

Cumulative Incidence of Infective Endocarditis in Patients with Congenital Heart Disease: A Nationwide, Case-Control Study Over Nine Decades

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Background. Congenital heart disease (CHD) is a lifelong predisposing condition for infective endocarditis (IE). As a consequence of advances in pediatric care, the number of adults with CHD is now exceeding the number of children. The goal of the present study was to determine the cumulative incidence of IE in patients with CHD and detect temporal changes compared with controls.

Methods. Nationwide registry-based case-control study of patients with CHD born 1930–2017 matched with 10 random controls. Infective endocarditis episodes were linked using the Swedish 10-digit personal identification number.

Results. In total, 89 541 patients with CHD and 890 470 matched controls were included. In patients with CHD, 1477 IE episodes were registered and 447 episodes in controls. Patients with CHD had 8.5% cumulative incidence of IE at age 87 years, compared with 0.7% in matched controls. Incidence rate of IE per 100 000 person-years was 65.5 (95% confidence interval [CI] 62.2–68.9) and 1.8 (95% CI: 1.7–2.0) in CHD patients and controls, respectively. By age 18 years, patients with CHD had an IE incidence similar to that of 81-year-old controls. Incidence of IE differed by age but not by birth year. Bacterial etiology was registered from 1997 in half of the IE episodes; among CHD IE cases, 43.3% were caused by streptococci and 29.8% by *Staphylococcus aureus*.

Conclusions. Infective endocarditis remains an important complication in patients with CHD. Incidence correlate with age and the number of IE episodes are expected to increase as the CHD population grow older.

Keywords. congenital heart disease; infective endocarditis; endocarditis/epidemiology.

Congenital heart disease (CHD) is present in approximately 1% of newborns and is recognized as a lifelong predisposing condition for infective endocarditis (IE) [1]. CHD predisposes to IE via several mechanisms such as the presence of a disturbed, nonlaminar blood flow causing shear stress and microdamage to endothelial cells, the presence of foreign intracardiac material such as prosthetic valves and implanted cardiac devices, cyanosis, and recurrent exposure to health care procedures. As a consequence of major advances in pediatric care for patients with CHD, an increasing number of children reach adulthood and grow older with a continuous risk for IE [2]. The number of adults with severe heart defects is now exceeding the number of

children with severe heart defects [3, 4]. In addition to ageing, patients with CHD exhibit greater cardiac complexity and higher rates of comorbidities compared with just a few decades ago [5].

IE is an important cause of morbidity and mortality in patients with CHD [6]. The overall incidence of IE is 20–70 times higher among patients with CHD than in the general population [7–9]. In addition to the expanding CHD population at risk, IE incidence is correlated with age [10, 11] and can be expected to increase further in an ageing CHD population.

IE carries considerable morbidity with prolonged courses of intravenous antibiotic therapy and cardiac surgery in many cases. Despite this, the short-term mortality of IE in patients with CHD is reported to be 15% [12]. Studies based on analyses of IE cases in a CHD population [6] or registry studies [13] may over- or underestimate the risk of IE owing to the lack of an adequate control group or skewed inclusion.

Our goal in the present study was to establish population-based estimates for incidence of IE in patients with CHD. The primary objective was to describe cumulative incidence of IE in patients with CHD born between 1930 and 2017 and to detect temporal changes in incidence in comparison with matched

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controls. A secondary objective was to estimate the incidence rate of IE and correlate to time of birth and to CHD lesion groups. Finally, we sought to investigate the microbiological etiology of IE.

