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Clinical Profile of Stroke in 900 Patients With Hypertrophic Cardiomyopathy

Barry J. Maron, MD, FACC,* Iacopo Olivotto, MD,† Pietro Bellone, MD,‡ Maria Rosa Conte, MD,§ Franco Cecchi, MD,† Björn P. Flygenring, MD, FACC,* Susan A. Casey, RN,* Thomas E. Gohman, BA,* Sergio Bongioanni, MD,§ Paolo Spirito, MD, FACC‖

Minneapolis, Minnesota; and Florence, Pietra Ligure, Turin and Genoa, Italy

OBJECTIVES We sought to assess the occurrence and clinical significance of stroke and peripheral arterial embolizations at non-central nervous system sites in a large, community-based cohort with hypertrophic cardiomyopathy (HCM).

BACKGROUND Such vascular events are insufficiently appreciated complications of HCM for which there is limited information on occurrence, clinical profile and determinants.

METHODS We assessed the clinical features of patients with stroke and other peripheral vascular events in a consecutive group of patients with HCM from four regional cohorts not subject to significant tertiary referral bias.

RESULTS Of the 900 patients, 51 (6%) patients experienced stroke or other vascular events over 7 ± 7 years, including 44 patients with stroke; 21 (41%) of these 51 patients died or were permanently disabled. The overall incidence was 0.8%/year and 1.9% for patients >60 years old. Age at first event ranged from 29 to 86 years (mean 61 ± 14 years). Most (n = 37; 72%) events occurred in those >50 years, although 14 (28%) younger patients (≤50 years) also had events. Multivariate analysis showed stroke and other peripheral vascular events to be independently associated with congestive symptoms and advanced age, as well as with atrial fibrillation (in 45 [88%] of 51 patients), at the initial evaluation. The cumulative incidence of these events among patients with atrial fibrillation was significantly higher in non-anticoagulated patients as compared with patients receiving warfarin (31% vs. 18%; $p < 0.05$).

CONCLUSIONS Stroke and peripheral embolizations showed a 6% prevalence rate and an incidence of 0.8%/year in a large, unselected HCM group. These profound complications of HCM, which may lead to disability and death, were substantially more common in the elderly, occurred almost exclusively in patients with paroxysmal or chronic atrial fibrillation and appeared to be reduced in frequency by anticoagulation. (J Am Coll Cardiol 2002;39:301–7) © 2002 by the American College of Cardiology

Hypertrophic cardiomyopathy (HCM) is a genetic disease with a broad clinical spectrum and diverse consequences (1–4). Stroke and systemic embolic events are known to occur as complications of HCM (5–8). However, few data are available regarding the frequency and determinants of these important cardiovascular events, and the clinical profile of patients with HCM and these complications has never been investigated systematically. This is a major clinical question, because the protective effect of anticoagulant treatment has clearly been established for patients at risk of developing cardioembolism (9–14). Consequently, to compensate for the limited available data, we developed a clinical profile of patients with HCM at high risk of developing stroke and other peripheral vascular events, from a large cohort of 900 patients gathered from regional populations largely free of tertiary center referral bias (15) and, therefore, most representative of the true disease state.

METHODS

Study Group

We reviewed the case records of patients with HCM evaluated between 1970 and 1998 in the outpatient and inpatient services of the four participating institutions. A consecutively enrolled and prospectively followed group of 900 patients with HCM was assembled, including: 1) the Minnesota cohort—295 patients from the Minneapolis Heart Institute, consisting primarily of Minnesota residents, but also from the adjacent states of Wisconsin, Iowa, North Dakota and South Dakota (16); 2) the Tuscany cohort—237 patients from the Careggi Hospital in Florence and predominantly from the Tuscany region in central Italy (17); 3) the Genoa cohort—210 patients from the Galliera Hospital, primarily from metropolitan Genoa and the adjacent regions of northwestern Italy (18); and 4) the Turin cohort—158 patients from the Rivoli Hospital and metropolitan Turin and the adjacent regions of northern Italy.

From the *Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; †Ospedale di Careggi, Florence, Italy; ‡Ospedale Santa Corona, Pietra Ligure, Italy; §Ospedale di Rivoli, Turin, Italy; and ‖Ente Ospedaliero Ospedali Galliera, Genoa, Italy. This study was supported in part by grants from the Consiglio Nazionale delle Ricerche and Telethon-Italy (P. S.), the Minneapolis Heart Institute Foundation and Paul G. Allen Foundation (B. J. M.), and the Italian Ministry for Scientific and Technocological Research (MURST—COFIN 2000) (I. O. and F. C.).

