**Comparison of Hypertrophic Cardiomyopathy in Afro-Caribbean versus White Patients in the United Kingdom**

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**ABSTRACT**

**Background:** This study investigated the influence of African/Afro-Caribbean (black) ethnicity on the clinical profile and outcomes in hypertrophic cardiomyopathy (HCM).

**Methods:**  425 consecutive HCM patients (163 black and 262 Caucasian [white]; mean age 52.5±16.6 years) were assessed at three cardiomyopathy centers. Repeat assessments were performed 6-12 monthly and mean follow-up was 4.3±3.0 years. The primary outcome was a composite of cardiovascular death, cardiac arrest or appropriate device therapy.

**Results:** A fortuitous diagnosis of HCM was more commonly made in black compared to white patients (31.3% versus 19.1%, p=0.004). An abnormal ECG at presentation was more frequent in black patients (98.2% versus 90.5%, p=0.002), with T-wave inversion being a common feature (91.4% versus 73.0%, p<0.001). Asymmetric septal hypertrophy was the predominant pattern in both ethnic groups; however, apical (22.2% versus 10.7%, p<0.001) and concentric (9.3% versus 1.5%, p<0.001) patterns were more prevalent in black patients. Hypertension was more frequent in black patients (58.3% versus 31.7%, p<0.001). There were no ethnic differences in risk factor profile or primary outcome. Independent predictors of the primary outcome were non-sustained ventricular tachycardia (hazard ratio 6.03, 95% confidence interval 3.06-11.91, p=<0.001) and hypertension at presentation (hazard ratio 2.02, 95% confidence interval 1.05-3.88, p=0.036), with an additive effect.

**Conclusions:** Ethnicity-specific phenotypic expressions and the high prevalence of hypertension potentially result in under diagnosis of HCM in black patients. HCM in isolation is associated with a relatively benign course in black patients. However, hypertension has an adverse effect on outcome and requires aggressive management, irrespective of ethnicity.

**INTRODUCTION**

Hypertrophic cardiomyopathy (HCM) is recognized for its diverse phenotypic expression.[1] The influence of ethnicity on clinical and morphological features is unknown. Observations from athletes[2,3] and hypertensive patients[4,5] reveal a high prevalence of ECG repolarization changes and left ventricular hypertrophy (LVH) in individuals of African/Afro-Caribbean (black) ethnicity. This combination creates diagnostic challenges with respect to the differentiation of morphologically mild HCM from other causes of LVH in this ethnic group.[2,5–8] The issue is confounded by the high prevalence of hypertension in the black population,[9,10] which has been associated with poor outcomes in Caucasian (white) HCM cohorts.[11] Furthermore, reports from the US reveal that deaths from HCM are more prevalent among black athletes,[12] raising the possibility that HCM may exhibit a more malignant course in black individuals. This study sought to address differences in the clinical phenotype, risk factor profile and outcome of HCM between black and white patients.

**METHODS**

**Patient Selection and Definitions**

Between 2001 and 2014, 425 consecutive patients with HCM (262 [61.6%] white and 163 [38.4%] black) were assessed in three specialist cardiomyopathy clinics in London, UK, which serve regions with a diverse ethnic composition. Ethnicity was self-assigned by patients and none were of mixed ethnicity. Patients were diagnosed after either: 1) primary care referral for symptoms and/or the detection of a murmur on examination; 2) investigation for an abnormal ECG; 3) cascade screening of family members of patients with HCM; 4) referral from another hospital for specialist evaluation; or 5) presentation with cardiac arrest.

HCM was diagnosed on the basis of LVH ≥15mm in any myocardial segment on echocardiography and/or cardiac magnetic resonance imaging (CMRI), in the absence of another condition capable of producing the same magnitude of LVH.[13] Patterns of LVH were categorized according to the location of the myocardial segment revealing the greatest degree of hypertrophy on echocardiography and/or CMRI. Concentric LVH was categorized as global myocardial hypertrophy with <2mm difference between adjacent segments. In cases of mild (<15mm) LVH (n=60; 14.1%), HCM was diagnosed in the context of supportive features, including: 1) an established pathogenic gene mutation (n=30); 2) a family history of HCM or sudden cardiac death (SCD) in a first-degree relative (n=17); 3) LVH confined to the apical segments (n=12); 4) presentation with cardiac arrest in the presence of mild asymmetric septal hypertrophy and unobstructed coronary arteries (n=1).

Hypertension was defined according to the Seventh Joint National Committee (JNC 7) criteria[14] as a blood pressure (BP) of ≥140/90mmHg on an average of ≥2 properly measured seated BP readings and/or patients on established antihypertensive therapy. Among patients with hypertension (n=178; 41.9%), HCM was diagnosed in the presence of severe LVH ≥20mm (n=36) or in the context of LVH ≥15mm in any myocardial segment and supportive features, including: 1) an established pathogenic gene mutation (n=31); 2) a family history of HCM or SCD in a first-degree relative (n=32); 3) non-concentric, segmental patterns of LVH confined to the apical segments (n=35), mid-septum (n=24), or anterior wall (n=3); and 4) systolic anterior motion of the mitral valve leaflets (n=17).[13,15–17]

**Clinical Evaluation**

All patients were investigated with history, physical examination, 12-lead ECG, 2-dimensional echocardiography, exercise testing and 24-hour ambulatory ECG monitoring. 246 (58%) patients also underwent CMRI. A proportion of patients (63 [38.7%] black and 132 [50.4%] white) underwent gene testing. All patients had repeat assessment on a 6-12 monthly basis. Analysis relating to electrocardiographic and structural data was performed on the presenting investigations by NS, MP and SS who were blinded to the ethnicity of the patient. Data from study entry to the last contact in clinic or death were used for the purposes of risk stratification and outcomes. Mean follow-up duration was 4.3±3.0 years (range 6 months to 13 years).

