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ORIGINAL INVESTIGATIONS

Incidence of and Risk Factors for Sick Sinus Syndrome in the General Population

Paul N. Jensen, MPH,*† Noelle N. Gronroos, MA, MPH,‡ Lin Y. Chen, MD, MS,§ Aaron R. Folsom, MD, MPH,‡ Chris deFilippi, MD,‖ Susan R. Heckbert, MD, PhD,*†¶ Alvaro Alonso, MD, PhD‡

ABSTRACT

BACKGROUND Little is known about the incidence of and risk factors for sick sinus syndrome (SSS), a common indication for pacemaker implantation.

OBJECTIVES This study sought to describe the epidemiology of SSS.

METHODS This analysis included 20,572 participants (mean baseline age 59 years, 43% male) in the ARIC (Atherosclerosis Risk In Communities) study and the CHS (Cardiovascular Health Study), who at baseline were free of prevalent atrial fibrillation and pacemaker therapy, had a heart rate of ≥50 beats/min unless using beta blockers, and were identified as of white or black race. Incident SSS cases were identified by hospital discharge International Classification of Disease-revision 9-Clinical Modification code 427.81 and validated by medical record review.

RESULTS During an average 17 years of follow-up, 291 incident SSS cases were identified (unadjusted rate 0.8 per 1,000 person-years). Incidence increased with age (hazard ratio [HR]: 1.73; 95% confidence interval [CI]: 1.47 to 2.05 per 5-year increment), and blacks had a 41% lower risk of SSS than whites (HR: 0.59; 95% CI: 0.37 to 0.98). Incident SSS was associated with greater baseline body mass index, height, N-terminal pro-B-type natriuretic peptide, and cystatin C, with longer QRS interval, with lower heart rate, and with prevalent hypertension, right bundle branch block, and cardiovascular disease. We project that the annual number of new SSS cases in the United States will increase from 78,000 in 2012 to 172,000 in 2060.

CONCLUSIONS Blacks have a lower risk of SSS than whites, and several cardiovascular risk factors were associated with incident SSS. With the aging of the population, the number of Americans with SSS will increase dramatically over the next 50 years. (J Am Coll Cardiol 2014;64:531–8) © 2014 by the American College of Cardiology Foundation.

From the *Cardiovascular Health Research Unit, University of Washington, Seattle, Washington; †Department of Epidemiology, University of Washington, Seattle, Washington; ‡Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota; §Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota; ‖Department of Medicine, University of Maryland, Baltimore, Maryland; and the ¶Department of Pharmacy, University of Washington, Seattle, Washington. The ARIC study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute (NHLBI) contracts HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C. This CHS study research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and NHLBI grant HL080295, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided by the National Institute on Aging grant AG023629. A full list of principal CHS investigators and institutions can be found at www.chs-nhlbi.org. This study was additionally funded by NHLBI grants R21 HL109611, T32 HL07770, and T32 HL007902. Ms. Gronroos is an employee of Blue Cross Blue Shield of Minnesota (hired after data analysis of this study was complete). Dr. deFilippi has received research funding from Roche Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CI = confidence interval

CKD = chronic kidney disease

CRP = C-reactive protein

CV = cardiovascular

ECG = electrocardiogram

HR = hazard ratio

ICD-9-CM = International Classification of Disease-revision 9-Clinical Modification

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SSS = sick sinus syndrome

Sick sinus syndrome (SSS) is a cardiac conduction disorder characterized by symptomatic dysfunction of the sinoatrial node. On the electrocardiogram (ECG), SSS usually manifests as sinus bradycardia, sinus arrest, or sinoatrial block, and is sometimes accompanied by supraventricular tachyarrhythmias ("tachy-brady" syndrome). Typical symptoms of SSS include syncope, dizziness, palpitations, exertional dyspnea, easy fatigability from chronotropic incompetence, heart failure, and angina (1-3). Clinically significant SSS typically requires pacemaker implantation. Approximately 30% to 50% of pacemaker implantations in the United States list SSS as the primary indication (4).

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Epidemiological information about SSS is limited. Although past studies have described the characteristics of individuals hospitalized for SSS, the incidence of SSS in the general population remains unclear. Additionally, no prior epidemiological studies have evaluated potential risk factors for incident SSS. The goals of this analysis were to determine the age and sex-specific incidence of SSS in white and black participants in the ARIC (Atherosclerosis Risk In Communities) study and the CHS (Cardiovascular Health Study), as well as to investigate associations of cardiovascular (CV) risk factors with incident SSS.