METHODS

Study Population

In the current study, data from the Swedish National Patient Register (NPR) and Cause of Death Register (CDR) were used to identify all patients with CHD. The NPR was initiated in 1964, and since 1987, it includes full nationwide coverage of all in-hospital admissions in Sweden. Additionally, all diagnoses from outpatient specialist clinics since 2001 are recorded in the NPR. The CDR began in 1961. To identify all patients with CHD, the NPR and CDR were linked using the unique Swedish 10-digit personal identification number. In our study, for each case of CHD, approximately 10 random controls were matched by birth year and sex from the Swedish Total Population Register. A total of 89 541 patients with CHD and 890 470 controls (ratio of 9.4 controls per case) born in 1930–2017 were identified and followed from birth until the end of study on 31 December 2017. Patients with CHD and controls were divided into 2 birth cohorts, 1930–1969 and 1970–2017. Previous validation studies of the NPR and CDR have shown high validity for cardiovascular disease [14] and for CHD spectrum diagnoses [15]. Episodes of IE in cases and controls were identified in the NPR. An IE episode was defined as an inpatient encounter with a diagnostic code for IE; repeat encounters within a 3-month period were discarded to account for transfers during the same IE episode. Relapse was defined as a new IE encounter more than 3 months after the previous episode. Data regarding type of CHD lesion, age, time of event, previous cardiac surgery, and bacterial etiology were registered. Mortality was defined as total mortality during follow-up.

Definition of Diagnoses

All diagnoses are coded according to the revisions of the International Classification of Diseases (ICD) system, ICD-8 (1968–1986), ICD-9 (1987–1996), and ICD-10 (1997 onward). [Supplementary Table 1](#) lists the specific diagnoses for CHD used in the NPR and CDR. Patients were grouped into 6 CHD lesion groups based on the hierarchical classification system [16] modified by Liu et al [17].

CHD lesion group 1 (conotruncal defects including common arterial trunk, transposition of the great arteries, tetralogy of Fallot, and aortopulmonary septum defects) and group 2 (non-conotruncal defects including endocardial cushion defects, common ventricle defects, and hypoplastic left heart syndrome) represent the most complex conditions. CHD lesion group

3 includes coarctation of the aorta, and CHD lesion groups 4 and 5 include ventricular and atrial septal defects, respectively. Lesion group 6 consists of CHD diagnoses not included in lesion groups 1–5, mainly congenital valve malformations. A more detailed list of diagnoses for CHD lesion groups is shown in [Supplementary Table 2](#). IE was defined using ICD-8 and ICD-9 codes 421 and ICD-10 codes I33, I38, and I39. Bacterial codes are listed in [Supplementary Table 3](#).

Statistical Analysis

All statistical analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Baseline characteristics are shown as continuous or categorical variables. Continuous variables are shown as mean (standard deviation [SD]) and categorical variables as number with percentage. The incidence of IE is estimated as the number of events divided by the total number of person-years, with 95% confidence interval (CI), separately for patients with CHD and controls. Cumulative incidence of IE for patients with CHD and controls was calculated according to the Fine-Gray method (using the R package `prodlm`).

Ethical Approval

The study was approved by the regional ethics board in Gothenburg (Gbg 912-16, T 619-18) and complied with the Declaration of Helsinki. As retrospective and pseudonymized registry data were used, the requirement for patient consent was waived.

RESULTS

A total of 89 541 patients with CHD and 890 470 matched controls were included in the study. In sum, 4 out of 5 patients were born 1970 or later, and 49% were women ([Table 1](#)). The mean follow-up of the study was 25.4 (SD 22.2) years in cases and 27.3 (SD 22.0) years in controls. Cardiovascular risk factors and comorbidities diagnosed before IE occurrence were uncommon in both groups but significantly more prevalent among patients with CHD. Patients with the most complex CHD diagnoses (lesion groups 1 and 2) constituted 13% of patients with CHD. The most common lesion type was ventricular septum defect, seen in 28% of cases.

In total, 1477 patients with CHD and 447 controls developed IE ([Table 2](#)). Nearly two-thirds of IE episodes occurred in men among in both groups. Patients with CHD were more than 20 years younger when they developed IE (mean age 36.2 ± 21.1 vs $57.1.0 \pm 18.8$ years, $P < .001$); cardiac surgery prior to IE diagnosis had been performed in 627 (42.5%) patients with CHD who had IE compared with 96 (21.5%) of controls ($P < .001$). Relapse of IE was found in 93 (6.7%) patients with CHD and in 16 (3.9%) of controls with IE ($P = .052$). Unadjusted total mortality during follow-up was higher in controls with IE compared with CHD patients with IE, 169/447 (41.6%) versus 387/1477 (28.0%), $P < .001$.