12-Lead Electrocardiography

Standard 12-lead electrocardiography was performed with individuals in the supine position. T-wave inversion of ≥-0.1 mV in two or more contiguous leads was considered significant other than in leads V1, aVR and III. Deep T-wave inversion was defined as a T-wave deflection of ≥-0.2 mV. ST-segment shift of ≥-0.1 mV in ≥2 contiguous leads was considered significant. Left ventricular hypertrophy was identified using the Sokolow–Lyon criterion.[18] Q-waves were considered pathological if ≥0.04 s in duration or ≥25% of the height of the ensuing R-wave.

Echocardiography

Standard views of the heart were obtained and analyzed in accordance with European Society of Echocardiography.[19] Left ventricular ejection fraction was calculated using Simpson’s method.[20] Indices of diastolic function were assessed in the apical 4-chamber view with pulsed-wave Doppler across the mitral valve and tissue Doppler imaging of the septal and lateral mitral valve annulus.[21]

Exercise Stress Testing

All patients were exercised to exhaustion using the standard Bruce protocol on an upright treadmill stress test.[22] Blood pressure measurements and ECG readings were taken at one-minute intervals and analyzed specifically for arrhythmias. A systolic BP rise of >25mmHg from baseline to peak exercise was considered normal.[23]

24-Hour Ambulatory ECG Monitoring

Ambulatory 24-hour ECG monitoring was performed specifically to detect supraventricular and/or ventricular arrhythmias.[24] All individuals were encouraged to continue their daily activities during monitoring. Non-sustained ventricular tachycardia (NSVT) was defined as three or more consecutive ventricular beats at a rate of >120 beats per minute with a duration of <30 seconds.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging was performed using methods previously described and analyzed with semi-automated software.[25–27] All volumes and masses were indexed for age and body surface area. Late gadolinium images were acquired after intravenous gadolinium-DTPA administration.[25] The presence or absence of late gadolinium enhancement was recorded as a binary variable.

**Risk Assessment, Events and Outcomes**

Conventional markers of SCD were used for risk stratification, namely: 1) history of unexplained syncope; 2) family history of SCD in 1 or more first degree relatives; 3) LVH of ≥30mm; 4) NSVT on ambulatory monitoring or exercise testing; 5) an abnormal systolic BP response to exercise.[13] The estimated 5-year risk of SCD was calculated using a recently proposed risk stratification tool by the European Society of Cardiology.[17,28] The primary outcome was a composite of cardiovascular death, cardiac arrest or appropriate device therapy, defined as appropriate anti-tachycardia pacing and/or shock delivery from an implantable cardioverter-defibrillator (ICD). Secondary outcomes included myocardial infarction and stroke. Of the cohort of 425 individuals, 16 were excluded from subsequent survival analysis due to a primary event prior to entry into the study. Of the remaining 409 patients, a further 16 had experienced a secondary event prior to entry into the study and were excluded from subsequent survival analysis for secondary events.

**Statistical Analysis**

The Kolmogorov-Smirnov test was used to evaluate whether each parameter followed a Gaussian distribution. Values are expressed as mean ± standard deviation or percentages, as appropriate. Comparisons were performed by Student’s t-test, Mann Whitney U test, and Chi-square test for normally distributed, non-normally distributed and categorical variables, respectively. Survival curves were constructed according to the Kaplan-Meier method, and comparisons were performed using the log-rank test. Hazard ratios and 95% confidence intervals (CI) were calculated with Cox proportional hazards regression models. A two-tailed p-value of <0.05 was considered significant throughout.

To determine predictors of the primary outcome, clinical variables were tested using univariate analysis. Variables with a p-value of <0.1 for univariate associations were entered into a backward stepwise multivariate Cox proportional hazards regression model to determine independent predictors of the primary outcome. All analyses were performed using SPSS software, version 20.0 (IBM, Chicago, Illinois).

**RESULTS**

**Baseline Demographics**

Baseline demographics, mode of presentation and co-morbidities in black versus white HCM patients are presented in Table 1. Hypertension at study entry was almost twice as common in black compared to white patients (58.3% versus 31.7%, p<0.001). Ninety-one (55.8%) black and 79 (30.2%) white patients were on anti-hypertensive treatment. The majority of patients with hypertension (145 out of 178, 81.5%) had good BP control (<140/90mmHg). Only 11 patients (2.6% of the entire cohort) exhibited persistently elevated BP during follow-up.

