

APPENDICES

Supplemental Table 1. Baseline and follow-up characteristics according to sex in the subgroups of patients presenting with heart failure, chest pain and arrhythmias at the onset.

| DATA AT BASELINE | | | | | | | | | |
|----------------------------------|---------------------|---------------------|------------------|--------------------|-----------------|--------------|-----------------------|-----------------------|--------------|
| | Chest Pain N = 187 | | | Arrhythmias N = 19 | | | Heart Failure N = 106 | | |
| Population | F = 51 (27 %) | M = 136 (73%) | p value | F = 7 (37%) | M = 12 (63%) | p value | F = 43 (41%) | M = 63 (59%) | p value |
| Age, (years) | 41 ± 22 | 34 ± 16 | 0.640 | 30 ± 10 | 44 ± 21 | 0.201 | 43 ± 17 | 40 ± 17 | 0.480 |
| SBP, (mmHg) | 121 ± 18 | 124 ± 14 | 0.156 | 124 ± 19 | 121 ± 17 | 0.749 | 115 ± 17 | 117 ± 19 | 0.731 |
| NYHA Class, no. (%) | | | | | | | | | |
| I | 29 (91%) | 89 (90%) | 0.955 | 6 (86%) | 9 (75%) | 0.718 | 9 (21%) | 12 (19%) | 0.765 |
| II | 1 (3%) | 5 (5%) | | 0 | 1 (8%) | | 12 (29%) | 18 (29%) | |
| III | 1 (3%) | 2 (2%) | | 0 | 0 | | 11 (26%) | 20 (32%) | |
| IV | 1 (3%) | 3 (3%) | | 1 (14%) | 2 (17%) | | 10 (24%) | 12 (19%) | |
| LVEF, (%) | 61 (55-65) | 59 (56-63) | 0.679 | 61 (50-69) | 56 (47-65) | 0.254 | 29 (23-40) | 29 (24-36) | 0.953 |
| LVEDVi, (mL/m2) | 43 ± 10 | 50±11 | <0.001 | 56 ± 27 | 65±21 | 0.340 | 81±36 | 83 ± 26 | 0.744 |
| Non ischemic LGE, no. (%) | 15 (29%) | 67 (49%) | <0.001 | 3 (42%) | 4(33%) | 0.858* | 5(12%) | 12 (19%) | 0.074 |
| Beta-blocker, no. (%) | 21 (46%) | 37 (34%) | 0.182 | 5 (83%) | 6 (60%) | 0.588* | 22 (81,5%) | 30 (77%) | 0.656 |
| ACE-i/ARB, no. (%) | 12 (26%) | 19 (18%) | 0.263 | 3 (60%) | 1 (14%) | 0.222* | 11 (92%) | 16 (84%) | 0.546 |
| | | | | | | | | | |
| DATA AT LAST AVAILABLE FOLLOW-UP | | | | | | | | | |
| | Chest Pain N = 181 | | | Arrhythmias N = 15 | | | Heart Failure N= 57 | | |
| Population | F = 50 | M =131 | p value | F = 6 | M = 9 | p value | F = 21 | M = 36 | p value |
| ICD at follow-up, no. (%) | 0 | 2 (2%) | 0.464 | 5(83) | 6 (67%) | 0.537* | 9 (42%) | 14 (39%) | 0.764 |
| LVEF follow-up, (%) | 62 (55-69) | 60 (57-64) | 0.567 | 63 (56-68) | 56 (47-65) | 0.254 | 50 (42-55) | 42 (29-51) | 0.004 |
| LVEDVi follow-up (mL/m2) | 44 ± 11 | 53 ± 11 | 0.002 | 46 ± 14 | 71 ± 20 | 0.019 | 63 ± 25 | 77 ± 30 | 0.048 |

Legend: ACE-i, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; ICD, implantable cardiac defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume indexed; LVESVi, left ventricular end-systolic volume indexed; NYHA, New York Heart Association; SBP systolic blood pressure. In bold p-value < 0.05. *Fisher exact Test

