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First report from the European registry for anomalous aortic origin of coronary artery (EURO-AAOCA)

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Abstract

OBJECTIVES: Anomalous aortic origin of a coronary artery (AAOCA) is a group of rare congenital heart defects with various clinical presentations. The lifetime-risk of an individual living with AAOCA is unknown, and data from multicentre registries are urgently needed to adapt current recommendations and guide optimal patient management. The European AAOCA Registry (EURO-AAOCA) aims to assess differences with regard to AAOCA management between centres.

METHODS: EURO-AAOCA is a prospective, multicentre registry including 13 European centres. Herein, we evaluated differences in clinical presentations and management, treatment decisions and surgical outcomes across centres from January 2019 to June 2023.

RESULTS: A total of 262 AAOCA patients were included, with a median age of 33 years (12–53) with a bimodal distribution. One hundred thirty-nine (53.1%) were symptomatic, whereas chest pain ($n = 74$, 53.2%) was the most common complaint, followed by syncope ($n = 21$, 15.1%). Seven (5%) patients presented with a myocardial infarction, 2 (1.4%) with aborted sudden cardiac death. Right-AAOCA was most frequent (150, 57.5%), followed by left-AAOCA in 51 (19.5%), and circumflex AAOCA in 20 (7.7%). There were significant differences regarding diagnostics between age groups and across centres. Seventy-four (28.2%) patients underwent surgery with no operative deaths; minor postoperative complications occurred in 10 (3.8%) cases.

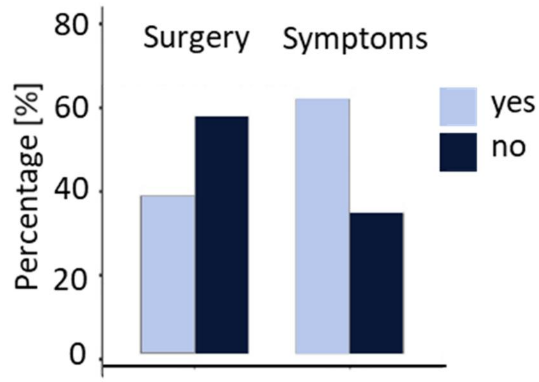
CONCLUSIONS: Currently, no uniform agreement exists among European centres with regard to diagnostic protocols and clinical management for AAOCA variants. Although surgery is a safe procedure in AAOCA, future longitudinal outcome data will hopefully shed light on how to best decide towards optimal selection of patients undergoing revascularization versus conservative treatment.

EACTS Annual Meeting 2023, Vienna

First Results from the European Registry for Anomalous Aortic Origin of Coronary Artery (EURO-AAOCA)

Summary

In a prospective study across 13 European centers between January 2019 and June 2023 we included 262 patients with an anomalous aortic origin (AAOCA). We evaluated differences in clinical presentation, diagnostic evaluation and treatment decision. We found that right AAOCA was the most common and currently no agreement regarding diagnostic- and clinical management exists.



Legend: Distribution of surgery and symptoms for patients with AAOCA.

Keywords: AAOCA • Europe • Multicentre • Prospective • Operative outcomes

ABBREVIATIONS

AAOCA	Anomalous aortic origin of a coronary artery
ACC	American College of Cardiology
AHA	American Heart Association
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CHSS	Congenital Heart Surgeons Society
CMR	Cardiovascular magnetic resonance imaging
ESC	European Society of Cardiology
EURO-AAOCA	European AAOCA Registry
FFR	Fractional flow reserve
IVUS	Intravascular ultrasound
L-AAOCA	Left anomalous aortic origin of a coronary artery
LGE	Late gadolinium enhancement
OR	Odds ratio
R-AAOCA	Right anomalous aortic origin of a coronary artery
SCD	Sudden cardiac death

