Long-term outcomes after myocardial infarction in middle-aged and older patients with congenital heart disease—a nationwide study

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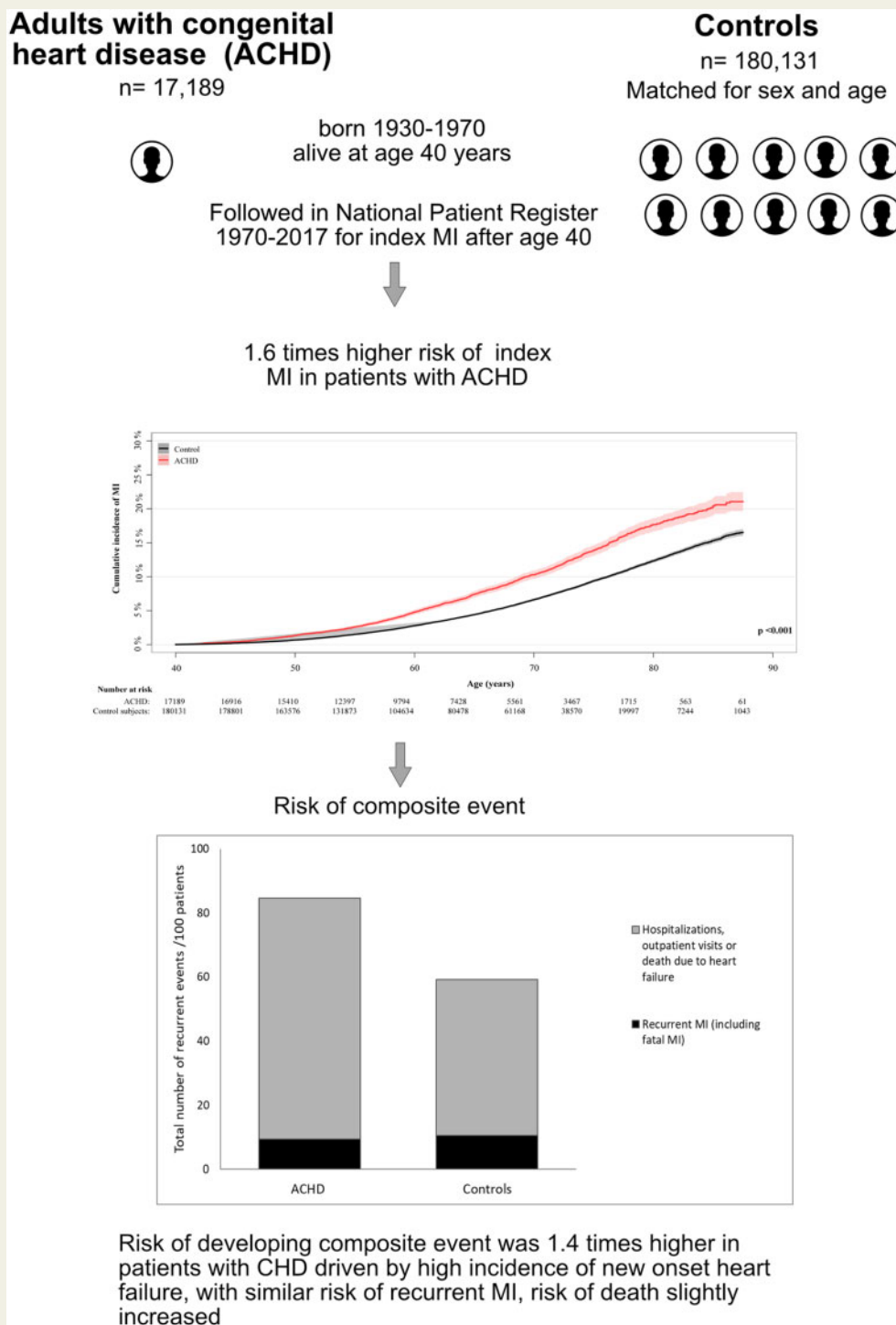|	
Aims	We aimed to describe the risk of myocardial infarction (MI) in middle-aged and older patients with congenital heart disease (ACHD) and to evaluate the long-term outcomes after index MI in patients with ACHD compared with controls.
Methods and results	A search of the Swedish National Patient Register identified 17 189 patients with ACHD (52.2% male) and 180 131 age- and sex-matched controls randomly selected from the general population who were born from 1930 to 1970 and were alive at 40 years of age; all followed up until December 2017 (mean follow-up 23.2 ± 11.0 years). Patients with ACHD had a 1.6-fold higher risk of MI compared with controls [hazard ratio (HR) 1.6, 95% confidence interval (CI) 1.5–1.7, $P < 0.001$] and the cumulative incidence of MI by 65 years of age was 7.4% in patients with ACHD vs. 4.4% in controls. Patients with ACHD had a 1.4-fold increased risk of experiencing a composite event after the index MI compared with controls (HR 1.4, 95% CI 1.3–1.6, $P < 0.001$), driven largely by the occurrence of new-onset heart failure in 42.2% ($n = 537$) of patients with ACHD vs. 29.5% ($n = 2526$) of controls.
Conclusion	Patients with ACHD had an increased risk of developing MI and of recurrent MI, new-onset heart failure, or death after the index MI, compared with controls, mainly because of a higher incidence of newly diagnosed heart failure in patients with ACHD. Recognizing and managing the modifiable cardiovascular risk factors should be of importance to reduce morbidity and mortality in patients with ACHD.

