



# Relationship Between Anemia and the Risk of Sudden Cardiac Arrest

— A Nationwide Cohort Study in South Korea —

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**Background:** The relationship between anemia and sudden cardiac arrest (SCA) is unclear in the general population, so we assessed it in a nationwide cohort.

**Methods and Results:** We studied 494,948 subjects (mean age, 47.8 years; 245,333 men [49.6%]) with national health check-up data from the Korean National Health Insurance Database Cohort. During a mean follow-up period of 5.4 years, SCA occurred in 616 participants (396 men, 220 women). The incidence rates of SCA increased across the 4 anemia groups in both men (0.3, 1.5, 5.3, and 4.5 per 1,000 person-years) and women (0.2, 0.5, 0.5, and 1.2 per 1,000 person-years). The SCA risk per 1-unit decrease in hemoglobin (Hb) increased by 21% and 24%, respectively, in multivariable models adjusted for cardiovascular factors, in men (95% confidence interval [CI], 13–29%;  $P < 0.001$ ) and women (95% CI, 13–37%;  $P < 0.001$ ). A negative correlation between QTc interval and Hb level was observed in men, and a trend was observed in women.

**Conclusions:** Anemia was associated with an increased risk of SCA even after accounting for concomitant conditions in a South Korean nationwide cohort. The correlation between anemia and SCA might be explained by an increase in arrhythmic risks, such as QTc prolongation.

**Key Words:** Anemia; General population; Sudden cardiac arrest

Anemia is common in patients with cardiovascular disease and is a multifactorial problem, especially in the elderly population.<sup>1</sup> The risks of mortality, morbidity and hospitalization in patients with anemia were similar to those of 4 other common cardiovascular risk factors: smoking, diabetes mellitus, arterial hypertension, and hypercholesterolemia.<sup>2</sup> Consequently, anemia has lately been characterized as “the fifth cardiovascular risk factor”.<sup>1</sup> Anemia is present in one-third of patients with acute coronary syndrome (ACS); in particular, in 12.8% of patients with acute myocardial infarction (MI), in 43% of the elderly patients with ST-elevation MI and in 5–10% of non-ST-elevation ACS patients.<sup>3</sup> Recently, it was reported that anemia is associated with increased mortality and sudden death in patients with diastolic heart failure (HF).<sup>4,5</sup>

There are approximately 300,000–350,000 cases of out-of-hospital sudden cardiac arrest (SCA) or sudden cardiac death in the USA yearly, imparting a substantial public health burden.<sup>6–8</sup> Factors that have been most commonly associated with the occurrence of SCA in the overall population include coronary artery disease and associated markers such as diabetes mellitus, left ventricular hypertrophy (LVH), hyperlipidemia, and cardiomyopathies.<sup>6,9–11</sup>

However, little is known about the association between anemia and the development of SCA in the general population. QT prolongation and LVH are risk factors of ventricular fibrillation.<sup>12</sup> However, it is not known whether the severity of anemia is related to QT prolongation and LVH. The aim of this study was to assess the effect of anemia on SCA in a general population by using a national

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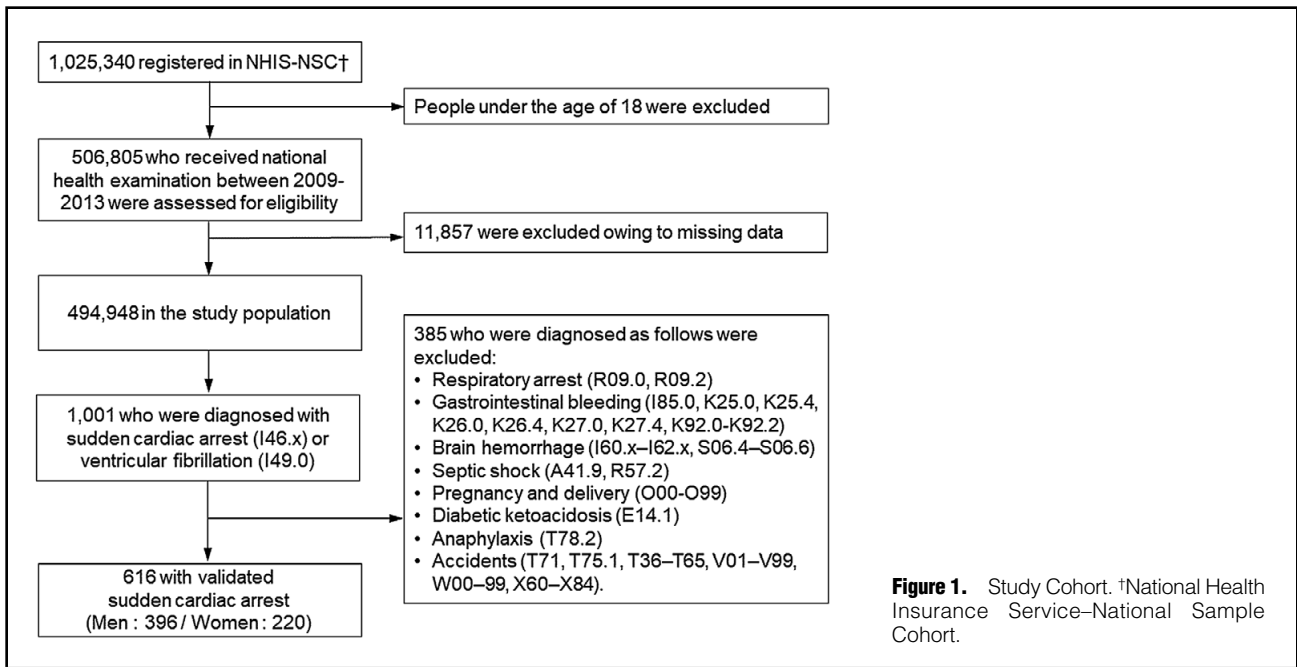
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cohort. Moreover, we analyzed ECG changes according to the severity of anemia by using a hospital cohort.