Table 1. Characteristics of Study Population

Characteristics	Patients With CHD	Controls	P value
	N = 89 541	N = 890 470	
Female sex	44 170 (49.3)	436 751 (49.0)	.108
Born in Sweden	83 088 (92.8)	719 530 (80.8)	<.001
Birth period			.437
1930–1969	17 601 (19.7)	176 010 (19.8)	
1970–2017	71 940 (80.3)	714 460 (80.2)	
Follow-up, years mean (SD)	25.4 (22.2)	27.3 (22.0)	<.001
Median (IQR)	18 (7.6–38.5)	21.5 (9.5–41.5)	
Hierarchical CHD classification, n (%)			
Lesion group 1	6326 (7.1)	63 040 (7.1)	
Lesion group 2	4831 (5.4)	48 200 (5.4)	
Lesion group 3	4599 (5.1)	45 870 (5.2)	
Lesion group 4	25 151 (28.1)	249 315 (28.0)	
Lesion group 5	20 929 (23.4)	208 091 (23.4)	
Lesion group 6	27 705 (30.9)	275 954 (31.0)	

Values are n (%), unless otherwise indicated.

Abbreviations: CHD, congenital heart disease; IQR, interquartile range; SD, standard deviation.

Cumulative Incidence of Infective Endocarditis in Patients with Congenital Heart Disease

In patients with CHD, the lifetime incidence of IE was 8.5%, compared with 0.7% in controls (Figure 1). At the age of 18 years, cumulative incidence of IE in patients with CHD reached the incidence of IE among controls at age 81 (0.5%), corresponding to 323 IE episodes in 71 940 patients with CHD compared with 11 IE cases in 714 460 controls. The incidence of IE was higher from birth in patients with CHD, as illustrated in Figure 2. To account for changing validity of IE diagnostic

codes during the study period, a sensitivity analysis was performed on IE events diagnosed after 2001, when the modified Duke criteria started to be applied. These findings were in concordance with the main analysis (Supplementary Figure 1). The cumulative incidence of IE in the different CHD lesion groups differed, with a similar incidence in lesion groups 1, 3, 4, and 6. However, IE during childhood was almost exclusively seen among patients with complex lesions (lesion groups 1 and 2) (Supplementary Figure 2).

Table 2. Characteristics of Infective Endocarditis (IE) Cases in Patients With and Without Congenital Heart Disease (CHD)

	IE in Patients With CHD	IE in Controls	P value
	N = 1477	N = 447	
Female sex	546 (37.0)	162 (36.2)	.573
Age at event (years)			<.001
Mean (SD)	36.2 (21.1)	57.1 (18.8)	
Median (IQR)	34.8 (20.2–51.8)	61.1 (44.9–72.2)	
Birth period			<.001
1930–1969	913 (61.8)	384 (85.9)	
1970–2017	564 (38.2)	63 (14.1)	
Period of diagnosis			<.001
1970–1987 (ICD-8)	244 (16.5)	16 (3.6)	
1988–1996 (ICD-9)	292 (19.8)	51 (11.4)	
1997–2017 (ICD-10)	941 (63.7)	380 (85.0)	
Prior cardiac surgery	627 (42.5)	96 (21.5)	<.001
Mechanical valve	163 (11.0)	27 (6.0)	.003
Bioprosthesis	80 (5.4)	41 (9.2)	.006
Relapse ^a	93 (6.7)	16 (3.9)	.052
Mortality during follow-up	480 (32.5)	210 (47.0)	<.001

Values are n (%), unless otherwise indicated.

Abbreviations: ICD, International Classification of Diseases; IQR, interquartile range; SD, standard deviation.

^aNew infective endocarditis diagnosed more than 3 months after the initial episode.

