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A National Population-based Study of Adults with Coronary Artery Disease and Coarctation of the Aorta

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Abstract

Adults with repaired coarctation of the aorta (CoA) suffer reduced long-term survival compared to the general population, in part due to coronary artery disease (CAD). There is conflicting evidence as to whether or not CoA is an independent risk factor for CAD. The primary aim was to determine if CoA is independently associated with premature myocardial infarction (MI) in the contemporary era. The secondary aim was to determine if CoA is independently associated with early coronary intervention. In a cross-sectional study using the National Inpatient Sample database from 2005–2014, we compared the age at MI and the age at coronary intervention (CABG or PCI, in the absence of MI diagnosis) in patients with and without CoA using weighted linear regression. Among 5,472,416 observations with a primary diagnosis of MI, 174 had a diagnosis of CoA. Patients with CoA had MI 7.2 years younger than those without CoA, after adjusting for potential confounders (95% CI –11.3, –3.1, $P = 0.001$). Among 3,631,718 patients without a diagnosis of MI who underwent CABG or PCI, 279 had a diagnosis of CoA. Patients with CoA who underwent coronary intervention were 15.6 years younger than those without CoA, after adjusting potential confounders (95% CI –18.3, –12.9, $P < 0.001$). In conclusion, patients with CoA have MI at a slightly younger age and undergo coronary intervention at a significantly younger age than those without CoA in the contemporary era. Our findings support continued close surveillance for and treatment of modifiable risk factors for CAD.

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Keywords

congenital heart disease; myocardial infarction; epidemiology

INTRODUCTION

Patients with coarctation of the aorta (CoA), a common form of congenital heart disease often repaired in early childhood, have reduced long-term survival relative to the general population.^{1,2} Coronary artery disease (CAD) has historically been reported as a common cause of premature death in these patients.^{3–6} However, a more recent study found that while the prevalence of CAD in patients with CoA was higher than in patients with ventricular septal defects, after adjusting for traditional risk factors, CoA was not independently associated with risk of CAD.⁷ It is not known if CoA is associated with premature myocardial infarction (MI) or coronary intervention in the contemporary surgical era in the United States. In addition, the associated morbidities of CoA patients who suffer MI or undergo coronary intervention and in-hospital mortality are unknown. We utilized the National Inpatient Sample (NIS) database, the largest all-payer inpatient database representing over 95% of the US population, to determine if CoA is independently associated with premature MI. Our secondary aim was to determine if CoA is independently associated with earlier coronary intervention [coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)] in the absence of acute MI.

METHODS

Methodology is adapted from our previously published study of stroke in adults with CoA.⁸ A cross-sectional study of patients 18 years of age included in the administrative NIS discharge database, provided by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality, was performed for the period 2005–2014. Each year of the NIS includes data from an estimated 35 million annual discharges.⁹ Our primary hypothesis was that patients with CoA are hospitalized with myocardial infarction at a younger age than patients without CoA. Our secondary hypothesis was that patients with CoA undergo coronary intervention, including CABG and PCI, at a younger age than the general population. Additional secondary outcomes included associated morbidities. Due to the use of publically available and anonymous data, the Boston Children's Hospital Institutional Review Board exempted the study and waived the requirement for informed consent.

CoA was defined by International Classification of Diseases, Ninth Revision (ICD-9) code 747.1.¹⁰ MI was defined by a primary diagnostic ICD-9 code of 410.x (excluding 410.x2, "subsequent episode of care").^{11,12} The positive predictive value of administrative codes for MI is 93%.¹² CABG was defined by a primary procedural ICD-9 code of 36.1, 36.2, or 36.3. PCI was defined by primary procedural ICD-9 code of 00.66, 17.55, or 36.0. Observations were excluded if there was a concomitant ICD-9 code indicating infective endocarditis (421.x), complex congenital heart disease (Supplementary Table 1), cardiac surgery other than CABG, or pregnancy as designated by HCUP. For the primary outcome

of MI, elective admissions were excluded. For the secondary outcome of coronary intervention, both elective and non-elective admissions were included and observations with a concomitant diagnosis of MI were excluded. If an observation had both a primary diagnosis of MI and underwent coronary intervention, it was included in the MI analysis only. Previously reported covariate ICD-9 definitions are shown in Supplementary Table 2.^{13–18} Median income quartiles based on ZIP code are provided by HCUP; the upper limit of quartile 1 is 150% of the federal poverty level. Per HCUP, race includes both race and ethnicity; in the case that the source data supplied both, ethnicity takes precedence over race.

