JACC: ADVANCES VOL. 3, NO. 7, 2024

ORIGINAL RESEARCH

RHYTHM DISORDERS AND ELECTROPHYSIOLOGY

Frequency of Electrocardiogram-Defined Cardiac Conduction Disorders in a Multi-Institutional Primary Care Cohort

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ABSTRACT

BACKGROUND Disorders affecting cardiac conduction are associated with substantial morbidity. Understanding the epidemiology and risk factors for conduction disorders may enable earlier diagnosis and preventive efforts.

OBJECTIVES The purpose of this study was to quantify contemporary frequency and risk factors for electrocardiogram (ECG)-defined cardiac conduction disorders in a large multi-institutional primary care sample.

METHODS We quantified prevalence and incidence of conduction disorders among adults receiving longitudinal primary care between 2001 and 2019, each with at least one 12-lead ECG performed prior to the start of follow-up and at least one ECG during follow-up. We defined conduction disorders using curated terms extracted from ECG diagnostic statements by cardiologists. We grouped conduction disorders by inferred anatomic location of abnormal conduction. We tested associations between clinical factors and incident conduction disease using multivariable proportional hazards regression.

RESULTS We analyzed 189,163 individuals (median age 55 years; 58% female). The overall prevalence of conduction disorders was 27% among men and 15% among women. Among 119,926 individuals (median age 55 years; 51% female), 6,802 developed an incident conduction system abnormality over a median of 10 years (Q1, Q3: 6, 15 years) of follow-up. Incident conduction disorders were more common in men (8.78 events/1,000 person-years) vs women (4.34 events/1,000 person-years, $P < 0.05$). In multivariable models, clinical factors including older age (HR: 1.25 per 5-year increase [95% CI: 1.24-1.26]) and myocardial infarction (HR: 1.39 [95% CI: 1.26-1.54]) were associated with incident conduction disorders.

CONCLUSIONS Cardiac conduction disorders are common in a primary care population, especially among older individuals with cardiovascular risk factors. (JACC Adv 2024;3:101004) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101004

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

ECG = electrocardiogram

EHR = electronic health record

PY = person-years

Conduction disorders are a primary cause of syncope,[1] which constitutes 1 to 5% of emergency department visits per year in the United States with associated costs in excess of 2.5 billion dollars annually.[2] In some cases, conduction disorders can result in sudden cardiac death.[3,4] Understanding the contemporary epidemiology and risk factors for conduction disorders may enable earlier diagnosis and potential preventive efforts to reduce downstream complications.

Prior estimates of the contemporary frequency of conduction disorders have been limited by either a narrow scope on specific conduction abnormalities[5-8] or very broad categorization of different underlying disorders.[9] Furthermore, since conduction abnormalities can be challenging to diagnose, prior estimates are subject to misclassification on the basis of self-report or diagnosis codes,[9,10] or limited generalizability due to examination of highly curated research cohorts.[11,12] As a result, estimates of the contemporary epidemiology of conduction system disorders defined using direct rhythm assessment within a real-world ambulatory care population represents an important gap in current knowledge.

Here, utilizing a unique resource of nearly 200,000 patients receiving longitudinal primary care in a large multi-institutional academic health care system with a baseline 12-lead electrocardiogram (ECG), we sought to define the contemporary epidemiology and risk factors for conduction system disease across a broad spectrum of specific conduction abnormalities.

METHODS

STUDY SAMPLE. We analyzed the Community Cohort Project (C3PO), a sample comprising over 500,000 adults receiving longitudinal primary care within the Mass General Brigham multi-institutional health care system.[13] Individuals in C3PO are linked to the full breadth of data available in the electronic health record (EHR), including demographics, anthropometrics, vital signs, narrative notes, laboratory results, medication lists, radiology and cardiology diagnostic tests, and procedure and diagnostic administrative billing codes spanning 2001 to 2019.

Given our intent to define conduction disorders using ECG diagnoses, we excluded individuals without a baseline ECG prior to the start of follow-up. Since the original indication for pacemaker therapy can be difficult to ascertain after implant and may not indicate a conduction disorder (eg, cardiac resynchronization therapy), we also excluded individuals with a pacemaker in situ, as well as those with history of cardiothoracic surgery prior to the start of follow-up (**Figure 1**). For analyses of incident disease, we excluded individuals with any existing conduction disorder at baseline.

CLINICAL FACTOR DEFINITIONS. As described previously, the start of follow-up in the sample was defined as the second of the earliest pair of qualifying primary care visits required for inclusion.[13] Age and sex were defined using the EHR. Potential risk factors for conduction disease were selected based on known or suspected associations with incident conduction disorders and included hypertension, diabetes, chronic kidney disease, coronary artery disease, myocardial infarction, atrial fibrillation, heart failure, valvular disease, and stroke/transient ischemic attack.[9,14] Risk factors were ascertained at the start of follow-up. Heart failure was defined using a previously described natural language processing-based algorithm with an area under the receiver operating characteristic curve of 0.91 for manually adjudicated heart failure.[15] The remaining clinical factors were defined using groupings of International Classification of Diseases-9th and -10th Revision (ICD-9 and -10) diagnosis codes[16-18] (Supplemental Table 2). Clinical factor definitions for hypertension, diabetes, chronic kidney disease, coronary artery disease, myocardial infarction, and valvular disease have been previously validated with positive predictive value ≥85%.[18] Anti-arrhythmic and atrioventricular nodal-blocking medications were ascertained using medication lists (Supplemental Table 3).

Pacemaker implantation and cardiothoracic surgery were identified using Current Procedural

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 26, 2023; accepted February 23, 2024.