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Graphical Abstract

Adults with congenital heart disease (ACHD)
n= 17,189

Controls
n= 180,131
Matched for sex and age

born 1930-1970
alive at age 40 years

Followed in National Patient Register
1970-2017 for index MI after age 40

1.6 times higher risk of index MI in patients with ACHD

Risk of composite event

Risk of developing composite event was 1.4 times higher in patients with CHD driven by high incidence of new onset heart failure, with similar risk of recurrent MI, risk of death slightly increased

Introduction

Congenital heart disease is the most common major birth defect, with an incidence of approximately 1% in newborns.[1] Because of advances in surgical and medical management of patients with congenital heart disease in recent decades, a growing proportion of children with congenital heart disease survive into adulthood,[2,3] thus increasing the population of adults with congenital heart disease (ACHD).[4–6] These older patients will be prone to develop atherosclerotic disease and other age-related disorders such as coronary artery disease (CAD), heart failure, and ischaemic stroke.[7–11]

Patients with ACHD have been reported to have an increased risk of CAD and myocardial infarction (MI) compared with controls[7,10,12] and it is unclear whether patients with ACHD are at increased risk of adverse outcomes such as recurrent MI, heart failure, or death compared with other patients with CAD. This represents an important knowledge gap considering that CAD is one of the main predictors of mortality in the constantly growing group of older patients with ACHD.[6]

CAD is the most common cause of heart failure in patients without ACHD.[13] In contrast, heart failure in patients with ACHD is mostly attributed to complications related to structural abnormalities.[9] Given the increased risk of MI in patients with ACHD, knowledge about the long-term outcomes after MI in patients with ACHD is important for secondary prevention measures and healthcare planning in this patient group.

Therefore, the present study aimed to: (i) describe the risk of index MI in middle-aged and older patients with ACHD compared with controls and (ii) evaluate the long-term outcomes after index MI [risk of a composite event of either a recurrent MI, new-onset heart failure, or cardiovascular disease (CVD) mortality] in patients with ACHD compared with controls.

Methods

Data sources

The present study used data from the Swedish National Patient Register (NPR) and Cause of Death Register. The NPR was initiated in 1964, with full coverage since 1987, and reporting to the register is mandatory for all hospitals. Since 2001, the NPR has also recorded all diagnoses from hospital outpatient clinics. Primary and secondary diagnoses in the NPR are coded in accordance with the International Classification of Disease (ICD) system. The Cause of Death Register contains information on all deaths of Swedish citizens from 1961 onwards.

Study population

The NPR was searched to identify all patients with at least one ACHD diagnosis who were born from 1930–1970 and were alive at the age of 40 years. Patients who were alive at ≥40 years of age and were diagnosed with an ACHD for the first time in the Cause of Death Register were also included. Each patient with ACHD was sex- and age-matched with ∼10 controls from the Total Population Register who did not have an ACHD diagnosis. All personal identifiers were replaced by anonymized codes in the final dataset. Patients and controls were followed from January 1970 to December 2017. For administrative reasons, cause of death information was unavailable for 2017.

The index MI population comprised all patients with ACHD and controls with a first diagnosis of MI at ≥40 years of age. Patients who were diagnosed with MI before the age of 40 years were excluded (59 patients with ACHD, 162 controls), as were patients with a ventricular septal defect (VSD) diagnosed for the first time on the same date or within 3 months of the MI diagnosis (n = 96), as these patients were considered more likely to have post-MI VSD.

Within the index MI population, patients with recurrent MI, new-onset heart failure, or CVD death were then identified. Patients with ACHD and controls were compared regarding: (i) incidence of index MI and (ii) risk of a composite event after index MI (either a recurrent MI, or new-onset heart failure, or CVD death, whichever happened first).

Definitions

Supplementary material online, Table S1 lists the ACHD diagnoses in the ICD versions 8, 9, and 10. The ACHD diagnoses were grouped into six lesion groups according to a hierarchical classification system based on lesion severity, originally presented by Botto et al.,[14] modified by Liu et al.[15] The lesion groups, corresponding diagnoses, and ICD codes are shown in Supplementary material online, Table S2. The ICD codes for the outcomes and cardiovascular risk factors, as well as definitions of cardiovascular risk factors and procedures, are shown in Supplementary material online, Table S3.

Recurrent MI was defined as a second hospitalization or death due to MI in the NPR or Cause of Death Register occurring ≥2 months after index MI. New-onset heart failure was defined as a heart failure diagnosis that was identified for the first time during the same admission as the index MI or any time after the index MI (either hospitalization or outpatient clinic visit or fatal heart failure).

Statistical analysis

Categorical data are presented as numbers and percentages, while continuous data are presented as means and standard deviations or medians and interquartile ranges. Incidence rates are reported as the number of events per 10 000 person-years and calculated as the number of events divided by the total follow-up time of patients and controls. The statistical analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Index myocardial infarction

Cumulative incidence function according to the Fine–Gray method was used to calculate the cumulative incidences of index MI in patients with ACHD and controls. Death due to other causes than MI was the competing event.

