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EXCESS MORTALITY AND SEX DIFFERENCES IN OUTCOME IN HYPERTROPHIC CARDIOMYOPATHY: A EUROPEAN MULTICENTRE STUDY

Presentata da:

Dr. Massimiliano Lorenzini

Coordinatore Dottorato **Supervisore**

Prof. Gaetano Domenico Gargiulo Prof. Claudio Rapezzi

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ABSTRACT

Background. Contemporary survival studies in hypertrophic cardiomyopathy (HCM) have shown that the prognosis for most individuals with the disease is much better than described previously, but it remains unclear whether HCM conveys an excess mortality when compared to the general population.

Methods. We conducted a retrospective, multicentre longitudinal cohort study of adult HCM patients from 7 European centers. To compare survival to the general population standardized mortality ratios (SMR) were calculated using data from Eurostat stratified by study period, country, sex and age, using a composite endpoint (all-cause mortality, sudden cardiac death (SCD) equivalent, and heart transplantation).

Results. The study population consisted of 4893 patients (mean age 49.2 ± 16.4 years; 64% male). After a median follow up of 6.1 years (IQR 3.0-9.8), 796 (16.3%) patients reached the composite endpoint. HCM had an excess mortality compared to the general population (SMR 2.23 (95% Confidence Interval (CI):1.66-2.94)). Females were older at presentation, more symptomatic at baseline (NYHA III/IV: 17.1% vs 7.5%) and more likely to have left ventricular outflow tract obstruction and atrial fibrillation. Female patients had a greater excess mortality than males (SMR 2.87 (95% CI: 2.57-3.19) vs 1.92 (95% CI: 1.76-2.11); p<0.001). Excess mortality in females was present throughout the age spectrum while mortality in male patients after the age of 65 years was similar to the normal population. Female sex was independently associated with a worse prognosis in the multivariable model for the primary composite endpoint (HR 1.19, 95% CI:1.06-1.30;p=0.007) and HF death or transplantation (HR 1.44, 95% CI:1.25-1.59;p<0.001), but not SCD or equivalent.

Conclusions. HCM is associated with a significant excess mortality throughout the life course. Women have a worse prognosis that is at least partly due to an excess HF mortality.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common genetic heart disease with a prevalence of at least 1 in 500 (1). The diagnosis is based on the presence of haemodynamically unjustified significant left ventricular (LV) hypertrophy (≥15mm on echocardiography or cardiac magnetic resonance), even though a positive family history lowers the diagnostic threshold (2). Approximately 50% of patients carry a mutation in a gene encoding a sarcomeric protein that is inherited as an autosomal dominant trait with incomplete prevalence (3). *MYH7* and *MYBPC3,* that encode components of the thick-filament, are the two most commonly responsible genes with a combined relative prevalence of 60-70%. Almost all remaining genotype-positive cases are due to mutations in 6 other sarcomeric genes (*TNNT2, TPM1, MYL2, MYL3, TNNI3* and *ACTC1*) (4–7). Phenotypic heterogeneity is well established in HCM with significant phenotype variation even within the same family, probably due to genetic and possibly acquired modifiers (6). Various attempts to establish genotype-phenotype correlations have been unsuccessful, but emerging evidence suggests a more aggressive phenotype in *MYH7* HCM, with a younger age at presentation and a higher heart failure (HF) mortality (7). Research into novel disease-causing genes is ongoing, but novel genes account only for a modest proportion of 'gene-negative' patients. In fact, a polygenic substrate is probably responsible for the remaining ~50% of HCM patients in whom a mutation in the main 8 sarcomeric genes is not found (8). It has however been quite well established that HCM patients with sarcomeric mutations have an overall worse prognosis compared to those whithout (6).

In HCM, LV hypertrophy is asymmetric in most cases, but can also be concentric or predominately apical (9). The associated mitral valve abnormalities (elongated leaflets and anteriorised antero-lateral papillary muscle (10)), along with the hypertrophy of the basal septum, lead to systolic anterior movement of the mitral valve leaflets, a dynamic LV outflow tract (LVOT) obstruction and, in most cases, a posteriorly directed mitral regurgitation (11). A

significant LVOT obstruction can be documented in around 30% of patients in resting conditions, and up to 70% on exercise echocardiography (12). It is responsible for a reduced exercise tolerance in most patients, but is also associated with an overall worse prognosis due to HF and sudden cardiac death (SCD) (13, 14). Long-term data support the use of surgical myectomy to improve HF symptoms and probably prognosis (15), while alcohol septal ablation should be reserved for patients who are not surgical candidates since it improves symptoms, but some concerns over long-term risk of ventricular arrhythmias persists (16).

LVOT obstruction however is not the only pathophysiological mechanism leading to HF in HCM. Diastolic dysfunction is a hallmark of HCM and has a complex pathogenesis that includes a combination of abnormal LV relaxation, abnormal intracellular calcium homeostasis and reduced chamber compliance (17). In some cases with a 'restrictive pathophysiology', no significant LVOT obstruction is present and LV ejection fraction is preserved, and a severe diastolic function is the prominent HF mechanism (18).

A subgroup of 3-5% patients go on to develop 'burn-out' HCM, with progressive LV remodelling, systolic dysfunction, extensive fibrosis (19) and wall thinning (20, 21). Prognosis in this subgroup is grim with a high mortality due mainly to refractory HF, but also SCD (20, 21). The pathogenesis of 'burn-out' HCM remains unclear, but based on the presence of large areas of transmural scar it has been suggested that microvascular ischemia has a prominent role (19–21). The only factors that have been associated with this disease progression are a family history of 'burn-out' HCM (21) and a higher − albeit modest − prevalence multiple sarcomeric mutations (13%) (22).

Atrial fibrillation has a prevalence of around 20% in HCM, plays a prominent pathophysiological role and has historically been considered a turning point in the natural history of the disease (23–25). This is due to the fact that it is often associated with the

occurrence (or worsening) of HF as the loss of atrial contribution to LV filling is poorly tolerated in these patients. It is also associated with a significant thromboembolic risk mandating anticoagulation (26, 27). However, a recent report suggests that the combination of an aggressive rhythm-control strategy and a low threshold for anticoagulation have significantly reduced its impact on disease-related morbidity and mortality (28).

Early HCM cohort studies reported a high mortality due to SCD and HF but were limited by a significant selection bias (29). Due to increased physician awareness, improved imaging techniques and systematic family screening, the number of mildly affected patients in contemporary cohorts has increased significantly and it is now well established that HCM has an extremely heterogeneous natural history (29–34). This ranges from young patients who experience SCD or develop refractory HF, to patients who are diagnosed incidentaly, remain completely asymptomatic throughout their lifetime and die of an unrelated cause. Contemporary management, that includes use of implantable defibrillators (ICD) (35, 36), improved SCD risk stratification (37), surgical myectomy (15) and early anticoagulation for atrial arrhythmias, has undoubtedly improved outcomes compared to the early cohorts, but a significant number of patients still experience HCM-related morbidity and mortality. In fact, whether HCM actually conveys an excess mortality compared to the general population remains to be established since the issue has only been investigated in small, selected subgroups (15, 32, 33, 38).

