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Original research

Influence of sex and phenotype on cardiac outcomes in patients with Fabry disease

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ABSTRACT

Objective This study describes the influence of sex and disease phenotype on the occurrence of cardiac events in Fabry disease (FD).

Methods Cardiac events from birth to last visit (median age 50 years) were recorded for 213 patients with FD. Patients were categorised as follows: men with classical FD (n=57), men with non-classical FD (n=26), women with classical FD (n=98) and women with non-classical FD (n=32), based on the presence of classical FD symptoms, family history (men and women), biomarkers and residual enzyme activity (men). Event rates per 1000 patient-years after the age of 15 years and median event-free survival (EVS) age were presented. Influence of disease phenotype, sex and their interaction was studied using Firth's penalised Cox regression.

Results The event rates of major cardiovascular events (combined endpoint cardiovascular death (CVD), heart failure (HF) hospitalisation, sustained ventricular arrhythmias (SVAs) and myocardial infarction) were 11.0 (95% CI 6.6 to 17.3) in men with classical FD (EVS 55 years), 4.4 (95% CI 2.5 to 7.1) in women with classical FD (EVS 70 years) and 5.9 (95% CI 2.6 to 11.6) in men with non-classical FD (EVS 70 years). None of these events occurred in women with non-classical FD. Sex and phenotype significantly influenced the risk of major adverse cardiovascular event. CVD was the leading cause of death (75%) to which HF contributed most (42%). The overall rate of SVA was low (14 events in nine patients (4%)).

Conclusions Sex and phenotype greatly influence the risk and age of onset of cardiac events in FD. This indicates the need for patient group-specific follow-up and treatment.

INTRODUCTION

Fabry disease (FD) is a rare X-linked lysosomal storage disease that is caused by mutations in the *Galactosidase alpha* gene, resulting in reduced alpha-galactosidase A enzyme activity.^{1 2} Accumulation of the enzyme's substrate globotriaosylceramide (Gb3) and its derivatives is the primary trigger for damage and dysfunction of various tissues and organs, including vascular endothelium and the heart.³⁻⁵

Due to the X-linked mode of inheritance, men are generally more severely affected and disease manifestations occur earlier compared with women. In addition, a distinction is made between classical and non-classical disease phenotypes, with significant differences in onset and progression of

symptoms, organ damage and outcome between these two groups. The classical form of FD in men is characterised by greatly reduced or absent alpha-galactosidase A activity, resulting in manifestations in multiple organs, starting from late adolescence.^{6 7} Non-classical disease manifests itself later in adulthood and often affects only the heart.⁸⁻¹⁰

Early cardiac manifestations of FD are bradycardia, shortened PQ interval, low native T1 value on cardiac MRI and, in male patients and a subset of female patients, cardiac hypertrophy.^{11 12} As the disease progresses, conduction abnormalities (CAs), supraventricular arrhythmias, ischaemic heart disease, diastolic and systolic dysfunctions and ultimately overt heart failure (HF), leading to cardiac death, may occur.^{3 13-22} On the other hand, a significant number of patients will remain asymptomatic, even at an advanced age.⁷ Limited evidence is available on the risk and timing of cardiac manifestations and events in different patient groups (ie, men vs women, classical vs non-classical FD phenotype).^{3 23} It is important to generate these data, as it will guide patient-specific follow-up and timing of treatment initiation, risk assessment (eg, for sudden cardiac death (SCD)) and evaluation of new FD therapies that are currently in various stages of development. To answer the open questions, we performed a retrospective study in an FD cohort under follow-up at the Amsterdam University Medical Centres (AUMC), which is unique in both its size, as well as the length of systematic follow-up of patients, providing detailed clinical data on cardiac outcome.

METHODS

Patient and public involvement

This is an observational longitudinal retrospective study, using data from all adult patients with a definite diagnosis of FD (figure 1) that have been under follow-up at any time at the AUMC, the national referral centre for patients with FD in the Netherlands (table 1).

Data collection

Patients were divided into four groups: men with classical FD, men with non-classical FD, women with classical FD and women with non-classical FD, based on the presence of classical FD symptoms (cornea verticillata, acroparesthesia or angiokeratoma), family history or known mutation-phenotype associations (men and women) and biomarkers and residual alpha-galactosidase A activity (men)^{7 24}



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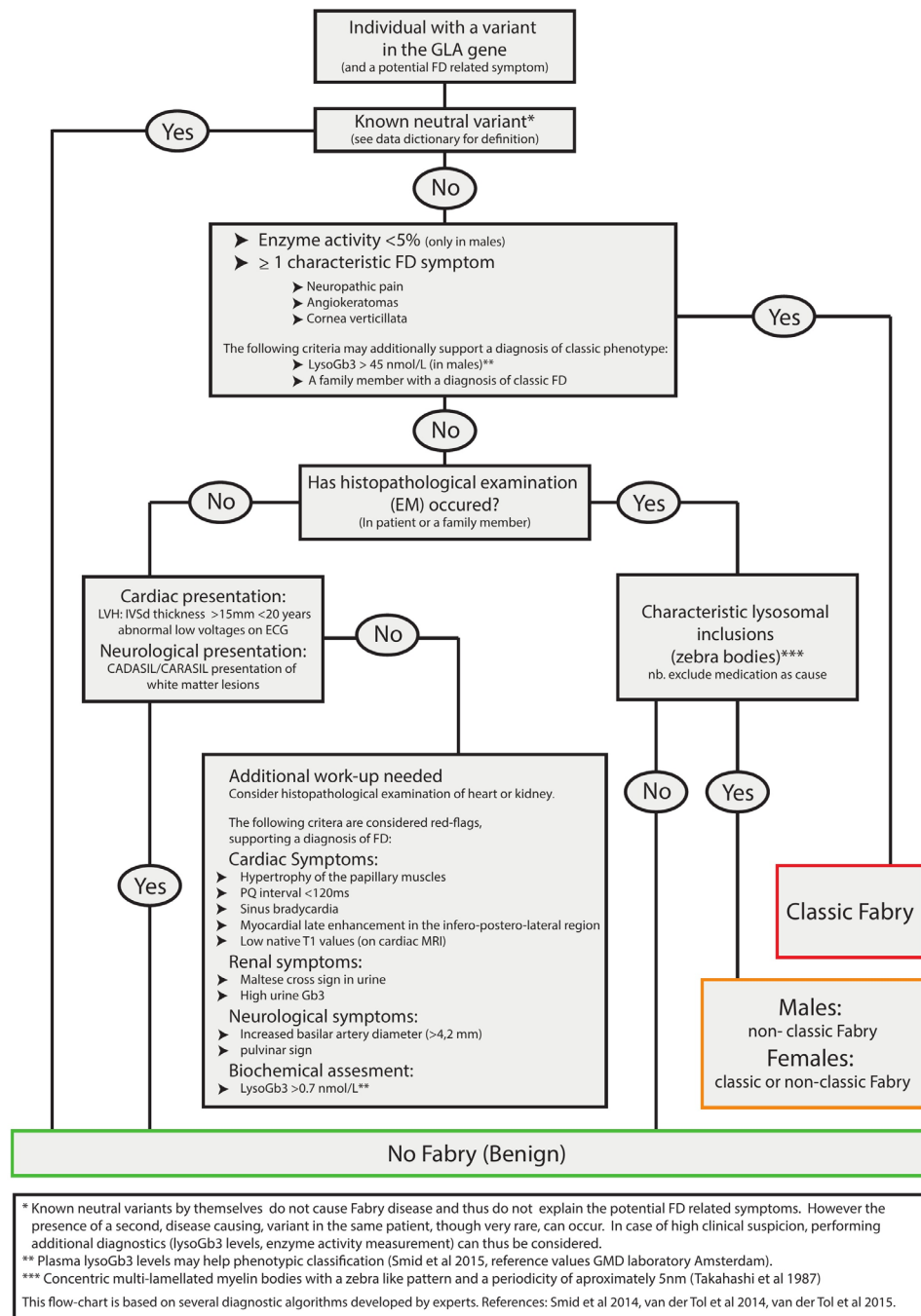


Figure 1 Flowchart for the diagnosis and phenotype allocation in FD. CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leucoencephalopathy; EM, electron microscopy; FD, Fabry disease; GLA, *galactosidase alpha*; IVSd, diastolic interventricular septum diameter.

(see figure 1 for details). Patients attended the clinic for standardised follow-up visits.

Between September 2018 and January 2019, all available patients charts, clinical letters, cardiac imaging reports from birth until the last outpatient clinic visit were investigated to record the following events: cardiovascular death (CVD), HF hospitalisation, sustained ventricular arrhythmias (SVA), myocardial infarction (MI), CA, pacemaker or implantable cardiac defibrillator (ICD) implantation, atrial fibrillation, coronary artery disease (CAD), percutaneous coronary intervention, coronary artery bypass graft surgery, systolic dysfunction on cardiac MRI or, if unavailable on echocardiography,

left ventricular outflow tract (LVOT) obstruction, moderate or severe valve disease and other heart surgery/intervention. The combined endpoint major adverse cardiovascular event (MACE) was defined as the occurrence of at least one of the following events: CVD, HF hospitalisation, SVA or MI. SVA included SCD, sudden cardiac arrest, sustained ventricular tachycardia lasting >30 s, appropriate ICD shock, and ventricular fibrillation. CA were defined as a composite of second-degree atrioventricular (AV) block type II, third-degree AV block, sinus arrest and device implantation for CA. Endpoint definitions are provided in online supplemental table 1). Events were adjudicated by a panel of experts consisting of

Table 1 Patient characteristics

	All	Men		Women	
		Classical	Non-classical	Classical	Non-classical
General					
Number of patients, n (%)	213 (100)	57 (27)	26 (12)	98 (46)	32 (15)
Age at last outpatient visit or death (years), median (range)	50 (19–83)	45 (19–66)	64 (26–78)	51 (19–83)	47 (23–79)
Cumulative follow-up from the age of 15 (years)	7090	1546	1190	3213	1140
Age at first outpatient clinic visit (years) median (range)	42 (3–77)	30 (3–58)	60 (22–70)	41 (7–71)	44 (19–77)
Comorbidities					
Number of patients with CVA at any time, n (%)	25 (12)	9 (16)	5 (19)	11 (11)	0 (0)
Obesity,* n (%)	30/198 (15)	1/51 (2)	4/24 (17)	16/93 (17%)	9/30 (30)
Smoking,* n (%)	75/177 (42)	17/44 (39)	14/23 (61)	35/87 (40)	9/23 (39)
Hypertension,* n (%)	48/199 (24)	8/51 (16)	11/26 (42)	18/95 (19)	11/27 (41)
Dyslipidaemia,* n (%)	14/187 (8)	0/43 (0)	7/23 (30)	5/91 (6)	2/30 (7)
Diabetes mellitus,* n (%)	4/203 (2)	0/52 (0)	2/25 (8)	1/96 (1)	1/30 (3)
Cardiac imaging					
Echocardiography					
Available echocardiography at any time, n (%)	181 (85)	49 (86)	21 (81)	87 (89)	24 (75)
Left ventricular hypertrophy on echocardiography at any time, n (%)†	90/181 (50)	24/49 (49)	16/21 (76)	43/87 (49)	7/24 (29)
Cardiac MR‡					
Available cardiac MR at last follow-up, n (%)	141 (66)	41 (72)	11 (42)	71 (73)	18 (56)
Left ventricular ejection fraction (%), median (range)	61 (24–84)	57 (24–70)	57 (48–67)	63 (51–84)	61 (57–70)
Available cardiac MR, where myocardial fibrosis was assessed by late gadolinium enhancement, n (%)	139/141 (99)	39/41 (95)	11/11 (100)	71/71 (100)	18/18 (100)
Myocardial fibrosis on cardiac MR, n (%)	54/139 (39)	13/39 (33)	6/11 (55)	29/71 (41)	6/18 (33)
ERT					
Patients on ERT, n (%)	128 (60)	47 (83)	12 (46)	62 (63)	7 (22)
Age start ERT (years), median (range)	42 (10–77)	27 (10–58)	59 (20–68)	46 (16–71)	60 (30–77)
Untreated patients, n (%)	85 (40)	10 (17)	14 (54)	36 (37)	25 (78)
Reasons for not starting ERT					
Diagnosis through family screening, absent or minimal organ involvement, n (%)	41 (19)	1 (2)	3 (12)	17 (17)	20 (63)
Diagnosis not through family screening, absent or minimal organ involvement, n (%)	2 (1)	0 (0)	0 (0)	1 (1)	1 (3)
Advanced disease stage, n (%)	18 (9)	2 (4)	9 (35)	5 (5)	2 (6)
Follow-up ended before ERT was available, n (%)	8 (4)	5 (9)	0 (0)	3 (3)	0 (0)
Other, n (%)	16 (8)	2 (4)	2 (8)	10 (10)	2 (6)

