SUPPLEMENTAL MATERIAL

Table S1. Characteristics and echocardiographic variables according to the flow and gradient state in reduced LVEF (N=227).

	LF-LG N=52 (23%)	NF-LG N=48 (21%)	LF-HG N=51 (22%)	NF-HG N=76 (33%)	P-value
Age, years	84 (79-89)	83 (78-87)	85 (82-89)*	86 (82-89)*	0.013
Male sex, n (%)	24 (46)	20 (42)	19 (37)	32 (42)	0.840
BSA, cm^2	1.41 (1.33-1.53)	1.42 (1.26-1.56)	1.41 (1.30-1.51)	1.43 (1.28-1.58)	0.875
STS PROM, %	8.5 (5.5-15.6)	7.6 (4.6-10.9)	8.4 (5.6-11.5)	7.8 (5.4-10.8)	0.587
NYHA class III/IV, n (%)	30 (58)	24 (50)	34 (67)	41 (54)	0.362
Hemoglobin, g/dl	11.4 (10.6-13.0)	10.5 (9.4-12.4)	11.7 (10.7-13.0)	11.3 (10.1-12.5)	0.061
BNP, pg/ml	774 (412-1210)*	362 (218-716)	825 (474-1556)*	704 (330-1213)*	0.003
AF, n (%)	9 (17)	6 (13)	11 (22)	9 (12)	0.444
CHF, n (%)	42 (81)	36 (75)	45 (88)	64 (84)	0.351
CAD, n (%)	28 (54)	26 (54)	14 (28)*#	26 (34)	0.007
Prior MI, n (%)	12 (23)	10 (21)	4 (8)	10 (13)	0.122
LVEDV, ml	120 (87-154)	127 (101-161)	103 (84-133)	121 (91-144)	0.117
LVESV, ml	80 (52-111)	70 (57-97)	57 (45-84)	70 (51-83)	0.060
LVEF, %	35 (27-41)*	41 (36-45)	41 (35-45)#	43 (37-47)#	<0.001
LVSVi, ml/m^2	29 (25-32)*	41 (38-46)	30 (24-33)*	43 (38-52)$#	<0.001
LV mass	135 (108-165)	138 (115-175)	142 (123-173)	150 (126-183)	0.221

index, g/m²					
LAD, mm	45 (41-48)	46 (39-49)	43 (38-49)	45 (40-49)	0.821
LAVi, ml/m²	56 (42-78)	58 (45-74)	57 (43-78)	63 (50-81)	0.270
E/A	0.87 (0.59-1.94)	0.63 (0.53-1.09)	0.65 (0.52-1.49)	0.66 (0.50-1.30)	0.269
E/e'	19 (15-25)	19 (11-27)	19 (15-28)	18 (14-24)	0.671
AV Vmax, m/sec	3.30 (2.92-3.64)	3.58 (3.21-3.99)	4.66 (4.25-5.16)*#	4.80 (4.40-5.32)*#	<0.001
AV mean PG, mmHg	26 (19-31)	29 (25-35)	55 (45-68)*#	56 (45-71)*#	<0.001
AVA, cm²	0.59 (0.48-0.69)*	0.75 (0.63-0.90)	0.36 (0.28-0.44)#*	0.55 (0.45-0.66)$*	<0.001
AVAi, cm²/m²	0.40 (0.35-0.49)*	0.51 (0.47-0.63)	0.27 (0.20-0.31)#*	0.38 (0.31-0.46)$*	<0.001
TR velocity, m/s	2.65 (2.30-3.07)	2.55 (2.29-2.93)	2.69 (2.29-3.24)	2.74 (2.35-3.03)	0.601
TAPSE, mm	15 (12-17)	17 (14-23)	16 (12-20)	17 (15-21)	0.047
S', cm/sec	8 (7-9)	11 (9-12)	7 (6-10)	10 (9-11)	0.013
FAC, %	35 (23-40)	39 (36-46)	38 (30-52)	44 (38-47)	0.074
LVGLS, %	5.4 (4.1-7.0)	7.6 (5.1-9.8)	6.0 (4.8-8.5)	8.7 (6.8-12.0)#$	<0.001
AR ≥moderate, n (%)	12 (23)	8 (17)	3 (6)	16 (21)	0.084
MR ≥moderate, n (%)	20 (39)	8 (17)	11(22)	13 (17)#	0.021
TR ≥moderate,	10 (19)	4 (8)	4 (8)	13 (17)	0.191

n (%)					

Continuous variables are expressed as median (interquartile range).

* p<0.008 for NFLG

# p<0.008 for LFLG

$ p<0.008 for LFHG

AF, atrial fibrillation; AR, aortic regurgitation; AV, aortic valve; AVA, aortic valve area; AVAi, aortic valve area index; BNP, B-type natriuretic peptide; BSA, body surface area; CAD, coronary artery disease; CHF, congestive heart failure; FAC, fractional area change; GLS, global longitudinal strain; HG, high-gradient; LAD, left atrial dimension; LAVi, left atrial volume index; LF, low-flow; LG, low-gradient; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSVi, left ventricular stroke volume index; MI, myocardial infarction; MR, mitral regurgitation; NF, normal-flow; NYHA, New York Heart Association; PG, pressure gradient; STS PROM, Society of Thoracic Surgeons predicted risk of mortality; TAVI, transcatheter aortic valve implantation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; Vmax, peak aortic valve velocity.

Table S2. Characteristics and echocardiographic variables according to the flow and gradient state in preserved LVEF (N=1,515).

	LF-LG N =91 (6%)	NF-LG N=295 (20%)	LF-HG N=140 (9%)	NF-HG N=989 (65%)	P-value
Age, years	84 (81-87)	84 (81-87)	85 (82-88)*	85 (81-88)	0.017
Male sex, n (%)	36 (40)	90 (31)	40 (29)	329 (33)	0.282
BSA, cm²	1.51 (1.36-1.63)	1.43 (1.33-1.59)	1.45 (1.34-1.59)	1.43 (1.32-1.56) #	0.017
STS PROM, %	5.9 (4.2-8.2)	5.3 (3.8-7.5)	5.6 (4.0-7.4)	5.6 (4.0-7.9)	0.284
NYHA class III/IV, n (%)	37 (41)	82 (28)	57 (41)*	286 (29)$	0.004
Hemoglobin, g/dl	11.6 (10.5-13.0)	11.3 (10.3-12.4)	11.7 (10.4-12.8)	11.2 (10.1-12.3)	0.018
BNP, pg/ml	249 (146-441)*	147 (70-304)	285 (130-534)*	207 (99-461)*	<0.001
AF, n (%)	39 (43)*	35 (12)	38 (27)*	79 (8)$#	<0.001
CHF, n (%)	58/91 (64)*	123/295 (42)	91/140 (65)*	573/985 (58)*	<0.001
CAD, n (%)	33/91 (36)	103/295 (35)	42/140 (30)	270/988 (27)	0.038
Prior MI, n (%)	9/91 (10)	15/295 (5)	2/140 (1)#	32/987 (3)#	0.004
LVEDV, ml	66 (53-85)	74 (62-92)	66 (52-82)*	79 (64-98)*#$	<0.001
LVESV, ml	25 (17-34)	24 (19-32)	24 (17-31)	27 (20-35)*$	<0.001
LVEF, %	63 (55-68)*	65 (60-70)	64 (60-69)	65 (60-69)#	0.001
LVSVi, ml/m²	30 (27-33)*	47 (41-55)	31 (28-33)*	50 (43-58)*#$	<0.001
LV mass	92 (76-114)	99 (81-120)	120 (96-143)*#	121 (101-148)*#	<0.001