**Table 1. Baseline demographic characteristics, mode of presentation and co-morbidities in black versus white HCM patients.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | | **Black Patients**  **(n=163)** | **White Patients**  **(n=262)** | | **p-value** | | |
| Age at diagnosis (years) | | 51.5±15.9 | 50.5±17.7 | | 0.712 | | |
| Age at first evaluation (years) | | 52.4±15.9 | 52.6±17.1 | | 0.883 | | |
| Male gender – no. (%) | | 107 (65.6) | 165 (66.8) | | 0.807 | | |
| Systolic Blood Pressure (mmHg) | | 130±15 | 125±17 | | 0.003 | | |
| Diastolic Blood Pressure (mmHg) | | 77±11 | 74±11 | | 0.017 | | |
| Follow-up duration (years) | | 3.8±3.1 | 4.2±3.6 | | 0.123 | | |
| **Mode of presentation – no. (%)** | | | | | | | |
| Cardiovascular symptoms | | 96 (58.9) | 166 (63.4) | | 0.929 | | |
| Familial Screening | | 11 (6.7) | 46 (17.6) | | 0.001 | | |
| Cardiac Arrest | | 5 (3.1) | 0 (0.0) | | 0.008 | | |
| Fortuitous | | 51 (31.3) | 50 (19.1) | | 0.004 | | |
| Abnormal ECG | | 44 (27.0) | 28 (10.7) | | <0.001 | | |
| Abnormal Examination | | 4 (2.5) | 17 (6.5) | | 0.062 | | |
| Pre-participation Screening | | 3 (1.8) | 5 (1.9) | | 0.960 | | |
| **Symptoms at initial evaluation – no. (%)** | | 134 (82.2) | 202 (77.1) | | 0.208 | | |
| Chest pain | | 83 (50.9) | 111 (42.4) | | 0.085 | | |
| Breathlessness | | 71 (43.6) | 127 (48.5) | | 0.323 | | |
| Palpitation | | 63 (38.7) | 97 (37.0) | | 0.736 | | |
| Pre-syncope | | 24 (14.7) | 42(16.0) | | 0.718 | | |
| Syncope | | 37 (22.7) | 43 (16.4) | | 0.107 | | |
| **Family History of hypertrophic cardiomyopathy – no. (%)** | | 31 (19.0) | 76 (29.0) | | 0.021 | | |
| **New York Heart Association Class at presentation – no. (%)** | | | | | | | |
| I | | 125 (77.6) | 182 (69.7) | | 0.008 | | |
| II | | 26 (16.1) | 71 (27.2) | |
| III | | 5 (3.1) | 7 (2.7) | |
| IV | | 5 (3.1) | 1 (0.4) | |
| **Prevalence of Co-morbidities – no. (%)** | | | | | | |
| History of hypertension | | 95 (58.3) | 83 (31.7) | | <0.001 | | |
| Atrial Fibrillation | 31 (21.5) | | | 68 (27.4) | | 0.196 |
| Coronary artery disease\* | 14 (10.1) | | | 23 (9.4) | | 0.810 |
| Myocardial bridge\* | 1 (1.5) | | | 5 (4.2) | | 0.311 |
| Coronary artery dissection\* | 3 (4.5) | | | 0 (0.0) | | 0.020 |
| Chronic obstructive pulmonary disease / Asthma | 9 (6.5) | | | 29 (11.8) | | 0.095 |
| Renal disease | 5 (3.6) | | | 7 (2.9) | | 0.680 |
| Diabetes | 20 (14.4) | | | 21 (8.6) | | 0.076 |
| Dyslipidaemia | 15 (10.9) | | | 30 (12.2) | | 0.688 |
| Cancer | 8 (5.8) | | | 10 (4.0) | | 0.436 |

**\*In 181 (44.3%) patients who underwent conventional or computed tomography coronary angiography (67 [43.8%] black and 114 [44.9%] white).**

**Mode of Presentation and Symptoms**

The diagnosis of HCM was triggered predominately by symptoms in both groups (Table 1). However, a fortuitous diagnosis of HCM was more common in black patients (31.3% versus 19.1%, p=0.004). In particular, black patients were more likely to be identified following investigation of an abnormal ECG performed for an unrelated reason (27.0% versus 10.7%, p<0.001). In contrast, white patients were more frequently diagnosed after familial screening (6.7% versus 17.6%, p=0.001). More black compared to white patients presented with cardiac arrest (3.1% versus 0.0%, p=0.008) or with New York Heart Association (NYHA) class IV symptoms (3.1% versus 0.4%, p=0.008).

**Electrocardiographic Changes**

A higher proportion of black patients exhibited an abnormal ECG (98.2% versus 90.5%, p=0.002) (Table 2). Although common in both ethnicities, repolarization abnormalities were more prevalent in black patients, particularly T-wave inversion (91.4% versus 73.0%; p<0.001), including lateral T-wave inversion (84.0% versus 68.0%, p<0.001) and deep T-wave inversion (80.2% versus 58.3%, p<0.001). The prevalence of ST-segment depression was also commoner in black patients (55.6% versus 45.6%, p=0.046), while pathological Q-waves were commoner in white patients (11.1% versus 23.2% p=0.002).