## Methods

### Source of Study Data

A national health insurance system in Korea was established in 1963 according to the National Health Insurance Act, and it is compulsory for all citizens in South Korea to participate. The National Health Insurance Service (NHIS) released the National Sample Cohort (2002–2013) database (NHIS-NSC [2002–2013]) in 2015. It consists of 1,025,340 Koreans as an initial 2002 cohort and followed up the subjects through 2013. The national cohort represents approximately 2.2% of the source population in 2002 (46,605,433). This is a semi-dynamic cohort database; namely, the cohort was followed up to either the time of the participant's disqualification from health services because of death or emigration, or the end of the study period. The national cohort contains eligibility and demographic information about health insurance and medical aid beneficiaries, medical bill details, medical treatment, disease histories, and prescriptions; such data are constructed after converting insurance claim information to the first day of medical treatment.

In the cohort, the subjects' disease information was classified according to the 10th revision of the International Classification of Diseases (ICD-10) codes, and the subjects' mortality data, as well as the cause of death, were obtained from the Korean National Statistical Office. As this study was based on data from the NHIS, informed consent was not specifically obtained individually. Data were fully anonymized and de-identified for the analysis. This study was approved by the Institutional Review Board of Severance Hospital.

### Study Population

A total of 506,805 subjects had a nationwide health

examination after 2009. However, 11,857 were excluded because of missing data in variables of the health examination. Finally, this study included 494,948 subjects older than 18 years, who had had a physical examination in 2009 and had follow-up data until December 2013 (Figure 1). To ensure diagnostic accuracy, we defined patients with comorbidities, including hypertension, diabetes mellitus, and HF, only when the condition was a discharge diagnosis or confirmed more than twice in the outpatient department.<sup>13,14</sup> Furthermore, the laboratory and survey questionnaire data of general and life-transition health examinations for all cohort members were merged.

Anemia was analyzed as both a continuous and a categorical variable. According to the World Health Organization criteria, anemia is defined as a hemoglobin (Hb) concentration <13 g/dL in men and <12 g/dL in women. We also defined mild anemia as an Hb concentration of 11 to <13 for men and 11 to <12 for women, moderate anemia as Hb 8 to <11 g/dL, and severe anemia as Hb <8 g/dL.<sup>15</sup> At the time of Hb measurement, systolic and diastolic pressures were also measured; serum samples for fasting glucose, Hb, and total cholesterol levels were also obtained after an overnight fast at each examination site. Detailed histories of smoking status, alcohol consumption, and physical activity (including amount and frequency) were obtained through questionnaires.

To evaluate the relationships between anemia and ECG parameters, including QT, QTc intervals (corrected QT interval), T-wave abnormality, and LVH, additional analyses were performed using the MUSE system in 11,782 individuals who were admitted to Severance Hospital from 2004 to 2009. QTc prolongation was defined as >450 ms in men and >470 ms in women. The study protocol was approved by the Institutional Review Board of Severance Hospital and complied with the Declaration of Helsinki.