METHODS

STUDY POPULATION. The prospective cohort ARIC study comprised 15,792 individuals aged 45 to 64 years of age when recruited between 1987 and 1989 from 4 U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi (blacks only); Washington County, Maryland; and the northwestern suburbs of Minneapolis, Minnesota. The prospective cohort CHS study consisted of 5,888 community-dwelling adults age 65 years of age or older from 4 U.S. communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. From 1989 to 1990, CHS recruited 5,201 participants; 687 blacks were included from 1992 to 1993. The ARIC and CHS design and recruitment are described in detail elsewhere (5-7).

IDENTIFICATION OF INCIDENT SSS. Incident SSS was ascertained during cohort follow-up from hospitalization records (8,9). Medical records were reviewed for hospitalizations that included International Classification of Disease-revision 9-Clinical Modification (ICD-9-CM) code 427.81 (SSS, sinoatrial node dysfunction, tachycardia-bradycardia syndrome, persistent sinus bradycardia) in any position. We considered SSS to be present if the medical record included a diagnosis of SSS and symptoms or signs consistent with SSS (e.g., syncope, dizziness, bradycardia, sinus pauses), with no evidence of other conditions responsible for the episode, such as atrioventricular block or medication use.

In the ARIC study, 294 individuals had ICD-9-CM code 427.81 in at least 1 hospitalization. Of these participants, we obtained medical records in 195, from which we confirmed 130 (67%) of the 195 cases after medical record review. In the CHS study, ICD-9-CM code 427.81 was present in 179 individuals, and medical records were available for 169, from which we confirmed 99 cases (59%) after record review.

To determine the negative predictive value of ICD-9-CM code 427.81 for SSS, we reviewed medical records for a random sample of participants with selected non-SSS ICD-9-CM codes (426.0 and 426.1, atrioventricular block; 426.6, other heart block; 427.89, other atrial arrhythmia; 37.8, insertion, placement, and revision of pacemaker; V45.01, status post-pacemaker implantation; and V53.31, fitting and adjustment of cardiac pacemaker). Among 178 ARIC and CHS participants with these selected ICD-9-CM codes, the medical records documented a diagnosis of SSS in 5 of them (2.8%), suggesting excellent negative predictive value for the absence of the 427.81 code.

In the incidence rate calculations, we included validated SSS cases and a random sample of 63% of the 109 individuals with ICD-9-CM code 427.81 for whom medical records were not available. This sampling proportion was based on the positive predictive value of the ICD-9-CM code 427.81 in those with available medical records. We included only validated cases in the risk factor analysis; unvalidated cases were classified as noncases.

RISK FACTOR ASCERTAINMENT. Similar methods were used in the ARIC and CHS studies to assess most risk factors, as described previously (10,11). Participants underwent a baseline study examination that included height and weight measurement, blood pressure measurement by a random-zero sphygmomanometer, and 12-lead resting ECG. Race, smoking, and alcohol consumption information were determined by self-report. Information was collected on medication use, and blood was collected with the participant in a fasting state, from which glucose, high-density lipoprotein and low-density lipoprotein cholesterol, C-reactive protein (CRP), N-terminal

pro-B-type natriuretic peptide (NT-proBNP), troponin T, cystatin C, and creatinine levels were measured (12,13). CRP, NT-proBNP, troponin T, and cystatin C were measured at baseline in CHS and 9 years after baseline in ARIC. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications by a participant who reported a physician diagnosis of hypertension. Diabetes was determined by either a fasting glucose level of ≥126 mg/dl or use of an oral hypoglycemic agent or insulin. Heart rate, PR interval, QRS interval, and right and left bundle branch block were identified on study ECGs analyzed at a central ECG laboratory. A history of chronic kidney disease (CKD) and major CV events, including coronary heart disease, myocardial infarction, heart failure, and stroke, was ascertained at baseline study examination (7,14). Events that occurred during follow-up were identified from hospitalization records, and ARIC and CHS study staff and investigators adjudicated these events (8,9). We defined CKD as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2; estimated glomerular filtration rate was estimated from serum creatinine levels (15).

STATISTICAL ANALYSES. Analyses were limited to white and black participants. Because of their small numbers, we excluded individuals from other racial/ethnic groups. Participants who at baseline had prevalent SSS or atrial fibrillation, a history of pacemaker implantation, or a heart rate <50 beats/min while not on beta-blockers also were excluded, because these conditions often coexist with SSS.