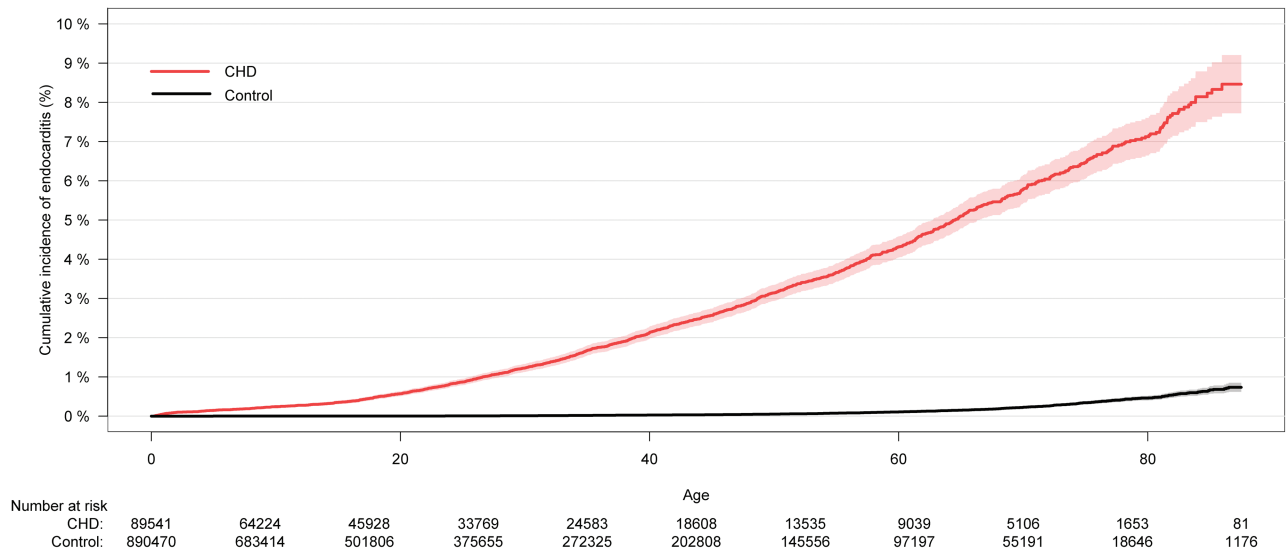


Figure 1. Cumulative incidence of infective endocarditis in patients with CHD and controls for up to 88 years of follow-up. Shaded area shows 95% confidence interval. Abbreviation: CHD, congenital heart disease.

Incidence Rate of Infective Endocarditis

The incidence rate of IE was 65.5 (95% CI: 62.2–68.9) per 100 000 person-years in patients with CHD compared with 1.8 (95% CI: 1.7–2.0) per 100 000 person-years in matched controls. Additionally, the incidence of IE per 100 000 person-years in the birth cohort (1930–1969) was higher in both cases, with 84.7 (95% CI: 79.3–90.4) and in controls, with 3.4 (95% CI: 3.1–3.4), as compared with the later birth cohort (1970–2017) with incidence rates of 47.9 (95% CI: 44.0–52.0) in patients with CHD and 0.5 (95% CI: .4–.6) in controls (Supplementary Table 4).

To analyze whether the difference in IE incidence rates between birth cohorts was affected by varying incidence during the 2 time periods or whether it was secondary to lower age and shorter duration of follow-up in patients born in 1970 or later, the cohort was divided into 5 age groups according to age at IE episode and then stratified by birth period, as shown in Figure 3. IE incidence did not differ by birth period before or after 1970. A higher incidence rate of IE was seen in all CHD lesion groups compared with controls; however, the rate differed with the highest IE incidence rate seen in lesion group 1 (158.1

