Supplementary Information

Anemia in Patients with Severe Aortic Stenosis

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Definitions of the clinical events

Major bleeding was defined as overt bleeding plus a decrease in hemoglobin of 3 g/dl to

<5 g/dl or bleeding requiring transfusion (BARC type 3a). Life-threatening/disabling

bleeding events were defined as overt bleeding plus a decrease in hemoglobin ≥5 g/dl or

bleeding requiring surgical intervention or intravenous vasoactive agents (BARC type 3b),

bleeding in a critical organ such as intracranial, intraocular (BARC type 3c) or fatal

bleeding (BARC type 5) [1, 2]. Death was regarded as cardiovascular in origin unless

obvious non-cardiovascular causes could be identified. Aortic valve (AV) procedure-

related death was defined as any death during the hospitalization for surgical aortic valve

replacement (AVR) or trans-catheter aortic valve implantation (TAVI). AV-related death

included AV procedure-related death, sudden death, and death due to heart failure

presumably related to aortic stenosis [3].

Supplemental Reference

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Supplemental Table S1. Univariate and Multivariable Logistic Regression Analyses for Factors Associated with Anemia

Variables	Univariate Analyses				Multivariable Analyses	
	Anemia		OR (95% CI)	P value	OR (95% CI)	P value
	Yes	No				
	N=2117	N=1286				
Age ≥80 years	1164 (55)	393 (31)	2.78 (2.40-3.21)	<0.001	2.27 (1.94-2.67)	<0.001
Women	1347 (64)	762 (59)	1.3 (1.04-1.39)	0.01	1.51 (1.26-1.80)	<0.001
BMI <22 kg/m^2	1432 (68)	634 (49)	2.15 (1.87-2.48)	<0.001	1.91 (1.64-2.24)	<0.001
Current smoking	88 (4)	87 (7)	0.6 (0.44-0.81)	0.001	0.9 (0.64-1.24)	0.5
Coronary artery disease	702 (33)	341 (27)	1.37 (1.18-1.60)	<0.001	1.32 (1.11-1.57)	0.002
Prior HF	433 (20)	158 (12)	1.84 (1.51-2.24)	<0.001	1.36 (1.09-1.70)	0.007

Prior symptomatic stroke	302 (14)	166 (13)	1.12 (0.92-1.38)	0.3	0.9 (0.73-1.14)	0.4
Atrial fibrillation or flutter	483 (23)	270 (21)	1.11 (0.94-1.32)	0.2	0.9 (0.71-1.05)	0.1
Malignancy	330 (16)	145 (11)	1.45 (1.18-1.79)	<0.001	1.44 (1.15-1.81)	0.002
Aortic/peripheral disease	379 (18)	156 (12)	1.58 (1.29-1.94)	<0.001	1.4 (1.11-1.73)	0.004
Liver cirrhosis	29 (1)	8 (1)	2.22 (1.06-5.22)	0.03	2.63 (1.19-6.48)	0.02
Chronic lung disease (moderate or severe)	41 (3)	64 (3)	0.95 (0.64-1.42)	0.8	0.9 (0.58-1.39)	0.6
Creatinine level above median (0.83 mg/dl)	1358 (73)	492 (27)	2.89 (2.50-3.33)	<0.001	3.06 (2.59-3.62)	<.0001
Vmax >5 m/s	402 (19)	261 (20)	0.9 (0.77-1.10)	0.4	1.09 (0.90-1.32)	0.4
LVEF <40 %	190 (9)	90 (7)	1.31 (1.01-1.71)	0.04	0.88 (0.66-1.18)	0.4

Any combined valvular disease (moderate or severe)	947 (45)	475 (37)	1.38 (1.20-1.59)	<0.001	1.07 (0.91-1.26)	0.4
TR pressure gradient ≥40 mm Hg	409 (19)	158 (12)	1.71 (1.40-2.09)	<0.001	1.34 (1.07-1.68)	0.01

Values are number (%), and OR (95%CI).

BMI=body mass index; CI=Confidence interval; HF=heart failure; LVEF=left ventricular ejection fraction; OR=odds ratio; TR=tricuspid regurgitation.

Supplemental Table S2. Detailed Data on Baseline Characteristics According to the Status of Anemia

Variables	No anemia	Mild anemia	Moderate/Severe anemia	P value
	Hb ≥13.0 g/dl for men, and ≥12.0 g/dl for women	Hb 11.0–12.9 g/dl for men, and 11.0–11.9 g/dl for women	Hb ≤10.9 g/dl	
	N=1286	N=835	N=1282	
Clinical characteristics				
Age, y* †	74.5 ± 9.9	78.0 ± 8.7	81.4 ± 8.7	<0.001
Age ≥80	393 (31)	372 (45)	792 (62)	<0.001
Men*	524 (41)	399 (48)	371 (29)	<0.001
BMI, kg/m^2	22.7 ± 3.7	22.0 ± 3.7	20.6 ± 3.6	<0.001
BMI <22 kg/m^2*	634 (49)	491 (59)	941 (73)	<0.001

Hypertension*	879 (68)	598 (72)	923 (72)	0.09
Current smoking*	87 (7)	51 (6)	37 (3)	<0.001
History of smoking	323 (25)	222 (27)	210 (16)	<0.001
Dyslipidemia	514 (40)	308 (37)	372 (29)	<0.001
On statin therapy	353 (27)	238 (29)	288 (22)	0.002
Diabetes mellitus	296 (23)	209 (25)	323 (25)	0.4
On insulin therapy*	39 (3)	59 (7)	78 (6)	<0.001
Coronary artery disease*	341 (27)	304 (36)	398 (31)	<0.001
Prior PCI	126 (10)	132 (16)	189 (15)	<0.001
Prior CABG	38 (3)	58 (7)	72 (6)	<0.001
Prior myocardial infarction*	73 (6)	78 (9)	132 (10)	<0.001