Cox proportional hazard regression models were performed to obtain the hazard ratios (HRs) and 95% confidence intervals (CIs) for the index MI in patients with ACHD and controls. Time zero in the analyses was age 40 years. Data are presented as Model 1 (unadjusted) and Model 2 (adjusted for diabetes mellitus, hypertension, and hypercholesterolaemia). In the regression models, patients were censored at the end of the study (2017) or death from other cause than MI. Because of non-proportionality of some of the regression models, follow-up was divided into intervals of 0–15, 15–30, and >30 years. After stratification for comorbidities, all final Cox proportional regression models met the requirement of proportionality.

Long-term outcomes after index myocardial infarction

Long-term outcomes after index MI were analysed in patients who survived their index MI. Within the index MI population, Kaplan–Meier
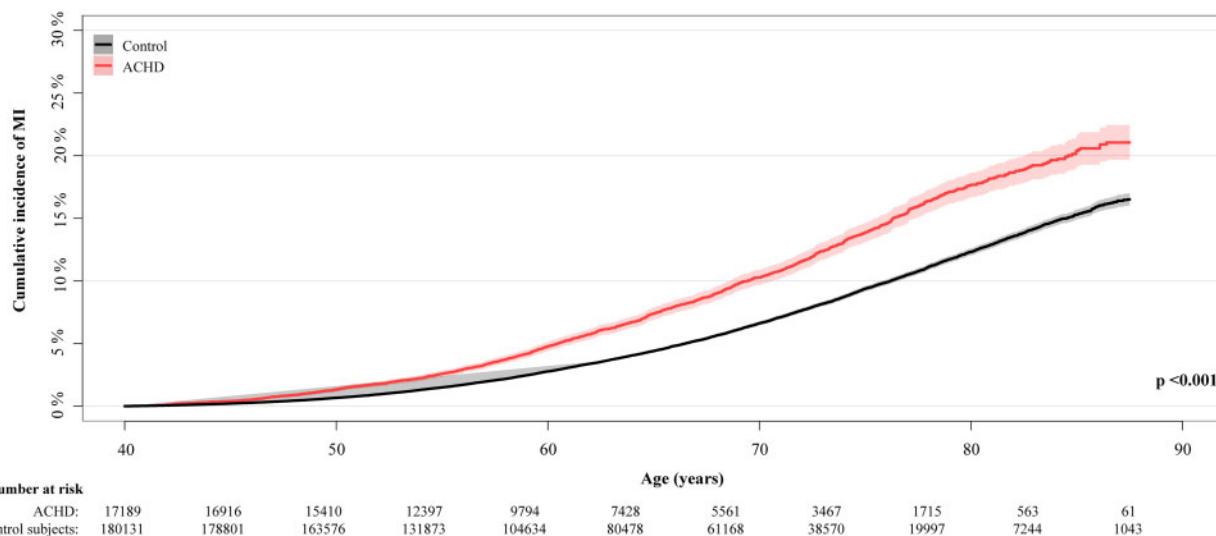
Figure 1 Cumulative incidence of index myocardial infarction in patients with congenital heart disease and controls ≥40 years of age. ACHD, adult congenital heart disease; MI, myocardial infarction.

survival analysis was performed to calculate the cumulative incidence of a composite event (either a recurrent MI, or new-onset heart failure, or CVD death, whichever happened first) in patients with ACHD and controls.

Cox proportional hazard regression models were performed to obtain the HRs and 95% CIs for the composite event after the index MI in patients with ACHD and controls. Data are presented as Model 1 (unadjusted) and Model 2 (adjusted for diabetes mellitus, hypertension, hypercholesterolaemia, and age at MI). The assumption of proportionality was tested and met the requirement of proportionality.

In the index MI population (for ACHD and controls), we also calculated the total number of recurrent events by adding the number of patients with one, two, three, or four episodes of recurrent MIs and heart failure-related hospitalizations and outpatients visits (including fatal MIs and heart failure), divided by total number of patients with index MI and multiplied by 100. The time frame was from index MI until the end of follow-up (2017).

Ethical approval

The study was approved by the regional ethics board in Gothenburg (Gbg 912-16, T 616-18) and complied with the Declaration of Helsinki. As retrospective and coded registry data were used, the need for patient consent was waived.

Results

Study population

The study cohort comprised 17 189 patients with ACHD (52.2% male) and 180 131 controls (52.3% male) (see Supplementary material online, *Table S4*). The mean follow-up duration was 23.2 ± 11.0 years in patients with ACHD and 23.4 ± 11.0 years in controls, comprising 387 368 person-years in the ACHD population and 4 147 183 person-years in controls.

Index myocardial infarction

Patients with ACHD had a 1.6-fold higher risk of MI compared with controls (HR 1.6, CI 1.5–1.7, $P < 0.001$). The cumulative incidence of MI by the age of 65 years was 7.4% in patients with ACHD vs. 4.4% in controls, and the cumulative incidence of MI up to 87 years of age in patients with ACHD was 21.1% compared with 16.5% of controls (*Figure 1*).