index, g/m²				
LAD, mm	45 (40-50)*	42 (37-45)	43 (38-48)*	42 (37-46)#	<0.001
LAVi, ml/m²	52 (38-73)	50 (38-64)	58 (39-75)	52 (41-64)	0.058
E/A	0.66 (0.55-0.79)	0.68 (0.59-0.86)	0.64 (0.52-0.80)	0.67 (0.55-0.82)	0.059
E/e'	15 (12-19)	16 (12-22)	17 (12-22)	18 (14-23)*#	<0.001
AV Vmax, m/sec	3.60 (3.20-3.90)	3.88 (3.52-4.06)	4.60 (4.30-5.01)*#	4.8 0(4.40-5.25)#*	<0.001
AV mean PG, mmHg	30 (23-34)	33 (28-37)	50 (44-63)#*	55 (46-67)#*	<0.001
AVA, cm²	0.63 (0.53-0.71)*	0.76 (0.67-0.86)	0.45 (0.37-0.55)*#	0.62 (0.52-0.74)*$	<0.001
AVAi, cm²/m²	0.41 (0.36-0.50)*	0.51 (0.45-0.60)	0.31 (0.26-0.37)*#	0.43 (0.36-0.50)*$	<0.001
TR velocity, m/s	2.55 (2.23-2.87)	2.50 (2.28-2.77)	2.53 (2.29-3.00)	2.55 (2.30-2.83)	0.278
TAPSE, mm	15 (13-20)*	20 (17-23)	17 (14-21)*	20 (18-22)$#	<0.001
S', cm/sec	10 (7-12)	11 (9-13)	10 (8-12)	11 (9-13)$	0.025
FAC, %	36 (28-43)	44 (39-49)	41 (34-46)	44 (40-50)#	0.002
LVGLS, %	11.7 (8.4-15.0)*	14.5 (11.0-17.0)	11.5 (8.2-13.5)*	12.7 (10.0-15.7)*$	<0.001
AR ≥moderate, n (%)	9 (10)	31 (11)	14 (10)	127 (13)	0.531
MR ≥moderate, n (%)	14 (15)	36 (12)	25 (18)	76 (8)$	<0.001
TR ≥moderate,	16 (18)	32 (11)	25 (18)	69 (7)#$	<0.001

n (%)					

Continuous variables are expressed as median (interquartile range).

* p<0.008 for NFLG

# p<0.008 for LFLG

$ p<0.008 for LFHG

AF, atrial fibrillation; AR, aortic regurgitation; AV, aortic valve; AVA, aortic valve area; AVAi, aortic valve area index; BNP, B-type natriuretic peptide; BSA, body surface area; CAD, coronary artery disease; CHF, congestive heart failure; FAC, fractional area change; GLS, global longitudinal strain; HG, high-gradient; LAD, left atrial dimension; LAVi, left atrial volume index; LF, low-flow; LG, low-gradient; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSVi, left ventricular stroke volume index; MI, myocardial infarction; MR, mitral regurgitation; NF, normal-flow; NYHA, New York Heart Association; PG, pressure gradient; STS PROM, Society of Thoracic Surgeons predicted risk of mortality; TAVI, transcatheter aortic valve implantation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; Vmax, peak aortic valve velocity.

Table S3. Details of events (N=1,742).

	All patients
Cardiovascular death and rehospitalization for cardiovascular events, n (%)	301 (17)
Cardiovascular death, n (%)	86 (5)
Rehospitalization for cardiovascular events, n (%)	254 (15)
Congestive heart failure	131 (8)
Arrhythmia	47 (3)
Newly developed coronary artery disease	18 (1)
TAVI valve related	19 (1)
Ischemic stroke	46 (3)
Hemorrhage stroke	5 (0.3)
New device implantation after discharge*	33 (2)
All-cause death, n (%)	290 (17)

TAVI, transcatheter aortic valve implantation.
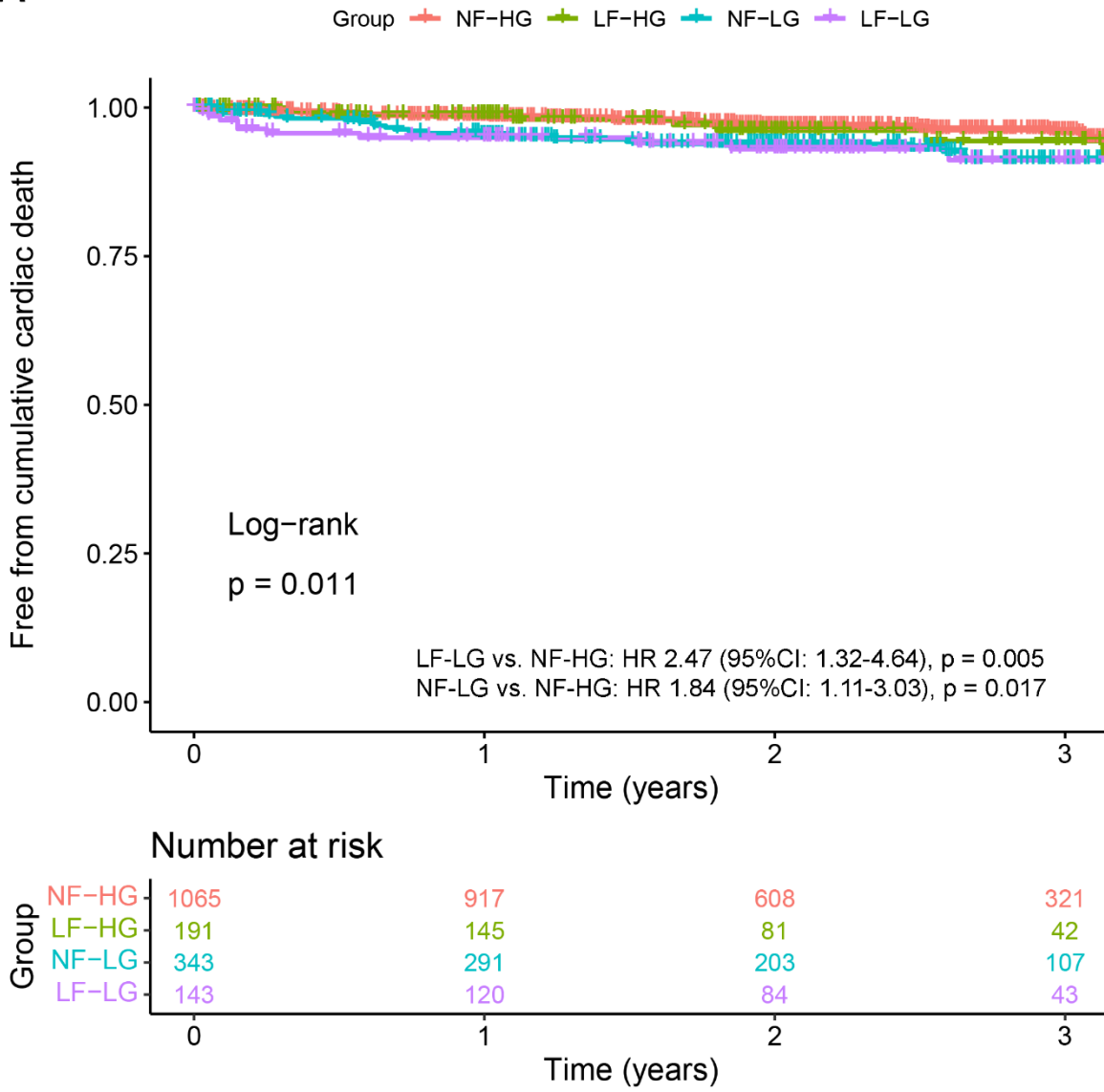
* All patients underwent permanent pacemaker implantation.