The presence of sex differences in HCM has been known for some time (39), with a male predominance and important baseline clinical differences, but it has only recently been suggested that female sex is associated with a worse survival (40, 41). The pathophysiology underlying this outcome difference remains to be investigated.

AIMS

1) Too compare the survival of patients with HCM in a large multicentre European cohort with that observed in the general population using contemporaneous country, age and sex-stratified European mortality data.
2) To investigate the presence of sex-related differences in baseline clinical profile, survival and mode of death.

METHODS

Study design and overview

The study was carried out using data from a retrospective, multicentre longitudinal cohort − the Hypertrophic Cardiomyopathy Outcome Investigators (www.HCMRisk.org)(37). The study conforms to the principles of the Helsinki declaration. The investigators from each centre guarantee the integrity of data from their institution.

Study population and participating centres

The study cohort consisted of all consecutive HCM patients with valid follow up who were evaluated between 1980 and 2013 at seven European centres: (i) The Heart Hospital, London, UK; (ii) A Coruña University Hospital, A Coruña, Spain; (iii) Unit of Inherited Cardiovascular diseases, 1st Department of Cardiology, University of Athens, Greece; (iv) Institute of Cardiology, Alma Mater University of Bologna, Italy; (v) University Hospital Virgen de la Arrixaca, Murcia, Spain; (vi) Monaldi Hospital, Università della Campania "Luigi Vanvitelli", Italy; and (vii) Hospital Universitario Puerta del Hierro, Madrid, Spain. Data from the Hypertrophic Cardiomyopathy Outcome Investigators cohort have been reported in other studies (26, 37, 42–45). Only adult patients (≥16 years of age) were included. HCM was defined as a maximum LV wall thickness ≥15mm unexplained solely by loading conditions (2) or in accordance with published criteria for the diagnosis of disease in relatives of patients with unequivocal disease (46). Patients with known inherited metabolic diseases or syndromic causes of HCM were excluded.

Patient assessment and data collection

Patients were reviewed every 6–12 months or earlier if there was a change in symptoms. At presentation, all patients underwent clinical assessment, pedigree analysis, physical

examination, resting and ambulatory electrocardiography (ECG), and transthoracic echocardiography. Each centre collected data independently using the same methodology.

Definition of baseline variables

Family history of sudden cardiac death (SCD) was defined as a history of sudden cardiac death in one or more first-degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post- or antemortem diagnosis)(14). Maximum left ventricular (LV) wall thickness was defined as the greatest thickness in the anterior septum, posterior septum, lateral wall, and posterior wall of the LV, measured at the level of the mitral valve, papillary muscles, and apex in the parasternal short-axis plane using 2-D echocardiography (47). LV ejection fraction was calculated using the Teichholz method (48). The left atrial (LA) diameter was determined by M-Mode or 2D echocardiography in the parasternal long axis plane (49). The maximum LV outflow gradient was determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three- and five-chamber views. Peak outflow tract gradients were determined using the modified Bernoulli equation (gradient = $4V^2$, where V is the peak aortic outflow velocity on continuous wave Doppler) (14). Non-sustained ventricular tachycardia was defined as ≥3 consecutive ventricular beats at a rate of ≥120 bpm and <30 s in duration on Holter monitoring (minimum duration 24 hours) at or prior to first evaluation (50). Syncope was defined as a history of unexplained syncope at or prior to first evaluation (49).

Outcomes

A composite endpoint was used for the main survival analysis, consisting of all-cause mortality, SCD or equivalent (aborted SCD, appropriate implantable cardioverter defibrillator (ICD) shock therapy) and heart transplantation. The cause of death was ascertained by experienced cardiologists at each centre using hospital and primary health care records, death certificates,

post-mortem reports, and interviews with witnesses (relatives and physicians). SCD was defined as witnessed sudden death with or without documented ventricular fibrillation or death within one hour of new symptoms or nocturnal deaths with no antecedent history of worsening symptoms (47). Successfully resuscitation from ventricular fibrillation or ventricular tachycardia during follow-up and appropriate ICD shock therapy were considered equivalent to SCD (13, 50–54), but anti-tachycardia pacing was not. Data on aborted SCD or sustained ventricular tachycardia (at a rate of ≥120 beats per minute lasting >30 seconds) preceding the presentation were collected, but not included in the study end-point. Other cardiovascular (CV) death included stroke, heart failure deaths and procedure-related deaths. Heart transplantation was considered equivalent to death from heart failure. The follow-up time for each patient was taken to be the time from diagnosis to the primary composite endpoint, end of study period or last follow-up date. Patients who were alive at the end of study period or who were lost to follow-up were treated as censored.

Ethical approval

Patients at A Coruña University Hospital (Spain), 1st Department of Cardiology, University of Athens (Greece), University Hospital Virgen de la Arrixaca (Spain), and Monaldi Hospital (Italy) provided written informed consent. Data collection at The Heart Hospital (UK) and Hospital Universitario Puerta de Hierro (Spain) was approved by the local ethics committees. The ethics committee at the Institute of Cardiology at the University of Bologna (Italy) were informed, but approval was not required under local research governance arrangements.

Statistical analysis

Statistical analyses were carried out with IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA) and STATA version 12. For descriptive statistics, variables are expressed as mean ± standard deviation (SD), median (interquartile range, IQR) or counts and

percentages as appropriate. The follow-up time for each patient was calculated from the date of first evaluation at participating centres to the date of the relevant endpoint or to the date of their most recent evaluation. For comparisons between groups, the chi-square test was used for categorical variables and Student's t-test or Mann–Whitney for continuous variables, as appropriate.

Standardized mortality ratios (SMR) were calculated as actual deaths/expected deaths ratio using data from Eurostat (55) extracted on 18/08/17. Eurostat is the statistical office of the European Union that supplies the public and European institutions with data and statistics with the objective of defining, implementing and analyzing European Union policies. Expected mortality was based on the mortality rates from the appropriate period for each centre and was stratified by country, sex and age at the end of follow up. Patient age at the end of follow up was used for the calculation of expected mortality based on yearly mortality rates by age in the general population. For the calculation of expected deaths, each patient contributed person-years to the different age categories he/she was assigned to from presentation and throughout follow up (e.g. a patient who presented aged 20 and died at 32 contributed 5 years follow up to the 20-25 age group, 5 to the 25-30 age group, and 2 to the 30-35 age group). SMRs were calculated using the main combined study endpoint; 95% confidence intervals and comparisons were estimated by Poisson regression. Indirectly adjusted mortality rates were obtained by multiplying the crude rate of the standard population by the SMRs and 95% confidence intervals were calculated as previously described (56).

