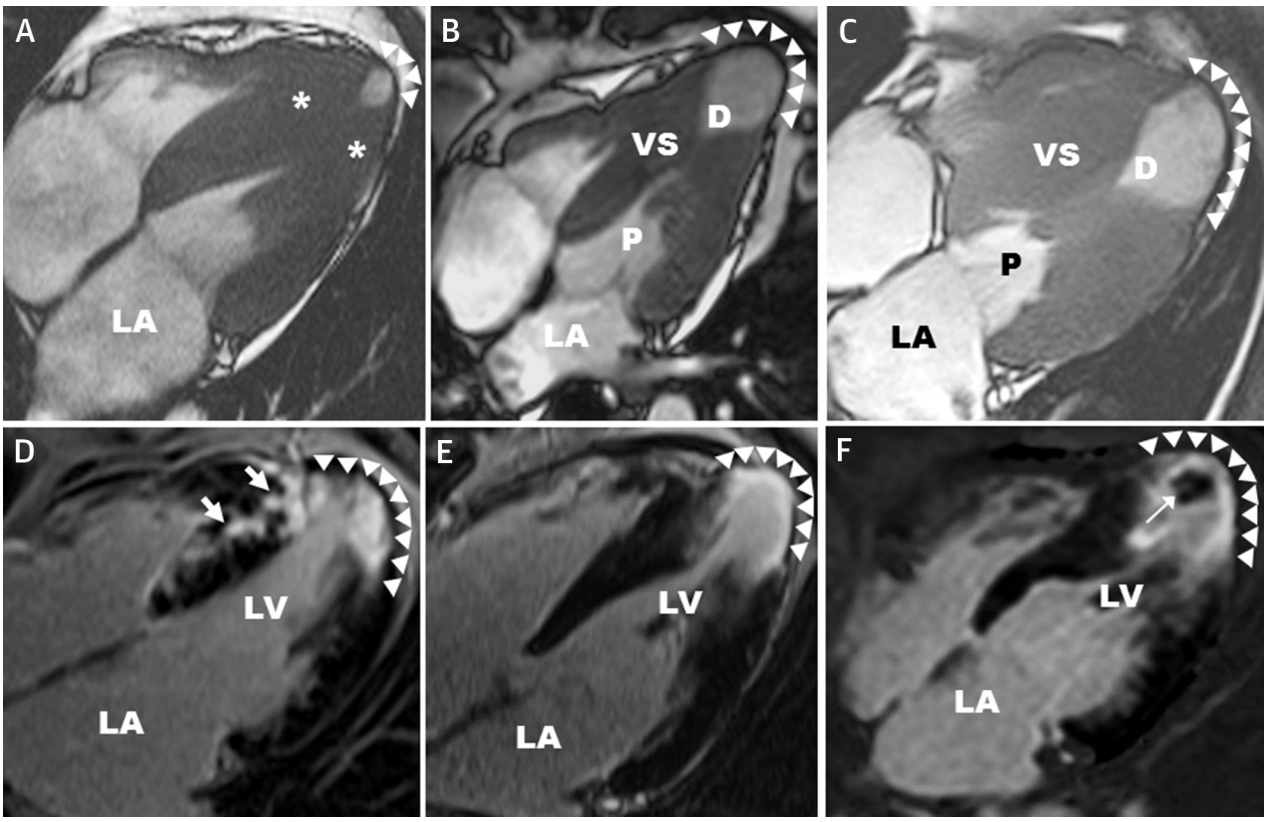
CENTRAL ILLUSTRATION **Diagnosis, Expanded Risk Stratification, and Management Implications in HCM Patients With High-Risk LV Apical Aneurysms**



Rowin, E.J. et al. J Am Coll Cardiol. 2017;69(7):761–73.

(A to D) *Aneurysms more reliably identified by cardiac magnetic resonance imaging (CMR) and contrast with echocardiography.* Echocardiogram **(A)** in 4-chamber view shows normal apical contour without evidence of apical aneurysm, whereas echocardiography with contrast **(B)** and CMR **(C)** in the same patient demonstrates medium-sized, thin-wall apical aneurysm **(arrowheads)** with associated hour-glass–shaped LV chamber **(D)**. *Aneurysms can raise risk of SD.* **(D)** In another patient, contrast-enhanced CMR image shows transmural LGE of aneurysm rim **(arrowheads)** with contiguous extension into the inferior **(short arrows)** and anterior LV walls **(long arrow)**, a potential nidus of monomorphic VT. *Aneurysms are sources of thromboemboli.* Marked signal intensity contrast between the bright aneurysm rim and hypointense mass **(yellow arrow)** confirms presence of a thrombus in the apical aneurysm. Below are management implications and effect of treatment interventions, including *prevention of SD* with ICDs, *radiofrequency ablation* of arrhythmic focus for refractory monomorphic VT **(E)**. and *stroke prophylaxis* with anticoagulation. **(E)** Electroanatomic endocardial voltage map in the right anterior oblique view of an apical aneurysm patient with recurrent VT. The **red dots** represent the ablation lesions delivered around the rim of the scarred aneurysm. ICD = implantable cardioverter defibrillator; LA = left atrium; LV = left ventricle; RV = right ventricle; SD = sudden death; VT = ventricular tachycardia.