Patients with ACHD were slightly younger than controls at the time of index MI (*Table 1*). Only 48 patients with ACHD (3.2%) and 110 controls (1.1%) with index MI were identified in the outpatient register (*Table 1*). The risk of MI in patients with ACHD compared with controls was the highest in the first 0–15 years of follow-up and decreased across the three follow-up periods (0–15, 15–30, and >30 years), but differences in HR across the follow-up periods were only minor from a clinical perspective (Supplementary material online, *Table S5*).

Overall, similar numbers of patients with ACHD and controls were diagnosed with MI during the same admission or within a month after a cardiac surgical procedure (other than CABG/coronary intervention): 50 patients with ACHD (6.4%) and 105 controls (6.0%). Almost half of the patients with ACHD with MI ($n = 725$, 48.9%) had a known and registered ACHD diagnosis at the time of MI.

Patients with conotruncal defects had the highest incidence of MI (48.3 events/10 000 patient-years) while moderately lower or similar incidences of MI were observed in all other ACHD diagnoses including coarctation of the aorta. For all lesion groups, the hazard for MI was significantly higher among patients with ACHD compared with controls (*Table 2*).

Among patients with MI, the most common cardiovascular risk factor in both the ACHD population and controls was hypertension, which was present in 43.5% ($n = 646$) of patients with ACHD and 42.9% ($n = 4268$) of controls (*Table 1*). After adjustment for cardiovascular risk factors (hypertension, diabetes mellitus, hypercholesterolaemia), the risk of MI remained higher in patients with ACHD compared with controls (HR 1.4, CI 1.3–1.5, $P < 0.001$).

Table 1 Clinical characteristics of and myocardial infarction-related information on patients with adult congenital heart disease and controls who experienced an index myocardial infarction

	Patients with ACHD with MI	Controls with MI
Number	1484	9954
Number surviving index MI, n (%)	1272 (85.7)	8572 (86.1)
Male, n (%)	946 (63.7)	6944 (69.8)
Age at index MI in years, median (IQR)	61.8 (54.3–69.7)	63.5 (55.5–71.3)
Diabetes mellitus, n (%)	275 (18.5)	2026 (20.4)
Hypertension, n (%)	646 (43.5)	4268 (42.9)
Atrial fibrillation, n (%)	297 (20.0)	623 (6.3)
Hypercholesterolemia, n (%)	326 (22.0)	2310 (23.2)
Previous diagnosis of heart failure, n (%)	257 (17.3)	597 (6.0)
Previous CABG, n (%)	99 (6.7)	296 (3.0)
Previous PCI, n (%)	15 (1.0)	216 (2.2)
Previous coronary angiogram, n (%)	119 (8.0)	327 (3.3)
MI-related information		
Coronary angiogram, n (%)	450 (30.3)	3711 (37.3)
CABG, n (%)	178 (12.0)	955 (9.6)
PCI, n (%)	323 (21.8)	3437 (34.5)

ACHD, adult congenital heart disease; CABG, coronary artery bypass grafting; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2 Incidence rates and hazard ratios of index myocardial infarction in patients with congenital heart disease and controls in accordance with the six lesion groups

ACHD lesion group	Total number of patients, n (%)		Number of patients with MI, n (%)		Incidence of index MI (per 10 000 patient-years)		Hazard ratio (95% confidence interval)	
	ACHD	Controls	ACHD	Controls	ACHD	Controls	Model 1: unadjusted	Model 2: adjusted*
All lesion groups	17 189	180 131	1484 (8.6)	9954 (5.5)	38.3	24.0	1.6 (1.5–1.7)	1.4 (1.3–1.5)
Lesion Group 1[a]	738 (4.3)	9594 (5.3)	65 (8.8)	419 (4.4)	48.3	22.3	2.3 (1.8–3.0)	3.2 (2.4–4.2)
Lesion Group 2[b]	878 (5.1)	10 297 (5.7)	79 (9.0)	520 (5.1)	40.1	22.2	1.8 (1.5–2.3)	1.3 (1.1–1.7)
Lesion Group 3[c]	1204 (7.0)	12 738 (7.1)	97 (8.1)	592 (4.7)	40.0	21.7	2.0 (1.6–2.4)	1.5 (1.2–1.8)
Lesion Group 4[d]	2079 (12.1)	22 763 (12.6)	162 (7.8)	1181 (5.2)	37.5	23.6	1.7 (1.4–2.0)	1.4 (1.2–1.7)
Lesion Group 5[e]	6398 (37.2)	63 557 (35.3)	582 (9.1)	4052 (6.4)	36.1	25.5	1.4 (1.3–1.5)	1.2 (1.1–1.4)
Lesion Group 6[f]	5892 (34.3)	61 182 (34.0)	499 (8.5)	3190 (5.2)	39.8	23.5	1.8 (1.6–2.0)	1.4 (1.3–1.6)

ACHD, adult congenital heart disease; MI, myocardial infarction.
*Adjusted for diabetes mellitus, hypertension, hypercholesterolaemia.
[a]Lesion Group 1 was defined as conotruncal defects [common arterial trunk, transposition of the great arteries (unrepaired lesions and surgically repaired with either arterial switch, atrial switch, or Rastelli), double-outlet right ventricle, double-outlet left ventricle, congenitally corrected transposition/discordant atrioventricular and ventriculoatrial connection, tetralogy of Fallot, and aortopulmonary septal defect].
[b]Lesion Group 2 was defined as severe non-conotruncal defects (endocardial cushion defect/atrioventricular septal defect, common ventricle, and hypoplastic left heart syndrome). This group contains univentricular heart defects, unpalliated or palliated with a systemic-to pulmonary shunt, or a Fontan circulation.
[c]Lesion Group 3 was defined as coarctation of the aorta.
[d]Lesion Group 4 was defined as ventricular septal defect.
[e]Lesion Group 5 was defined as atrial septal defect.
[f]Lesion Group 6 was defined as all other heart and circulatory system anomalies that were not included in the other lesion groups.