Cox proportional hazards modelling

Univariable and multivariable Cox regression models were fitted for each endpoint and tested for non-linearity of continuous predictors by inclusion of quadratic terms. The correct functional forms of continuous predictor variables were also assessed by visual analysis of

cumulative plots of Martingale residuals. Candidate predictor variables were selected based previous description of an association with the study endpoint or pathophysiological plausibility. Sample size guidelines for Cox regression suggest that at least 10 events per candidate variable are required to obtain unbiased parameter estimates (coefficients and HRs) with correct standard errors (57). The proportional hazards assumption was verified using Schoenfeld residuals (58). To determine the degree of bias due to missing data, the characteristics of patients with missing information were compared with those with complete information. Logistic regression was used to identify the predictors of missingness. Data were assumed to be missing at random, and values for the missing predictors were imputed using multiple imputation techniques based on chained equations (59). All predictors of missingness were included in the multiple imputation model, together with the outcome, potential predictors and the estimate of the cumulative hazard function (60). The number of imputations was based on the percentage of missingness and the estimates were combined using Rubin's rules (61).

RESULTS

The study population consisted of 4893 patients that were followed for a total of 33,717.3 person-years. **Table 1** reports the baseline characteristics of the study population and **Figure 1** shows the distribution by age at presentation.

Outcomes

After a median follow up of 6.1 years (IQR 3.0-9.8), 796 patients (16.3%) reached the composite primary endpoint. Of these, 263 patients (5.4%) met the SCD or equivalent endpoint (137 (2.8%) SCD, 96 (2%) appropriate ICD shocks and 30 (0.6%) aborted SCD); 200 (4.1%) met the heart failure (HF) death or equivalent endpoint (123 (2.5%) actual HF death, 77 (1.6%) cardiac transplant); 103 (2.1%) died of other CV causes; 210 (4.3%) died from non-CV causes and 20 (0.4%) of unknown causes. During follow up 390 (8%) patients underwent septal reduction treatment [282 (5.8%) septal myectomy, 93 (1.9%) alcohol septal ablation and 15 (0.3%) both procedures].

Overall, patients with HCM had an excess mortality compared to the general population (SMR 2.23 (95% CI: 1.66-2.94). **Figure 2A** shows the calculated SMR by age, with values >1 indicating excess mortality compared to the general population; **Figure 2B** reports the indirectly adjusted mortality rates by age in the study population. The main cause of death in younger patients was SCD (or equivalent), but this accounted for progressively smaller percentage of total deaths with advancing age, while HF death or cardiac transplantation accounted for a similar proportion of events throughout the age spectrum. Other CV and non-CV causes increased progressively after the age of 45 years (**Figure 3**). **Figure 4** shows the event rates according to age at presentation. The rate of SCD varied with age, while the rate of HF death or transplantation, other CV and non-CV death increased after the age of 65.

Sex differences

Male and female patients had a different baseline clinical profile (**Table 2**). Females were older at presentation, more symptomatic (NYHA III/IV: 17.1% vs 7.5%) and more likely to have a family history of SCD and a history of syncope. LV wall thickness and systolic function were similar in men and women, but females were more likely to have LVOT obstruction. Women were also more likely to have or develop atrial fibrillation (AF) during the study (**Table 3**) and have a history of hypertension.

Female patients had a greater excess mortality than males (SMR 2.87 (95% CI: 2.57-3.19) vs 1.92 (CI 1.76-2.11); p<0.001). Excess mortality in females was present throughout the age spectrum while mortality in male patients after the age of 65 years was similar to the normal population (**Figure 5**). **Figure 6** reports the event rates by sex and age at presentation.

More than 10 events per predictor were present for each of the multivariable models. Female sex was independently associated with a worse prognosis in the multivariable model for the composite study endpoint (HR 1.19, 95% CI: 1.06-1.30; p=0.007. **Table 4**) and HF death or transplantation (HR 1.44, 95% CI: 1.25-1.59; p<0.001. **Table 5**), but not SCD or equivalent (**Table 6**). In the multivariable model for the primary composite endpoint septal myectomy had a protective effect, but no interaction between sex and septal myectomy was present (HR 1.06, 95% CI 0.53-2.14; p= 0.862).

DISCUSSION

In a large, international multicentre cohort we show that adult patients with HCM have an excess mortality compared to the general population. Female patients have a greater excess mortality than men, and this is at least partly due to heart failure.

Outcomes in HCM

Previous studies have described HCM-related mortality in specific age groups (30–32), and a very recent report from the SHaRe registry (62) described the outcomes in a large multicentre HCM population in greater detail, but this is the first and largest study to compare survival in adult patients of all ages with contemporaneous national survival data from European countries. Our findings are consistent with previous studies showing that SCD is the predominant cause of death in younger adults, whereas HF deaths occurs throughout the life course. The rate of SCD is in line with previous reports and our data confirm the role of known important risk factors (47, 49, 51, 52). Overall, we confirmed that mortality is lower than reported in historical cohorts (29) and this is probably due to a significant selection bias. However, our data show that – even in the modern era – a diagnosis of HCM confers an excess mortality compared to the normal population.

Most previous studies comparing survival in HCM with the general population focused on small subgroups of HCM patients (15, 32, 33, 38) and cannot be used to compared our findings. The only comparable data from the SHaRe registry (62), found that HCM patients treated in the US had a worse survival than the general population only in the younger (age 20-29) and older age groups (age 50-69). No survival difference compared to the general population was found when analysing the small subgroup (370 patients) with ‘non-familial HCM’ (defined as having negative genetic testing and no family history of HCM). The authors carried out an elegant analysis of lifetime disease burden in relation to genotype in mildly smaller cohort than

the present one, but the survival comparison with the general population was rudimentary. The incident Kaplan-Meier derived mortality over a 10-year period in the HCM cohort was simply compared to age-adjusted mortality in the overall US population. The analysis did not adjust for factors that significantly impact mortality such as sex, geographic location and study period, was only carried out in the subgroup of US patients (n=2029) and only up to the age of 69. These differences explain the fact that in a larger cohort and adjusting for more confounders, we documented an excess mortality throught the age spectrum.

Sex differences in HCM

A male predominance around 60% is a constant finding in large HCM cohorts (39, 41, 62–64) and significant sex-related differences in clinical profile at presentation have been known for some time. In line with our own observations, female HCM patients have been previously found to be older at presentation, more symptomatic and with a greater degree of LV outflow tract obstruction (39–41). Regarding outcome, recent reports in Chinese and North American populations have reported higher all-cause mortality in female patients (40, 41), in contrast to previous studies that had shown an excess HF and stroke mortality in women, but no difference in overall survival (39). In this study, we show that the excess mortality compared to the general population is greater in women than in men, and that this excess persists into the later decades of life in women in contrast to men over the age of 65 who have a similar mortality to the general population. With respect to the mode of death, SCD predominates in younger men whereas HF is the major cardiovascular cause of death in older women.

