Myocardial Infarction in Adults With Congenital Heart Disease

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We compared the incidence and 30-day mortality of myocardial infarction (MI) in adults with congenital heart disease (CHD) relative to the general population. This cohort study used nationwide population-based medical databases to identify individuals born before 1982 and diagnosed with CHD in Denmark between 1963 and 2012. Patients were followed for first-time MI using data from the Danish National Registry of Patients. For each subject with CHD, we identified 10 controls from the general population, matched by sex and birth year. A unique personal identifier enabled follow-up for migration, death, or MI. We computed cumulative incidences and hazard ratios (HR) adjusted for birth year and sex for MI and 30-day mortality after MI. We identified 10,501 CHD adults alive at 30 years. By 70 years of age, the cumulative incidence of MI was 10% versus 6.5% for controls. The overall HR of MI in subjects with CHD compared with controls was 2.0 (95% CI 1.7 to 2.3). The 30-day mortality was 18% for the 296 subjects with CHD experiencing an MI during follow-up. The overall HR comparing 30-day mortality after MI between subjects with CHD and controls was 1.4 (95% CI 1.0 to 1.8). The greatest mortality was observed in adults with severe CHD (HR 2.7 [95% CI 1.5 to 5.0]). In conclusion, the incidence of MI and the 30-day mortality after MI for severe CHD were increased in adults with CHD compared with the general population. Underlying mechanisms need to be clarified. **(Am J Cardiol 2017;120:2272–2277)**

There are inherent and nonmodifiable myocardial infarction (MI) risk factors related to congenital heart disease (CHD) pathophysiology and surgical treatment, such as abnormal congenital origin and course of the coronary arteries or necessary surgical management choices that may decrease coronary perfusion.[1] In addition to these examples, as the median age of the CHD population increases, potentially modifiable MI risk factors such as sedentary lifestyle and type 2 diabetes mellitus, which may be more frequent in individuals with CHD,[2,3] may interact with these nonmodifiable risk factors to further increase MI risk. Furthermore, several studies have also demonstrated impaired vascular function in the CHD population.[4,5] Despite the growth of the population of adults with CHD, there are very little data on the incidence and outcome of MI. The purpose of this study was to compare the incidence and 30-day mortality of MI in adults with CHD with that of the general population.

Methods

Our nationwide population-based cohort study was conducted in Denmark, with a current population of approximately 5.6 million individuals. We used 2 nationwide population-based medical databases to identify individuals diagnosed with CHD in Denmark between 1963 and 1974 (before 15 years of age) and from 1977 to 2012 (at any age). We included only CHD survivors alive at age 30 years. Subjects with CHD diagnosed between 1963 and 1974 were identified based on review of medical records in all Danish pediatric and medical departments.[6,7] The review was done in the years 1970 to 1974 and the diagnoses were later translated from the International Society of Cardiology (1970) classification to the International Classification of Diseases Tenth Revision (ICD-10).[8] CHD survivors diagnosed after 1977 were identified by use of the Danish National Registry of Patients (DNRP). The DNRP contains information on all hospital admissions in Denmark and includes subjects' civil registration numbers, dates of admission and discharge, surgical procedures, and up to 20 discharge diagnoses coded by physicians according to the ICD.[9,10] We used a previously described algorithm to exclude patients with invalid CHD or inaccurate coding in the DNRP.[11] CHD survivors were categorized according to complexity using a hierarchical algorithm based on the location of the provider issuing the diagnosis and the physiologic complexity. When a subject's CHD ICD codes were inconsistent across different providers, those issued

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See page 2277 for disclosure information.

