# Myocardial Disease and Ventricullar Arrhythmia in Marfan Syndrome – A Prospective Study

**Laura Muino Mosquera** ( laura.muinomosquera@uzgent.be )
Universitair Ziekenhuis Gent https://orcid.org/0000-0002-3094-7807
**Hans De Wilde**
Universitair Ziekenhuis Gent
**Daniel Devos**
Universitair Ziekenhuis Gent
**Danilo Babin**
Universiteit Gent
**Luc Jordaens**
Universitair Ziekenhuis Gent
**Anthony Demolder**
Universiteit Gent
**Katya De Groote**
Universitair Ziekenhuis Gent
**Daniel De Wolf**
Universitair Ziekenhuis Gent
**Julie De Backer**
Universitair Ziekenhuis Gent

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# Abstract

**Background:** Aortic root dilatation and -dissection and mitral valve prolapse are established cardiovascular manifestations in Marfan syndrome (MFS). Heart failure and arrhythmic sudden cardiac death have emerged as additional causes of morbidity and mortality.

**Methods:** To characterize myocardial dysfunction and arrhythmia in MFS we conducted a prospective longitudinal case-control study including 86 patients with MFS (55.8% women, mean age 36.3yr - range 13-70yr-) and 40 age- and sex-matched healthy controls. Cardiac ultrasound, resting and ambulatory ECG (AECG) and NT-proBNP measurements were performed in all subjects at baseline. Additionally, patients with MFS underwent 2 extra evaluations during 30±7months follow-up. To study primary versus secondary myocardial involvement, patients with MFS were divided in 2 groups: without previous surgery and normal/mild valvular function (MFS-1; N=55) and with previous surgery or valvular dysfunction (MFS-2; N=31).

**Results:** Compared to controls, patients in MFS-1 showed mild myocardial disease reflected in a larger left ventricular end-diastolic diameter (LVEDD), lower TAPSE and higher amount of (supra) ventricular extrasystoles ((S)VES). Patients in MFS-2 were more severely affected. Seven patients (five in MFS-2) presented decreased LV ejection fraction. Twenty patients (twelve in MFS-2) had non-sustained ventricular tachycardia (NSVT) in at least one AECG. Larger LVEDD and higher amount of VES were independently associated with NSVT.

**Conclusion:** Our study shows mild but significant myocardial involvement in patients with MFS. Patients with previous surgery or valvular dysfunction are more severely affected. Myocardial function should be evaluated in all patients with MFS, especially those with valvular disease and cardiac surgery.


# Introduction

Marfan syndrome (MFS) (OMIM #154700, ORPHA #284963) is an inherited connective tissue disorder caused by pathogenic variants in the fibrillin-1 gene (*FBN1*), encoding for the extracellular matrix protein, fibrillin-1[1]. Although aortic root dilatation and -dissection and mitral valve prolapse (MVP) are the most common and best studied cardiovascular manifestations in MFS, heart failure and sudden cardiac death, presumably secondary to ventricular arrhythmia, seem to be additional causes of morbidity and mortality to consider in at least some of these patients[2,3].

Ventricular myocardial dysfunction in MFS is usually mild and affects 7–68% of the patients, depending on the studied cohort, the technique used and the definition of ventricular dysfunction[4–10]. End-stage heart failure is less common and occurs only in minority of patients[3,11,12]. Left ventricular enlargement and myocardial dysfunction in MFS can result from valvular disease, but primary biventricular myocardial involvement in patients with MFS without valvular pathology has been shown by several independent groups[5–10]. Furthermore, mild myocardial impairment and abnormal myocardial signaling

have been shown in 2 different murine models of MFS (*fbn1*$^{mgR/mgR}$ and *fbn1* $^{C1039G/+}$)[13,14]. Using one of these models (*fbn1* $^{C1039G/+}$), Rouff and colleagues further showed that hemodynamic overload by TAC ligation (transverse aortic constriction), was less well tolerated in MFS mice than in wild-type littermates[15]. This finding supports the idea that secondary hemodynamic overload in a myocardium primarily predisposed to disease might cause more damage.

Next to ventricular enlargement or dysfunction, myocardial disease might manifest as ventricular arrhythmia. The prevalence of sustained ventricular tachycardia (VT) and sudden cardiac death (SCD) in MFS is approximately 10% and 4% respectively[2,4,16]. An enlarged left ventricle [4,16,17] and high levels of NT-proBNP[2,16] seem to be the most consistent features related to ventricular arrhythmia. Isolated MVP without regurgitation, although associated with ventricular arrhythmia and SCD in non-MFS populations [18], has not shown a consistent relation with arrhythmia in MFS[2,4,16,17].

Genotype-phenotype correlations have been studied by a few groups. Aalberts and colleagues found a higher prevalence of left ventricular dilatation in non-missense *FBN1* variant carriers[19] and Aydin and colleagues found that patients carrying a *FBN1* missense variant were more likely to present ventricular ectopy[16]. Given the known relation between left ventricular dimension and the presence of ventricular ectopy, these results seem contradictory and warrant further study.

To study myocardial disease in patients with MFS, we conducted a prospective longitudinal case-control study. The aims of the study were: 1. Compare the prevalence of myocardial dysfunction and arrythmia between patients with MFS and sex- and age-matched healthy controls. 2. Distinguish primary versus secondary myocardial involvement. 3. Identify factors predisposing to myocardial disease and genotype-phenotype correlations.

# Materials And Methods

# Subjects

Patients with a clinical diagnosis of MFS according to the revised Ghent nosology[1] older than 12 year and in whom a (likely) pathogenic *FBN1* gene variant was confirmed, were asked to participate in the study. Of the 108 patients evaluated in our institution between January 2015 and June 2016 and fulfilling the inclusion criteria, 86 agreed to participate in this longitudinal study. Six patients were excluded due to psychosocial problems (N = 5) or residency outside Belgium (N = 1), 11 patients declined participation, 4 patients were not included because of (planned) pregnancy and 1 patient because of a medical history of heart transplantation. Forty age- and sex-matched healthy volunteers were also recruited (Fig. 1). To participate in the study, controls could not have a (family) history of bicuspid aortic valve, thoracic aortic disease or cardiomyopathy.

In all control and MFS subjects, personal medical and family history, medication use and conventional cardiovascular risk factors (self-reported diabetes, hypercholesterolemia and smoking habits) were

documented. Anthropometric data and blood pressure after 10 min resting were assessed. A 12-lead electrocardiogram (ECG), a 24-hour ambulatory ECG (AECG) and a standard cardiac ultrasound were performed. NT-proBNP was measured at baseline. Additionally, patients with MFS were followed for a mean duration of 30 ± 7months. During follow-up, they underwent annual ECG and 24 h AECG recording, cardiac ultrasound and measurement of NT-proBNP. Since thyroid function is associated with higher risk of arrythmia[20,21], levels of TSH were measured in all patients at the end of the study to rule out (sub)clinical thyroid disease.