Comparing our findings to the only other large study that specifically investigated sex differences in HCM some significant study design differences should be noted. The Mayo Clinic data (40) originate from a single referral centre, where a third of patients underwent septal reduction therapy (compared to 8% in our cohort). The study endpoint used was all-

cause mortality and did not including SCD and HF death equivalents, thereby only partially capturing the HCM-related events throughout the long study period (1975-2012) during which treatment has improved significantly. Finally, cause of death was not reported. Our study confirms these findings, clarifying that sex-related differences in outcome are part of the disease natural history and not a difference in response to treatment. Importantly, our data also clarifies that the worse prognosis in female patients is at least partially due to a greater HF mortality, but unfortunately based only on the baseline phenotypic variables, our data does not allow us to establish the exact pathophysiology of this HF mortality. The available literature does not provide a possible explanation as no significant sex imbalance has been recorded in the available series of HCM patients with 'burn-out' progression and LV systolic dysfunction (18, 21, 22) or those with advanced HF with a preserved EF (18).

The explanation for these sex differences in phenotype and outcome in HCM is not straightforward. The available evidence has started to explain why sex differences exist, but does not help us understand the different phenotype and the worse outcome in female patients. The male predominance and younger age of males at presentation could actually reflect a greater and earlier penetrance in males, as suggested in some small series of patients with sarcomeric mutations (65–68), however in larger series of patients with a clinical diagnosis of HCM, female sex has been associated with a higher prevalence of sarcomeric mutations on genetic testing (62, 69, 70). Murine models also suggest an earlier phenotypic expression in males (71–73), and phenotype (consisting of LV hypertrophy, function and fibrosis) appears to be the result of a complex interaction between sex, sex hormones, genotype (specific sarcomeric mutation, but also other genes such as androgen receptors) and hypertrophic stimuli (71–77). Mouse studies also suggest a different electrophysiological phenotype according to sex, but this does not help explain our findings since male mice have been found to be more predisposed to ventricular arrhythmias (71, 78), and the observed survival difference in patients

does not seem to be related to SD in both our data or previously published cohorts (39, 41). It is interesting to note however, that while in the general population the risk of atrial fibrillation is higher in males (79), the opposite appears to be true in HCM (45), and this could be related to higher LV filling pressures (E/e') (40). Female sex is not however associated with a greater thrombo-embolic risk in HCM (26).

In the broader context of HF of any aethiology, limited data is available regarding sex differences, but some large datasets have shown a worse survival in male patients (80). This has been attributed to the greater prevalence of LV systolic dysfunction in males, while females have been found to be older and more frequently have a preserved ejection fraction (81).

Non-biological factors may also contribute to sex differences in HCM outcome, since women have been shown to have a reduced awareness of cardiovascular risk (82), a longer delay in seeking medical attention in acute coronary syndromes (83, 84) and have less access to screening programs (85, 86).

CONCLUSIONS

HCM is associated with a significant excess mortality throughout the course of life. Women have a worse prognosis that is at least partly due to an excess HF mortality.

In spite of the undoubted success of modern treatments for HCM, the implications of our findings are that further research into the causes of this excess mortality is required. Areas of interest include better risk stratification for both sudden and HF-related death as well as systematic exploration of therapies with the potential to attenuate or prevent adverse ventricular remodelling.

LIMITATIONS

Due to the historic nature of a considerable part of the study cohort, baseline cardiac MRI data were not collected in this dataset. Information on genotype was not collected in the present dataset and this leaves a number of unanswered questions that will require dedicated studies to investigate the relationship between genotype, sex and outcomes in HCM.

A degree of survivor bias cannot be excluded in the present study, since it is possible that some patients died prior to evaluation in a referral centre or clinical diagnosis. Finally, all the participating centres are longstanding HCM referral units and a degree of referral bias is possibly present.

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TABLES

Table 1: Baseline characteristics of the study population (n=4893)

Age at presentation (yrs)		49.2 ± 16.4
Male sex		3126 (63.9%)
Country:	Greece	566 (11.6%)
	Spain	1497 (30.6%)
	Italy	733 (15%)
	UK	2097 (42.9%)
Family history of sudden death		1127/4752 (23.7%)
Previous VF/sustained VT		134 (2.7%)
NYHA class	I	2560 (54.6%)
	II	1613 (34.4%)
	III/IV	514 (11%)
Unexplained syncope		725/4846 (15%)
Non-sustained VT on Holter		924/4204 (22%)
ICD		816 (16.7%)
Previous atrial fibrillation		653 (13.3%)
Hypertension		1446/4783 (30.2%)
Maximum LV wall thickness (mm)		19 (IQR 16-22)
LV end-diastolic diameter (mm)		44.8 ± 6.5
LV Ejection fraction ≤50%		396/4428 (8.9%)
Maximum LVOT gradient (mmHg)		9 (IQR 4-50)
LVOT gradient >50 mmHg		1087/4238 (25.6%)
Left atrial diameter (mm)		44.1 ± 7.8

HCM: hypertrophic cardiomyopathy; VF: ventricular fibrillation; VT: ventricular tachycardia; ICD: implantable cardioverter defibrillator; LV: left ventricle; LVOT: left ventricular outflow tract obstruction.

Table 2: Characteristics of the study population according to sex.

		Females (n=1767)	Males (n=3126)	P- value
Age at presentation (yrs)		52.9 ± 17.2	47.1 ± 15.6	<0.001
Follow up duration (yrs)		5.8 (IQR 2.8-9.5)	6.3 (IQR 3.1-9.9)	0.003
Family history of sudden death		467/1709 (27.3%)	660/3043 (21.7%)	<0.001
Previous VF/sustained VT		40 (2.3%)	94 (3%)	0.126
NYHA class	I II III/IV	695 (41.2%) 703 (41.7%) 288 (17.1%)	1865 (62.1%) 910 (30.3) 226 (7.5%)	<0.001
Unexplained syncope		289/1746 (16.6%)	436/3100 (14.1%)	0.020
Non-sustained VT on Holter		296/1496 (19.8%)	628/2708 (23.2%)	0.011
ICD		281 (15.9%)	535 (17.1%)	0.275
Hypertension		616/1732 (35.6%)	830/3051 (27.2%)	<0.001
Maximum LV wall thickness (mm)		18 (IQR 16-22)	19 (IQR 16-22)	0.003
LV end-diastolic diameter (mm)		42.5 ± 6.2	46.1 ± 6.3	<0.001
LV ejection fraction (%)		66 ± 12	65 ± 12	<0.001
LV Ejection fraction ≤50%		8.3%	9.3%	0.251
Maximum LVOT gradient (mmHg)		10 (IQR 4-64)	8 (IQR 4-44)	<0.001
LVOT gradient >50 mmHg		463/1545 (30%)	624/2693 (23.2%)	<0.001
Left atrial diameter (mm)		43 ± 7.6	44.8 ± 7.9	<0.001
AF at baseline or during follow up		591 (33.4%)	939 (30%)	0.014

HCM: hypertrophic cardiomyopathy; VF: ventricular fibrillation; VT: ventricular tachycardia; ICD: implantable cardioverter defibrillator; LV: left ventricle; LVOT: left ventricular outflow tract obstruction; AF: atrial fibrillation.