**Table 2. Electrical, structural and genetic characteristics of black versus white HCM patients.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Black Patients**  **(n=163)** | **White Patients**  **(n=262)** | **p-value** |
| **Heart rate (bpm)** | **67.1±14.4** | **67.9±13.3** | **0.601** |
| **ECG parameters – no. (%)** |  |  |  |
| Abnormal ECG | 160 (98.2) | 237 (90.5) | 0.002 |
| Rhythm | | | |
| Sinus rhythm | 156 (95.7) | 241 (92.0) | 0.289 |
| Atrial fibrillation/flutter | 5 (3.1) | 17 (6.5) |
| Paced Rhythm | 2 (1.2) | 4 (1.5) |
| Sokolow-Lyon voltage criteria for left ventricular hypertrophy | 89 (54.9) | 94 (36.3) | <0.001 |
| Left bundle branch block | 6 (3.7) | 12 (4.6) | 0.646 |
| Pathological Q-waves | 18 (11.1) | 60 (23.2) | 0.002 |
| T-wave Inversion | 148 (91.4) | 189 (73.0) | <0.001 |
| TWI confined to V1–V4 | 7 (4.3) | 5 (1.9) | 0.152 |
| TWI involving the inferior leads | 5 (3.1) | 8 (3.1) | 0.999 |
| TWI involving the lateral leads | 136 (84.0) | 176 (68.0) | <0.001 |
| Deep T-wave inversion | 130 (80.2) | 151 (58.3) | <0.001 |
| ST-segment elevation | 87 (53.7) | 101 (39.0) | 0.003 |
| ST-segment depression | 90 (55.6) | 118 (45.6) | 0.046 |
| **Structural characteristics on echocardiography** | | | |
| Left atrial dimension (mm) | 40.8±6.1 | 41.7±7.9 | 0.231 |
| Left ventricular end-diastolic dimension (mm) | 44.9±6.9 | 45.5±7.1 | 0.369 |
| Maximum left ventricular wall thickness (mm) | 19.0±5.0 | 18.8±5.2 | 0.846 |
| Simpson’s Ejection fraction (%) | 64.7±10.5 | 63.6±10.1 | 0.593 |
| Complete SAM at rest – no. (%) | 20 (12.5) | 79 (30.2) | <0.001 |
| Resting left ventricular outflow tract gradient ≥30 mmHg at rest – no. (%) | 12 (7.5) | 55 (21.4) | <0.001 |
| E/A ratio | 1.19±0.57 | 1.21±0.60 | 0.685 |
| Average E/E’ | 12.0±4.8 | 13.0±6.5 | 0.126 |
| **Left ventricular hypertrophy pattern – no (%)** | | | |
| Septal | 52 (32.1) | 142 (54.2) | <0.001 |
| Apical | 36 (22.2) | 28 (10.7) |
| Concentric | 15 (9.2) | 4 (1.5) |
| Mixed Patterns | 59 (36.4) | 88 (33.6) |
| **CMRI – no. (%)** | **99 (60.7)** | **147 (56.1%)** | 0.347 |
| Left ventricular mass index (g/m2) | 105±44 | 103±40 | 0.703 |
| Left ventricular end diastolic volume index (ml/m2) | 71±21 | 72±19 | 0.911 |
| Late gadolinium enhancement – no. (%) | 53 (55.8) | 102 (70.3) | 0.021 |
| **Genetic Testing – no. (%)** | **63 (38.7)** | **132 (50.4)** | **0.018** |
| Gene positive (% of those tested) | 34 (54.0) | 67 (50.8) | 0.675 |
| MYBPC3 | 23 (36.5) | 34 (25.8) | 0.220 |
| MYH7 | 3 (4.8) | 16 (12.1) |
| TNNI3 | 4 (6.3) | 3 (2.3) |
| TNNT2 | 2 (3.2) | 8 (6.1) |
| Other (MYH6, MYL3, MYL3) | 2 (3.2) | 6 (4.5) |

**bpm beats per minute; CMRI, cardiac magnetic resonance imaging; E/A, ratio of early to late diastolic inflow velocities; E/E’, ratio of early diastolic inflow to early myocardial relaxation velocity; MYBPC3, myosin binding protein C; MYH6, myosin heavy chain 6; MYH7, myosin heavy chain 7; MYL3, myosin light chain 3; TNNI3, troponin I type 3; TNNT2, troponin T type 2; SAM, systolic anterior motion of the mitral valve leaflets; and TWI, T-wave inversion.**

**Structural Changes**

There were no ethnic differences in mean left atrial dimension, left ventricular dimensions, maximum left ventricular wall thickness, left ventricular mass or left ventricular systolic function (Table 2). Though common in both groups, asymmetric septal hypertrophy was observed in only a third of black patients compared to over half of white patients. In contrast, both apical and concentric patterns of LVH were commoner in black patients. Importantly, almost 10% of black patients (n=16) revealed a concentric pattern of LVH. Of these, 4 had a positive gene test, 3 had a family history of HCM, 2 exhibited LVH of ≥20mm, and 1 experienced a cardiac arrest. The remaining 5 individuals had no history of hypertension or other condition capable of producing the same magnitude of LVH. Of the patients subjected to a CMRI, the presence of late gadolinium enhancement was commoner in white patients (55.8% versus 70.3%, p=0.022).

**Genetic Analysis**

Of the 63 (38.7%) black and 132 (50.4%) white patients referred for genetic testing, a recognized disease causing mutation was identified in a similar proportion of individuals (54.0% versus 50.8%, respectively, p=0.675) (Table 2).

**Risk Factor Profile for Sudden Cardiac Death**

Among 409 patients eligible for survival analysis, there were no ethnic differences in the overall risk of SCD based on conventional risk markers or the recently proposed European Society of Cardiology risk stratification tool (Table 3).[17,28] Regarding individual risk factors, a history of syncope was more common in black patients whereas an abnormal BP response to exercise was more common in white patients (Table 3).