To test our primary hypothesis, we compared the age at hospitalization with a primary diagnosis of MI in patients with and without a diagnosis of CoA using simple and multivariable weighted linear regression. Covariates included sex, race, atrial fibrillation or flutter, chronic kidney disease, diabetes mellitus, hyperlipidemia, hypertension, tobacco use, alcohol dependence or abuse, and median income by ZIP code. Sample weights were applied to patient-level discharge observations to generate a nationally representative estimate of US hospitalizations per recommendations from the Healthcare Cost and Utilization Project Methods Series.¹⁹ To account for a change in sampling frame in 2012, revised trend weights supplied by the Agency for Healthcare Research and Quality were used. Stata statistical software (version 14.2) svy commands were used to account for sample weights and clustering in the NIS survey design.

Interactions between CoA and hypertension and sex were assessed using interaction terms. In addition, a second model excluding hypertension was evaluated for both outcomes to determine if inclusion of hypertension, which may be an intermediary in the causal pathway from CoA to age at MI or coronary intervention, attenuated the effect of CoA on the outcome. Income was missing in 2.4% of observations and race in 15.9%, therefore, multiple imputation was used to impute the incomplete observations based on the values of all other covariates (Stata mi commands). Multinomial regression was used for both income and race, and 10 imputed datasets were created. Weighted linear regression models were run for each of the imputed datasets and combined to give the final results. Relationships between secondary outcomes and patient characteristics were assessed using logistic regression. For all analyses, the statistical significance level was set at 0.05 and hypothesis tests were 2-sided.

Codes for bicuspid aortic valve (BAV), which is present in over 50% of patients with CoA, have limited accuracy in administrative databases.^{20,21} It may be coded as either bicuspid aortic valve/congenital aortic insufficiency (746.4) or congenital aortic stenosis (746.3). To determine the impact of inclusion of observations with BAV on the association of CoA with age at MI and coronary intervention, we repeated analyses adjusting for the presence of these codes.

RESULTS

An estimated 5,472,416 patients were hospitalized with a primary diagnosis of myocardial infarction from 2005–2014. There were 174 patients with a secondary diagnosis of CoA.

Patient characteristics are summarized in Table 1. The only statistically significant difference between the two groups with respect to clinical comorbidities and sociodemographic characteristics was in the sex distribution. Twenty percent of patients with CoA were female versus 39.9% of patients without CoA ($P = 0.016$). Hyperlipidemia and hypertension were common comorbidities in both those with and without CoA, but the frequency did not differ between the two groups.

Patients with CoA were admitted with MI at a median age of 60 years (interquartile range (IQR) 50–71), compared to median age of 68 years (IQR 57–79) in those without CoA (Figure 1). After adjusting for potential confounders, CoA patients had MI 7.2 years younger than patients without CoA (95% CI –11.3, –3.1, Table 5). Stratification by the presence of hypertension or sex was not performed as the interaction terms did not reach statistical significance. In addition, inclusion of hypertension in the model did not significantly affect the estimate for CoA (Table 5). Only 8.8% of CoA patients and 0.06% of non-CoA patients had a diagnostic code for BAV or congenital aortic stenosis, which is significantly less than the established prevalence of BAV in CoA. When BAV was included in the model, there was no significant change in the association of CoA with age at MI (β –6.6, 95% CI –10.7, –2.4, $P = 0.002$).

An estimated 3,631,718 patients without a diagnosis of acute MI underwent CABG or PCI from 2005–2014. There were 279 patients with a diagnosis of CoA. Patient characteristics are summarized in Table 2. Hyperlipidemia was less common in patients with CoA (44.7%) compared to those without CoA (69.8%, $P < 0.001$). Hypertension was common in both groups (77.0% and 68.6% in those with and without CoA, respectively, $P = 0.17$). Most coronary interventions were percutaneous (70.6%) and there was no significant difference in the proportion of PCI versus CABG in those with and without CoA.

Patients with CoA underwent CABG or PCI at a median age of 53 years (IQR 35–60), compared to a median age of 66 years (IQR 57–74) in those without CoA (Figure 2). After adjusting for potential confounders, CoA patients underwent coronary intervention 15.6 years younger than patients without CoA (Table 3). As in the primary analysis, the interaction term for CoA and hypertension did not reach statistical significance. In addition, exclusion of hypertension from the model did not affect the beta estimate for CoA (Table 3). As in the analysis for the primary outcome of MI, BAV was more common in those with CoA (12.5% vs. 0.08%, $P < 0.001$) but less than the established prevalence. When BAV was included in the model, there was no significant change in the association of CoA with age at coronary intervention (β –15.1, 95% CI –17.8, –12.4, $P < 0.001$).