Table 3. Events during follow up according to sex

	Females (n=1767)	Males (n=3126)	P- value
Septal myectomy	118 (6.7%)	179 (5.7%)	0.180
Alcohol septal ablation	47 (2.7%)	61 (2%)	0.105
Sudden cardiac death (SCD)	36 (2.0%)	101 (3.2%)	na
Aborted SCD	10 (0.6%)	20 (0.6%)	na
Appropriate ICD shock	25 (1.4%)	71 (2.3%)	na
Heart failure death	70 (4.0%)	53 (1.7%)	na
Heart transplantation	36 (2.0%)	41 (1.3%)	na
Other CV death	51 (2.9%)	52 (1.7%)	na
Non-CV death	96 (5.4%)	114 (3.6%)	na
Unknown cause of death	11 (0.6%)	9 (0.3%)	na

ICD: implantable cardioverter defibrillator; CV: cardiovascular.

Table 4: Univariable and multivariable predictors of the primary composite endpoint.

PRIMARY COMPOSITE ENDPOINT (all-cause mortality, transplantation, aborted SCD, appropriate ICD shock)						
	Univariable analysis			Multivariable analysis		
Predictor	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age at presentation (10 yrs)	1.39	1.32-1.45	<0.001	1.34	1.27-1.42	<0.001
Female sex	1.28	1.17-1.37	<0.001	1.19	1.06-1.30	0.007
Previous VF/VT	4.26	3.29-5.5	<0.001	3.82	2.93-4.99	<0.001
NYHA II	1.43	1.21-1.68	<0.001	1.11	0.93-1.31	<0.001
III/IV	3.51	2.92-4.22		2.14	1.74-2.63	
Syncope	1.4	1.17-1.67	<0.001	1.23	1.03-1.48	0.025
EF ≤50%	3.29	2.73-3.95	<0.001	2.11	1.73-2.57	<0.001
MWT (5mm)	1.99	1.35-2.94	0.001	1.30	0.87-1.94	0.201
$[MWT (5mm)]^2$	0.94	0.88-0.98	0.003	0.98	0.94-1.03	0.435
LA diameter (5mm)	1.34	1.29-1.39	<0.001	1.22	1.17-1.28	<0.001
LVOT max (25mmHg increase)	1.06	1.01-1.11	0.011	1.02	0.97-1.07	0.520
AF	1.56	1.36-1.8	<0.001	1.24	1.10-1.36	0.001
NSVT on Holter	1.75	1.49-2.06	<0.001	1.29	1.08-1.54	0.005
Family history of SD	1.12	0.96-1.31	0.157	1.30	1.10-1.54	0.002
Stroke	1.67	1.35-2.07	<0.001	1.24	0.99-1.56	0.059
Hypertension	1.21	1.03-1.41	0.018	1.28	1.15-1.39	<0.001
Septal myectomy	0.63	0.45-0.89	0.009	0.56	0.39-0.80	0.002
ASA	0.78	0.47-1.27	0.312	0.67	0.97-1.07	0.520

Previous VF/VT: previous aborted sudden cardiac death or sustained ventricular tachycardia; EF: left ventricular (LV) ejection fraction; MWT: LV maximum wall thickness (for 5mm increase); LA diameter: left atrial diameter (for 5mm increase); LVOT max: maximum LV outflow tract gradient (for 25mmHg increase); AF: atrial fibrillation at baseline or during follow up; NSVT: non-sustained ventricular tachycardia; SD: sudden death; ASA: alcohol septal ablation.

Table 5: Univariable and multivariable predictors of heart failure endpoint.

HEART FAILURE DEATH OR TRANSPLANTATION						
	Univariable analysis			Multivariable analysis		
Predictor	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age at presentation (10yrs)	1.31	1.20-1.44	<0.001	1.09	0.98-1.21	0.133
Female sex	1.53	1.38-1.65	<0.001	1.44	1.25-1.59	<0.001
Previous VF/VT	3.3	1.88-5.79	<0.001	2.58	1.41-4.71	0.002
NYHA II	1.8	1.24-2.61	<0.001	1.46	0.99-2.16	<0.001
III/IV	9.16	6.46-13.01		4.71	3.15-7.05	
EF ≤50%	7.48	5.52-10.13	<0.001	4.13	2.95-5.79	<0.001
MWT (5mm)	0.95	0.83-1.08	0.429	0.96	0.83-1.11	0.592
LA diameter (5mm)	3.46	1.79-6.70	<0.001	3.13	1.58-6.21	0.001
[LA diameter (5mm)]^2	0.96	0.93-0.99	0.015	0.96	0.93-0.99	0.012
LVOTmax (25mmHg increase)	0.83	0.67-1.02	0.077	0.77	0.62-0.96	0.023
[LVOTmax (25mmHg increase)]^2	1.03	1.00-1.06	0.044	1.04	1.01-1.08	0.020
AF	2.71	2.02-3.63	<0.001	1.08	0.77-1.52	0.656
NSVT on Holter	1.81	1.32-2.49	<0.001	1.18	0.80-1.72	0.400
Hypertension	1.02	0.65-1.29	0.898	1.47	1.24-1.63	0.001
Septal myectomy	0.78	0.41-1.48	0.451	0.52	0.26-1.05	0.069
ASA	1.2	0.53-2.71	0.655	1.08	0.47-2.51	0.851

Previous VF/VT: previous aborted sudden cardiac death or sustained ventricular tachycardia; EF: left ventricular (LV) ejection fraction; MWT: LV maximum wall thickness (for 5mm increase); LA diameter: left atrial diameter (for 5mm increase); LVOT max: maximum LV outflow tract gradient (for 25mmHg increase); AF: atrial fibrillation at baseline or during follow up; NSVT: non-sustained ventricular tachycardia; SD: sudden death; ASA: alcohol septal ablation.

Table 6: Univariable and multivariable predictors of sudden death endpoint.