To evaluate primary versus secondary myocardial disease, patients with MFS were divided in two groups: The 1st group without medical history of cardiovascular surgery (aortic root replacement (AoRR) or isolated mitral valve surgery) and without moderate to severe mitral or aortic regurgitation. This group is further referred in the text as MFS-1 (N = 55). The 2nd group of patients with either cardiovascular surgery or with valvular disease (or both), is further referred in the text as MFS-2 (N = 31).

# Study procedures

Cardiac ultrasound was performed with a Vivid S60N®, GE Healthcare, equipped with a 5S probe. Aortic diameters, valvular function as well as cardiac chamber dimensions and -function were measured according to the guidelines of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI)[22,23]. Data were stored and analyzed offline using an ultrasound workstation (EchoPAC, GE Healthcare, version 201). For the continuous variables, an average of 3 consecutive measurements was calculated. Aortic and mitral valve regurgitation were graded into mild, moderate or severe and mitral valve prolapse was considered if there was a superior mitral leaflet displacement of more than 2 mm in systole. Z-scores of the aortic sinus and proximal ascending aorta were calculated according to Campens and colleagues[24]. For evaluation of diastolic function, a combination of pulsed wave and tissue doppler imaging (TDI) was used. LV ejection fraction (EF) was calculated from a 2D image in parasternal long-axis view ($LVEF = LVEDD^2\text{-}LVESD^2/LVEDD^2*100 + k$, where LVEDD = left ventricular end diastolic diameter, LVESD = left ventricular end systolic diameter, k = correction for apical contraction). Systolic dysfunction was defined as LVEF < 55%[23]. An LVEDD was considered enlarged if indexed for body surface area (BSA)(LVEDDi) was above 30 $mm/m^2$ [23]. The tricuspid annular plane systolic excursion (TAPSE) viewed from the four-chamber view was used to evaluate right ventricular function. TAPSE was considered abnormal if ≤ 16 mm.

A routine 12-lead ECG was recorded using an available commercial system (MAC 5500 HD, GE Healthcare). Regular measurements of P-wave width and height, P-wave axis, PR-interval, QRS width and axis, and QTc interval using Bazett's formula were calculated. The U-wave was included in the measurement of the QTc interval if > 50% of the T-wave height. A standard AECG was performed and analyzed using 2 semi-automatic software packages (Philips DigiTrack XT®, Philips and Trillium Platinum TM®, Forest Medical). Minimum, maximum and average heart rate, number of supraventricular- (SVES) and ventricular extrasystoles (VES) were recorded. Atrial runs and non-sustained ventricular tachycardia (NSVT) were defined as 3 or more consecutive atrial or ventricular beats. Sustained

ventricular tachycardia (VT) was defined if VT lasted 30 seconds or more. Ventricular ectopy (VE) was defined if more than 10 VES/h. Heart rate variability (HRV) was studied using the standard deviation of the normal-to-normal interval (SDNN) and the square root of the mean squared difference of successive normal-to-normal intervals (RMSDD).

# Classification of the genetic variants

To study genotype-phenotype correlations, variants in the *FBN1* gene were classified according to their effect on the DNA structure as missense (single nucleotide change), in-frame (indels not causing alteration in the reading frame), frameshift (indels causing an alteration in the reading frame), nonsense (single nucleotide change causing a premature stop-codon) and splice-site variants (indels or single nucleotide change in a place where splicing occurs).

Variants were also classified according to the expected effect at the protein level[25]. Frameshift and nonsense variants not affecting exon 65 or the last 50 nucleotides of exon 64 were considered to have an haploinsufficient (HI) effect, leading to the production of a reduced amount of normal fibrillin-1 (derived from the non-mutated allele). The other frameshift and nonsense variants and all missense variants were considered to have a dominant negative (DN) effect, leading to a shorter or a structurally abnormal but stable protein. These predictions were confirmed by the Mutation Taster software[26]. To classify the effect of the splice-site variants we used the Human Splicing Finder Software[27]. Splice-site variants causing a change in the reading frame were considered as HI, while variants affecting splicing but not causing a change in the reading frame were considered as DN.

Furthermore, we considered variants affecting exon 24–32 separately because these have been previously associated with higher ventricular ectopy [16].

# Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25 package (SPSS Inc., Chicago, IL, USA).

Continuous variables are expressed as mean and standard deviation or as median and interquartile range (IQR). Categoric variables are expressed as absolute value and percentage.

The Kolmogorov-Smirnov test was used to determine normality. Continuous variables were analyzed either using the unpaired sample t-test and the Mann-Whitney-U if two groups were compared or the ANOVA and Kruskal-Wallis if more than 2 groups were compared. For the categorical variables Chi-square test or the Fisher exact test were used. Variables were adjusted for confounders using either linear regression for continuous variables or logistic regression for categoric variables. Those variables with a p-value < 0.2 were considered as possible confounders. Since NT-ProBNP and the amount of ventricular extrasystoles (VES) in 24 h were extremely skewed, a logarithmic transformation was performed to include them in the multivariable analysis.

# Ethical issues

The study was approved by the local Independent Ethics Committee and the Institutional Review Board (IRB) of our hospital. All subjects participating in the study gave written informed consent.

# Results

Baseline characteristics and comparison between Marfan syndrome patients and control subjects

Eighty-six patients with MFS (55.8% female, 36.3 ± 14.3 year -range 13–70 year-) and 40 age- and sex-matched controls (52.5% female, 37.9 ± 14.4 year -range 16–69 year) were included in the study. One of the study patients declined AECG (Fig. 1). Table 1 shows the baseline characteristics of the MFS group.

