**SEX DIFFERENCES ON MORTALITY AFTER AORTIC VALVE REPLACEMENT IN PATIENTS WITH PARADOXICAL LOW FLOW SEVERE AORTIC STENOSIS**

Online Supplementary Material

**Table S1. Implanted valve types and sizing**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Size** | | |
| **Prosthethic valve model** | **≤21 mm** | **22-25 mm** | **>25 mm** |
| **Mechanical valves** | | | |
| St. Jude Medical Standard | **14** | **18** | **3** |
| St Jude Medical Regent | **23** | **13** | **1** |
| Carbomedics Standard and TopHat | **6** | **21** | **5** |
| MCRI On-X | **16** | **10** | **0** |
| Medtronic Advantage | **10** | **30** | **0** |
| ATS Medical | **0** | **5** | **0** |
| **Stented bioprosthetic valves** | | | |
| Carpentier-Edwards Magna | **368** | **513** | **46** |
| Medtronic Mosaic | **15** | **74** | **23** |
| Sorin Mitroflow | **42** | **34** | **4** |
| St. Jude Medical Epic | **26** | **39** | **1** |
| St. Jude Medical Trifecta | **31** | **36** | **1** |
| **Stentless bioprosthetic valves** | | | |
| Medtronic Freestyle | **3** | **5** | **1** |
| Sorin Freedom SOLO | **11** | **23** | **8** |
| **Sutureless bioprosthetic valves** | | | |
| ATS Enable | **0** | **3** | **0** |
| Perceval | **0** | **0** | **8** |

**Table S2. Baseline characteristics according to transvalvular flow**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Normal flow**  (n=1006, 67%) | **Paradoxical Low Flow**  (n=484, 33%) | **P value** |
| **Clinical data** |  |  |  |
| Age, yrs | 70±10 | 70±10 | 0.48 |
| Female sex | 358 (36) | 186 (38) | 0.29 |
| Body surface area, m2 | 1.81±0.20 | 1.86±0.22 | **<0.001** |
| Systolic blood pressure, mmHg | 129±19 | 129±19 | 0.84 |
| Diastolic blood pressure, mmHg | 71±10 | 74±10 | **<0.001** |
| Heart rate, beats/min | 65±11 | 71±12 | **<0.001** |
| Symptomatic | 877 (87) | 428 (88) | 0.49 |
| NYHA functional class III-IV | 371 (37) | 200 (41) | 0.10 |
| Hypertension | 713 (71) | 355 (73) | 0.32 |
| Diabetes | 264 (26) | 165 (34) | **0.002** |
| COPD | 117 (12) | 63 (13) | 0.44 |
| CAD | 490 (49) | 237 (48) | 0.93 |
| Previous myocardial infarction | 143 (14) | 78 (16) | 0.33 |
| Concomitant CABG | 475 (47) | 230 (48) | 0.91 |
| Chronic kidney disease | 42 (4) | 23 (5) | 0.61 |
| Atrial fibrillation | 70 (7) | 61 (13) | **0.001** |
| Parsonnet risk score | 2 [2-4] | 3 [2-4] | 0.06 |
| Valve weight, g | 2.83±1.33 | 2.65±1.25 | **0.025** |
| Anatomically severe AS | 676 (88) | 324 (84) | **0.045** |
| **Echocardiographic data** | | | |
| **Before AVR** | | | |
| LV end-diastolic diameter, cm | 4.65±0.60 | 4.52±0.53 | **<0.001** |
| LV end-diastolic volume, ml | 102±32 | 95±26 | **<0.001** |
| Relative wall thickness ratio | 0.48±0.11 | 0.50±0.11 | **0.001** |
| LV mass index, g.m-2 | 113±33 | 107±30 | **0.001** |
| Peak aortic jet velocity, m.s-1 | 4.2±0.7 | 4.1±0.8 | **<0.001** |
| Mean gradient, mm Hg | 45±16 | 42±17 | **0.01** |
| Mean gradient <40 mmHg | 405 (40) | 238 (49) | **0.001** |
| LVOT diameter, cm | 2.18±0.20 | 2.09±0.18 | **<0.001** |
| Aortic valve area, cm2 | 0.79±0.20 | 0.65±0.20 | **<0.001** |
| Indexed aortic valve area, cm2.m-2 | 0.44±0.11 | 0.35±0.10 | **<0.001** |
| Zva, mmHg.ml-1.m-2 | 4.1±0.8 | 5.6±1.1 | **<0.001** |
| LV ejection fraction, % | 63±7 | 61±7 | **<0.001** |
| LVEF 50-59% | 162 (16) | 110 (23) | **0.002** |
| Mean transvalvular flow, ml.s-1 | 253±51 | 194±37 | **<0.001** |
| Stroke Volume, ml | 78±15 | 57±9 | **<0.001** |
| SVi, ml.m-2 | 43±7 | 31±3 | **-** |
| **After AVR** | | | |
| SVi - Discharge, ml.m-2 | 34±8 | 31±30 | **<0.001** |
| Patient-prosthesis mismatch |  |  | 0.59 |
| Moderate | 176 (19.0) | 88 (19.2) |  |
| Severe | 4 (0.4) | 4 (0.9) |  |