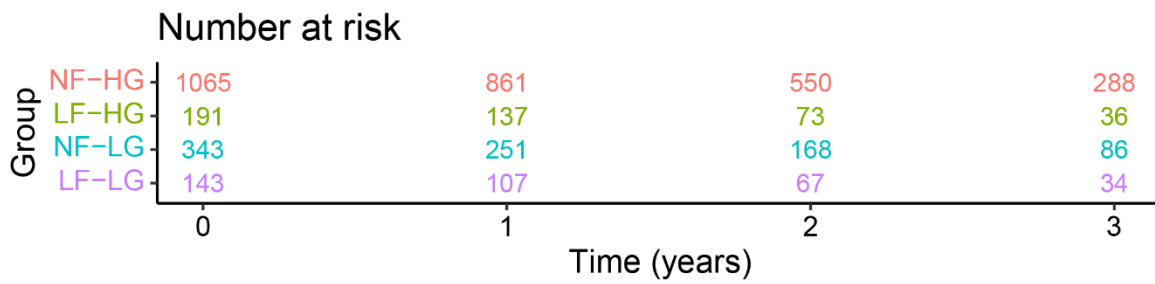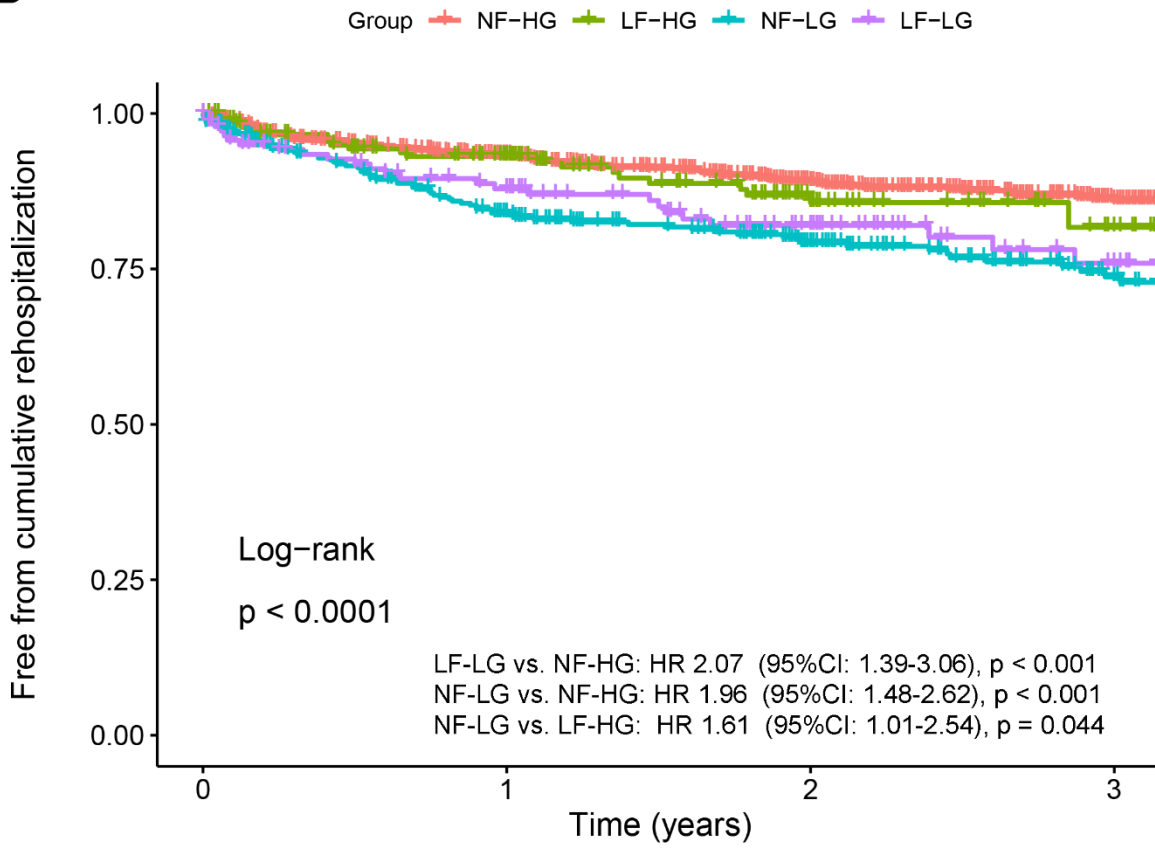**Table S4. Model for the composite outcome in the subgroup with GLS evaluation (N=993).**

	Multivariable	
	HR (95%CI)	**P-value**
Prior cardiac surgery	1.97 (1.22-3.18)	0.005
AF	1.89 (1.18-3.03)	0.008
NYHA class III/IV	1.46 (1.02-2.08)	0.040
STS PROM, %	1.02 (1.00-1.05)	0.048
Low-gradient: mean PG <40 mmHg	1.67 (1.17-2.39)	0.005
LVGLS	0.95 (0.92-0.99)	0.019