FIGURE 1 CMR Images in 6 HCM Patients With Thin-Walled LV Apical Aneurysms



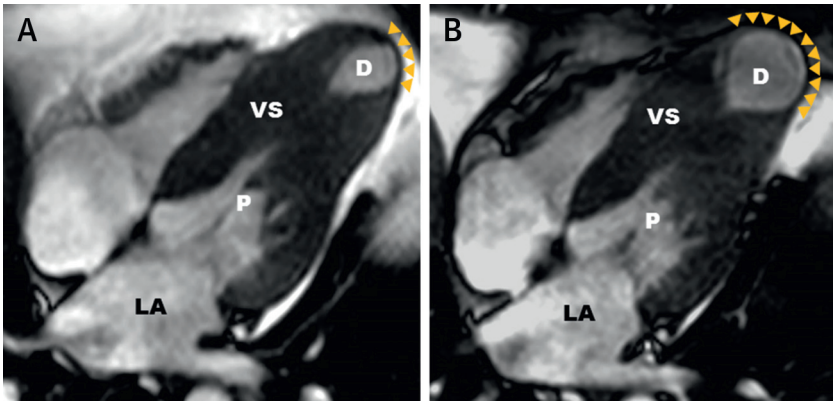
(A to C) CMR images in mid-systole demonstrating various sizes of aneurysms. **(A)** Small apical aneurysm (1.6-cm transverse dimension; **arrowheads**), identified only by CMR, in a 42-year-old man with hypertrophy localized to distal LV **(asterisks)**. **(B)** A 62-year-old asymptomatic woman with medium-size apical aneurysm (3.2 cm; **arrowheads**), with mid-ventricular muscular apposition of the septum and LV free wall producing distinct proximal (P) and distal (D) chambers and an intracavitary gradient of 50 mm Hg. **(C)** Large apical aneurysm (4.9 cm; **arrowheads**) in a 49-year-old man with similar hourglass-shaped LV chamber as in **B**. A primary prevention ICD was placed on the basis of the presence of the scarred apical aneurysm, in the absence of other conventional risk factors, with appropriate shock for rapid monomorphic ventricular tachycardia 1 year after device placement. **(D to F)** Contrast-enhanced CMR images in end-diastole demonstrating LV scar contiguous with the aneurysm. **(D)** A 41-year-old man with medium-sized apical aneurysms and transmural LGE of the aneurysm rim **(arrowheads)**, with extension into the contiguous ventricular septum **(arrows)**, as well as extensive LGE in other regions of LV (occupying 27% of the LV mass). **(E)** A 44-year-old man with LGE localized to the aneurysm rim **(arrowheads)**. Patient experienced an appropriate ICD intervention for VT 4 years after primary prevention implant. **(F)** Transmural LGE in medium-sized apical aneurysm **(arrowheads)** of a 56-year-old man with a intracavitary thrombus within the aneurysm **(arrow)**. CMR = cardiac magnetic resonance; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricle/ventricular; VS = ventricular septum.

replacement. Of these 10 patients, 3 had an adverse non-fatal HCM related event 2 to 13 years before death, including thromboembolic stroke in 2 and appropriate ICD intervention in one.

NONFATAL ADVERSE HCM-RELATED EVENTS. Over the follow-up period, 26 of the 80 surviving patients (33%) had nonfatal, adverse disease-related events (Figure 3), whereas the remaining 54 (67%) were free of adverse events after 4.5 ± 3 years (up to 12 years).

