Coronary artery disease in adults with anomalous aortic origin of a coronary artery

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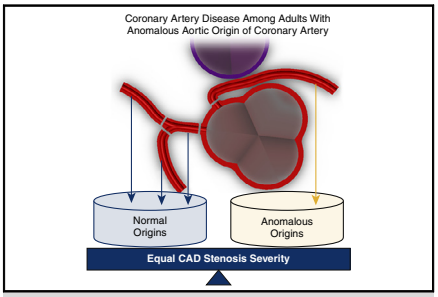
ABSTRACT

Objectives: This study sought to characterize coronary artery disease (CAD) among adults diagnosed with an anomalous aortic origin of a coronary artery (AAOCA). We hypothesized that coronaries with anomalous origins have more severe CAD stenosis than coronaries with normal origins.

Methods: This single-center study of 763 adults with AAOCA consisted of 620 patients from our cardiac catheterization database (1958-2009) and 273 patients from electronic medical records query (2010-2021). Within left main, anterior descending, circumflex, and right coronary arteries, the CAD stenosis severity, assessed by invasive or computer tomography angiography, was modeled with coronary-level variables (presence of an anomalous origin) and patient-level variables (age, sex, comorbidities, and which of the four coronaries was anomalous).

Results: Of the 763 patients, 472 (60%) had obstructive CAD, of whom, 142/472 (30%) had obstructive CAD only in the anomalous coronary. Multivariable modeling showed similar CAD stenosis severity between coronaries with anomalous versus normal origins ($P = .8$). Compared with AAOCA of other coronaries, the anomalous circumflex was diagnosed at older ages (59.7 $\pm$ 11.1 vs 54.3 $\pm$ 15.8 years, $P < .0001$) and was associated with increased stenosis in *all* coronaries (odds ratio, 2.7; 95% confidence interval, 2.2-3.4, $P < .0001$).

Conclusions: Among adults diagnosed with AAOCA, the anomalous origin did not appear to increase the severity of CAD within the anomalous coronary. In contrast to the circumflex, AAOCA of the other vessels may contribute a greater ischemic burden when they present symptomatically at younger ages with less CAD. Future research should investigate the interaction between AAOCA, CAD, and ischemic risk to guide interventions. (JTCVS Open 2022;10:205-21)



Atherosclerotic stenosis severity in coronaries among patients with AAOCA.

CENTRAL MESSAGE

Anomalous origin does not increase the atherosclerotic stenosis severity in the anomalous coronary. The anomalous circumflex artery is diagnosed in patients with greater stenosis in all coronaries.

PERSPECTIVE

Coronary artery disease is poorly characterized in patients with anomalous coronary arteries. Among 793 adults diagnosed with an anomalous aortic origin of a coronary artery, those with an anomalous circumflex presented later and with more stenosis, suggesting that coronary artery disease in other anomalous coronaries (right, left main, and anterior descending) causes symptoms at earlier stages.

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Abbreviations and Acronyms

AAOCA = anomalous aortic origin of a coronary artery
CABG = coronary artery bypass grafting
CAD = coronary artery disease
LAD = left anterior descending coronary artery
LCx = left circumflex
LMCA = left main coronary artery
RCA = right coronary artery

Anomalous aortic origin of a coronary artery (AAOCA) is a congenital malformation in which a coronary artery arises from the aorta other than the natural sinus of Valsalva.[1,2] Published literature about AAOCA has focused on young patients (<30 years of age) due to the malformation's association with ischemia and notoriety as the second leading cause of sudden cardiac death in athletes and military recruits.[3-5] Meanwhile, the significance of AAOCA in older patients, who typically present with cardiac symptoms such as chest pain and dyspnea, is unclear.[6] The presence of concomitant acquired cardiac pathologies obfuscate the cause of ischemia and optimal treatment. Furthermore, comorbid coronary artery disease (CAD) highlighted the possibility that AAOCA may increase the risk of CAD formation, as is seen with myocardial bridges.[7,8]

Literature exploring the relationship between AAOCA and CAD is limited to small cohort studies that yield conflicting results. While some publications found no association between AAOCA and CAD,[9,10] others showed an increased CAD within anomalous vessels.[11-14] Previous studies of adults with AAOCA also lacked anatomic details about the anomalous coronaries' proximal course type that may affect the pattern of CAD formation. The intramural course travels circumferentially within the wall of the aorta, and the interarterial course travels between the great arteries; both of these courses are associated with ischemia and sudden death.[1,15] In addition, the intraseptal course, traveling within the interventricular septum, is increasingly recognized as a potential cause of ischemia.[16] Hemodynamic changes due to ischemia-associated course types may also predispose the anomalous coronary to CAD formation.

Therefore, we sought to elucidate the association between AAOCA and CAD by characterizing patients with AAOCA who underwent invasive or computed tomography angiography. We hypothesized that among patients with AAOCA, anomalous-origin coronaries have more severe stenosis compared with the normal-origin coronary arteries. If true, patients with AAOCA may require more aggressive medical management of CAD risk or more frequent surveillance for surgical intervention.

METHODS

Patients

We confirmed the presence of AAOCA among 793 patients who had CAD characterization by invasive or computed tomography angiography at Cleveland Clinic from 2 data sources: (1) our cardiac catheterization database capturing data from 1958 to 2009, and (2) the electronic medical record identifying potential cases after 2010 (Figure E1). Cleveland Clinic's Institutional Review Board approved the use of these data for research, with patient consent waived (study number 17-1087, approved August 15, 2017). Our inclusion criteria for AAOCA included any adult (age ≥18 years) with an anomalous left main (LMCA), left anterior descending (LAD), left circumflex, (LCx), or right coronary artery (RCA) arising from an incorrect sinus of Valsalva or above the sinotubular junction. Similar to the Congenital Heart Surgeons' Society registry of patients with AAOCA, we excluded individuals with other hemodynamically significant congenital cardiac malformations that would have independently required surgical intervention.[5]

The diagnostic catheterization database comprises 118,167 patients, of whom 1323 (1.1%) had AAOCA. Most cases of AAOCA (750/1325, 53%), had missing values for the percent diameter stenosis in all 4 of the major coronaries (LMCA, LAD, LCx, or RCA). Although the missing values were likely due to the absence of any CAD, the uncertainly led us to omit coronaries with missing stenosis values, leaving 620 patients from the catheterization dataset for analysis. Because discrete coding of the coronary anatomy in the catheterization database stopped in 2009 and never included the proximal course description, we queried our electronic medical record and billing databases from January 2010 to March 2021 for diagnosis codes of "AAOCA" or "coronary malformation," yielding 888 potential cases (Figure E1). After reviewing the corresponding imaging and operative reports, we confirmed the presence of AAOCA in 275 patients, of whom 273 (99%) had imaging reports that specified the percent diameter stenosis.

Among our overall cohort of 793 patients, the majority were male (575/793, 73%), with an average age of 56.2 ± 14.2 years at the time of CAD imaging (Table E1). AAOCA was typically diagnosed on the most recent CAD imaging study, with a mean interval time between diagnosis and CAD imaging of zero years (85th percentile of 0.16 years). The most common anomalous coronary was the LCx (343/793, 43%), followed by the RCA (306/793, 39%), LMCA (108/793, 14%), LAD (27/793, 3%), and multiple coronaries (9/793, 1%) (Table 1). Stratification of baseline characteristic by the anomalous coronary indicated that the anomalous LCx was diagnosed at a later age (59.7 ± 11.1 vs 54.3 ± 15.8 years, $P < .0001$) (Table E2).