AF, atrial fibrillation; CI, confidence interval; GLS, global longitudinal strain; HR, hazard ratio; LV, left ventricular; NYHA, New York Heart Association; PG, pressure gradient; STS PROM, Society of Thoracic Surgeons risk score risk of mortality.
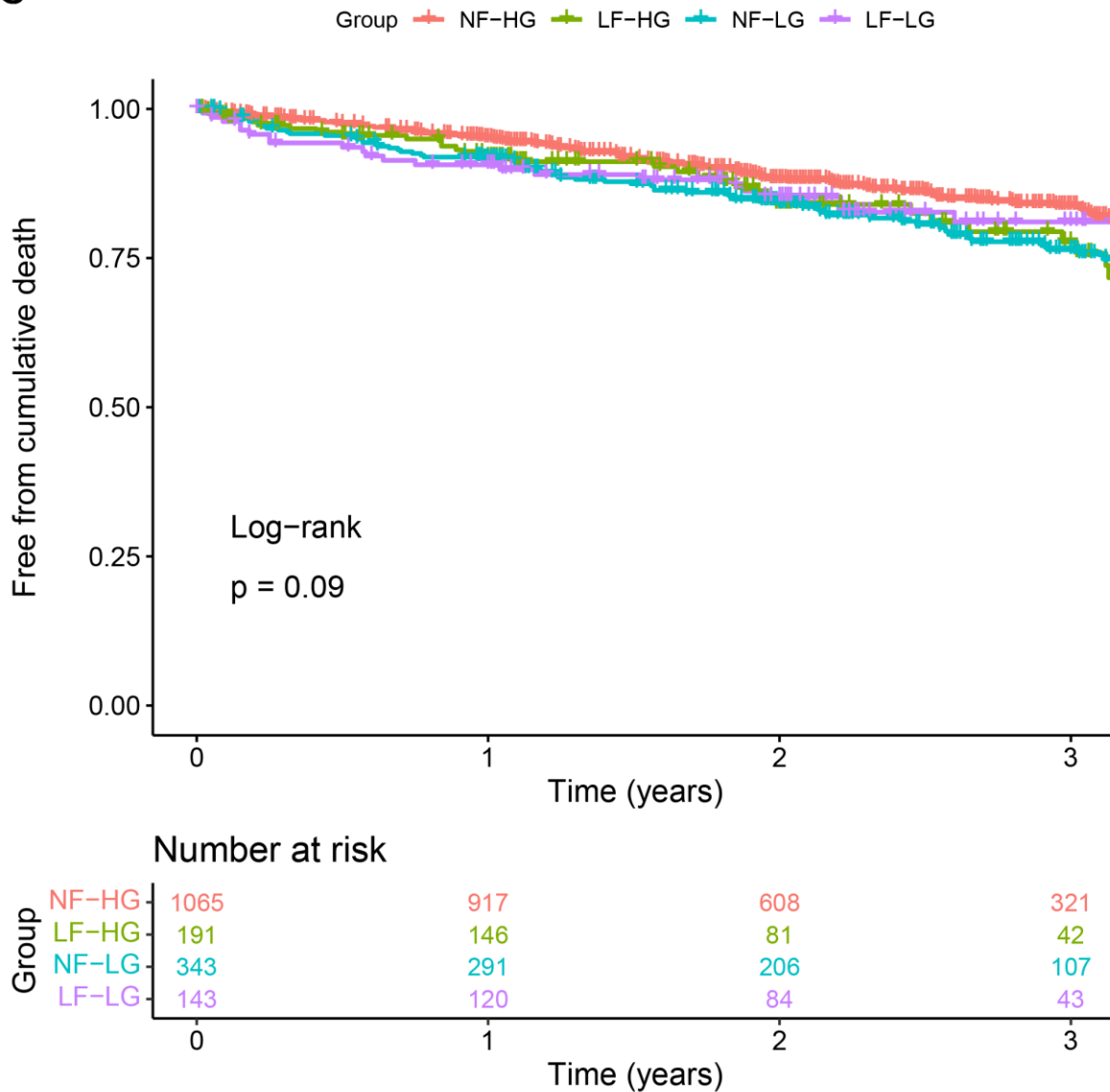
Figure S1. Impact of flow-gradient patterns on the secondary outcome in severe AS after TAVI (N=1,742).

B

Group ┼ NF−HG ┼ LF−HG ┼ NF−LG ┼ LF−LG

Log−rank

p < 0.0001

LF-LG vs. NF-HG: HR 2.07 (95%CI: 1.39-3.06), p < 0.001
NF-LG vs. NF-HG: HR 1.96 (95%CI: 1.48-2.62), p < 0.001
NF-LG vs. LF-HG: HR 1.61 (95%CI: 1.01-2.54), p = 0.044