Terminology (CPT) codes (Supplemental Table 4). An individual was considered to have a pacemaker if they had either: 1) ≥1 CPT code for pacemaker insertion; or 2) ≥2 CPT codes indicating the presence of a pacemaker (eg, interrogation) on at least 2 different days. The pacemaker definition was validated in a random sample of 40 patients by a study author blinded to the algorithm result (J.S.H.) and was found to have a positive predictive value of 95%. An individual was considered to have undergone cardiothoracic surgery if they had ≥1 corresponding CPT code for cardiothoracic surgery, which has previously been found to have a positive predictive value of 96%.[19]

CONDUCTION DISORDER DEFINITIONS. For the purposes of classifying prevalent and incident conduction disease, we analyzed cardiologist-entered diagnostic statements of 12-lead ECGs performed in the context of clinical care. Study sample ECGs were acquired using GE Healthcare machines (models MAC5000 and MAC5500). ECG diagnostic statements were accessed via: 1) the MUSE Cardiology Information System database of Mass General Brigham (GE Healthcare, "MUSE" software versions 8.0 and 9.0); and 2) the Mass General Brigham Research Patient Data Registry ('RPDR'). The MUSE database contains quantitative ECG measurements (intervals, axes, lead-specific voltage measurements), cardiologist-entered diagnostic statements, and corresponding tracings from the 2 largest hospitals in the Mass General Brigham system (Massachusetts General Hospital and Brigham and Women's Hospital). RPDR is a legacy data warehouse that includes quantitative ECG measurements and cardiologist-entered diagnostic statements across the larger Mass General Brigham health care system, but does not contain ECG tracings. Although the data sources contain substantial overlap, both were included to maximize capture of conduction diagnoses. In the case of duplicate entries, MUSE database entries were used preferentially (Supplemental Figure 1). To minimize inclusion of individuals with a prior history of conduction disease which may not be captured on the baseline ECG, we considered ICD-9/-10 code diagnoses only for the purposes of excluding individuals from incident analyses (N = 844, 1% of all individuals excluded from incident analyses). We did not include ICD-9/-10 code-based diagnoses toward estimates of prevalent or incident conduction disease.

Since the clinical implications of disorders affecting atrioventricular conduction may vary by physiologic mechanism and anatomic location, we grouped specific conditions by inferred anatomic region of abnormal conduction (based on information available on surface ECG) and the presence or absence of atrioventricular node conduction block (**Figure 1**).[5,20] We therefore grouped first-degree atrioventricular block and second-degree atrioventricular block type 1 as *nodal delay*; right/left bundle branch block, incomplete right/left bundle branch block, interventricular conduction delay, left anterior/posterior fascicular block, bifascicular block, and so-called trifascicular block (ie, first-degree atrioventricular block with bifascicular block) as *infranodal delay*; and second-degree atrioventricular block type 2 or third-degree atrioventricular block as *nodal/infranodal block*. We also defined *any conduction disorder* as the composite of *nodal delay*, *infranodal delay*, and *nodal/infranodal block*. Conduction disorder diagnoses were not mutually exclusive.

To classify conduction disorders using cardiologist-entered ECG diagnostic statements, we developed sets of regular expressions corresponding to the specific conduction disorders outlined above and informed by recommended standards of ECG interpretation[21] (Supplemental Table 3). Each search term was validated across a random sample of twenty diagnostic statements containing the term (or the total number of statements containing the term for those with fewer than twenty) by a study author (J.S.H.) blinded to the automated result. Each term had a positive predictive value ≥95% for representing the target abnormality, using the reviewer's clinical interpretation of the diagnostic statement as the reference standard.

For 486 individuals with an ECG diagnosis of second-degree atrioventricular block not further delineated as type 1 or type 2, 254 had a corresponding ECG tracing available for review by study authors (J.S.H. and V.N.) who further classified the type of atrioventricular block. The remaining 232 individuals without ECG tracings available for manual review, as well as an additional 233 individuals with an ECG diagnosis of second-degree atrioventricular block with 2:1 conduction, were grouped into the *any conduction disorder* category only.

STATISTICAL ANALYSES. We first estimated the point prevalence of conduction disorders prior to the start of follow-up. We then calculated the incidence rate of conduction disorders as the number of incident events divided by total person-time, among individuals without a prevalent conduction disorder. Incidence rates were stratified by sex and age (10-year increments). CIs were calculated using the exact binomial method. We then plotted the cumulative incidence of conduction disorders using the Kaplan-Meier method, stratified across broader age