INTRODUCTION

Coronary artery anomalies are a rare form of congenital heart disease. Notably, a specific subset, anomalous aortic origin of a coronary artery (AAOCA), is proven to have the potential to lead to adverse cardiac outcomes [1]. Especially AAOCA variants with an interarterial course between the great arteries and an intramural course (proximal coronary segment within the aortic wall of the tunica media) are associated with an anticipated higher risk of sudden cardiac death (SCD) [2, 3]. In fact, AAOCA contributed to up to one-third of the deaths documented in autopsy reports of young athletes and military recruits who died during intense physical exertion [3, 4]. Although, autopsy do not accurately reflect the real risk in general population of individuals living with AAOCA [5], traditionally surgical repair was recommended for all patients. Nevertheless, recommendations have recently slightly changed: The European Society of Cardiology (ESC) 2020 guidelines have given a class IC indication for surgery in patients with right-AAOCA (R-AAOCA) or left-AAOCA (L-AAOCA) and typical angina, who present with evidence of stress-induced myocardial ischaemia in a matching territory or high-risk anatomy [6]. Comparably, the American Heart Association (AHA)/American College of Cardiology (ACC) 2018 guidelines giving a class IC recommendation for surgery L-AAOCA and R-AAOCA with symptoms or diagnostic evidence consistent with coronary ischaemia attributable to the anomalous coronary artery [7].

Diagnostic and treatment approaches are varying across centres, complicating generation of evidence on optimizing the management of AAOCA. Therefore, evaluating the true risk of different AAOCA variants, comparing anatomical and functional evaluation, and selecting patients who need surgery to reduce the burden of AAOCA healthcare costs while not overtreating or unnecessarily restricting AAOCA individuals from competitive sports is a matter of current research. There are several retrospective registries existing for the American [8, 9], European [10–12] and Japanese [13] cohorts. However, there is a lack of data from prospective studies.

The European AAOCA Registry (EURO-AAOCA) was established to prospectively include all AAOCA cases from different centres in Europe, and to compare the findings across them. In this 1st analysis, we aimed to evaluate findings of clinical presentations, diagnostics, treatment and immediate surgical outcome across centres.

METHODS

Ethical statement

The overall study was approved by the Ethics Committee 'Comitato etico per la sperimentazione clinica della Provincia di Padova' (approval number 4901/AO/20). Individual consent was obtained from the enrolling centre. Formal consent was obtained from the patient or if minor, by the patient's parent/guardian.

Enrolment

This is a prospective observational multicentre registry study, which includes all patients with a diagnosis of AAOCA who presented at one of the participating centres between January 2019 and June 2023. Patients are followed annually for up to 5 years. Thirteen centres have been enrolled so far to the time of analysis: Athens, Bern, Bruxelles, Gent, Groningen, London, Madrid, Milan, Padua Paediatric Cardiac Center, Padua Adult Cardiology, Parma, Treviso and Verona. All clinical data were de-identified and collected using REDCap platform hosted at the University Hospital of Padova.

Exclusion criteria were coronary anomalies with normal origin, but anomalous course, and coronary artery anomalies in association to major congenital heart disease (i.e. Tetralogy of Fallot, transposition of the great arteries, anomalous origin of a coronary from the pulmonary artery).

All patients with a diagnosis of AAOCA, Right coronary artery (RCA) from the left coronary sinus (left coronary artery (LCA) from the right coronary sinus, high coronary take-off ($\geq$1 cm) or other coronary anomalies not fitting the exclusion criteria (either referred to surgery or to medical follow-up) were included in this analysis. Patients' demographics and diagnostic tests performed were described. In particular, the anatomical pattern and morphology of the coronary artery, the appearance of symptoms during stress tests and the surgical indication were included. Intraoperative and postoperative data were analysed, and immediate postoperative outcomes were reported.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median and interquartile range based on normality. We assessed normal distribution using Shapiro–Wilk test. Categorical variables were presented as frequency and % of the population. Patient characteristics and global findings are reported for the entire cohort. We conducted a sub-analysis by dividing the population, based on literature and on cohort distribution, into patients with an age <30 years and $\geq$30 years. These groups were compared using a chi-square test with Yates' continuity correction, an independent samples *t*-test, or a Wilcoxon rank sum test for categorical or continuous variables, respectively. Univariable logistic regression analysis was performed to identify variables that predict referral to surgery. Variables with <50 values were excluded. The results were expressed as odds ratios (ORs) with a 95% confidence interval. Due to multiple testing and the exploratory nature of the study, statistical significance was defined with a two-sided *P*-value of <0.005 for comparison between groups. For the logistic regression model, a false discovery rate correction was applied. All statistical analysis was performed with the help of R software version 4.2.3 (R Foundation for Statistical Computing, Vienna Austria).