### Definition and Validation of SCA

In the NHIS-NSC, the cause of deaths was coded using the

**Table 1. Baseline Characteristics of Participants and Incidence of Sudden Cardiac Arrest by Severity of Anemia Among South Koreans**

	Men				Women			
	None (n=232,401)	Mild anemia (n=11,337)	Moderate anemia (n=1,451)	Severe anemia (n=144)	None (n=202,982)	Mild anemia (n=30,848)	Moderate anemia (n=14,872)	Severe anemia (n=913)
Age, years	46.0±13.7	59.8±14.3	63.3±13.8	59.6±14.6	48.6±14.5	50.1±15.4	48.9±15.1	47.1±11.6
BMI	24.3±3.1	23.0±3.1	22.3±3.2	22.4±3.2	23.3±3.5	22.8±3.2	22.7±3.3	22.9±3.3
Systolic BP, mmHg	124.8±14.2	125.2±15.9	125.9±17.6	124.2±18.0	119.9±15.8	118.6±15.8	118.6±15.5	117.4±13.9
Diastolic BP, mmHg	78.1±9.9	76.3±10.3	75.6±10.7	73.9±10.7	74.4±10.1	73.0±10.0	72.9±10.1	71.4±9.3
Hypertension	46,283 (19.9)	4,995 (44.1)	805 (55.5)	55 (38.2)	46,108 (22.7)	7,518 (24.4)	3,264 (21.9)	111 (12.2)
Diabetes mellitus	28,326 (12.2)	3,429 (30.2)	599 (41.3)	38 (26.4)	25,625 (12.6)	4,366 (14.2)	2,113 (14.2)	80 (8.8)
HF	4,001 (1.7)	719 (6.3)	154 (10.6)	12 (8.3)	5,603 (2.8)	1,148 (3.7)	649 (4.4)	20 (2.2)
Dyslipidemia	40,321 (17.3)	3,596 (31.7)	547 (37.7)	37 (25.7)	43,023 (21.2)	6,661 (21.6)	2,723 (18.3)	90 (9.9)
CKD	11,269 (4.8)	1,755 (15.5)	459 (31.6)	28 (19.4)	11,636 (5.7)	2,618 (8.5)	1,589 (10.7)	57 (6.2)
ESRD	65 (0.1)	93 (0.8)	68 (4.7)	3 (2.1)	76 (0.1)	41 (0.1)	59 (0.4)	1 (0.1)
COPD	12,559 (5.4)	9,719 (14.3)	256 (17.6)	11 (7.6)	13,709 (6.8)	2,426 (7.9)	1,054 (7.1)	32 (3.5)
Previous MI	2,579 (1.1)	378 (3.3)	76 (5.2)	3 (2.1)	1,486 (0.7)	325 (1.1)	182 (1.2)	4 (0.4)
Previous ischemic stroke	5,279 (2.3)	939 (8.7)	177 (12.2)	12 (8.3)	5,306 (2.6)	1,096 (3.6)	558 (3.8)	23 (2.5)
Malignancy	14,114 (6.1)	1,924 (17.0)	387 (26.7)	22 (15.3)	13,856 (6.8)	2,316 (7.5)	1,075 (7.2)	44 (4.8)
Smoking, pack-years	11.6±14.2	14.1±17.9	13.4±17.8	13.3±18.8	0.4±2.6	0.3±2.1	0.2±1.8	0.2±1.9
Creatinine, mg/dL	1.2±1.3	1.2±1.4	1.7±2.2	1.6±2.3	1.0±0.9	1.0±0.9	1.1±1.2	1.0±0.7
eGFR, mL/min/1.73m <sup>2</sup>	89.3±20.3	80.6±22.3	69.6±29.2	78.1±27.3	90.0±20.7	89.0±21.8	89.0±24.0	94.0±22.0
Total cholesterol, mg/dL	194.5±36.3	181.4±38.6	166.7±36.7	146.8±33.8	197.1±37.7	191.1±36.8	185.4±35.4	164.1±30.2
No. of events/person-years	304/909,660	64/43,095	26/4,892	2/448	131/768,343	55/118,119	30/55,106	4/3,245
SCA incidence per 1,000 person-years	0.3	1.5	5.3	4.5	0.2	0.5	0.5	1.2

Continuous variables are expressed as mean±standard deviation. Numbers in parenthesis are percentage value. The Hb categories are as follows: normal, ≥13g/dL for men and ≥12g/dL for women; mild anemia, 11 to <13g/dL for men and 11 to <12g/dL for women; moderate anemia, 8 to <11g/dL; and severe anemia, <8g/dL. BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Hb, hemoglobin; HF, heart failure; MI, myocardial infarction; SCA, sudden cardiac arrest.