Prior open heart surgery	73 (6)	82 (10)	111 (9)	<0.001
Prior HF	158 (12)	119 (14)	314 (24)	<0.001
Prior symptomatic stroke*	166 (13)	128 (15)	174 (14)	0.30
Atrial fibrillation or flutter* †	270 (21)	172 (21)	311 (24)	0.06
Aortic/peripheral vascular disease*	156 (12)	152 (18)	227 (18)	<0.001
Serum creatinine, mg/dl*	0.8 (0.6–1.0)	0.9 (0.7–1.2)	1.1 (0.8–2.3)	<0.001
Creatinine >2 mg/dl	40 (3)	124 (15)	360 (28)	<0.001
eGFR, ml/min/1.73m^2	64 ± 22	51 ± 26	39 ± 27	0.001
Hemodialysis*	36 (3)	105 (13)	230 (18)	<0.001
Hemoglobin, g/dl	13.4 (12.7–14.2)	11.6 (11.3–11.9)	9.7 (8.7–10.4)	<0.001
BNP, pg/ml	143 (57–432)	216 (97–615)	554 (202–1357)	<0.001

CRP, mg/dl	0.13 (0.06–0.36)	0.2 (0.08–0.64)	0.43 (0.1–2.2)	<0.001
Liver cirrhosis (Child-Pugh B or C)*	8 (1)	8 (1)	21 (2)	0.04
Malignancy	145 (11)	114 (14)	216 (17)	<0.001
Malignancy currently under treatment* †	33 (3)	39 (5)	71 (6)	<0.001
Chronic lung disease	159 (12)	88 (11)	119 (9)	0.04
Chronic lung disease (moderate or severe)*	41 (3)	21 (3)	43 (3)	0.5
Logistic EuroSCORE, %	7.0 (4.2–12.0)	9.4 (6.2–16.0)	14.2 (9.0–23.0)	<0.001
EuroSCORE II, %	1.9 (1.2–3.5)	2.8 (1.7–4.5)	4.1 (2.7–6.8)	<0.001
STS score (PROM), %	2.5 (1.6–4.0)	3.8 (2.4–5.9)	6.1 (3.7–1.0)	<0.001
Echocardiographic variables				
Vmax, m/s	4.2±0.9	4.2±0.9	4.1±0.9	0.01

Vmax >5 m/s	261 (20)	171 (20)	231 (18)	0.2
Vmax >4 m/s* †	790 (61)	491 (59)	713 (56)	0.01
Mean aortic PG, mmHg	42±20	42±21	41±20	0.09
AVA (equation of continuity), cm^2	0.73±0.18	0.72±0.18	0.69±0.19	<0.001
Low gradient AS (Vmax ≤4m/s and mean aortic PG ≤40mmHg, but AVA <1.0 cm^2)	537 (42)	356 (43)	597 (47)	0.04
LV end-diastolic diameters, mm	46±7	46±7	46±7	0.5
LV end-systolic diameters, mm	30±8	30±8	31±8	<0.001
LVEF, %*	64±13	63±13	61±14	<0.001
<40%	90 (7)	57 (7)	133 (10)	0.002
<50%	178 (14)	117 (14)	263 (21)	<0.001

IVST in diastole, mm	11.5±2.4	11.5±2.3	11.2±2.2	0.002
PWT in diastole, mm	11.1±2.0	11.1±2.2	10.9±2.0	0.04
Any combined valvular disease (moderate or severe)*†	475 (37)	324 (39)	623 (49)	<0.001
Moderate or severe AR	280 (22)	174 (21)	263 (21)	0.7
Moderate or severe MS	51 (4)	24 (3)	46 (4)	0.4
Moderate or severe MR	191 (15)	152 (18)	362 (28)	<0.001
Moderate or severe TR	159 (12)	124 (15)	289 (23)	<0.001
TR pressure gradient ≥40 mm Hg*	158 (12)	117 (14)	292 (23)	<0.001
Symptomatic status at index UCG				
Chest pain	176 (14)	142 (17)	154 (12)	0.02

Syncope	66 (5)	53 (6)	74 (6)	0.5
HF	494 (38)	302 (36)	727 (57)	<0.001
NYHA III or IV	172 (35)	127 (42)	414 (57)	<0.001
Asymptomatic	637 (50)	407 (49)	455 (35)	<0.001
Admission for HF at index echocardiography* †	194 (15)	123 (15)	454 (35)	<0.001
Therapeutic strategy*				
Initial AVR	549 (43)	316 (38)	313 (24)	<0.001
Conservative	737 (57)	519 (62)	969 (76)	<0.001

Values are mean ± SD, median (interquartile range), or number (%).

The values of CRP and BNP were obtained in 2914 (76%) and 1801 (47%) patients, respectively. The NYHA class was obtained in 1500 (44.1%) patients.