RESULTS

Two hundred sixty-two patients from 13 centres were included (median 22 patients/centre, IQR 6–28). The median age was 36 years (IQR 12–55) with a bimodal distribution (Figs 1 and 2), and 86 (32.8%) were women. The AAOCA age distribution across centres is presented in Fig. 2.

Anatomy and symptoms

The most commonly diagnosed anomaly was R-AAOCA in 150 (57.5%) patients and the 2nd most common anomaly was L-AAOCA in 51 patients (19.5%), followed by the circumflex AAOCA) in 20 subjects (7.6%). The most common course was interarterial (202; 77.7%). Other anatomical high-risk features included presence of intramural segment in 142 (55.3%), slit-like ostium in 112 (51.9%) and an acute take-off angle in 129 (61.1%). There were no differences in anatomical high-risk features between patients <30 and $\geq$30 years. Symptoms were present in 139 (53.1%), with chest pain in 74 (53.2%), followed by syncope in 21 (15.1%). Seven (5%) patients presented with a myocardial infarction at baseline [3 with concomitant coronary artery disease (CAD) and 4 without] and 2 with an aborted SCD (1.4%). Patients with <30 years presented more frequently with syncope compared to $\geq$30 years (28.6% vs 7.8%, $P=0.003$). There were no differences for myocardial infarction and aborted SCD between the groups (Table 1).

Diagnostics

The use of invasive coronary angiography, cardiovascular magnetic resonance imaging (CMR), single-photon emission computer tomography and coronary computed tomography angiography (CCTA) were different between centres (Fig. 3). Invasive coronary angiography was performed in 145 patients (55.3%) and more often in patients $\geq$30 years (80.6% vs 28.9%, $P<0.001$). CAD was only present in patients $\geq$30 years [i.e. 21 (15.7%)]. Advanced interventional procedures such as intravascular ultrasound (IVUS) and Fractional Flow Reserve (FFR) measurements were only performed in a portion of all coronary angiographies [i.e. IVUS in 71 (27.1%), FFR in 49 (18.7%)]. CMR was performed in 100 (38.2%) patients and showed late gadolinium enhancement (LGE) in 24 (9.2%) patients. LGE was present in 17/65 (26.2%) patients with R-AAOCA and 4/16 (25.0%) patients with L-AAOCA. Furthermore, a patient with a high-origin left coronary artery, a patient with a left coronary artery from RCA and 1 with an RCA from left coronary artery presented with LGE. An ischaemic pattern was present in 11/24 (45.8%). Single-photon emission computer tomography was performed in 64 (24.4%)

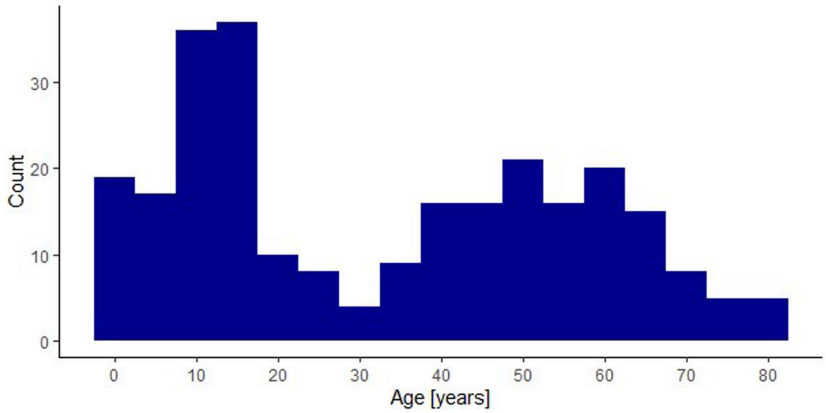


Figure 1: The age distribution of all patients, showing a clear bimodal pattern.