For the subcohort of 273 cases dated after 2010, detailed notes and imaging reports within the electronic medical record revealed how the patients presented for AAOCA diagnosis and allowed more complete anatomic characterization per the nomenclature set by the Congenital Heart Surgeons' Society.[5] Within this modern subcohort, 155 of 273 (57%) were male, with an average age of 52.5 ± 17.5 years (Table E3). Most were diagnosed after coronary imaging evaluation of cardiac symptoms (195/273,

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71%). Common presenting symptoms included chest pain (169/273, 62%) and dyspnea (181/273, 66%). The RCA was the most common anomalous coronary artery (162/273, 59%), followed by the LMCA (53/273, 19%), LCx (47/273,17%), LAD (7/273, 2.6%), and multiple (4/273, 1.5%) (Tables E4 and E5). A high proportion had detailed coronary morphology documented; 88 of 190 (46%) had a slit-like orifice, 150 of 233 (64%) had an interarterial course, 102 of 211 (48%) had an intramural course, and 33 of 196 (17%) had an intraseptal course.

Data Abstraction

Variables in the overall cohort were restricted to those available within the cardiac catheterization database: which coronary was anomalous, the severity of stenosis in each coronary, demographics, and comorbidities. However, the modern subcohort derived from manual review of electronic medical records captured additional details, including symptoms at presentation, the presence of a slit-like orifice, course types, and operative procedures. When adjudicating conflicting reports about coronary anatomy, we followed a hierarchy of truth, preferentially using available data from the operative note, then imaging report(s) in descending preference: computed tomography angiography, magnetic resonance imaging, cardiac catheterization, and echocardiography.

To characterize the severity of atherosclerotic CAD, we compiled the percent diameter stenosis in the LMCA, LAD, LCx, and RCA (Figure 1). Stenosis in the ramus and other branches such as the marginal, diagonal, and septal were omitted. CAD data were abstracted from the most recent imaging study before AAOCA repair or any coronary revascularization. Because the distribution of percent diameter stenosis was irregularly clustered (Figure E2), we could not analyze the stenosis as a continuous variable and instead categorized the stenosis severity in each coronary as an ordinal variable: 0% as none, 1% to 24% as minimal, 25% to 49% as mild, 50% to 69% as moderate, 70% to 99% as severe, and 100% as occluded.[17] Clinically significant, obstructive CAD was defined as ≥50% stenosis in the LMCA and ≥70% stenosis in all other coronary arteries.[18]

Statistics

Descriptive statistics used mean ± standard deviation for normally distributed data and median, with 15 and 85 percentiles, for continuous variables with non-normal distribution. Counts and frequencies describe categorical data. χ^2 testing evaluated associations between categorical variables such as which coronary was anomalous and location of obstructive CAD (none, only in the anomalous coronary, or within normal-origin coronaries). Post-hoc analyses compared each of the 3 subgroups of CAD location with the 2 other subgroups (independently and combined) using the Bonferroni correction for significance. Separate multivariable cumulative logistic regressions were performed, using the stenosis severity in each of the four coronaries as individual responses and as a combined patient-clustered response. Covariates were assigned at the coronary or patient level in this multilevel model.[19] First, at the coronary level, we categorized the origin as normal or anomalous. Next, at the patient level, covariates considered included age, sex, comorbidities (congestive heart failure, pulmonary disease, diabetes, peripheral artery disease, hypertension, and tobacco use). To account for how the anomalous origin affects the stenosis in the other normal-origin coronaries within a patient, we also included which of the 4 coronaries was anomalous at the patient level. In the secondary analysis with the modern subcohort, we also considered among the coronary-level variables the presence of a slit-like orifice, intramural course, interarterial course, and intraseptal course. Multivariate imputation by chained equations for missing data and bootstrap aggregation for variable selection were employed.[20,21] Statistical analyses were conducted in SAS 9.4 (SAS Institute, Inc).

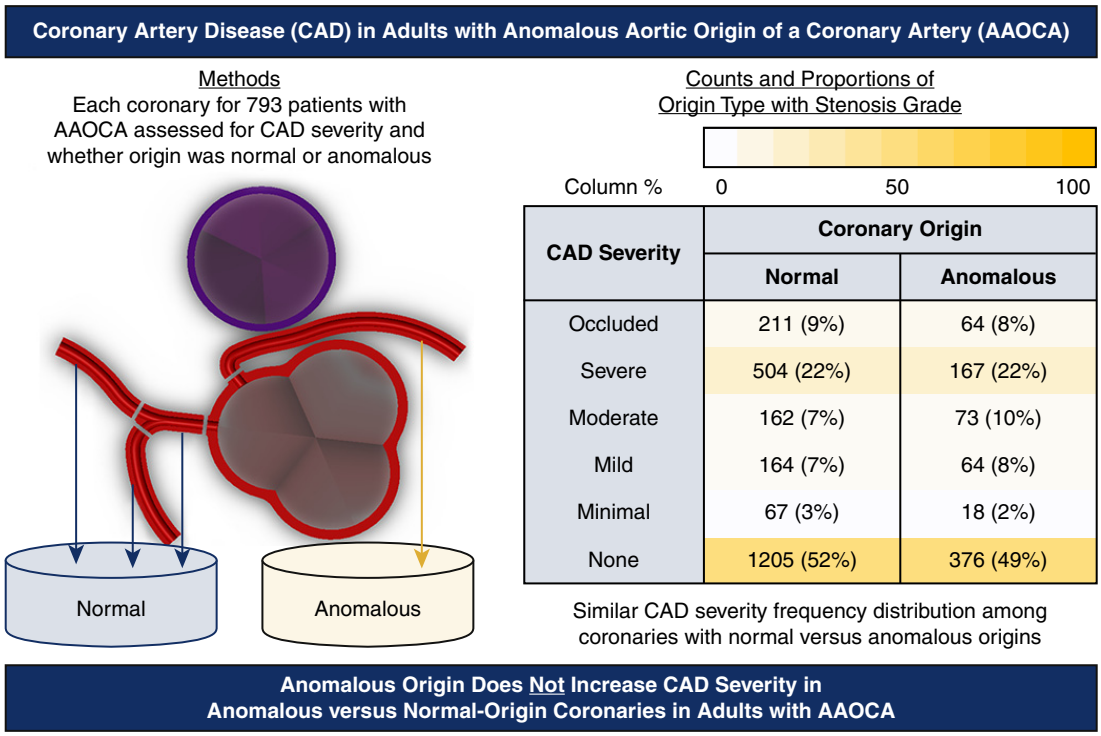

FIGURE 1. Coronary stenosis severity in patients with anomalous aortic origin of a coronary artery (*AAOCA*). Among 793 adults with an AAOCA, the maximum severity of coronary artery disease (*CAD*) stenosis was characterized for the left main, anterior descending, circumflex, and right coronary arteries. The heatmap depicts the proportions of anomalous and normal-origins coronaries with each stenosis severity. The stenosis in coronary arteries with normal origins was similar to those with anomalous origins after adjusting for age, sex, and comorbidities.

