Relationship Between Anemia and Sudden Cardiac Death in Patients With Severe Aortic Stenosis

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Aortic stenosis (AS) is associated with significant morbidity and mortality, including sudden cardiac death (SCD). Anemia is a known risk factor for mortality in patients with AS. We sought to understand the prognostic implications between anemia and SCD in severe AS. The Mayo Clinic AS database includes 8,357 adults with severe AS (mean gradient ≥40 mm Hg, aortic valve area ≤1 cm^2, or peak aortic jet velocity ≥4 m/s) enrolled between January 1, 1995 and April 30, 2015. Survival and cause of death were ascertained from the National Death Index and SCD from medical records. We excluded patients with multiple valvular abnormalities, leaving 7,292 subjects. The median (interquartile range, [IQR]) age was 76 (68, 82) years with 56% male, and median (IQR) hemoglobin level was 12.9 (11.6, 14.1) g/dl. The frequency of anemia (hemoglobin <13.0g/dl for men, <12.0 g/dL for women) was 40%. During median (IQR) follow up of 4.4 (1.8, 8.1) years, 4,056 died (10-year survival 38%) including 225 with SCD (10-year cumulative incidence 5%). In a multivariate model including age, sex, body-mass index, hypertension, diabetes mellitus, myocardial infarction, estimated glomerular filtration rate, and time dependent aortic valve replacement, anemia was associated with increased all-cause mortality (hazard ratios 1.75, 95%CI 1.64, 1.87; p < 0.001) and increased SCD mortality (hazard ratios 1.42, 95%CI 1.07, 1.86; p = 0.01). In conclusions, anemia is a frequent finding in patients with severe AS and independently associated with increased all-cause mortality and SCD. Anemia may be a useful prognostic marker and a modifiable therapeutic target in managing patients with severe AS **(Am J Cardiol 2020;136:107−114)**

Aortic stenosis (AS) is the most prevalent valvular abnormality warranting treatment in the United States.[1,2] As AS progresses, impedance of blood flow results in increasing left ventricular pressure overload, hypertrophy, and decreased compliance which ultimately impairs cardiac output and coronary blood flow. As such, AS is associated with significant comorbidity and mortality including sudden cardiac death (SCD). The onset of symptoms in AS is associated with a marked increase in mortality. Even asymptomatic patients with severe AS are at increased risk of SCD death events with an estimated even rate of 1% per year.[1−3] However, it is difficult to predict which patients with AS will suffer from SCD and the exact mechanisms are unclear. Furthermore, AS is a progressive condition with both an age-related prevalence and severity, and patients often have other comorbidities. Anemia is a known risk factor for mortality in patients with AS and a potentially treatable risk factor. Importantly, anemia has negative consequences for cardiac function.[4] In particular, anemia has been associated with left ventricular hypertrophy, which exacerbates myocardial ischemia by increasing oxygen demand.[5] We hypothesized that anemia in AS is associated with increased risk of SCD. The aim of this study was to assess the relationships between anemia and SCD in patients with severe AS.

Methods

We utilized the Mayo Clinic AS database which contains a total of 8,357 patients with severe AS, defined as mean gradient ≥40 mm Hg, aortic valve area ≤1 cm^2, or peak aortic jet velocity ≥4 m/s,[7] enrolled from January 1, 1983 through April 30, 2015. We excluded patients from this database who were <18 years of age, had subvalvular or supravalvular AS, concomitant ≥moderate aortic regurgitation, ≥moderate mitral regurgitation, ≥moderate tricuspid

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regurgitation, ejection fraction <50% and those who had missing laboratory data of hemoglobin or creatinine within 1 year of echocardiographic assessment showing severe AS. All participants were evaluated with a full clinical history, physical examination and transthoracic echocardiogram. The study was approved by the Mayo Clinic Institutional Review Board (10-007230).

Data regarding past medical history, cardiac risk factors, echocardiographic variables, and laboratory measurements were collected for each patient. Baseline clinical laboratory values were obtained within 1 year of diagnosis of severe AS. When multiple laboratory values were available, those closest in time to the echocardiogram were included.