FIGURE 1 Study Sample and Conduction Disease Groupings

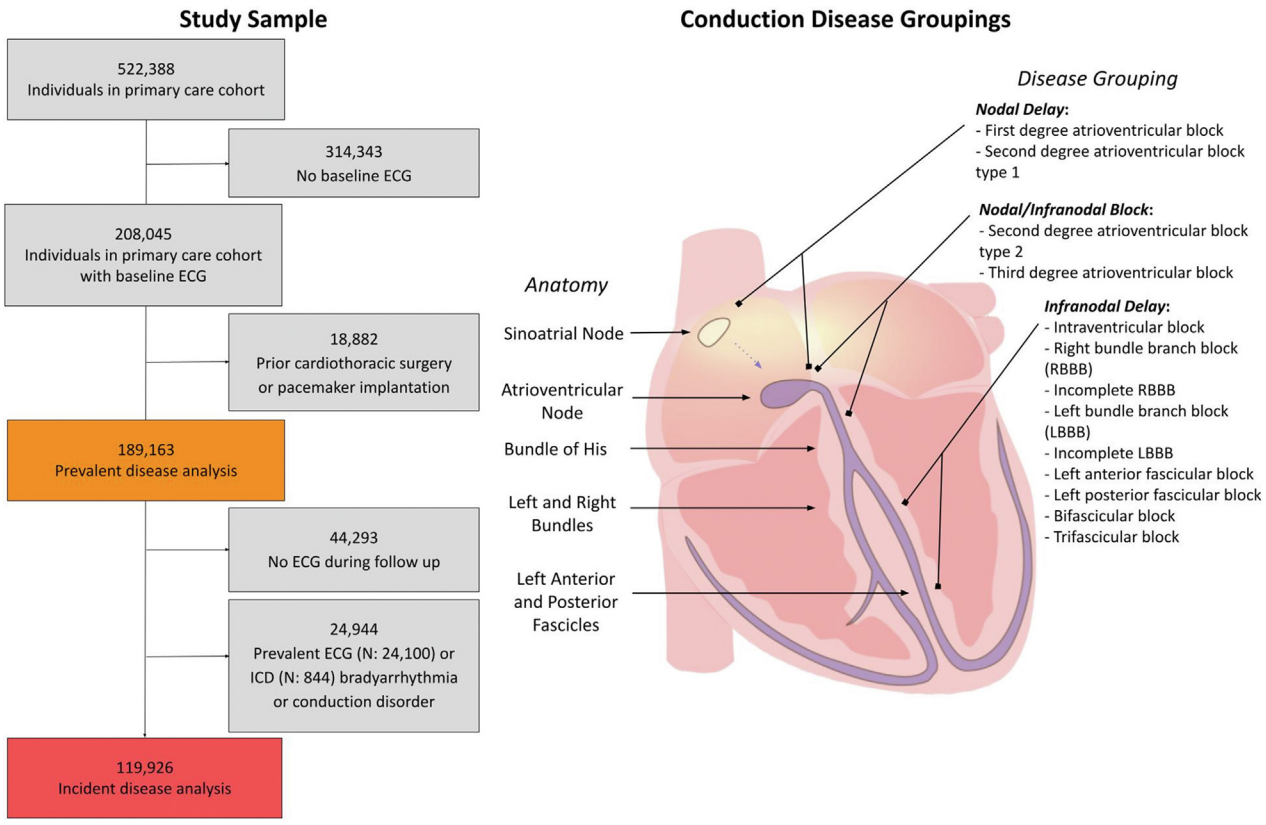


Figure depicts an overview of the study design. The left panel outlines flow through the study, Including inclusion and exclusion criteria and sample sizes. The right panel shows a schematic of the cardiac conduction system with anatomical landmarks and the corresponding categories of conduction diseases used in the current study, informed by the inferred anatomic location based on available information within the surface electrocardiogram (ECG).

categories based on approximate tertiles of age (<55, 55-75, >75 years). In all analyses, person-time spanned from start of follow-up to the earliest of death, pacemaker implantation, cardiothoracic surgery, last known clinical encounter, or August 31, 2019 (the administrative censoring date for the sample).[13] Pacemaker implantation and cardiothoracic surgery were treated as censoring events.

To identify risk factors for incident conduction disorders, we fit separate multivariable Cox proportional hazards models each with incident *nodal delay*, *infranodal delay*, *nodal/infranodal block*, and *any conduction disorder* as the outcomes. Covariates common to each model included age, sex, diabetes mellitus, coronary artery disease, obesity, chronic kidney disease, hypertension, valvular disease, myocardial infarction, atrial fibrillation, heart failure, stroke/transient ischemic attack, anti-arrhythmic use, and atrioventricular nodal-blocker use.

We performed several secondary analyses. First, we repeated the association testing outlined above with the inclusion of body mass index (BMI) as an additional covariate, within the subset of individuals with an available weight measurement within 3 years prior to the start of follow-up and an available height measurement at any point in the EHR. Second, to assess the degree to which identified conduction abnormalities may result in clinical action, we compared rates of incident pacemaker implant following development of an incident conduction disorder, utilizing an incidence density matching design (Supplemental Methods). Briefly, individuals

with an incident conduction disorder were matched 1:1 with individuals of the same age, sex, and accrued follow-up at the time of an ECG showing no conduction disorder.

We considered associations statistically significant if the 2-sided *P* value was <0.05. All analyses were performed in Python v3.0 (packages 'pandas' and 'lifelines').[22,23]

RESULTS

PREVALENT CONDUCTION DISORDERS. A total of 189,163 individuals were included in the analysis sample (median age 55 years [IQR: 44-67 years], 58% female, 75% White, median 2 ECGs per individual [IQR: 1-4]) (**Table 1**). Individuals excluded for absence of a baseline ECG had similar demographics but lower comorbidity burden (Supplemental Table 1).

A total of 37,906 individuals had a prevalent conduction disorder (prevalence 20.0%, 95% CI: 19.9-20.2) (Supplemental Table 4). *Infranodal delay* was the most common conduction disorder (prevalence 15.0%, 95% CI: 14.9-15.2), while *nodal/infranodal block* was rare (prevalence 0.1%, 95% CI: 0.0-0.2). Prevalence of conduction disorders increased with older age and male sex (**Central Illustration**, **Figure 2**, Supplemental Tables 5 and 6).

INCIDENT CONDUCTION DISORDERS. There were 119,926 individuals without a baseline conduction disorder (median age 55 years [IQR: 45-66 years], 61% female, 76% White, median 4 ECGs per individual [IQR: 2-9]) (**Table 1**). Median follow-up time was 10 years [IQR: 6.0-15.5 years] and the overall mortality rate was 12.0 per 1,000 PY (95% CI: 11.8-12.2).

