

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).