TABLE 1. Frequency of anomalous coronary in overall cohort stratified by presence and location of obstructive CAD

Anomalous coronary	All (N = 793) n (%)	Absent CAD (N = 321) n (%)	Only anomalous coronary with CAD (N = 142) n (%)	Normal-origin coronary with CAD (N = 330) n (%)
LMCA	108 (14)	61 (19)	20 (14)	27 (8.2)
LAD	27 (3.4)	9 (2.8)	2 (1.4)	16 (4.8)
LCx	343 (43)	57 (18)	77 (54)	209 (63)
RCA	306 (39)	188 (59)	41 (29)	77 (23)
Multiple	9 (1.1)	6 (1.9)	2 (1.7)	1 (0.3)

The presence of obstructive coronary artery disease (*CAD*) was defined as obstructive lesions with >50% stenosis in the left main coronary artery (*LMCA*) or >70% stenosis in the right coronary artery (*RCA*), left anterior descending (*LAD*), or left circumflex (*LCx*) coronary artery. The frequencies of patients with AAOCA affecting each of the 4 or multiple coronaries were stratified based on the presence and location of any CAD. Patients with obstructive CAD only in the anomalous coronary were compared with those without any CAD and those with CAD in normal-origin vessels. The results of a χ^2 test found a difference in the presence and location of CAD among AAOCA based on which coronary was anomalous ($P < .0001$). *AAOCA*, Anomalous aortic origin of a coronary artery.

RESULTS

Presence and Location of Obstructive CAD

Most patients had obstructive CAD in at least one coronary (472/793, 60%), of whom 142 of 472 (30%) had CAD only in the anomalous coronary (Table 1). The remainder of patients with CAD had coronary atherosclerosis in coronaries with normal origins, with or without concomitant disease in the anomalous coronary. Compared with those without CAD, the subgroup with obstructive CAD was older (60.3 ± 10.5 vs 51.3 ± 16.9 years, $P < .0001$), had more men (391/472, 83% vs 184/321, 57%, $P < .0001$), more anomalous LCx cases (286/427, 61% vs 57/321, 18%, $P < .0001$), fewer anomalous LMCA (47/427, 10% vs 61/321, 19%, $P = .0003$), and fewer anomalous RCA cases 118/427, 25% versus 188/321, 59%, $P < .0001$). No associations were found when we compared the coronary anatomy or baseline characteristics between those with CAD located only within the anomalous coronary and the two other subgroups (Table 1 and Table E1).

CAD Severity in Coronaries With Normal Versus Anomalous Origin

Among the 4 major coronaries in the 739 patients with AAOCA, 3075 had the severity of CAD graded. Of these assessed coronaries, the CAD was occluding in 275 (49%), severe in 671 (22%), moderate in 235 (8%), mild in 228 (7%), minimal in 85 (3%), and completely free in 1581 (51%). The distribution of CAD severity was similar between coronaries with anomalous origins and those without (Figure 1).

Multivariable modeling also showed no association between the presence of an anomalous origin and CAD stenosis severity in the corresponding coronary ($P = .8$). Meanwhile, older age ($P < .0001$), male sex ($P < .0001$), and various comorbidities were associated with increased stenosis within the 4 coronaries (as a patient-clustered response) (Table E6). Another patient-level response associated with increased CAD in all coronaries was the presence of an anomalous LCx ($P < .0001$). Similar associations were seen with the CAD severity when each of the four coronaries was analyzed as separate response variables (Tables E7-E10). The corresponding odds ratio for increased likelihood of greater CAD severity in all coronaries (as a patient-clustered response) was 2.7 (95% confidence interval, 2.2-3.4) (Table 2). Male sex had a similar odds ratio of 2.5 (95% confidence interval, 1.9-3.2).

Subcohort Analysis

Analyses were conducted separately using the modern subcohort of 273 patients, in which only 31 (13%) had obstructive CAD (Table E3). When CAD was present, it

TABLE 2. Odds ratio of each coronary having more severe stenosis based on the location of the anomalous coronary in the overall cohort

Stenosis severity in:	Age*	Male	Anomalous LMCA	Anomalous LAD	Anomalous LCx	Anomalous RCA
Overall (clustered)	↑	2.5 (1.9-3.2)			2.7 (2.2-3.4)	
RCA	↑	2.5 (1.8-3.4)			2.0 (1.4-3.0)	
LMCA	↑	1.6 (1.2-2.2)		†	†	
LAD	↑	3.3 (2.4-4.6)			4.5 (3.3-6.0)	
LCx	↑	2.6 (2.0-3.4)			2.1 (1.6-2.7)	

Odds ratios and 95% confidence intervals are shown for statistically significant correlations in multivariable modeling that adjusted for age, sex, comorbidities, and which coronary was anomalous. Blank cells indicate no statistical association. *LMCA*, Left main coronary artery; *LAD*, left anterior descending coronary artery; *LCx*, left circumflex; *RCA*, right coronary artery. *In all coronaries, the stenosis severity increased with age, which was modeled with nonlinear transform specified in Tables E6-E10. †The LMCA does not exist when the LAD or LCx is anomalous.

was isolated to only the anomalous coronary in 19 of 31 (61%). On univariable analyses, the presence of CAD was not associated with the anatomic features of AAOCA, including which coronary was anomalous ($P = .19$) and course type: intramural ($P = .34$), interarterial ($P = .39$), and intraseptal ($P = .38$) (Table E5). Meanwhile, the presence of an anomalous LCx was associated with absences of the intramural course, interarterial, and intraseptal course ($P < .0001$) (Table E5).

The multivariable mixed-effect model of the modern subcohort also found similar results as that of the total cohort (Table E11). CAD severity increased with increased age, male sex, and the presence of an anomalous LCx ($P = .0005$, $P < .0001$, and $P = .006$, respectively). However, at the coronary level, the presence of an anomalous origin was not associated with a change in CAD stenosis severity within the specific coronary artery ($P = .3$). Also, no association was seen with comorbidities, orifice shape, or course-types: intramural ($P = .4$), interarterial ($P = .8$), and intraseptal ($P = .6$).

AAOCA Repair and Outcomes

The majority of patients with AAOCA in the modern subcohort underwent some cardiac surgery (134/273, 52%), of which 92 of 134 (69%) involved the anomalous coronary (Table E12). A small proportion of AAOCA operations (11/134, 8%) were performed at outside hospitals before the patient was evaluated at our center. Unroofing of an intramural course was most common (64/92, 70%) and preferred in the absence of obstructive CAD, which was present in only 5 of 92 (5%) of patients who underwent AAOCA repair. Reimplantation was used in cases in which there was a very short (or no) intramural course (8/92, 8.7%). Coronary artery bypass grafting (CABG) was used in specific cases (16/92, 17%), such as when there was significant CAD stenosis within the anomalous coronary or for the intraseptal course before the introduction of the Najm transconal unroofing procedure.[22] A third of AAOCA repairs (34/92, 37%) underwent concomitant cardiac surgical procedures (CABG to a normal-origin coronary, aortic root valve surgery, and or aortic root surgery). Percutaneous interventions were never used to directly address the anomalous origin but were used to revascularize some coronaries with obstructive CAD.

Postoperative complications were rare and insufficient to determine associations with CAD. There were no deaths. One patient arrived in cardiogenic shock and required emergency off-pump CABG and postoperative extracorporeal membrane oxygenation support. After stabilization, the patient underwent elective AAOCA unroofing and survived. Another patient required reoperation, in which the initial saphenous vein bypass graft to an anomalous right coronary (without CAD stenosis) at an outside hospital failed after a year and required coronary reimplantation. Three other patients required reoperations for cardiac pathologies other than AAOCA.