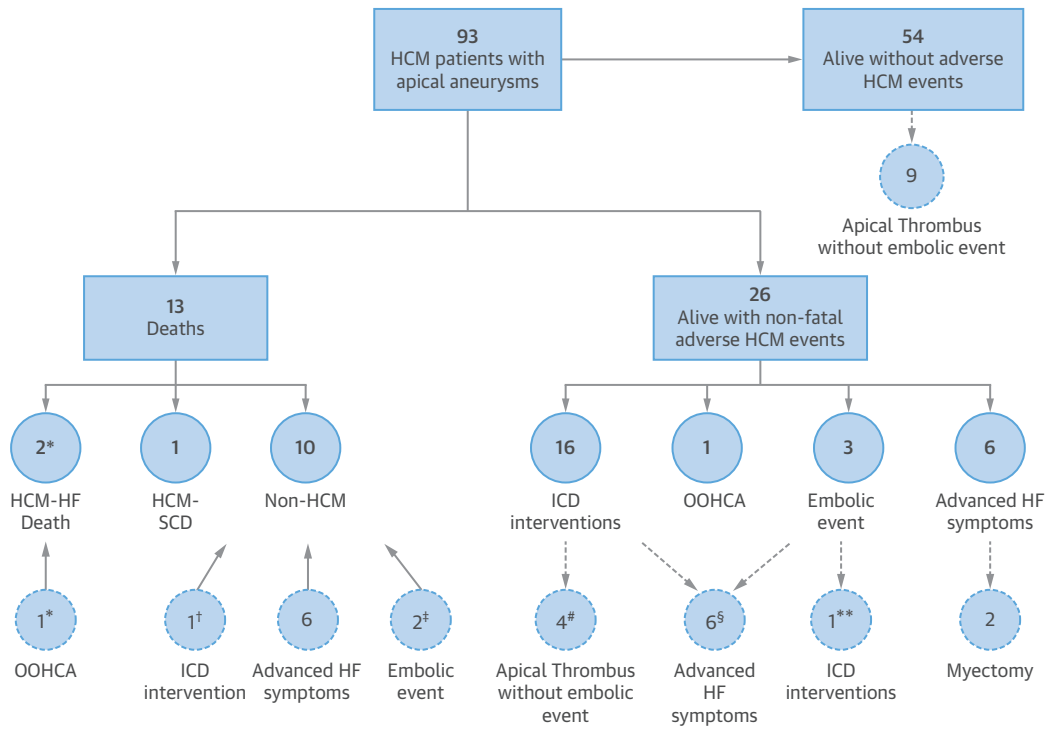
APPROPRIATE ICD INTERVENTIONS AND RESUSCITATED CARDIAC ARRESTS. Of the 54 patients with primary prevention ICDs, 18 experienced an aborted SD event with ≥1 appropriate ICD interventions for monomorphic VT (n = 16) or VF (n = 2) (4.0%/year) (Table 2), including 9 of 33 (27%) who were implanted solely or largely for a perceived increase in SD risk related specifically to the apical aneurysm. Initial ICD discharge occurred at 52 ± 13 years (range 29 to 71 years), and interval from implant to first appropriate ICD intervention was 3.5 ± 3.3 years. Two other patients were successfully resuscitated from out-of-hospital cardiac arrest. Eighteen of these 20 patients have survived 4.7 ± 3.5 years after the initial appropriate ICD intervention/cardiac arrest, currently mean age 56 ± 13 years (range 42 to 72 years). The majority of

FIGURE 2 Expansion of an LV Apical Aneurysm in a 57-Year-Old Man



(A) Initial CMR image demonstrated a medium sized apical aneurysm **(arrowheads)** with maximum transdimensional width of 2.2 cm, with mid-ventricular muscular apposition of the septum and LV free wall producing distinct proximal (P) and distal (D) chambers. **(B)** CMR image in identical imaging plane performed 8 year later demonstrated expansion of apical aneurysm **(arrowheads)** 1.9-fold to a maximum transdimensional width of 4.2 cm. Although aneurysm size increased in this individual patient, overall there was no significant increase in aneurysm size in the remaining 24 patients over 4.2 ± 3 years of follow-up. Abbreviations as in Figure 1.

FIGURE 3 Flow Diagram Showing Clinical Outcome and Events in 93 Patients With LV Apical Aneurysm



*OOHCA 3 years before heart failure-related death; †ICD intervention 13 years before noncardiac death. ‡Two patients with thromboembolic events 2 and 7 years before non-HCM death. #Includes 4 patients with apical thrombus identified after appropriate ICD therapy. §Includes 1 patient with heart transplant 3 years after appropriate ICD intervention, 1 transplanted 9 months after ICD shock; 1 currently on transplant list. **Includes 1 patient with ICD intervention 9 years following stroke. HF = heart failure; NYHA-FC = New York Heart Association functional class; OOHCA= resuscitated out-of-hospital cardiac arrest; SCD = sudden cardiac death; other abbreviations as in Figure 1.