Anemia was defined as hemoglobin <13.0 g/dl for males, and <12.0 g/dl for females, as per our institution's laboratory standardized age- and sex-specific reference ranges.[6] Comorbidities were collected if present at any time prior to and up to 1 month after the diagnosis of severe AS. These included hypertension, defined as blood pressure >140/90 mm Hg or treated with current anti-hypertensive medications; diabetes mellitus (DM; defined as fasting blood sugar >126 mg/dl on 2 occasions or treatment with anti-diabetic therapies); renal insufficiency, defined as estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m^2; chronic lung diseases, including asthma (requiring treatment), chronic obstructive pulmonary disease (with a forced expiratory volume in the first second and/or forced vital capacity <70%; 50% forced expiratory volume in the first second < 80% predicted), cystic fibrosis, and idiopathic pulmonary fibrosis. Patients were censored at the time of intervention on their valve.

Pressure gradients were estimated using Doppler echocardiography and the modified Bernoulli equation, with aortic valve area determined by the continuity equation. Left ventricular ejection fraction and left atrial volume index were calculated using Simpson's biplane method of discs.[7] Early (E) and late (A) transmitral inflow velocity signals were obtained by pulsed-wave Doppler sampling at the mitral valve (MV) leaflet tips. Tissue Doppler imaging of the mitral annulus (e') was performed according to standardized methods, using the septal e'.[8] An E/e' ≥15 was indicative of an elevated left ventricular filling pressure. Peak pulmonary artery systolic pressure was estimated from the tricuspid valve regurgitation continuous-wave Doppler peak velocity and the estimated right atrial pressure.[7,9,10,11]

Survival status was ascertained using the National Death Index to December 31, 2016. Outcomes including death were categorized as all-cause death, cardiac-related death (i.e., coronary artery disease, arrhythmic deaths, myocardial infarction (MI), peripheral arterial disease, (excluding stroke), cardiovascular (CV)-related (i.e., cardiac-related and with stroke), and SCD. Each SCD case was individually and manually reviewed using the electronic health record, obituaries, autopsy reports, and the National Death Index. In addition, each case was validated using the American Heart Association definition as death occurring within 60 minutes of the onset of symptoms or within 24 hours of the onset of symptoms if nonwitnessed.[12]

Continuous variables are described as means with standard deviation (SD) and categorical variables as frequencies. Continuous variables were compared using *t* tests or nonparametric tests for non-Gaussian distribution. Categorical variables were compared using chi-square or Fisher's exact test. Mortality was estimated using Kaplan-Meier plots and groups tested using the log-rank test. Univariate and multivariate Cox proportional hazards regression modeling were used to determine hazard ratios (HR) which are provided with 95% confidence intervals (CI). Selection of candidate variables for model building were based on biological plausibility and established risk factors and included: age, sex, eGFR, body mass index, hypertension, DM, previous MI, time dependent aortic valve replacement aortic valve replacement (AVR) treatment (surgical valve replacement surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation [TAVI]). Survival c-statistics were used to summarize the discriminatory ability of models, specifically 500 bootstrap samples were used to calculate the increase in c-statistic when adding anemia or hemoglobin to models without these variables. The increase in c-statistic was summarized with along with 95%CI and the bootstrap standard error was used to create a test of significance. A secondary outcome analysis was performed after propensity matching those with anemia to those without anemia based on demographics, comorbidities, medications, and AS severity. Logistic regression methods were used to create a propensity score for anemia and a greedy matching algorithm was used to create a matched group. Absolute standardized differences were examined to compare the groups after matching and showed good balance. Cox regression was then performed on the matched groups. Competing risk analyses were used to plot cumulative incidence of cardiac death and SCD accounting for competing risk of other deaths. Competing risk analysis was also used to plot the incidence of each type of AVR (SAVR or TAVI), accounting for the other type. A 2-way *a priori* alpha level of 0.05 was considered significant and the study powered at 80% with a beta of 0.2. SAS version 9.4[13] was used for analyses.

Results

A total of 7,292 subjects from the Mayo Clinic AS database met inclusion criteria. Table 1 summarizes the baseline clinical and echocardiographic characteristics of the subjects. Of the 2,887 (40%) with anemia, 131 (5%) were microcytic (mean corpuscular volume [MCV] <78.2 fl), 363 (13%) macrocytic (MCV >97.9 fl) and the remaining 2,393 (83%) were normocytic (MCV 78.2 to 97.9 fl). Anemic patients were older (78 vs 74 years old, $p < 0.001$), had worse renal function (creatinine 1.2 vs 1.1 mg/dl; eGFR: 53.4 vs 60.9 mL/min/1.73m^2, $p < 0.001$), and had more comorbidities including hypertension, type 2 DM, coronary artery disease, chronic obstructive pulmonary disease, and stroke ($p < 0.001$; all) (Table 1).