Age-, sex-, and race-specific SSS incidence rates were calculated for each age/sex/race category as the number of SSS cases divided by the number of person-years at risk in that category. Participants began accruing time at risk upon their baseline examination and were followed to the earliest of hospitalization with SSS, death, loss to follow-up, or December 2009 (ARIC) or June 2008 (CHS).

TABLE 1 Baseline Characteristics of Included Participants in ARIC and CHS

	ARIC		CHS	
	Whites (n = 11,226)	Blacks (n = 4,089)	Whites (n = 4,427)	Blacks (n = 830)
Age, yrs	54 ± 5.7	54 ± 5.8	73 ± 6	73 ± 6
Male	47%	37%	42%	36%
High school graduate	83%	59%	73%	54%
BMI, kg/m^2	27 ± 4.9	30 ± 6.2	26 ± 4	29 ± 6
Height, cm	169 ± 9.4	168 ± 8.9	165 ± 9	165 ± 9
Systolic blood pressure, mm Hg	119 ± 17	129 ± 22	135 ± 21	143 ± 23
Hypertension	27%	56%	56%	75%
Impaired fasting glucose	38%	34%	14%	12%
Diabetes	9%	20%	14%	26%
HDL-cholesterol, mg/dl	50 ± 17	55 ± 78	54 ± 16	58 ± 15
LDL-cholesterol, mg/dl	138 ± 38	138 ± 43.2	131 ± 35	129 ± 36
C-reactive protein, mg/dl*	4 ± 7	7 ± 7	5 ± 8	6 ± 9
NT-proBNP, ng/l*	211 ± 4,503	224 ± 3,107	242 ± 661	245 ± 1,047
Troponin T, ng/l*	7 ± 10	8 ± 25	8 ± 17	12 ± 53
Cystatin C, mg/l*	0.9 ± 0.3	0.8 ± 0.4	1.1 ± 0.3	1.1 ± 0.3
Heart rate, beats/min	67 ± 10	67 ± 11	65 ± 10	68 ± 11
PR interval, ms	161 ± 26	170 ± 29	170 ± 29	173 ± 30
QRS interval, ms	98 ± 13	97 ± 13	93 ± 17	93 ± 19
Right bundle branch block	0.9%	0.9%	4.2%	5.3%
Left bundle branch block	0.5%	0.4%	1.6%	2.5%
Current smoker	25%	30%	12%	16%
Past smoker	35%	24%	42%	35%
Cigarette pack-yrs	17 ± 22	12 ± 20	36 ± 29	28 ± 26
≥1 Alcoholic drink/week	39%	23%	32%	19%
Drinks/week†	3 ± 7	2 ± 7	8 ± 9	8 ± 12
Coronary heart disease	5%	4%	19%	18%
Chronic kidney disease	5%	4%	26%	19%
Heart failure	4%	7%	3%	6%
Stroke	2%	2%	3%	6%

Values are mean ± SD or %. *Measured 9 years after baseline in ARIC (Atherosclerosis Risk in Communities) study. †Among those who reported ≥1 alcoholic drink per week.

BMI = body mass index; CHS = Cardiovascular Health Study; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

We estimated the number of annual incident SSS cases occurring in the U.S. population age 45 years of age and older during the period 2012 to 2060, by applying age-specific incidence rates from the ARIC and CHS cohorts to the U.S. Census Bureau population

TABLE 2 Incidence Rates of SSS Among Women in ARIC and CHS

	White Women				Black Women			
Age Group (yrs)	SSS Cases	Person-Years	Incidence (per 1,000)	95% CI	SSS Cases	Person-Years	Incidence (per 1,000)	95% CI
45–54	1	17,699	0.06	0.00–0.31	1	8,627	0.12	0.00–0.65
55–64	8	46,164	0.17	0.07–0.34	2	19,775	0.10	0.01–0.37
65–74	37	50,755	0.73	0.51–1.01	10	17,171	0.58	0.28–1.07
75–84	61	29,887	2.04	1.56–2.62	16	6,854	2.33	1.43–4.07
85+	19	6,428	2.96	1.79–4.63	5	1,206	4.15	1.35–9.68

CI = confidence interval; SSS = sick sinus syndrome; other abbreviations as in Table 1.