TABLE 2 HCM Patients With LV Apical Aneurysms and HCM-Related Death or Life-Threatening Events/Interventions

Patient #	Sex	Age, yrs: Initial Eval, Yrs	Age, yrs: Death/Event, Yrs	NYHA Functional Class: Initial	NYHA Functional Class: Last	Max. LV Thickness, mm	Aneurysm Size	EF, %	Peak Intracavity Gradient	% LGE on CMR	Comment
HCM-related deaths											
Sudden cardiac death											
1	F	38	39	1	1	17	Small	60	0	6.4	LV aneurysm only risk marker
Advanced heart failure death without transplant											
1	M	43	44	3	–	25	Medium	30	36	–	Post-op death (aneurysm resection)
Advanced heart failure death with prior resuscitated cardiac arrest											
1*	M	39	42	3	–	22	Small	35	0	–	Died HF awaiting transplant; resuscitated cardiac arrest 3 yrs prior
Noncardiac death with prior nonfatal HCM events											
Non-HCM death with prior appropriate ICD interventions											
1	M	46	61	1	3	18	Large	50	50	–	Appropriate ICD interventions for VT (ages 47, 49, 56, 57 yrs [electrical VT storm]); death due to cancer at age 61 yrs
Non-HCM death with prior thromboembolic event											
1	F	51	52	1	1	23	Medium	50	0	–	Thromboembolic renal infarct (age 44 yrs); death due to cancer at age 52 yrs
2	F	76	81	2	2	25	Large	50	50	7.4	Embolic stroke (age 78 yrs), death due to COPD at age 81 yrs

Continued on the next page

patients with SD events (15 of 21; 71%) had medium or large aneurysms.

Notably, 13 of the 18 patients (70%) had ≥2 appropriate interventions including 4 patients with ≥4 interventions (range to 10). Eight patients with ICDs experienced electrical VT storms, with ≥3 sustained episodes of VT over 24 h.

Seven patients with recurrent symptomatic monomorphic VT (including 5 with a VT storm) underwent mapping and radiofrequency ablation to obliterate a ventricular arrhythmia focus in the area of scar contiguous with the rim of the aneurysm (**Central Illustration**). Two patients had 1 ablation and 5 required multiple procedures (up to 4) to successfully ablate the arrhythmia focus. After the most recent radiofrequency ablation, 6 of the 7 patients had no further recurrence of VT over 1.9 ± 1.1 years (range to 6 years).

THROMBOEMBOLIC EVENTS. Nonfatal embolic events occurred in 5 patients (5.0%; 1.1%/year), including cerebral (n = 3), myocardial (n = 1), and renal infarction (n = 1). At the time of these events, patients were in sinus rhythm and did not receive anticoagulation. Each patient was without another identifiable thromboembolic source, and the event was judged secondary to clot formation in the dyskinetic/akinetic apex. In 13 other patients without a thromboembolic event, a thrombus was identified in the apical aneurysm by CMR or cardiac computed tomography only (n = 6), contrast echocardiography (n = 4), or both echocardiography and CMR (n = 3) (**Central Illustration**). Apical thrombi or embolic events occurred most commonly in medium and large aneurysms (14 of 18; 78%), but notably in 4 patients with small (<2 cm) aneurysms (**Table 3**). All 18 patients with apical thrombus or an embolic event were subsequently treated with anticoagulants, predominantly warfarin (n = 14), and none have experienced a thromboembolic event over 4.0 ± 2.8 years. Anticoagulation therapy for primary prevention of thromboembolism was offered to the remaining 75 apical aneurysm patients, of whom 25 elected to initiate anticoagulants, including warfarin (n = 21), each without a thromboembolic event.

HEART FAILURE. Advanced HF symptoms were present in 18 aneurysm patients (19%), including 6 in class III/IV at study entry and 12 who progressed to severe symptoms. These symptoms were associated with systolic dysfunction in 8, and preserved EF in 10. No consistent relation was evident between aneurysm size and advanced HF, although 8 patients had large or medium-sized aneurysms that could potentially contribute to symptoms. There was no consistent relationship between diastolic filling patterns and development of advanced HF (grade I in 7; grade II in 5; grade III in 4) (Online Table 1). In addition, these patients showed a wide range in E/E′ (range 7 to 26), including 10 with E/e′ ≤15, most consistent with indeterminate or normal LV filling pressures (Online Table 1).