Table 2 summarizes the echocardiographic characteristics between patients with and without anemia. Median left ventricular ejection fraction was higher (65%) in the nonanemic patients in comparison to the anemic patients (62%) ($p < 0.001$). Right ventricular systolic pressure was higher in the anemic patients (44 mm Hg) in comparison to the

Table 1
Baseline characteristics of all severe aortic stenosis patients with and without anemia

Variable	Total (n = 7,292)	Hemoglobin (g/L)		p value
		≥12 (Female) ≥13 (Male) (n = 4,405)	<12 (Female) <13 (Male) (n = 2,887)	
Age	76 (68,82)	74 (66, 81)	78 (71, 84)	<0.001
Men	4105 (56%)	2476 (56%)	1629 (56%)	0.86
Body mass index (kg/m2)	27.6 (24.4, 31.6)	27.8 (24.6, 31.8)	27.3 (24.1, 31.4)	0.003
Hypertension	4119 (56%)	2384 (54%)	1735 (60%)	<0.001
Diabetes mellitus	1655 (23%)	811 (18%)	844 (29%)	<0.001
Previous myocardial infarction	645 (9%)	281 (6%)	364 (13%)	<0.001
Coronary artery disease	3808 (52%)	2153 (49%)	1655 (57%)	<0.001
Atrial fibrillation	931 (13%)	485 (11%)	446 (15%)	<0.001
Stroke	1664 (23%)	902 (20%)	762 (26%)	<0.001
Chronic obstructive pulmonary disease	930 (13%)	463 (11%)	467 (16%)	<0.001
Prior malignancy	1586 (22%)	899 (20%)	687 (24%)	<0.001
Antiplatelet/anticoagulant	578 (8%)	409 (9%)	169 (6%)	<0.001
Beta blocker	535 (7%)	387 (9%)	148 (5%)	<0.001
Calcium channel blocker	193 (3%)	134 (3%)	59 (2%)	0.009
Hemoglobin	12.9 (11.6, 14.1)	13.9 (13.2, 14.7)	11.1 (10.1, 11.9)	<0.001
Microcytic	160 (2%)	29 (1%)	131 (5%)	<0.001
Normocytic	6458 (89%)	4065 (92%)	2393 (83%)	
Macrocytic	674 (9%)	311 (7%)	363 (13%)	
Ferritin [N=1199]	96 (38, 274)	88 (45, 237)	101 (35, 292)	0.40
Total Iron Binding Capacity [N=1144]	286 (230, 338)	296 (259, 338)	280 (219, 338)	<0.001
Creatinine	1.1 (0.9, 1.3)	1.1 (0.9, 1.2)	1.2 (0.9, 1.5)	<0.001
Estimated Glomerular Filtration Rate	59.2 (47.2, 71.5)	60.9 (51.9, 72.5)	53.4 (38.9, 69.0)	<0.001
Transcatheter aortic valve implantation				<0.001
1 year rate	367 (13%)	156 (10%)	211 (18%)	
5 year rate	444 (18%)	189 (13%)	255 (27%)	
Surgical aortic valve replacement				<0.001
1 year rate	3883 (52%)	2616 (60%)	1267 (41%)	
5 year rate	4341 (59%)	2950 (77%)	1391 (46%)	

Continuous variables are median (Q1, Q3).

nonanemic patients (36 mm Hg) ($p < 0.001$). Other echo parameters including left ventricular stroke volume index (57.4 ml/m^2 vs 57.4ml/m^2, $p = 0.90$), were similar between anemic and nonanemic patients.