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Abbreviations and Acronyms
AF = atrial fibrillation
CNS = central nervous system
HCM = hypertrophic cardiomyopathy
LV = left ventricular
NYHA = New York Heart Association
TIA = transient ischemic attack

Echocardiography

Echocardiographic studies were performed with commercially available Hewlett-Packard and Toshiba instruments. Left ventricular (LV) wall thickness, left atrial size and other echocardiographic dimensions were measured as previously described (19). The peak instantaneous LV outflow gradient was estimated with continuous wave Doppler echocardiography under basal conditions (19). Mitral regurgitation was estimated with color flow imaging by measuring the maximal regurgitant jet area in cross-sectional planes (20).

Definitions

HCM. In each patient, the diagnosis of HCM was based on the two-dimensional echocardiographic identification of a hypertrophied and nondilated LV (wall thickness ≥15 mm in adults, or the equivalent, relative to body surface area, in children) (21) in the absence of another cardiac or systemic disease capable of producing a comparable magnitude of LV hypertrophy (19). Portions of these databases have been utilized in other clinical studies (16–18).

Stroke. Stroke was defined as transient or permanent neurologic impairment and disability due to vascular causes, including episodes lasting <24 h which were regarded as transient ischemic attacks (TIAs). Patients with hemorrhagic strokes or neurologic impairment due to nonvascular causes (e.g., brain tumor) were excluded from the analysis. Given the retrospective nature of this study, as well as the well-recognized difficulties in establishing the etiology of ischemic stroke subtypes, no attempt was made to distinguish cardioembolic stroke from other ischemic subtypes in the present study.

Embolizations to non-central nervous system (CNS) sites. Arterial embolism causing acute ischemia to the limbs, kidney and spleen was diagnosed based on an abrupt onset of localized pain associated with cold and pulseless extremities or hematuria. This diagnosis was usually confirmed by Doppler echocardiography and/or angiography (for the limbs and kidney) or abdominal ultrasound (for the kidney or spleen). For the purpose of this study, we considered the cumulative prevalence of stroke and arterial embolizations at non-CNS sites.

Statistics

The cumulative incidence of stroke and other peripheral vascular events was calculated as the ratio of the number of patients with this complication (at the end of the study period) to the total number of study patients. The incidence of these clinical events was compared in different patient subgroups by using the Fisher exact test. All continuous variables were compared by the Student *t* test for independent samples; categorical variables, expressed as proportions, were compared by the chi-square test. All tests were two-tailed.

To assess the risk of stroke or other peripheral vascular events associated with the principal clinical variables of our study patients, Cox proportional hazards regression analysis was performed using the SPSS, version 8.0 statistical package (SPSS Inc., Chicago, Illinois). The variables were initially tested in the univariate model; variables that were significantly associated with the risk of stroke on univariate analysis were subsequently included in a multivariate analysis for the assessment of independent risk. The 95% confidence limits of rates were calculated using the Poisson distribution.

RESULTS

Overall HCM Group

At the initial evaluation, the 900 study patients ranged in age from 29 to 86 years (mean 46 ± 20 years); 551 patients (61%) were male (Table 1). The period of follow-up to the most recent assessment or to death was 7 ± 7 years for the overall study group. At entry, 827 patients (92%) were asymptomatic or had only mild symptoms (New York Heart Association [NYHA] functional class I or II), and 73 patients (8%) had severe symptoms (NYHA functional class III or IV). Basal LV outflow obstruction (gradient ≥30 mm Hg) was present in 215 patients (24%) (Table 1).

Patients With Stroke or Other Peripheral Vascular Events

Prevalence. In 843 (94%) of the 900 study patients, the clinical history excluded events consistent with stroke or systemic thromboembolization. Of the other 57 patients, 6 were diagnosed with stroke of hemorrhagic origin or due to a brain tumor.

The remaining 51 patients (6%) experienced one or more cerebrovascular or other peripheral vascular event involving organs other than the CNS (Fig. 1); 38 patients (75%) had a single event, but 13 patients (25%) had multiple occurrences (up to 7) (Table 2). The incidence of these events was 0.8%/year, 0.3% in those ≤40 years old and 1.9% in those >60 years (Table 2).