Long-term outcomes after index myocardial infarction

A total of 1272 patients with ACHD (85.7%) and 8572 controls (86.1%) survived the index MI. The mean follow-up duration after index MI was 6.2 ± 6.5 years in patients with ACHD and 6.9 ± 7.1 years in controls.

The cumulative incidence of a composite event up to 2 and 10 years after the index MI was 31.1% and 54.2% in patients with ACHD

and 24.0% and 41.4% in controls, respectively. This was largely driven by 42.2% (*n* = 537) of patients with ACHD experiencing new-onset heart failure vs. 29.5% (*n* = 2526) of controls (*P* < 0.001), while recurrent MI was slightly more common among controls [9.6% (*n* = 820)] than patients with ACHD [8.5% (*n* = 108)] (*P* = 0.241). *Figure 2* shows a Kaplan-Meier curve of freedom from composite event after index MI in patients with ACHD and controls.

Patients with ACHD had a 1.4-fold higher risk of a composite event compared with controls (HR 1.4, CI 1.3–1.6, *P* < 0.001), and the increased risk in patients with ACHD persisted after adjustment for age at index MI, hypertension, diabetes mellitus, and hypercholesterolaemia (HR 1.5, CI 1.4–1.6, *P* < 0.001). Patients with conotruncal defects and coarctation of the aorta had the highest risk of a composite event relative to controls (*Table 3*).

ACHD was associated with a higher incidence of total events after index MI (total number of recurrent non-fatal/fatal MIs, heart failure-related hospitalizations, outpatient visits, and fatal heart failure in patients with new-onset heart failure) compared with controls (84.6 events/100 patients with ACHD vs. 59.2 events/100 controls; *Figure 3*, *P* < 0.001). ACHD was also associated with markedly more hospitalizations, outpatient visits for heart failure, and fatal heart failure events compared with controls (75.3/100 patients vs. 48.8/100 controls), while the incidence of recurrent MI was similar in both groups.

All-cause mortality after index MI was also slightly higher in patients with ACHD vs. controls (Supplementary material online, *Figure S1*); the cumulative incidence of all-cause mortality up to 38 years of follow-up after index MI was 90.8% in patients with ACHD and 89.4% in controls.

Take home figure summarizes the methods and the main findings of the study.

Discussion

The present study revealed that in comparison with controls, ACHD was associated with a higher risk of MI and a higher long-term risk of a composite event of either a recurrent MI, new-onset heart failure, or CVD death. The increased risk of any of these events in patients with ACHD was mainly explained by an increased risk of new-onset heart failure in patients with ACHD vs. controls.

Patients with ACHD have an increased risk of heart failure compared with controls,[16,17] related to complexity of lesion.[9] Our results indicate that patients with ACHD are also more prone to developing heart failure related to MI, possibly due to structural ACHD-related factors that predispose to heart failure, such as valvular disease and systemic right ventricles, univentricular circulation, injury of coronary arteries during surgical repair, or coronary anomalies. While MI in patients with ACHD may unmask previously undiagnosed heart failure, heart failure might also be over-diagnosed in patients with ACHD during admission for an MI (e.g. in patients with systemic right ventricles and univentricular circulation systems), as these patients habitually show a decreased ejection fraction.