**TABLE 3. Risk factor profile, events and treatment strategies in black versus white HCM patients eligible for survival analysis (n=409).**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | | **Black Patients**  **(n=155)** | | **White Patients**  **(n=254)** | | **p-value** |
| **Prevalence of conventional risk factors – no. (%)** | | | | | | |
| History of Syncope | | 36 (23.2) | | 38 (15.0) | | 0.035 |
| Family history of sudden death | | 30 (19.4 | | 47 (18.5) | | 0.831 |
| NSVT at entry to study | | 23 (16.1) | | 29 (11.8) | | 0.236 |
| NSVT at any time since diagnosis | | 34 (23.8) | | 60 (24.5) | | 0.874 |
| Left ventricular wall thickness ≥30mm | | 9 (5.8) | | 9 (3.5) | | 0.273 |
| Abnormal blood pressure response to exercise | | 15 (13.3) | | 47 (23.7) | | 0.026 |
| 0 risk factors | | 73 (47.1) | | 119 (46.9) | | 0.961 |
| 1 risk factor | | 56 (36.1) | | 86 (33.9) | | 0.640 |
| ≥2 risk factors | | 26 (16.8) | | 49 (19.3) | | 0.523 |
| **European Society of Cardiology Risk stratification model** | | | | | | |
| Overall HCM Risk Score | | 3.45±3.94 | | 3.45±3.59 | | 0.483 |
| HCM Risk Score High – no. (%) | | 19 (13.4) | | 27 (11.4) | | 0.566 |
| **Deaths – no. (%)** | | **12 (7.7)** | | **21 (8.3)** | | **0.850** |
| Cardiovascular deaths | | 9 (5.8) | | 16 (6.3) | | 0.939 |
| Sudden death secondary to arrhythmia | | 2 (1.3) | | 4 (1.6) | | 0.352 |
| Myocardial Infarction | | 1 (0.6) | | 2 (0.8) | |
| End stage heart failure\* | | 1 (0.6) | | 7 (2.8) | |
| Other† | | 3 (1.9) | | 2 (0.8) | |
| Stroke‡ | | 2 (1.3) | | 1 (0.4) | |
| Non-cardiovascular deaths | | 3 (1.9) | | 5 (2.0) | | 0.939 |
| Cancer | | 2 (1.3) | | 3 (1.2) | | 0.979 |
| Other | | 1 (0.6) | | 2 (0.8) | |
| **Primary Outcome Events – no. (%)** | | **20 (12.9%)** | | **22 (8.7%)** | | **0.170** |
| Cardiovascular cause of death | | 9 (5.8) | | 15 (5.9) | | 0.089 |
| HCM-related§ | | 5 (3.2) | | 11 (4.3) | |
| Non-HCM related | | 4 (2.6) | | 4 (1.6) | |
| Aborted Cardiac arrest | | 6 (3.9) | | 1 (0.4) | |
| Appropriate ICD therapy|| | | 5 (3.2) | | 6 (2.4) | |
| **Secondary Outcome Events – no. (%)** | | **17 (11.0)** | | **25 (9.8)** | | **0.716** |
| Non-fatal Stroke | | 12 (7.7) | | 17 (6.7) | | 0.921 |
| Non-fatal Myocardial Infarction | | 5 (3.2) | | 8 (3.1) | |
| **Pharmacological Therapy – no. (%)** | | | | | | | |
| Beta-blockers | 84 (58.7) | | 131 (53.7) | | 0.334 | | |
| Verapamil | 8 (5.6) | | 24 (9.8) | | 0.144 | | |
| Disopyramide | 4 (2.8) | | 22 (9.0) | | 0.018 | | |
| Angiotensin converting enzyme inhibitor or Angiotensin II receptor blocker | 60 (42.0) | | 73 (29.9) | | 0.016 | | |
| Diuretics | 49 (34.3) | | 51 (20.9) | | 0.004 | | |
| **Non-Pharmacological Therapy – no. (%)** | | | | | | | |
| Pacemaker | 8 (5.2) | | 17 (6.7) | | 0.530 | | |
| ICD | 14 (9.0) | | 28 (11.0) | | 0.520 | | |
| Alcohol septal ablation | 1 (0.6) | | 2 (0.8) | | 1.000 | | |
| Myectomy | 2 (1.9) | | 22 (8.7) | | 0.006 | | |

**HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; NSVT, non-sustained ventricular tachycardia**

**\*Heart failure death secondary to systolic dysfunction**

**†Fatal aortic aneurysm or cardiac tamponade.**

**‡Two out of three stroke deaths occurred in the context of atrial fibrillation off anticoagulation (anticoagulation declined by one patient and contraindicated in the other)**

**§ HCM-related deaths refer to (i) sudden death secondary to arrhythmia; (ii) death due to end stage heart failure; (iii) stroke deaths**

**||In 42 (10.3%) patients with an implantable cardioverter-defibrillator (ICD) (14 [9.0%] black and 28 [11.0%] white).**

**Primary and Secondary Outcomes**

During the study period, a similar proportion of black and white patients experienced primary and secondary outcome events (Table 3). Of the 409 patients eligible for survival analysis, 24 (5.9%) died from cardiovascular causes, 7 (1.7%) survived a cardiac arrest and 11 (2.7%) received appropriate ICD therapy. Kaplan-Meier survival analysis demonstrated no differences in estimated freedom from primary outcome in black versus white patients at 5 (82.5% versus 92.1%) or 10 years (71.1% versus 74.1%), respectively (p log-rank=0.095, Figure 1A). Similarly, Kaplan-Meier survival analysis demonstrated no ethnic differences in estimated freedom from stroke or myocardial infarction at 5 or 10 years.

Determinants of the Primary Outcome

Univariate analysis demonstrated an association between the primary outcome and several cohort characteristics (Table 4A). However, on multivariate analysis (Table 4B), only hypertension (hazard ratio 2.02, 95% CI 1.05-3.88, p=0.036) and NSVT (hazard ratio 6.03, 95% CI 3.06-11.91, p=<0.001) remained independent predictors of the primary outcome. Kaplan-Meier survival analysis demonstrated an additive detrimental effect on freedom from primary outcome among patients with hypertension and NSVT (Figure 1B).

**TABLE 4. Results of univariate (A) and multivariate (B) analysis for predictors of the primary endpoint (cardiac death, appropriate ICD therapy or cardiac arrest) in the total cohort of black and white HCM patients eligible for survival analysis (n=409).**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Hazzard ratio** | **95% CI** | **P-value** |
| **A: UNIVARIATE ANALYSES\*** | | | |
| Age at first evaluation | 1.02 | 1.00 – 1.04 | 0.063 |
| Black Ethnicity | 1.67 | 0.91 – 3.06 | 0.098 |
| Male Gender | 0.65 | 0.36 – 1.21 | 0.174 |
| Family history of sudden cardiac death | 0.68 | 0.29 – 1.62 | 0.388 |
| Syncope | 1.92 | 1.00 – 3.71 | 0.051 |
| History of hypertension at first evaluation | 1.78 | 0.97 – 3.29 | 0.064 |
| Left atrial size (mm) | 1.05 | 1.00 – 1.09 | 0.059 |
| Left ventricular wall thickness ≥30mm | 4.02 | 1.77 – 9.14 | 0.001 |
| History of non-sustained ventricular tachycardia at baseline visit | 4.94 | 2.55 – 9.55 | <0.001 |
| Abnormal blood pressure response to exercise | 1.97 | 0.85 – 4.54 | 0.113 |
| Resting left ventricular outflow tract gradient ≥30mmHg at rest | 0.70 | 0.329 | 1.465 |
| Late Gadolinium enhancement on cardiac magnetic resonance imaging | 1.21 | 0.39 – 3.82 | 0.741 |
| **B: MULTIVARIABLE ANALYSES USING BACKWARD STEPWISE (LIKELIHOOD RATIO) METHOD†** | | | |
| History of hypertension at first evaluation | 2.02 | 1.05 – 3.88 | 0.036 |
| History of non-sustained ventricular tachycardia at baseline visit | 6.03 | 3.06 – 11.91 | <0.001 |