Among admissions for CABG or PCI, 45% were elective. In this elective intervention group, CoA patients underwent coronary intervention at an average age 20.0 years younger than those without CoA, after adjusting for potential confounders (β –20.0; 95% CI –22.5, –15.5; $P < 0.001$). Among non-elective admissions, CoA patients underwent coronary intervention at an average age 10.2 years younger than those without CoA, after adjusting for confounders (β –10.2; 95% CI –14.5 –5.9; $P < 0.001$).

DISCUSSION

In this nationally representative analysis of hospitalizations in the United States, we found that patients with CoA suffered MI at only a slightly younger age (7.2 years) and underwent coronary intervention at a significantly younger age (16 years) than those without CoA.

The younger age at MI in those with CoA may be due to increased risk of MI, potentially due to long-standing hypertension.²² However, alternative explanations exist. The age difference may be explained by overall decreased survival in patients with CoA, for a variety of reasons, and does not necessarily imply increased risk of MI. The life expectancy of patients with CoA has been reported to be 5–10 years shorter than the age- and sex-matched United Kingdom population.¹ Cerebrovascular disease, both ischemic and hemorrhagic, is also a significant contributor to early morbidity and mortality.^{1,8} Therefore, our results support, but do not definitively prove the hypothesis that there is an increased risk for premature MI in this population. This finding is consistent with the case-control study by Roifman et al., which found an increased prevalence of CAD in patients with CoA compared to those with ventricular septal defects; this difference was, however, entirely attributable to increased prevalence of traditional risk factors.⁷

Despite the relatively modest difference in age at MI, patients with CoA underwent coronary intervention in the absence of MI at a substantially younger age than those without CoA. This difference in age was most prominent in patients who underwent elective interventions. There are several possible explanations for these findings. First, patients with CoA may be subjected to closer surveillance and thus CAD may be detected and intervened upon sooner. Of note, it is unknown if intervening upon coronary disease identified by more aggressive screening is appropriate or provides clinical benefit, and practice patterns on coronary revascularization for asymptomatic patients have shifted. It is also possible that historical concern for increased risk of MI in patients with CoA may lead to more aggressive diagnostic testing and intervention when CAD is detected. While PCI has not been shown to decrease mortality or risk of MI in the general population with stable CAD, the impact of coronary intervention in patients with CoA remains unknown.^{23,24} Finally, patients with CoA develop hypertension at a young age and over 50% are hypertensive by middle-age even in the absence of restenosis.²² While inclusion of hypertension in the models of MI or coronary intervention did not significantly attenuate the effect of CoA on age at outcome, duration of hypertension and treatment-response may impact age at coronary artery disease, which could not be accounted for in our analyses. Further research is needed to understand the drivers of early age of coronary intervention and whether or not it reduces the risk of premature MI.

Many of the limitations of this study are intrinsic to the use of an administrative database. First, we do not have data on type or timing of CoA repair or the presence of residual aortic obstruction, factors which may contribute to development of premature CAD. Second, the interaction terms for hypertension and CoA were statistically insignificant in the models of both outcomes; however, power was limited to detect effect modification. Third, body mass index could not be ascertained given the poor predictive value of ICD-9 codes for obesity.²⁵ Fourth, it is likely that CoA is not routinely coded in all admitted patients with CoA

resulting in an underestimation of its prevalence, though this would not affect the estimates of age at MI or coronary intervention. Finally, information regarding medication use or duration of treatment for comorbidities, such as hypertension, was not available.

In conclusion, patients with CoA in the United States suffer MI at a slightly younger age and undergo coronary intervention at a significantly younger age than patients without CoA in the contemporary era. Further research is needed to determine the drivers of early intervention and its effects on premature morbidity and mortality in patients with CoA. In the interim, our findings support continued close surveillance for and treatment of modifiable risk factors for coronary artery disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Age at Myocardial Infarction and Coronary Intervention in Patients with and without Coarctation of the Aorta

Box-plot diagram showing age of myocardial infarction and coronary intervention [coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)] in those with and without coarctation of the aorta (CoA). The central line is the median and the box ranges from the 25th-75th percentile with bars encompassing 95% confidence interval. P-values are derived from univariate weighted linear regression. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; CoA = coarctation of the aorta.