TABLE 3 Incidence Rates of SSS Among Men in ARIC and CHS

	White Men				Black Men			
Age Group (yrs)	SSS Cases	Person-Years	Incidence (per 1,000)	95% CI	SSS Cases	Person-Years	Incidence (per 1,000)	95% CI
45–54	1	13,272	0.08	0.00–0.42	0	4,766	0.00	0.00–0.77
55–64	14	38,162	0.37	0.20–0.62	3	10,807	0.28	0.06–0.81
65–74	43	41,075	1.05	0.76–1.41	6	9,411	0.64	0.23–1.39
75–84	47	20,807	2.26	1.66–3.00	2	3,435	0.58	0.07–2.10
85+	15	3,926	3.82	2.14–6.30	0	399	0.00	0.00–9.25

Abbreviations as in Tables 1 and 2.

projections through 2060 (16), and assumed that no other factors influenced SSS rates other than changes in the population age structure. We repeated these calculations using the lower and upper limits of the 95% confidence intervals (CIs) of the age-specific rates.

To assess the association between potential risk factors and incident SSS, we used Cox proportional hazards models that adjusted for age, sex, race, clinic, and traditional CV risk factors at baseline (hypertension, diabetes, smoking, low-density lipoprotein cholesterol, body mass index [BMI], and history of a major CV event [myocardial infarction, heart failure, stroke]). In the ARIC study, models that included CRP, NT-proBNP, troponin T, and cystatin C levels were left-truncated at 9 years after baseline, the point at which these biomarkers were assessed. For sensitivity analyses, we examined models that adjusted only for age, sex, race, and clinic, and also models that adjusted for baseline age, sex, race, and clinic, and traditional CV risk factors as time-dependent covariates. Continuous risk factors were scaled to their standard deviations to facilitate comparisons of hazard ratios (HRs) of risk factors measured on different scales. High-sensitivity CRP and NT-proBNP were transformed by log base 2, because their distributions were right skewed. Cox proportional hazards models were fit separately for ARIC and CHS samples; cohort-specific HRs were combined using fixed-effects meta-analysis (17).

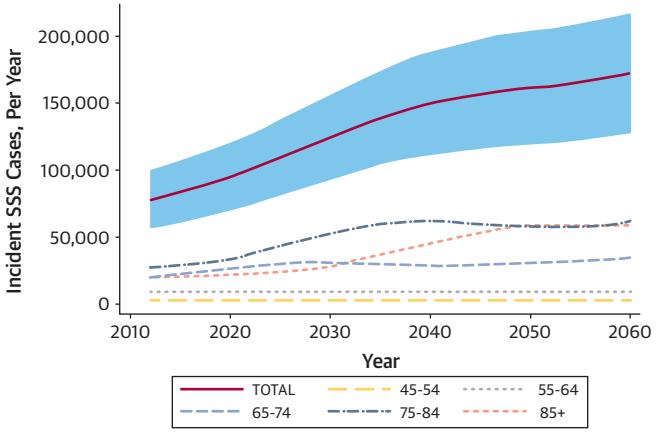


FIGURE 1 Estimated Number of Incident SSS Cases per Year, Overall and by Age Group, United States, 2012 to 2060

The **shaded area** corresponds to the range of estimates on the basis of the 95% confidence intervals of age-specific rates. SSS = sick sinus syndrome.

RESULTS

From among ARIC (N = 15,792) and CHS (N = 5,888) participants, those who at baseline had evidence of prevalent SSS, atrial fibrillation, or pacemaker (37 in ARIC; 385 in CHS), had a heart rate of <50 beats/min without using beta-blockers (339 in ARIC; 217 in CHS), or did not report white or black race (101 in ARIC; 29 in CHS) were excluded from the analyses.

Baseline characteristics of the remaining 20,572 participants are reported in Table 1. The average age of participants was 59 years of age, and 44% were male. Because of the study design, CHS participants were older than ARIC participants upon enrollment (CHS mean age 73 years; ARIC mean age 54 years). As expected, CHS participants had a higher prevalence of conditions associated with advanced age, including hypertension, diabetes, coronary heart disease, and CKD. Blacks had a higher prevalence of traditional CV risk factors than whites.