Table 1
Baseline characteristics of the patients with Marfan syndrome

| Parameter | Marfan (N = 86) |
|---|---|
| Female (%) | 48 (55.8) |
| Age | 36.3 ± 14.3 |
| FBN1 variant type (%) | |
| Missense | 43 (50.6) |
| Frameshift | 20 (23.5) |
| Nonsense | 15 (15.6) |
| Splice-site | 7 (8.2) |
| De novo (%) | 26 (30.2) |
| Systemic score [a] | 7.9 ± 3.2 |
| EL (%) | 47 (54.7) |
| **Medical history** | |
| AoRR (%) | 22 (25.6) |
| Valve sparing (%) | 16 (72.7) |
| Valve replacement (%) | 6 (27.3) |
| MVP (%) | |
| Bulging | 24 (28.9) |
| Prolapse | 16 (19.3) |
| MV surgery (%) | 3 (3.5) |
| Valvuloplasty and ring (%) | 1 (1.2) |
| Bioprosthesis (%) | 1 (1.2) |
| Mechanical valve (%) | 1 (1.2) |
| Atrial arrhythmia (%)[b] | 8 (9.3) |
| Afib (%) | 4 (4.6) |
| Other SVT (%) | 4 (4.6) |
| Symp. VE (%)[b] | 3 (3.5) |
| Treatment | |

| Parameter | Marfan (N = 86) |
|---|---|
| None (%) | 19 (22.1) |
| BB alone (%) | 35 (40.7) |
| ARB alone(%) | 9 (10.5) |
| ACEi alone (%) | 1 (1.2) |
| BB + ARB (%) | 21 (24.4) |
| BB + ACEi (%) | 1 (1.2) |
| **Cardiovascular risk factors** | |
| BMI ≥ 25 kg/m² (%) | 20 (23.2) |
| Smoking (%) | |
| Never | 60 (69.8) |
| Ex-smoker | 17 (19.8) |
| Current | 9 (10.5) |
| AHT (%) | 8 (9.3) |
| Hyperlipidaemia (%) | 8 (9.3) |
| Diabetes (%) | 3 (3.5) |

[a] Marfan systemic score is a scoring system which takes into consideration several characteristic features of MFS and assigns each of them a value between 1–3, 3 being the most specific for the disease. A score of ≥ 7 is considered abnormal and in combination with aortic disease and/or ectopia lentis is diagnostic of MFS

[b] Patients reporting palpitations in the past were not included. Only confirmed atrial and ventricular ectopy for which treatment was implemented were considered

Abbreviations: ACEi: angiotensin converting enzyme inhibitor, Afib: atrial fibrillation, AoRR: aortic root replacement, ARB: angiotensin II receptor blocker antagonist, BB: beta-blocker, BMI: body mass index, EL: ectopia lentis, HTA: arterial hypertension, MV: mitral valve, MVP: mitral valve prolapse, SVT: supraventricular tachycardia, VE: ventricular ectopy.

Twenty-four patients had undergone cardiovascular surgery at baseline (21 AoRR, 2 mitral valve surgery alone and 1 patient both). Eleven patients had moderate to severe valvular disease (5 mitral valve regurgitation, 4 aortic valve regurgitation and 1 both) of whom 7 had not undergone cardiovascular surgery. These 31 patients formed the MFS-2 group. Eight patients had previously been treated or were currently under treatment for atrial arrhythmia (4 atrial fibrillation and 4 with another type of

supraventricular tachycardia) and 3 patients had been treated for symptomatic ventricular ectopia (2 medical treatment and 1 ablation). In the control group, except for one woman of 69yrs old who had undergone coiling for a cerebral aneurysm, no one had a significant medical history. Two controls had smoked in the past, 2 were treated for arterial hypertension and 7 reported to have hyperlipidemia.

As shown in Table 2, while 7 (8.1%) of the patients with MFS had decreased LVEF (5 in the MFS-2 group), decreased LVEF was no present in control subjects. Demographic characteristics in the group with decreased LVEF were similar to the rest of the MFS cohort (supplemental table 1). Median LVEF in this group was 53.1% (IQR 47.1 – 53.7%). As expected, LVEDDi and LVESDi were significantly higher in patients with decreased LVEF (28.2 ± 3.5 mm/m² versus 25.3 ± 3.5 mm/m², $p = 0.038$ and 21.7 ± 2.6 mm/m² versus 16.6 ± 2.7 mm/m², $p < 0.001$, respectively). Nine patients (10.5%) had a TAPSE value ≤ 16 mm (6 in the MFS-2 group).

To assess whether myocardial involvement in MFS has a primary component, we compared control subjects with those MFS-1 patients without previous surgery or valvular disease. As shown in Table 2, mild biventricular myocardial involvement in MFS-1 was evidenced by significantly higher NT-proBNP, left ventricular dimension, E/Em ratio and lower TAPSE. Furthermore, MFS-1 patients showed higher QRS-duration and QTc time at rest ECG. NSVT only occurred in patients with MFS. SDNN and RMSDD were significantly higher in MFS-1 even after adjusting for beta-blocker use ($p = 0.008$ and $p = 0.027$, respectively).

Table 2
Comparison between control subjects and patients with Marfan syndrome with and without valvular disease and/or cardiovascular surgery

| | Control subjects | patients with Marfan syndrome | | | p-value | p-value | p-value |
|---|---|---|---|---|---|---|---|
| | N = 40 | All<br>N = 86 | No surgery<br>No valvular disease<br>N = 55 (MFS-1) | Surgery<br>Valvular disease<br>N = 31 (MFS-2) | Control vs<br>MFS All | Control vs<br>MFS-1 | MFS-1<br>vs<br>MFS-2 |
| **Female (%)** | 22 (55) | 48 (55.8) | 31 (56.4) | 17 (54.8) | 0.728 | 0.895 | 0.891 |
| **Age (%)** | 37.9 ± 14.4 | 36.3 ± 14.3 | 35.1 ± 14.7 | 38.5 ± 13.7 | 0.586 | 0.370 | 0.295 |
| **Height (cm)** | 173 ± 10 | 183.4 ± 10.4 | 183.2 ± 11 | 183.9 ± 9.5 | **< 0.001** | **< 0.001** | 0.771 |
| **Weight (kg)** | 68.3 ± 9.2 | 74.1 ± 17.9 | 74.2 ± 17.9 | 74.1 ± 18.3 | **0.018** | **0.041** | 0.987 |
| **BSA (m²)** | 1.8 ± 0.1 | 1.9 ± 0.3 | 1.9 ± 0.2 | 1.9 ± 0.2 | **0.001** | **0.001** | 0.923 |
| **SBP (mmHg)** | 121.1 ± 12.7 | 123.4 ± 14.1 | 121 ± 12.6 | 127.3 ± 15.9 | 0.472 | 0.899 | **0.049** |
| **DBP (mmHg)** | 73.7 ± 9.6 | 69.8 ± 11 | 71.6 ± 70 | 67 ± 10.1 | 0.076 | 0.361 | 0.067 |
| **BB Use (%)[a]** | 0 (0) | 57 (66.3) | 32 (58.2) | 25 (80.6) | n.a | n.a | **0.034** |
| **Cardiac ultrasound** | | | | | | | |
| **Ao sinus (mm)** | 30.5 ± 2.9 | 40 ± 5.3 | 39.8 ± 5.1 | 41.1 ± 6.6[b] | **< 0.001** | **< 0.001** | 0.498 |
| **z-score sinus** | -0.8 ± 0.7 | 2.7 ± 1.4 | 2.5 ± 1.4 | 3.3 ± 1.1[b] | **< 0.001** | **< 0.001** | 0.094 |
| **LVEDDi (mm/m²)** | 24.7 ± 2.4 | 25.5 ± 3.5 | 24.8 ± 3.4 | 26.7 ± 3.5 | 0.127 | 0.795 | **0.020** |
| **LVEDDi ≥ 30 mm/m² (%)** | 0 (0) | 9 (10.5) | 5 (9.1) | 4 (12.9) | 0.056 | **0.050** | 0.717 |
| **LVEF (%)** | 68.3 ± 7.2 | 64.8 ± 7.5 | 66 ± 7.2 | 62.5 ± 7.6 | **0.013** | 0.131 | **0.034** |
| **LVEF < 55%** | 0 (0) | 7 (8.1) | 2 (3.6) | 5 (16.1) | 0.096 | 0.507 | 0.093 |
| **E/A** | 1.5 (1.2-2) | 1.7 ± 0.6 | 1.6 (1.3-2) | 1.6 (1.2–2.1) | 0.338 | 0.351 | 0.975 |