*Cardiovascular risk factors assessed at first outpatient clinic visit: obesity: Body Mass Index ≥ 30 kg/m²; smoking: patients who have ever smoked; hypertension: antihypertensive medication use or systolic blood pressure of >140 mm Hg and/or diastolic blood pressure of >90 mm Hg, measured at least twice; dyslipidaemia: elevated levels of total cholesterol (>6.5 mmol/L) or low-density lipoprotein cholesterol (>2.5 mmol/L) or triglycerides (>3.0 mmol/L), or low levels of high-density lipoprotein cholesterol (men: <1.0 mmol/L, women: <1.2 mmol/L) or medication prescribed for the indication dyslipidaemia; diabetes mellitus: type 1 or type 2, if reported by a medical doctor in the medical chart or when the patient is using antidiabetic medication.

†The included cardiac MRIs were obtained at the time of the last follow-up (with a maximum range of 2 years between the MRI and the last follow-up date). Severely affected patients with Fabry disease with a non-MRI compatible cardiac device were not included in the routine imaging follow-up.

‡Definition of cardiac hypertrophy on echocardiography: men >51 g/m^{2.7} and women >48 g/m^{2.7}, calculated with the Devereux formula: $0.8\{1.04[(LVEDD+IVSd+PWd)^3-LVEDD^3]\}+0.6$. LVEDD, IVSd and PWd are in millimetre.

CVA, cerebrovascular accident; ERT, enzyme replacement therapy; IVSd, interventricular septal thickness at end diastole; LVEDD, left ventricular end diastolic dimension; MR, magnetic resonance; PWd, posterior wall thickness at end diastole.

two cardiologists (AH and MB) and one metabolic specialist (ML).

Statistical analysis

For all cardiac events, the event rate per 1000 patient-years was calculated in order to correct for unequal follow-up duration between the different patient groups. The corresponding 95% CIs were reported for both individual and composite cardiac events, using the mid-P exact test (table 2 and online supplemental table 2). For the event rates calculation, follow-up duration from the age of 15 years onwards was used, because this study shows that cardiac events do not occur before the age of 15 years (figure 2, table 2 and online supplemental table 2) and the event-free follow-up duration of

especially the younger men with classical FD would impact unevenly on the event rate without this correction.

Event-free survival (EVS) was analysed using the Kaplan-Meier (KM) method, in which patients were stratified according to phenotype and sex. If less than 50% of the patients developed a specific event, the median age of onset for those patients who experienced the event was reported instead. Pairwise comparison between patients with FD groups was performed using a log-rank test, with Bonferroni correction. Next, these analysis were performed correcting for competing risks (CRs) (eg, non-CVD for the outcome of CVD, online supplemental figures 2–6). Cox regression analyses were performed to assess the effect of phenotype and sex and the interaction between these variables on the

Table 2 Prevalence, event rates and age at onset of death and cardiovascular events

	Men (N=83)			Women (N=130)	
	All (N=213)	Classical (n=57)	Non-classical (n=26)	Classical (n=98)	Non-classical (n=32)
Death					
Number of patients, n (%)	24 (11)	15 (26)	3 (12)	6 (6)	0 (0)
Deaths per 1000 person-years (from the age of 15 years), with 95% CI	3.4 (2.2 to 5.0)	9.7 (5.7 to 15.6)	2.5 (0.6 to 6.9)	1.9 (0.8 to 3.9)	0 (–)
Age at death (years), median (range)	58 (26–77)	56 (26–66)	65 (64–68)	72 (57–77)	(–)
Cause of death: HF, n (%)	10 (42)	4 (27)	2 (67)	4 (67)	0 (0)
Cause of death: MI, n (%)	2 (8)	2 (13)	0 (0)	0 (0)	0 (0)
Cause of death: ischaemic or haemorrhagic cerebrovascular accident, n (%)	4 (17)	2 (13)	0 (0)	2 (33)	0 (0)
Cause death: SCD during haemodialysis	2 (8)	2 (13)	0 (0)	0 (0)	0 (0)
Cause death: other, n (%)	6 (25)	5 (33)	1 (33)	0 (0)	0 (0)
Major adverse cardiovascular events*					
Number of patients, n (%)	38 (18)	17 (30)	7 (27)	14 (14)	0 (0)
Event rate, with 95% CI	5.4 (3.9 to 7.3)	11.0 (6.6 to 17.3)	5.9 (2.6 to 11.6)	4.4 (2.5 to 7.1)	0 (–)
Age at first event (years)	54 (33–75)	52 (33–66)	64 (34–67)	54 (34–75)	(–)
CVD					
Number of patients, n (%)	18 (9)	10 (18)	2 (8)	6 (6)	0 (0)
Event rate, with 95% CI	2.5 (1.6 to 3.9)	6.5 (3.3 to 11.5)	1.7 (0.3 to 5.6)	1.9 (0.8 to 3.9)	0 (–)
Age at CVD (years)	58 (47–77)	55 (47–66)	66 (65–68)	72 (57–77)	(–)
HF hospitalisation					
Number of patients, n (%)	18 (9)	8 (14)	4 (15)	6 (6)	0 (0)
Event rate, with 95% CI	2.5 (1.6 to .9)	5.2 (2.4 to 9.8)	3.4 (1.1 to 8.1)	1.9 (0.8 to 3.9)	0 (–)
Age at first event (years)	63 (43–77)	54 (43–66)	68 (64–69)	69 (52–77)	(–)
SVAs†					
Number of patients, n (%)	9 (4)	4 (7)	3 (12)	2 (2)	0 (0)
Event rate, with 95% CI	1.3 (0.6–2.3)	2.6 (0.8–6.2)	2.5 (0.6–6.9)	0.6 (0.1–2.6)	0 (–)
Age at first event (years)	56 (46–73)	48 (46–56)	67 (64–67)	62 (51–73)	(–)
MI					
Number of patients, n (%)	22 (10)	8 (14)	4 (15)	10 (10)	0 (0)
Event rate, with 95% CI	3.1 (2.0 to 4.6)	5.2 (2.4 to 9.8)	3.4 (1.1 to 8.1)	3.1 (1.6 to 5.6)	0 (–)
Age at first event	51 (33–75)	51 (33–58)	57 (34–67)	51 (34–75)	(–)
CAs‡					
Number of patients, n (%)	29 (14)	7 (12)	8 (50)	12 (12)	2 (6)
Event rate, with 95% CI	4.1 (2.8 to 5.8)	4.5 (2.0 to 9.0)	6.7 (3.1 to 12.8)	3.7 (2.0 to 6.4)	1.8 (0.3 to 5.8)
Age at first documentation (years)	60 (48–74)	56 (48–60)	62 (50–65)	63 (49–74)	72 (71–72)
Atrial fibrillation					
Number of patients, n (%)	44 (21)	20 (35)	7 (27)	16 (16)	1 (3)
Event rate, with 95% CI	6.2 (4.6 to 8.3)	12.9 (8.1 to 19.6)	5.9 (2.6 to 11.6)	5.0 (3.0 to 7.9)	0.9 (0.04 to 4.3)
Age at first event (years)	55 (18–69)	49 (18–61)	57 (34–69)	58 (47–67)	68 (–)

Data are presented as number (percentage) or median (range). All event rates are per 1000 patient-years from the age of 15 years onwards.

*Major adverse cardiac events: composite of CVD, HF hospitalisation, SVAs and MI.

†SVAs: composite of SCD, sudden cardiac arrest, sustained ventricular tachycardia, including appropriate ICD shock, and ventricular fibrillation.

‡CAs: composite of second-degree AV block Mobitz II, third-degree AV block, sinus arrest and pacemaker or ICD device implantation for CAs.

AV, atrioventricular; CA, conduction abnormality; CVD, cardiovascular death; HF, heart failure; ICD, implantable cardiac defibrillator; MI, myocardial infarction; SCD, sudden cardiac death.

occurrence of events. Since no events occurred in the subgroup of women with non-classical FD, we used Firth's penalised Cox regression to obtain stable models. P values of <0.008 (after Bonferroni correction) were considered statistically significant. SPSS V.25 and R V.3.6.1 were used for statistical analysis.

RESULTS

A total of 213 patients were included: 57 (27%) men and 98 (46%) women with classical FD, and 26 (12%) men and 32 (15%) women with non-classical FD. The median age at last outpatient visit or death was 50 years (range 19–83). Patient characteristics

are described in table 1. Figure 2 shows the occurrence of cardiac events for all patients in the four different groups.