During a mean 17 years of follow-up, 291 incident SSS cases were identified, 246 in whites and 45 in blacks. The crude incidence rate of SSS in ARIC and CHS was 0.8 (95% CI: 0.7 to 0.9) per 1,000 person-years. Incidence estimates were similar in ARIC and CHS (Online Tables 1 and 2). SSS incidence increased with age and was similar in men and women (Tables 2 and 3). Using the combined ARIC and CHS populations as the standard population, the age- and

sex-standardized rate of SSS was 0.9 (95% CI: 0.8 to 1.0) per 1,000 person-years in whites and 0.7 (95% CI: 0.5 to 0.8) per 1,000 person-years in blacks (adjusted rate ratio 0.75, 95% CI: 0.54 to 1.03, comparing blacks vs. whites). The age- and race-standardized rate of SSS was 0.8 (95% CI: 0.7 to 0.9) per 1,000 person-years in women and 0.9 (95% CI: 0.7 to 1.1) per 1,000 person-years in men (adjusted rate ratio: 1.17, 95% CI: 0.93 to 1.48, comparing men vs. women).

On the basis of ARIC and CHS age-specific rates of SSS and U.S. Census Bureau population projections for the United States between 2012 and 2060, we estimated that there were approximately 78,000 (95% CI: 57,113 to 99,725) incident cases of SSS in 2012, and that this number would increase to almost 172,000 (95% CI: 127,939 to 216,692) per year by 2060 (Fig. 1). Most of this increment would be caused by an increased number of SSS events among individuals age 75 years of age and older.

In models adjusted for age, sex, race, clinic, and CV risk factors, incident SSS was associated with greater BMI, height, NT-proBNP, and cystatin C, with longer QRS interval, with lower heart rate, and with prevalent hypertension, right bundle branch block, and history of a major CV event (Fig. 2). Although male sex was not associated with incident SSS (HR: 1.25; 95% CI: 0.73 to 2.50), blacks appeared to have a lower risk of SSS than whites (HR: 0.59; 95% CI: 0.37 to 0.98) after adjustment for age, sex, and CV risk factors. Results were similar for all risk factors in the ARIC and CHS cohorts. We found that the use of minimally adjusted models or models with time-varying adjustment for traditional CV risk factors resulted in similar associations between investigated risk factors and incident SSS (Online Tables 3 and 4).

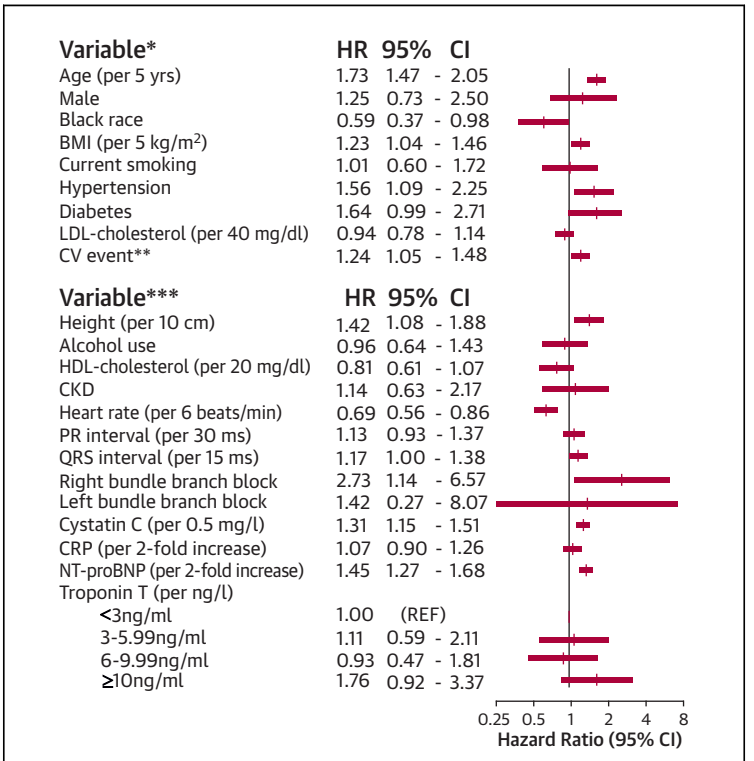


FIGURE 2 Meta-Analyzed Multivariate Adjusted HRs of Incident SSS According to Participant Characteristics