In the 18 patients with advanced HF symptoms, 2 patients received a heart transplant and have

TABLE 2 Continued

Patient #	Sex	Age, yrs: Initial Eval, Yrs	Age, yrs: Death/Event, Yrs	NYHA Functional Class: Initial	NYHA Functional Class: Last	Max. LV Thickness, mm	Aneurysm Size	EF, %	Peak Intracavity Gradient	% LGE on CMR	Comment
Non-fatal HCM-related major events											
Resuscitated cardiac arrest											
1*	F	60	67	2	2	16	Small	65	0	–	Resuscitated cardiac arrest (age 55 yrs) without subsequent events
Appropriate ICD interventions											
1	F	26	29	2	2	17	Large	60	48	6.4	ICD placement due only to aneurysm
2	M	36	45	1	1	18	Large	65	45	–	ICD placement predominantly due to aneurysm; ICD interventions at age 37 yrs (×2), 38 yrs (electrical storm), 39 yrs (×2). Endocardial RF ablation at ages 38 and 39 yrs; epicardial RF ablation at age 39 yrs.
3*	M	37	42	2	2	35	Medium	50	0	–	Electrical VT storm at age 37 yrs
4	M	39	40	1	1	19	Large	55	21	12	ICD placement due only to aneurysm. Electrical VT storm (age 40 yrs) with subsequent endocardial RF ablation.
5	M	44	50	1	1	21	Medium	55	30	3.3	ICD placement due predominantly to aneurysm. ICD intervention ×2 (age 48 yrs)
6	M	45	52	1	1	17	Medium	60	40	–	ICD placement due only to aneurysm; Appropriate ICD interventions at ages 45 yrs (electrical VT storm), 50 and 51 yrs (electrical VT storm). Endocardial RF VT ablation at age 45 and 51 yrs.
7	M	48	55	2	1	16	Small	65	50	2.7	ICD placement due only to aneurysm
8	M	53	64	1	1	30	Medium	55	50	5.5	
9	M	56	66	1	1	19	Small	60	0	4.4	ICD placement due only to aneurysm
10	M	61	64	1	1	16	Small	55	0	–	ICD placement due only to aneurysm; Appropriate ICD shock at ages 62 and 63 yrs (×2; including electrical VT storm). Epicardial and endocardial RF VT ablation at age 63 yrs.
11	M	63	68	1	1	17	Medium	75	0	22.2	ICD placement due only to aneurysm; ICD interventions at age 68 ×3 yrs
12*	M	65	73	2	2	17	Medium	60	21	–	ICD intervention at age 64 yrs; subsequently at ages 66 (×3), 67, 72 (×5) yrs. Endocardial RF VT ablation ×2 at age 72 yrs.
13*	M	67	72	1	1	18	Medium	55	75	–	ICD intervention at age 66 yrs, subsequently at ages 67, 69 yrs. Endocardial RF VT ablation at ages 67 and 69 yrs.
Appropriate ICD interventions and heart transplant											
1*	M	55	58	1	1	13	Medium	40	0	–	ICD intervention age 54 yrs, subsequently at age 57 yrs; advanced symptoms at age 56 yrs with transplant at age 58 yrs
2	M	62	64	3	1	20	Medium	45	0	–	Appropriate ICD intervention at age 63 yrs; transplant at age 64 yrs
Appropriate ICD intervention and active on heart transplant list											
1	F	37	43	2	3	26	Medium	53	0	–	ICD intervention (age 37 yrs), subsequently at ages 38 yrs (VT storm), 39, 42 (VT storm) yrs. Endocardial/epicardial RF ablations, but with recurrent VT.
Appropriate ICD interventions and thromboembolic event											
1	M	47	48	1	1	32	Medium	70	0	17	VT storm (age 48 yrs), 15 appropriate ICD shocks/24 h. Embolic stroke (age 47 yrs).
Thromboembolic event											
1	M	29	36	1	1	16	Small	55	0	1.0	Right coronary artery thrombus (age 36 yrs)
2	F	59	66	3	2	14	Large	50	40	–	Embolic stroke (age 66 yrs)

*Appropriate ICD intervention or out-of-hospital cardiac arrest prior to first visit; a dash indicates that CMR was not performed.
EF = ejection fraction; HF = heart failure; RF = radiofrequency; other abbreviations as in Table 1.

survived without cardiovascular symptoms over 3.5 and 5.4 years. Eight other patients died, either in the setting of disabling HF (n = 1), post-operatively after aneurysm resection (n = 1), or due to non-HCM-related causes (n = 6), and 6 have survived without transplant, including 5 who declined or did not qualify, and 1 currently listed. The remaining 2 patients (both with small aneurysms) had severe

TABLE 3 Relationship of LV Apical Aneurysm Size to HCM-Related Events

Clinical Course	n	Aneurysm Size: Small (n = 53)	Medium (n = 30)	Large (n = 10)	p Value
Sudden death events	21	6 (29)	10 (47)	5 (24)	0.10
Advanced heart failure symptoms NYHA functional class III/IV	18	10 (56)	4 (22)	4 (22)	0.06
Thromboembolic event/apical clot	18	4 (22)	11 (61)	3 (17)	0.02*†

Values are n (%) except as noted. *Significant difference between small and medium aneurysms. †Significant difference between medium and large aneurysms.