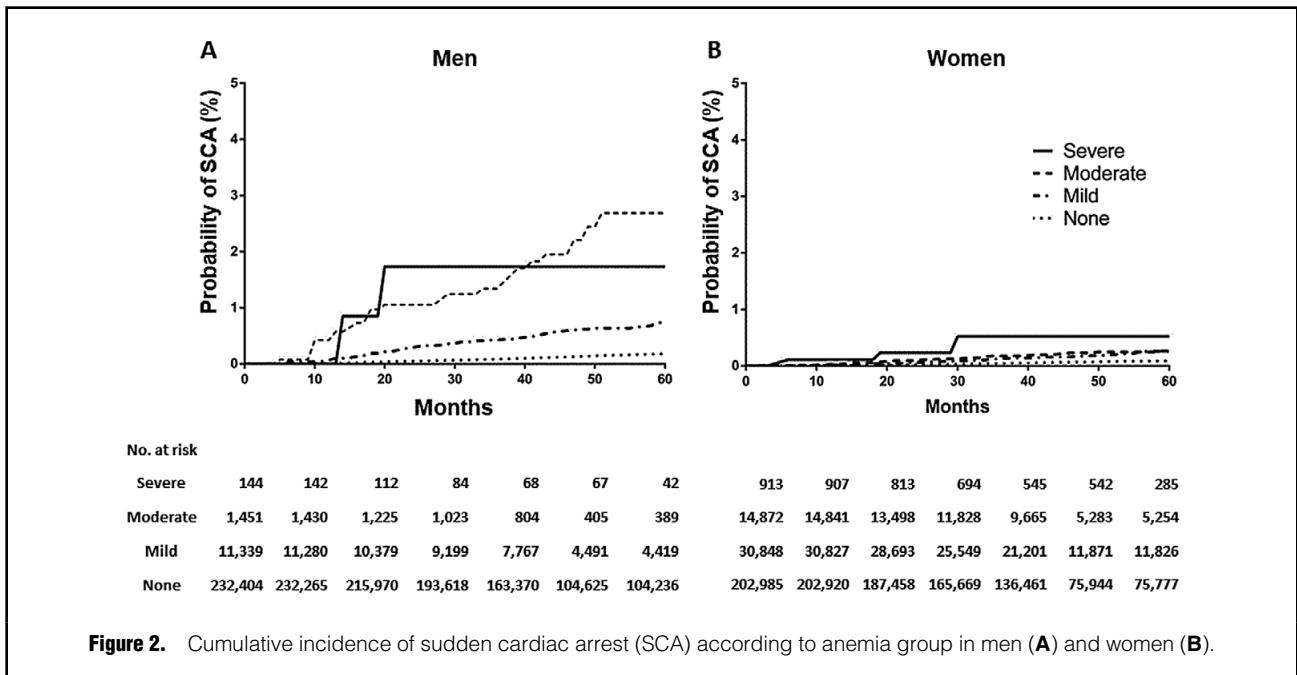
ICD-10 codes. We identified 1,001 patients (men 651, women 350) with SCA and ICD-10 codes I46.x (cardiac arrest) and I49.0 (ventricular fibrillation). To exclude patients with non-cardiac arrest, we excluded 385 patients (men 255, women 130) with a diagnosis of SCA accompanied by respiratory arrest (R09.0, R09.2), gastrointestinal bleeding (I85.0, K25.0, K25.4, K26.0, K26.4, K27.0, K27.4, K92.0–K92.2), brain hemorrhage (I60.x–I62.x, S06.4–S06.6), septic shock (A41.9, R57.2), pregnancy and delivery (O00–O99), diabetic ketoacidosis (E14.1), anaphylaxis (T78.2), and accidents including asphyxiation, drowning, poisoning, traffic accident, fall, and suicide (T71, T75.1, T36–T65, V01–V99, W00–99, X60–X84) (**Figure 1**).

To evaluate the accuracy of our definition of SCA, we conducted a validation study with the medical records of 2 independent tertiary hospitals from 2009 to 2013. We found 731 patients with code I46.x or I49.0 after excluding those with diagnostic codes for non-cardiac causes, as mentioned before. Their medical records were then reviewed by 5 physicians, and we ascertained the patients with true SCA. The positive predictive value was 80.2% (586 of 731) using our criteria of SCA, suggesting good diagnostic accuracy of our definition. False-positive cases were respiratory arrest (7.0%), history of SCA (4.2%), arrest caused by cancer progression (1.9%), accidents (1.8%), bleeding (1.8%),

metabolic acidosis (1.0%), septic shock (0.8%), stroke (0.5%), and others (0.9%).

### Statistical Analysis

The baseline characteristics of the 2 groups were compared by Student's t-test for continuous variables, and by chi-square test or Fisher's exact test for categorical variables. The matched patient groups were compared by paired t-test for continuous variables and by McNemar's test for categorical variables. We used a sex-specific Kaplan-Meier plot for the presentation of survival curves in the anemia group and a log-rank test to assess whether the survival curves were statistically significantly different. To investigate the association between anemia or anemia category and the risk of SCA, we used a sex-specific Cox's proportional hazard regression model with adjustment for clinical variables including age, body mass index, chronic kidney disease or end-stage renal disease, chronic obstructive pulmonary disease, diabetes mellitus, dyslipidemia, hypertension, HF, interim MI and HF, malignancy, previous MI, previous ischemic stroke, and smoking pack-years. The 4 anemia categories were modeled with 3 predictor variables (for mild, moderate, and severe anemia). We also estimated other models with an ordinal predictor variable for the anemia category to test for a linear trend across anemia