DISCUSSION

Prevalence of CAD in Patients Diagnosed With AAOCA

The rate of obstructive CAD (60% of the overall cohort) is slightly greater than that in multi-institutional elective angiography registries in which the median is 45% with an interquartile range of 39% to 52%.[23] The similar anatomic and baseline characteristics between patients with CAD in only the anomalous coronary and patients with CAD in normal-origin coronaries, AAOCA was typically diagnosed incidentally due to ischemic symptoms from CAD leading to coronary imaging. Interestingly, our modern subcohort showed a much lower prevalence of obstructive CAD at 13%, which may be due to a referral bias for second opinions or surgical management of AAOCA with a lower burden of CAD. The decrease in CAD severity in the modern subcohort may be attributable to increased statin use and reduced tobacco use, though these associations were not directly explored in our analyses.[24] The decrease in male predominance within the newer era also highlights the increased recognition and diagnosis of cardiovascular disease within women, a population with less frequent obstructive CAD and more microvascular disease.[25]

Association Between AAOCA and CAD

Our study, which is the largest single-center study on adult patients with AAOCA, demonstrates that the anomalous origin does not increase the stenosis severity of CAD in the anomalous vessel itself. However, the anomalous LCx was associated with increased stenosis in not only the LCx itself but all the other coronaries. Similarly, a study of 34 AAOCA cases by Eid and colleagues9 found no increase in coronary stenosis in anomalous coronaries overall, and, when present, CAD tended to be in the anomalous LCx. Suryanarayana and colleagues[10] also found no difference in the prevalence of CAD in anomalous vessels as compared with normal-origin coronaries of 147 patients with AAOCA. In contrast, studies by Click and colleagues[13] and Samarendra and colleagues[14] found increased CAD stenosis in the anomalous coronaries, but this was typically limited to the anomalous LCx. Meanwhile, Çanga colleagues[26] found mixed results for 98 patients with AAOCA among whom there was less CAD in the anomalous LAD but similar CAD risk in the anomalous LCx and RCA. These conflicting findings may be attributed to the limited sample sizes and heterogeneity of the anomalous coronary definition. Before recommending for or against more intensive medical management or surveillance for CAD, in patients with AAOCA compared with the general population, investigations with more sensitive modalities such as

intravascular ultrasound are needed (when previous invasive and computed tomography angiography studies failed to consistently show increased CAD in the anomalous coronary).[27]

A strength of our study includes the implementation of sophisticated multivariable models that adjusted for both the patient-level and individual coronary-level relationships, as we posited that an anomalous coronary origin may change the flow distributions among the remaining coronary arteries as well. This led to our unexpected finding that the anomalous LCx was associated with increased severity of CAD in all coronaries of that patient. Significant covariates in our model known to increase the risk of CAD included male sex, older age, diabetes, peripheral artery disease, and tobacco use. Patients with congestive heart failure or pulmonary disease were less likely to have CAD, presumably due to coronary imaging for symptoms due to the comorbid condition before significant CAD developed. Hypertension had an unexpected negative association with CAD, possibly due to the association with antihypertensive therapy (not collected in our study). These comorbidities were not strongly associated with CAD in the modern subcohort likely due to the decreased comorbidity frequency and smaller sample size. Similarly, the lack of association between CAD stenosis and other anatomic details (ie, the interarterial and intramural courses) may be a type II error. The complexity of the statistical model precluded a precise power calculation, but the positive association found for CAD severity with sex, age, and the presence of an anomalous LCx, in both the total cohort and the modern subcohort, suggests that the statistical power was sufficient.

We speculate that the increased CAD severity in the presence of an anomalous LCx may be attributable to two possible mechanisms. First, the anomalous LCx may not only alter the hemodynamics downstream in the LCx but also the flow distribution to the remaining coronaries. By taking a retroaortic course, the LCx may have a longer and tortuous path, promoting greater CAD development within the LCx itself.[13] If the anomalous LCx is smaller, the other coronaries may compensate with increased flow velocity, potentially increasing the shear forces and likelihood of developing CAD. Second, the anomalous LCx may simply represent a more benign variant, such that a greater degree of stenosis or occlusion (either within the LCx itself or the other coronaries) is necessary before the patient becomes symptomatic, prompting coronary imaging. Furthermore, the LCx never had an interarterial and intramural course, 2 risk factors for ischemia that existed for the RCA and LMCA and would likely warrant surgical repair (Table E1).[15,28] Therefore, the diagnosis of non-LCx coronaries may have resulted from the presence of greater-risk AAOCA variants causing ischemia in coronaries that lack significant CAD.

Surgical Management of CAD in AAOCA

Various surgical approaches exist to restore the physiologic coronary anatomy for patients with AAOCA.[1] We generally use the same criteria for surgical revascularization in concomitant stable CAD as for normal-origin coronaries.[18] Specifically, we do not lower the CAD stenosis threshold for the anomalous coronary, because the dynamic effect of the anomalous origin or course type restricting coronary perfusion generally only occurs during exercise. At rest, the coronary perfusion is presumed to be similar to coronaries with normal origins and carries a similar risk of graft failure in the absence of critical stenosis unless the proximal segment of the anomalous coronary is ligated (which was performed in 2 cases).[1,6]

Knowledge about the outcomes of AAOCA operations in the setting of concomitant CAD has been limited, since the largest registry of patients with AAOCA, led by Congenital Heart Surgeons' Society, is limited to those diagnosed before 30 years of age.[29] Other single-institution studies of AAOCA surgeries had few older adults or excluded patients with concomitant CAD in the anomalous coronary.[30,31] Although AAOCA surgeries have favorable mortality up to 10-year follow-up, some have wondered if sympathetic denervation from coronary reimplantation may decrease vasoreactivity and thereby accelerate CAD progression.[29,32,33] Longer follow-up over decades is needed to characterize CAD progression after AAOCA surgery.

Limitations

We only compared the CAD within patients diagnosed with AAOCA and lacked propensity-matched patients without AAOCA as true controls. Although we adjusted for confounding variables, our single-center cohort likely has a surgical referral bias. Without longitudinal coronary imaging and objective measures of provocative ischemia, our conclusions presumed that the indication for imaging that diagnosed AAOCA was based on similar levels of ischemia for the anomalous coronaries. Uncertainty about the exact etiology of symptoms or ischemia risk prevented us from determining the exact primary indication for cardiac surgery when concomitant procedures were performed in this retrospective study. Finally, the stenosis data were largely based on angiography, and we only characterized the most severe stenosis in the four major coronary arteries, omitting CAD in distal branches, cumulative effects of smaller stenosis, and microvascular dysfunction. More accurate quantification of ischemia severity with advanced techniques, such as intravascular ultrasound and dobutamine-stress instantaneous wave-free ratio studies are the subject of future work by our group.[34,35]

CONCLUSIONS

In summary, both symptoms of CAD and significant CAD are common among adults diagnosed with AAOCA,

and CAD is usually diffuse, affecting multiple vessels (not limited to the anomalous coronary). Anomalous origin did not increase the severity of CAD in the affected vessel. In contrast to those with an anomalous RCA, LMCA, or LAD coronary artery, adults with an anomalous LCx coronary artery had more severe CAD stenosis in all coronary arteries, suggesting that a greater CAD burden may be necessary to trigger diagnostic coronary imaging. Importantly, AAOCA affecting non-LCx coronary arteries may be susceptible to ischemia despite less severe CAD stenosis. Further research should focus on the interaction between CAD and AAOCA on ischemic risk and strategies for surgical intervention.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

The Congenital Heart Surgeon's Society Data Center guided the database design for this project. At Cleveland Clinic, Areatha Lockridge completed database queries. Tanya Ashinhurst managed the REDCap database. Moses Anabila performed statistical analyses.