The present study is the first to compare long-term outcomes after MI in patients with and without ACHD. Notably, there was no markedly increased risk of recurrent MI or all-cause death after index MI in patients with ACHD compared with controls. It is
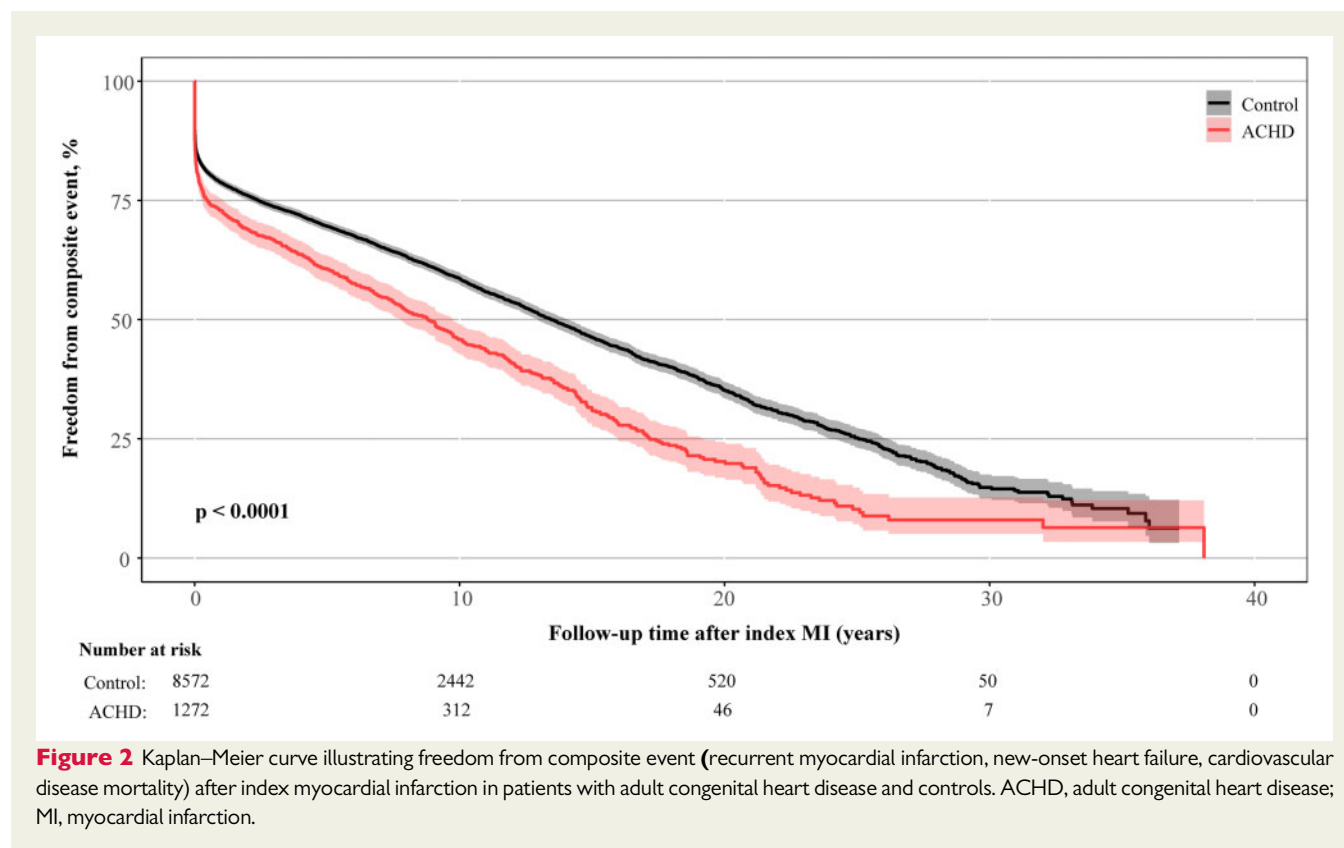

Figure 2 Kaplan–Meier curve illustrating freedom from composite event (recurrent myocardial infarction, new-onset heart failure, cardiovascular disease mortality) after index myocardial infarction in patients with adult congenital heart disease and controls. ACHD, adult congenital heart disease; MI, myocardial infarction.

Table 3 Risk of a composite event after the index myocardial infarction in patients with adult congenital heart disease compared with controls in accordance with the adult congenital heart disease lesion group

ACHD lesion group	Hazard ratio (95% confidence interval), model 1, unadjusted	Hazard ratio (95% confidence interval), model 2, adjusted*
All lesion groups	1.4 (1.3–1.6)	1.5 (1.4–1.6)
Lesion Group 1[a]	2.1 (1.5–3.1)	2.5 (1.7–3.7)
Lesion Group 2[b]	1.5 (1.1–2.1)	1.4 (1.0–2.0)
Lesion Group 3[c]	2.2 (1.7–3.1)	2.2 (1.6–3.0)
Lesion Group 4[d]	1.5 (1.2–1.9)	1.5 (1.2–1.9)
Lesion Group 5[e]	1.3 (1.2–1.5)	1.4 (1.2–1.6)
Lesion Group 6[f]	1.4 (1.2–1.6)	1.4 (1.2–1.6)

ACHD, adult congenital heart disease.

*Adjusted for age at myocardial infarction, hypertension, diabetes mellitus, and hypercholesterolaemia.

[a]Lesion Group 1 was defined as conotruncal defects [common arterial trunk, transposition of the great arteries (unrepaired lesions and surgically repaired with either arterial switch, atrial switch or Rastelli), double-outlet right ventricle, double-outlet left ventricle, congenitally corrected transposition/discordant atrioventricular and ventriculoatrial connection, tetralogy of Fallot, and aortopulmonary septal defect].

[b]Lesion Group 2 was defined as severe non-conotruncal defects (endocardial cushion defect/atrioventricular septal defect, common ventricle, and hypoplastic left heart syndrome). This group contains univentricular heart defects, unpalliated or palliated with a systemic-to pulmonary shunt or a Fontan circulation.