Abbreviations as in Table 1.

limiting HF symptoms in New York Heart Association functional class III due to LV outflow obstruction from marked SAM (gradients 70 and 100 mm Hg), and underwent surgical myectomy with relief of symptoms over 4 and 5 years follow-up.

MID-VENTRICULAR OBSTRUCTION. Thirty-four of the 93 patients (37%) had intraventricular mid-cavity pressure gradients (44 ± 26 mm Hg) in the absence of subaortic obstruction due to SAM. Of these 34 patients, only 5 (15%) developed advanced HF symptoms (2.5%/year). Of the 55 patients without mid-cavity (or subaortic) obstruction, 11 developed advanced HF symptoms (20%; 2.7%/year), not significantly different from patients with mid-cavity obstruction ($p = 0.53$).

OVERALL EVENT RATES. Combining HCM mortality and nonfatal adverse disease-related events apical aneurysm patients experienced a 3-fold greater event rate than the 1,847 HCM patients without aneurysms (6.4%/year vs. 2.0%/year; $p < 0.001$) (**Figures 4 and 5**), as well as a 5-fold higher rate of arrhythmic events (4.7%/year vs. 0.9%/year; $p < 0.001$) (**Central Illustration**). HCM-related mortality was low both in patients with and those without apical aneurysms (0.8%/year vs. 0.6%/year; $p = 0.64$) (**Figure 4**).

Thromboembolic events were 2-fold more common in patients with apical aneurysms than non-aneurysm patients (1.1%/year vs. 0.5%/year), although this difference did not achieve statistical significance ($p = 0.06$). In 13 other patients without embolic events, a thrombus was identified in the aneurysm.

ESC SD RISK SCORE. Of the 21 LV aneurysm patients with arrhythmic events, only 2 (10%) were judged at high risk sufficient to recommend an ICD based on the ESC risk score (>6%/5 years). Thirteen of the 21 patients (62%) were judged to be at the lowest risk (<4%/5 years), considered inconsistent with an ICD recommendation.

DISCUSSION

Within the clinical spectrum of HCM, increased recognition of an unusual phenotype with thin-walled, scarred LV apical aneurysms has recently emerged (4,11,22). This finding raises a number of management considerations, including risk stratification for SD (4,8-10,23). However, due to the relatively small numbers of previously recognized aneurysm patients and short follow-up periods, the precise risk and clinical implications associated with this subgroup have remained incompletely defined (4-18).

Our data underscore concerns that HCM patients with LV apical aneurysm represent a high-risk subgroup within the disease spectrum, with more than 25% having died from their disease or experienced an adverse-disease-related complication such as ICD interventions for VT/VF, resuscitated out-of-hospital cardiac arrest, progressive HF requiring cardiac transplant or transplant listing, or thromboembolic events. Indeed, HCM patients with apical aneurysm experienced an adverse event rate of 6.4%/year, more than 3-fold greater than that of our HCM cohort without aneurysms.