A total of 6,802 individuals (5.7%) developed an incident conduction disorder (incidence rate 6.0 per 1,000 PY [95% CI: 5.8-6.1]). Incidence rates of specific conduction disease categories (per 1,000 PY) were *nodal delay* 2.9 [95% CI: 2.8-3.0], *infranodal delay* 4.0 [95% CI: 3.9-4.1], and *nodal/infranodal* block 0.04 [95% CI: 0.03-0.05] (Supplemental Table 7). The incidence of conduction disorders was also associated with older age and male sex (**Figures 2 and 3**, Supplemental Tables 7 and 8).

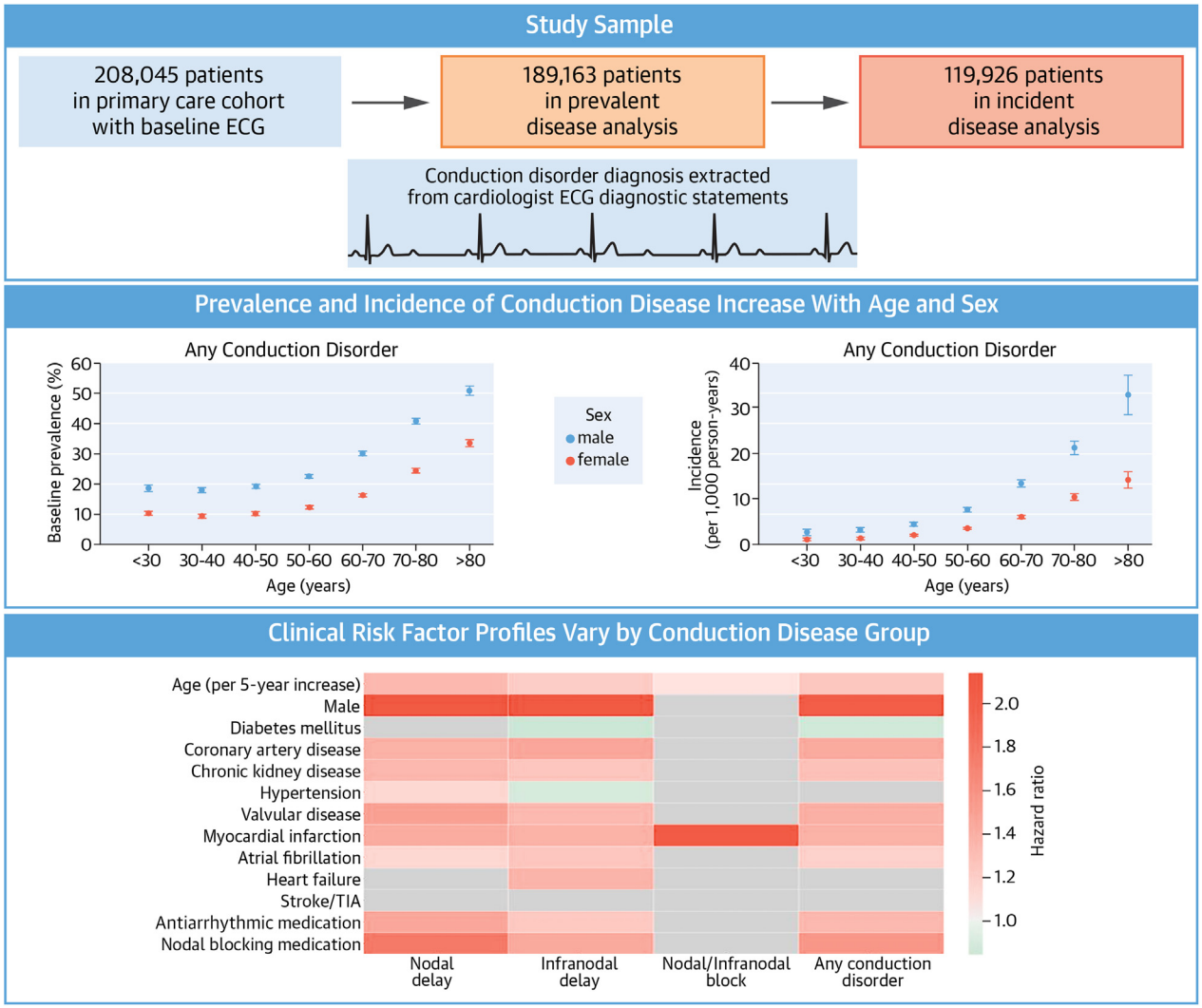
ASSOCIATION OF CLINICAL FACTORS AND INCIDENT CONDUCTION DISEASE. In multivariable analysis, several clinical factors were associated with incident conduction disease including older age (HR: 1.25 per 5-year increase [95% CI: 1.24-1.26]), male sex (HR: 2.05 [95% CI: 1.95-2.15]), and prior myocardial infarction (HR: 1.39 [95% CI: 1.26-1.54]). Risk factor profiles differed among the conduction disorder groups (**Central Illustration**, **Figure 4**, Supplemental Figure 2, Supplemental Table 9). For example, heart failure was significantly associated with *infranodal delay* (HR: 1.38 [95% CI: 1.03-1.84]) but not the other conduction disorder categories. Although myocardial infarction was significantly associated with all conduction disorder categories, the effect size was largest for *nodal/infranodal block* (HR: 2.09 [95% CI: 1.00-4.33]) compared to *any conduction disorder* (HR: 1.39 [95% CI: 1.26-1.54]), *nodal delay* (HR: 1.42 [95% CI: 1.25-1.62]), or *infranodal delay* (HR: 1.40 [95% CI: 1.24-1.58]). Male sex was also significantly associated with *nodal delay* (HR: 2.14 [95% CI: 2.00-2.29]) and *infranodal delay* (HR: 2.13 [95% CI: 2.01-2.26]) but not *nodal/infranodal block* (HR: 1.07 [95% CI: 0.79-1.47]). Antiarrhythmic use was associated with *nodal delay* (HR: 1.47 [95% CI: 1.18-1.83]) and *infranodal delay* (HR: 1.23 [95% CI: 1.00-1.51]) but not with *nodal/infranodal block*. Similarly, nodal blocking medications were associated with *nodal delay* (HR: 1.78 [95% CI: 1.65-1.93]) and *infranodal delay* (HR: 1.46 [95% CI: 1.36-1.56]). In a subset of 67,379 individuals with baseline BMI (mean 28.8 kg/m^2, standard deviation 6.6 kg/m^2), greater BMI was associated with slightly lower risk of *infranodal delay* (HR: 0.95 [95% CI: 0.91-0.98]) and *any conduction disorder* (HR: 0.97 [95% CI: 0.94-1.00]) (Supplemental Table 10).