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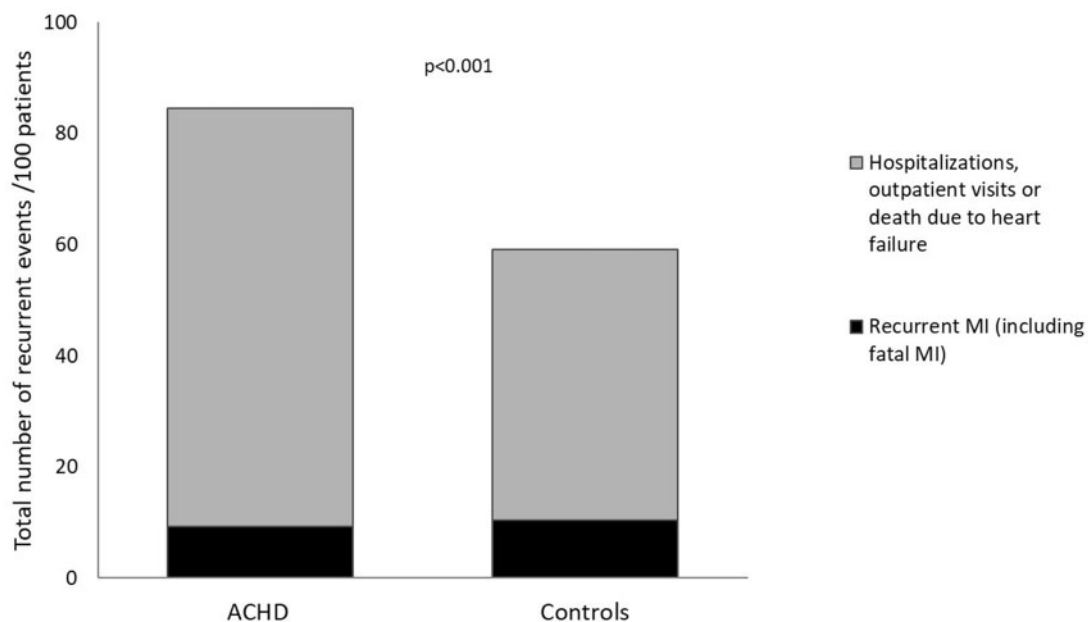

Figure 3 Total number of events after index myocardial infarction in patients with adult congenital heart disease and controls. Total number of events included all registered episodes of recurrent myocardial infarction (including fatal myocardial infarctions), hospitalizations or outpatient visits for heart failure, as well as fatal heart failure events in patients with new-onset heart failure. ACHD, adult congenital heart disease; MI, myocardial infarction.

possible that for middle-aged and older patients with ACHD who survive their index MI, having an ACHD lesion is less important than other factors regarding the risk of recurrent MI or all-cause mortality.

The mortality rates in conjunction with MI in the present study were higher than previously reported.[18] Our study included MI that took place before the era of percutaneous coronary intervention and highly sensitive troponins and included patients with MI identified in

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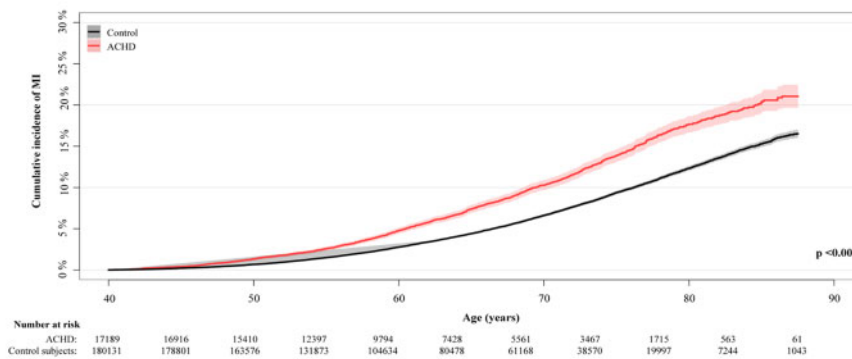Followed in National Patient Register
1970-2017 for index MI after age 40

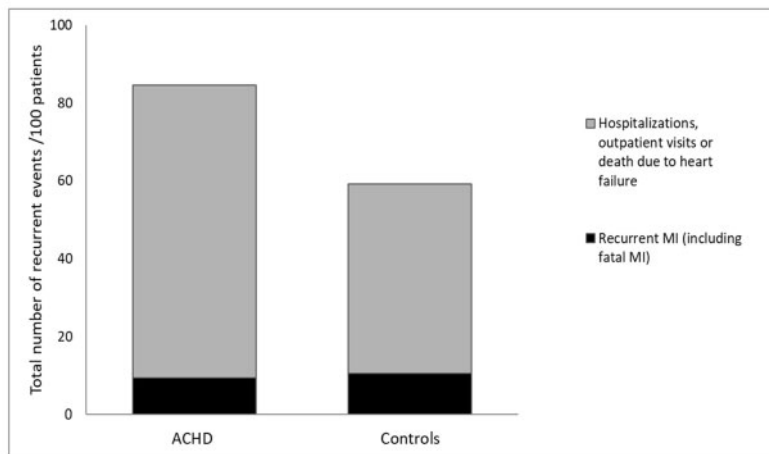1.6 times higher risk of index
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Risk of composite event

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Take home figure Long-term outcomes after myocardial infarction in middle-aged and older patients with congenital heart disease. ACHD, adult congenital heart disease; MI, myocardial infarction.

the death register as well as MI identified in outpatient clinics. We found that ~50% of the patients with an MI had a registered ACHD diagnosis at the time of their MI. This is most likely due to a significant number of the patients had not been hospitalized before their index MI, or the hospitalizations occurred before the year 1970 when the follow-up in the registers began. The outpatient register was initiated first in 2001.