Enzyme replacement therapy (ERT)

Sixty per cent (128/213) of the included patients were treated with ERT. Decisions to initiate treatment were based on the presence of symptoms as described earlier²⁵ or based on the recommendations of the European Fabry Working Group once they became available.²⁶ The majority of the untreated patients were either diagnosed through family screening, without signs of organ involvement at the last follow-up (48% of untreated

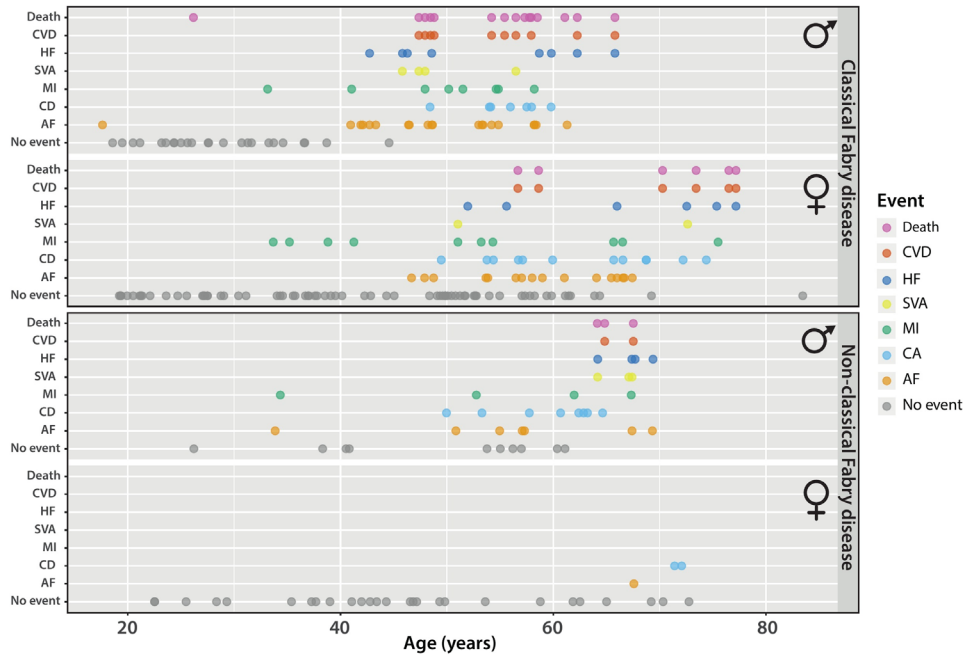


Figure 2 Occurrence of cardiac events for all 213 patients with FD, stratified by sex and phenotype. Included events are death, CVD, HF hospitalisation (first event), SVAs (first event), MI (first event), CA (first recorded) and AF (first recorded). No event was scored if none of the predefined events was recorded at the time of the last outpatient visit. ♂, men; ♀, women; AF, atrial fibrillation; CA, conduction abnormality; CVD, cardiovascular death; HF, heart failure; MI, myocardial infarction; SVA, sustained ventricular arrhythmia.

patients) or diagnosed at an advanced disease stage, at which point no benefit of ERT was to be expected (21%) (table 1).

Major adverse cardiovascular events

The event rate (after age 15 years) for MACE was 11.0 per 1000 patient-years (95%CI 6.6 to 17.3) for men with classical FD vs 4.4

(95% CI 2.5 to 7.1) in women with classical FD and 5.9 (95% CI 2.6 to 11.6) in men with non-classical FD. None of the women with non-classical FD developed MACE. KM analysis showed a significant difference between the four subgroups (figure 3; see online supplemental figure 2 for CR analysis). Having a classical phenotype and being male significantly increased the risk of MACE (table 3).

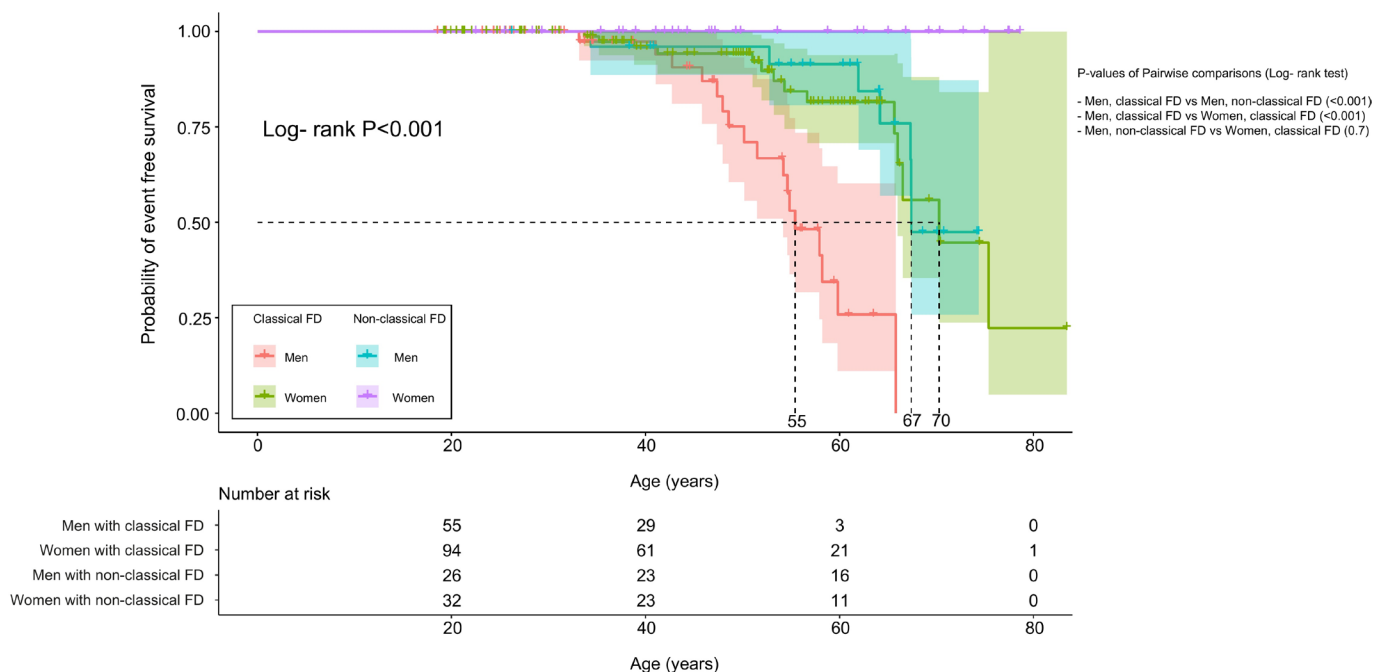


Figure 3 Kaplan-Meier curves (with 95% CIs) including data of 213 patients with FD, stratified by sex and phenotype, for major adverse cardiovascular events (clustered endpoint of cardiovascular death, heart failure hospitalisation, sustained ventricular arrhythmias and myocardial infarction). Patients are censored if a MACE did not occur at the time of the last follow-up contact. Median event-free survival is given for each group. Pairwise comparisons between patient groups are given. FD, Fabry disease.

Table 3 Firth's penalised Cox regression

Outcome	Covariate	Coef	Exp (coef)	95% CI
MACE	Phenotype, classical	2.99	19.89*	2.61 to 2554.03
	Sex, male	2.79	16.35*	1.94 to 2138.95
	Phenotype:sex	-1.19	0.31	0.002 to 2.96
CVD	Phenotype, classical	2.29	9.84†	1.13 to 1292.61
	Sex, male	1.88	6.56	0.51 to 916.78
	Phenotype:sex	0.81	2.25	0.01 to 38.56
HF hospitalisation	Phenotype, classical	2.36	10.56†	1.23 to 1383.10
	Sex, male	2.35	10.51†	1.08 to 1407.18
	Phenotype:sex	0.38	1.47	0.01 to 22.14
SVA	Phenotype, classical	1.07	2.91	0.23 to 404.25
	Sex, male	1.81	6.14	0.58 to 831.73
	Phenotype:sex	0.55	1.74	0.01 to 39.94
MI	Phenotype, classical	2.42	11.19†	1.41 to 1446.63
	Sex, male	2.21	9.12	0.94 to 1221.07
	Phenotype:sex	-1.28	0.28	0.00 to 3.26

*P<0.008.

†P<0.05.

coeff, coefficient; CVD, cardiovascular death; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; SVA, sustained ventricular arrhythmia.

HR for MACE in men with a classical versus non-classical phenotype was 6.1 (95% CI 2.4-17.0), and that in men vs women with a classical disease phenotype was 5.0 (95% CI 2.3-11.0) (table 4). Of the patients who developed MACE, MI was the first recorded event in 47% of men with classical FD, 64% of women with classical FD and 57% of men with non-classical FD. Excluding MI from the MACE analysis did not change the observed differences between the patient groups (see online supplemental results).

Cardiovascular death

In men with classical FD, 10 out of 15 deaths (67%) were CVDs (event rate 6.5 per 1000 patient years). CVD was also the major cause of death in women with classical FD (6/6 deaths (100%), event rate 1.9) and men with non-classical FD (2/3 deaths (67%), event rate 1.7). KM analysis showed a significant difference between the four subgroups (figure 4A; see online supplemental figure 3 for CR analysis). Having a classical phenotype increased the risk of CVD, but this effect did not hold after correcting for multiple testing (table 3). Group comparisons showed significant higher risk in men with classical versus non-classical disease (HR: 22.2, 95% CI: 5.0-19.3) and men versus women with classical disease (HR: 14.8, 95% CI: 4.3-67.0) (table 4). HF was an important cause of CVD (40% of CVD in men with classical FD, 67% in women with classical FD and 100% in men with non-classical FD) (table 2 and online supplemental table 2).

HF hospitalisation

The event rate for HF hospitalisation was 5.2 in men with classical FD vs 1.9 in women with classical FD. In men with non-classical FD, the event rate was 3.4. KM analysis showed

a significant difference between the four subgroups (figure 4B; see online supplemental figure 4 for CR analysis). Classical phenotype and male sex increased the risk of HF hospitalisation, but this effect did not hold after correcting for multiple testing (table 3). Group comparisons showed significant higher risk in men with classical versus non-classical disease (HR: 15.5, 95% CI: 3.7-82.7) and men versus women with classical disease (HR: 15.4, 95% CI: 4.1-73.8) (table 4). The left ventricle ejection fraction prior or at the time of the event was known in 17 out of 18 patients, who were hospitalised because of HF. In 12/17 patients (71%), the ejection fraction was <50% (5/7 in men with classical FD, 3/6 in women with classical FD and 4/4 in men with non-classical FD).

SVAs and ICD device implantation

The event rate of SVA was low (14 events in nine patients in the total cohort) (figure 4C; see online supplemental figure 5 for CR analysis; for between-group comparison, see tables 3 and 4). The first SVA episode occurred at the time of an MI in two patients and in one patient at the time of HF hospitalisation. Of the remaining six patients who experienced an SVA, two had an ejection fraction of <35%; in two patients, the first event occurred during haemodialysis, and in one patient, an allergic reaction to clopidogrel was described as a possible trigger. In the last patient, no trigger could be identified. Of all patients who suffered SVA, three died as a result of the first episode (one due to MI and two during haemodialysis); one patient died 3 years after the first SVA episode due to MI. The other five patients had an ICD implanted after the first event. In three patients, the ICD successfully aborted an episode of ventricular arrhythmia during follow-up. Of these three patients, two died of HF, respectively, 22 months and 6 years after ICD implantation. One patient was alive at the last follow-up (ICD was 4.8 years in situ). In two patients, no shocks were administered by the ICD. Of these two, one patient died 9 months after ICD implantation as a result of HF (no documented SVA), whereas in the other patient, no shocks were documented at the time of a sudden cardiac arrest with pulseless electrical activity. He was resuscitated and survived the episode. In the entire cohort of 213, 19 patients (including the 5 patients described earlier) had an ICD implanted. The total time the 19 ICDs were in situ was 71 years (range 0.1-9.3 years per patient).