SUDDEN DEATH, ABORTED SCD OR APPROPRIATE ICD SHOCK						
	Univariable analysis			Multivariable analysis		
Predictor	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age at presentation (10yrs)	0.89	0.83-0.97	0.005	0.89	0.82-0.98	0.016
Female sex	0.57	0.12-0.91	0.010	0.80	0.40-1.10	0.207
Previous VF/VT	10.74	7.84-14.69	<0.001	6.21	4.50-8.86	<0.001
NYHA II	0.96	0.74-1.25	0.946	0.87	0.66-1.16	0.466
III/IV	1.02	0.66-1.56		0.92	0.58-1.46	
EF ≤50%	2.33	1.63-3.32	<0.001	1.80	1.25-2.61	0.002
MWT (5mm)	3.06	1.56-6.02	0.001	2.30	1.16-4.56	0.018
$[MWT (5mm)]^2$	0.91	0.85-0.98	0.013	0.93	0.87-1.00	0.060
LA diameter (5mm)	1.21	1.13-1.30	<0.001	1.16	1.06-1.26	0.001
LVOTmax (25mmHg increase)	1.01	0.93-1.10	0.797	1.05	0.96-1.16	0.289
AF	1.14	0.89-1.46	0.315	0.83	0.62-1.10	0.188
NSVT on Holter	2.62	2.01-3.4	<0.001	2.15	1.62-2.84	<0.001
Family history of SD	1.77	1.37-2.27	<0.001	1.59	1.22-2.07	<0.001
Syncope	2.16	1.64-2.84	<0.001	1.74	1.31-2.32	<0.001
Septal myectomy	0.63	0.34-1.15	0.131	0.57	0.30-1.07	0.081
ASA	0.44	0.14-1.36	0.153	0.52	0.16-1.63	0.260

Previous VF/VT: previous aborted sudden cardiac death or sustained ventricular tachycardia; EF: left ventricular (LV) ejection fraction; MWT: LV maximum wall thickness (for 5mm increase); LA diameter: left atrial diameter (for 5mm increase); LVOT max: maximum LV outflow tract gradient (for 25mmHg increase); AF: atrial fibrillation at baseline or during follow up; NSVT: non-sustained ventricular tachycardia; SD: sudden death; ASA: alcohol septal ablation.

FIGURES

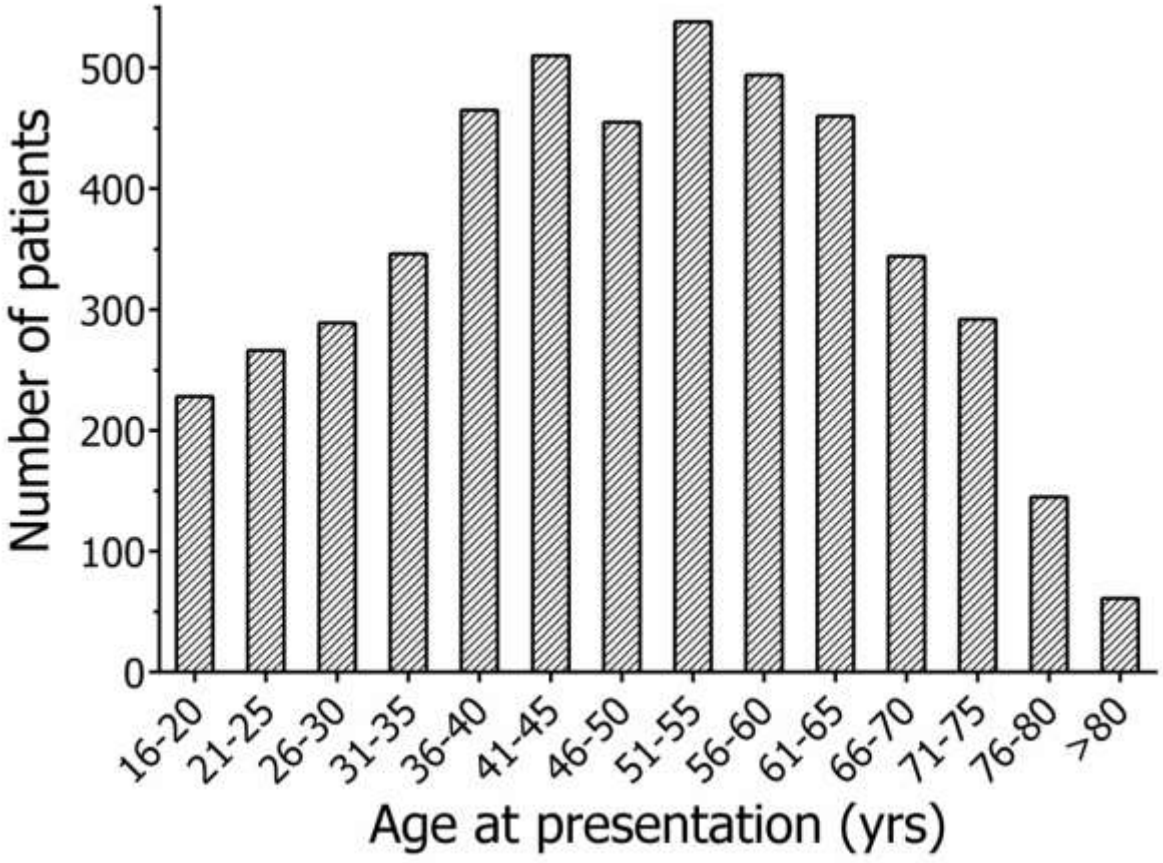

Figure 1: Distribution of study cohort by age at presentation.