In the present study, ~60% of patients with ACHD and 45% of controls experienced recurrent MI, new-onset heart failure, or CVD death during follow-up after index MI. Our findings are in line with a previous report of outcomes after MI in the general population where 20% of MI-survivors experienced a recurrent cardiovascular event in the first year and an additional 20% within the next 2 years.[19]

Our findings are consistent with other registry studies on the risk of MI or acute coronary syndrome (ACS) in patients with ACHD. Olsen et al.[7] found that the risk of MI in patients with ACHD who are older than 30 years is doubled compared with controls (HR 2.0, CI 1.7–2.3). Saha et al.[10] found that the risk of ACS and other cardiovascular endpoints in patients with lower-complexity ACHD is approximately twice as high as that of controls, after adjustment for cardiovascular risk factors. Whether an 'ACHD-related' factor[10] or traditional cardiovascular risk factors[20] is the most important for the development of CAD in patients with ACHD is not known.

The present study supports the hypothesis that 'ACHD-related' factors contribute to the increased risk of cardiovascular events in patients with ACHD, as the risk of MI in patients with ACHD remained higher than that in controls even after adjustments for diabetes mellitus, hypertension, and hypercholesterolaemia. Other studies have also reported that the risk of ischaemic heart disease and ACS is up to 16.5 times higher in young patients with ACHD than in controls.[11,12] Furthermore, the present study found that the relative risk of MI was highest in the youngest patients (follow-up period 0–15 years), suggesting that the 'ACHD-related' factor is more important in younger patients. The increased risk may be due to factors such as previous surgical treatments (manipulation of coronary arteries in the arterial switch procedure) and coronary anomalies.[21,22] Screening for modifiable cardiovascular risk factors in patients with ACHD should be considered, and good risk factor control is likely to be very important in order to further improve the long-term survival of patients with ACHD.

Strengths and limitations

The present study had several strengths. First, the nationwide coverage enabled the study of all patients with ACHD throughout Sweden born from 1930 to 1970, with a mean follow-up duration of ~23 years and minimal loss to follow-up by linkage between the NPR and the Cause of Death register. Our study is also the first to report long-term outcomes after MI in patients with ACHD, including risk of recurrent MI, new-onset heart failure, and CVD death. Second, the present study specifically evaluated the risk of MI in patients with ACHD, which is the most serious presentation of ischaemic heart disease other than sudden cardiac death. Third, the present study included patients with ACHD who were ≥40 years, which is the age when atherosclerotic disease starts to clinically manifest.

Our study also had several limitations. First, the ACHD and outcome diagnoses were based on ICD codes. As with all registry data, there is the potential for miscoding and misclassification of the diagnoses. Furthermore, as the 8th, 9th, and 10th versions of the ICD were used, there might have been inaccuracies in the translation of the ACHD diagnoses between versions. However, a previous study validated many of the diagnoses in the NPR, including MI.[23] We used a hierarchical classification system that classifies the ACHD diagnoses into six different lesion groups. However, there is a potential that the patients within each group are somewhat heterogeneous in the ACHD severity. Hence, we believe that there is scope for larger, more detailed datasets to be examined before we can draw firm conclusions on the more precise or isolated ACHD diagnoses. Second, as the follow-up started in 1970, we do not have reliable information on the incidence of MI and death in patients with ACHD before 1970, leading to an immortal time bias. Also, data on emigration were not available. Third, it was not possible to reliably establish how many patients underwent surgical procedures and how previous surgeries affected the risk of MI. Fourth, we did not have access to individual patient's medical records to ascertain the clinical details of the MI type and cardiovascular risk factors such as smoking, cholesterol, and physical activity levels. Furthermore, some cardiovascular risk factors (such as hypercholesterolaemia and hypertension) are not reliably registered in the NPR, as they are often treated in primary care only. However, to minimize the risk of missing potential cardiovascular risk factors, patients were considered to have hypertension, hypercholesterolaemia, and diabetes mellitus if the diagnoses were discovered before or within 1 year of the index MI. Nevertheless, adjusting for the risk factors did not differ significantly between the adjusted and unadjusted models. Fifth, since the patients had their MI between 1970 and 2017, a substantial proportion of patients were treated in the pre-interventional era when mortality after MI was higher compared to the current era. The total proportion of patients who underwent interventional treatment was therefore lower compared to present time. Finally, as primary care diagnoses are not reported to the NPR, a small proportion of patients with primarily mild ACHD lesions who never presented to a hospital may not have been identified in the NPR.

Conclusion

Compared with controls, patients with ACHD who were older than 40 years had a 1.6-fold increased risk of MI and this increased risk persisted after adjustment for cardiovascular risk factors. After index MI, patients with ACHD had a 1.4-fold higher risk of a composite event (recurrent MI, new-onset heart failure, or CVD death) and a greater number of total events after MI compared with controls, which were driven mainly by patients with ACHD experiencing markedly more heart failure-related hospitalizations, outpatient visits, and deaths due to heart failure compared with controls. The long-term risk of mortality was only slightly higher in patients with ACHD compared with controls. Recognizing and managing the modifiable cardiovascular risk factors should be of importance to reduce the morbidity and mortality in patients with ACHD.

Data availability statement

All relevant aggregated data underlying this article are available in the article and in its Supplementary material online.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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