*AS: aortic stenosis, AVR: aortic valve replacement, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, CABG: coronary artery bypass graft, LV: left ventricle, LVOT: left ventricular outflow tract, SVi: stroke volume index, PPM: patient-prosthesis mismatch*

**Table S3. Background model for multivariate predictors of overall mortality**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Predictor** | **Increment** | **HR** | **95% CI** | **P value** |
| **Age** | **1 year** | **1.05** | **1.03-1.07** | **<0.01** |
| Sex | Female | 1.06 | 0.76-1.49 | 0.73 |
| **NYHA III-IV** | **Yes** | **1.57** | **1.15-2.16** | **<0.01** |
| CAD | Yes | 1.08 | 0.77-1.52 | 0.66 |
| **Diabetes** | **Yes** | **1.52** | **1.10-2.11** | **0.01** |
| **COPD** | **Yes** | **1.56** | **1.06-2.29** | **0.02** |
| AF | Yes | 1.24 | 0.79-1.95 | 0.34 |
| **CKD** | **Yes** | **2.75** | **1.76-4.31** | **<0.01** |
| Hypertension | Yes | 1.39 | 0.93-2.08 | 0.10 |
| LVEF 50-59% | Yes | 1.30 | 0.92-1.85 | 0.14 |

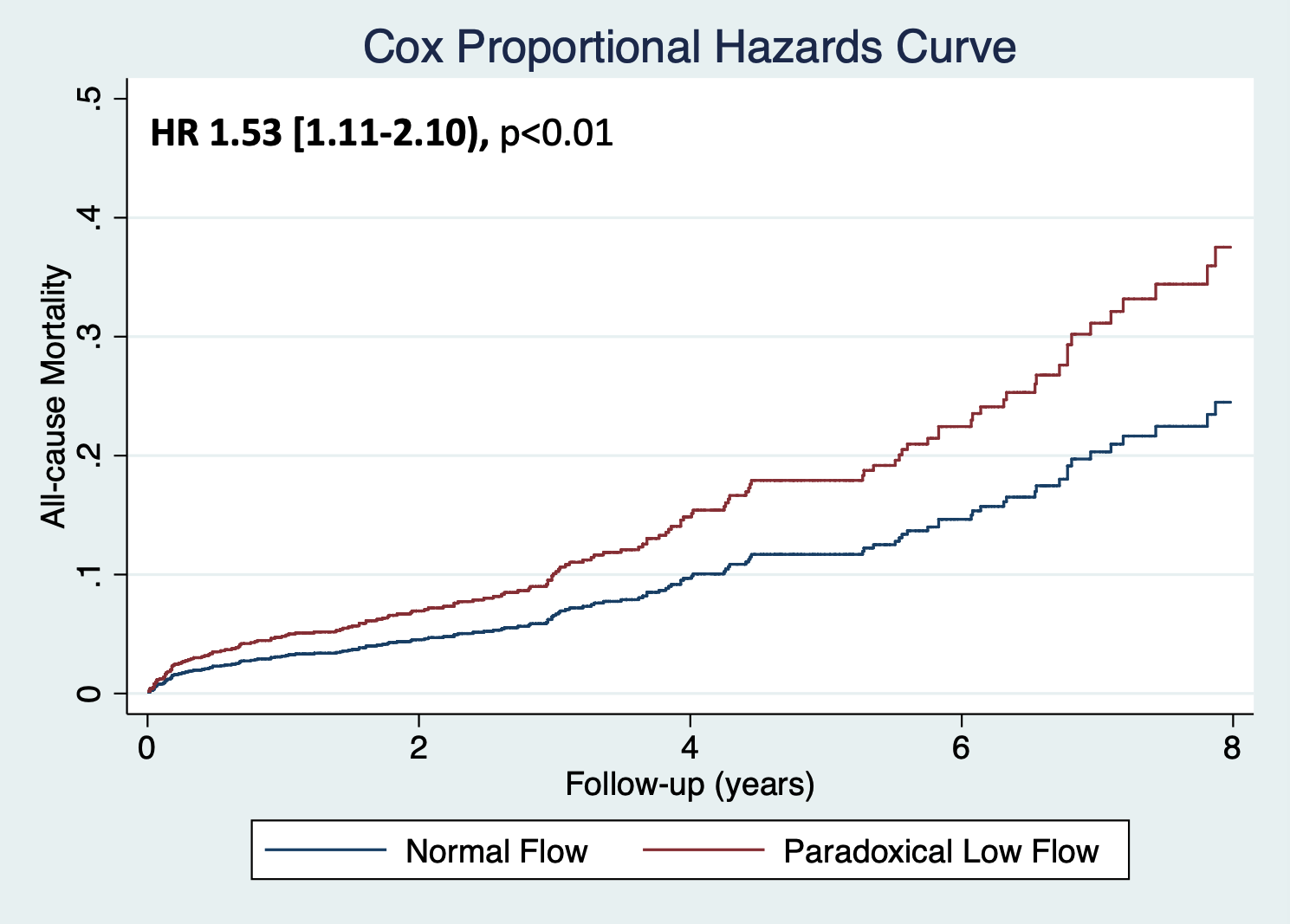
Background model adjusted for all listed variables, stroke volume index and mean gradient. HR: hazard ratio; CI: confidence interval; COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, CKD: chronic kidney disease, AF: atrial fibrillation, LVEF: left ventricular ejection fraction.

**Table S4. Additive models of multivariate analyses of overall mortality**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Clinical variables**  Chi2=84.79 | | | **+ LVEF**  Chi2=87.03 (p=0.14)  NRI=-0.09±0.10 (p=NS) | | | **+ Mean Gradient**  