Model	Men		Women	
	HR (95% CI)	P value	HR (95% CI)	P value
<b>With Hb as a continuous variable (per 1 g/dL decrease)</b>				
Age adjusted	1.26 (1.18–1.35)	<0.001	1.32 (1.20–1.45)	<0.001
Adjusted for clinical variables†	1.32 (1.13–1.29)	<0.001	1.25 (1.13–1.38)	<0.001
Adjusted for clinical variables and interim MI, HF†	1.21 (1.13–1.29)	<0.001	1.24 (1.13–1.37)	<0.001
<b>With anemia as a categorical variable*</b>				
None	1		1	
Mild anemia	1.50 (1.13–1.99)	<0.001	1.88 (1.37–2.59)	<0.001
Moderate anemia	4.01 (2.64–6.08)	<0.001	1.86 (1.23–2.81)	<0.001
Severe anemia	6.19 (1.53–25.01)	<0.001	8.77 (3.22–23.86)	<0.001
Trend across categories	4.25 (1.03–17.65)	0.05	5.77 (2.03–16.36)	<0.001

The Hb categories are as follows: normal,  $\geq 13$  g/dL for men and  $\geq 12$  g/dL for women; mild anemia, 11 to  $< 13$  g/dL for men and 11 to  $< 12$  g/dL for women; moderate anemia, 8 to  $< 11$  g/dL; and severe anemia,  $< 8$  g/dL. \*Adjusted for clinical variables including age, BMI, CKD or ESRD, COPD, diabetes mellitus, dyslipidemia, hypertension, HF, interim MI and HF, malignancy, previous MI, previous ischemic stroke, regular use of cigarettes in the prior year. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

categories. We studied whether anemia predisposed patients to SCA through an interim MI or HF event. We used a linear-by-linear association trend test for the calculation of the rates of QTc prolongation and LVH, as well as T-wave abnormality according to the severity of anemia. All statistical analyses were performed using SPSS software version 20.0 (IBM Corp., Chicago, IL, USA). Statistical significance was established at a  $P < 0.05$ .

## Results

### Study Subjects

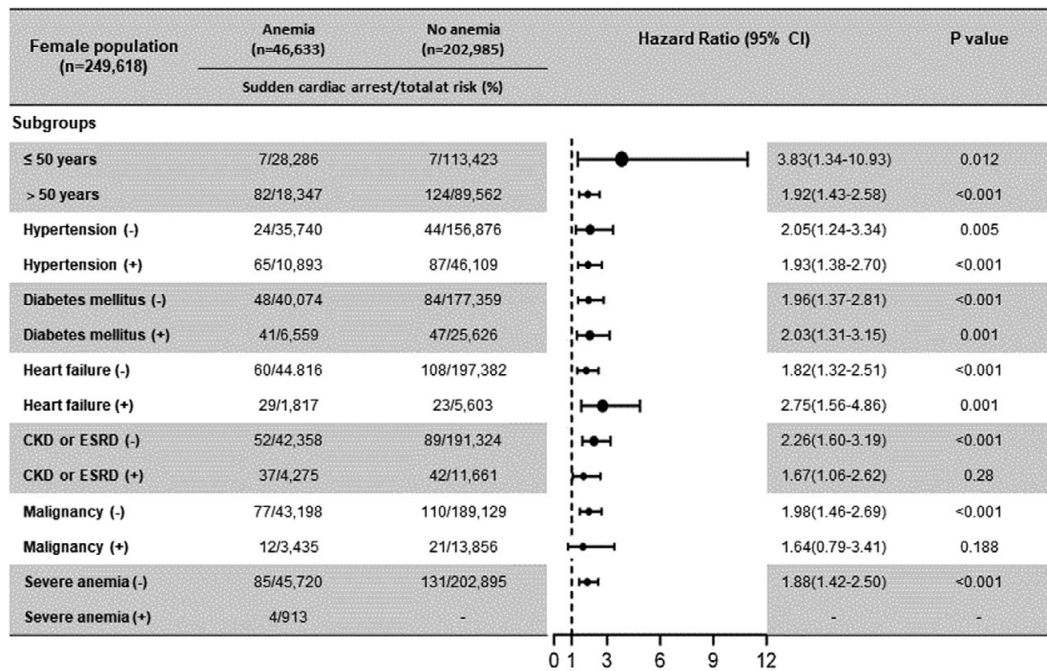
The baseline characteristics of the study are presented in **Table 1**. The mean age was 47.8 (range, 18–98) years in men and 47.8 (range, 18–98) years in women. Of the 494,948 participants, 59,565 (12.0%) were anemic, including 42,185, 16,323, and 1,057 with mild, moderate, and severe

anemia, respectively; 12,932 (5.3%) men and 46,633 (18.8%) women had anemia. Anemia was more common in women than in men ( $P < 0.001$ ). Participants with anemia were older, and more frequently had comorbidities than those without anemia.