Myocardial infarction

MI occurred in 22 patients. MI event rate was 5.2 in men with classical FD, 3.1 in women with classical FD and 3.4 in men with non-classical FD. The median EVS was not significantly different between the three affected patient groups, although the KM curves do show a similar pattern as seen for the other cardiac events (figure 4D and online supplemental figure 6). A classical phenotype increased the risk of MI, but this effect did not hold after correcting for multiple testing (table 3). Group comparisons showed no significant differences in the HRs between the

Table 4 HRs for the comparison of different patient groups

Comparison	MACE	CVD	HF	SVA	MI
Men with classical FD versus men with non-classical FD	6.1 (2.4-17.0)*	22.2 (5.0-19.3)*	15.5 (3.7-82.7)*	5.1 (0.9-41.1)	3.1 (1.0-11.7)
Men with classical FD versus women with classical FD	5.0 (2.3-11.0)*	14.8 (4.3-67.0)*	15.4 (4.1-73.8)*	10.7 (1.9-92.0)*	2.5 (1.0-6.7)
Men with non-classical FD versus women with classical FD	0.8 (0.3-2.0)	0.7 (0.1-2.7)	1 (0.3-3.4)	2.1 (0.4-13.0)	0.8 (0.2-2.4)

These HRs were obtained from Firth's penalised COX regression models in which sex and phenotype were combined in one variable with four patient groups.

*P<0.008.

CVD, cardiovascular death; FD, Fabry disease; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; SVA, sustained ventricular arrhythmia.

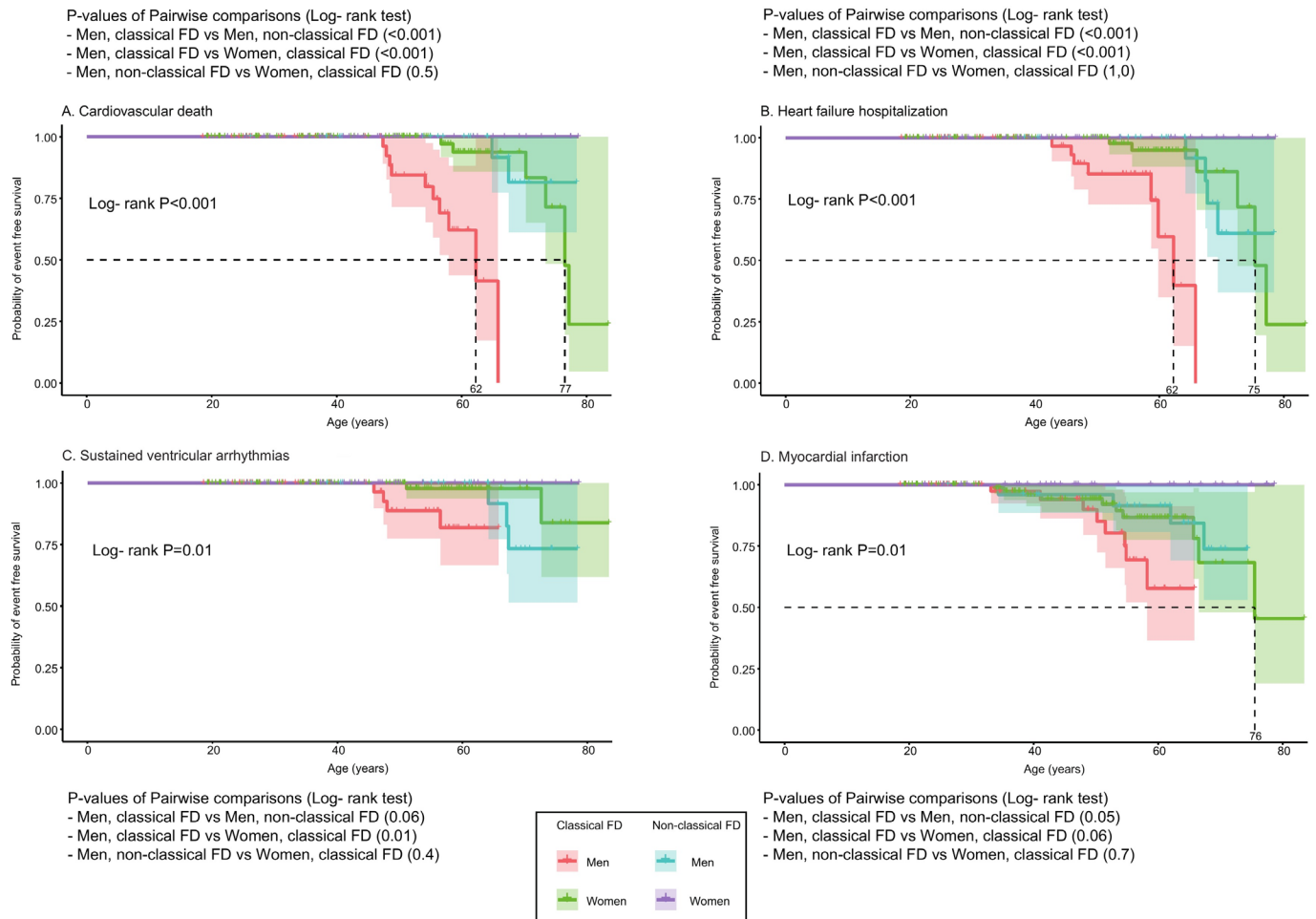


Figure 4 Kaplan-Meier curves (with 95% CIs) including data of 213 patients with FD, stratified by sex and phenotype for (A) cardiovascular death, (B) heart failure hospitalisation, (C) sustained ventricular arrhythmias and (D) myocardial infarction. Patients are censored if the event did not occur at the time of the last follow-up contact. Median event-free survival is given for each group in which events occurred. Pairwise comparisons between patient groups are given for each cardiac outcome. FD, Fabry disease.

patient groups (table 4; for further MI classification, see online supplemental table 3). Cardiovascular risk factors (obesity, smoking, hypertension, dyslipidaemia and diabetes mellitus) in patients suffering from an MI were present in 4 out of 8 men with classical FD (data not available for two patients), in 8 out of 10 women with classical FD and in 4 out of 4 men with non-classical FD (data not shown).

Data on other non-major cardiac events can be found in the online supplemental results section.

DISCUSSION

This is the first longitudinal study that describes the prevalence and timing of cardiac events in a large cohort of male and female patients with FD, categorised into classical and non-classical patient groups. The results show that these sex-defined and phenotype-defined patient groups differ substantially in terms of their risk of major cardiac events. The risk for all events showed the same trend: highest in men with a classical FD, intermediate in women with classical FD and in men with non-classical FD, and low in women with non-classical FD. For the individual events, differences between the groups were not always significant due to the relative low event rate. In men with classical FD, events occurred mainly from the fifth decade of life onwards, resulting in a reduced life expectancy (no men with classical FD in our cohort survived beyond 66 years of age). In women with

classical FD and men with non-classical FD, events are observed from the sixth decade onwards, with more variability regarding the age of onset. MI is the first major adverse cardiac event observed in 21/38 (55%) of patients with a MACE. Most likely, both macrovascular and microvascular CADs contribute to the development of ischaemia due to endothelial dysfunction and cardiac hypertrophy in FD.^{17 27 28} The relative contribution of FD-related endothelial pathology and hypertrophy versus that of general risk factors (eg, smoking) cannot easily be determined, given that the majority of patients had cardiovascular risk factors at the time of MI.

Importantly, none of the women with non-classical FD developed a MACE. This variation means that if 'cardiac events' is a clinical endpoint in an FD treatment study, men with classical FD should be treated as a separate group from women with classical FD and men with non-classical FD, and women with non-classical FD should not be included at all. This also means that results from previous clinical trials, in which phenotypical distinction was not made, should be interpreted with caution.

Fabry cardiomyopathy is associated with a risk of SCD, and in advanced disease, ICD implantation should be considered.^{15 29} The most frequently observed cause of death in the current study was HF (42% of all deaths), whereas SCD comprised 17% of all deaths. This finding is in contrast with a recent meta-analysis of Baig *et al*, which identified SCD as the most common cause of

death (62% of all deaths). However, the context of SCD and the FD phenotype of the included patients were not clear for most studies included in this meta-analysis. In addition, most included studies were performed in small cohorts, with a relatively short follow-up duration. In our patients with FD cohort, the SVA rate was low and more than half of the patients developed their first event in the context of either an MI or HF (hospitalisation or ejection fraction <35%). An earlier study of Vijapurapu *et al*²⁹ reported a higher event rate in patients with FD with an ICD, but sex and phenotype distributions in this group were not reported. Large multicentre cohort studies are needed to develop an FD SCD risk calculator to guide ICD implantation decision making.

Our findings, if confirmed in other longitudinal cohort studies, may change decision making regarding ICD implantation policy in FD. With the knowledge that HF is the main contributor to death in FD, future studies should aim to detect and treat HF in a much earlier phase of the disease. This highlights the urgent need for biomarkers that predict future development of HF, separating low-risk and high-risk patients, as clearly not all women with classical FD and men with non-classical FD develop HF.

A limitation of the current study is its retrospective design, which may lead to under-recording and subsequent underestimation of the event risk, even though we accessed historical files for the majority of patients. Nevertheless, we cannot rule out that for some deceased patients, especially those who died over a decade ago, some cardiac events may have been missed. In addition, the reported age of onset of cardiac manifestations such as

systolic dysfunction, LVOT obstruction and heart valve disease depends on the time at which imaging was performed and may thus not be fully accurate. The contribution of enrolment bias on the observed outcomes between sexes remains unknown. In theory, more women could have been identified through family screening and more men because of clinical manifestations, which could have contributed to the observed differences in the occurrence of cardiac events. The influence of chronic kidney disease on MACE occurrence, which may have increased the risk, was not analysed as the sample size and differences in follow-up duration between patients did not allow for this analysis. However, a glomerular filtration rate below 60 mL/min was present only in 20% of classically affected male patients and only in a single patient from other groups (online supplemental table 4). In addition, the effect of ERT on the occurrence of cardiac events was not analysed, because of the same reasons, as well as variability in the age of therapy initiation and indication bias for start of treatment.

An important strength of the study is the fact that it was a long-term longitudinal study on a large FD cohort, and the detailed data on predefined clinical cardiac events, in contrast to earlier studies, which often used composites for cardiac involvement in FD, including symptoms of angina pectoris, palpitations and microscopic Gb3 storage.^{22 23}

CONCLUSIONS

This large longitudinal study confirms that men with classical FD develop severe cardiac events, mainly from the fifth decade of life onwards. For women with classical FD and men with non-classical FD, cardiac events occur approximately a decade later and in a smaller proportion of patients. None of the non-classically affected women in this cohort developed a major cardiac event. More than half of the first observed SVAs occurred in the context of either an MI or HF, and HF was the most common cause of death. These findings shed new light on the clinical course and cardiac outcomes in FD cardiomyopathy and emphasise the need for new treatments, primarily to prevent HF in FD.

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Contributors MES: study design, acquisition, analysis and interpretation of data, first draft of manuscript. AH: study design, interpretation of data, critical revision of manuscript. MB: study design, interpretation of data, critical revision of manuscript. LvD: analysis and interpretation of data, critical revision of manuscript. MD: data extraction from electronic clinical report files, data processing, critical revision of manuscript. CH: study concept, study design, interpretation of data and critical revision of manuscript. ML: study concept, study design, study supervision, interpretation of data and critical revision of manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The medical ethics review committee of the Amsterdam University Medical Centres confirmed that the Medical Research Involving Human Subjects Act does not apply to this study (W19-438 # 19.505) because of the retrospective character of this work, using historical data obtained in the context of

Key messages

What is already known on this subject?