Number at risk

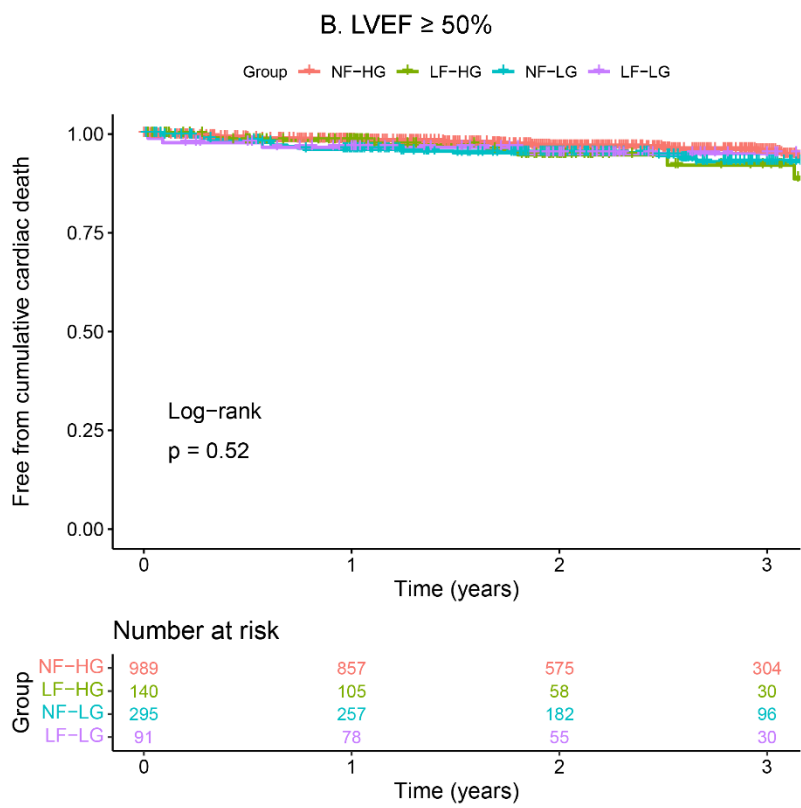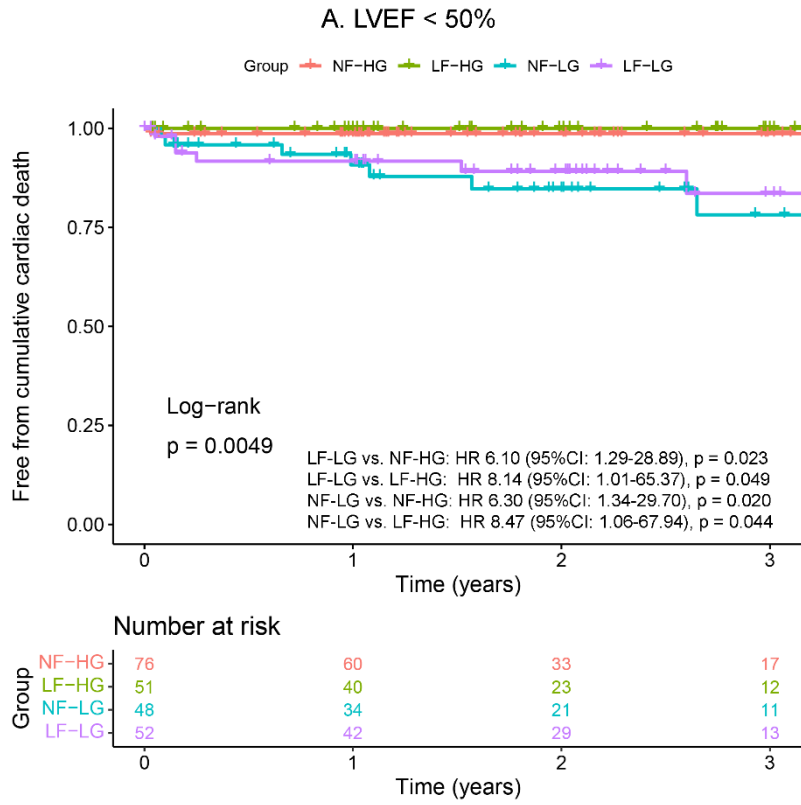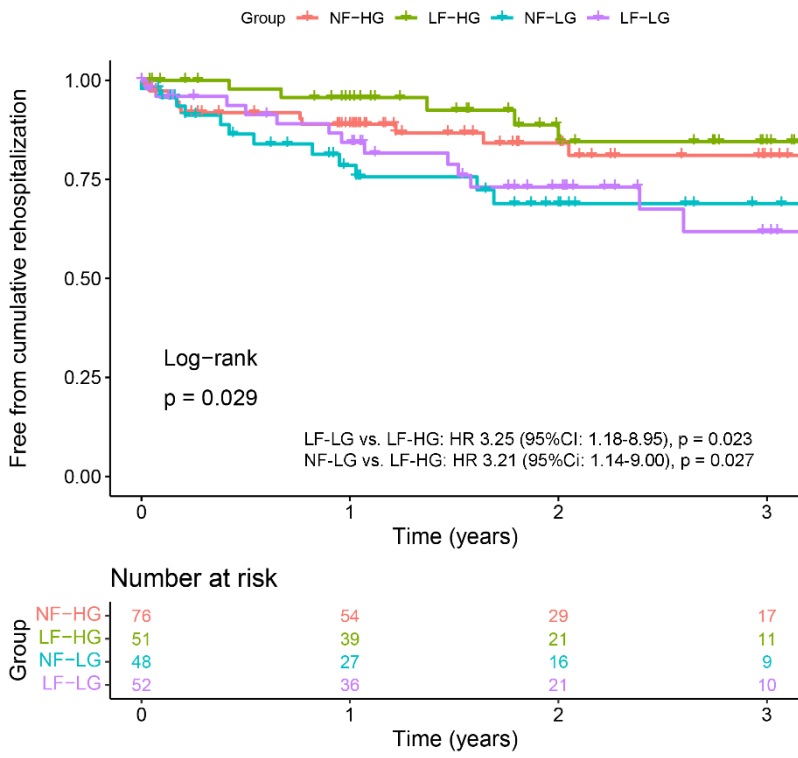| Group	0	1	2	3
NF−HG	1065	861	550	288
LF−HG	191	137	73	36
NF−LG	343	251	168	86
LF−LG	143	107	67	34

Kaplan–Meier curves demonstrate freedom from cumulative cardiovascular death (A), rehospitalization for cardiovascular events (B), and all-cause death (C) in our study population stratified by the pressure gradient and flow status. Three-year event-free survival rates for secondary outcome in each groups are as follows: cardiac death, LF-LG 91.2% (95% CI: 85.7–97.0), NF-LG 91.2% (95% CI: 87.5–94.9), LF-HG 94.4% (95% CI: 89.7–99.3), and NF-HG 95.9% (95% CI: 94.5–97.4); cardiovascular rehospitalization, LF-LG 75.9% (95% CI: 67.2–85.7), NF-LG 73.7% (95% CI: 68.3–79.6), LF-HG 81.7% (95% CI: 74.1–90.0), and NF-HG 86.0% (95% CI: 83.4–88.6); and all-cause death, LF-LG 81.1% (95% CI: 73.9–88.9), NF-LG 76.4% (95% CI: 71.2–82.0), LF-HG 77.6% (95% CI: 69.8–86.4), and NF-HG 83.8% (95% CI: 81.1–86.6). NF-HF, normal-flow, high-gradient; LF-HG, low-flow, high-gradient; NF-LG, normal-flow, low-gradient; LF-LG, low-flow, low-gradient; TAVI, transcatheter aortic valve implantation; AS, aortic stenosis; HR, hazard ratio; CI, confidence interval.
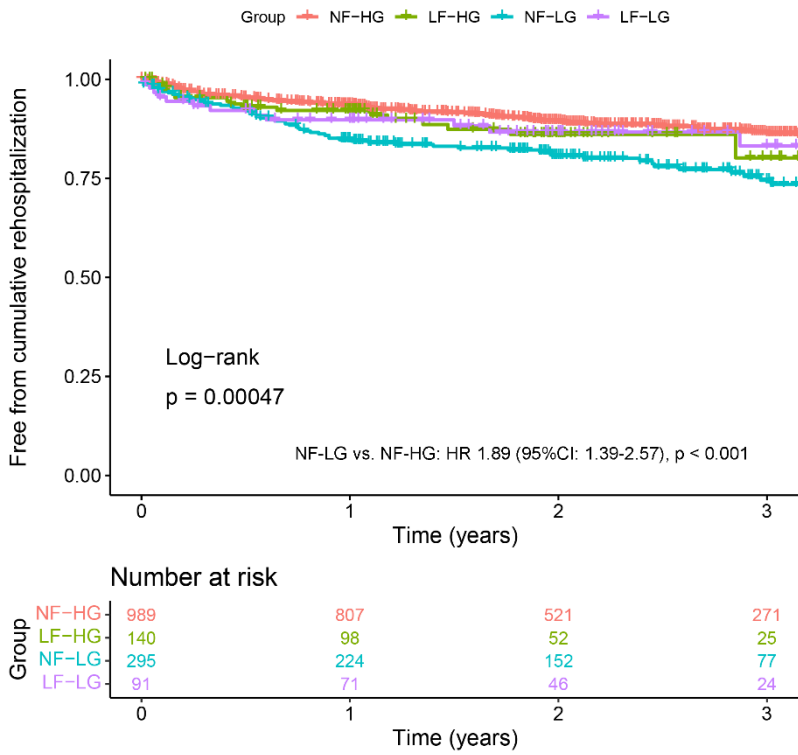
Figure S2. Impact of flow-gradient patterns on the secondary outcome according to baseline EF.
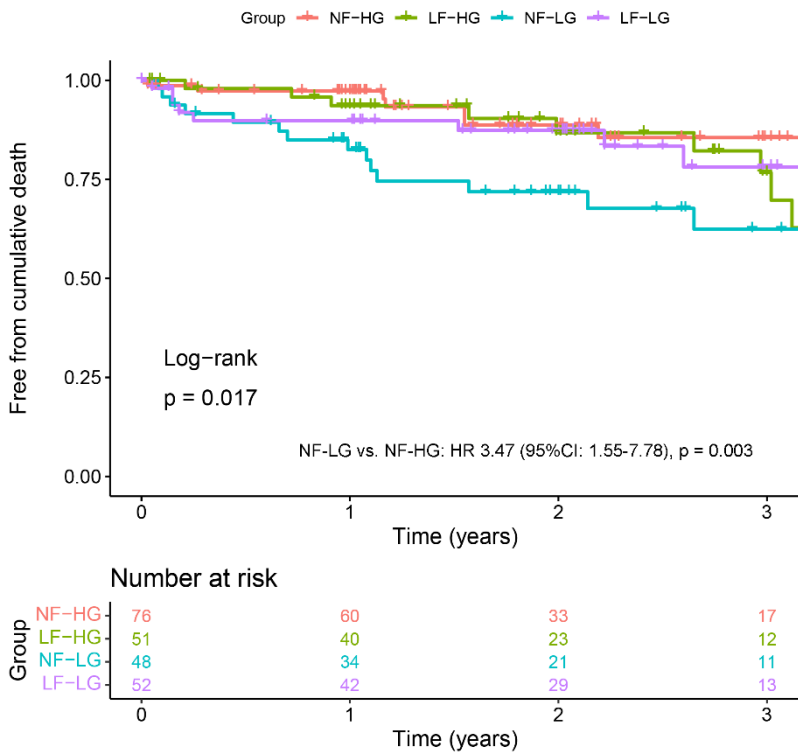
A. LVEF < 50%