### Incidence of SCA

During a mean follow-up of 5.4 years, 616 participants (men 396, women 220) had a SCA. Demographics of participants with SCA are presented in **Table S1**. Of the 616 participants, 181 (29.7%) were anemic. A total of 92 (23.2%) men and 89 (40.5%) women had anemia. Before developing SCA, 930 men and 364 women had experienced MI, and 1,513 men and 1,384 women had experienced HF. During the follow-up period, 6,219 participants (4,003 men, 2,216 women) died.

The age-adjusted incidence rates of SCA are presented



**Figure 3.** Forest plot of the anemia effect on sudden cardiac arrest in subgroups. CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease.

in **Table 1**. The incidence rates of SCA increased across the categories of anemia in men (0.3, 1.5, 5.3, and 4.5 per 1,000 person-years) and women (0.2, 0.5, 0.5, and 1.2 per 1,000 person-years), respectively. **Figure 2** shows the Kaplan-Meier curves for SCA in patients with different categories of anemia. The probability of developing SCA over time increased across the categories of anemia.

### Risk of SCA According to Anemia

The results of the multivariable Cox's proportional hazard regression are shown in **Table 2**. After adjustment for age alone, each 1-unit decrease in Hb was associated with an increase of 26% for men ( $P<0.001$ ) and 32% for women ( $P<0.001$ ). These relations remained significant in the multivariable-adjusted models, with an increase in the risk of SCA per 1-unit decrease in Hb of 32% for men ( $P<0.001$ ) and 25% for women ( $P<0.001$ ). Similarly, the age-adjusted and fully adjusted hazard ratios (HRs) for SCA increased across Hb categories in both men and women (**Table 2**). The multivariable-adjusted HRs for SCA were 1.50 (95% confidence interval [CI], 1.13–1.99) for mildly anemic men and 1.88 (95% CI, 1.36–2.59) for mildly anemic women. These findings were not attenuated in models adjusting for interim MI or HF in addition to baseline covariates. Each 1-unit decrease in Hb was associated with an increase of 21% for men ( $P<0.001$ ) and 24% for women ( $P<0.001$ ).

The association between Hb and the risk of SCA did not vary by age, sex, or systolic blood pressure ( $P>0.10$  for all interaction terms). To assess the influence of different degrees of anemia, we estimated regressions with 4 Hb categories (normal, mild, moderate, and severe anemia). The respective age-adjusted HRs for SCA increased progressively across the 4 Hb categories in men (1.00, 1.72

[95% CI, 1.30–2.28], 5.33 [95% CI, 3.53–8.03], 5.82 [95% CI, 1.45–23.41];  $P=0.001$  for trend) and women (1.00, 2.04 [95% CI, 1.48–2.80], 2.35 [95% CI, 1.57–3.52], 10.10 [95% CI, 3.73–27.34];  $P=0.001$  for trend). After adjustment for clinical variables and interim MI or HF, these findings remained significant in men (1.00, 1.50 [95% CI, 1.13–1.99], 4.01 [95% CI, 2.64–6.08], 6.19 [95% CI, 1.53–25.01];  $P=0.001$  for trend) and women (1.00, 1.88 [95% CI, 1.37–2.59], 1.86 [95% CI, 1.23–2.81], 8.77 [95% CI, 3.22–23.86];  $P=0.001$  for trend).