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Key Words: congenital heart disease, adult congenital heart disease, coronary artery disease, coronary artery imaging, coronary surgery

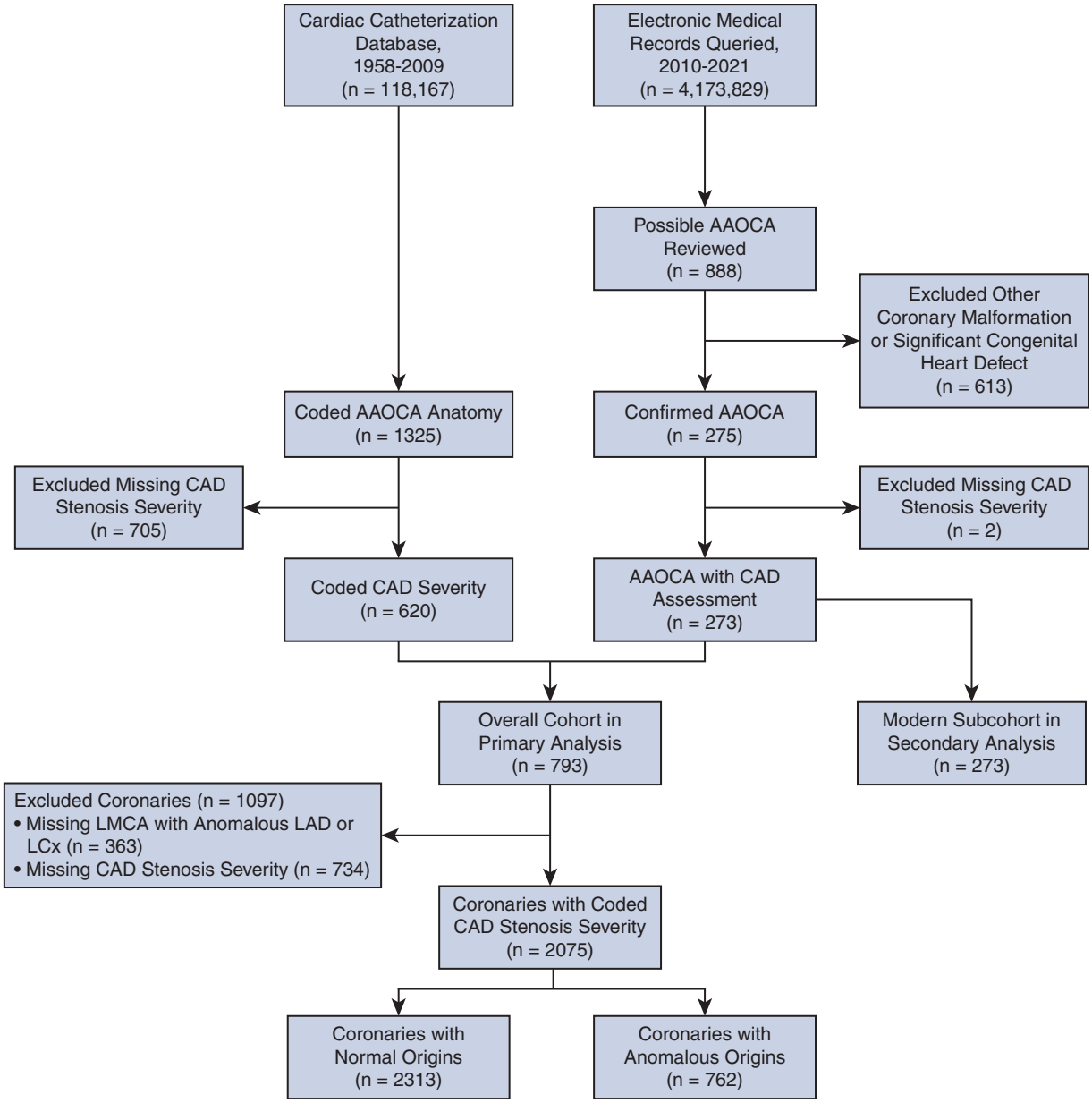

FIGURE E1. Flow diagram of overall cohort and modern subcohort. The cardiac catheterization database identified 620 patients who were previously coded for an anomalous aortic origin of a coronary artery (*AAOCA*) and atherosclerotic coronary artery disease (*CAD*) severity. An additional 273 patients were identified by querying the electronic medical records database and reviewing all available coronary imaging reports to confirm the presence of AAOCA and CAD assessment by invasive or computed tomography angiography. The combined cohorts of patients with AAOCA formed the overall cohort (n = 793) used in the primary analysis. The modern subcohort (n = 273) included more detailed coronary anatomy and was used for the secondary analysis. *LMCA*, Left main coronary artery; *LAD*, left anterior descending; *LCx*, left circumflex.

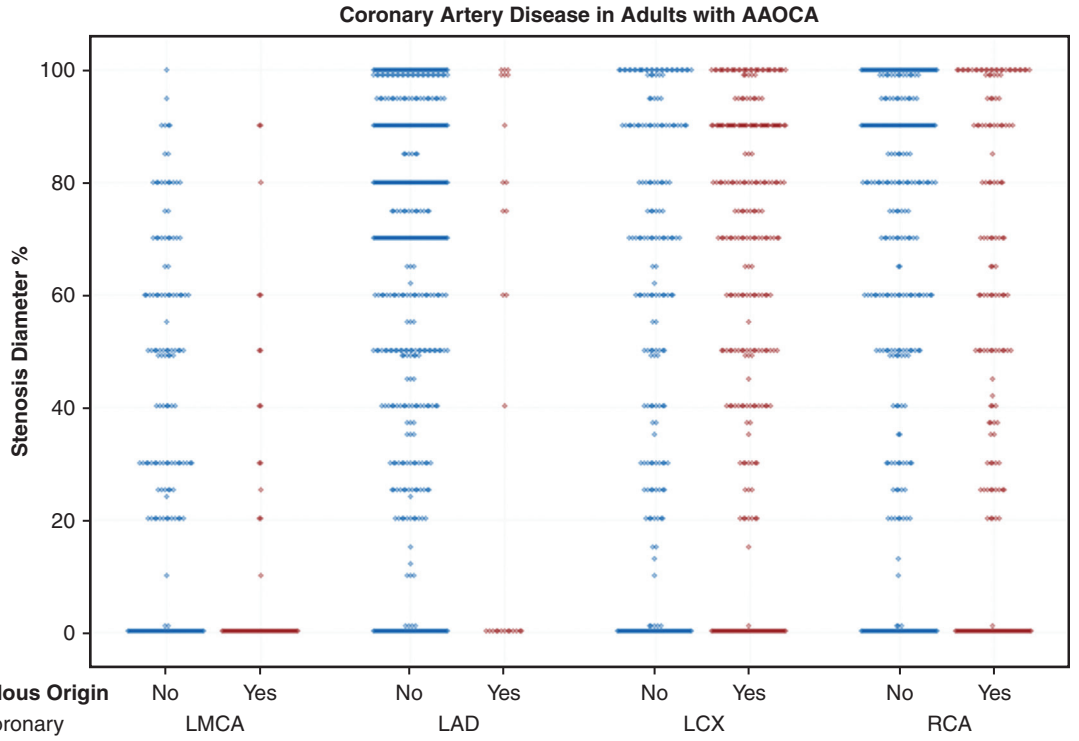

FIGURE E2. Dot plot of coronary artery disease stenosis stratified by the coronary and anomalous origin, Percent diameter stenosis due to coronary artery disease stratified first by the coronary and then by whether that coronary was anomalous. *AAOCA*, Anomalous aortic origin of a coronary artery; *LMCA*, left main coronary artery; *LAD*, left anterior descending; *LCx*, left circumflex; *RCA*, right coronary artery.