Supplemental Table S3. List of adjusting variable in the Cox proportional hazard models

Adjusting variables in the Cox proportional hazard models	Adjusting variables in the parsimonious Cox proportional hazard models
Age	Age
Men	Vmax >4m/s
BMI <22 kg/m2	Any combined valvular disease (moderate or severe)
Therapeutic strategy	Atrial fibrillation or flutter
LVEF	Malignancy currently under treatment
TR pressure gradient ≥40 mmHg	Admission for HF at index echocardiography
Vmax >4m/s	
Any combined valvular disease (moderate or severe)	

Prior myocardial infarction

Prior symptomatic stroke

Atrial fibrillation or flutter

Chronic lung disease (moderate or severe)

Malignancy currently under treatment

Aortic/peripheral vascular disease

Liver cirrhosis (Child-Pugh B or C)

Hemodialysis

Admission for HF at index echocardiography

Hypertension

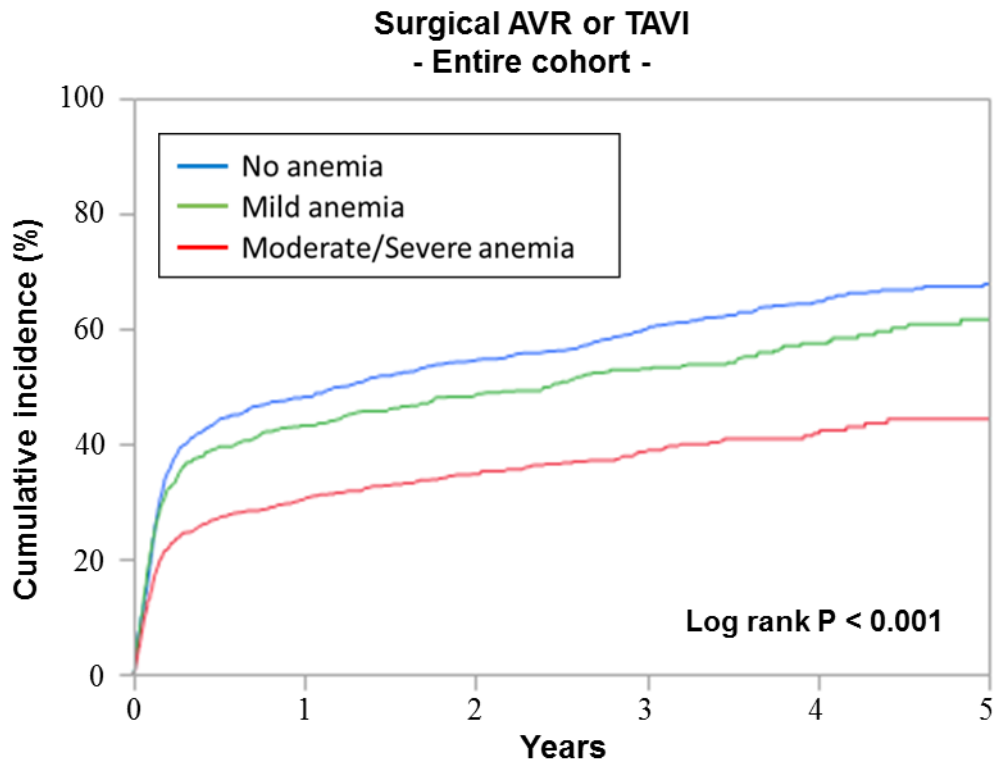Current smoking

On insulin therapy

Coronary artery disease

Serum creatinine

BMI=body mass index; HF=heart failure; LVEF=left ventricular ejection fraction; TR=tricuspid regurgitation; Vmax=peak aortic jet

velocity.

Supplemental Figure S1

A.

	0	1 year	2 year	3 year	4 year	5 year
No anemia						
N of patients at risk	1286	585	458	309	180	81
N of patients with event		597	667	715	745	757
Cumulative incidence		48%	55%	60%	65%	68%
Mild anemia						
N of patients at risk	835	385	297	198	96	42
N of patients with event		342	375	398	411	418
Cumulative incidence		43%	49%	53%	57%	62%
Moderate/Severe anemia						
N of patients at risk	1282	573	390	236	114	50
N of patients with event		349	380	400	409	413
Cumulative incidence		30%	35%	39%	42%	44%