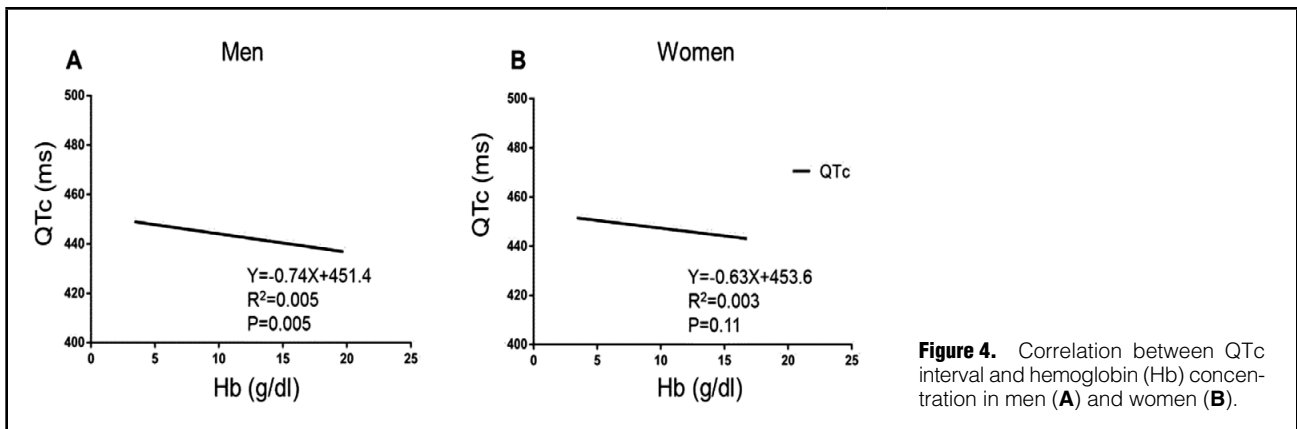
In a secondary analysis restricted to mild-moderate anemia, the association between anemia and the risk of SCA remained significant (sex-pooled multivariable-adjusted HR per 1-unit increase in Hb, 1.50 [95% CI, 1.34–1.67];  $P<0.001$ ). Additionally, the relationship between anemia and the risk of SCA in the female population is presented in **Figure 3**. Adjusted HRs significantly increased in premenopausal women (3.83 [95% CI, 1.34–10.93,  $P=0.012$ ]). Adjusted HRs for SCA also significantly increased in patients without hypertension (2.05 [95% CI, 1.24–3.34,  $P=0.005$ ]), diabetes mellitus (1.96 [95% CI, 1.37–2.81,  $P<0.001$ ]), HF (1.82 [95% CI, 1.32–2.51,  $P<0.001$ ]), chronic kidney disease or end-stage renal disease (2.26 [95% CI, 1.60–3.19,  $P<0.001$ ]), malignancy (1.98 [95% CI, 1.46–2.69,  $P<0.001$ ]) and severe anemia (1.88 [95% CI, 1.42–2.50,  $P<0.001$ ]), respectively.

### ECG Changes Associated With Anemia

The relationship between anemia and QTc prolongation was evaluated in 11,782 individuals (mean age:  $61.2\pm 14.4$  years; 6,151 [52.2%] women), who were admitted to Severance Hospital between 2004 and 2009. Their characteristics are presented in **Table 3**. The overall rate of QTc

Table 3. Characteristics of the Study Population by Severity of Anemia					
	None (n=7,056)	Mild anemia (n=2,214)	Moderate anemia (n=2,122)	Severe anemia (n=390)	P value
Age, years	60.4±14.3	63.6±13.7	62.2±14.9	57.9±17.1	<0.001
Hb, g/dL	14.0±1.3	11.8±0.5	9.8±0.8	6.7±1.1	<0.001
MCV, fL	91.6±4.9	91.8±6.3	90.8±7.7	88.3±11.9	<0.001
Serum iron, µg/dL	61.6±59.5	60.1±50.1	57.4±52.0	65.1±95.7	0.13
TIBC, µg/dL	228.3±89.2	226.3±81.2	229.9±81.6	259.9±135.5	<0.001
Transferrin saturation, %	29.0±24.1	29.8±30.0	28.6±25.8	28.0±29.8	0.02
Ferritin, ng/mL	693.5±2,209.7	602.9±2,091.5	498.3±1,429.2	876.3±3,429.8	0.01
QTc, ms	443.8±25.1	444.9±25.0	446.4±24.5	447.7±25.9	<0.001
QTc prolongation					
Overall	2,027 (28.7)	744 (33.6)	667 (31.4)	141 (36.2)	<0.001
Men	1,405 (43.0)	567 (44.4)	472 (51.4)	89 (53.3)	<0.001
Women	622 (16.4)	177 (18.9)	195 (16.2)	52 (23.3)	0.13
T-wave abnormality					
Overall	2,205 (31.2)	716 (32.3)	729 (34.4)	120 (30.8)	0.04
Men	821 (25.1)	346 (27.1)	286 (31.1)	36 (21.6)	0.01
Women	1,384 (36.5)	370 (39.4)	443 (36.8)	84 (37.7)	0.57
LVH					
Overall	828 (11.7)	277 (12.5)	272 (12.8)	44 (11.3)	0.29
Men	478 (14.6)	180 (14.1)	146 (15.9)	26 (3.1)	0.45
Women	350 (9.2)	97 (10.3)	126 (10.5)	18 (81)	0.41

Continuous variables are expressed as mean±standard deviation. Numbers in parenthesis are percentage value. MCV defined as follows: microcytic, <80 fL; normocytic, 80 to ≤100 fL; macrocytic, >100 fL. fL indicates femtoliters (10<sup>-15</sup>). LVH, left ventricular hypertrophy; MCV, mean cell volume; QTc, corrected QT interval; TIBC, total iron binding capacity.



**Figure 4.** Correlation between QTc interval and hemoglobin (Hb) concentration in men (A) and women (B).

prolongation was 28.7%, 33.6%, 31.4% and 36.2% in normal, mild, moderate and severe anemia, respectively ( $P < 0.001$  for trend). A significant negative correlation between QTc interval and Hb level was observed in men (Figure 4). The associations between anemia and other ECG characteristics, including LVH and T-wave abnormality, were not observed.