**\*The table depicts statistically significant variables and variables considered to be associated with an increased risk of sudden cardiac death in hypertrophic cardiomyopathy.**

**†All variables that that demonstrated a p-value of <0.1 in the univariate analyses were included in the multivariable model.**

**Influence of Hypertension on the HCM Phenotype**

Based on the high prevalence of co-existent hypertension and its association with the primary outcome, we performed a separate comparison between the hypertensive and normotensive group (Table 5). Of interest, HCM patients with hypertension were on average 15 years older at the time of diagnosis compared to normotensive patients (59.5±13.3 versus 44.7±16.7 years, p<0.001). However, there were no differences between the two groups with respect to the magnitude and pattern of LVH, prevalence of resting left ventricular outflow tract obstruction, the proportion with a disease causing genetic mutation, or conventional risk factors for SCD, with the exception of a family history of SCD which was commoner in the normotensive group (22.7% versus 13.5% p=0.017). Hypertensive patients demonstrated inferior indices of diastolic function (as assessed by E/E’) compared to normotensive patients (Table 5).

**TABLE 5. Differences in characteristics of HCM patients with and without hypertension.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HCM with hypertension**  **n=178** | **HCM without hypertension**  **n=247** | **p-value** |
| Age at diagnosis (years) | 59.5±13.3 | 44.7±16.7 | <0.001 |
| Black ethnicity – no. (%) | 95 (53.4) | 68 (27.5) | <0.001 |
| Male gender – no. (%) | 100 (56.2) | 182 (73.7) | <0.001 |
| Family History of HCM – no. (%) | 24 (13.5) | 83 (33.6) | <0.001 |
| Implantable cardioverter-defibrillator – no. (%) | 15 (8.4) | 31 (12.6) | 0.177 |
| Abnormal ECG – no. (%) | 169 (94.9) | 228 (92.3) | 0.280 |
| Left atrial dimension (mm) | 42.5±7.3 | 40.6±7.2 | 0.010 |
| LV end diastolic dimension (mm) | 45.8±7.0 | 44.9±7.0 | 0.217 |
| Maximum left ventricular wall thickness (mm) | 19.3±4.3 | 18.5±5.6 | 0.089 |
| Simpson’s Ejection fraction (%) | 66.0±10.0 | 62.6±10.5 | 0.118 |
| E/A ratio | 1.10±0.58 | 1.28±0.58 | 0.002 |
| Average E/E' | 13.81±5.49 | 11.75±6.03 | 0.001 |
| Complete SAM at rest – no. (%) | 39 (21.9) | 60 (24.6) | 0.521 |
| Resting gradient ≥30mmHg – no. (%) | 29 (16.6) | 38 (15.7) | 0.812 |
| Left ventricular hypertrophy pattern – no. (%) | | | |
| Pure Septal | 75 (42.1) | 119 (48.4) | 0.226 |
| Pure Apical | 34 (19.1) | 30 (12.2) |
| Pure Concentric | 7 (3.9) | 12 (4.9) |
| Mixed Patterns | 62 (34.8) | 85 (34.6) |
| **Cardiac MRI – no. (%)** | 107 (60.1) | 139 (56.3) | 0.429 |
| LV mass index (g/m2) | 111±44 | 98±38 | 0.045 |
| LV end diastolic volume index (ml/m2) | 69±20 | 75±19 | 0.138 |
| Late gadolinium enhancement – no. (%) | 68 (64.8) | 87 (64.4) | 0.959 |
| **Number Gene Tested – no. (%)** | 64 (36.0) | 131 (53) | <0.001 |
| Gene Positive of those tested – no. (%) | 31 (48.4) | 70 (53.4) | 0.512 |
| **Conventional Risk Factors – no. (%)** |  |  |  |
| History of Syncope | 32 (18.0) | 48 (19.4) | 0.705 |
| Family history of SCD | 24 (13.5) | 56 (22.7) | 0.017 |
| Ventricular tachycardia | 45 (26.2) | 57 (24.9) | 0.772 |
| LV wall thickness ≥30mm | 6 (3.4) | 12 (4.9) | 0.442 |
| Abnormal BP response to exercise | 21 (17.6) | 41 (20.2) | 0.575 |
| 1 risk factor | 56 (31.5) | 88 (35.6) | 0.371 |
| ≥2 risk factors | 30 (16.9) | 52 (21.1) | 0.279 |
| **European Society of Cardiology Risk Stratification Model** | | | |
| Overall HCM Risk Score | 3.12±2.99 | 3.89±4.50 | 0.024 |
| High Risk (≥6% 5-year risk of SCD) – no. (%) | 21 (12.7) | 29 (12.9) | 0.944 |

**BP blood pressure; HCM, hypertrophic cardiomyopathy; LV, left ventricular; SAM, systolic anterior motion of the mitral valve leaflets; SCD, sudden cardiac death.**

**DISCUSSION**

Hypertrophic cardiomyopathy is a relatively common and treatable condition with a relatively benign course in most patients.[1] Despite being recognized as a global disorder, data relating to the phenotypic manifestations and natural history in black patients are scarce.[12,29–34] Additionally, black patients have a high prevalence of hypertension, which is conventionally regarded as an exclusion criterion for the diagnosis of HCM; therefore the diagnosis of HCM is probably under-reported in this cohort. However, black ethnicity modulates a number of cardiovascular diseases, including myocardial infarction,[35] stroke,[36] and heart failure.[37] The present study provides a comprehensive description of the clinical phenotype and natural course of HCM in a well-characterized cohort of black and white patients in the UK with equal access to a national health care system.