B.
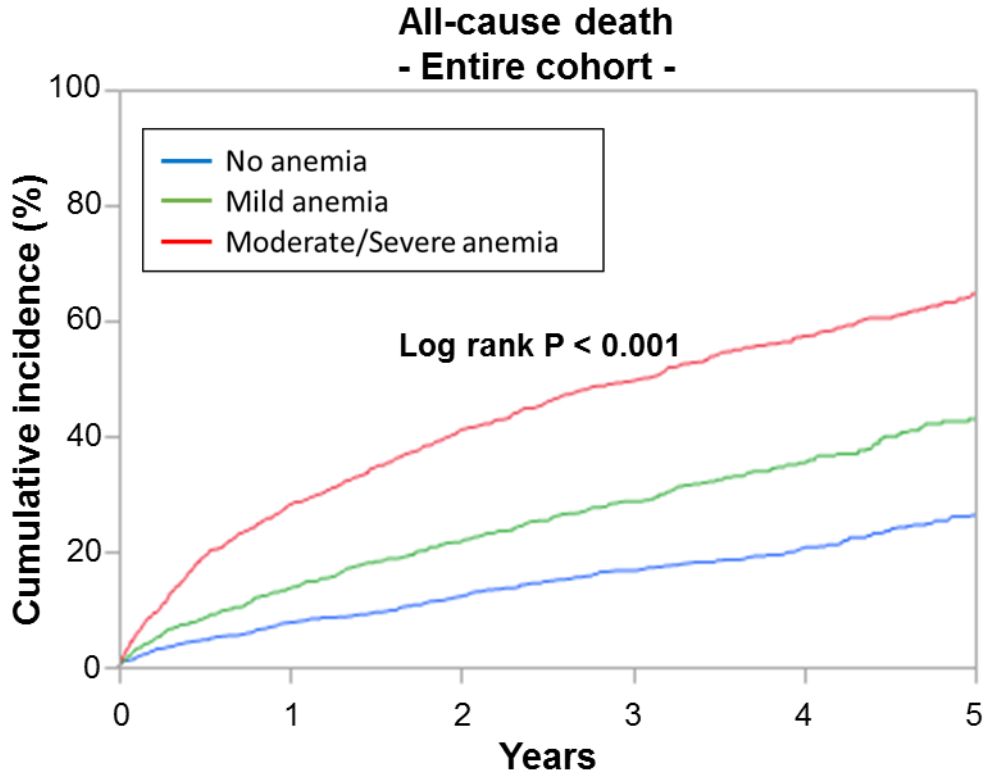
All-cause death
- Entire cohort -

	0	1 year	2 year	3 year	4 year	5 year
No anemia						
N of patients at risk	1286	1144	1061	808	517	279
N of patients with event		98	153	203	234	263
Cumulative incidence		8%	12%	17%	21%	26%
Mild anemia						
N of patients at risk	835	685	598	439	259	134
N of patients with event		111	175	224	258	282
Cumulative incidence		14%	22%	29%	35%	43%
Moderate/Severe anemia						
N of patients at risk	1282	857	672	459	239	114
N of patients with event		345	499	588	646	677
Cumulative incidence		28%	41%	50%	57%	65%

C.

Cardiovascular death
- Entire cohort -
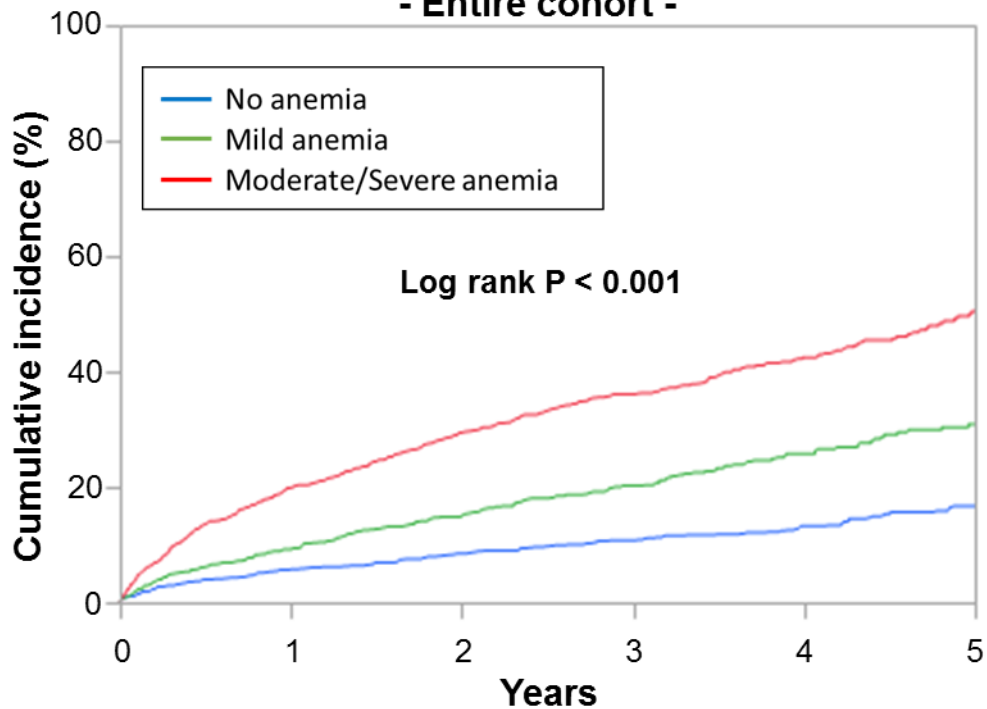
	0	1 year	2 year	3 year	4 year	5 year
No anemia						
N of patients at risk	1286	1144	1061	808	517	279
N of patients with event		72	105	129	147	163
Cumulative incidence		6%	9%	11%	13%	17%
Mild anemia						
N of patients at risk	835	685	598	439	259	134
N of patients with event		73	117	150	175	189
Cumulative incidence		9%	15%	20%	26%	31%
Moderate/Severe anemia						
N of patients at risk	1282	857	672	459	239	114
N of patients with event		233	332	388	424	448
Cumulative incidence		20%	30%	36%	42%	50%

D.