Chi2=96.72 (p<0.01)  NRI=0.17±0.11 (p=NS) | | | | **+ Stroke Volume Index**  Chi2=102.76 (p=0.01)  NRI=0.23±0.10 (p=0.026) | | |
| **Predictor** | **Increment** | **HR** | **95% CI** | **P value** | **HR** | **95% CI** | **P value** | **HR** | **95% CI** | **P value** | **HR** | | **95% CI** | **P value** |
| Age | 1 year | 1.05 | 1.03-1.07 | <0.01 | 1.05 | 1.03-1.07 | <0.01 | 1.05 | 1.03-1.07 | <0.01 | 1.05 | | 1.03-1.07 | <0.01 |
| Sex | Female | - | - | - | - | - | - | - | - | - | - | | - | - |
| NYHA III-IV | Yes | 1.56 | 1.14-2.14 | <0.01 | 1.55 | 1.13-2.12 | <0.01 | 1.58 | 1.15-2.16 | <0.01 | 1.56 | | 1.13-2.14 | <0.01 |
| CAD | Yes | - | - | - | - | - | - | - | - | - | - | | - | - |
| Diabetes | Yes | 1.51 | 1.09-2.09 | 0.01 | 1.50 | 1.09-2.08 | 0.01 | 1.53 | 1.10-2.11 | 0.01 | 1.47 | | 1.06-2.03 | 0.02 |
| COPD | Yes | 1.49 | 1.02-2.18 | 0.03 | 1.51 | 1.03-2.22 | 0.04 | 1.52 | 1.04-2.23 | 0.03 | 1.54 | | 1.05-2.26 | 0.03 |
| AF | Yes | - | - | - | - | - | - | - | - | - | - | | - | - |
| CKD | Yes | 2.71 | 1.73-4.25 | <0.01 | 2.71 | 1.73-4.25 | <0.01 | 2.74 | 1.75-4.28 | <0.01 | 2.72 | | 1.73-4.3 | <0.01 |
| Hypertension | Yes | - | - | - | - | - | - | - | - | - | - | | - | - |
| LVEF 50-59% | Yes |  |  |  | **1.41** | **1-1.99** | **0.05** | 1.39 | 0.98-1.96 | 0.062 | 1.29 | | 0.90-1.83 | 0.16 |
| Mean gradient | 5 mmHg increase |  |  |  |  |  |  | **1.07** | **1.02-1.13** | **<0.01** | **1.08** | | **1.03-1.13** | **<0.01** |
| Stroke volume index | 5 ml.m-2 decrease |  |  |  |  |  |  |  |  |  | **1.13** | | **1.02-1.24** | **0.015** |