- ▶ Early cardiac manifestations of Fabry disease (FD) are left ventricular hypertrophy, fibrosis formation and conduction abnormalities. As the disease progresses, cardiac complications, such as arrhythmias and heart failure (HF), occur in a significant proportion of patients with FD, yet others remain asymptomatic throughout long-term follow-up. The evolution of cardiac events and the influence of sex and disease phenotypes on this trajectory have not been described previously.

What might this study add?

- ▶ This is the first large longitudinal cohort study describing the effect of disease phenotype and sex on the occurrence of cardiac events in FD. The event rates of major adverse cardiovascular events (combined endpoint cardiovascular death (CVD), HF hospitalisation, sustained ventricular arrhythmias (SVA) and myocardial infarction) were 11.0 in men with classical FD (95% CI 6.6 to 17.3) (event-free survival (EVS) 55 years), 4.4 (95% CI 2.5 to 7.1) and in women with classical FD (EVS 70 years) and 5.9 (2.6–11.6) in men with non-classical FD (EVS 70 years). None of these events occurred in women with non-classical FD. CVD was the leading cause of death (75%), to which HF contributed most (42%). The overall rate of SVAs was low (14 events in nine patients (4%))

How might this impact on clinical practice?

- ▶ Cardiac care in FD should be tailored to the sex and disease phenotypes of the patient and should focus on early detection and treatment of HF.

regular patient care. The study was conducted in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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Supplemental table 1 Definitions of cardiac events	
Events	Definition
<i>Major adverse cardiovascular events (MACE): composite of cardiovascular death, heart failure hospitalization, sustained ventricular arrhythmias (SVA) and myocardial infarction</i>	
1. Cardiovascular death*	Death as a result of one of the following diseases/ syndromes: <ul style="list-style-type: none"> - Acute coronary syndrome - Sudden cardiac death (SCD) - Hypertensive crisis - Ischemic or hemorrhagic stroke - Cardiomyopathy - Other cardiovascular cause such as: pulmonary embolism, peripheral vascular disease
2. Heart failure hospitalization*	Hospital admission (at least one night) with the following clinical manifestations of heart failure: dyspnea, reduced exercise tolerance, fluid retention in peripheral and/ or splanchnic vessels, seen as peripheral edema
3. Sustained ventricular arrhythmia (SVA)	composite of sudden cardiac death (SCD), sudden cardiac arrest (SCA), sustained ventricular tachycardia (VT) including appropriate ICD shock, and ventricular fibrillation (VF)
4. Myocardial infarction*	Acute myocardial injury with clinical evidence of acute myocardial ischemia. Definition according to the Fourth Universal Definition of Myocardial Infarction

<i>Sustained ventricular arrhythmias (SVA): composite of sudden cardiac death (SCD), sudden cardiac arrest (SCA), sustained ventricular tachycardia (VT) including appropriate ICD shock, and ventricular fibrillation (VF)</i>	
5. Sudden cardiac death*	Sudden cessation of cardiac activity, resulting in hemodynamic collapse and death. Often typically due to sustained ventricular arrhythmias (VT, VF). This occurs either : <ul style="list-style-type: none"> - \leq 1 hour after observed cardiac symptoms/ abnormalities <i>or</i> - If the patient is found dead, he or she was seen alive in the previous 24 hours without cardiac symptoms. Trauma, overdose, drowning and suicide exclude SCD
6. Sudden cardiac arrest*	Sudden cessation of cardiac activity so that the person becomes unresponsive, with no normal breathing and no signs of circulation
7. Sustained ventricular tachycardia*	Ventricular tachycardia lasting for >30 seconds or ended <30 seconds by a defibrillator
8. Ventricular fibrillation*	Inconsistent depolarization of the ventricles with AV- dissociation resulting in mechanical cardiac arrest (resuscitation and/or defibrillation often necessary)
<i>Conduction abnormalities (CA): composite of second-degree atrioventricular (AV) block Mobitz II, third-degree AV block, sinusarrest (SA) and pacemaker (PM) or implantable cardiac defibrillator device (ICD) implantation for conduction abnormalities</i>	
9. Second-degree AV block, Mobitz II	Intermittent nonconducted P waves not preceded by PR prolongation and not followed by PR shortening.
10. Third-degree AV block	Interruption of impulse transmission from the atria to the ventricles

11. Sinusarrest	An alteration in discharge by the sinusnode pacemaker, resulting in no P- waves and associated QRS-T during sinus pause. This pause is sometimes followed by junctional rhythm or idioventricular rhythm. Absence of escape rhythm results in asystole
12. Implantable cardiac defibrillator implantation*	First ICD or Cardiac resynchronization therapy device (CRT-D) implantation, indication of primary or secondary prevention was registered
13. Pacemaker implantation*	First pacemaker implantation, indication for implantation was registered
<i>Other events or interventions</i>	
14. Atrial fibrillation	Irregular heart rhythm without identifiable p-waves recorded on ECG
15. Coronary artery disease*	At least 50% stenosis of luminal diameter of left main coronary artery or at least 70% stenosis of luminal diameter of at least one of the major epicardial coronary arteries on coronary angiogram. Patients were also classified as having coronary atherosclerosis if there was a clear indication of myocardial ischemia on non-invasive imaging (i.e. stress CMR, SPECT)
16. Percutaneous coronary intervention (PCI)	Non-surgical intervention in which coronary stenosis is resolved with coronary angioplasty with or without the placement of a coronary stent
17. Coronary artery bypass graft (CABG) surgery	Open heart surgery where a bypass is placed around one or more (stenotic) coronary arteries
18. Systolic dysfunction on MRI or echocardiography	Left ventricular ejection fraction <50% on MRI. If no MRI is available: left ventricular ejection fraction <55% on echocardiography

19. Left ventricular outflow tract (LVOT) obstruction	Dynamic gradient of ≥ 30 mmHg on echocardiogram in the left ventricular outflow tract measured at rest, during Valsalva procedure or during exercise
20. Moderate or severe valve disease	First ultrasound report mentioning moderate to severe stenosis of insufficiency of the mitral, tricuspid or aortic valve. Or heart valve dysfunction that required surgery where no previous ultrasound reports were available
21. Heart surgery ⁺	Heart surgery, with exception of isolated CABG or PCI. This includes: myectomy due to LVOT obstruction with dynamic gradient, heart valve surgery, pulmonary vein isolation (PVI), or other interventions
<i>* Events discussed with the expert panel</i>	

Supplemental table 2 Prevalence, event rates and age at onset of individual outcomes †					
	All (213)	Men (83)		Women (130)	
		Classical (57)	Non-classical (26)	Classical (98)	Non-classical (32)
1. Sudden cardiac death					
Number of patients	4 (2%)	4 (7%)	0 (0%)	0 (0%)	0 (0%)
Event rate, with 95%-CI	0.6 (0.2-1.4)	2.6 (0.8-6.2)	0 (-)	0 (-)	0 (-)
Age at death	48 (47-56)	48 (47-56)	(-)	(-)	(-)
2. Sudden cardiac arrest					
Number of patients	6 (3%)	1 (2%)	3 (12%)	2 (2%)	0 (0%)
Event rate, with 95%-CI	0.8 (0.3-1.8)	0.6 (0.03-3.2)	2.5 (0.6-6.9)	0.6 (0.1-2.1)	0 (-)
Age at first event	66 (46-73)	46 (-)	67 (64-67)	65 (57-73)	(-)
3. Sustained ventricular tachycardia					
Number of patients	4 (2%)	0 (0%)	2 (8%)	2 (2%)	0 (0%)

Event rate, with 95%-CI	0.6 (0.2-1.4)	0 (-)	1.7 (0.3-5.6)	0.6 (0.1-2.1)	0 (-)
Age at first event	66 (51-73)	(-)	66 (64-67)	62 (51-73)	(-)
4. Ventricular fibrillation					
Number of patients	2 (1%)	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Event rate, with 95%-CI	0.3 (0.1-0.9)	0.6 (0.03-3.2)	0 (-)	0.3 (0.02-1.5)	0 (-)
Age at first event	59 (46-73)	46 (-)	(-)	73 (-)	(-)
5. Second- degree AV block, Mobitz II					
Number of patients	1(1%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Event rate, with 95%-CI	0.1 (0.01-0.7)	0 (-)	0.8 (0.04-4.1)	0 (-)	0 (-)
Age at first documentation	65 (-)	(-)	65 (-)	(-)	(-)
6. Third- degree AV block					
Number of patients	9 (4%)	1 (2%)	4 (15%)	4 (4%)	0 (0%)
Event rate, with 95%-CI	1.3 (0.6-2.3)	0.6 (0.03-3.2)	3.4 (1.1-8.1)	1.2 (0.4-3.0)	0 (-)

Age at first documentation	60 (50-72)	60 (-)	58 (50-63)	59 (54-72)	(-)
7. Sinusarrest					
Number of patients	7 (3%)	3 (5%)	2 (8%)	2 (2%)	0 (0%)
Event rate, with 95%-CI	1.0 (0.4-2.0)	1.9 (0.5-5.3)	1.7 (0.3-5.6)	0.6 (0.1-2.1)	0 (-)
Age at first documentation	58 (48-69)	58 (48-60)	60 (58-62)	59 (49-69)	(-)
8. PM, ICD and CRT-D implantation					
Number of patients	36 (17%)	9 (16%)	11 (42%)	14 (14%)	2 (6%)
PM	14 (7%)	4 (7%)	3 (12%)	5 (5%)	2 (6%)
PM + ICD upgrade at later stage	3 (1%)	0 (0%)	2 (8%)	1 (1%)	0 (0%)
ICD	7 (3%)	0 (0%)	3 (12%)	4 (4%)	0 (0%)
DDD-ICD	9 (4%)	3 (5%)	2 (8%)	4 (4%)	0 (0%)
CRT-D	2 (1%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)

PM + CRT-D upgrade at later stage	1 (0.5%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)
9. Coronary artery disease					
Number of patients	18 (9%)	9 (16%)	3 (12%)	6 (6%)	0 (0%)
Event rate, with 95%-CI	2.5 (1.6-3.9)	5.8 (2.8-10.7)	2.5 (0.6-6.9)	1.9 (0.8-3.9)	0 (-)
Age at first documentation	55 (39-77)	51 (46-64)	55 (53-67)	57 (39-77)	(-)
10. Percutaneous coronary intervention					
Number of patients	7 (3%)	3 (5%)	2 (8%)	2 (2%)	0 (0%)
Event rate, with 95%-CI	1.0 (0.4-2.0)	1.9 (0.5-5.3)	1.7 (0.3-5.6)	0.6 (0.1-2.1)	0 (-)
Age at first documentation	53 (39-67)	50 (48-64)	61 (55-67)	46 (39-53)	(-)
11. Coronary artery bypass graft surgery					
Number of patients	4 (2%)	3 (5%)	1 (4%)	0 (0%)	0 (0%)
Event rate, with 95%-CI	0.6 (0.2-1.4)	1.9 (0.5-5.3)	0.8 (0.04-4.1)	0 (-)	0 (-)
Age at first surgery	58 (54-69)	58 (54-58)	69	(-)	(-)