Heart failure hospitalization
- Entire cohort -
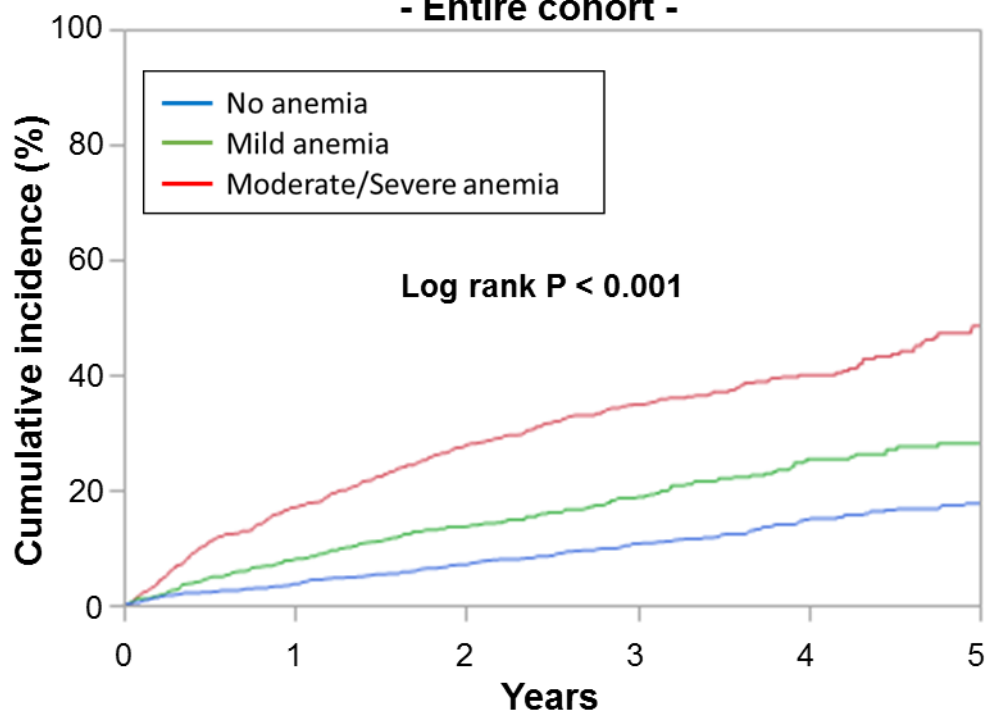
	0	1 year	2 year	3 year	4 year	5 year
No anemia						
N of patients at risk	1286	1114	1011	751	466	256
N of patients with event		45	73	35	146	158
Cumulative incidence		4%	7%	11%	15%	18%
Mild anemia						
N of patients at risk	835	648	546	385	225	118
N of patients with event		61	99	127	152	158
Cumulative incidence		8%	14%	19%	25%	28%
Moderate/Severe anemia						
N of patients at risk	1282	770	568	367	181	78
N of patients with event		179	273	322	344	362
Cumulative incidence		17%	28%	35%	40%	48%

E.

Aortic valve-related death
- Entire cohort -
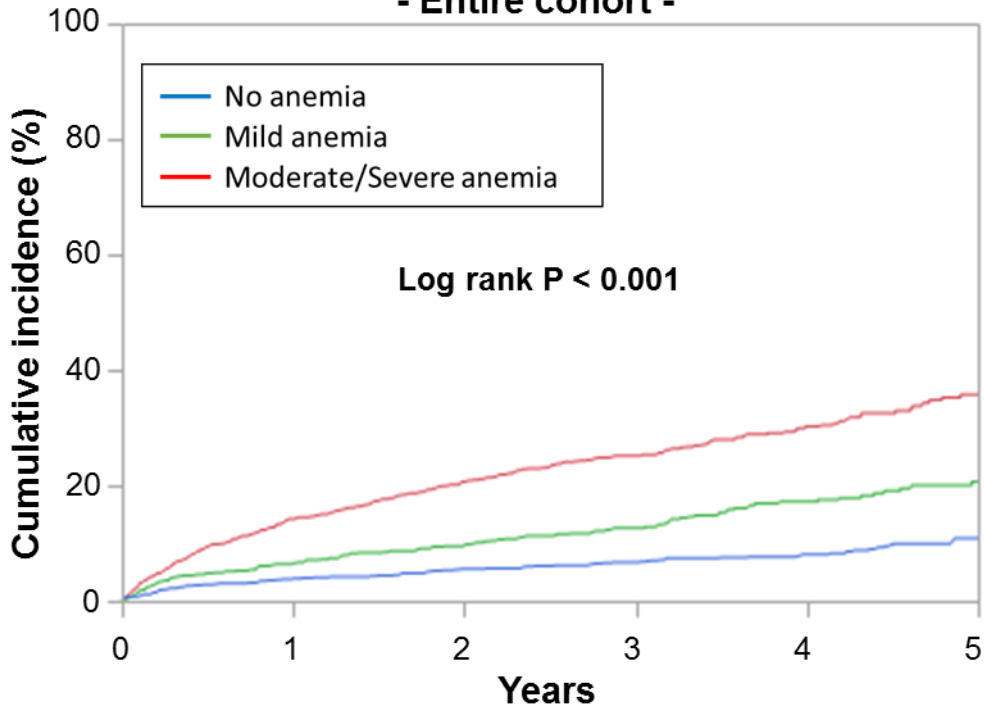
	0	1 year	2 year	3 year	4 year	5 year
No anemia						
N of patients at risk	1286	1144	1062	808	517	279
N of patients with event		48	68	79	89	101
Cumulative incidence		4%	6%	7%	8%	11%
Mild anemia						
N of patients at risk	835	685	598	439	260	134
N of patients with event		51	74	92	111	119
Cumulative incidence		6%	10%	13%	17%	21%
Moderate/Severe anemia						
N of patients at risk	1282	857	672	459	239	114
N of patients with event		161	222	255	279	293
Cumulative incidence		14%	21%	25%	30%	36%