Supplemental Table 2. Incidence rates of events as number of events per 100 patients/years.

| | Females (n 101, 32%) | | | | Males (n 211, 68%) | | | |
|------------------------------|----------------------|---------|----------------|---------|--------------------|----------|-----------------|---------|
| | All (101) | CP (51) | Arrhythmia (7) | HF (43) | All (211) | CP (136) | Arrhythmia (12) | HF (63) |
| ICD appropriate intervention | 0.5 | 0 | 2.1 | 0.7 | 0.5 | 0.2 | 2.4 | 0.7 |
| Death | 0.6 | 0 | 0 | 1.3 | 1.4 | 0.6 | 2.2 | 2.8 |
| HTx | 0.5 | 0 | 1.3 | 0.9 | 1.4 | 0.6 | 2.2 | 2.8 |
| Death or HTx | 0.9 | 0 | 1.3 | 1.6 | 2 | 0.8 | 2.2 | 4.1 |

Legend: CP. chest pain; HTx. heart transplantation; HF. heart failure; ICD. implantable cardiac defibrillator.

Supplemental Table 3. Baseline and follow-up characteristics according to the primary outcome of death for all cause/heart transplant.

| DATA AT BASELINE | | | |
|---|----------------------------------|----------------------------|------------------|
| Population N=312 | Death/HTx free N= 272 | Death/HTx N= 44 | p-value |
| Age, (years) | 38±17 | 37±19 | 0.740 |
| Male Sex no. (%) | 178 (65) | 36 (82) | 0.031 |
| NYHA Class, no. (%) | | | <0.001 |
| I | 146 (53) | 11(25) | |
| II | 24 (9) | 13 (29) | |
| III | 28 (10) | 6 (14) | |
| IV | 15 (6) | 14 (32) | |
| Chest Pain onset no. (%) | 178 (65) | 9 (20) | <0.001 |
| Arrhythmias onset no. (%) | 15 (6) | 4 (9) | 0.355* |
| Heart Failure onset no. (%) | 75 (28) | 31 (70) | <0.001 |
| Diabetes mellitus, no. (%) | 10 (4) | 1 (2) | 0.522* |
| Hypertension, no. (%) | 41 (15) | 1 (2) | 0.104* |
| Family History for DCM, no. (%) | 11 (4) | 2 (4) | 0.942* |
| LVEF baseline, (%) | 51±15 | 31±13 | <0.001 |
| LVEDVi baseline, (mL/m2) | 56±22 | 84±34 | <0.001 |
| Restrictive pattern, no. (%) | 34 (13) | 29 (66) | <0.001 |
| Non ischemic LGE, no. (%) | 103 (38) | 3 (7) | 0.319* |
| Beta-blocker, no. (%) | 109 (40) | 12 (27) | 0.208 |
| ACE-i/ARB, no. (%) | 59 (22) | 3 (7) | 0.094* |
| MRA, no. (%) | 29 (11) | 2 (4) | 0.748* |
| Diuretics, no. (%) | 44 (16) | 17 (39) | <0.001 |
| DATA AT LAST AVAILABLE FOLLOW-UP | | | |
| Population N= 255 | | | |
| ICD, at follow-up, no. (%) | 32 (13) | 4 (9) | 0.865* |
| LVEF at follow-up, (%) | 55±12 | 37±11 | <0.001 |
| LVEDVi at follow-up, (mL/m2) | 58±22 | 88±32 | 0.002 |
| LVESVi at follow-up, (mL/m2) | 28±19 | 54±23 | 0.003 |

Legend: ACE-i, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; HTx, heart transplantation; ICD, implantable cardiac defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume indexed; LVESVi, left ventricular end-systolic volume indexed; MRA mineral corticoid antagonists; NYHA, New York Heart Association. In bold p-value < 0.05.
*Fisher exact Test