Log-rank

p = 0.0049

LF-LG vs. NF-HG: HR 6.10 (95%CI: 1.29-28.89), p = 0.023
LF-LG vs. LF-HG: HR 8.14 (95%CI: 1.01-65.37), p = 0.049
NF-LG vs. NF-HG: HR 6.30 (95%CI: 1.34-29.70), p = 0.020
NF-LG vs. LF-HG: HR 8.47 (95%CI: 1.06-67.94), p = 0.044

Number at risk

Group	0	1	2	3
NF-HG	76	60	33	17
LF-HG	51	40	23	12
NF-LG	48	34	21	11
LF-LG	52	42	29	13

B. LVEF ≥ 50%

Log-rank

p = 0.52

Number at risk

Group	0	1	2	3
NF-HG	989	857	575	304
LF-HG	140	105	58	30
NF-LG	295	257	182	96
LF-LG	91	78	55	30

C. LVEF < 50%

Group — NF-HG — LF-HG — NF-LG — LF-LG

Log-rank
p = 0.029

LF-LG vs. LF-HG: HR 3.25 (95%CI: 1.18-8.95), p = 0.023
NF-LG vs. LF-HG: HR 3.21 (95%Ci: 1.14-9.00), p = 0.027

Number at risk

Group	0	1	2	3
NF-HG	76	54	29	17
LF-HG	51	39	21	11
NF-LG	48	27	16	9
LF-LG	52	36	21	10

D. LVEF ≥ 50%

Group — NF-HG — LF-HG — NF-LG — LF-LG

Log-rank
p = 0.00047

NF-LG vs. NF-HG: HR 1.89 (95%CI: 1.39-2.57), p < 0.001

Number at risk

Group	0	1	2	3
NF-HG	989	807	521	271
LF-HG	140	98	52	25
NF-LG	295	224	152	77
LF-LG	91	71	46	24

E. LVEF < 50%

Group — NF–HG — LF–HG — NF–LG — LF–LG

Log-rank
p = 0.017

NF-LG vs. NF-HG: HR 3.47 (95%CI: 1.55-7.78), p = 0.003

Number at risk

Group	0	1	2	3
NF–HG	76	60	33	17
LF–HG	51	40	23	12
NF–LG	48	34	21	11
LF–LG	52	42	29	13

F. LVEF ≥ 50%

Group — NF–HG — LF–HG — NF–LG — LF–LG

Log-rank
p = 0.66

Number at risk

Group	0	1	2	3
NF–HG	989	857	575	304
LF–HG	140	106	58	30
NF–LG	295	257	185	96
LF–LG	91	78	55	30

Survival analysis was performed separately for reduced (N=227) and preserved EF (N=1,515).

Kaplan–Meier curves demonstrate freedom from cumulative cardiovascular death (A, B),

rehospitalization for cardiovascular events (C, D), and all-cause death (E, F) in our study population stratified by the pressure gradient and flow status. LV, left ventricular; EF, ejection fraction; NF-HF, normal-flow, high-gradient; LF-HG, low-flow, high-gradient; NF-LG, normal-flow, low-gradient; LF-LG, low-flow, low-gradient; HR, hazard ratio; CI, confidence interval.

Figure S3. Estimated cumulative incidence curves of the primary endpoint (N=1,742).
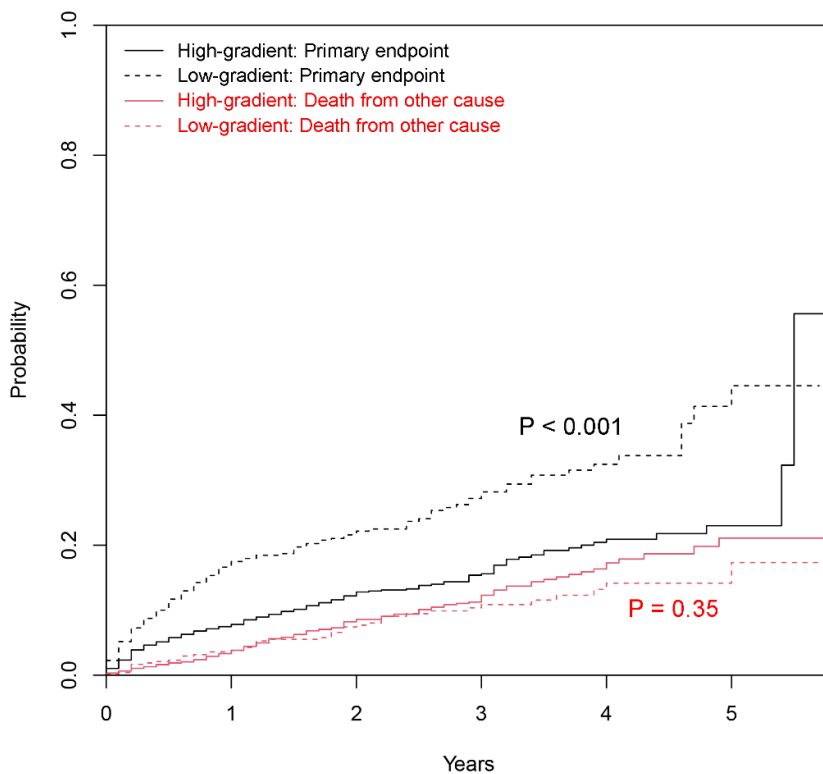
Patients were stratified according to the pressure gradient (<40 mmHg, low gradient; ≥40 mmHg, high gradient), and the cumulative probability of events was calculated separately for both events. The black line shows the cumulative incidence curves of the primary endpoint, composite of cardiovascular death, and rehospitalization for cardiovascular events, whereas the red line shows the cumulative incidence of mortality due to other causes. Patients with low-gradient show a significantly higher probability of the primary endpoint than those with high-gradient. There is no significant difference in the probability of competing events of all-cause death.