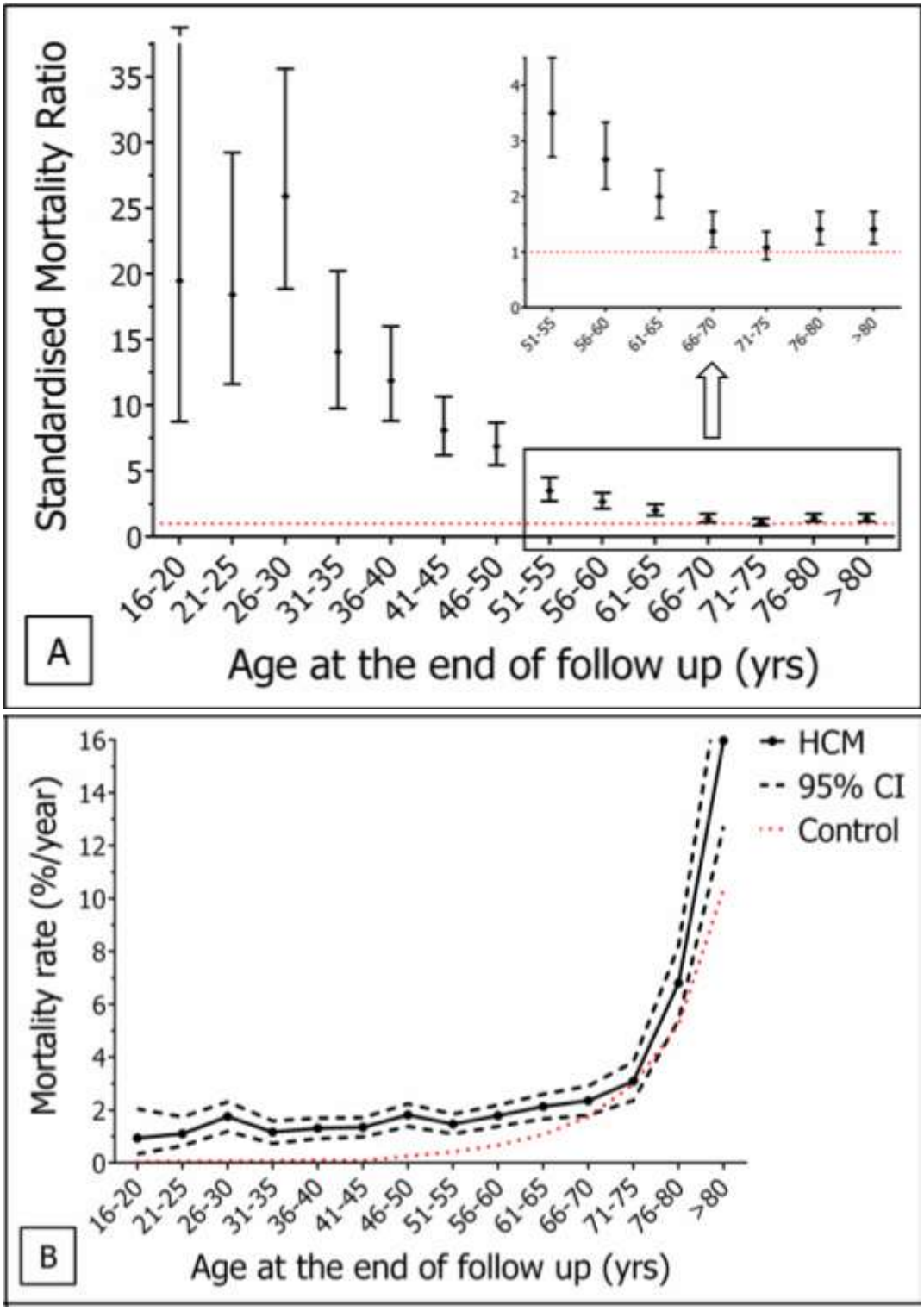

Figure 2: Standardised mortality ratios (SMR) in the study population reported by age (A; values >1 indicate an excess mortality compared to the general population), and indirectly adjusted mortality rates by age in the study population (B). HCM: hypertrophic cardiomyopathy. Age group 16-20 SMR clipped upper CI limit = 43.36. Age group >80 adjusted mortality clipped upper CI limit 19.2%.

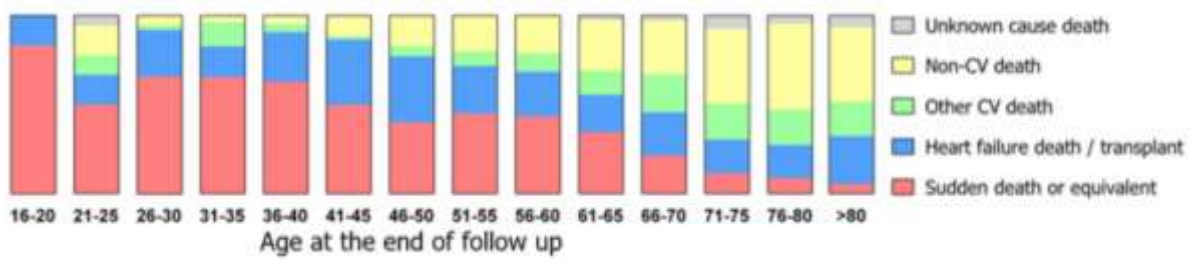

Figure 3: Cause of death in the study population by age group; CV: cardiovascular.

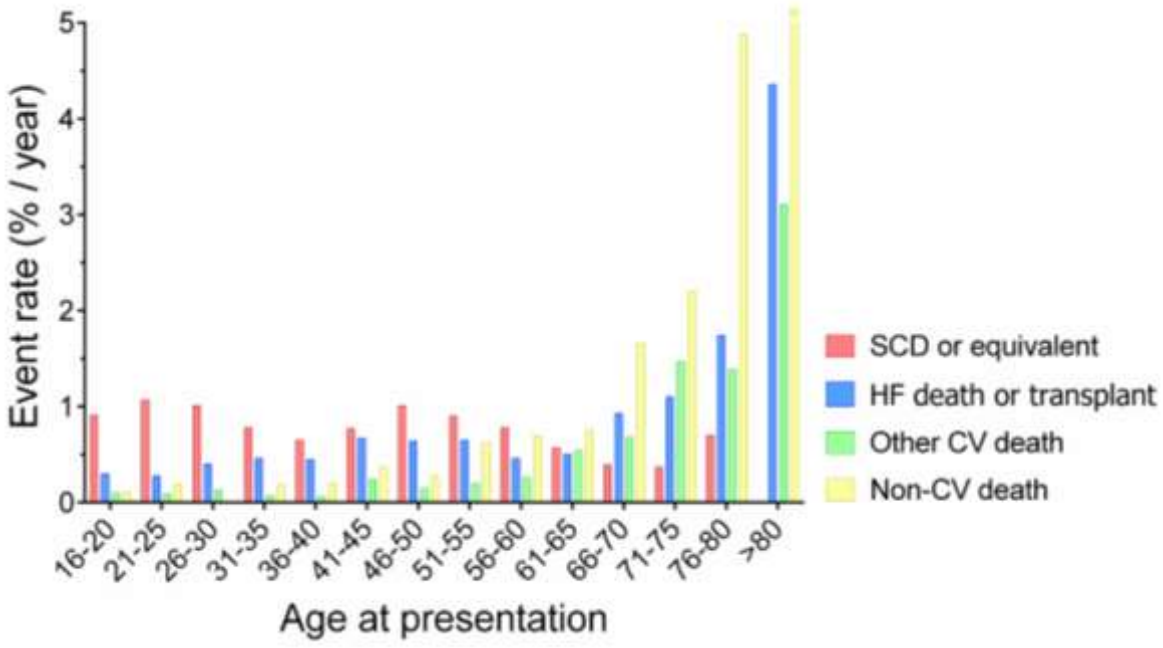

Figure 4: Events rates in the study population according to age at presentation. SCD: sudden cardiac death; HF: heart failure; CV: cardiovascular. Rate of non-CV death in patients aged >80: 6.2%/yr.