Values are given as mean ± SD, median (IQR) or number (%)

| | Control subjects | patients with Marfan syndrome | | | p-value | p-value | p-value |
|---|---|---|---|---|---|---|---|
| | N = 40 | All<br>N = 86 | No surgery<br>No valvular disease<br>N = 55 (MFS-1) | Surgery<br>Valvular disease<br>N = 31 (MFS-2) | Control vs<br>MFS All | Control vs<br>MFS-1 | MFS-1 vs<br>MFS-2 |
| **E/E'** | 6.4 (5.1–7.6) | 7.8 (6.9–10.4) | 7.8 (6.6–9.3) | 8.6 (7-12.8) | **< 0.001** | **< 0.001** | 0.051 |
| **LAVi (ml/m²)** | 21.2 ± 5.5 | 21.4 ± 9.1 | 21.4 ± 1.3 | 26.4 ± 11.3 | 0.685 | 0.945 | **0.038** |
| **MVP (%)[c]** | 1 (2.5) | 16 (18.6) | 8 (14.5) | 8 (26.7) | **0.011** | **0.045** | 0.185 |
| **TAPSE (mm)** | 24.5 ± 2.8 | 21.1 ± 4.2 | 22.1 ± 4.3 | 19.5 ± 3.8 | **< 0.001** | **0.003** | **0.010** |
| **TAPSE ≤ 16 mm (%)** | 0 (0) | 9 (10.5) | 3 (6.4) | 6 (20.7) | **0.027** | 0.250 | 0.077 |
| **Blood test** | | | | | | | |
| **NT-ProBNP (pg/ml)** | 30 (19-44.5) | 68.50 (35.3-149.3) | 53.5 (30-74.2) | 129 (82-235.2) | **< 0.001** | **0.001** | **< 0.001** |
| **Electrocardiographic data** | | | | | | | |
| **Min HR (bpm)** | 50.5 (44-55.5) | 46 (42-50.2) | 45 (41.5–49) | 48 (44–55) | **0.037** | **0.004** | **0.026** |
| **Average HR (bpm)** | 74.2 ± 8.3 | 65.5 (50.7–72.2) | 64 (56.5–71.5) | 67 (58.5–73) | **< 0.001** | **< 0.001** | 0.205 |
| **QRS width (ms)** | 80 (80–90) | 96 (84.5–104) | 96 (86–104) | 98 (86–106) | **< 0.001** | **< 0.001** | 0.639 |
| **QTc (ms)** | 380.2 ± 24.5 | 415 (400.2-435.7) | 414 (388-433.5) | 426 (407–445) | **< 0.001** | **< 0.001** | **0.028** |
| **QTc > 460 ms (%)** | 0 (0) | 4 (4.6) | 0 (0) | 4 (12.9) | n.a | n.a | n.a |
| **SVES/24 h** | 2 (0.25–4.7) | 11 (2-41.75) | 7 (2-37.5) | 17 (1–56) | **< 0.001** | **< 0.001** | 0.560 |
| **Atrial runs (%)** | 2 (5) | 26 (30.2) | 14 (26.4) | 12 (41.4) | **0.002** | **0.015** | 0.318 |

Values are given as mean ± SD, median (IQR) or number (%)

| | Control subjects | patients with Marfan syndrome | | | p-value | p-value | p-value |
|---|---|---|---|---|---|---|---|
| | N = 40 | All<br>N = 86 | No surgery<br>No valvular disease<br>N = 55 (MFS-1) | Surgery<br>Valvular disease<br>N = 31 (MFS-2) | Control vs MFS All | Control vs MFS-1 | MFS-1 vs MFS-2 |
| **VES/24 h** | 0 (0-5.7) | 7.5 (1–98) | 6 (1-69.5) | 14 (1.5-373.5) | **< 0.001** | **< 0.001** | 0.312 |
| **VE (%)** | 5 (12.5) | 27 (32.9) | 14 (26.4) | 13 (41.9) | **0.017** | 0.099 | 0.090 |
| **Vent couplets (%)** | 2 (5) | 17 (20.7) | 9 (17) | 8 (25.8) | **0.032** | 0.077 | 0.270 |
| **NSVT (%)** | 0 (0) | 10 (12.5) | 5 (9.1) | 5 (17.2) | **0.030** | **0.050** | 0.273 |
| **SDNN (ms)** | 147 (116-185.2) | 176 (138–208) | 185 (156.2-219.2) | 132 (95.4–191) | **0.034** | **0.001** | **0.003** |
| **RMSDD (ms)** | 53 (36.2–84) | 79.5 (58.2-111.5) | 82.5 (66.2–82.5) | 59.3 (42.7–112) | **0.003** | **< 0.001** | **0.040** |
| Values are given as mean ± SD, median (IQR) or number (%) | | | | | | | |

[a] Beta-blocker alone or in combination

[b]Only those patients with valvular pathology without aortic root replacement are considered for the mean value of the sinus and the z-score.

[c] Only those patients with true mitral valve prolapse considered here. Those with mitral valve bulging were not included in this calculation.

Abbreviations: Ao: aortic, BB: beta-blocker, BSA: Body surface area, DBP: Diastolic blood pressure, Dec Time: Deceleration time, HR: Heart Rate, LAVi: left atrium volume index, LVEDDi: Left ventricular end diastolic diameter index, LVEF: Left ventricular ejection fraction, MFS: Marfan syndrome, MVP: mitral valve prolapse, NSVT: Non-sustained ventricular, RMSDD: mean squared difference of successive NN intervals, SBP: Systolic blood pressure, SDNN: Standard deviation of the NN interval, SVES: Supraventricular extrasystoles, VES: Ventricular extrasystoles, TAPSE: Tricuspid annular plane systolic excursion, VE: ventricular ectopy.