CI: confidence interval, HR: hazard ratio, NRI: net reclassification improvement p value next to Chi2 represents the result of likelihood ratio tests.

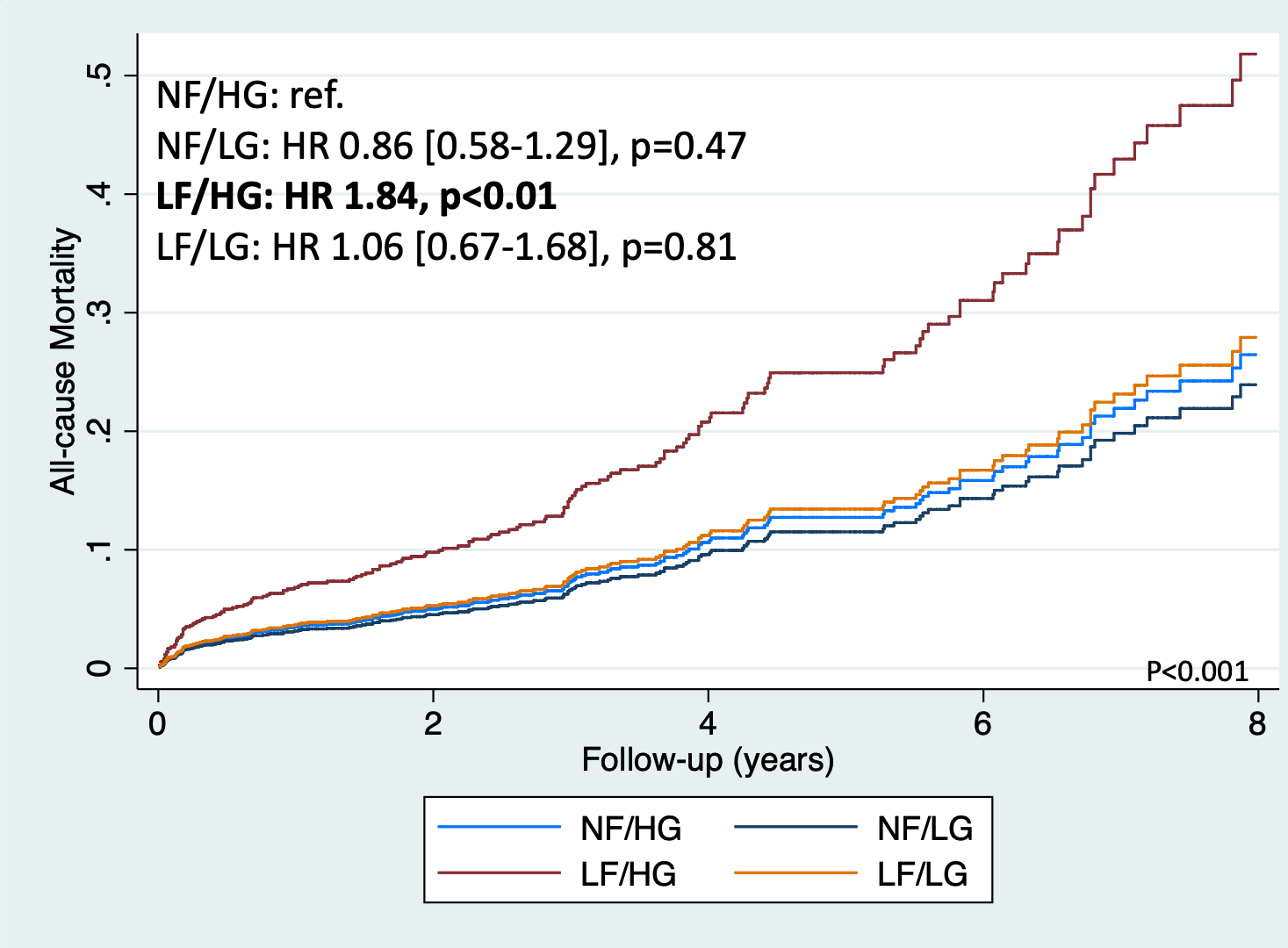
**Figure S1.** Cox-adjusted Proportional Hazards Curve of Normal Flow vs Paradoxical Low Flow