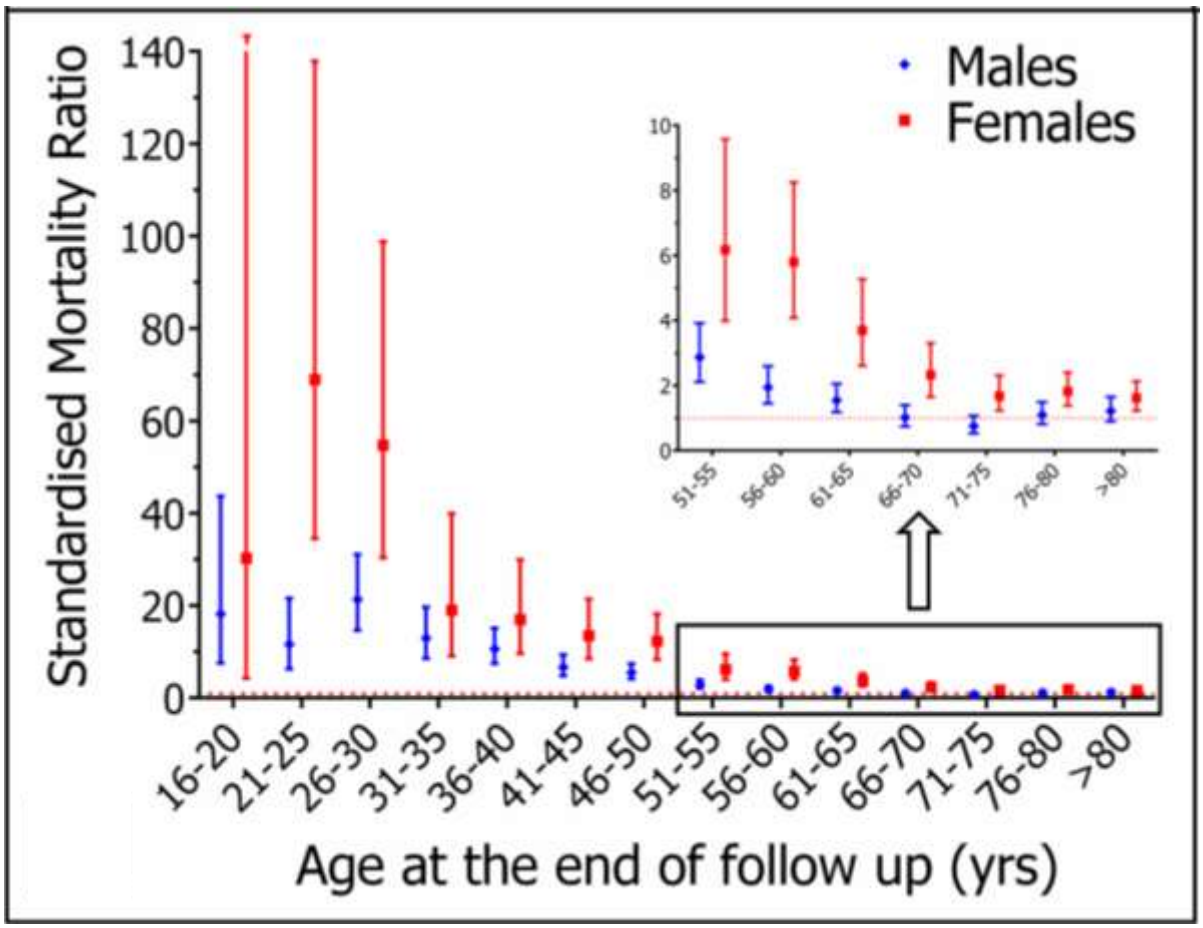

Figure 5: Standardised mortality ratios (SMR) in the study population by age and sex (values >1 indicate an excess mortality compared to the general population). Females aged 16-20: clipped upper CI limit = 215.12.

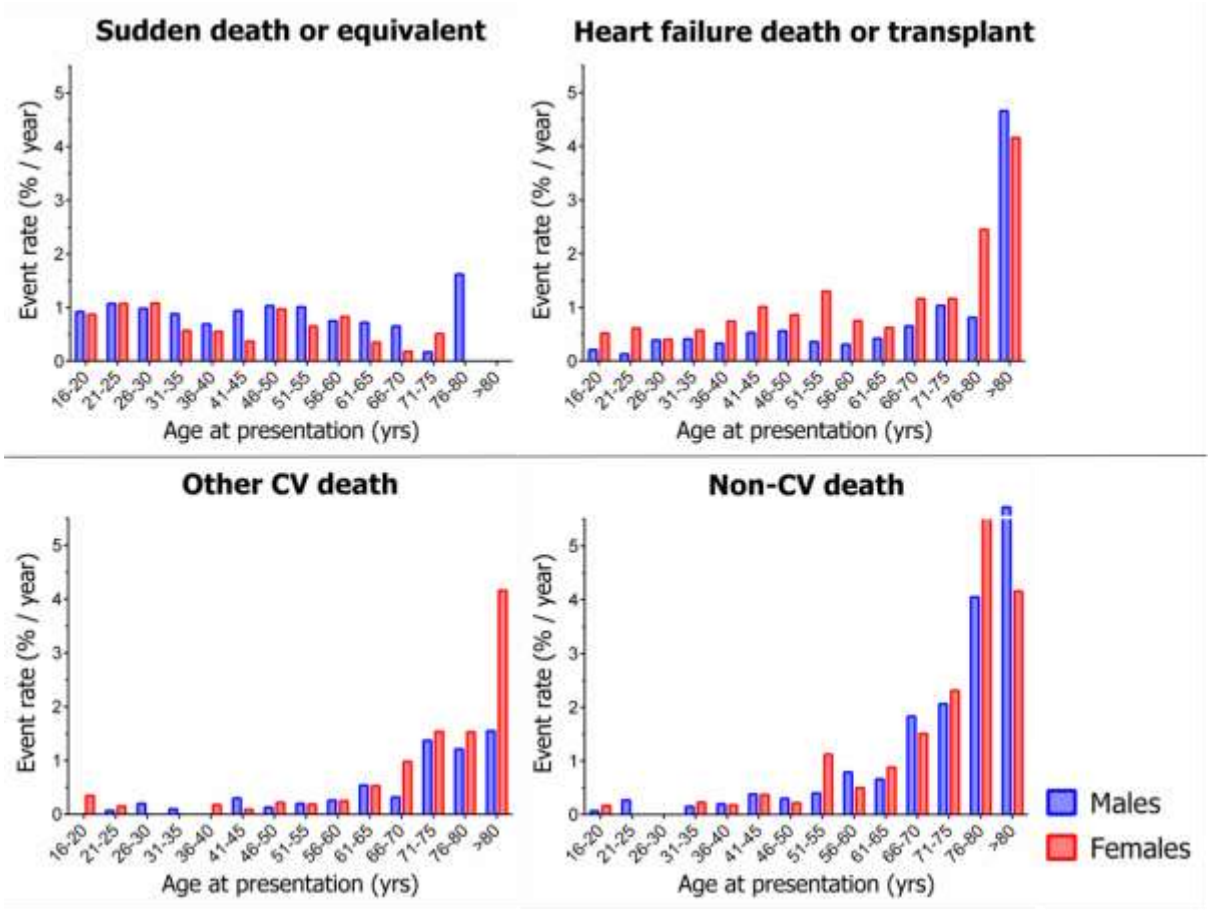

Figure 6: Events rates in the study population by sex, according to age at presentation. CV: cardiovascular.