Table 1.**Characteristics of Patients with Myocardial Infarction**

Variable	Coarctation of Aorta		P-value
	Yes (N = 174)	No (N = 5,472,242)	
Female	35 (20.0%)	1,798,033 (39.9%)	0.016
Atrial Fibrillation or Flutter	35 (22.9%)	778,722 (17.0%)	0.40
Chronic Kidney Disease	[†]	773,446 (16.5%)	0.10
Diabetes Mellitus	59 (37.0%)	1,677,262 (36.5%)	0.97
Hyperlipidemia	93 (61.7%)	2,573,525 (56.3%)	0.55
Hypertension	102 (69.6%)	3,220,471 (70.5%)	0.89
Tobacco Use	53 (36.0%)	1,612,868 (35.3%)	0.91
Alcohol Dependence or Abuse	[†]	128,512 (2.9%)	0.98
Race			0.76
White	116 (78.2%)	3,452,330 (76.5%)	
Black	[†]	449,506 (10.0%)	
Hispanic	14 (9.2%)	332,680 (7.4%)	
Asian or Pacific Islander	[†]	99,405 (2.2%)	
Native American	-	25,102 (0.6%)	
Other	-	138,394 (3.2%)	
Median Income by ZIP Code (Quartile)			0.69
1	46 (27.3%)	1,284,758 (28.5%)	
2	51 (35.8%)	1,189,017 (27.2%)	
3	20 (17.7%)	1,069,789 (24.0%)	
4	33 (19.2%)	953,854 (20.3%)	

Total numbers (N) are weighted estimates rounded to the nearest whole number.

Covariates are defined in Supplemental Table 2. There were no CoA patients of Native American or other race, denoted by “-”.

[†] Healthcare Cost and Utilization Project data use agreement prohibits reporting of fewer than 11 observations. CoA = coarctation of the aorta.

Table 2.

Characteristics of Patients with Coronary Intervention (PCI or CABG)

Variable	Coarctation of Aorta		P-value
	Yes (N = 279)	No (N = 3,631,439)	
Female	72 (32.4%)	1,206,827 (29.2%)	0.55
Atrial Fibrillation or Flutter	28 (14.7%)	564,515 (13.7%)	0.81
Chronic Kidney Disease	[†]	381,992 (3.4%)	0.12
Diabetes Mellitus	63 (39.3%)	1,495,004 (27.7%)	0.11
Hyperlipidemia	115 (44.7%)	2,631,265 (69.8%)	<0.001
Hypertension	172 (77.0%)	2,907,850 (68.6%)	0.17
Tobacco Use	67 (32.7%)	1,240,477 (25.6%)	0.24
Alcohol Dependence or Abuse	[†]	64,343 (3.5%)	0.32
			0.97
White	183 (72.9%)	2,980,624 (79.7%)	
Black	14 (5.5%)	275,009 (7.4%)	
Hispanic	54 (21.6%)	242,732 (6.5%)	
Asian or Pacific Islander	-	83,683 (2.3%)	
Native American	-	20,846 (0.6%)	
Other	-	132,748 (3.6%)	
Median Income by ZIP Code (Quartile)			0.93
1	68 (26.7%)	1,013,805 (24.4%)	
2	53 (26.9%)	980,533 (24.0%)	
3	95 (24.7%)	897,508 (39.4%)	
4	34 (21.7%)	843,796 (12.3%)	

Total numbers (N) are weighted estimates rounded to the nearest whole number.

Covariates are defined in Supplemental Table 2. There were no CoA patients of Asian or Pacific Islander, Native American, or other race, denoted by “-”.

[†] Healthcare Cost and Utilization Project data use agreement prohibits reporting of fewer than 11 observations.

CoA = coarctation of the aorta.

Table 3.

Multivariable Linear Models of Relationship between Coarctation of the Aorta and Age at Myocardial Infarction and Coronary Intervention with and without Hypertension

Primary Diagnosis	β for CoA (years)	95% CI	P-value
Myocardial Infarction			
Model 1	-7.1	-11.3, -3.0	0.001
Model 2	-7.2	-11.3, -3.1	0.001
Coronary Intervention			
Model 1	-15.6	-18.4, -12.9	<0.001
Model 2	-15.6	-18.3, -12.9	<0.001

Model 1: adjusted for sex, atrial fibrillation or flutter, chronic kidney disease, diabetes mellitus, hyperlipidemia, tobacco use, alcohol dependence or abuse, race, and income

Model 2: adjusted for all Model 1 variables and hypertension

CoA = coarctation of the aorta