TABLE 1 Study Baseline Characteristics

	Prevalent Disease Analysis (n = 189,163)	Incident Disease Analysis (n = 119,926)
Age (y)	55 (44, 67)	55 (45, 66)
Follow-up duration (y)	-	10 (6, 15)
Female	109,502 (57.9)	72,616 (60.6)
Race and ethnicity		
White	142,554 (75.4)	90,787 (75.7)
Black	16,989 (9.0)	10,955 (9.1)
Hispanic	10,546 (5.6)	6,690 (5.6)
Asian	6,124 (3.2)	3,595 (3.0)
Mixed	13 (0.0)	6 (0.0)
Unknown	6,330 (3.3)	3,598 (3.0)
Other	6,607 (3.5)	4,295 (3.6)
Hypertension	99,107 (52.4)	64,449 (53.7)
Diabetes	30,070 (15.9)	19,152 (16.0)
Coronary artery disease	30,921 (16.3)	17,942 (15.0)
Chronic kidney disease	12,558 (6.6)	7,091 (5.9)
Valvular disease	7,657 (4.0)	4,195 (3.5)
Myocardial infarction	7,700 (4.1)	4,103 (3.4)
Atrial fibrillation	12,214 (6.5)	6,574 (5.5)
Heart failure	1,791 (0.9)	782 (0.7)
Stroke/transient ischemic attack	5,537 (2.9)	3,158 (2.6)
Anti-arrhythmic medication	3,448 (1.8)	1,718 (1.4)
Atrioventricular nodal blocking medication	52,942 (28.0)	32,717 (27.3)

Values are median (Q1, Q3) or n (%).

CENTRAL ILLUSTRATION **Frequency of Electrocardiogram-Defined Cardiac Conduction Disorders in a Multi-Institutional Primary Care Cohort**



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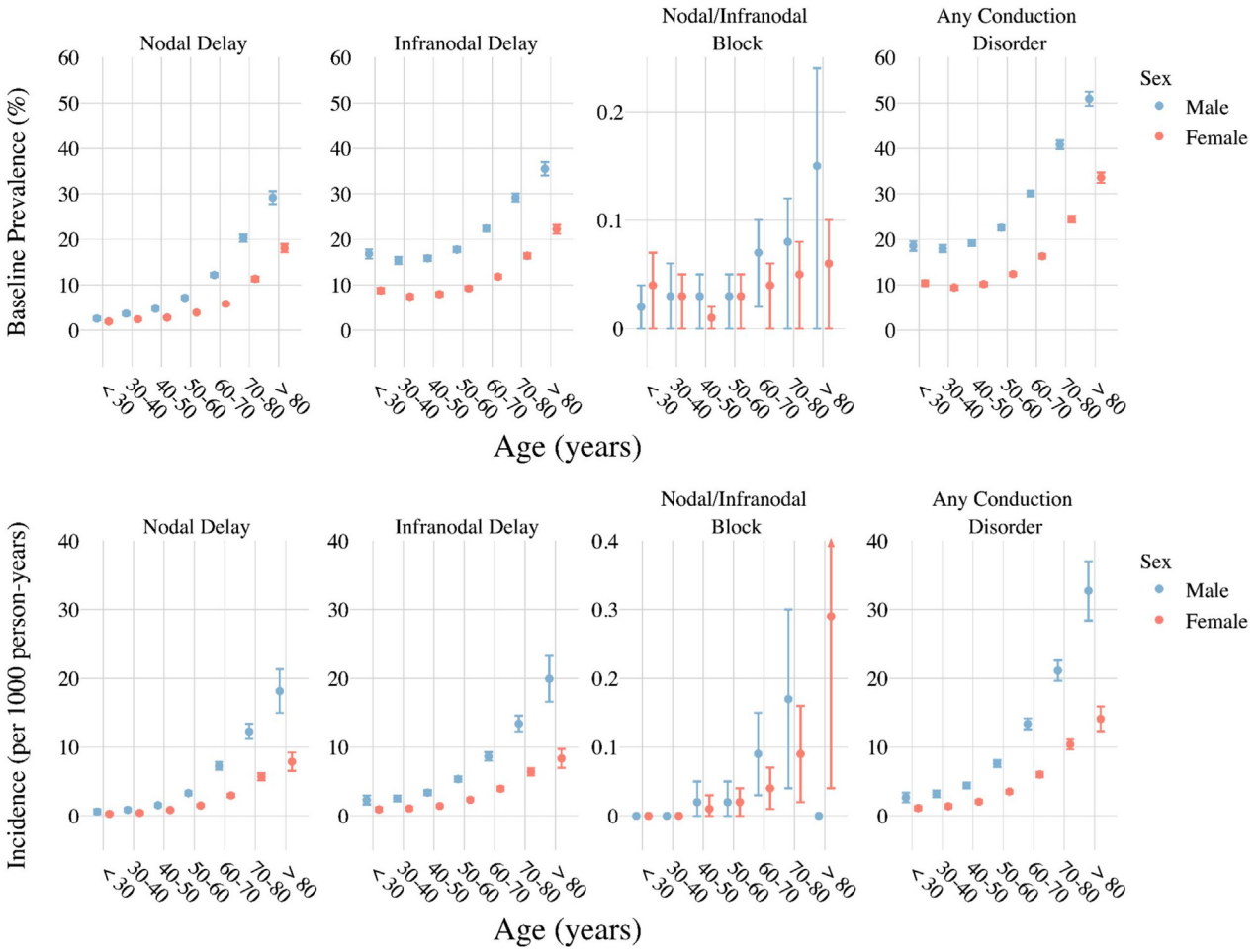
The study analyzed 189,163 individuals to assess prevalence of conduction disorders, and 119,926 individuals without prevalent conduction disease to assess incidence of a new conduction disorder. Conduction diseases were grouped according to inferred anatomic location based on available information within the surface ECG. The prevalence and incidence of conduction disease were substantial and increased consistently with age and sex. Although risk factor profiles varied across specific conduction disorder categories, older age, male sex, and traditional cardiovascular risk factors were generally associated with increased risk of an incident conduction disease.