In comparison to MFS-1 patients, at baseline MFS-2 patients showed significantly larger left ventricular dimensions and lower left ventricular ejection fraction, higher NT-proBNP, longer QTc time and decreased TAPSE. QTc time was abnormal (> 460 ms) in 4 patients in the MFS-2 group. Systolic blood pressure was

also slightly but significantly higher in MFS-2 patients (Table 2). SDNN and RMSDD were significantly lower in MFS-2 and similar to the control population.

Events during follow-up and AECG characteristics in subsequent examinations

During a follow-up period of 30 ± 7months 3 patients died from (suspected) aortic dissection or rupture (2 type A and 1 type B). Two of them died just after completing the 3rd visit (Fig. 1). Four other patients survived a dissection (1 coronary dissection, 1 type B dissection and 2 type A dissections). Prophylactic AoRR was performed in 6 patients and aortic valve replacement with mechanical prosthesis in an additional patient who had previous AoRR.

All patients except 4 (one of the patients who died, 2 patients who declined further participation after visit 1 and one patient who could not attend the last visit -figure 1-) completed the study.

The overall amount of VES on 24 h AECG in patients with MFS at baseline was low (7.5 VES/24 h IQR 1–98). However, 20 patients (23.3%) showed NSVT on one or more of the 24 h AECG (10 at the 1st exam, 10 additionally during the 2 consecutive exams). 80% of these patients was under treatment with a beta-blocker (Table 3). Only one patient in this group, showed sustained VT during follow-up despite beta-blocker therapy. He was 30yrs old at the time of the first sustained VT episode and had had AoRR and MV surgery 4 months earlier. No patients in the study developed SCD or arrhythmogenic syncope during the study period.

To identify factors associated with NSVT we compared the 20 patients having NSVT with the rest of the MFS cohort. Univariate analysis showed that LVEDDi, LVESDi, NT-proBNP and the amount of VES/24 h were significantly higher in the group with NSVT (Table 3). Furthermore, NSVT during follow-up occurred more frequently in the MFS-2 group than in the MFS-1 group (40% versus 14.5%, p = 0.008). In multivariate analysis, however, only LVEDDi and VES/24 h were independently associated with NSVT (Fig. 2). These 2 variables were associated independently from each other.

Table 3
Comparison between patients with and without non-sustained ventricular tachycardia

| | Non-sustained ventricular tachycardia | | |
|---|---|---|---|
| | **Present (n = 20)** | **Absent (n = 65[b])** | **p-value** |
| Female (%) | 10 (50) | 37 (59.7) | 0.604 |
| Age (yrs) | 40.3 ± 15.7 | 35.2 ± 13.8 | 0.170 |
| BSA (kg/m²) | 21.3 (19-25.5) | 21.4 (18.6–24.8) | 0.821 |
| SBP (mmHg) | 124.3 ± 12.8 | 122.1 ± 14.5 | 0.549 |
| DBP (mmHg) | 67.7 ± 5.7 | 70.1 ± 10.9 | 0.365 |
| BB Use (%) | 16 (80) | 39 (62.9) | 0.157 |
| MFS systemic score[a] | 8 (4–11) | 8 (6–10) | 0.657 |
| MFS group | | | **0.008** |
| MFS-1 (N = 55) (%) | 8 (40) | 47 (72.3) | |
| MFS-2 (N = 30[b]) (%) | 12 (60) | 18 (27.7) | |
| **Cardiac ultrasound** | | | |
| Ao sinus (mm) | 39.9 ± 4.3 | 40.1 ± 5.6 | 0.906 |
| MVP (%) | 7 (35) | 9 (15.3) | 0.058 |
| LVEDDi (mm/m²) | 27.9 ± 3.6 | 24.8 ± 3.2 | **< 0.001** |
| LVESDi (mm/m²) | 18.4 ± 3. | 16.7 ± 2.7 | **0.028** |
| LVEF (%) | 63.6 ± 8.2 | 65.2 ± 7.4 | 0.419 |
| RVOTi (mm/m²) | 15.9 ± 2.4 | 15.4 ± 2.7 | 0.476 |
| TAPSE (mm) | 20.8 ± 3.7 | 21.7 ± 4.2 | 0.448 |
| LAVi (mm/m²) | 24.2 (14-29.2) | 21.2 (15.2–28.6) | 0.854 |
| E/A ratio | 1.6 ± 0.6 | 1.7 ± 0.6 | 0.723 |
| E/Em ratio | 9.5 (7.1–11.7) | 7.8 (6.6–9.7) | 0.100 |
| **Serologic test** | | | |
| NT-ProBNP (pg/ml) | 112 (78.5-216.5) | 60 (31–129) | **0.017** |

Values are given as mean ± SD, median (IQR) or number (%)

| | Non-sustained ventricular tachycardia | | |
|---|---|---|---|
| **Ambulatory ECG** | | | |
| Min HR (bpm) | 47 (42–51) | 46 (42.2–50) | 0.792 |
| Average HR (bpm) | 67 (58–72) | 65.5 (57.2–72.7) | 0.991 |
| Max HR (bpm) | 122 (100–133) | 120.5 (101–142) | 0.684 |
| QRS width (ms) | 100 (90.5-109.5) | 96 (82.5-101.5) | 0.075 |
| Qtc time (ms) | 426 (403-443.2) | 413 (385.2–432) | 0.199 |
| VES/24 h | 345 (9-3727) | 4 (1–35) | **0.001** |
| SDNN (ms) | 177 (126.1-264.6) | 176 (140-203.5) | 0.620 |
| RMSDD (ms) | 74 (58-159.9) | 79.5 (57.9–109) | 0.790 |
| Values are given as mean ± SD, median (IQR) or number (%) | | | |

[a] MFS systemic score is a scoring system which takes into consideration several characteristic features of MFS and assigns each of them a value between 1–3, 3 being the most specific for the disease. A score of ≥ 7 is considered abnormal and in combination with aortic disease and/or ectopia lentis is diagnostic of MFS.