F.
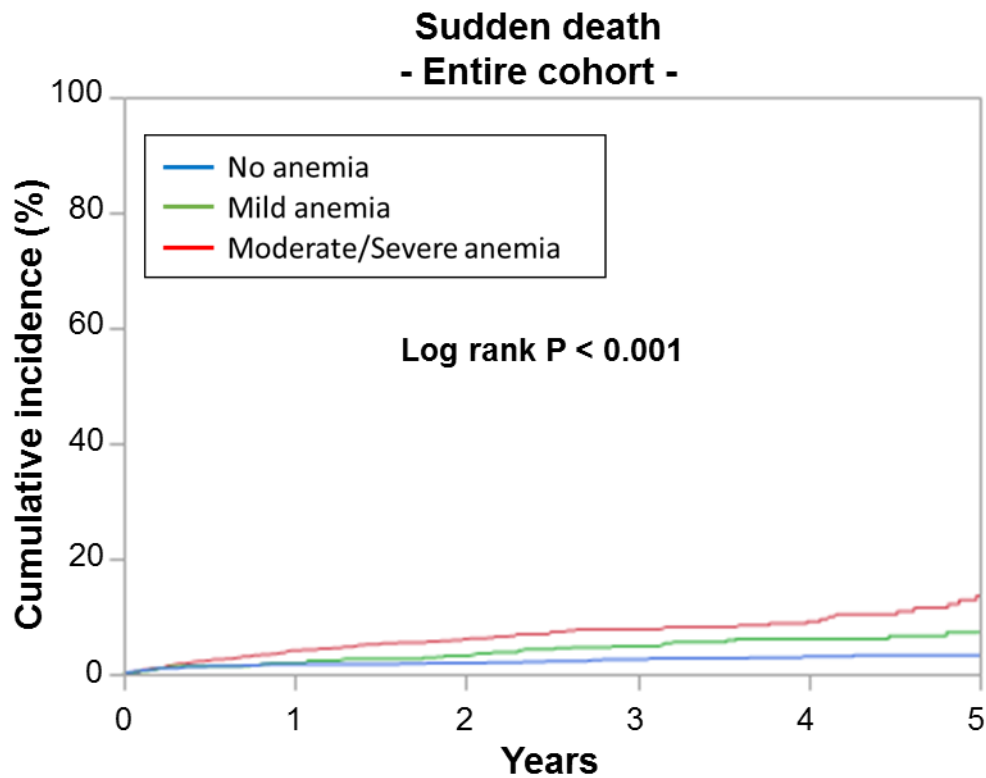
Sudden death
- Entire cohort -

	0	1 year	2 year	3 year	4 year	5 year
No anemia						
N of patients at risk	1286	1144	1062	808	517	279
N of patients with event		21	24	30	33	34
Cumulative incidence		2%	2%	3%	3%	3%
Mild anemia						
N of patients at risk	835	685	598	439	260	134
N of patients with event		15	23	33	38	40
Cumulative incidence		2%	3%	5%	6%	7%
Moderate/Severe anemia						
N of patients at risk	1282	857	672	459	239	114
N of patients with event		43	60	70	75	83
Cumulative incidence		4%	6%	8%	9%	14%

G.

Non-cardiovascular death
- Entire cohort -
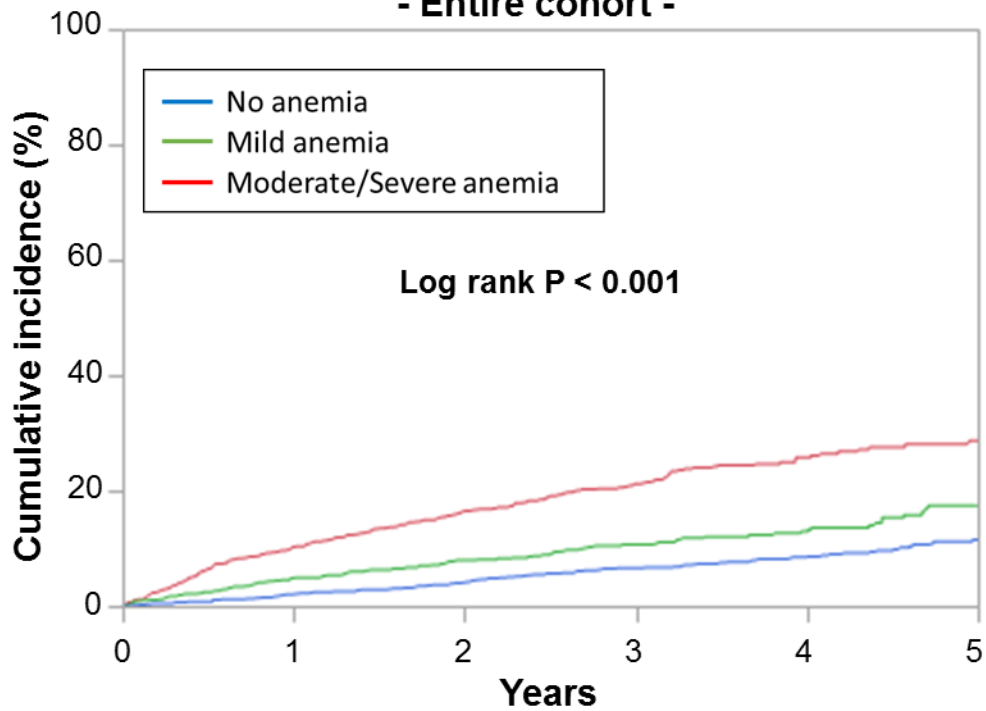
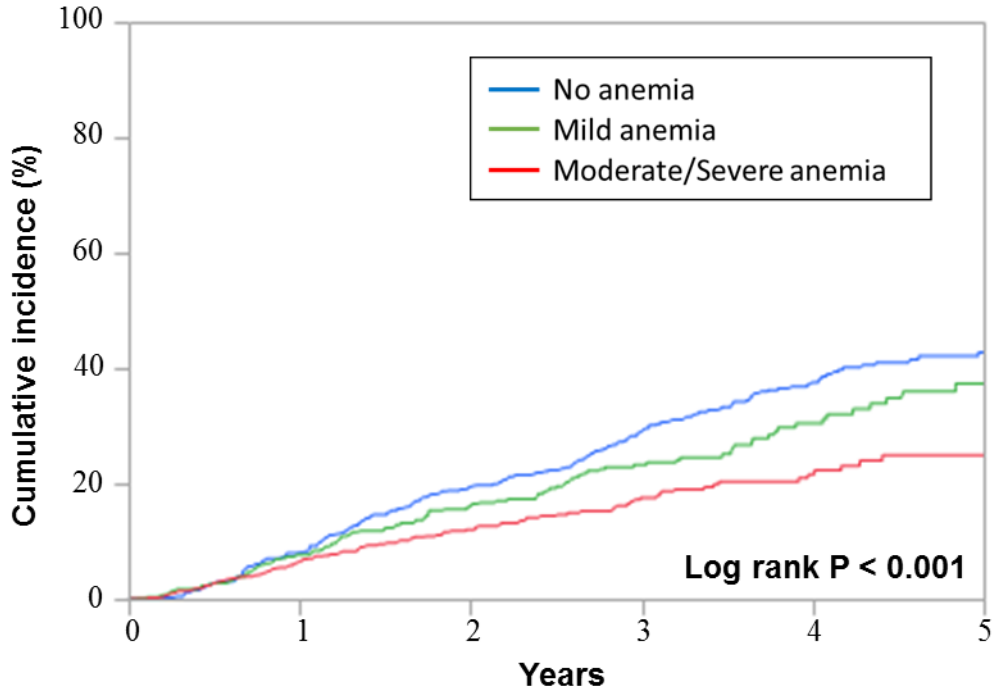|	0	1 year	2 year	3 year	4 year	5 year
No anemia						
N of patients at risk	1286	1144	1062	808	517	279
N of patients with event		26	48	74	87	100
Cumulative incidence		2%	4%	7%	8%	12%
Mild anemia						
N of patients at risk	835	685	598	439	259	134
N of patients with event		38	58	74	83	93
Cumulative incidence		5%	8%	11%	13%	17%
Moderate/Severe anemia						
N of patients at risk	1282	857	672	459	239	114
N of patients with event		112	167	200	222	229
Cumulative incidence		10%	17%	21%	26%	29%