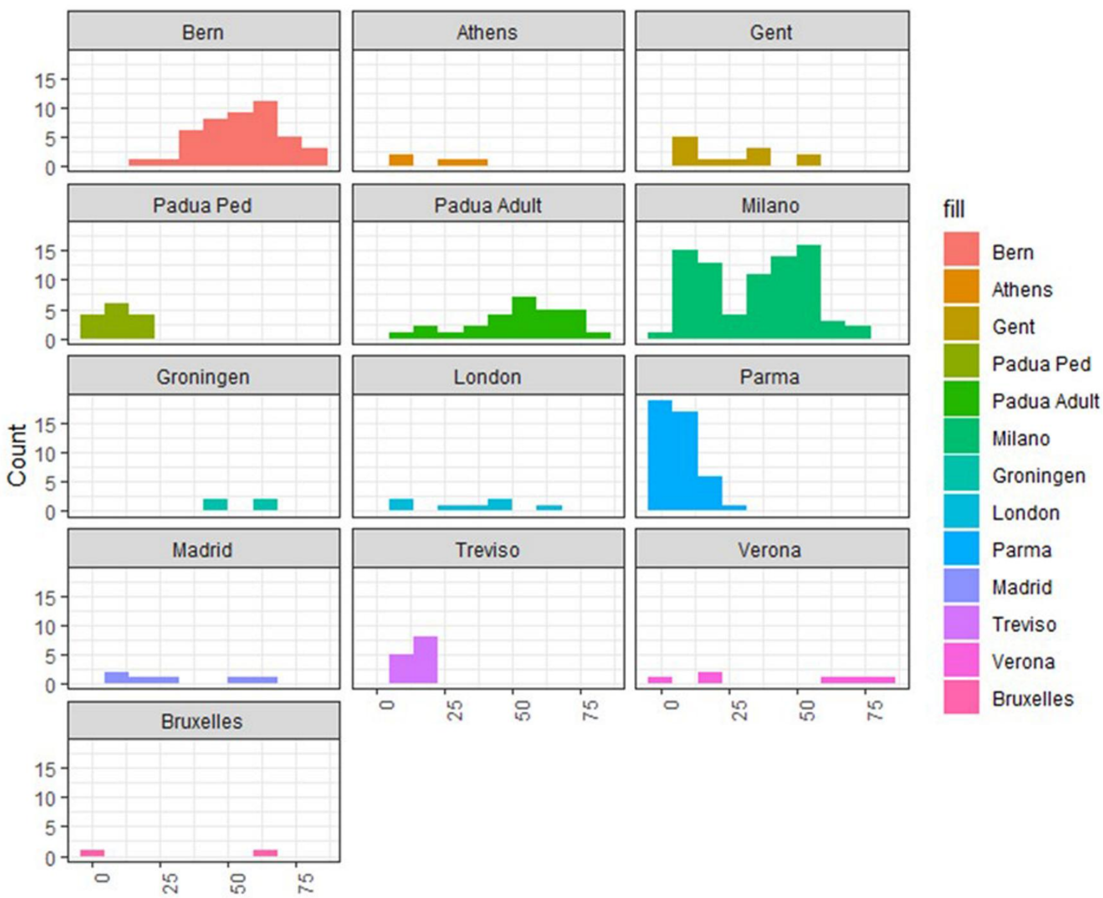


Figure 2: The different age distributions displayed for the different participating centres.

patients and was pathologic in 12 of them (18.8%). In 210 (80.2%) patients, a CCTA was performed and was less frequent in the <30 years cohort compared to ≥30 years cohort (68.8% vs 91.0%, $P < 0.001$). The different diagnostic tests performed in patients <30 and ≥30 years are summarized in Table 2.