**Phenotypic Difference between Black and White Patients**

Almost all (n=160, 98.2%) black patients exhibited an abnormal ECG, with a high prevalence of T-wave inversion (n=148, 91.4%), which was frequently deep (n=130, 80.2%) and involved the lateral leads (n=136, 84.0%). In contrast, almost 10% of white patients revealed a normal ECG. Given that the reported prevalence of repolarization changes in black hypertensive patients is ≤30%,[17,38] the diagnosis of HCM should be considered in any black hypertensive individual with LVH on imaging studies who exhibits marked ECG repolarization anomalies, particularly if there is persistence of ECG changes and LVH despite good BP control.[39,40]

A third of black patients exhibited apical or concentric patterns of hypertrophy compared to only 12% of white patients. Both patterns of hypertrophy may be responsible for failure to diagnose HCM in black individuals leaving them vulnerable to complications. In the context of hypertension, concentric LVH may be mistaken for hypertensive heart disease, while apical hypertrophy may go undetected on conventional echocardiography and the associated marked repolarization changes falsely attributed to “left ventricular strain pattern”. The observation that patients with a history of hypertension (mainly black) were diagnosed with HCM, on average, 15 years later than normotensive patients and that 3% of black patients compared to none of the white patients presented with cardiac arrest supports this theory.

**Ethnic Differences in HCM Risk Profile**

Black patients did not exhibit a higher prevalence of conventional risk markers for SCD or higher 5-year risk.[17,28] In addition, ethnicity was not a determinant of the composite primary outcome of death, cardiac arrest or appropriate ICD therapy. Therefore, our findings do not indicate a more malignant course of HCM in black patients. In contrast, data from a registry of SCD in young athletes in the US reported a higher number of HCM related SCDs in black athletes.[12,41] Although an increased predisposition to fatal arrhythmias during strenuous exercise on the HCM phenotype in black athletes cannot be excluded, the registry findings are likely to reflect relatively higher participation rates, lower accessibility to healthcare, or under diagnosis of HCM in black athletes during pre-participation evaluation.[2,3]

**The Influence of Hypertension on Outcome in HCM**

The prevalence of hypertension in our cohort was similar to that reported in the general black and white population[42] and some HCM cohorts,[43] although higher that that reported in other studies of HCM patients.[44] Multivariate analysis identified NSVT and hypertension as independent predictors of primary outcome irrespective of ethnicity, gender or age (Table 4). Non-sustained ventricular tachycardia conferred a 6-fold increased risk of reaching the primary outcome occurring during the study period. Hypertension was present in 40% of the overall cohort and was more prevalent in black patients. Although hypertension had limited influence on the phenotypic expression of HCM (Table 5), it was associated with a 2-fold increased risk of reaching the primary outcome occurring during the study period. The combination of NSVT and hypertension had a significant additive impact, further reducing event-free survival (Figure 1B). These findings are unsurprising given that hypertension adversely affects several disease processes and that NSVT is a well-established risk marker for SCD in HCM. However, the observations nevertheless have important implications for the HCM population given the considerable overlap between hypertension and HCM in clinical practice, underscoring the need for good BP control in HCM patients.

**Study Limitations**

It is possible that a small proportion of patients with genuine hypertensive heart disease were misclassified as having HCM. However, the similarities between the hypertensive and normotensive groups of both ethnicities (Table 5) and the lack of any reversal of the ECG and echocardiographic anomalies despite good BP control in the great majority of subjects make this less likely.[39,40] The additive effect of hypertension on mortality in patients with HCM was probably underestimated by this study, as the great majority of hypertensive patients were well-controlled. The authors appreciate that numbers in this study were small, which may limit the degree to which our outcome findings can be generalized to the entire population of black patients with HCM or to black patients with differing ethnic origins. Finally the natural history of HCM reported in this study refers only black patients who were referred and treated in tertiary referral centers.

**CONCLUSION**

Ethnicity appears to be an important determinant of the phenotypic expressions of HCM. Apical and concentric LVH are more common in black patients and, coupled with a higher incidence of hypertension, may potentially contribute to a lower detection rate for HCM in the black population. T-wave inversion is almost universal in black patients with HCM, suggesting the need for comprehensive investigation and follow-up of black individuals exhibiting marked repolarization anomalies, regardless of co-existing hypertension. Our results indicate that HCM, in isolation, is associated with a relatively benign course in black patients. However, our results suggest that concomitant hypertension may have a negative impact on mortality and highlight the importance of good BP control in all patients with HCM.

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**Competing Interests:** None.

**Ethics Approval:** Ethical approval was granted by the local research ethics committee in accordance with the Declaration of Helsinki and patients provided oral consent for their anonymized data to be used for this study.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

**Data sharing statement:** All additional unpublished information is kept on a secure server in the institution and only available to the first, second and senior authors of the manuscript.