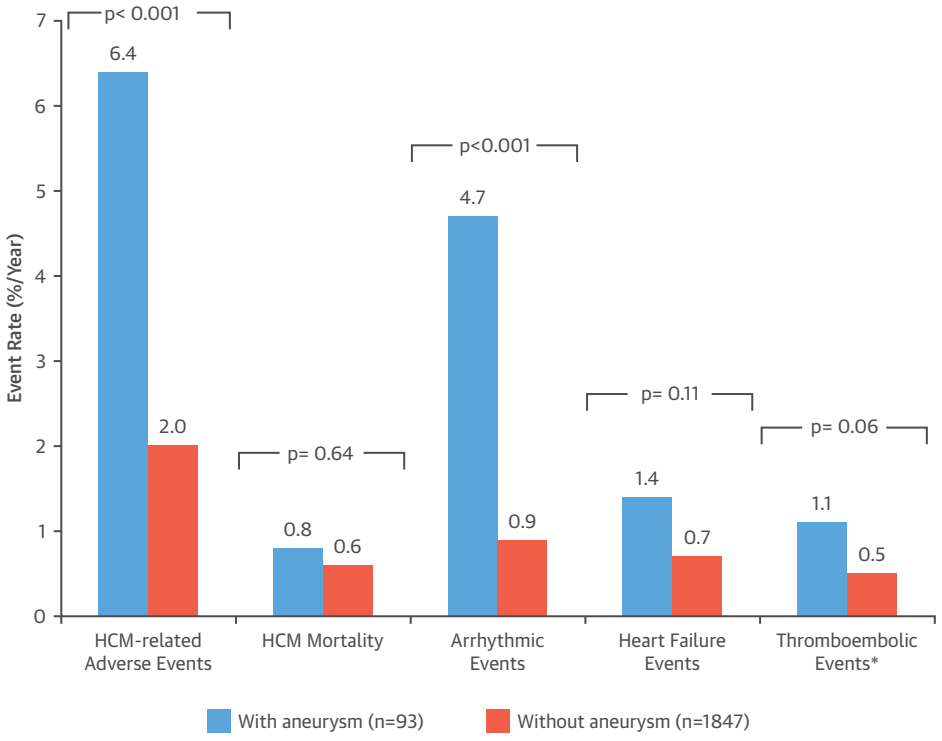
Areas of myocardial scarring contiguous with the scarred rim of the aneurysm at the junction of viable and abnormal tissue where re-entry circuits occur represent the primary arrhythmogenic substrate for the generation of malignant ventricular tachyarrhythmias independent of aneurysm size, and also are where effective radiofrequency ablation has been targeted (24-31).

Indeed, about 20% of the aneurysm patients in our cohort experienced potentially life-saving ICD interventions for VT/VF. In almost one-half of patients, an ICD was placed solely or largely because of the aneurysm itself. This translates to an arrhythmic event rate of almost 5%/year, more than 5-fold greater than that of our cohort of patients without aneurysms, and equivalent to other high-risk HCM populations with conventional SD risk markers (23).

SD events in the aneurysm patients occurred over a wide range of ages (7 patients ≥60 years), suggesting that advanced age may not be associated with lower risk in this particular subgroup (1,2). Nevertheless, the HCM-related mortality rate reported here was low (0.8%/year), similar to that of HCM patients without aneurysms, and attributable to our aggressive management strategy of recommending primary prevention ICDs for HCM patients with apical aneurysms. Of particular note, a subgroup of HCM patients has been recognized to be at risk for SD despite the absence of conventional markers (32). It is possible that in some of these patients, undetected LV apical aneurysms may have been responsible for SD.

A striking proportion of aneurysm patients with ICD events (70%) experienced multiple recurrent interventions for ventricular tachyarrythmias,

FIGURE 4 Clinical Outcome in 93 Patients With LV Apical Aneurysm Compared With HCM Cohort Without Aneurysm (n = 1,847)



*Does not include 13 patients with apical aneurysms who had intracavitary thrombus, but did not experience embolic events. Abbreviations as in Figure 1.

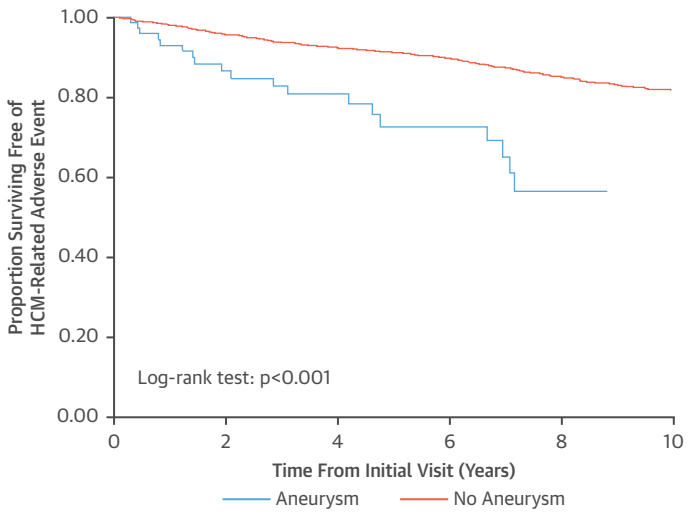
including 9 patients with ≥4 separate arrhythmic events aborted by the ICD, or a VT storm. This frequent occurrence of ventricular tachyarrhythmias in implanted patients differs distinctly from other high-risk HCM patients, in which ICD interventions are uncommon over long periods of time (23). These arrhythmic events were predominantly monomorphic VT (90%) and amenable to successful mapping and radiofrequency ablation (26-31). Such apical aneurysm patients represent the only subgroup within the broad spectrum of HCM for which VT ablation is an effective therapeutic option for refractory ventricular tachyarrthymias (24-31). Notably, the ESC mathematical risk score model to identify HCM patients at high risk who become ICD candidates does not include LV apical aneurysm patients (20).