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by 1 of the 4 academic medical centers in Denmark were selected in place of those issued by community hospitals. When there was inconsistency within an academic center, we selected the most complex diagnosis. The hierarchy of physiologic complexity included the following: univentricular > biventricular complex > biventricular simple (isolated or in combination: ventricular septal defect, atrial septal defect, and persistent ductus arteriosus, as well as isolated coarctation of the aorta) > biventricular without history of surgery or intervention. Since 1968, a unique 10-digit civil personal registration number has been assigned to all residents of Denmark. Civil personal registration numbers are used in all Danish registries, permitting unambiguous individual-level linkage of data from all sources used in this study. This provided us with virtually complete follow-up until death, emigration, or the outcome under study. The Civil Registration System also made it possible to identify a general population comparison cohort.[12] For each subject with CHD, we identified 10 population-comparison cohort members from the general population using the Civil Registration System, matched by sex and birth year. Matched controls were assigned an index date, corresponding to the date of CHD diagnosis of the respective CHD subjects. Subjects were followed during 1977 to 2012 for first-time MI using data from the DNRP. This registry allowed identification of persons with any in- or outpatient hospital contact involving MI. The positive predictive value of the MI diagnoses recorded in the DNRP is greater than 90%.[9] However, misclassification may be higher in subjects with CHD owing to abnormal baseline electrocardiograms and the potential for atypical presentation of MI. As a result, we conducted a sensitivity analysis where we restricted the outcome to MI diagnoses that (1) were followed, within 30 days, by coronary artery bypass graft surgery or percutaneous coronary intervention, or (2) had a length of stay of at least 7 days, or (3) were followed, within 30 days, by death because of MI. Cause of death was identified using the Cause of Death Registry. We identified dates of death using the Civil Registration System.[12] We identified the highest educational level attained by study subjects in data provided by Statistics Denmark.[13] Follow-up of subjects with CHD and comparison cohort members began at CHD diagnosis or index date, age 30 years, or January 1, 1977, whichever came later. Follow-up continued until death, emigration, MI, or end of study on January 1, 2013, whichever came first. We computed incidence rates of MI per 100,000 person-years according to age groups. We computed cumulative incidence curves for the CHD cohort and comparison cohort while taking account of the competing risk of death. Using Cox's proportional hazards regression, we computed hazard ratios (HR) to compare the risk of MI in subjects with CHD with that of the matched general population cohort. The regression analyses were adjusted for sex and birth year (model 1). Age was used as the underlying time scale. In an additional model, we adjusted for history of cancer, history of chronic obstructive pulmonary disease, and educational level (model 2). Analyses were done overall and in subgroups according to sex, year of birth, age at CHD diagnosis, CHD complexity, specific CHD diagnosis, and period of follow-up (1977 to 1999, 2000 to 2012). The overall analysis was repeated in a sensitivity analysis using more strict criteria of the MI outcome. The assumption of proportional hazards was graphically assessed and found to be valid. We computed Kaplan-Meier curves of mortality by time from MI diagnosis in days until 30 days after MI for subjects with CHD and comparison cohort members experiencing MI. The corresponding HRs, computed for subgroups according to CHD complexity, were adjusted for sex and the categories of birth year. Analyses were performed using the Stata 14 package (StataCorp LP, Ontario, TX). The study was approved by the Danish Data Protection Agency that protects the privacy of individuals whose data are recorded in Danish registries. No informed consent was required for this study.

Results

We identified 10,501 subjects with CHD (Table 1). The incidence rate of MI increased with age for both CHD subjects and comparison cohort members (Figure 1). By 70 years of age, the cumulative incidence of MI was 10% in subjects with CHD and 6.5% in controls (Figure 2). The risk of MI was elevated in the overall CHD cohort compared with the general population (model 1: HR 2.0, 95% CI 1.7 to 2.3;

Table 1
Characteristics of 10,501 congenital heart disease survivors born in Denmark from 1890 to 1982

Variable	CHD Cohort	General Population Cohort
All	10,501 (100%)	101,661 (100%)
Man	4,848 (46%)	46,638 (46%)
Birth Year		
1890–1939	1,348 (13%)	13,042 (13%)
1940–1959	2,581 (25%)	25,369 (25%)
1960–1982	6,572 (63%)	63,250 (62%)
Educational level*		
Basic	5,293 (50%)	47,309 (47%)
Medium	1,343 (13%)	14,278 (14%)
High	2,106 (20%)	24,229 (24%)
Missing	1,759 (17%)	15,845 (16%)
Cancer	202 (2%)	1,583 (2%)
Chronic obstructive pulmonary disease	199 (2%)	746 (1%)
Severity of CHD		
Mild (biventricular, no surgery)	4,645 (44%)	-
Moderate (biventricular, surgery)	2,163 (21%)	-
Severe	2,046 (19%)	-
Univentricular	61 (1%)	-
Not classified	1,586 (15%)	-
Age at CHD diagnosis (Years)		
0–10	4,392 (42%)	-
above 10	6,109 (58%)	-
Major CHD diagnoses		
Atrial septal defect	2,651 (25%)	-
Ventricular septal defect	2,362 (22%)	-
Persistent ductus arteriosus	881 (8%)	-
Coarctation of the aorta	731 (7%)	-
Tetralogy of Fallot	414 (4%)	-
Transposition of the great arteries	159 (2%)	-
Other	3,303 (31%)	-

* Basic: completion of primary education (7 to 10 years), Medium: vocational training (3 to 4 year programs completed after primary education) or high school (3 year secondary education known as gymnasium), High: University education, bachelor or master level.