All-cause mortality in Normal Flow (Blue Line) and Paradoxical Low Flow (Red Line). HR: Hazard-Ratio.

Adjusted for age, sex, coronary artery disease, NYHA class 3/4, systemic hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, left ventricular ejection fraction and mean transvalvular gradient.

**Figure S2.** Cox-adjusted Proportional Hazards Curve of Flow-Gradient Patterns



All-cause mortality according to Flow-Gradient Patterns: Normal Flow/High Gradient (light blue line), Normal Flow/Low Gradient (dark blue line), Low Flow/High Gradient (brown Line) and Low Flow/Low Gradient (orange line).

Adjusted for age, sex, coronary artery disease, NYHA class 3/4, systemic hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, chronic kidney disease and left ventricular ejection fraction.

HR: Hazard-Ratio, NF: Normal Flow (Stroke volume index ≥35 ml/m2), LF: Low Flow (Stroke volume index <35 ml/m2)

**IMPACT OF LOW-FLOW: SUBGROUP ANALYSES**

**Figure S3 Panel A. Forest plot showing subgroup analysis of effect of low-flow (guidelines threshold) on mortality**

**A screenshot of a cell phone

Description automatically generated**

Estimated effect of low-flow (stroke volume index < 35 ml/m2) across various patient subgroups. Solid blue line represents the line for no effect (HR=1 and dashed blue-line represents the point estimate of effect for the whole cohort (HR=1.60). MG: mean transvalvular gradients, AVR: aortic valve replacement, CABG: coronary artery bypass graft surgery, LVEF: left ventricular ejection fraction, MI: myocardial infarction

**Figure S3 Panel B. Forest plot showing subgroup analysis of effect of low-flow (sex-specific thresholds) on mortality**

**A screenshot of a cell phone

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Estimated effect of low-flow (stroke volume index < 40 ml/m2 in men and <32 ml/m2 in women) across various patient subgroups. Solid blue line represents the line for no effect (HR=1 and dashed blue-line represents the point estimate of effect for the whole cohort (HR=1.65). MG: mean transvalvular gradients, AVR: aortic valve replacement, CABG: coronary artery bypass graft surgery, LVEF: left ventricular ejection fraction, MI: myocardial infarction