TABLE E1. Overall cohort demographics and comorbidities stratified by presence and location of obstructive CAD

	All (N = 793) Mean ± SD or n (%)	No CAD (N = 321) Mean ± SD or n (%)	Only anomalous coronary with CAD (N = 142) Mean ± SD or n (%)	Normal- origin coronary with CAD (N = 330) Mean ± SD or n (%)	*P* value
Demographics					
Age at CAD imaging, y	56.6 ± 14.2	51.3 ± 16.9	59.4 ± 9.95	60.7 ± 10.7	<.0001
Male	575 (73)	184 (57)	120 (85)	271 (82)	<.0001
Comorbidities					
Hypertension	445/789 (56)	212/319 (66)	74/141 (52)	159/329 (48)	<.0001
Tobacco use	367/780 (47)	118/320 (37)	78/139 (56)	171/321 (53)	<.0001
Arrhythmias	220/774 (32)	177/306 (58)	19/110 (17)	24/263 (9.1)	<.0001
Heart failure	152/780 (19)	81/317 (26)	25/138 (18)	46/325 (14)	.0012
Diabetes	149/774 (19)	60/320 (19)	31/137 (23)	58/317 (18)	.54
Pulmonary disease	121/776 (16)	95/318 (30)	10/137 (7.3)	16/321 (5)	<.0001
Peripheral artery disease	69/774 (8.9)	15/316 (4.8)	13/137 (9.5)	41/321 (13)	.0018

Baseline characteristics of 793 adult patients diagnosed with AAOCA are shown as counts (and relative frequencies) stratified by the presence and location. Obstructive coronary artery disease (*CAD*) was defined as >50% stenosis in the left main coronary artery (*LMCA*) or >70% stenosis in the right coronary artery (*RCA*), left anterior descending (*LAD*), or left circumflex (*LCx*) coronary artery. The frequencies of patients with AAOCA affecting each of the 4 or multiple coronaries were stratified based on the presence and location of any CAD. *P* value resulted from χ^2 tests comparing patients with no CAD, CAD in only the anomalous coronary, and CAD in normal-origin coronaries. *SD*, Standard deviation; *AAOCA*, anomalous aortic origin of a coronary artery.

TABLE E2. Overall cohort demographics and comorbidities stratified by anomalous coronary

	Anomalous coronary					
	LMCA, N = 108	**LAD, N = 27**	**LCx, N = 343**	**RCA, N = 306**	**Multiple, N = 9**	
	Mean ± SD or 15/50/85 percentile or n (%)	**Mean ± SD or 15/50/85 percentile or n (%)**	**Mean ± SD or 15/50/85 percentile or n (%)**	**Mean ± SD or 15/50/85 Percentile or n (%)**	**Mean ± SD or 15/50/85 percentile or n (%)**	***P* value**
Demographics						
Age, y	55.2 ± 16.1	57.5 ± 10.3	59.7 ± 11.1	53.6 ± 16.2	57.3 ± 9.63	.0002
Interval, AAOCA diagnosis to CAD imaging, y	0/0/0.68	0/0/1.83	0/0/0	0/0/0.43	0/0/5.45	
Male	72/108 (67)	22/27 (81)	276/343 (80)	201/306 (66)	4/9 (44)	<.0001
Comorbidities						
Congestive heart failure	30/108 (28)	6/26 (23)	57/335 (17)	58/303 (19)	1/8 (13)	.16
Arrhythmias	39/99 (39)	7/22 (32)	51/269 (19)	119/282 (42)	4/7 (57)	<.0001
Pulmonary disease	24/107 (22)	4/26 (15)	28/331 (8.5)	63/304 (21)	2/8 (25)	.0001
Diabetes	20/104 (19)	7/26 (27)	60/331 (18)	60/304 (20)	2/9 (22)	.85
Peripheral artery disease	9/107 (8.4)	4/26 (15)	31/329 (9.4)	25/303 (8.3)	0/8 (0)	.66
Hypertension	68/108 (63)	13/27 (48)	167/340 (49)	191/305 (63)	6/9 (67)	.0044
Tobacco use	46/105 (44)	11/26 (42)	178/336 (53)	127/304 (42)	5/9 (56)	.059

Patient demographics and comorbidities were stratified by which coronary was anomalous: left main (*LMCA*), left anterior descending (*LAD*), left circumflex (*LCx*), right (*RCA*), or multiple coronary arteries. *P* values corresponded with the χ^2 test for differences between all 5 groups, of which coronary was anomalous. *SD*, Standard deviation; *AAOCA*, anomalous aortic origin of a coronary artery; *CAD*, coronary artery disease.

TABLE E3. Modern subcohort baseline patient characteristics stratified by presence and location of obstructive CAD

	All (N = 273)	No CAD (N = 242)	Only anomalous coronary with CAD (N = 19)	Normal- origin coronary with CAD (N = 12)	
	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	*P* value
Demographics					
Age at CAD imaging, y	52.5 ± 17.5	50.7 ± 17.3	64.1 ± 9.72	70.9 ± 13.6	<.0001
Male	155 (57)	95 (39)	9 (47)	7 (58)	.03
Indication for diagnostic AAOCA imaging					
Symptomatic cardiac evaluation	195 (71)	175 (72)	13 (68)	7 (58)	.55
Cardiac surgery evaluation	45 (16)	37 (15)	5 (26)	3 (25)	.33
Noncardiac surgery evaluation	13 (4.8)	12 (5)	0 (0)	1 (8.3)	.52
Noncoronary imaging	7 (2.6)	7 (2.9)	0 (0)	0 (0)	.63
Routine screening	3 (1.1)	2 (0.83)	0 (0)	1 (8.3)	.046
Other	7 (2.6)	6 (2.5)	1 (5.3)	0 (0)	.65
Unknown	3 (1.1)	3 (1.2)	0 (0)	0 (0)	.82
Symptoms					
Chest pain	169 (62)	147 (61)	13 (68)	9 (75)	.51
Dyspnea	181 (66)	161 (67)	12 (63)	8 (67)	.96
Syncope	46 (17)	43 (18)	3 (16)	0 (0)	.27
Arrhythmia	159 (58)	143 (59)	9 (47)	7 (58)	.61
Myocardial infarction	25 (9.2)	16 (6.6)	5 (26)	4 (33)	.0002
Aborted SCD	6 (2.2)	5 (2.1)	1 (5.3)	0 (0)	.57
None	18 (6.6)	13 (5.4)	3 (16)	2 (17)	.075
Comorbidities					
Valve dysfunction	128 (47)	110 (45)	10 (53)	8 (67)	.31
Cardiomyopathy	36 (13)	32 (13)	2 (11)	2 (17)	.88
Heart failure	68 (25)	58 (24)	5 (26)	5 (42)	.38
Arrhythmia	165 (60)	147 (61)	10 (53)	8 (67)	.71
Congenital heart disease	35 (13)	32 (13)	2 (11)	1 (8.3)	.84
Cerebrovascular disease	21 (7.7)	18 (7.4)	2 (11)	1 (8.3)	.89
Pulmonary disease	81 (30)	74 (31)	4 (21)	3 (25)	.64
Liver disease	54 (20)	45 (19)	5 (26)	4 (33)	.35
Renal disease	32 (12)	25 (10)	5 (26)	2 (17)	.098
Diabetes	58 (21)	44 (18)	9 (47)	5 (42)	.0024
Peripheral arterial disease	11 (4)	9 (3.7)	1 (5.3)	1 (8.3)	.7
Hypertension	195 (71)	168 (69)	16 (84)	11 (92)	.11
Hyperlipidemia	168 (62)	140 (58)	17 (89)	11 (92)	.0022
Tobacco use	89 (33)	77 (32)	8 (42)	4 (33)	.65
None	42 (15)	42 (17)	0 (0)	0 (0)	.042

P values compared the CAD-free, CAD-only, and all-others categories. Origin refers to that of the anomalous coronary. Symptoms and comorbidities were not mutually exclusive.
CAD, Coronary artery disease; *AAOCA*, anomalous aortic origin of a coronary artery; *SCD*, sudden cardiac death.