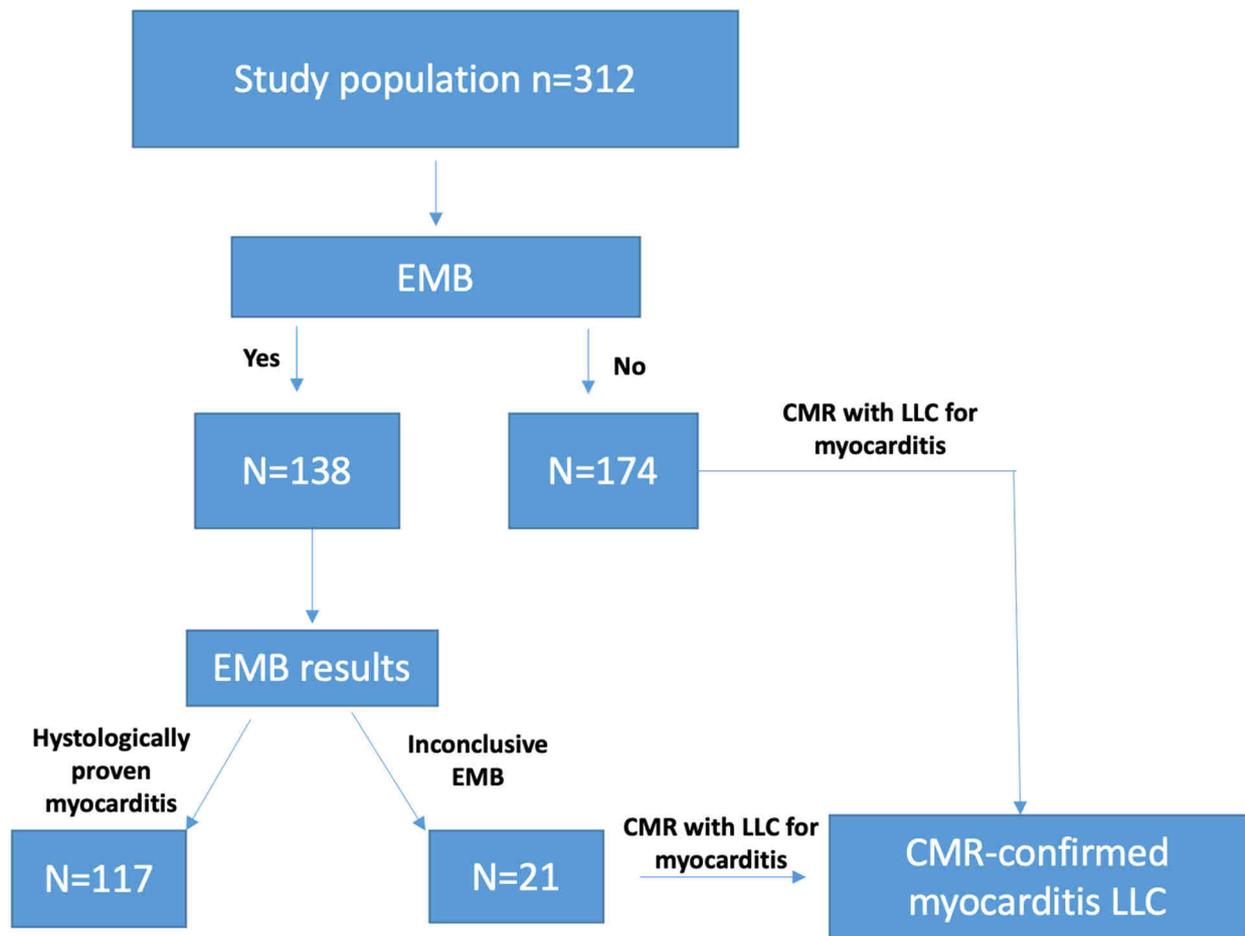
Supplemental Table 4. Different multivariable Cox models, each time maintaining male sex and changing the combination of the other covariates.