Clinical profile. At their first event, the 51 patients were 29 to 86 years (mean 61 ± 14 years); 37 patients (72%) were >50 years, but 14 patients (28%) were ≤50 years, including 2 patients who were ≤40 years old (Fig. 2). At the time of the initial event, 32 patients (63%) were asymptomatic or mildly symptomatic (NYHA functional class I or II), and 19 patients (37%) had severe symptoms (NYHA functional class III or IV), including 7 patients in the end-stage phase (22) with systolic ventricular dysfunction. Of the 51 patients with events, only 4 patients (8%) had severe mitral regurgitation (by color flow Doppler imaging), each associated with atrial fibrillation (AF).

Table 1. Clinical and Demographic Features of 900 Patients With Hypertrophic Cardiomyopathy With and Without Stroke and Other Peripheral Vascular Events

Variable	Overall Population (n = 900)	With Events (n = 51)	Without Events (n = 849)	p Value
Gender (male)	551 (61%)	25 (49%)	526 (62%)	NS
Age at initial evaluation (yrs)	46 ± 20	58 ± 17	45 ± 20	<0.001
Duration of follow-up (yrs)	7 ± 7	6 ± 6	7 ± 6	NS
Severe symptoms (NYHA functional class III/IV)				
At initial evaluation	73 (8%)	10 (20%)	63 (7%)	<0.005
At most recent evaluation	154 (17%)	19 (36%)	135 (16%)	<0.001
Maximal LV wall thickness (mm)	21 ± 5	23 ± 5	21 ± 5	NS
Outflow obstruction*	215 (24%)	19 (37%)	196 (23%)	<0.05
LV end-diastolic cavity (mm)	44 ± 8	44 ± 7	44 ± 8	NS
LA dimension (mm)†	42 ± 9	49 ± 8	42 ± 9	<0.001
Atrial fibrillation	192 (21%)	45 (88%)	147 (17%)	<0.001
Chronic	98 (11%)	28 (54%)	70 (8%)	<0.001
Paroxysmal	94 (10%)	17 (33%)	77 (9%)	<0.001

*Peak instantaneous outflow tract gradient ≥30 mm Hg, estimated by continuous wave Doppler echocardiography. †At most recent evaluation. Data are presented as the number (%) of patients, or the mean value ± SD.
LA = left atrium; LV = left ventricular; NYHA = New York Heart Association.

Stroke. Of the 51 study patients with vascular events, 44 patients (70%) had experienced a stroke. Based on the overall clinical profile, a cardioembolic origin of stroke was judged to be definite in 8 of these patients (with AF and non-CNS embolization) and very probable in 31 patients (with AF) (23). Ten of these patients had neurologic impairment for <24 h (i.e., TIAs).

Of the 44 patients with stroke, 34 patients survived (including 11 patients with varying degrees of permanent neurologic impairment, such as aphasia or hemiparesis). The other 10 patients (20%) died as a direct consequence of their event, one day to four months later (age range 29 to 86 years; mean 69 years) (Fig. 2).

Arterial embolizations at non-CNS sites. Seven patients had embolic events to organs other than the brain, associated with AF in five (Fig. 1). These thromboemboli involved the kidney (n = 2), limbs (n = 3), kidney and limbs (n = 1) or spleen (n = 1). None of the patients died or had permanent impairment after these embolic events.

AF and Left Atrial Dimension

Of the 900 patients, 708 were in sinus rhythm, and only 6 of these patients experienced events throughout follow-up (0.8% cumulative incidence). By comparison, the 192 patients with paroxysmal or chronic AF had a 23% cumulative incidence of vascular events, or 2.5%/year (Table 2).

Atrial fibrillation was documented in 45 (88%) of the 51 patients with vascular events, either as one or more paroxysmal episode (n = 17) or chronic AF (n = 28); these events were most common in patients with chronic AF (28% vs. 20% for paroxysmal AF). Atrial fibrillation was five times more common in patients with stroke and other peripheral vascular events than in those without (88% vs. 17%; p < 0.001).