12. Systolic dysfunction on MRI or echocardiography					
Number of patients	28 (13%)	11 (19%)	8 (31%)	8 (8%)	1 (3%)
Event rate, with 95%-CI	3.9 (2.7-5.6)	7.1 (3.7-12.4)	6.7 (3.1-12.8)	2.5 (1.2-4.7)	0.9 (0.04-4.3)
Age at first documentation	60 (29-77)	52 (29-64)	64 (53-69)	65 (54-77)	72 (-)
13. Left ventricular outflow tract obstruction					
Number of patients	8 (4%)	2 (4%)	1 (4%)	4 (4%)	1 (3%)
Event rate, with 95%-CI	1.1 (0.5-2.1)	1.3 (0.2-4.3)	0.8 (0.04-4.1)	1.2 (0.4-3.0)	0.9 (0.04-4.3)
Age at first documentation	56 (31-65)	43 (31-55)	58 (-)	57 (46-61)	65 (-)
14. Moderate or severe heart valve disease					
Number of patients	39 (18%)	14 (25%)	6 (23%)	16 (16%)	3 (9%)
Event rate, with 95%-CI	5.5 (4.0-7.4)	9.1 (5.2-14.8)	5.0 (2.0-10.5)	5.0 (3.0-7.9)	2.6 (0.7-7.2)
Age at first documentation	58 (36-77)	51 (36-61)	65 (51-70)	61 (47-77)	74 (65-76)

15. Heart surgery/ intervention*					
Number of patients	10 (5%)	2 (4%)	3 (12%)	5 (5 %)	0 (0%)
Event rate, with 95%-CI	1.4 (0.7-2.5)	1.3 (0.2-4.3)	2.5 (0.6-6.9)	1.6 (0.6-3.5)	0 (-)
Age at first surgery/ intervention	63 (49-72)	53 (49-57)	64 (64-68)	61 (52-72)	(-)

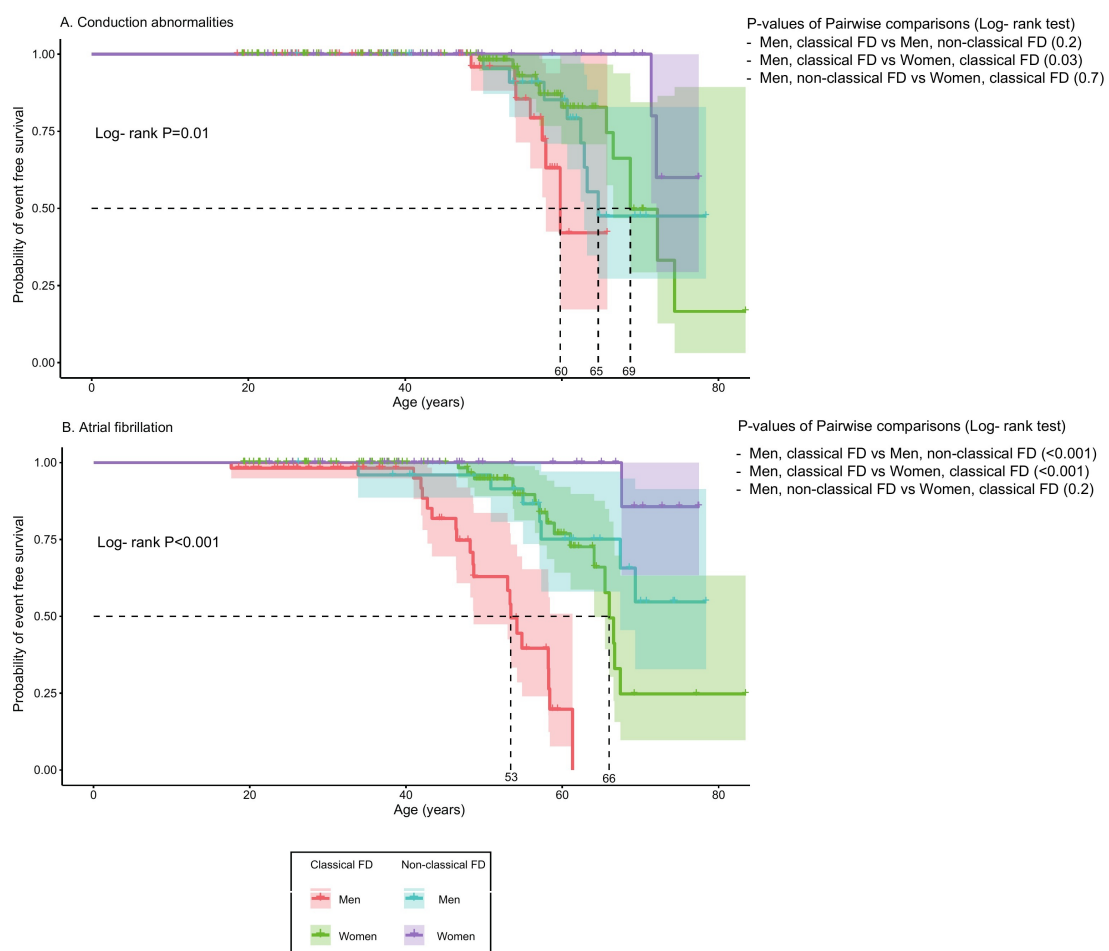
Data are presented as number (percentage) or median (range). All event rates are per 1000 patient years from age 15 onwards.

† Events per 1000 person years from age of 15 = (Number of events/ Cumulative follow up from age 15)x1000

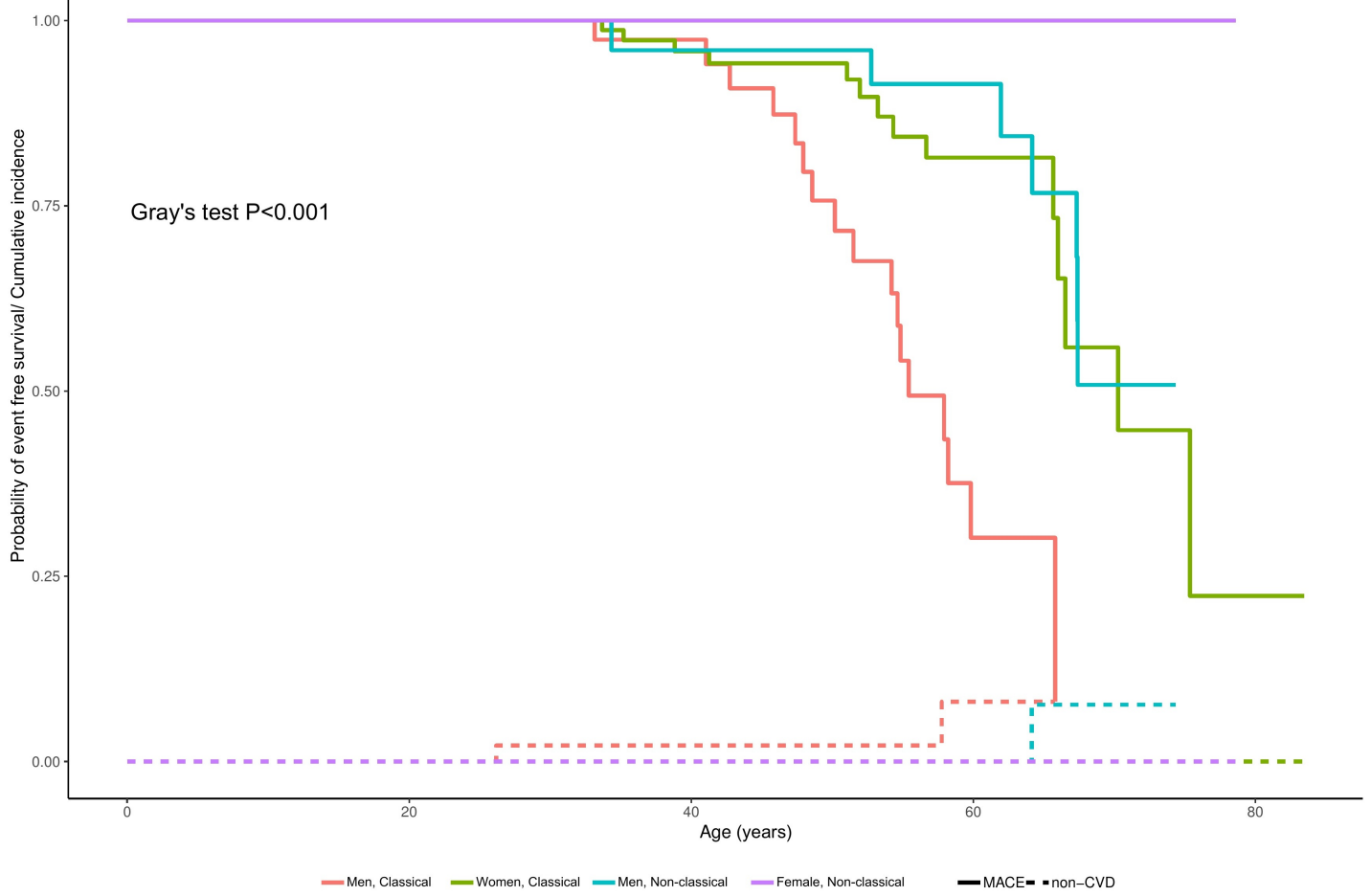
* heart surgery or intervention other than percutaneous coronary intervention or coronary artery bypass graft surgery

AV = atrioventricular; CRT = cardiac resynchronization therapy; ICD = implantable cardiac defibrillator; PM = pacemaker