Supplemental Figure S2

Variables	Subpopulation	Severity of anemia	Cumulative 5-year incidence/Number at risk (Cumulative 5-year event rate %)	Unadjusted HR (95% CI)	P value	Adjusted HR (95%CI)	P value	Adjusted HR (95% CI) 0.1 1 10	P for interaction
Age	Age <80	No	109/893 (16%)	1 (reference)		1 (reference)			0.09
		Mild	95/463 (26%)	1.75 (1.35-2.27)	<0.001	1.06 (0.8-1.41)	0.7		
		Moderate/Severe	150/490 (42%)	3.29 (2.61-4.17)	<0.001	1.65 (1.25-2.18)	<0.001		
	Age ≥80	No	100/393 (38%)	1 (reference)		1 (reference)			
		Mild	119/372 (48%)	1.34 (1.04-1.74)	0.02	1.46 (1.12-1.92)	0.006		
		Moderate/Severe	332/792 (68%)	2.23 (1.8-2.78)	<0.001	1.52 (1.19-1.93)	<0.001		
AS-related symptoms	Asymptomatic	No	78/638 (17%)	1 (reference)		1 (reference)			0.5
		Mild	98/408 (34%)	2.11 (1.6-2.79)	<0.001	1.57 (1.16-2.12)	0.004		
		Moderate/Severe	117/455 (41%)	2.92 (2.23-3.84)	<0.001	1.88 (1.38-2.57)	<0.001		
	Symptomatic	No	131/648 (26%)	1 (reference)		1 (reference)			
		Mild	116/427 (34%)	1.46 (1.15-1.86)	0.002	1.12 (0.87-1.45)	0.4		
		Moderate/Severe	365/827 (64%)	3.12 (2.58-3.8)	<0.001	1.43 (1.14-1.79)	0.002		
Severity of AS	Vmax <5m/s	No	177/1025 (24%)	1 (reference)		1 (reference)			1
		Mild	178/664 (37%)	1.74 (1.42-2.12)	0.005	1.34 (1.09-1.65)	0.006		
		Moderate/Severe	398/1051 (58%)	3.24 (2.73-3.84)	<0.001	1.63 (1.34-1.99)	<0.001		
	Vmax ≥5m/s	No	32/261 (14%)	1 (reference)		1 (reference)			
		Mild	36/171 (26%)	1.7 (1.08-2.69)	0.02	1.17 (0.7-1.97)	0.6		
		Moderate/Severe	84/231 (47%)	3.72 (2.54-5.55)	<0.001	1.33 (0.83-2.13)	0.2		
LV systolic function	EF ≥50%	No	164/1108 (20%)	1 (reference)		1 (reference)			0.3
		Mild	167/718 (32%)	1.65 (1.35-2.03)	<0.001	1.24 (1.002-1.53)	0.048		
		Moderate/Severe	354/1019 (52%)	3.31 (2.78-3.95)	<0.001	1.62 (1.32-1.98)	<0.001		
	EF <50%	No	45/178 (32%)	1 (reference)		1 (reference)			
		Mild	47/117 (48%)	1.99 (1.33-2.99)	<0.001	1.48 (0.93-2.34)	0.09		
		Moderate/Severe	128/263 (71%)	2.86 (2.05-4.06)	<0.001	1.52 (1-2.3)	0.0501		
Renal function	CRE ≤2mg/dl	No	192/1246 (21%)	1 (reference)		1 (reference)			<0.001
		Mild	175/711 (33%)	1.68 (1.38-2.04)	<0.001	1.41 (1.15-1.72)	<0.001		
		Moderate/Severe	337/922 (54%)	3.31 (2.80-3.93)	<0.001	1.73 (1.42-2.1)	<.0001		
	CRE >2mg/dl or hemodialysis	No	17/40 (52%)	1 (reference)		1 (reference)			
		Mild	39/124 (44%)	0.66 (0.38-1.19)	0.2	0.4 (0.22-0.77)	0.005		
		Moderate/Severe	145/360 (63%)	0.96 (0.60-1.65)	0.9	0.5 (0.3-0.95)	0.03		