[b] One patient declined 24 h AECG

Abbreviations: Ao: aortic, AoRR: Aortic root replacement, AR: Aortic regurgitation, BB: Beta-blocker, BSA: Body surface area, DBP: Diastolic blood pressure, ECG: Electrocardiogram, HR: Heart Rate, LAVi: left atrium volume index, LVEDDi: Left ventricular end diastolic diameter index, LVESDi: Left ventricular end systolic diameter index, LVEF: Left ventricular ejection fraction, LVMi: Left ventricular mass index, MFS: Marfan syndrome, MR: Mitral regurgitation, MV: Mitral valve, MVP: Mitral valve prolapse, NSVT: Non-sustained ventricular, RAVi: Right atrium volume index, RMSDD: mean squared difference of successive NN intervals, RVOT: Right ventricular outflow track, SBP: Systolic blood pressure, SDNN: Standard deviation of the NN interval, SVES: Supraventricular extrasystoles, TAPSE: Tricuspid, annular, plane systolic excursion, VES: Ventricular extrasystoles.

Other factors such as the presence of MVP or increased E/Em ratio tended to be higher in the group with NSVT but this was not statistically significant. We could not identify variables on the resting ECG or parameters of HRV associated with the presence of NSVT.

Seven patients were under treatment for thyroid disease during the study period (6 women for hypothyroidism with levothyroxine and 1 male for hyperthyroidism with thiamazole). Within the patients with hypothyroidism, one had NSVT during FU and one a history of Afib. All other patients, except for 1

with slightly elevated TSH (5.4 mU/l), had normal values (reference value in our institution 0.4-4 mU/l). This patient showed no arrhythmic events on his three AECGs.

# Genotype-phenotype correlations

As shown in Table 4, the presence of NSVT was not associated with a specific type of *FBN1* variant. We observed, however, that those patients carrying a missense variant tended to have less arrhythmia. Four out of the 7 patients (57.1%) with decreased LVEF carried a frameshift variant. This was significantly higher than in the group with normal LVEF (20.5%, p = 0.050). No other genotype-phenotype correlations were found.

Table 4
Comparison of the genotype between patients with and without arrhythmia and with normal or decreased ejection fraction

| | **Non-sustained ventricular tachycardia** | | | **Left-ventricular ejection fraction** | | |
|---|---|---|---|---|---|---|
| | **Present (n = 20)** | **Absent (n = 64)[a]** | **p-value** | **< 55% (n = 7)** | **≥ 55% (n = 77)** | **p-value** |
| Type of variant | | | | | | |
| Missense (%) | 7 (35) | 35 (54.7) | 0.100 | 1 (14.3) | 41 (52.6) | 0.058 |
| Inframe (%) | 1 (5) | 0 (0) | 0.238 | 0 (0) | 1 (10.3) | 0.918 |
| Frameshift (%) | 5 (25) | 14 (21.9) | 0.494 | 4 (57.1) | 16 (20.5) | **0.050** |
| Nonsense (%) | 4 (20) | 11 (17.2) | 0.747 | 0 (0) | 15 (19.2) | 0.243 |
| Splice-site (%) | 3 (15) | 4 (6.3) | 0.349 | 2 (28.6) | 5 (6.4) | 0.100 |
| Effect on the protein | | | | | | |
| Haploinsufficiency (%) | 9 (45) | 24 (37.5) | 0.128 | 4 (57.1) | 30 (38.5) | 0.283 |
| Localization: exon | | | | | | |
| Exon 24–32 (%) | 2 (10) | 8 (12.5) | 0.559 | 0 (0) | 10 (12.8) | 0.402 |

Values are given as number (%)

[a] Variant details were lacking in one patient. Another patient declined ambulatory ECG

# Discussion

In our study, we show mild myocardial involvement in patients with MFS, even in those without valvular disease or previous cardiovascular surgery. Prevalence of NSVT was rather high in MFS, presenting in

almost a quarter of the patients either at baseline or during follow-up. Those patients with valvular and/or cardiovascular surgery in the past seemed to have higher risk of myocardial disease.

Mild but significant myocardial dysfunction in patients with MFS has been reported earlier in several independent studies [4–10]. Myocardial involvement in patients without valvular disease or past history of cardiovascular surgery strongly suggests primary myocardial involvement. The fact that the majority of the patients with reduced ejection fraction were carrying a truncating variant suggests that there is a genetic predisposition, independent of hemodynamic overload, to develop myocardial dysfunction. These findings are in line with the findings of Aalberts and colleagues[19] and with the general observation that variants causing a HI effect (like most of the truncating variants) are associated with a more severe cardiovascular phenotype[28–31]. On the other hand we demonstrate that those patients with valvular disease and past history of cardiovascular surgery, have larger left ventricular diameters and lower ejection fraction, indicating that hemodynamic overload (as expected) also plays an important role in the pathophysiology of MFS cardiomyopathy.

So far, 6 studies, ours included, have investigated ventricular arrhythmia in MFS in detail[2,4,16,17,32]. Additional values of our study are the inclusion of a control population and the availability of serial 24 h AECGs in patients with MFS. Although in control subjects isolated ventricular extrasystoles are a relatively common finding, present in 12.5% of the subjects, NSVT was only present in patients with MFS. Two questions which we have not been able to resolve however, are (1) does the presence of NSVT predispose to life threatening arrhythmias and (2) is it necessary to treat NSVT to prevent adverse events. The prognostic value of NSVT in non-MFS patients is very variable[33] and the available evidence to answer this question for patients with MFS is very limited. Yetman and colleagues found that ventricular ectopy (defined as > 10VES/h, the presence of couplets or NSVT) was an independent risk factors of SCD[4]. Although Hoffman and colleagues[2] and Aydin and colleagues[16] found a higher amount of NSVT in those patients with ventricular arrhythmic events, these differences were not significant after multivariate analysis. In our study, no patient presented SCD or arrhythmogenic syncope and therefore we were not able to assess the predictive value of NSVT, but the high prevalence of NSVT contrasts with the low prevalence of SCD in our study. In our cohort, the only patient developing sustained VT, showed progressive ventricular ectopy under beta-blocker treatment and episodes of sustained VT were only controlled after treatment with amiodarone. In the study of Yetman and colleagues.[4], 2 of the 3 cases of SCD were under treatment with beta-blocker. Therefore, based on this very limited evidence, treatment of ventricular ectopy with beta-blockers alone seems insufficient, but further study in a larger cohort is warranted.

Another matter of debate is the underlying mechanism responsible for the ventricular ectopy. So far an enlarged LV diameter seems to be the most consistent independent factor associated with an arrhythmic event[4,16,17]. Although in the publication of Hoffman and colleagues, LV diameter was not independently associated with SCD and sustained VT, NT-proBNP, a marker of myocardial disease, showed to be a good predictor of these events. NT-proBNP, in our cohort, was also higher in those patients with NSVT, but we

could not find a very strong association. The levels of NT-proBNP in our patients with MFS were overall within normal values (68.50 pg/ml, IQR 35.3-149.3) which might explain the lack of association.