**Figure S4.** Mortality curves in Women and Men according to flow-status

A close up of a map

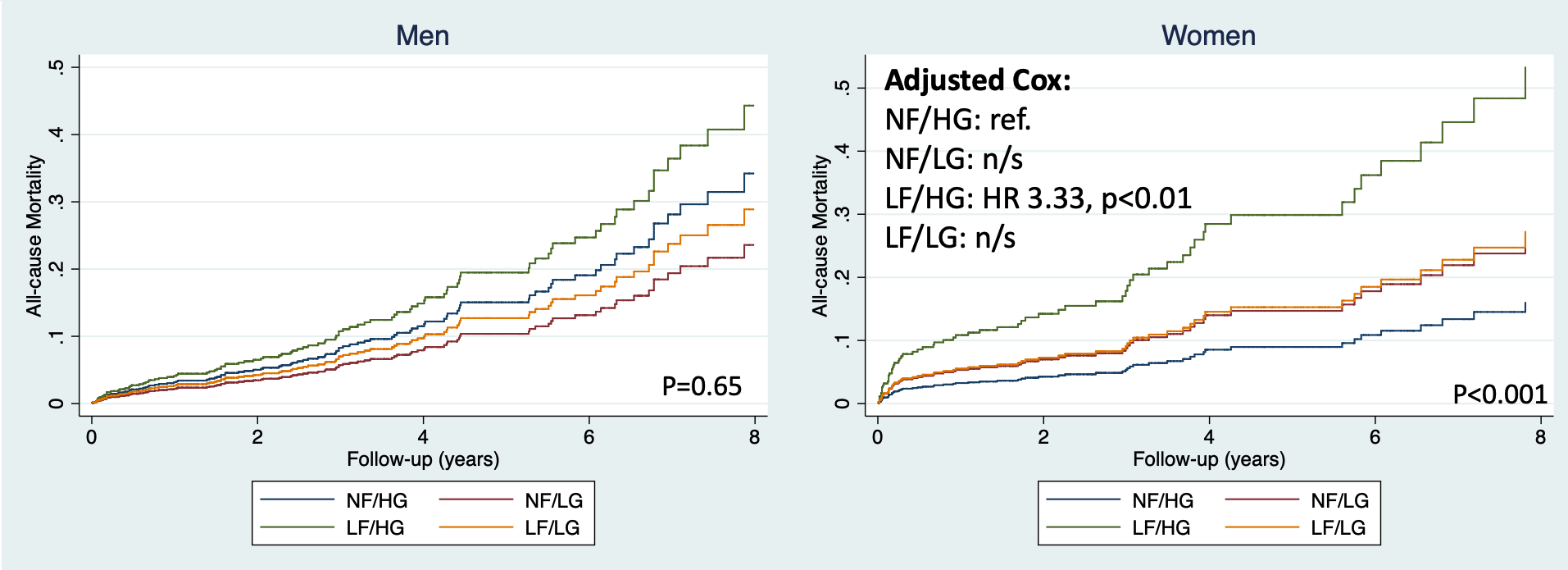
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Kaplan-Meier curves of all-cause mortality in Normal Flow (Blue Line) and Paradoxical Low Flow (Red Line) in Women (panels A and C) and Men (panels B and D) according to established (top) and new-proposed sex-specific (bottom) thresholds

\*Adjusted for age, sex, coronary artery disease, NYHA class 3/4, systemic hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, left ventricular ejection fraction and mean transvalvular gradient.