| | HR (95% C.I.) | p-value |
|----------------------------------|------------------------------|----------------|
| Male sex. No. (%) | 2.416 (1.072 – 5.447) | 0.033 |
| Onset with chest pain | 0.512 (0.079-3.315) | 0.482 |
| LVEF < 50% at baseline | 6.491 (0.980-43.010) | 0.053 |
| LVEDVi at baseline | 1.006 (0.991-1.020) | 0.448 |
| Male sex. No. (%) | | |
| Male sex. No. (%) | 2.600 (1.167-5.792) | 0.020 |
| Onset with HF | 0.540 (0.111-2.634) | 0.446 |
| Onset with chest pain | 0.306 (0.043-2.159) | 0.235 |
| LVEF < 50% at baseline | 11.442 (1.696-77.206) | 0.012 |
| Male sex. No. (%) | | |
| Male sex. No. (%) | 2.530 (1.132-5.657) | 0.024 |
| Onset with HF | 2.139 (0.480-9.538) | 0.319 |
| Onset with chest pain | 0.293 (0.056-1.535) | 0.146 |
| LVEDVi at baseline | 1.007 (0.995-1.020) | 1.007 |
| Male sex. No. (%) | | |
| Male sex. No. (%) | 2.600 (1.163-5.809) | 0.020 |
| Onset with HF | 0.970 (0.234-4.026) | 0.996 |
| Restrictive pattern | 2.682 (1.243-5.788) | 0.012 |
| LVEF < 50% at baseline | 11.496 (1.964-67.277) | 0.007 |
| Male sex. No. (%) | | |
| Male sex. No. (%) | 2.547 (1.142-5.678) | 0.022 |
| Onset with HF | 4.398 (1.535-12.605) | 0.006 |
| Restrictive pattern | 2.913 (1.317-6.444) | 0.008 |
| LVEDVi at baseline | 1.002 (0.988-1.015) | 0.817 |

| | | |
|----------------------------------|------------------------------|-------------------|
| Male sex. No. (%) | 2.460 (1.094-5.533) | 0.030 |
| Onset with HF | 0.996 (0.235-4.221) | 0.995 |
| LVEF < 50% at baseline | 14.541 (2.424-87.233) | 0.003 |
| LVEDVi at baseline | 1.006 (0.993-1.018) | 0.939 |
| | | |
| Male sex. No. (%) | 2.520 (1.124-5.650) | 0.025 |
| Restrictive pattern | 3.036 (1.289-7.150) | 0.011 |
| LVEF < 50% at baseline | 11.583 (2.822-47.541) | < 0.001 |
| LVEDVi at baseline | 0.998 (0.982 – 1.014) | 0.793 |
| | | |
| Male sex. no. (%) | 2.591 (1.160-5.789) | 0.020 |
| Onset with chest pain | 0.625 (0.088-4.456) | 0.639 |
| Restrictive pattern | 2.583 (1.191-5.602) | 0.016 |
| LVEF < 50% at baseline | 7.690 (1.106-53.474) | 0.039 |
| | | |
| Male sex. no. (%) | 3.169 (1.456-6.900) | 0.021 |
| Onset with HF | 1.404 (0.489-4.026) | 0.528 |
| Onset with chest pain | 0.327 (0.100-1.074) | 0.065 |
| Restrictive pattern | 2.678 (1.371-5.231) | 0.004 |
| | | |
| Male sex. no. (%) | 2.596 (1.164-5.791) | 0.020 |
| Onset with chest pain | 0.225 (0.074-0.689) | 0.009 |
| Restrictive pattern | 2.913 (1.316-6.447) | 0.008 |
| LVEDVi at baseline | 1.004 (0.991-1.016) | 0.553 |

Legend: HF, heart failure; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction. In bold p-value < 0.05.

Supplemental Figure 1: Consort flow diagram of the population.



Legend: CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy; LLC, Lake Louise Criteria.

Supplemental Figure 2: Long-term HTx-free survival according to the sex in the subgroups of patients presenting with chest pain (panel A). arrhythmias (panel B). heart failure (panel C). HTx indicates heart transplantation. Interestingly, no female experienced the outcome measure in chest pain group vs. 9 (6%) males. $p=0.1$. The subgroup of patients with HF at the onset experienced more adverse events than the other groups. $p=0.019$.