The prevalence of QTc prolongation, T-wave abnormality and LVH did not differ among microcytic, normocytic and macrocytic anemia in either men or women (Table S2).

## Discussion

The National Health Insurance Database Cohort-based data indicate that anemia is a risk factor for SCA. The association of anemia with the subsequent development

of SCA persists even after accounting for concomitant conditions such as hypertension, diabetes mellitus, and MI. The validity of our results is supported by the large sample size and their consistency in multiple analyses adjusting for known confounders in men and women. Finally, our findings have biological plausibility because QTc prolongation and LVH, which are associated with SCA, increased with the severity of anemia.

## Anemia, Cardiovascular Disease, and SCA

The association between anemia and cardiovascular disease is well known. Anemia is present in one-third of patients with ACS, especially in the 12.8% of patients with acute MI and the 43% of elderly patients with ST-elevation MI.<sup>3</sup> A clear correlation between anemia and death has been reported in patients with ACS.<sup>3,16–19</sup> Hb <11 g/dL is related

to a significant risk of cardiovascular death in patients with ACS. However, it is also worth mentioning that Hb >17 g/dL confers very serious risks.<sup>20</sup> The frequency of anemia is constantly increasing in HF. It is estimated that anemia is present in approximately 9.0–15.6% of patients with HF in the USA.<sup>21</sup> Moreover, the prevalence of anemia increases with worsening functional class, from 9% for New York Heart Association (NYHA) class I to 79% for NYHA class IV.<sup>22</sup> Anemia is considered an independent risk factor for LV dysfunction and is associated with increased risks of morbidity and mortality.<sup>23,24</sup> However, the association between SCA and anemia has not been revealed. This study showed that anemia was an independent risk factor of SCA even after accounting for concomitant conditions such as MI and HF. However, further studies are needed to verify the associations and proper mechanisms between anemia and SCA.

### ECG Change by Anemia

In this study, the QTc interval increased with the severity of anemia. Anemia is associated with increased inflammation markers and aggravated oxidative stress condition.<sup>25,26</sup> Notably, oxidative stress in cardiomyocytes has been shown to activate Ca<sup>2+</sup>/calmodulin-dependent protein kinase II,<sup>27</sup> sequentially inducing the prolongation of the APD and QT intervals.<sup>28</sup> Moreover, reduced Hb concentration is associated with impaired oxygen delivery, salt and water retention, and chronic volume overload.<sup>29</sup> However, the negative correlation between QTc prolongation and Hb was weak in women. This might be related to a sex difference in the definition of QTc prolongation. Second, compared with men, women had low hematocrit and hypochromic states related to menstruation.<sup>30</sup> These chronic anemic conditions might induce the increased QTc prolongation across Hb categories and decrease the statistical power in women.

### Study Limitations

First, we identified patients with SCA by using ICD-10 codes I46.x (cardiac arrest) and I49.0 (ventricular fibrillation). SCA was confirmed by emergency medical service personnel or during hospitalization. However, we cannot exclude the possibility that some episodes of SCA were missed or overestimated. To resolve this problem, we excluded patients with SCA diagnosis accompanied by other diseases. With this method, we confirmed that the positive predictive value of our criteria of SCA was 80.2%. Moreover, such misclassification would not be expected to differentially affect persons with and without anemia. Second, we only analyzed anemia at entry in this study, and we did not consider possible changes in Hb levels during the follow-up period. Third, serum iron, ferritin, and total iron binding capacity were not available in the national cohort. Therefore, we analyzed the relationship between the type of anemia and ECG parameters using an additional hospital cohort. There was no statistically meaningful association between the type of anemia and ECG parameters. Fourth, we adjusted for multiple confounders but it is possible that residual confounding influenced the results. Finally, inherited arrhythmic disorders such as long QT syndrome, Brugada syndrome, and short QT syndrome are well-known causes of SCA. These channelopathies might be affected by anemia, which could impair cardiac autonomic function<sup>31–33</sup> and worsen metabolic condition such as metabolic acidosis,<sup>34</sup> increased

inflammation and aggravated oxidative stress.<sup>25,26</sup> Thus, further studies are necessary to understand the association of anemia and inherited arrhythmic disorders that precedes SCA.

### Conclusions

Anemia was associated with an increased the risk of SCA even after accounting for concomitant conditions in a South Korean nationwide cohort. The correlation between anemia and SCA might be explained by the increase in arrhythmic risks, such as QTc prolongation.

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### Disclosures

The authors have no conflicts of interest to disclose.

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### Supplementary Files

#### Supplementary File 1

**Table S1.** Demographics of the study population with sudden cardiac arrest according to severity of anemia

**Table S2.** Incidence of QTc prolongation by the mean cell volume category

Please find supplementary file(s);  
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