HR: Hazard-Ratio

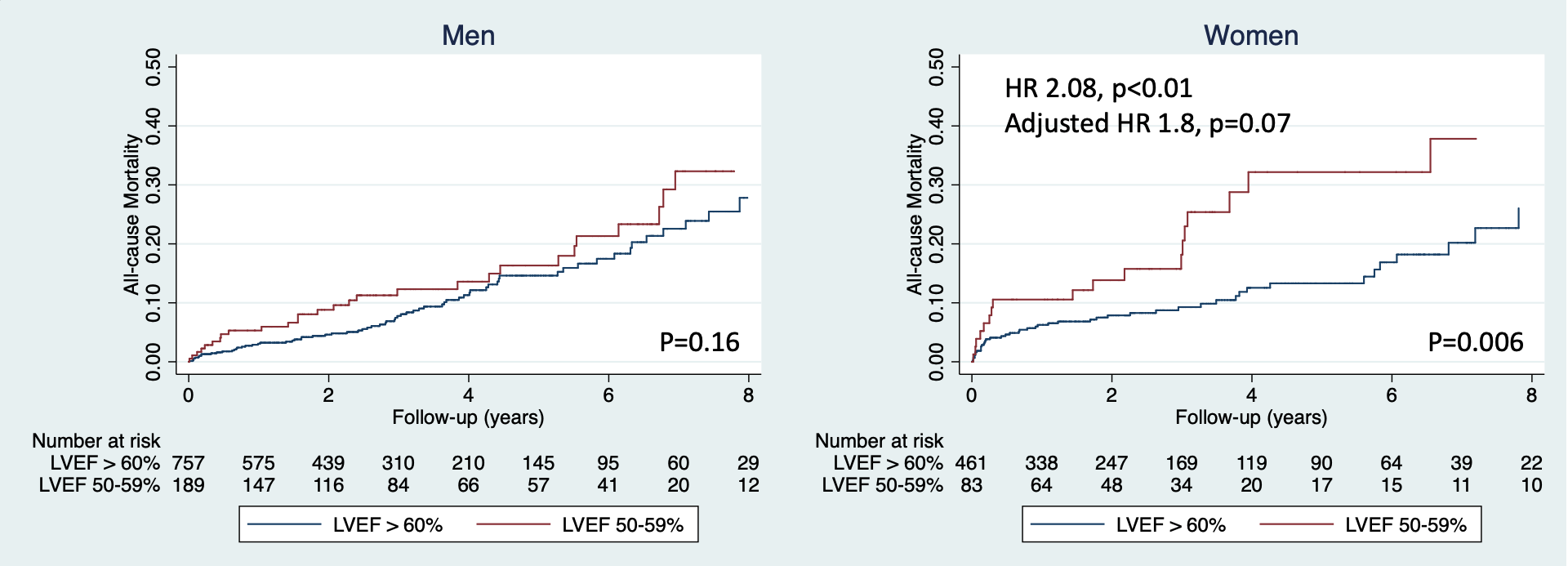
**Figure S5.** Cox-adjusted mortality curves according to sex and flow-gradient patterns.



Cox-adjusted mortality curves according to sex and flow-gradient patterns in men (left panel) and women (right panel): Normal Flow/High Gradient (blue line), Normal Flow/Low Gradient (maroon line), Low Flow/High Gradient (green line) and Low Flow/Low Gradient (orange line).

Adjusted for age, coronary artery disease, NYHA 3-4, hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, chronic kidney disease and LVEF. HR: hazard ratio.

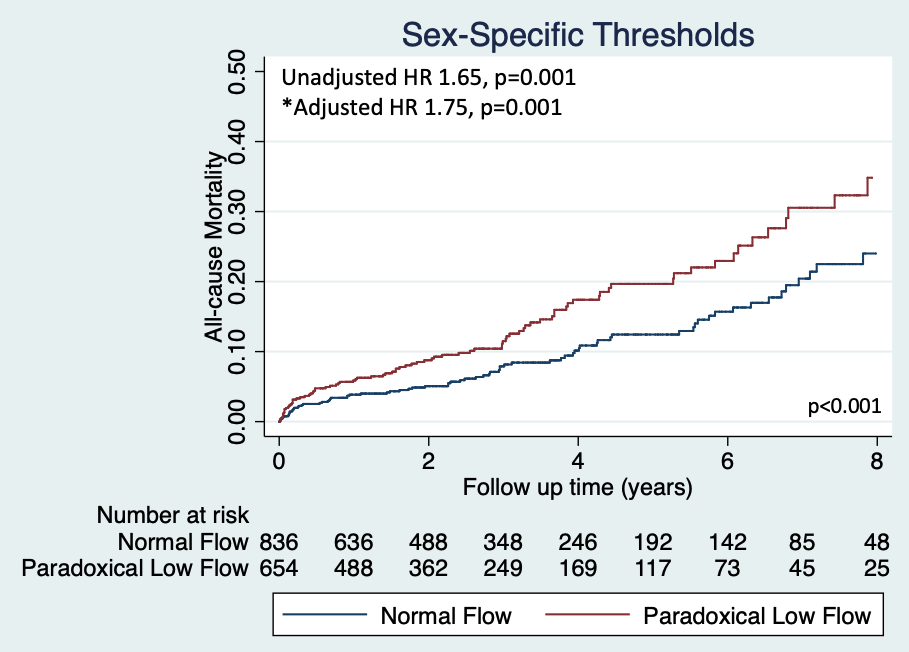
**Figure S6.** Overall mortality according to LVEF and Sex



Kaplan-Meier curves of all-cause mortality in LVEF>60% (blue line) and LVEF 50-59% (red line) in men (left panel) and women (right panel).