ASSOCIATION OF INCIDENT CONDUCTION DISEASE AND SUBSEQUENT PACEMAKER IMPLANTATION. The 10-year cumulative risk of pacemaker implantation following a conduction disorder was 8.7% [95% CI: 7.4%-10.1%] for *nodal delay*, 5.7% [95% CI: 4.9%-6.7%] for *infranodal delay*, 67.9% [95% CI: 41.2%-91.2%] for *nodal/infranodal block*, and 6.3% [95% CI: -6.3%] for any conduction disorder diagnosis. Cumulative risk of pacemaker implantation following conduction disorder diagnosis was substantially higher than that observed for individuals without a conduction disorder diagnosis matched on age, sex, and duration of follow-up time ($P < 0.05$ for all comparisons) (Supplemental Figure 3).

FIGURE 2 Age- and Sex-Stratified Prevalence and Incidence of Conduction Disorders



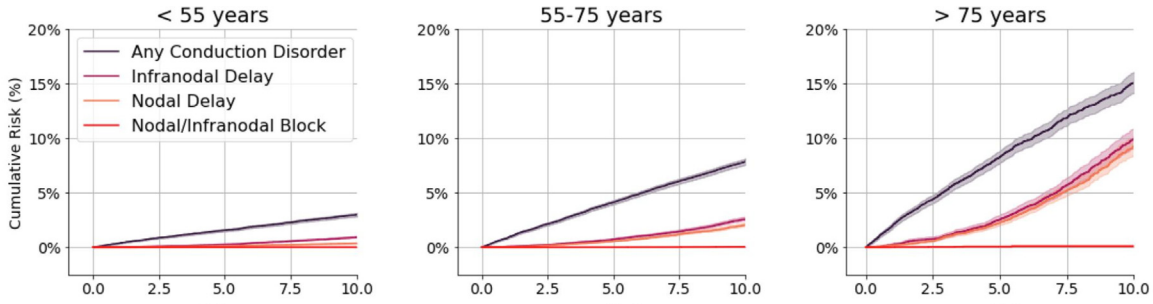
The upper panels depict age- and sex-stratified prevalence of conduction disorder groups. The lower panels depict age- and sex-stratified incidence (per 1,000 person-years) of the same conduction disorder groups. In all plots, bars represent 95% CIs.

DISCUSSION

In this contemporary analysis of nearly 200,000 individuals receiving longitudinal primary care within a multi-institutional health care system, the frequency of conduction disorders was substantial. Based on ECG interpretations performed by board-certified cardiologists, 1 in 5 individuals had a prevalent conduction disorder, of which 75% of conditions were forms of infranodal delay. New conduction disorders occurred at a rate of approximately 0.6%/year over a median follow-up of 10 years. Importantly, we observed that the incidence of conduction disease was greater in the presence of older age, male sex, and common cardiovascular risk factors such as chronic kidney disease and prior myocardial infarction. Overall, our findings provide a robust characterization of the contemporary burden of conduction system abnormalities in a primary care population, demonstrating that conduction disorders are common and that cardiovascular risk factors may identify individuals at greatest risk for developing a new conduction abnormality.

Our work supports and extends prior research by providing a robust and systematic quantification of the frequency of cardiac rhythm disorders using a large corpus of ECGs obtained within a well-curated primary care sample. In a broad survey of rhythm disorders in a national UK-based research cohort, Khurshid et al[9] reported a prevalence of bradyarrhythmias and conduction system diseases of 1% and an incidence rate of 2 to 3 events per 1,000 PY. In the