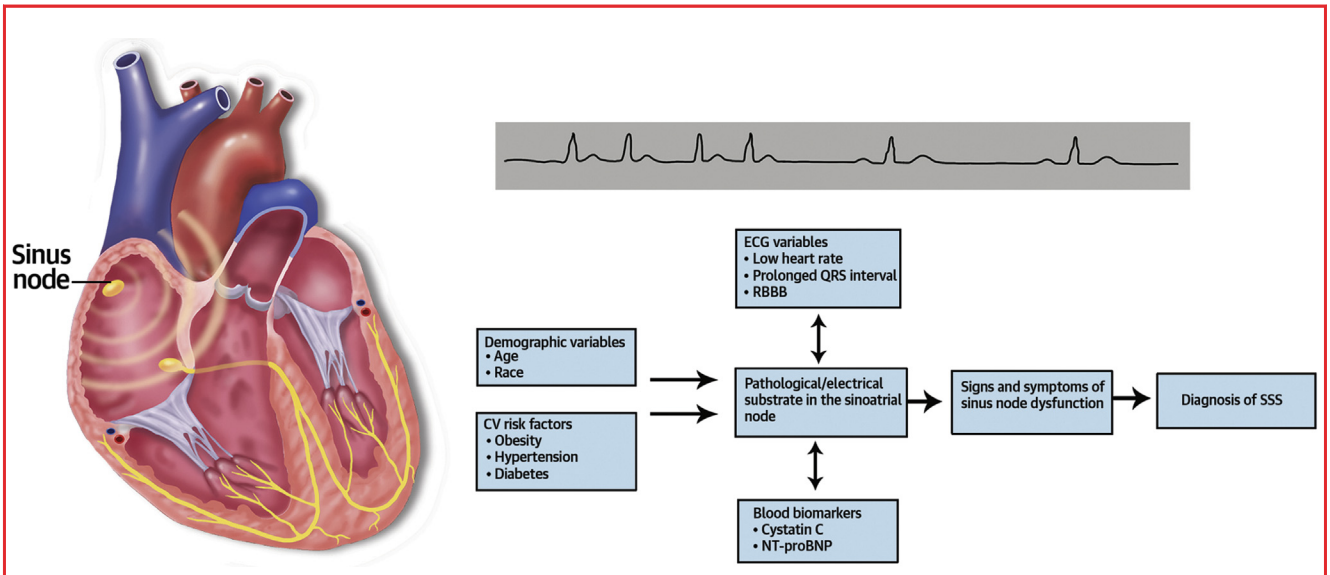
The * indicates the results are from 1 multivariate model that includes all of the listed variables and study clinic as covariates. The ** indicate that the cardiovascular (CV) event denotes a history of myocardial infarction (MI), heart failure (HF), or stroke at baseline. The *** indicate that each row represents a separate multivariable model; each model was adjusted for baseline age, sex, race, study clinic, hypertension, diabetes, body mass index (BMI), current smoking, low-density lipoprotein (LDL) cholesterol, and history of a CV event at baseline (MI, HF, or stroke). CI = confidence interval; CKD = chronic kidney disease; CRP = C-reactive protein; HDL = high-density lipoprotein; HR = hazard ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SSS = sick sinus syndrome.

DISCUSSION

In 2 large, prospective cohorts with an average follow-up of 17 years, we observed that the incidence of SSS increases with age, does not differ between men and women, but may be lower among blacks than whites. The age- and sex-standardized incidence of SSS was 0.9 per 1,000 person-years in whites and 0.7 per 1,000 person-years in blacks; after adjustment for age, sex, and CV risk factors, blacks had a 41% lower risk of SSS than whites. We identified a number of risk factors for SSS, including greater BMI, height, NT-proBNP level, and cystatin C level, longer QRS interval, lower heart rate, prevalent hypertension, and right bundle branch block, and a history of a CV event at baseline (Central Illustration). This is the first prospective, population-based study, to our knowledge, to report the incidence of SSS and to investigate risk factors for SSS in the U.S. population (18).

We estimated that the overall annual incidence of SSS in individuals age 45 years of age and older was close to 1 per 1,000. Our rates are consistent with a previous study of SSS-related hospitalizations in the Medicare population, which reported age-specific hospitalization rates ranging from 0.5 to 3.5 per 1,000 person-years (19). This study by Baine et al. (19) in the Medicare population, however, did not differentiate between incident SSS and repeated hospitalizations, nor did it validate SSS diagnoses.