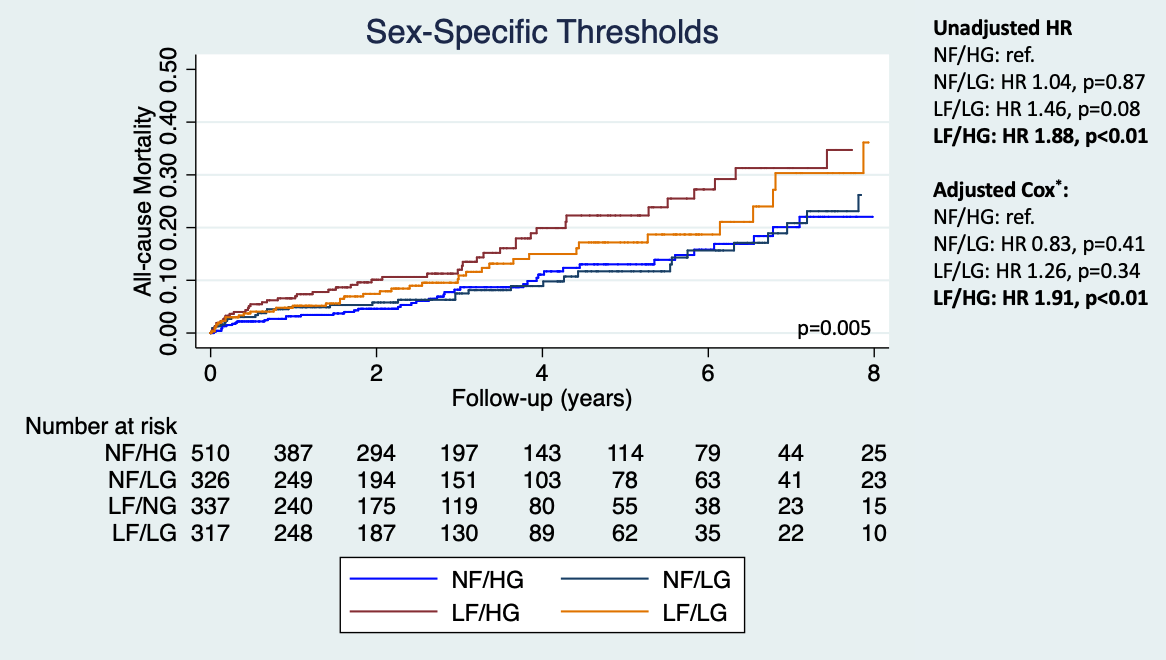
Adjusted for age, coronary artery disease, NYHA 3-4, hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary disease and chronic kidney disease. HR: hazard ratio, LVEF: left ventricular ejection fraction.

**Figure S7:** Kaplan-Meier curves of Normal Flow vs Paradoxical Low Flow according to proposed sex-specific thresholds

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All-cause mortality in Normal Flow (Blue Line) and Paradoxical Low Flow (Red Line) according to newly proposed sex-specific thresholds (Men: 40 ml/m2 and Women: 32 ml/m2). HR: Hazard-Ratio. Adjusted for age, sex, coronary artery disease, NYHA class 3/4, systemic hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, left ventricular ejection fraction and mean transvalvular gradient.

**Figure S8:** Kaplan-Meier Curves of Flow-Gradient Patterns according to proposed sex-specific thresholds



All-cause mortality according to Flow-Gradient Patterns: Normal Flow/High Gradient (light blue line), Normal Flow/Low Gradient (dark blue line), Low Flow/High Gradient (brown Line) and Low Flow/Low Gradient (orange line) using newly proposed sex-specific thresholds (Men: 40 ml/m2 and Women: 32 ml/m2).

\*Adjusted for age, sex, coronary artery disease, NYHA class 3/4, systemic hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, chronic kidney disease and left ventricular ejection fraction.

HR: Hazard-Ratio, NF: Normal Flow (Stroke volume index ≥35 ml/m2), LF: Low Flow (Stroke volume index <35 ml/m2), HG: high gradient (≥40 mmHg), LG: low gradient: <40 mmHg