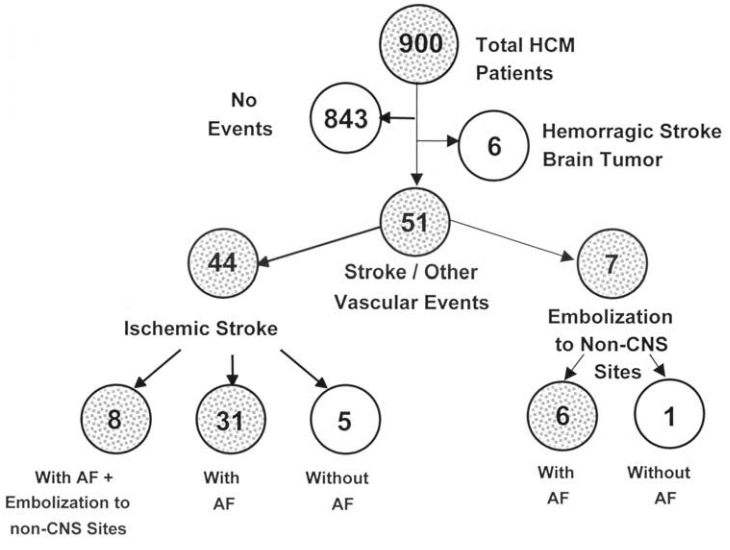

Figure 1. Profile of stroke and other peripheral vascular events among 900 patients with hypertrophic cardiomyopathy (HCM). AF = atrial fibrillation; CNS = central nervous system.

Table 2. Relationship Between Clinical, Morphologic and Functional Features at Initial Evaluation and Occurrence of Stroke or Other Peripheral Vascular Events in 900 Patients With Hypertrophic Cardiomyopathy

	n (%)	Follow-Up (years)	With Events (n)	Multiple Events (n)	≥1 Ischemic Stroke (n)	≥1 Embolism to Non-CNS Sites* (n)	Cumulative Incidence of First Event† (%)	Annual Incidence of First Event† (%)	Overall p Value and RR (95% CI) With Univariate Analysis‡ (First Event)	Overall p Value and RR (95% CI) With Multivariate Analysis‡ (First Event)
Overall	900	7.4 ± 6.6	51	13	44	15	5.7	0.77		
Gender									*p = 0.06*	*p = 0.5*
Men	551 (61%)	7.8 ± 6.7	25	8	20	8	4.5	0.58		
Women	349 (39%)	6.9 ± 6.3	26	5	24	7	7.4	1.08	1.8 (0.9–3.2)	
Age (yrs)									*p < 0.005*	*p < 0.005*
≤40	360 (40%)	8.7 ± 7.6	10	0	9	8	2.8	0.32		
41–60	327 (36%)	7.6 ± 6.2	21	7	14	5	6.4	0.85	2.5 (1.2–5.4)	1.6 (0.8–3.6)
>60	213 (24%)	4.9 ± 4.3	20	6	21	2	9.4	1.92	11.4 (4.9–25.3)	8.2 (3.9–21.6)
NYHA functional class									*p < 0.005*	*p < 0.05*
I–II	827 (92%)	7.5 ± 6.6	41	11	37	11	5.0	0.66		
III–IV	73 (8%)	5.9 ± 5.7	10	2	7	4	13.7	2.32	5.1 (2.4–9.6)	2.4 (1.2–5.0)
LVOT obstruction (≥30 mm Hg)									*p < 0.05*	*p = 0.2*
Absent	685 (76%)	7.4 ± 6.6	32	7	27	12	4.7	0.63		
Present	215 (24%)	7.4 ± 6.7	19	6	17	3	8.8	1.19	1.9 (1.1–3.6)	
Maximal LV thickness (mm)									*p = 0.25*	NI
≤25	749 (83%)	7.0 ± 6.3	35	8	30	10	4.7	0.67		
>25	151 (17%)	9.7 ± 7.6	16	5	14	5	10.6	1.09		
LA size (mm)									*p < 0.005*	*p = 0.7*
≤40	392 (44%)	7.1 ± 6.0	7	2	4	3	1.8	0.30		
41–50	369 (41%)	7.1 ± 6.5	19	4	19	5	5.1	0.79	2.5 (1.3–5.2)	
>50	139 (15%)	9.2 ± 8.0	25	7	21	7	18.0	1.95	4.4 (2.1–9.2)	
LVED (mm)									*p = 0.6*	NI
≤40	286 (32%)	7.9 ± 6.2	18	4	17	5	6.3	0.80		
41–50	463 (51%)	7.4 ± 6.7	24	8	15	6	5.2	0.70		
>50	151 (17%)	7.0 ± 7.1	9	1	12	4	6.0	0.85		
Atrial fibrillation									*p < 0.0001*	*p < 0.0001*
Absent	708 (79%)	6.8 ± 6.1	6	0	5	2	0.8	0.12		
Present	192 (21%)	9.4 ± 7.6	45	13	39	13	23.4	2.49	12.3 (6.1–28.4)	10.2 (4.6–25.0)