The median follow-up duration was 4.4 (IQR: 1.8, 8.1) years with a total follow-up of 40,292 person-years. A total of 4,879 patients underwent intervention on the aortic valve, including 4,412 (90%) with SAVR and 467 with

Table 2
Baseline echocardiographic features of all severe aortic stenosis patients with and without anemia

Echocardiography parameters	Total (n = 7,292)	Hemoglobin (g/L)		p value
		≥12 (Female) ≥13 (Male) (n = 4,405)	<12 (Female) <13 (Male) (n = 2,887)	
Heart rate [N=6906]	68 (60,78)	68 (60,76)	70 (61,79)	<0.001
Left ventricular diastolic diameter, mm [N=6552]	49 (45,53)	49 (45,53)	50 (45,54)	<0.001
Left ventricular systolic diameter, mm [N=6059]	30 (27, 35)	30 (26,34)	31 (27,36)	<0.001
Left ventricular stroke volume index, ml/m^2 [N=6869]	57 (49, 66)	57 (49,66)	57 (49,67)	0.90
Left ventricular ejection fraction, % [N=6202]	64 (56, 68)	65 (58, 69)	62 (54, 68)	<0.001
Left ventricular mass index, g/m^2 [N=6171]	120 (100,144)	117 (97,141)	124 (105,149)	<0.001
Calculated Aortic valve area (cm2) [N=7285]	0.8 (0.7, 0.90)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.02
Aortic valve area index, cm^2/m^2 [N=6998]	0.5 (0.5, 0.6)	0.5 (0.5, 0.6)	0.5 (0.5,0.6)	0.04
Aortic valve peak velocity, m/s	4.6 (4.3, 4.9)	4.6 (4.3, 4.9)	4.5 (4.3, 5.0)	0.57
Aortic valve mean gradient, mm Hg [N=7291]	50 (44, 59)	50 (44, 59)	49 (43, 59)	0.05
Transmital inflow early diastole velocity/mitral annular early diastole velocity (E/e' ratio) [N=4693]	17 (12, 23)	16 (12,20)	20 (14,26)	<0.001
Right ventricular systolic pressure	39 (32,51)	36 (30,46)	44 (34,56)	<0.001

Continuous variables are median (Q1, Q3).

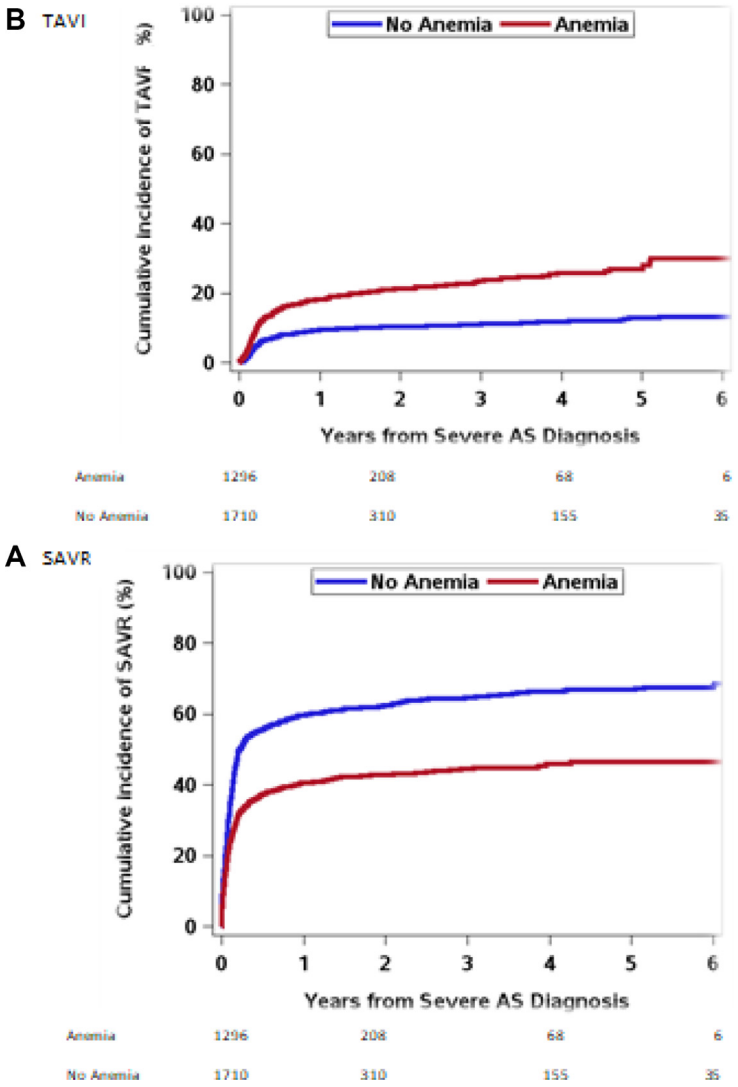

Figure 1. The cumulative incidence of TAVI and SAVR in patients with severe aortic stenosis when comparing anemic versus nonanemic patients after 2009. Anemic patients have an increased incidence of TAVI while nonanemic patients were more likely to receive SAVR. AS = aortic stenosis; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.