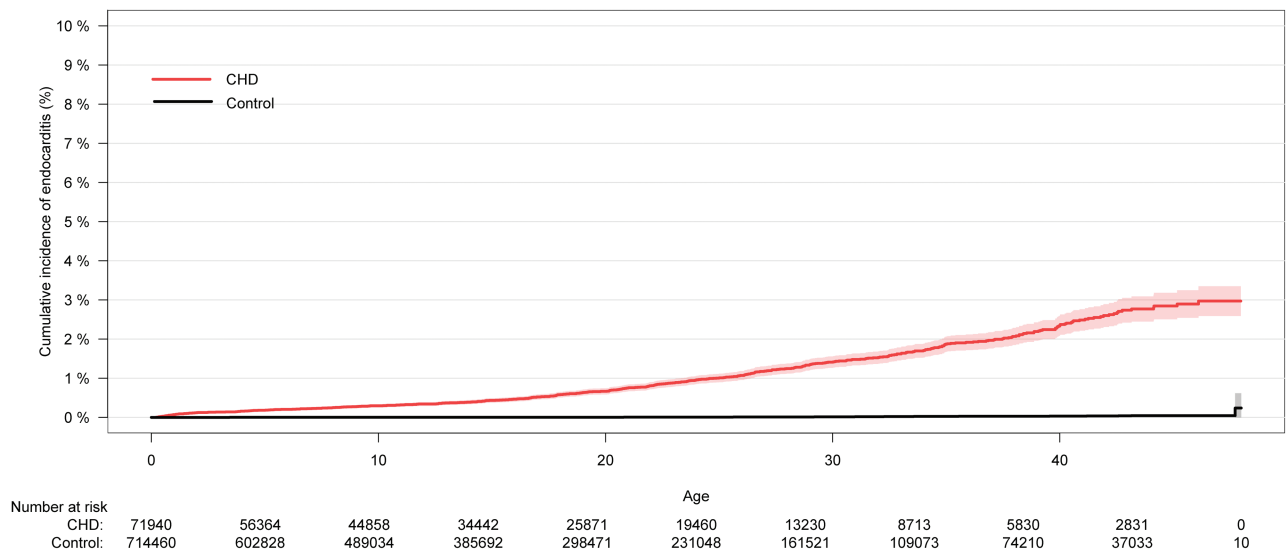


Figure 2. Cumulative incidence of infective endocarditis in patients with CHD and controls born 1970–2017. Shaded area shows 95% confidence interval. Abbreviation: CHD, congenital heart disease.

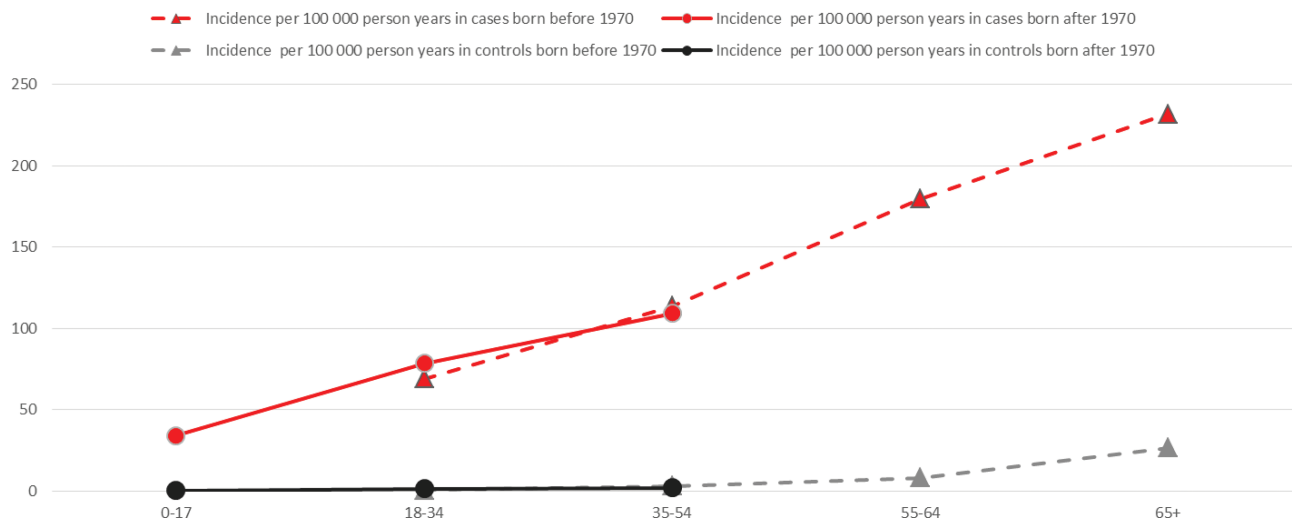


Figure 3. Incidence rate of infective endocarditis per 100 000 person-years in cases and controls stratified for age and birth period.

per 100 000 person-years) and the lowest in patients with atrial septal defect (27.8 per 100 000 person-years).