Supplemental Figure S3

A.

	0	1 year	2 year	3 year	4 year	5 year
No anemia						
N of patients at risk	737	584	457	308	180	81
N of patients with event		54	124	172	202	214
Cumulative incidence		8%	20%	29%	38%	43%
Mild anemia						
N of patients at risk	519	382	295	197	95	42
N of patients with event		34	67	89	102	109
Cumulative incidence		8%	16%	23%	30%	37%
Moderate/Severe anemia						
N of patients at risk	969	569	388	234	114	50
N of patients with event		46	76	96	105	109
Cumulative incidence		6%	12%	18%	22%	25%

B.

Surgical AVR or TAVI
- Initial AVR stratum -
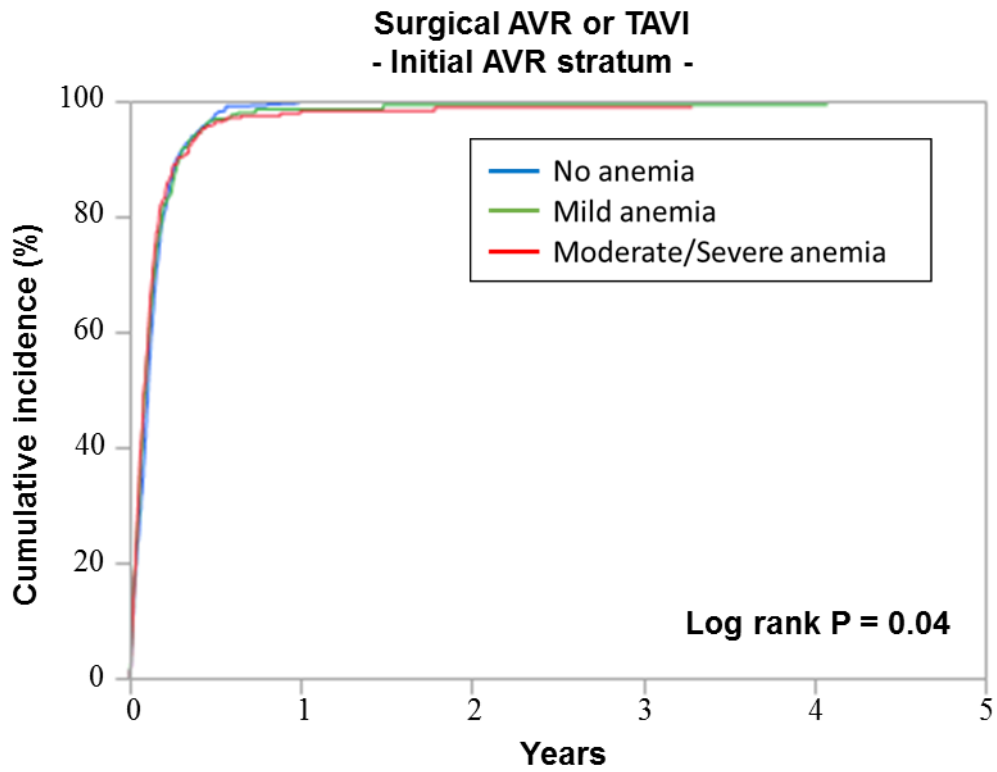
	0	1 year
No anemia		
N of patients at risk	549	1
N of patients with event		543
Cumulative incidence		100%
Mild anemia		
N of patients at risk	316	2
N of patients with event		308
Cumulative incidence		99%
Moderate/Severe anemia		
N of patients at risk	313	4
N of patients with event		303
Cumulative incidence		98%

Supplemental Figure Legends

Supplemental Figure S1

Cumulative incidences of surgical AVR or TAVI and the secondary outcome measures in

the no, mild, and moderate/severe anemia groups in the entire cohort.

AVR=aortic valve replacement; TAVI=transcatheter aortic valve implantation

Supplemental Figure S2

Subgroup analyses for the crude risks of mild and moderate/severe anemia relative to no

anemia for the primary outcome measure.

AS=aortic stenosis; EF=ejection fraction; eGFR=estimated glomerular filtration rate;

HR=hazard ratio; LV=left ventricular

Supplemental Figure S3

Kaplan–Meier curves for the cumulative incidences of surgical AVR or TAVI in the

conservative stratum (A) and in the initial AVR stratum (B).

AVR=aortic valve replacement; TAVI=transcatheter aortic valve implantation