TAVI. Since 2009, with the advent of TAVI as an option for valve replacement, anemia was associated with a higher rate of TAVI and a lower rate of SAVR ($p < 0.001$; all) (Figure 1A and B). A total of 4,056 subjects died over the study period with a 10-year survival of 38%. Of these 4,056 overall deaths, 2,285 were post-AVR. Of all deaths, 225 (6%) were confirmed as SCD events with a 10-year cumulative incidence of 5%. One hundred (44%) of the 225 SCD events occurred after AVR. However, we found that AVR (either SAVR or TAVI) was protective of having a future sudden cardiac event (HR = 0.40) and this was independent of whether the patient had anemia or not prior to the procedure.

Figure 2 demonstrates the cumulative incidence of SCD for both anemic and nonanemic patients. Anemic patients had an increased incidence of SCD at all time points in comparison to nonanemic patients ($p < 0.001$). Similarly, anemic patients had an increased incidence of all-cause and CV-related mortality at all time points. Figure 3 demonstrates the cumulative incidence of SCD amongst anemic patients with severe AS according to the MCV. There was no SCD in patients with microcytosis; however, macrocytosis was associated with an increased risk of overall mortality in comparison to normocytosis with a HR 1.53 (CI 1.35, 1.73, $p < 0.001$) after adjustment for age and sex.

Anemia was associated with increased all-cause mortality with an age- and sex-adjusted HR 1.46 (95%CI 1.42, 1.51, $p < 0.001$) for each SD decrease in hemoglobin. When restricted to SCD events, anemia was associated with a HR 1.65 (95%CI 1.26, 2.15, $p < 0.001$) in AS patients. A multivariate Cox proportional hazards model was constructed using the significant univariate determinants of age, sex, body mass index, hypertension, DM, MI, eGFR, time dependent AVR, and anemia. Tables 3 and 4 demonstrates the univariate and multivariate hazard models for mortality in all AS patients. Anemia was independently associated with increased all-cause mortality (HR 1.75, 95%CI 1.64 to 1.87, $p < 0.001$) and increased SCD mortality (HR 1.42, 95%CI 1.08 to 1.87, $p = 0.01$) following adjustment. Each 1 SD decrease in hemoglobin was

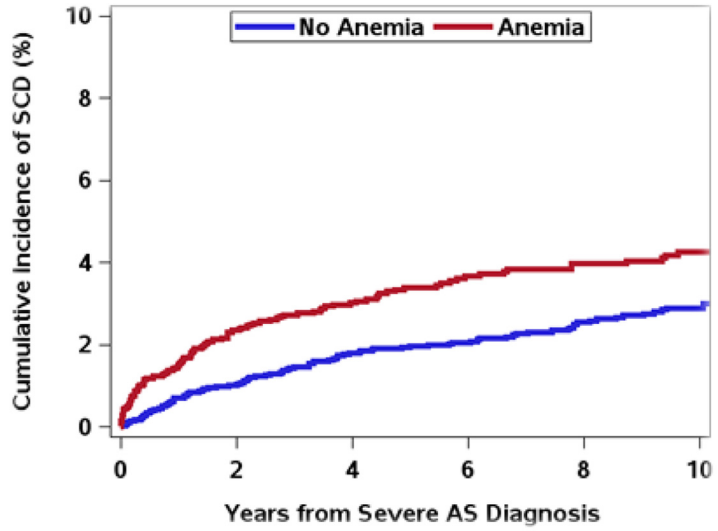

Figure 2. The cumulative incidence of SCD in patients with severe AS when comparing anemic versus nonanemic patients. Anemic patients had an increased incidence of SCD at all time points in comparison to nonanemic patients, $p < 0.001$. AS = aortic stenosis; SCD = sudden cardiac death.