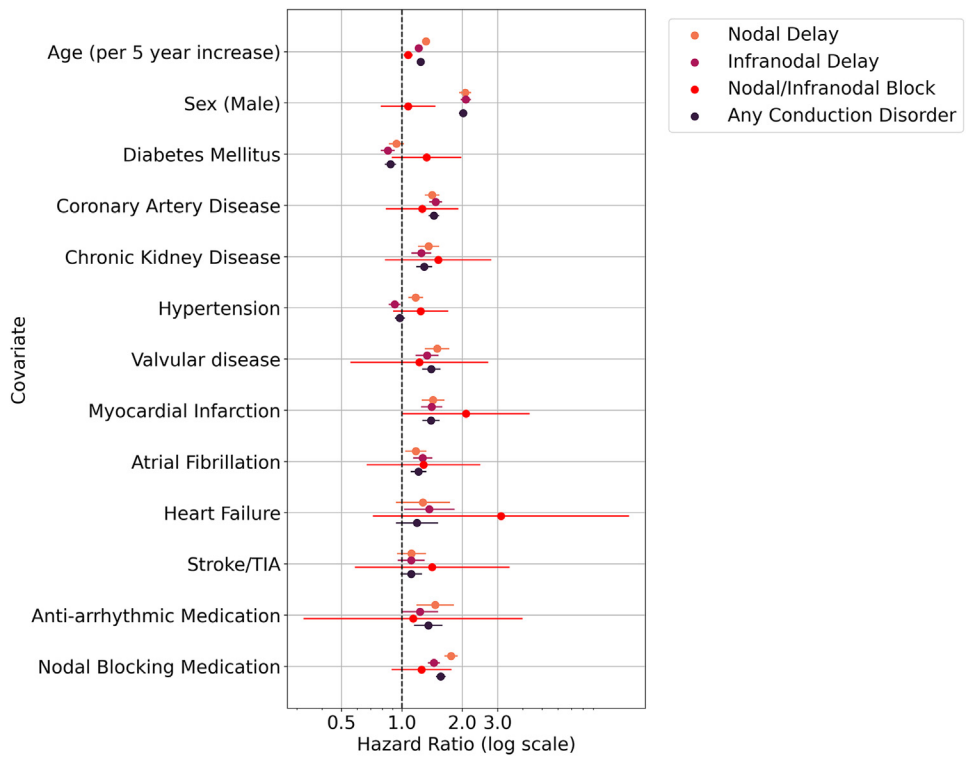
FIGURE 3 Cumulative Risk of Conduction Disorders by Age



At Risk									
Any Disorder	56836	44995	31405	50521	36075	22136	12542	5986	1892
Nodal/Infranodal Delay	56836	45623	32273	50521	37419	23761	12542	6422	2131
Nodal Delay	56836	45623	32273	50521	37419	23761	12542	6422	2131
Infranodal Block	56836	45623	32273	50521	37419	23761	12542	6422	2131

Each plot depicts the cumulative risk of conduction disorders for ages <55, 55 to 75, and >75 years, plotted using the Kaplan-Meier method. Each conduction disorder is depicted with a varying shade of Red. Individuals at risk for each conduction disorder category are shown below.

FIGURE 4 Forest Plot of Associations of Clinical Risk Factors and Incident Conduction Disorders



Depicted is a forest plot of associations between clinical factors and incident conduction disease in multivariable Cox proportional hazards models. Each conduction disorder is represented by a different shade of red. HRs are shown on log-scale with error bars corresponding to the corresponding 95% CI.

current study, we observed a twenty-fold higher prevalence and roughly twice the incidence of conduction disease, with differences likely due to our analysis of a real-world primary care sample, as well as the requirement for cardiologist-entered ECG diagnostic statements for disease ascertainment as opposed to billing codes and self-report.[24] We also required an ECG for inclusion in the study sample, which may select for individuals with greater cardiovascular comorbidity. At the same time, use of ECG diagnoses likely facilitated detection of certain conduction system disorders which may be asymptomatic yet retain clinical and prognostic relevance (eg, left bundle branch block).[25] Although our sample comprises individuals receiving primary care in varying settings (eg, community health centers, on-campus clinics), our analysis may be enriched for individuals more likely to engage in preventive health measures. Therefore, the frequency of conduction disorders in samples with poorer cardiovascular health and lower access to care may be even greater. Overall, however, our results suggest that conduction system disease appears more common than previously appreciated.

Our study suggests that the burden of conduction system abnormalities is only likely to increase as a result of population aging. While prior work has shown that conduction disorders are generally more common among older individuals, our findings demonstrate that the association of age appears generally uniform across various forms of atrioventricular conduction disease. In particular, there was a considerable increase in the frequency of *nodal/infranodal block* among older individuals, with an incidence rate of 0.2 events per 1,000 PY in adults over 80 years old compared to no events observed in adults younger than 40 years old. Therefore, conduction disorders, including those associated with *nodal/infranodal block*, are expected to increase with expected aging-related demographic shifts.[26] We also observed that conduction disease appears more common among men across all age categories. Importantly, in secondary analyses, we found that the incidence of pacemaker implant following a new conduction system disorder diagnosis was substantial, ranging from approximately 6% following a diagnosis of *infranodal delay* to roughly 70% after *nodal/infranodal block*. Although we acknowledge our estimates are subject to bias on the account of requiring the presence of a cardiologist interpreted clinical ECG for analysis, we submit our findings provide important contemporary estimates with greater precision than that afforded by typical approaches to the analysis of real-world health care samples (eg, diagnostic codes). Overall, especially given the substantial morbidity associated with certain conduction diseases including *nodal/infranodal block*, our estimates may be particularly useful for clinicians treating older individuals, as well as future studies evaluating strategies for early detection and treatment of conduction disease.[27]

Our observations suggest an important role of traditional cardiovascular risk factors in the development of conduction disease.[9,28] We observed that factors such as chronic kidney disease, myocardial infarction, and atrial fibrillation were each strongly associated with future conduction disease. Chronic kidney disease may lead to the development of conduction system disease through fibrosis and metabolic disarray, which places patients on hemodialysis at particular risk during the interdialytic period.[29] Atrioventricular block, which occurs in 2 to 5% of acute myocardial infarctions,[30,31] may be caused by ischemia and fibrosis of the conduction system and portends worse prognosis due to correlation with infarct size as well as association with increased risk of sudden death.[30] Even less severe forms of post-infarct conduction disease such as right and left bundle branch blocks have also been associated with increased mortality.[32,33] Associations between atrial fibrillation and conduction system disease have been previously described and are likely multifactorial, but in some cases may include shared genetic mechanisms related to cardiac development and ion channel function.[34-37] Consistent with expectations, we observed that the use of nodal blockers and antiarrhythmic drugs was also associated with the development of new conduction disorders, which we submit is likely related to direct effects on cardiac conduction, although use of such medications may also signal the presence of more severe cardiac disease. In contrast to recent evidence linking higher BMI with conduction disease, we observed modest associations between higher BMI and lower risk of incident conduction disease.[38-40] Since we adjusted for an array of concurrent obesity-related metabolic factors (eg, hypertension, diabetes, chronic kidney disease), we suspect low BMI may be acting as a marker of general medical comorbidity or frailty, although our observation merits further investigation. Overall, our findings highlight important associations between traditional risk factors and incident