A substantial proportion of our patients were identified with thrombus formation within the aneurysm or experienced a thromboembolic event, including 4 patients who had only small aneurysms (6). This observation suggests that the dyskinetic/akinetic apical aneurysm, can provide a structural nidus for intracavitary thrombus formation independent of size (7,8), raising strong consideration for anticoagulation in all patients with aneurysms. No embolic events occurred over the follow-up period in patients receiving prophylactic anticoagulation.

Advanced HF symptoms (class III/IV) occurred in a relatively small subgroup and were largely associated with adverse LV remodeling, either with systolic dysfunction or with preserved EF (33-35). The prevalence of end-stage HCM observed was higher than that previously reported in general HCM populations (33), suggesting that the remodeling process responsible for aneurysm formation may, in some susceptible patients, involve other portions of the LV chamber. In about 20% of these HF patients, the aneurysm was large and could have contributed to HF, but in 50% of these patients, aneurysms were small and probably should be regarded only as markers for adverse clinical course.

Additionally, the intracavitary gradients associated with mid-cavity muscular apposition are, in our judgment, unlikely to be responsible for limiting HF symptoms. Only a small minority of aneurysm

FIGURE 5 Survival Free of HCM-Related Adverse Events



Kaplan-Meier survival free of HCM-related adverse events in 93 HCM patients with LV apical aneurysms compared with HCM cohort of 1,847 patients without aneurysm. Abbreviations as in Figure 1.

patients with mid-cavity obstruction developed advanced symptoms—not significantly different then aneurysm patients without mid-cavity obstruction. This would be explained by the observation that only a portion of the LV chamber, the thin-walled, dyskinetic (fibrotic) aneurysm, is exposed to increased systolic pressures from the mid-cavity obstruction. It is unlikely that increased LV systolic pressures confined to the nonviable myocardium could promote the same pathophysiological mechanisms responsible for HF symptoms as in the much more common form of subaortic obstruction due to SAM (1). For these reasons, we have not advocated surgical midventricular muscular resection for such patients. Finally, because no study patient experienced ventricular rupture over follow-up, despite marked thinning of the aneurysm wall, our data do not support prophylactic surgical resection of the aneurysm itself.

We did not identify a consistent relation between size of the aneurysms and clinical outcome. However, about 20% of thromboembolic events and apical clot formation occurred in small aneurysms, while about 70% of SD events were in patients with medium-to-large aneurysms.

Nearly one-third of our aneurysm patients have a family history of HCM and/or a disease-causing sarcomeric protein mutation, although a specific mutation does not appear responsible for this unique phenotype (4). Nevertheless, genetic predisposition to this phenotype is suggested by aneurysm identification in 2 pairs of siblings (including 1 set of twins) among this patient cohort (7,17).

STUDY LIMITATIONS. In our study population, the prevalence of LV apical aneurysms was about 5%, although potentially an underestimate, given that all aneurysms cannot be reliably detected by echocardiography. In addition, the number of paired imaging studies was small and more extended follow up may be necessary to clarify the uncertainty regarding change in aneurysm size overtime.

CONCLUSIONS

HCM patients with LV apical aneurysms represent a high-risk subgroup associated with a number of adverse disease-related consequences, including arrhythmic SD events, thromboembolism, and end-stage HF. The SD event rate of almost 5%/year substantiates that LV apical aneurysms represent a novel risk marker in HCM. Because aneurysms are uncommon within the HCM disease spectrum, a high index of suspicion is necessary for detection often requiring CMR or contrast echocardiography. Complications of apical aneurysms in HCM are effectively treatable with contemporary management strategies, including primary prevention ICD therapy, radiofrequency ablation for recurrent VT, and prophylactic anticoagulation for stroke prevention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with hypertrophic cardiomyopathy and LV apical aneurysm are at increased risk of sudden death and thromboembolic events for which effective treatment modalities are available, including implantable defibrillators, anticoagulation, and catheter-based ablation procedures.

TRANSLATIONAL OUTLOOK: Future studies should focus on the mechanism of LV apical aneurysm formation in patients with hypertrophic cardiomyopathy and the development of therapeutic interventions to mitigate aneurysm formation.

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KEY WORDS hypertrophic cardiomyopathy, sudden death, VT ablation

APPENDIX For a supplemental table, please see the online version of this paper.