TABLE E4. Modern subcohort AAOCA anatomic characteristics stratified by presence and location of obstructive CAD

	All (N = 273)	No CAD absent (N = 242)	Only anomalous coronary with CAD (N = 19)	Normal- origin coronary with CAD (N = 12)	
	n (%)	n (%)	n (%)	n (%)	*P* value
Anomalous coronary					.19
RCA	162 (59)	147 (61)	10 (53)	5 (42)	
LMCA	53 (19)	48 (20)	4 (21)	1 (8.3)	
LAD	7 (2.6)	6 (2.5)	1 (5.3)	0 (0)	
LCx	47 (17)	37 (15)	4 (21)	6 (50)	
Multiple	4 (1.5)	4 (1.7)	0 (0)	0 (0)	
Origin					.93
Opposite sinus	201 (74)	180 (74)	12 (63)	9 (75)	
Noncoronary sinus	1 (0.37)	1 (0.41)	0 (0)	0 (0)	
Suprasinus	35 (13)	30 (12)	4 (21)	1 (8.3)	
Opposite coronary	36 (13)	31 (13)	3 (16)	2 (17)	
Slit-like orifice	88/190 (46)	82/175 (47)	5/12 (42)	1/3 (33)	.85
Course					
Interarterial	150/233 (64)	139/212 (66)	9/16 (56)	2/5 (40)	.39
Intramural	102/211 (48)	96/193 (50)	5/14 (36)	0/4 (0)	.38
Intraseptal	33/196 (17)	32/177 (18)	1/14 (7)	0/5 (0)	.34

AAOCA, Anomalous aortic origin of a coronary artery; *CAD*, coronary artery disease; *RCA*, right coronary artery; *LMCA*, left main coronary artery; *LAD*, left anterior descending coronary artery; *LCx*, left circumflex.

TABLE E5. Modern subcohort demographics and coronary anatomic features stratified by anomalous coronary

	Anomalous coronary					
	LMCA	LAD	LCx	RCA	Multiple	
	Mean ± SD or 15/50/85 percentile or n (%)	Mean ± SD or 15/50/85 percentile or n (%)	Mean ± SD or 15/50/85 percentile or n (%)	Mean ± SD or 15/50/85 percentile or n (%)	Mean ± SD or 15/50/85 percentile or n (%)	*P* value
Demographics						
Age	51.3 ± 16.6	54.6 ± 13.6	61.7 ± 15.8	50.7 ± 17.8	58.2 ± 5.52	.0025
Interval, AAOCA diagnosis to CAD imaging	0/0.11/3.79	0/0.07/3.91	0/0/1.53	0/0/0.57	0/0/0.05	
Male	31/53 (58)	3/7 (43)	27/47 (57)	93/162 (57)	1/4 (25)	.68
Comorbidities						
Congestive heart failure	19/53 (36)	2/7 (29)	13/47 (28)	34/162 (21)	0/4 (0)	.18
Arrhythmias	30/53 (57)	5/7 (71)	31/47 (66)	97/162 (60)	2/4 (50)	.83
Pulmonary disease	20/53 (38)	3/7 (43)	11/47 (23)	46/162 (28)	1/4 (25)	.51
Diabetes	10/53 (19)	0/7 (0)	16/47 (34)	32/162 (20)	0/4 (0)	.093
Peripheral artery disease	3/53 (5.7)	0/7 (0)	1/47 (2.1)	7/162 (4.3)	0/4 (0)	.86
Hypertension	36/53 (68)	5/7 (71)	36/47 (77)	114/162 (70)	4/4 (100)	.62
Tobacco use	17/53 (32)	0/7 (0)	16/47 (34)	54/162 (33)	2/4 (50)	.4
Arise from						<.0001
Opposite sinus	40/53 (75)	5/7 (71)	28/47 (60)	126/162 (78)	2/4 (50)	
Noncoronary sinus	0/53 (0)	0/7 (0)	0/47 (0)	1/162 (0.62)	0/4 (0)	
Opposite artery	11/53 (21)	2/7 (29)	19/47 (40)	4/162 (2.5)	0/4 (0)	
Suprasinus	2/53 (3.8)	0/7 (0)	0/47 (0)	31/162 (19)	2/4 (50)	
Morphology and course						
Slit-like Orifice	8/42 (19)	0/4 (0)	1/15 (6.7)	79/126 (63)	0/3 (0)	<.0001
Acute angulation	11/45 (24)	0/4 (0)	3/17 (18)	64/109 (59)	1/3 (33)	<.0001
Greater-risk course (any of 3 to follow)	37/52 (71)	5/5 (100)	1/33 (3)	133/152 (88)	3/4 (75)	<.0001
Intramural course	11/47 (23)	0/3 (0)	0/22 (0)	91/135 (67)	0/4 (0)	<.0001
Interarterial course	27/50 (54)	3/3 (100)	0/32 (0)	118/145 (81)	2/3 (67)	<.0001
Intraconal or intraseptal course	25/47 (53)	4/5 (80)	1/24 (4.2)	2/117 (1.7)	1/3 (33)	<.0001
Dominance						
Left	1/50 (2)	1/7 (14)	4/44 (9.1)	16/151 (11)	0/4 (0)	
Right	49/50 (98)	6/7 (86)	39/44 (89)	120/151 (79)	4/4 (100)	.088
Codominant	0/50 (0)	0/7 (0)	1/44 (2.3)	15/151 (9.9)	0/4 (0)	

LMCA, Left main coronary artery; *LAD*, left anterior descending coronary artery; *LCx*, left circumflex; *RCA*, right coronary artery; *SD*, standard deviation; *AAOCA*, anomalous aortic origin of a coronary artery; *CAD*, coronary artery disease.

TABLE E6. Factors associated with greater severity of coronary artery stenosis

Factor	Coefficient ± SE	*P* value
Coronary-level variables		
Anomalous origin	0.029 ± 0.071	.8
Patient-level variables		
Anomalous coronary: LCx	1.0 ± 0.11	<.0001
Male	0.92 ± 0.13	<.0001
Older age*	1.1 ± 0.10	<.0001
Diabetes	0.41 ± 0.14	.004
Peripheral artery disease	0.57 ± 0.18	.002
Tobacco use	0.37 ± 0.11	.0006
Hypertension (lower risk)	−0.27 ± 0.12	.02
Congestive heart failure (less risk)	−0.33 ± 0.15	.02
Pulmonary disease (lower risk)	−0.96 ± 0.17	<.0001

Using the 4 coronary stenosis measurements as a patient-cluster response and cumulative logistic mixed-effects model, associations with the presence of an anomalous coronary, demographics, and comorbidities were considered. The presence of an anomalous origin did not increase the likelihood of greater CAD severity. At the patient level, the presence of anomalous LCx increased the severity of CAD in all coronary arteries (with and without anomalous origins). *SE*, Standard error; *LCx*, left circumflex; *CAD*, coronary artery disease. *$[Age/50]^2$, squared transformation.