A peculiar finding was that the 2 parameters of heart rate variability (SDNN and RMSDD) were increased in patients with MFS without valvular disease or surgery independently of beta-blocker use. Heart rate variability refers to the fluctuation in the beat-to-beat interval of a patient's heart rate and reflects the autonomic activity of the heart. Lower values of heart rate variability have been related to left ventricular dysfunction and a higher incidence of arrhythmia after myocardial infarction in the general population[34]. In patients with MFS, however, its use has been very limited and actually, higher values of heart rate variability have been associated with cardiovascular risk. Hoffman and colleagues showed significantly higher RMSSD in those patients reaching the composite end point (ventricular tachycardia or fibrillation, arrhythmogenic syncope or sudden cardiac death)[2] and Mah and colleagues showed higher values of the triangular index (another parameter of heart rate variability) in those patients with worse aortic outcome[17]. In our study, we could not establish an association between heart rate variability and NSVT or reduced left ventricular function. Further study of autonomic function in patients with MFS could be interesting to gain a better understanding of its relation to the clinical outcome.

# Limitations and future perspectives

One of the most important limitations of our study is the sample size and the low number of events. These have prevented us from answering some important questions.

The underlying cause of ventricular ectopy should be better elucidated. For example, we did not address myocardial fibrosis as underlying mechanism of ventricular dysfunction and arrhythmia. A small study with cardiac MRI in 35 children with MFS (N = 14) and Loeys-Dietz syndrome (N = 21) showed increased markers of myocardial fibrosis in patients compared to an age-matched control population[35]. Another clue to better understand the pathophysiology of arrhythmia, could be determining the location of the ventricular ectopy. In our study, solely based on the 24 h AECG, it was challenging to accurately determine the ectopic foci. Therefore, electrophysiologic studies in a selected group of patients might be useful. Furthermore, in our study, mitral valve prolapse in itself did not seem to be highly correlated with higher incidence of ventricular arrhythmia, however other studies did find this correlation. It is possible that not so much mitral valve prolapse, but mitral valve annular disjunction (MAD) might be the underlying cause of arrhythmia in MFS, as it has been shown in non-MFS patients with MAD[36]. This correlation should be studied more in-depth.

## Conclusion

Patients with MFS have mild but significant myocardial dysfunction and a higher frequency of ventricular arrhythmia in comparison to healthy subjects. Although the overall amount of VES in patients with MFS was low, almost a quarter of the patients presented NSVT. Based on these facts we recommend surveillance of myocardial function and arrhythmia in all patients with MFS. Those patients with

increased LV diameter, decreased LV function, palpitations or additional cardiovascular risk factors including valvular disease and surgery, form a higher risk population.

# Abbreviations

ACEi: angiotensin converting enzyme inhibitor

AECG: ambulatory electrocardiogram

Afib: atrial fibrillation

AoRR: aortic root replacement

ARB: angiotensin receptor blocker

ASE: America Society of Echocardiography

BB: beta-blocker

BMI: body mass index

BSA: body surface area

DBP: diastolic blood pressure

DecTime: deceleration time

DN: dominant negative

EACVI: European Association of Cardiovascular Imaging

ECG: electrocardiogram

EL: ectopia lentis

FBN1: fibrillin-1 gene

HI: haploinsufficient

HR: heart rate

HRV: heart rate variability

HTA: arterial hypertension

LAVi: indexed left atrial volume

LVEDD: left ventricular end diastolic diameter

LVEDDi: indexed left ventricular end-diastolic diameter

LVEF: left ventricular ejection fractions

LVESD: left ventricular end-systolic diameter

MAD: mitral valve disjunction

MFS: Marfan syndrome

MV: mitral valve

MVP: mitral valve prolapse

NSVT: non-sustained ventricular tachycardia

RAVi: indexed right atrial volume

RMSDD: mean squared difference of successive normal to normal intervals

RVOT: right ventricular outflow track

SBP: systolic blood pressure

SCD: sudden cardiac death

SDNN: standard deviation of the normal-to-normal interval

SVES: supraventricular extrasystoles

TAC ligation : transverse aortic constriction ligation

TAPSE: tricuspid annular plane systolic excursion

TDI: tissue dopple imaging

VE: ventricular ectopy

VES: ventricular extrasystoles

VT: ventricular tachycardia

Yr: years

# Declarations

## Ethics approval and consent to participate

The study was approved by the local Independent Ethics Committee (IEC) and the Institutional Review Board (IRB) of of the Ghent University Hospital. Review identification number: EC: 2014/1198

All subjects participating in the study gave written informed consent.

## Consent for publication

All subjects participating in the study gave written informed consent.

## Availability of data and materials

The datasets generated and analysed during the current study are not publicly available because it could compromise the anonymity and confidentiality of the patient data but are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.


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## Author’s contributions

LMM, DDW and JDB contributed substantially to the conception and design of the work. LMM, HDW, DD, DB, LJ, AD, KDG and JDB contributed substantially to the acquisition, analysis and interpretation of the data. LMM, DDW, AD and JDB have drafted the work or substantively revised it.

All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.