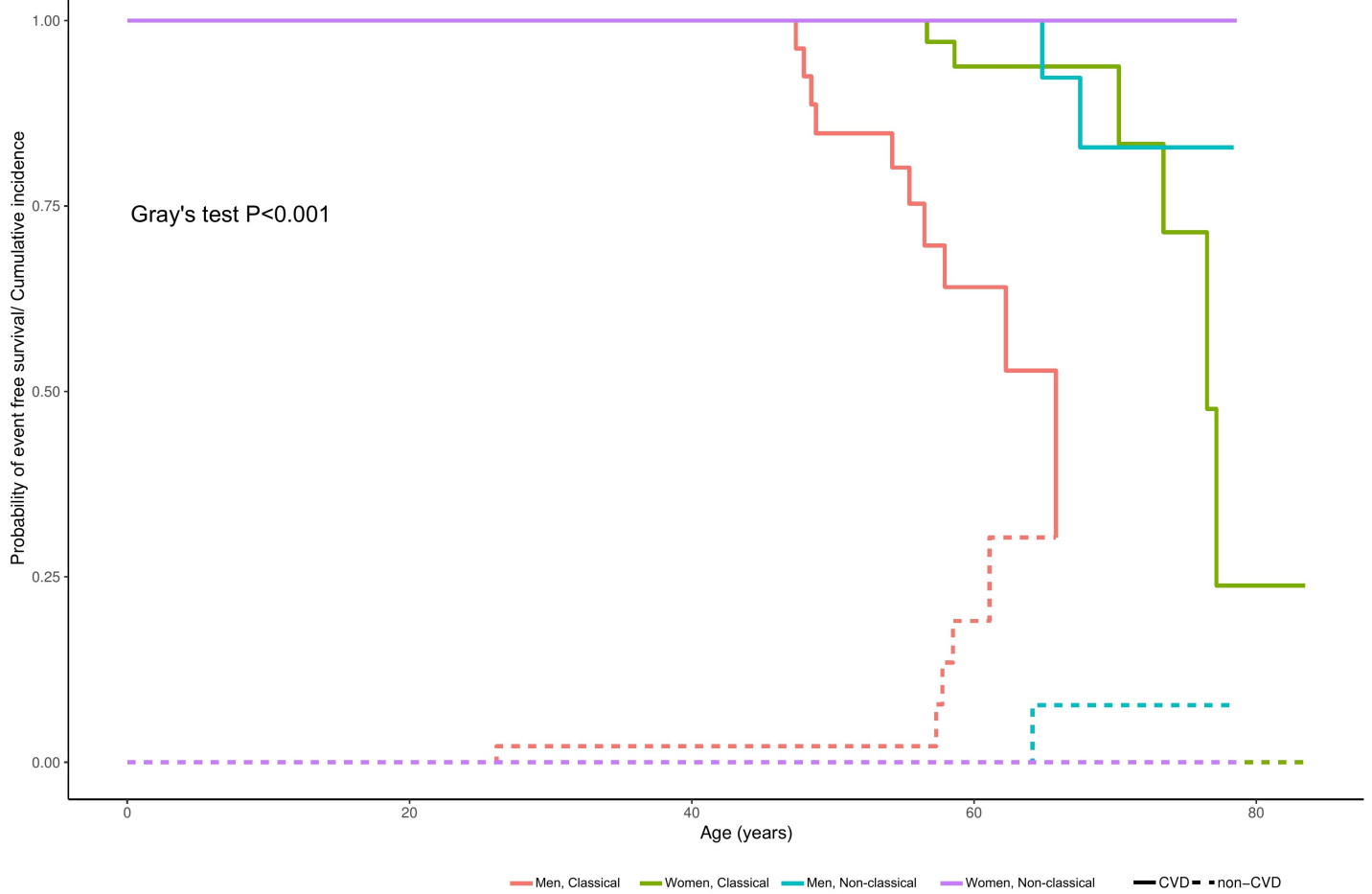
Supplemental figure 1



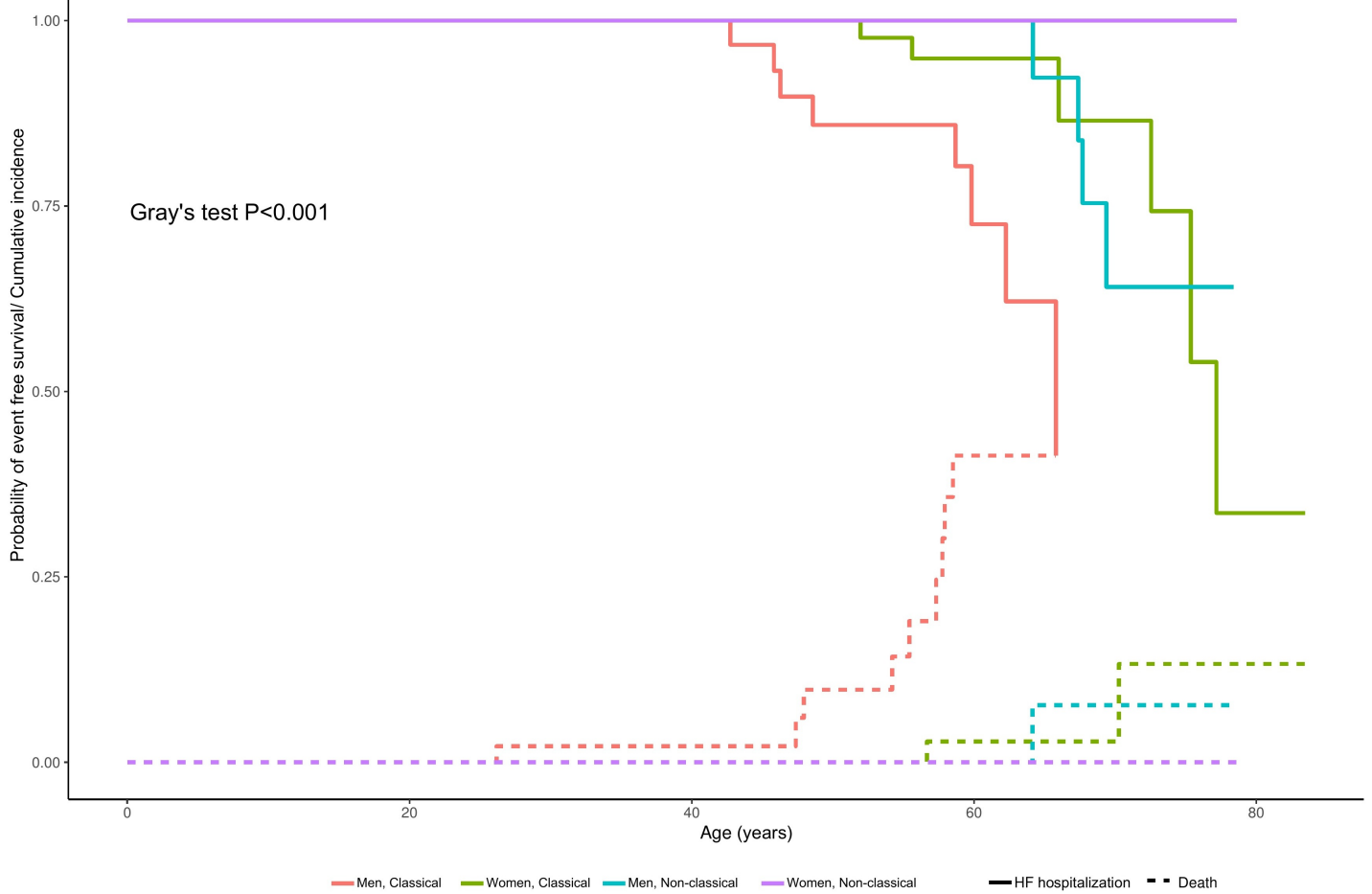
Supplemental figure 2: Major adverse cardiovascular events, competing risk= non-CVD



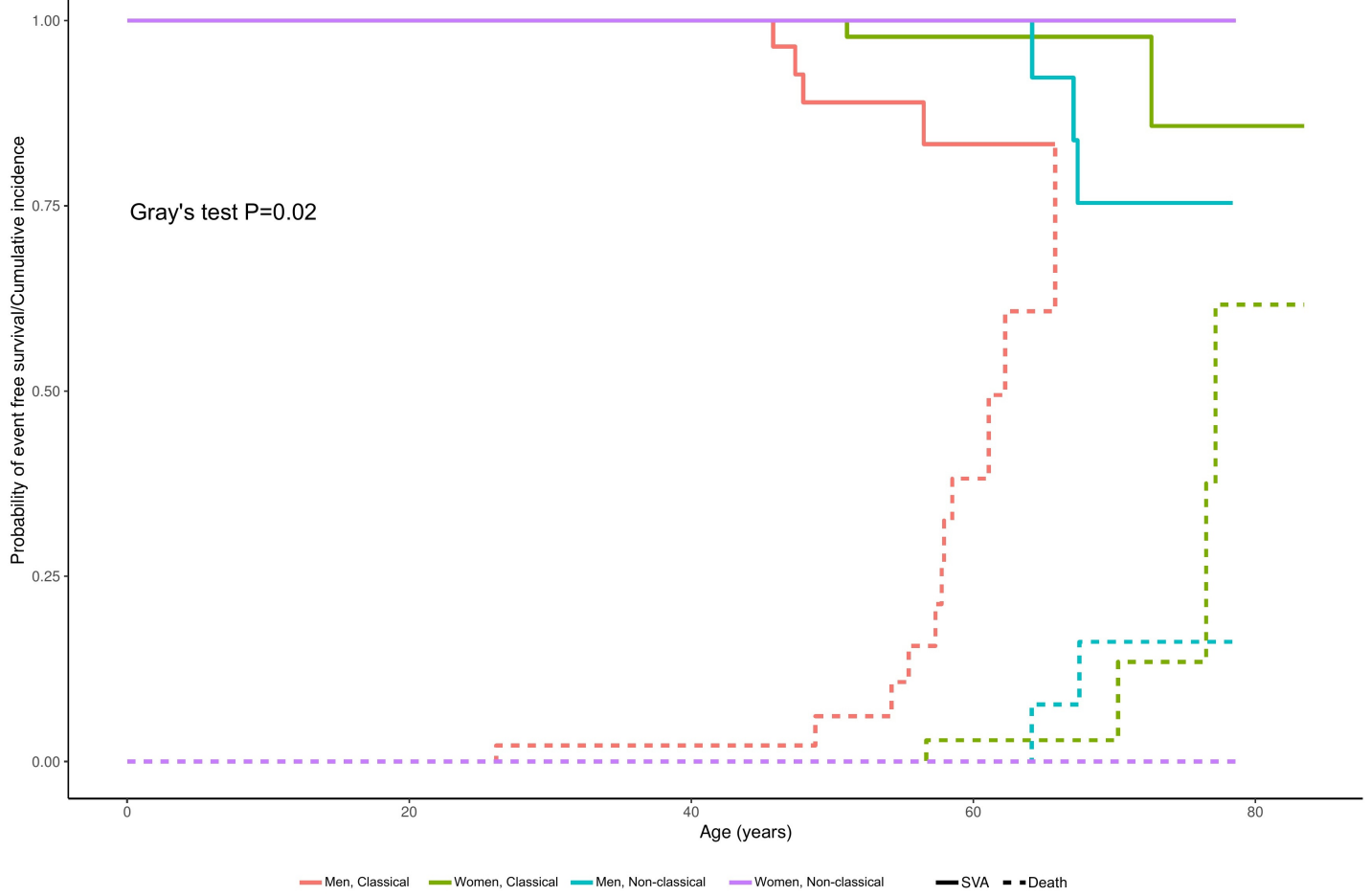
Supplemental figure 3: Cardiovascular death, competing risk= non-CVD



Supplemental figure 4: Heart failure hospitalization, competing risk= non-CVD



Supplemental figure 5: Sustained ventricular arrhythmias, competing risk= death (not included in the definition of SVA)



Supplemental results

Conduction abnormalities

Occurrence of CA showed the same distribution pattern across the four patient groups ($p=0.03$ for comparison of men with classical FD versus women with classical FD; $p=0.18$ for men with classical FD versus men with non-classical FD; and $p=0.005$ for men with classical FD versus women with non-classical FD) (Supplemental figure 1A). The median event-free survival was: 60, 69, and 65 years for men and women with classical FD and men with non-classical FD, respectively. CA were present in two women with non-classical disease .

Atrial fibrillation

The event rate for AF was 12.9 per 1000 patient-years in men with classical FD, 5.0 in women with classical FD and 5.9 in men with non-classical FD. Median event-free survival to first recorded AF event in men with classical FD was 53 years, compared to 66 years in women with classical FD. The median age of AF onset in men with non-classical FD was 57 years. Results of the log-rank test were $p<0.001$ for men with classical FD versus both other patient groups, (Supplemental figure 1B, table 2).

Systolic dysfunction, left ventricular outflow tract obstruction, and heart valve disease

The event rate for systolic dysfunction was the highest in men with classical and non-classical FD (7.1 and 6.7 respectively) and was substantially lower in women with classical and non-classical FD (2.5 and 0.9, respectively). First detection of systolic dysfunction occurred approximately a decade earlier in men with classical FD (median age 52, range 29-64) compared to women with classical FD (median age 65 years, range 54-77) and men with non-classical FD (64 years, range 53-69). For moderate/severe heart valve disease comparable results were found: men with classical FD had the highest event rate (9.1) and the lowest median age of onset (51 years, range 36-61) in comparison with the other 3 patient groups (supplemental table 2). The event rate of LVOT obstruction was low (1.1) in the total cohort (supplemental table 2).