Bacterial Etiology

Bacterial etiology was only sporadically registered prior to 1997 when the ICD-10 was taken into use; to account for this, a subgroup analysis of IE as coded in the ICD-10 was undertaken. Hence, from 1997 onward, codes for bacterial etiology were registered in approximately half of IE cases (668/1321, 50.6%), with a lower proportion of bacteria coding among CHD IE cases compared with non-CHD IE cases (450/941, 47.8% vs 228/380, 60.0%, $P < .001$). Among CHD IE cases with an associated bacteria code, 195 (43.3%) and 134 (29.8%) were caused by streptococci and *Staphylococcus aureus*, compared with 59 (25.9%) and 109 (47.8%) in non-CHD IE patients ($P < .001$ for both comparisons) (Table 3). The frequency of codes for enterococci and miscellaneous bacteria was similar in both groups.

DISCUSSION

In this nationwide, registry-based case-control study, we found a high long-term risk of IE in patients with CHD, with 8.5% cumulative incidence at age 87 years compared with 0.7% in controls. IE was more common in patients with CHD in all

age groups and in all CHD lesion groups. These results verify the clinical impression that IE is an important complication in patients with CHD, which has been described previously [7, 8, 12]. However, our data are unique in that we compared the development of IE in patients with CHD to matched controls in a large, national, unselected population of patients with CHD over almost 9 decades. In a recent study from Denmark using nationwide registries to follow patients with IE, the cumulative incidence of IE after 10 years in patients with CHD was 1.3% during 1996–2015, which parallels our findings [18]. To describe the incidence of IE in the diverse group of CHD patients during their lifespan is important to evaluate evolving management strategies.

As expected, the incidence of IE was correlated with age among both patients with CHD and in the control population, and incidence increased according to age in both cohorts. The age-related relative increase in incidence was less pronounced in the CHD group, mirroring the prevalence of non-age-related risk factors present since birth. A striking finding was that by the age of 18 years, patients with CHD had a similar IE incidence as that of 81-year-old controls. Furthermore, by the age of 40 years, the IE incidence was more than 75 times higher in patients with CHD than in

Table 3. Bacterial Etiology in Infective Endocarditis (IE) Cases With Bacteria Code Registered 1997–2017

Bacteria	IE With Bacteria Code in Patients With CHD	IE With Bacteria Code in Controls	P value
	n = 450	n = 228	
Streptococci	195 (43.3)	59 (25.9)	<.001
<i>S. aureus</i>	134 (29.8)	109 (47.8)	<.001
Enterococci	25 (5.5)	15 (6.6)	.60
Miscellaneous	96 (10.2)	45 (11.8)	.67

Values are n (%), unless otherwise indicated.

Abbreviation: CHD, congenital heart disease.

controls; by the end of study, the risk was 12 times higher in patients with CHD up to age 87 years. IE is rarely seen in children and young adults without risk factors; although especially among children with complex congenital heart lesions, IE is not uncommon and poses a substantial threat. The incidence rate of 34 per 100 000 person-years in patients with CHD aged 1–17 years in our study is similar to the rate found by Rushani et al [19]. Despite this markedly elevated risk of IE in children and younger adults, most IE cases occurred in patients with CHD born before 1970. In the oldest age group, ≥ 65 years, nearly 7000 patients with CHD remained at risk for IE. This complication has not been studied extensively in this age group previously, albeit IE in older people has attracted substantial interest among patients without CHD [20–22].