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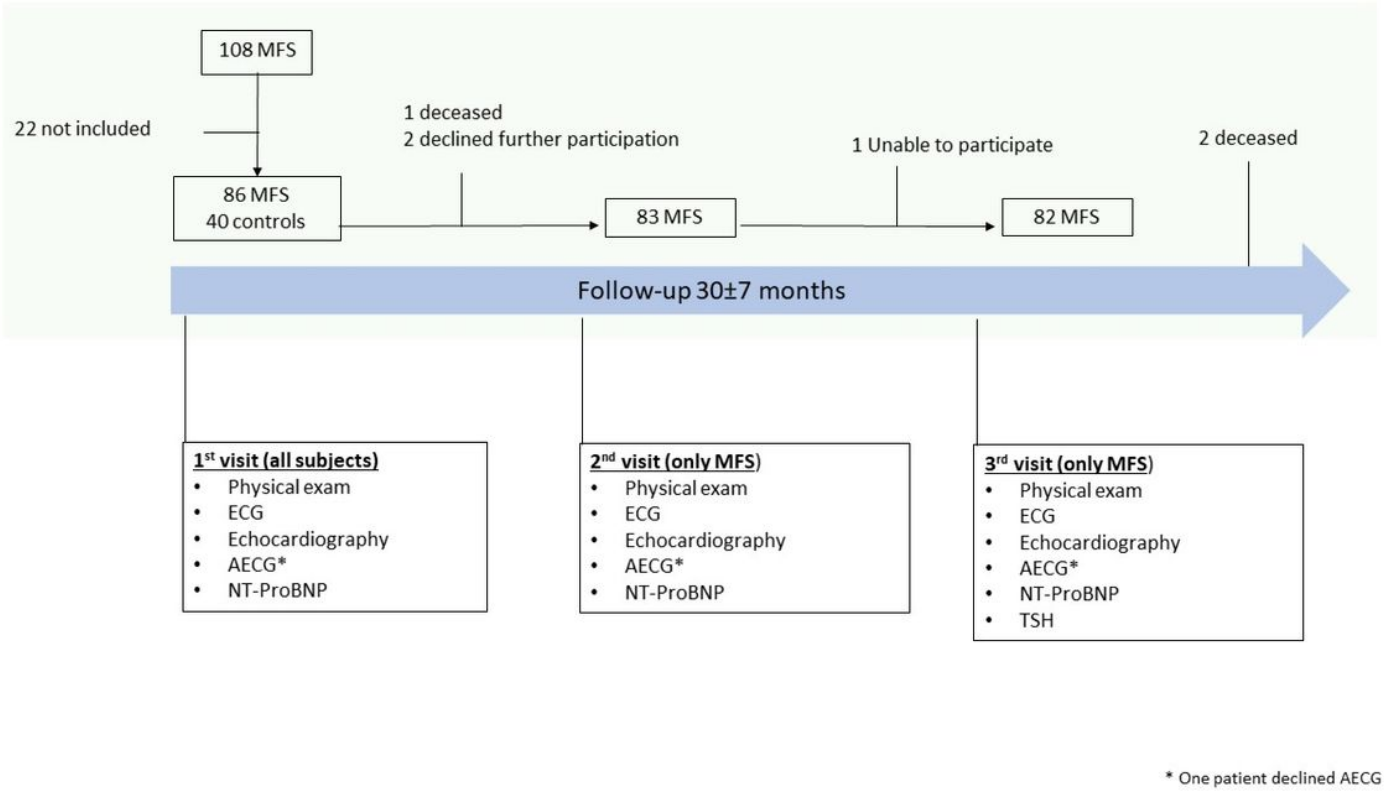
# Figures




## Figure 1

Inclusion procedure and investigations at baseline and during follow-up Eighty-six patients with MFS and 40 age- and sex matched controls were included in the study. At baseline all subjects underwent physical examination, resting and ambulatory ECG, cardiac ultrasound and dosing of NT-proBNP. In patients with MFS these investigations were repeated twice, in a mean period of 30±7months and TSH level was determined at the end of the study. Additionally, a subset of 45 patients underwent cardiac MRI with angiography and measurement of PWV. Eighty-two patients completed all 3 visits. Three patients died during study, 2 of them after completing the 3rd visit. Two patients declined further participation after the 1st visit and 1 patient could not attend the last visit. Abbreviations: AECG: Ambulatory ECG, ECG: Electrocardiogram, MFS: Marfan syndrome, MRI: Magnetic Resonance Image

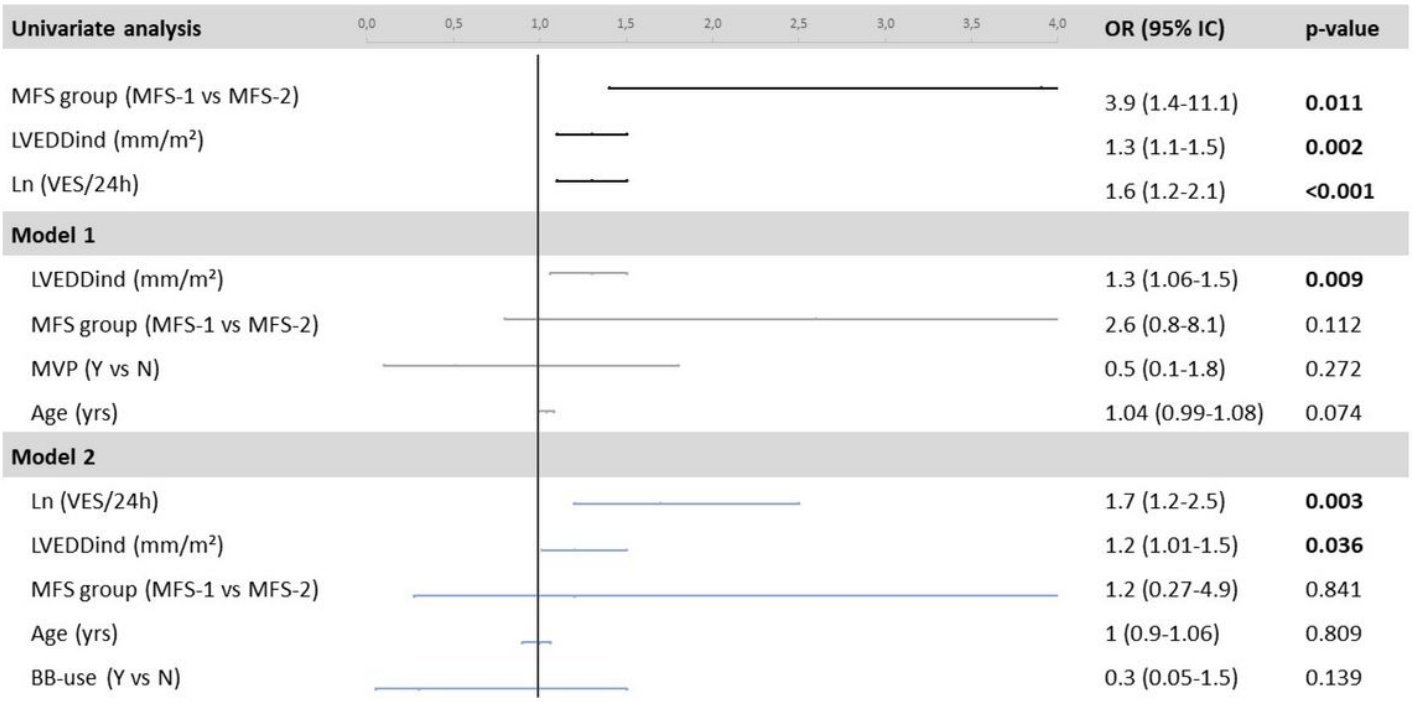



**Figure 2**

Multivariate analysis to identify independent associations with NSVT in patients with Marfan syndrome Multivariate analysis shows that higher left ventricular dimension and higher amount of VES in the AECG are the only independent factors of the presence of NSVT. Abbreviations: ln: logarithm, LVEDDind: left ventricular end diastolic diameter index, MFS: Marfan syndrome, ln: logarithm, yr: year, VES: ventricular extrasystoles.

# Supplementary Files

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- Supplemental.docx