arrhythmias, and future work is warranted to assess the potential value of novel biomarkers, including emerging artificial intelligence-based measures extracted from the ECG (eg, ECG-based physiologic age), in stratifying arrhythmia risk.[41,42]

Our analysis must be interpreted in the context of study design. First, to comprehensively ascertain conduction system disorders, including those which may be asymptomatic, we utilized cardiologist interpretations of 12-lead ECGs to define conditions. Limiting our sample to individuals with a 12-lead ECG introduces bias, as individuals excluded for an absent baseline ECG had similar demographic composition but lower comorbidity burden. Additionally, we may miss diagnoses of conduction disorders present on ECGs which were not formally interpreted by a cardiologist. Nevertheless, we submit that use of direct rhythm assessment leads to more accurate ascertainment of conduction system disorders compared to alternative approaches such as self-report, diagnostic, or billing codes. Second, use of 12-lead ECG diagnostic statements is subject to misdiagnosis, as well as imperfect sensitivity for paroxysmal arrhythmias which may be observed only using continuous monitoring (eg, inpatient telemetry, loop recorder, or surface monitor).[43] Use of regular expressions to classify diagnostic statements may contribute to misclassification, especially for conditions with uncommon terminology or abbreviations. However, we did ensure that our regular expression terms were precise when a condition was identified (ie, positive predictive value ≥95% for each). Third, since we excluded individuals with pacemakers implanted before start of follow-up, the prevalence of conduction disorders associated with atrioventricular block may be underestimated. Fourth, risk factors were ascertained primarily using diagnosis codes, which may introduce misclassification. Fifth, generalizability of our findings may be affected by geographic and demographic specificity on account of analyzing a primary care population from the New England region of the United States (eg, predominantly White). Conduction disorders may be even more common in populations with greater comorbidity burden and less ready access to care.[44] Future research across multiple sites and geographic locations is needed to better understand the effects of social determinants of health on conduction disease. Sixth, although our sampling approach has been previously shown to result in greater data density and less bias compared to alternative EHR sampling designs, misclassification of risk factors and outcomes due to a failure to capture events occurring outside the health care system remains possible.[13] Seventh, since our study was observational, we cannot exclude residual confounding in the analyses of risk factors.

CONCLUSION

The contemporary prevalence and incidence of conduction disorders in a large primary care sample is substantial. Up to 20% of individuals have a conduction disorder at baseline, and over 6% of the study sample developed a new conduction disorder over 10 years of follow-up. Risk of various conduction abnormalities appears uniformly higher in the presence of older age, male sex, and traditional cardiovascular risk factors. Future work is warranted to evaluate the incidence and risk factors for conduction disease in varied patient populations and to assess prospectively whether optimal cardiovascular risk factor management may reduce the incidence of conduction disease.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Lubitz is a full-time employee of Novartis as of July 2022. He received sponsored research support from Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, Fitbit, Medtronic, Premier, and IBM, and has consulted for Bristol Myers Squibb, Pfizer, Blackstone Life Sciences, and Invitae. Dr Ellinor receives sponsored research support from Bayer AG and IBM and has consulted for Novartis, MyoKardia, and Bayer AG. Dr Ho has received sponsored research support from Bayer AG. Dr Batra receives sponsored research support from Bayer AG and IBM and has consulted for Novartis and Prometheus Biosciences. Dr Philippakis is a Venture Partners and employee at GV, has consulted for Novartis and Rakuten, and receives sponsored research support from Verily, Microsoft, IBM, Intel, Pfizer, Abbvie, Biogen, Ionnis and Bayer. Investigators were supported by National Institutes of Health grants K23HL169839-01 (Dr Khurshid), R38HL150212 (Dr Haimovich); R01HL139731 (Dr Lubitz), R01HL157635 (Dr Lubitz), R01HL134893 (Dr Ho), R01HL140224 (Dr Ho), K24HL153669 (Dr Ho), 2R01HL092577 (Dr Ellinor), and 1R01AG066010, R01HL092577 (Dr Benjamin); American Heart Association grants 18SFRN34250007 (Dr Lubitz), AF 18SFRN34110082 (Dr Benjamin), 2023CDA1050571 (Dr Khurshid) and 18SFRN34110082 (Dr Ellinor); and by a grant from the European Union, MAESTRIA 965286 (Dr Ellinor). Dr Kornej has received funding from the Marie Sklodowska-Curie Actions under the European Union's Horizon 2020 research and innovation programme (Agreement No 838259). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Disorders of cardiac conduction are common and are expected to increase in frequency with population aging and growing prevalence of cardiovascular risk factors.

TRANSLATIONAL OUTLOOK: In our study, risk of various conduction abnormalities was uniformly higher in the presence of older age, male sex, and traditional cardiovascular risk factors. Therefore, future efforts are warranted to assess the effectiveness of cardiovascular risk factor optimization to reduce the incidence of conduction disease.

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KEY WORDS conduction disease, electrocardiogram, epidemiology

APPENDIX For supplemental methods, tables, figures, and references, please see the online version of this paper.