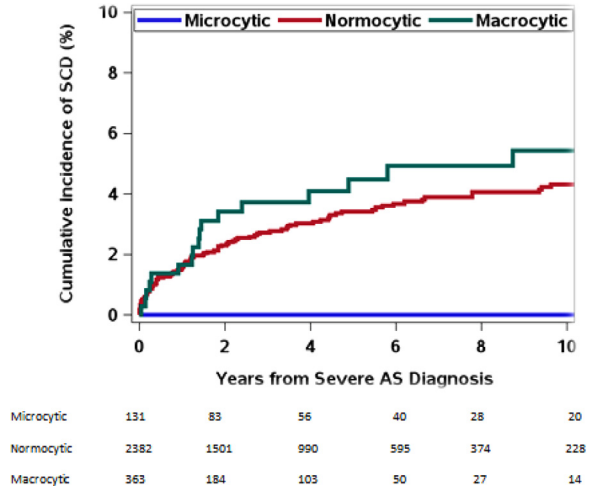

Figure 3. The cumulative incidence of SCD in patients with anemia and severe AS according to MCV. AS = aortic stenosis; MCV = mean corpuscular volume; SCD = sudden cardiac death.

associated with increased SCD risk (HR 1.30, 95%CI 1.13, 1.50, $p < 0.001$). With multivariate adjustment, c-statistics significant increased ($p < 0.001$ for both) for all-cause mortality when both anemia (Δ c-stat = 0.017) and hemoglobin (Δ c-stat = 0.021) were added to the models (Supplemental Table 1 and 2). For SCD, the increase in c-statistics was more modest and was not significant for anemia ($p = 0.11$) but did reach significance for hemoglobin (Δ c-stat = 0.011, $p = 0.03$). Propensity matching was used to balance the important covariates and results from outcome models were very similar (Supplemental Table 1).

Discussion

In this study of 7,292 patients with severe AS, anemia was prevalent, observed in 40% of patients. Additionally, and to our knowledge not previously reported, anemia was found to be independently associated with an increased risk of SCD in patients with severe AS. Moreover, while it has been previously shown that patients with severe AS and anemia are at an increased risk of mortality, our study replicates these findings in a large independent cohort.

Anemia is a frequent finding with increasing age and is broadly divided into categories based on MCV which narrows down etiologies: microcytic including any cause of iron deficiency (occult blood loss from peptic ulcer or intestinal neoplasia), sideroblastic anemia, thalassemias and anemia of chronic disease; macrocytic which includes megaloblastic (folate and vitamin B12 deficiency) and alcohol; and normocytic which includes intrinsic hemoglobinopathies, autoimmune disease and aplastic anemia. In the majority of our cohort, anemia was normocytic, possibly related to chronic disease. The mechanisms of anemia in AS also include an acquired coagulopathy known as Heyde's syndrome.[14] As red blood cells pass through the diseased valve, the increased shear stress causes degradation of the von Willebrand factor multimers. The large multimers are involved in platelet-mediated hemostasis, which are important in particular for the small vessels that form angiodysplastic lesions in the gastrointestinal tract. The coagulopathy causes increased propensity to bleed from the small angiodysplastic lesions, which is often subclinical and detected as iron deficiency anemia or prolonged bleeding time on routine laboratory evaluation. Just as AS increases in incidence with increasing age, so does the presence of angiodysplastic lesions in the gastrointestinal tract and these patients have increased risk of anemia. The acquired von Willebrand factor deficiency seen in Heyde's syndrome is postulated to reverse following replacement of the aortic valve, as the shear stress is reduced.[15]

Anemia has negative consequences for cardiac function, which compounds the effects of AS. AS alone leads to increased hypertrophy of the left ventricle, increased