Even though SSS can occur in the context of well-defined conditions, such as cardiac amyloidosis and other cardiomyopathies, or in the context of ischemic heart disease, most cases of SSS are due



CENTRAL ILLUSTRATION **Epidemiology of Sick Sinus Syndrome**

Demographic variables, such as increasing age, white race, and cardiovascular risk factors (obesity, hypertension, diabetes) may affect the sinoatrial node promoting the pathological and electrical substrate of sick sinus syndrome (SSS). Variables in the electrocardiogram (ECG) and blood biomarkers could be used to characterize the substrate. Eventually, alterations in the sinoatrial node will lead to signs and symptoms of sinus node dysfunction resulting in a clinical diagnosis of SSS.
CV = cardiovascular; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RBBB = right bundle branch block.

to degenerative idiopathic fibrotic infiltration of the sinus node (3). Older age and factors associated with atrial stretch and remodeling, such as hypertension or heart failure, have been associated with diffuse atrial fibrosis and electrical remodeling (20–23). The increased risk of SSS associated with older age, hypertension, elevated levels of NT-proBNP, and history of CV disease in the ARIC and CHS cohorts suggest that atrial fibrosis could specifically affect the sinus node and other atrial regions involved in pacemaker activity. In addition, we observed that greater height, cystatin C level (a marker of kidney dysfunction), and white race (vs. black) were associated with an elevated risk of SSS. Similar associations have been described for atrial fibrillation (24–27). Because atrial fibrillation and SSS frequently coexist—as 1 component of the so-called "tachy-brady syndrome"—the fact that these 2 conditions share risk factors is not surprising.

Strengths of this study include the large number of participants in ARIC and CHS, a long duration of follow-up, validation of most hospitalizations with a 427.81 (SSS) ICD-9-CM code, and detailed and thorough assessment of risk factors. In addition, the risk factors examined in this analysis were assessed using similar methodologies in both studies, which enabled a combining of estimates across cohorts using fixed-effects models.

STUDY LIMITATIONS. First, because SSS is a rare outcome, we were only able to identify a limited number of SSS cases, particularly among black participants. The available person-time in black men older than 75 years of age was quite limited. In addition, it is possible that differential access to health care by race and sex may have contributed to the small number of SSS cases identified in black men (28). A previous study of Medicare claims also reported that black men were less likely than white men to be hospitalized for SSS (19). Second, we were not able to review medical records for all participants with an ICD-9 code for SSS. Because we classified these participants as noncases in the risk factor analysis, if missing records were unrelated to the validity of the ICD-9 code, this misclassification likely attenuated associations of risk factors with SSS. Third, because we relied upon inpatient hospitalization records to identify SSS cases, we may have missed asymptomatic cases, which were less severe than those that resulted in an inpatient hospitalization, or cases diagnosed in an outpatient setting. Fourth, even though the negative predictive value of our case ascertainment was excellent (>97%), some SSS cases were not identified using ICD-9 code 427.81. Therefore, our incidence rate estimates represent a conservative estimate of the true rate in the general population. Finally, our

estimates of new SSS events occurring in the United States should be interpreted with caution because they are derived from 2 cohorts that are not representative of the entire U.S. population.

No previous studies have examined potential risk factors for SSS in the general population. Given the exploratory nature of this analysis, our examination of a large number of potential risk factors resulted in multiple comparisons, which may lead to the appearance of some associations as a result of chance. However, the directionality and strength of associations between risk factors and incident SSS were largely similar in independent ARIC and CHS models, which decreases the likelihood that these associations are spurious. Regardless, these findings are exploratory in nature; future research is needed to confirm these associations.

CONCLUSIONS

This study reports that the incidence of SSS increases with age, and does not differ between men and women. We also show that the expected number of SSS diagnoses in the United States will more than double over the next 50 years. We identified a number of risk factors for SSS, including greater BMI, height, NT-proBNP level, and cystatin C level, longer QRS interval, lower heart rate, and prevalent hypertension, right bundle branch block, and a history of a CV event at baseline. Further study is needed to confirm these findings and to further explore the difference in incidence by race.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Alvaro Alonso, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 South 2nd Street, Suite 300, Minneapolis, Minnesota 55454. E-mail: alonso@umn.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In addition to age, clinical characteristics associated with sick sinus syndrome include white race, hypertension, diabetes, obesity, right bundle branch block, and elevated serum levels of NT-proBNP and cystatin C.

TRANSLATIONAL OUTLOOK: Further study is needed to clarify the cellular and biochemical mechanisms that causally link these risk factors to degenerative fibrotic infiltration of the sinus node and related disease of the cardiac conducting system, and both elucidate and validate preventive strategies.

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APPENDIX For supplemental tables, please see the online version of this article.