*Including limbs, kidneys and spleen. †Calculated on 899 patients, excluding one patient who had a stroke before the initial diagnosis of hypertrophic cardiomyopathy. ‡First category of each variable was used as the reference for the calculation of odds ratios. Data are presented as the number (%) of patients or mean value ± SD. All p values are italicized in table.

CI = confidence intervals; CNS = central nervous system; LA = left atrial; LV = left ventricular; LVED = left ventricular end-diastolic dimension; LVOT = left ventricular outflow tract; NI = not included (in the multivariate analysis); NYHA = New York Heart Association; RR = relative risk.

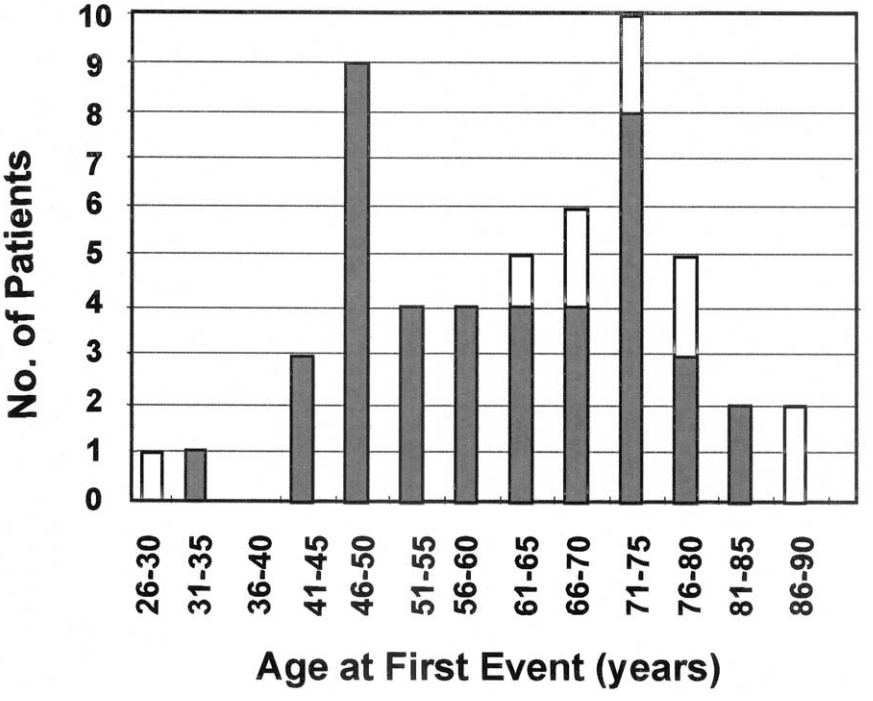

Figure 2. Distribution of ages at the time of the initial vascular event in 51 patients with hypertrophic cardiomyopathy (HCM), shown separately for those patients who survived **(shaded areas of bars)** or died **(open areas of bars)**.

In the 51 patients with events, left atrial size was 38 to 72 mm and was normal (≤40 mm) in only 4 patients (8%), including 2 patients with AF. Left atrial dimension was significantly greater in patients with events than in those without ($p < 0.001$) (Table 1; Fig. 3).

Variables Associated With Increased Risk of Vascular Events

Univariate analysis of the relationship between vascular events (stroke or peripheral arterial embolizations at non-CNS sites) and several clinical variables at the initial evaluation is shown in Table 2. There were statistically significant relationships for advanced NYHA functional classes III and IV ($p < 0.005$), outflow obstruction ($p < 0.05$), left atrial size ($p < 0.005$), a history of AF ($p < 0.0001$) and older age ($p < 0.005$). In the Cox multivariate regression model, only paroxysmal or chronic AF, severe symptoms at study entry (NYHA functional classes III and IV) and older age at the time of the clinical event proved to