Table 3
Univariate hazard ratios for mortality in all aortic stenosis patients

Outcome	Variable	Univariate (95% confidence interval)	p value
All-cause mortality	Age per 10 years	1.90 (1.83-1.96)	<0.0001
	Male sex	0.92 (0.87-0.98)	0.01
	Body mass index per 5 kg/m^2	0.91 (0.89-0.94)	<0.0001
	Anemia	2.22 (2.08-2.36)	<0.0001
	Diabetes mellitus	1.45 (1.35-1.56)	<0.0001
	Hypertension	1.38 (1.30-1.47)	<0.0001
	Myocardial infarction	1.72 (1.55-1.90)	<0.0001
	Estimated glomerular filtration rate per standard deviation	0.63 (0.60-0.65)	<0.0001
	Left ventricular end diastolic diameter per 10mm	1.00 (0.95-1.06)	0.90
	Aortic valve peak velocity (m/s)	0.78 (0.73-0.82)	<0.0001
	Aortic valve replacement (time dependent)	0.57 (0.53-0.60)	<0.0001
Sudden cardiac death	Age per 10 years	1.81 (1.56-2.09)	<0.0001
	Male	1.12 (0.86-1.46)	0.41
	Body mass index per 5 kg/m^2	0.92 (0.81-1.03)	0.15
	Anemia	1.93 (1.48-2.51)	<0.0001
	Diabetes mellitus	1.61 (1.20-2.15)	0.002
	Hypertension	1.46 (1.12-1.92)	0.006
	Myocardial infarction	2.04 (1.39-3.01)	0.0003
	Estimated glomerular filtration rate per standard deviation	0.64 (0.55-0.75)	<0.0001
	Left ventricular end diastolic diameter per 10mm	0.90 (0.72-1.13)	0.36
	Aortic valve peak velocity (m/s)	0.83 (0.65-1.06)	0.13
	Aortic valve replacement (time dependent)	0.40 (0.30-0.53)	<0.0001

afterload, and, over time, reduced cardiac output. Likewise, anemia leads to reduced oxygen delivery, decreased tissue perfusion, increased left ventricular hypertrophy and worsening heart failure.[5] As outlined in Figure 4, the presence of both risk factors increases the detrimental effects on the heart which lead to increased mortality. With regard to SCD, the mechanisms in AS are not completely clear but may involve 1 or more of the following mechanisms: (1) AS leads to hypertrophy of the left ventricle which can induce ventricular tachycardias causing hypotension, low cardiac output, and coronary hypoperfusion;[16,17] (2) stenosis of the aortic valve can affect the His-Purkinje system leading to atrioventricular conduction disturbances; and (3) patients with AS have an abnormal Bezold-Jarisch reflex,

Table 4
Univariate and multivariate hazard models for mortality in all aortic stenosis patients

Outcome	Variable	Age/sex adjusted hazard ratios (95% confidence interval) p value	Multivariate adjusted* hazard ratios (95% confidence interval) p value
All-cause mortality	Anemia	Hazard Ratio=1.93 (1.82 − 2.06) p<0.001 Δ c-stat=0.029 (0.024, 0.035), p<0.001	Hazard Ratio =1.75 (1.64 − 1.87) p<0.001 Δ c-stat=0.017 (0.013, 0.021), p<0.001
	Hemoglobin per 1 standard deviation decrease	Hazard Ratio =1.46 (1.42 − 1.51) p<0.001 Δ c-stat=0.035 (0.029, 0.042), p<0.001	Hazard Ratio =1.39 (1.35 − 1.44) p<0.001 Δ c-stat=0.021 (0.016, 0.025), p<0.001
Sudden cardiac death	Anemia	Hazard Ratio =1.65 (1.26 − 2.15) p<0.001 Δ c-stat=0.020 (0.003, 0.036), p=0.02	Hazard Ratio =1.42 (1.07 − 1.86) p=0.01 Δ c-stat=0.007 (-0.002, 0.015), p=0.11
	Hemoglobin per 1 standard deviation decrease	Hazard Ratio =1.40 (1.22 − 1.60) p<0.001 Δ c-stat=0.030 (0.010, 0.049), p=0.003	Hazard Ratio =1.30 (1.13 − 1.50) p<0.001 Δ c-stat=0.011 (0.001, 0.021), p=0.03

Δ c-stat = change in survival c-statistic from model without anemia/Hemoglobin estimate, Confidence interval, and p-value calculated based on 500 bootstrap samples.

* adjustment variables include age, sex, estimated glomerular filtration rate, body mass index, hypertension, diabetes mellitus, previous myocardial infarction, time dependent aortic valve replacement surgery.