TABLE E7. Factors associated with a greater grade of LMCA stenosis

Factor	Coefficient ± SE	*P* value
Anomalous coronary: left main	−0.066 ± 0.31	.8
Male	0.46 ± 0.24	.05
Older age*	1.1 ± 0.18	<.0001
Pulmonary disease (less risk)	−0.93 ± 0.37	.01

No association was found between which coronary was anomalous and the LMCA stenosis grade. *LMCA*, Left main coronary artery; *SE*, standard error. *$[Age/50]^2$, squared transformation.

TABLE E8. Factors associated with greater severity of LAD stenosis

Factor	Coefficient ± SE	*P* value
Anomalous coronary: LAD	0.28 ± 0.38	.5
Anomalous coronary: LCx	1.5 ± 0.15	<.0001
Male	1.2 ± 0.17	<.0001
Older age*	0.53 ± 0.087	<.0001
Peripheral artery disease	0.72 ± 0.25	.004
Pulmonary disease (less risk)	−1.1 ± 0.22	<.0001

Increased CAD severity in the LAD coronary was associated with the presence of an anomalous LCx coronary and not the presence of an anomalous LAD coronary. *LAD*, Left anterior descending coronary artery; *SE*, standard error; *LCx*, left circumflex. *exp [Age/50], exponential transformation.

TABLE E9. Factors associated with greater severity of LCx stenosis

Factor	Coefficient ± SE	*P* value
Anomalous coronary: LCx	0.73 ± 0.14	<.0001
Male	0.96 ± 0.13	<.0001
Older age*	0.93 ± 0.13	<.0001
Pulmonary disease (less risk)	−0.88 ± 0.22	<.0001

The presence of an anomalous LCx, male sex, and older age are associated with a greater likelihood of more severe CAD stenosis in the anomalous LCx. *LCx*, Left circumflex; *SE*, standard error; *CAD*, coronary artery disease. *$[Age/50]^2$, squared transformation.

TABLE E10. Factors associated with greater severity of RCA stenosis

Factor	Coefficient ± SE	*P* value
Anomalous coronary: RCA (less risk)	−0.25 ± 0.20	.2
Anomalous coronary: LCx	0.70 ± 0.20	.0003
Male	0.90 ± 0.17	<.0001
Older age*	2.5 ± 0.34	<.0001
Diabetes	0.47 ± 0.18	.01
Peripheral artery disease	0.64 ± 0.24	.008
Tobacco use	0.57 ± 0.14	<.0001
Hypertension (less risk)	−0.54 ± 0.16	.0001
Pulmonary disease (less risk)	−1.2 ± 0.23	.0005

Patients with anomalous LCx were significantly associated with a greater grade of RCA stenosis. The presence of an anomalous RCA had no association with the CAD severity in the RCA. *RCA*, Right coronary artery; *SE*, standard error; *LCx*, left circumflex; *CAD*, coronary artery disease. *Log [Age], logarithmic transformation.

TABLE E11. Factors associated with a greater overall coronary artery stenosis within modern subcohort

Factor	Coefficient ± SE	*P* value	R (%)*
Coronary-level			
Anomalous origin	0.16 ± 0.38	.6	4.3
Intramural	0.45 ± 0.52	.4	15
Interarterial	−0.096 ± 0.52	.8	2
Intraseptal	−0.38 ± 0.75	.6	3
Patient-level			
Anomalous coronary: LCx	0.97 ± 0.44	.03	74
Male	1.3 ± 0.36	.0004	99
Older age at assessment†	1.5 ± 0.21	<.0001	100

There was no association between the CAD severity and the presence of an anomalous origin, slit-like orifice, acute angulation, interarterial course, intramural course, intraseptal course, or any of the presumed high-risk courses were combined. Older age, male sex, and AAOCA affecting the anomalous left circumflex were associated with a greater grade of coronary artery stenosis overall. *SE*, Standard error; *LCx*, left circumflex; *CAD*, coronary artery disease; *AAOCA*, anomalous aortic origin of a coronary artery. *Bagging reliability represents the proportion of 1000 bootstrap logistic regression models, with the assumption of independence, in which the variable was retained with $P < .05$. †Exp [Age/50], exponential transformation.

TABLE E12. Surgical treatment and outcomes of patients with AAOCA in modern subcohort stratified by presence and location of obstructive CAD

	All	No CAD	Only anomalous coronary with CAD	Normal- origin coronary with CAD	
	n (%)	n (%)	n (%)	n (%)	*P* value
AAOCA repair	92/273 (34)	87/242 (36)	4/19 (21)	1/12 (8)	.068
AAOCA repair type					.025
Unroofing	64/92 (70)	63/87 (72)	1/4 (25)	0/1 (0)	
CABG	16/92 (17)	14/87 (16)	1/4 (25)	1/1 (100)	
Reimplantation	8/92 (8.7)	7/87 (8)	1/4 (25)	0/1 (0)	
Aortocoronary Window	2/92 (2.2)	1/87 (1.1)	1/4 (25)	0/1 (0)	
Other	2/92 (2.2)	2/87 (2.3)	0/4 (0)	0/1 (0)	
Concomitant cardiac procedures	34/92 (37)	30/87 (35)	4/4 (100)	0/1 (0)	.025
Aortic valve replacement/ repair	20/92 (22)	19/87 (22)	1/4 (25)	0/1 (0)	.83
Aortic root replacement/ repair	10/92 (11)	9/87 (10)	1/4 (25)	0/1 (0)	.44
CABG to another coronary	9/92 (10)	7/87 (8)	2/4 (50)	0/1 (0)	.0018
Symptom change					.049
Improved	55/92 (60)	51/87 (64)	2/4 (50)	0/1 (0)	
Same	22/92 (24)	19/87 (24)	2/4 (50)	0/1 (0)	
Worse	0/92 (0)	0/87 (0)	0/4 (0)	0/1 (0)	
Unknown	11/92 (12)	10/87 (13)	0/4 (0)	1/1 (100)	
Symptom change					
Improved	55/92 (60)	51/87 (64)	2/4 (50)	0/1 (0)	.049
Same	22/92 (24)	19/87 (24)	2/4 (50)	0/1 (0)	
Worse	0/92 (0)	0/87 (0)	0/4 (0)	0/1 (0)	
Unknown	11/92 (12)	10/87 (13)	0/4 (0)	1/1 (100)	
Complications					*
Arrhythmia	13/92 (14)	12/87 (14)	1/4 (25)	0/1 (0)	
Wound infection	1/92 (1)	1/87 (1.1)	0/4 (0)	0/1 (0)	
Postpericardotomy syndrome	1/92 (1)	1/87 (1.1)	0/4 (0)	0/1 (0)	
Pneumothorax	4/92 (4)	4/87 (4.6)	0/4 (0)	0/1 (0)	
ECMO	1/92 (1)	1/87 (1.1)	0/4 (0)	0/1 (0)	

Counts and frequency of patients that underwent *P* values compared categories in which the CAD was absent, CAD was in only the anomalous coronary, and CAD was in the normal-origin coronary. *AAOCA*, Anomalous aortic origin of a coronary; *CAD*, coronary artery disease; *CABG*, coronary artery bypass graft; *ECMO*, extracorporeal membrane oxygenation. *Complications were too infrequent to calculate a *P* value.