**Figure S4. Estimated cumulative incidence curves of the primary endpoint.**
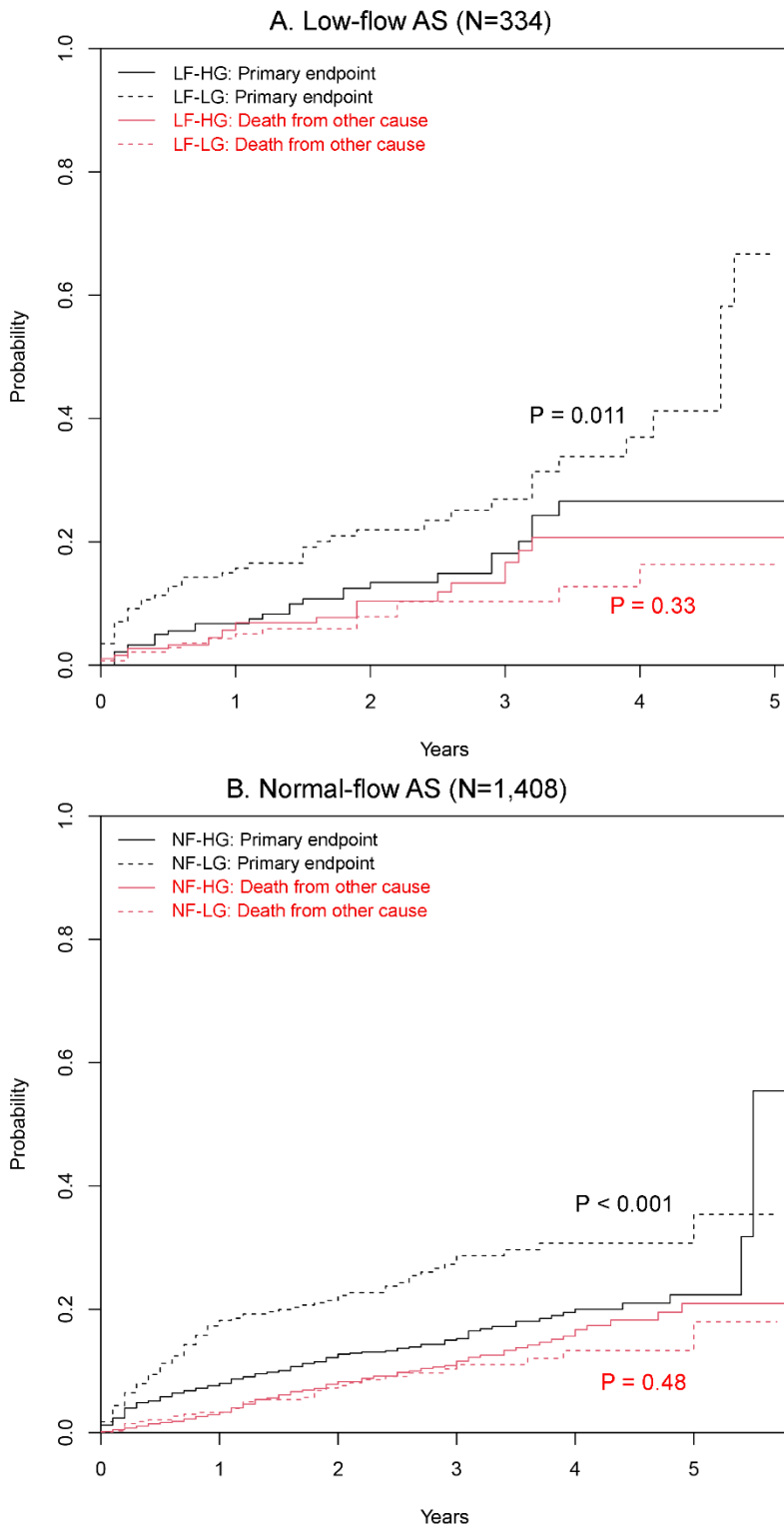
A) LF-AS (N=334) and B) NF-AS (N=1,408). Patients were stratified according to the pressure gradient (<40 mmHg, low gradient; ≥40 mmHg, high gradient), and the cumulative probability of events was calculated separately for both events. The black line shows the cumulative incidence curves

of the primary endpoint, composite of cardiovascular death, and rehospitalization for cardiovascular events, and the red line shows the cumulative incidence of mortality due to other causes. Low-gradient patients show a significantly higher probability of the primary endpoint than high-gradient patients among both low-flow and normal-flow AS patients. There are no significant differences in the probability of competing events for all-cause death. AS, aortic stenosis; HG, high-gradient; LF, low-flow; LG, low-gradient; NF, normal-flow.