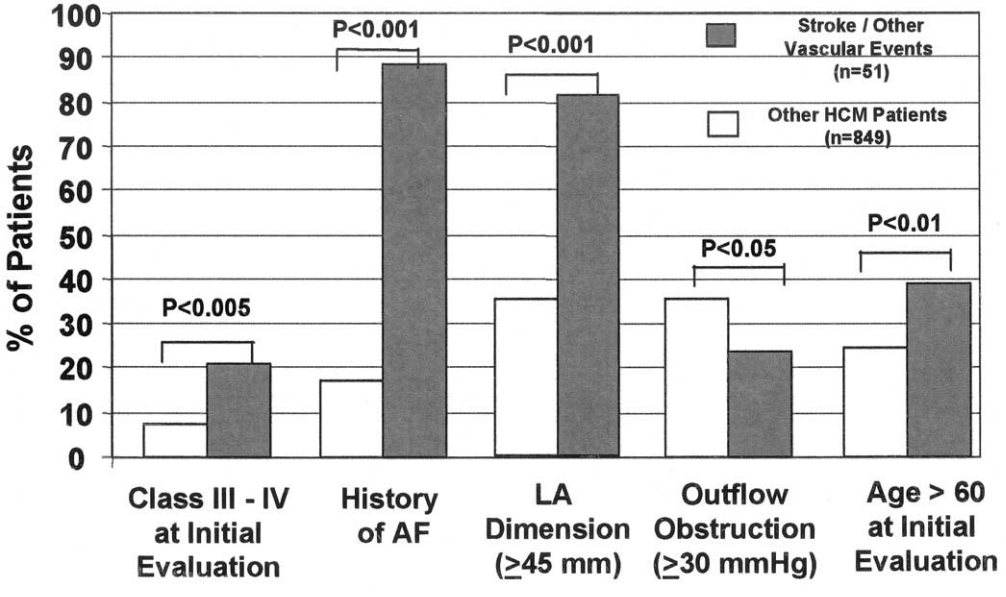

Figure 3. Comparison of selected clinical features of hypertrophic cardiomyopathy (HCM) in patients with (n = 51) or without (n = 849) stroke and other peripheral vascular events, based on univariate analysis. AF = atrial fibrillation; LA = left atrial.

be independently related to stroke and other peripheral vascular events (Table 2).

Preventive Treatment

Of the 190 patients with a history of chronic or paroxysmal AF, 82 patients received long-term anticoagulation with warfarin. The cumulative incidence of stroke and peripheral arterial embolizations among non-anticoagulated patients with AF was twice that of patients with AF who received warfarin (33 [31%] of 108 patients vs. 15 [18%] 82 patients; $p < 0.05$).

Of the 51 study patients who experienced confirmed events, 15 patients (29%) had received warfarin on a daily basis and in standard doses, due to a history of AF. Of these 15 patients, 6 patients were known to have international normalized ratios maintained within or near the target therapeutic range of 2 to 3 before their event (i.e., 1.8 to 2.5), whereas in 9 patients, regulation of warfarin administration appeared to be inadequate or was uncertain.

A major hemorrhagic complication as a consequence of anticoagulation occurred in one patient, a 70-year-old man who died of cerebral hemorrhage. Other cardioactive medications administered to patients with events included beta-blockers (n = 23), verapamil (n = 25) and amiodarone (n = 23).

DISCUSSION

Complications of HCM

Acute vascular events, including stroke and peripheral arterial embolizations, are not sufficiently appreciated as important and occasionally devastating consequences of the natural history of HCM. The frequency with which these complications occur as part of HCM, as well as their clinical determinants, has not yet been systematically characterized. Access to the present consecutive community-based and regional HCM population of 900 patients, relatively unselected and free of tertiary-center referral bias, afforded us the unique opportunity to establish a credible estimate of the prevalence and incidence of stroke and other peripheral vascular events in HCM, as well as the clinical features associated with these disease complications. Indeed, our unusually large study group is particularly well suited for the characterization of uncommon clinical events in a relatively uncommon disease such as HCM (18,24). This would not have been accessible using smaller cohorts, or a purely prospective study design (given the particularly long follow-up period required), nor as relevant if assessed in highly selected tertiary-center patient cohorts less representative of the overall HCM population (15,25).