The present study did not identify a change in IE risk related to birth year in patients with CHD. On the contrary, a similar incidence rate by age group was seen in CHD patients born before and after 1970, which was also the case in controls. If this is a correct finding remains unproven but to some extent the case-control design of the present study accounts for possible bias.

Nearly all studies of IE include more men than women [7, 23] although a few population-based studies have an even sex distribution [24, 25]. CHD, however, occurs in a similar proportion in male and female individuals but with variations between different types of cardiac lesions [26]. In our study, we identified a similar number of male and female patients with CHD, but male patients constituted two-thirds of IE cases. The reason for this uneven sex distribution in IE is unclear, but the data are in accordance with other studies [13].

The bacterial etiology of endocarditis has changed in Western countries over the past decades with *S. aureus* now being the most commonly reported cause [11], usually presenting with an acute sepsis-like illness. However, among patients with predisposing cardiac conditions, this etiological switch has not been seen [6, 27]. In our cohort, bacterial etiology was not coded in ICD-8 and 9; however, in the subgroup analyses of IE episodes in the ICD-10, streptococcal etiology was more common in patients with CHD and IE, and *S. aureus* was more common in controls with IE. A significantly lower proportion of IE episodes among patients with CHD had a bacteria code, but our data did not allow for further exploration. Tentative explanations may be owing to construction of the Duke modified endocarditis criteria [28], where CHD, as an important risk factor for IE, is a minor criterion itself. Hence, there is greater likelihood that a CHD patient who has fever and suggestive echocardiographic findings will be diagnosed with IE, also in the absence of documented bacteremia, than will patients who do not have CHD. Additionally, patients with CHD who have bacteremia with streptococci, *S. aureus*, or enterococci will be diagnosed with IE, even in the absence of endocarditis lesions

visualized by echocardiography, corresponding to possible IE in the modified Duke criteria. This reflects the complex anatomy influencing the echocardiographic characteristics of patients with CHD. Vegetations and other findings considered typical echocardiographic features of IE can be more difficult to visualize in patients with CHD [29], and the need for specialized approaches to echocardiography in adults with CHD is well recognized [30].

Mortality during follow-up was higher among controls with IE than in patients who have CHD with IE; there are several possible reasons for this, mainly that controls were more than 20 years older when contracting IE compared with their counterparts with CHD. Age is a major determinant of outcome in IE, with twice the in-hospital mortality rate in patients above age 65 years [31]. Additional factors influencing mortality include the lower proportion of *S. aureus* in patients with CHD and IE.

Our study had several limitations. First, a major limitation is that this study is based only on administrative registry data, without the inclusion of clinical information. Misclassification of both CHD diagnoses and IE cannot be ruled out, but recent data from a Danish study indicate a positive predictive value of 80% of IE diagnosis in the Danish National Patient Registry [32]. Additionally, data extraction spans the ICD 8-10 and alterations in coding as well as definitions of IE may have affected the comparability of patients over time. To account for this bias, a sensitivity analysis on IE cases diagnosed from 2001 was performed. Another limitation is that bacterial etiology was registered only from 1997 onward; also, in this part of the cohort, bacteria codes were missing in half of patients. Finally, the Swedish NPR started in 1964, with full nationwide coverage from 1987, and the CDR began in 1961; patients with CHD who died prior to these years were not included in the study, creating an immortal time bias. IE occurring in cases or controls before the start of the NPR was not registered. However, most patients were born after 1970, and IE incidence was strongly correlated with age, which is why a major influence on cumulative incidence is unlikely.

CONCLUSION

In this registry-based nationwide case-control study, cumulative incidence of IE at age 87 years was 8.5% in patients with CHD compared with 0.7% in controls. The relative risk of IE in patients with CHD, compared with controls, was highest in children and young adults and we found a similar IE incidence in 18-year-old patients with CHD as in 81-year-old controls. However, because IE incidence was strongly correlated with age also among patients with CHD, most IE cases were seen in older patients with CHD. No change in IE incidence was detected in patients with CHD born before or after 1970. Streptococci was the most frequently registered bacterial etiology in patients

with CHD who had IE and *S. aureus* was more common in IE among controls.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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