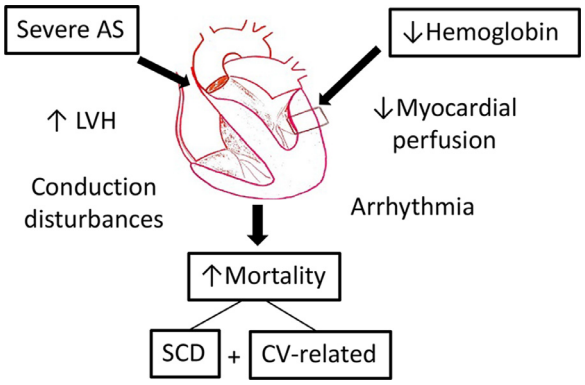

Figure 4. A proposed mechanism for anemia and severe AS leading to increased mortality and sudden cardiac death. Severe AS causes increased left ventricular hypertrophy which disturbs cardiac conduction and when combined with decreased hemoglobin causes decreased myocardial perfusion and cardiac arrhythmias. Together anemia and AS increases the risk of mortality, specifically SCD and CV-related mortality. AS = aortic stenosis; CV = cardiovascular; LVH = left ventricular hypertrophy; SCD = sudden cardiac death.

where stimulation of left ventricular baroreceptors cause hypotension, fall in venous return, and bradycardia, which may result in SCD.[18]

Interestingly, previous studies have demonstrated that replacing the diseased aortic valve can nearly normalize the prolonged bleeding time and incidence of gastrointestinal bleeding in patients with AS. One recent study demonstrated that the increased mortality risk associated with anemia in AS also normalizes with replacing the valve.[4] However, as our study demonstrates, patients with anemia and AS also tend to be older with worse renal function and more comorbidities, often precluding them from surgical replacement and TAVI intervention. Determining reversible causes of anemia in this subset of patients is particularly important. As there is some evidence in heart failure that treating anemia can improve symptoms, functional capacity, and quality of life,[19] treating anemia in AS patients may conceivably improve symptoms, risk of mortality and SCD.

Finally, in our study, anemia was associated with increasing age which is well documented in previous studies.[20] In fact, anemia has been shown to be independently associated with increased frailty and mortality in older adults.[21,22] Evidence demonstrating the temporal changes in anemia and its association with frailty and mortality are lacking but is proposed to be due to adverse outcomes associated with poor oxygen delivery such as fatigue, cognitive decline, and decreased muscle strength.[23] There are many unmeasured variables such as poorer nutrition, social status, and overall inflammatory milieu that likely contribute. While our study did not address frailty per se, the high prevalence of anemia in our patient population demonstrates how vulnerable this population is and how important it is to treat the reversible causes of anemia.

The limitations of our study include those inherent to retrospective analysis which may have introduced selection bias and makes it difficult to assess causation. Our analysis also depended on correct documentation of the cause of death and circumstances around the time of death. However, we attempted to minimize this risk by manually validating each SCD case both with our electronic health record but also the National Death Index and performed statistical analysis to minimize competing risks of other deaths. Last, we did not have sufficient data from our large cohort to assess the etiology of anemia in our patient population with variables such as alcohol consumption, liver disease, and iron deficiency, which may have informed us on the etiologies of macrocytosis, microcytosis, and normocytosis.

In conclusion, anemia is common in patients with AS and is independently associated with increased mortality, in particular SCD. Anemia may be a useful prognostic and therapeutic factor in patients with AS.

Authors' Contribution

Allison Ducharme-Smith: Data curation, Investigation, Methodology,Writing- Original Draft, Writing- Review and Editing; C. Anwar A. Chahal: Visualization, Investigation, Writing- Original Draft, Writing- Review and Editing; Hiroyiku Sawatari: Methodology, Software; Alex Podboy: Data curation, Investigation; Sherif: Data curation; Christopher G. Scott: Software, Formal analysis; Peter A. Brady: Writing- Review and Editing; Bernard J. Gersh: Writing- Review and Editing; Virend K. Somers: Conceptualization, Validation, Writing- Review and Editing, Supervision, funding acquisition; Vuyisile T. Nkomo: Validation, Writing- Review and Editing; Patricia A. Pellikka: Validation, Writing- Review and Editing, Supervision, Project administration.

Disclosures

VKS has served as a consultant to U-Health, GlaxoSmithKline, Price Waterhouse Coopers, Rhonda Grey, Dane Garvin, Philips, ResMed, Sorin Inc., and is working with Mayo Health Solutions and their industry partners on intellectual property related to sleep and CV disease. The Mayo Foundation has received a gift from the Philips Respironics Foundation for the study of sleep and CV disease. However, none of these entities were involved in this study in any way. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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