Prevalence and Demographic Data

Our data show that these complications are not particularly rare in HCM and may have an important clinical impact on many patients, particularly those >50 years. Over the seven-year follow-up period, stroke and peripheral vascular events occurred in >5% of the patients, and >70% of these events were in patients >50 years of age, in contrast to other adverse consequences of HCM, such as sudden death, which has a predilection for the young (1,3,4). Furthermore, in almost 40% of those patients with vascular events, the consequences were devastating, in terms of disability or death, and 25% had multiple events. Indeed, the incidence and impact of stroke in our HCM cohort appear to far exceed that reported in the general population of comparable age groups (23,26).

Role of AF

The present data also suggest that AF (paroxysmal or chronic), a common arrhythmia in HCM (16,17), is a major determinant of stroke and other peripheral vascular events (26,27). Approximately 90% of our patients with such events had experienced AF (incidence of 2.5%/year), although there appears to be little risk of stroke in the absence of AF (<1%/year). This should be a source of reassurance for the large proportion of patients with HCM in sinus rhythm (including those with an enlarged left atrium), who do not require warfarin. Although all AF episodes tabulated in this data analysis were documented by electrocardiography, we cannot exclude the possibility that those patients with vascular events, but no history of AF (~10%), may have experienced asymptomatic episodes of this arrhythmia. Therefore, patients with HCM and AF represent a vulnerable subset in which >25% developed events of proven or probable embolic etiology. This strong association between AF and the risk of stroke and other peripheral vascular events exceeds that previously reported in HCM (6,7), as well as in other cardiovascular conditions (23,26–28).

The segment of the HCM cohort with advanced age (>50 years old) was most vulnerable to stroke and other peripheral vascular events, and this risk progressed with age, probably due largely to the more frequent occurrence of AF in older patients. However, an important exception is that subset of patients (i.e., ~25%) in whom such clinical events occurred before 50 years of age, and in patients as young as age 29. Hence, stroke in HCM does not occur exclusively in older patients, and the possibility of potentially catastrophic cerebral infarcts should be considered in adult patients with HCM of almost any age, particularly in the presence of chronic or paroxysmal AF.

Anticoagulation

Anticoagulation with warfarin has proved highly effective in reducing the incidence of ischemic stroke in patients with AF in conditions other than HCM, particularly in those >60 years (9–14). Our data provide substantiation for this effective prevention of stroke, by showing that prophylactic warfarin treatment was associated with a marked reduction of these ominous and profound complications of HCM. Therefore, we believe that it is warranted to consider such therapy in patients with HCM and chronic AF or one or more paroxysmal episode, after considering the small pos-

sibility of hemorrhagic complications and also the necessity for close long-term follow-up and patient compliance. Indeed, because patients with HCM are almost always identified *before* a stroke occurs, time is still available for effective prevention of these ominous clinical events.

Our study also raises some important considerations regarding anticoagulant therapy. Warfarin administration for the prevention of cardioembolism did not appear to be absolutely protective, possibly due to inadequate patient compliance or suboptimal drug administration, or to marked degrees of blood stagnation in patients in the end-stage phase (22). Approximately 10% of patients with stroke (who were taking warfarin at the time of their event) were judged to have achieved satisfactory anticoagulant regulation in the optimal therapeutic range, and therefore appear to represent true treatment breakthroughs. It should also be noted that an important proportion of our patients with AF were not on anticoagulant therapy, because their events occurred before the efficacy of warfarin had been established (9,13).

Study Limitations

The present investigation was necessarily retrospective, given the uncommon occurrence of HCM in the general population and the relative infrequency of stroke and other peripheral vascular events as complications of HCM. Furthermore, because of acknowledged difficulties in definitively discerning cardioembolic from other stroke subtypes in individual patients, we elected to prudently present our data without making a distinction between embolic and nonembolic stroke. However, in the vast majority of patients in our study cohort judged to have stroke (39 of 44 patients; 88%), these events occurred in the presence of a high-risk source of cardiac emboli, such as AF, and thus are most likely to be cardioembolic in origin according to standard criteria (29). Finally, we believe that the substantial size of the study group (the largest series reported to date for HCM), as well as the long follow-up period, confers substantial power to our data and largely compensates for the retrospective design of the study and the possible uncertainty regarding the etiologic diagnosis of stroke.

Reprint requests and correspondence: Dr. Barry J. Maron, Minneapolis Heart Institute Foundation, 920 East 28th Street, Suite 60, Minneapolis, Minnesota 55407. E-mail: hcm.maron@mhif.org.

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