STROBE Statement—checklist of items that should be included in reports of observational studies

|  |  |  |
| --- | --- | --- |
|  | Item No | Recommendation |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract **Page 1** |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2** |
| Introduction | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported **Page 3** |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses **Page 3** |
| Methods | | |
| Study design | 4 | Present key elements of study design early in the paper **Pages 3-7** |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Pages 3-7** |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  **Pages 3-7**  *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| (*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **N/A**  *Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Pages 3-7; page 23** |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Pages 5-7** |
| Bias | 9 | Describe any efforts to address potential sources of bias **Page 5** |
| Study size | 10 | Explain how the study size was arrived at **Page3** |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page7** |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding **Page 7** |
| (*b*) Describe any methods used to examine subgroups and interactions **Page 7** |
| (*c*) Explain how missing data were addressed **Page 7** |
| (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **N/A**  *Case-control study*—If applicable, explain how matching of cases and controls was addressed  *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| (*e*) Describe any sensitivity analyses **N/A** |

Continued on next page

|  |  |  |
| --- | --- | --- |
| Results | | |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 3; page 7** |
| (b) Give reasons for non-participation at each stage |
| (c) Consider use of a flow diagram |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Pages 8-10** |
| (b) Indicate number of participants with missing data for each variable of interest |
| (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Page 5** |
| Outcome data | 15\* | *Cohort study*—Report numbers of outcome events or summary measures over time **Pages 15-16** |
| *Case-control study—*Report numbers in each exposure category, or summary measures of exposure |
| *Cross-sectional study—*Report numbers of outcome events or summary measures |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 8-20** |
| (*b*) Report category boundaries when continuous variables were categorized |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Pages 18-20** |
| Discussion | | |
| Key results | 18 | Summarise key results with reference to study objectives **Pages21-23** |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 23** |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Pages 23** |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results **Page 23** |
| Other information | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page24** |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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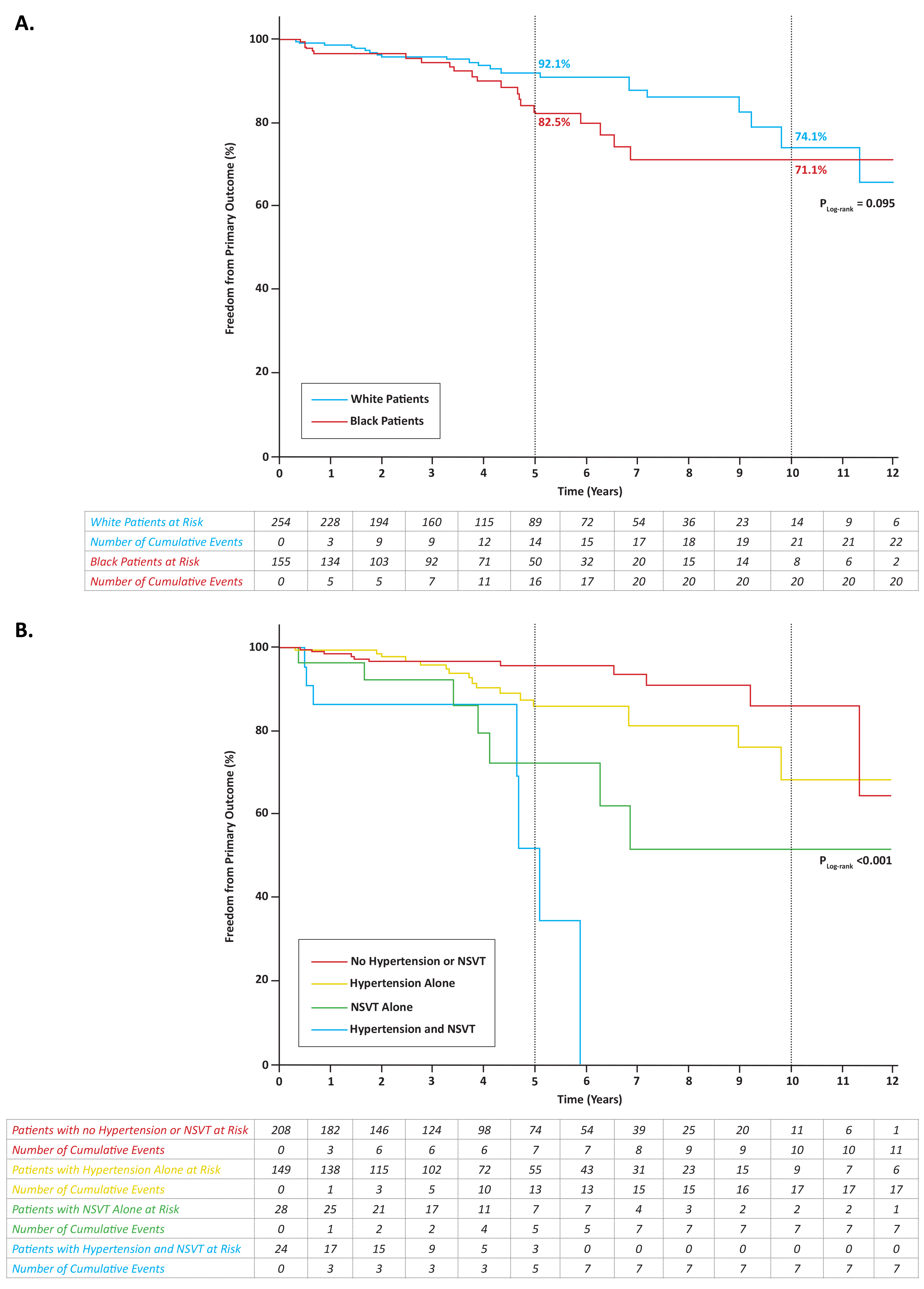
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**FIGURES AND FIGURE LEGENDS**



**Figure 1.** Kaplan-Meier curves illustrating freedom from the primary outcome during the study. A: according to ethnicity; B: According to the presence or absence of non-sustained ventricular tachycardia and/or hypertension, in various combinations, for the overall cohort of black and white patients eligible for survival analysis (n=409). NSVT indicates non-sustained ventricular tachycardia.