Heart surgery/ intervention

Rates of cardiothoracic surgery/ interventions (other than PCI and CABG surgery) were low in all

patient groups (17 interventions in 10 patients), with the highest event rate (2.5) in men with non-classical FD (supplemental table 2). Types of surgery/interventions were heart valve repair and/ or replacement (n=9), ablation after ventricular or supraventricular arrhythmias (n=5), myectomy because of severe LVOT obstruction (n=2), and correction of an anomalous pulmonary vein (n=1). Of the total cohort, 7 patients underwent PCI and 4 CABG surgery. There were no patients who underwent a heart transplantation.

Cardiac events in female patients with non-classical Fabry disease

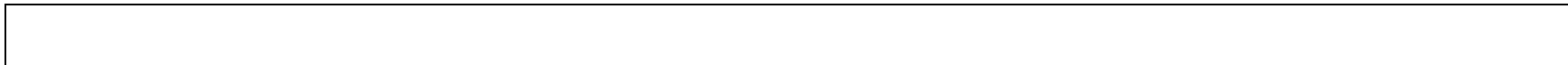
No MACEs were detected in women with non-classical FD. A total of 5 patients developed 8 non-major cardiac events (2 CA (1 tachycardia- bradycardia syndrome and 1 left/right bundle branch block for which a pacemaker was implanted, 1 AF, 3 moderate/ severe heart valve disease, 1 systolic dysfunction and 1 LVOT obstruction). All events in this group occurred from age 65 years onwards.

MACE (excluding MI from the analysis)

13 men with classical FD, 4 men with non-classical FD and 8 women with classical FD experienced a MACE. None of the women with non-classical FD developed MACE. The event rate (after age 15 years) for MACE was 8.4 per 1000 patient-years for men with classical FD, versus 2.5 in women with classical FD, and 3.4 in men with non-classical FD.

Median event-free survival was 60 years in men with classical FD, 75 years for women with classical FD. The median age of onset for MACE in men with non-classical FD was 67 years ($p < 0.001$ for comparison men with classical FD versus the other three patient groups; $p = 0.11$ for comparison men and women with classical FD).

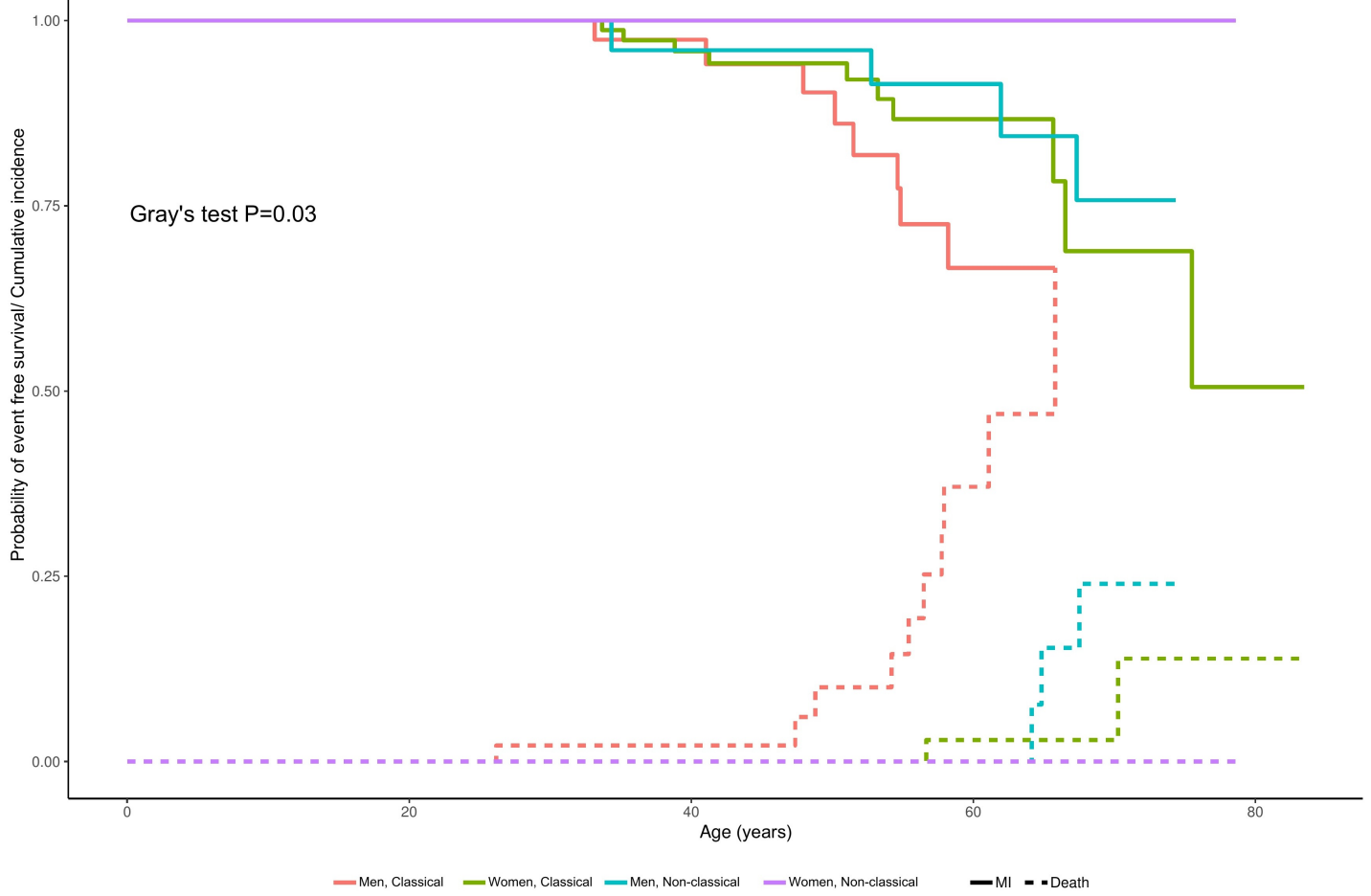
Supplemental table 3: Classification of myocardial infarctions					
	All (213)	Men (83)		Women (130)	
		Classical (57)	Non-classical (26)	Classical (98)	Non-classical (32)
Type I, n	7	3	1	3	0
STEMI, n	3	1	1	1	-
NSTEMI, n	3	1	0	2	-
Unknown, n	1	1	0	0	-
Type II, n	5	2	0	3	0
NSTEMI, n	5	2	-	3	-
Unknown type of infarction, n	10	3	3	4	0
NSTEMI, n	4	1	1	2	-
Unknown, n	6	2	2	2	-
n = number of patients; STEMI = ST-segment elevation myocardial infarction; NSTEMI = Non-ST-segment elevation myocardial infarction					



Supplemental table 4: Patient kidney characteristics					
	All (213)	Men (83)		Women (130)	
		Classical (57)	Non-classical (26)	Classical (98)	Non-classical (32)
KDIGO CKD stages**					
Patients with a known CKD stage, n (%)	152 (71%)	41 (72%)	13 (50%)	82 (84%)	16 (50%)
G1 (eGFR >90), n (%)	75 (49%)	23 (56%)	3 (23%)	37 (45%)	12 (75%)
G2 (eGFR 60-89), n (%)	48 (32%)	9 (22%)	4 (31%)	33 (40%)	2 (13%)
G3a (eGFR 45-59), n (%)	13 (9%)	1 (2%)	2 (15%)	8 (10%)	2 (13%)
G3b (eGFR 30-44), n (%)	12 (8%)	7 (17%)	2 (15%)	3 (4%)	0 (0%)
G4 (eGFR 15-29), n (%)	3 (2%)	1 (2%)	1 (8%)	1 (1%)	0 (0%)
G5 (eGFR <15), n (%)	1 (1%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)
Proteinuria (microalbuminuria > 300 milligrams/ 24 hours)**					

Patients with a known proteinuria status, n (%)	71 (33%)	16 (28%)	7 (27%)	41 (42%)	7 (22%)
Present proteinuria, n (%)	12 (17%)	4 (25%)	3 (43%)	5 (12%)	0 (0%)
Absent proteinuria, n (%)	59 (83%)	12 (75%)	4 (57%)	36 (88%)	7 (100%)
<p>KDIGO= Kidney Disease Improving Global Outcomes; CKD= Chronic Kidney Disease; eGFR= estimated Glomerular Filtration Rate, according to the Chronic Kidney Disease Epidemiology Collaboration equation and measured in milliliters/ minute per 1.73 meter²</p> <p>** The KDIGO CKD and proteinuria status are measurements, which are known at the time of the last follow-up (with a minimum and maximum range of 1 year between the measurement and the last follow-up date).</p>					

Supplemental figure 6: Myocardial infarction, competing risk= death



Supplemental figures legends

Supplemental figure 1 legend: Kaplan-Meier curves (with 95%-confidence intervals) including data of 213 FD patients, stratified by sex and phenotype for A. Conduction abnormalities, B. Atrial fibrillation. Patients are censored if event did not occur before last follow up. Median event-free survival is given for each group in which events occurred. Pairwise comparisons between patient groups are given.

Supplemental figure 2 legend: The smooth lines represent the Kaplan-Meier curves including data of 213 FD patients, stratified by sex and phenotype, for Major adverse cardiovascular events (clustered endpoint of cardiovascular death, heart failure hospitalization, sustained ventricular arrhythmias, and myocardial infarction). The broken lines represent the cumulative incidence curves from the competing risk (CR) analyses, where non-cardiovascular death is accounted as competing risk. The Event-free survival in men with classical FD is 55 years and in women with classical FD 70 years. The P- value of the Gray's test is given.

Supplemental figure 3 legend: The smooth lines represent the Kaplan-Meier curves including data of 213 FD patients, stratified by sex and phenotype, for Cardiovascular death. The broken lines represent the cumulative incidence curves from the competing risk (CR) analyses, where non- cardiovascular death is accounted as competing risk. The Event-free survival in men with classical FD is 66 years and in women with classical FD 77 years. The P- value of the Gray's test is given.

Supplemental figure 4 legend: The smooth lines represent the Kaplan-Meier curves including data of 213 FD patients, stratified by sex and phenotype, for Heart failure hospitalization. The broken lines represent the cumulative incidence curves from the competing risk (CR) analyses, where non- cardiovascular death is accounted as competing risk. The Event-free survival in men with classical FD is 66 years and in women with classical FD 77 years. The P- value of the Gray's test is given.

Supplemental figure 5 legend: The smooth lines represent the Kaplan-Meier curves including data of 213 FD patients, stratified by sex and phenotype, for Sustained ventricular arrhythmias. The broken lines represent the cumulative incidence curves from the competing risk (CR) analyses, where death is accounted as competing risk. The P- value of the Gray's test is given.

Supplemental figure 6 legend: The smooth lines represent the Kaplan-Meier curves including data of 213 FD patients, stratified by sex and phenotype, for Myocardial infarction. The broken lines represent the cumulative incidence curves from the competing risk (CR) analyses, where death is accounted as competing risk. The P- value of the Gray's test is given.