Figure S5. Changes in LV and AV parameters after TAVI according to the pressure gradient in patients with preserved EF and reduced EF (N=1,239).
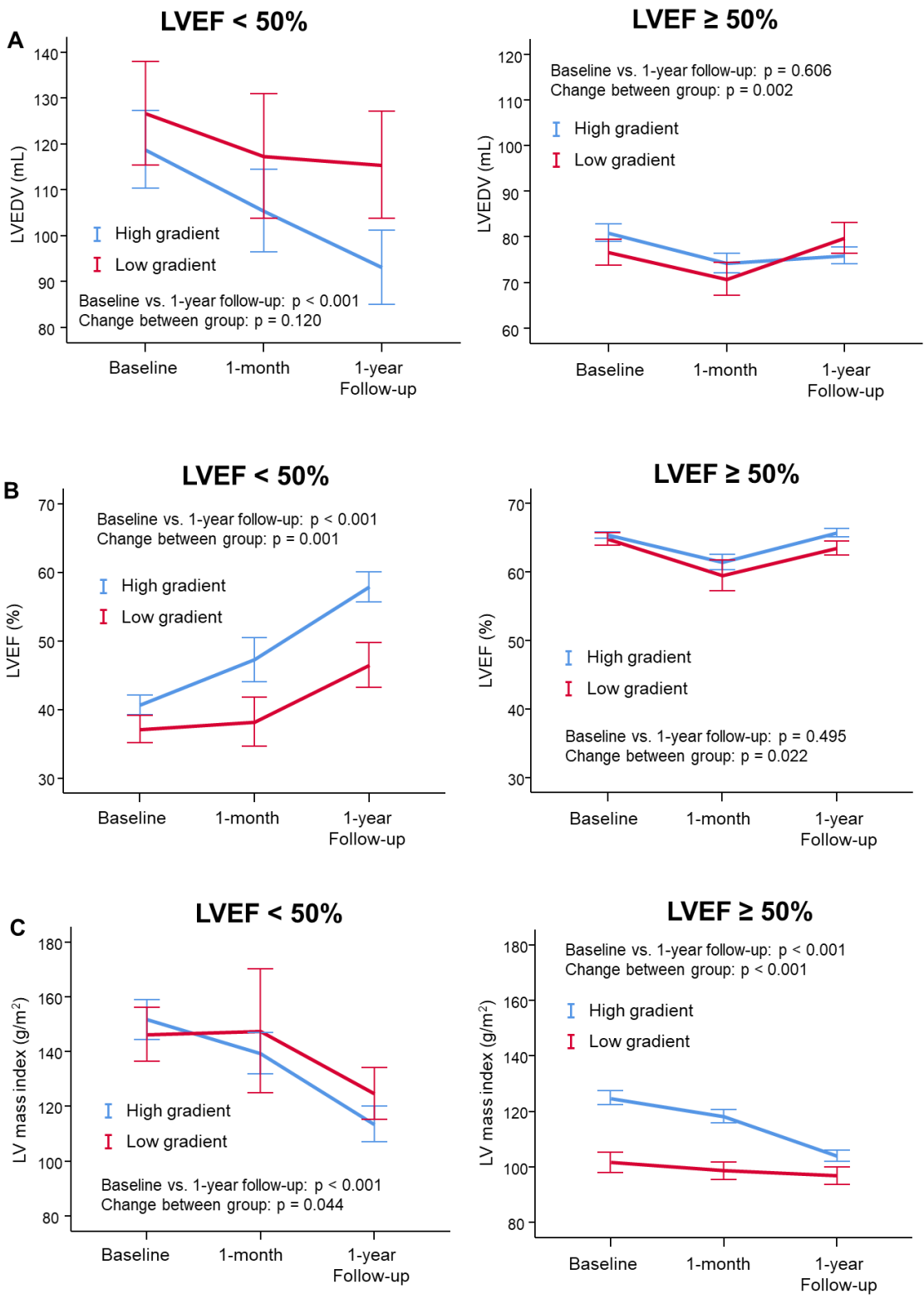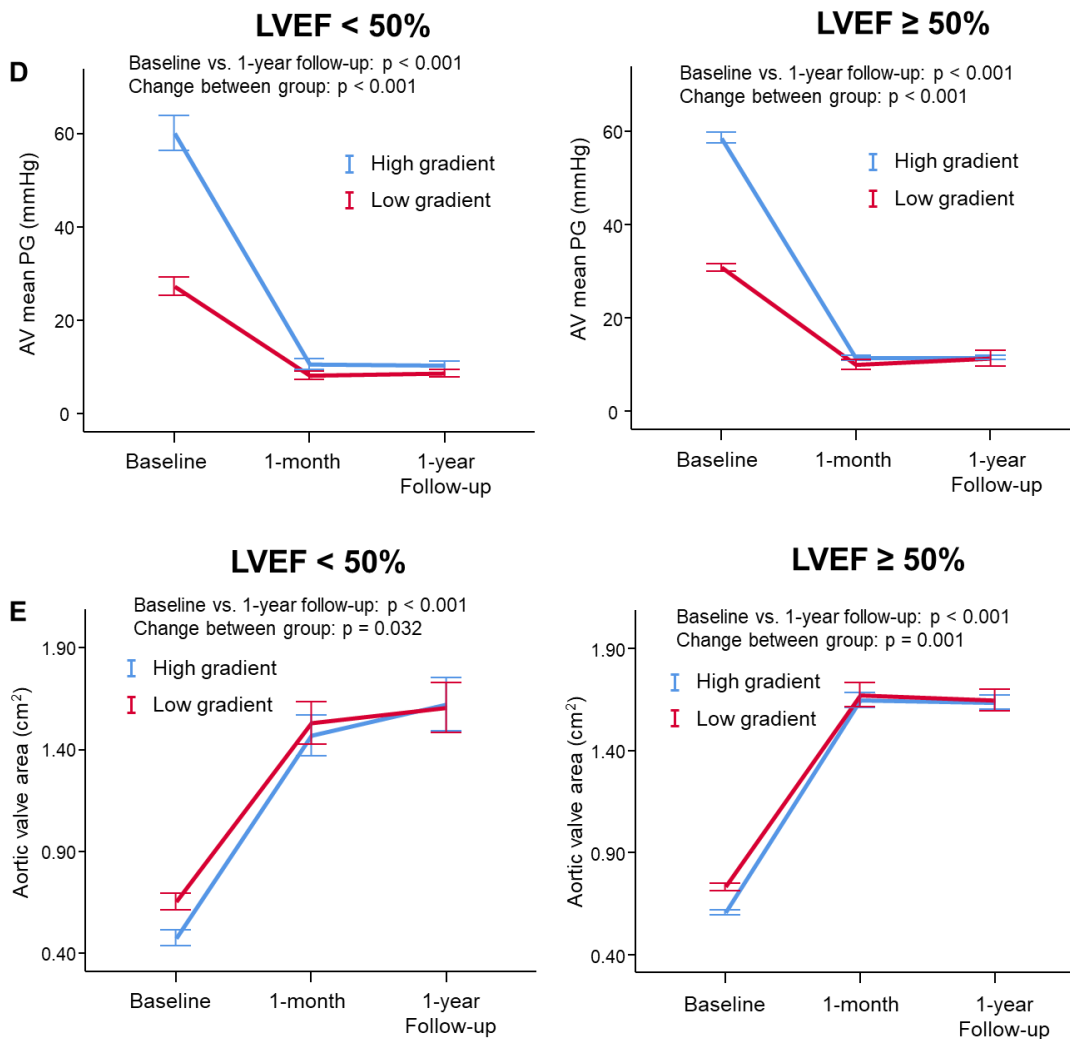
Changes in the LVEDV (A), LVEF (B), LV mass index (C), AV mean pressure gradient (D), and aortic valve area (E) between low-gradient and high-gradient AS. Data were analyzed separately for preserved and reduced EF. Markers represent the median of the observed data obtained before TAVI, at 1-month, and at the 1-year follow-up. Error bars represent 95% confidence intervals. The mixed model was constructed with patient groups, changes over time, and interactions between groups and changes. P-values for changes over time and differences in the magnitude of change between groups are shown as "Baseline vs. 1-year follow-up" and "Change between groups," respectively.

AS, aortic stenosis; AV, aortic valve; EF, ejection fraction; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; TAVI, transcatheter aortic valve implantation.