Therapy

Surgery was performed in 74 (28.2%) patients and the most frequent surgical procedure was the unroofing of the intramural segment [55 (74.3%) patients]. The median aortic cross-clamp time was 54.5 (IQR 46–69) min. Intraoperative complications occurred in 7 patients (9.5%), of which 3 were due to coronary lesions, 2 with bleeding, 1 with a change of surgical procedure and 1 with perioperative ischaemia.

The immediate postoperative outcome was favourable, with no operative deaths. Postoperative complications were observed in 10 (13.9%) patients; 2 had pericardial effusion necessitating drainage, 1 had pleural effusion necessitating drainage, 3 developed postoperative arrhythmia and 1 showed persistent neurological deficit upon discharge. In the remaining 3, they were

Table 1: Baseline characteristics anatomy and symptoms

	All ($n = 262$)	≥30 years ($n = 134$)	<30 years ($n = 128$)	*P*-value
Age, median (interquartile range)	36 (12–55)	54.2 ± 12.5	12 (7–16)	**<0.001**
Female sex, *n* (%)	86 (32.8)	46 (34.3)	40 (31.3)	0.69
BMI, median (interquartile range)	22.8 (18.7–26.9)	26.3 ± 4.1	19 (16.3–21.8)	**<0.001**
Type of coronary anomaly, *n* (%)	261 (99.6)	134 (100)	127 (99.2)	
R-AAOCA	150 (57.5)	86 (64.2)	64 (50.4)	0.033
L-AAOCA	51 (19.5)	24 (17.9)	27 (21.3)	0.60
LCA from RCA	7 (2.7)	5 (3.7)	2 (1.6)	0.49
RCA from LCA	2 (0.8)	2 (1.5)	0 (0)	0.50
High origin LCA	5 (1.9)	2 (1.5)	3 (2.4)	0.95
high origin RCA	16 (6.1)	1 (0.7)	15 (11.8)	**0.001**
Cx-AAOCA	20 (7.7)	13 (9.7)	7 (5.5)	0.30
Other	10 (3.8)	1 (0.7)	9 (7)	0.019
Anomalous course, *n* (%)	260 (99.2)	134 (100)	126 (98.4)	
Interarterial course	202 (77.7)	110 (82.1)	92 (73)	0.108
Retroaortic course	27 (10.4)	16 (11.9)	11 (8.7)	0.52
Subpulmonic course	12 (4.6)	5 (3.7)	7 (5.6)	0.69
Prepulmonic	7 (2.7)	2 (1.5)	5 (4)	0.40
Other	12 (4.6)	1 (0.7)	11 (8.7)	0.005
Anatomical high-risk features, *n* (%)	257 (98.1)	131 (97.8)	126 (98.4)	
Intramural course	142 (55.3)	80 (61.1)	62 (49.2)	0.074
Slit like ostium, *n* (%)	112 (43.6)	69 (52.7)	43 (34.1)	0.46
Acute take-off angle	129 (50.2)	72 (55)	57 (45.2)	0.81
R-AAOCA with all high-risk features, *n* (%)	71 (27.1)	49 (36.6)	22 (17.2)	**0.001**
L-AAOCA with all high risk features, *n* (%)	7 (2.7)	2 (1.5)	5 (3.9)	0.40
Symptoms type, *n* (%)	139 (53.1)	90 (67.2)	49 (38.3)	**<0.001**
Chest pain	74 (53.2)	52 (57.8)	22 (44.9)	0.20
Syncope	21 (15.1)	7 (7.8)	14 (28.6)	**0.003**
Dyspnoea	11 (7.9)	9 (10.0)	2 (4.1)	0.37
Myocardial infarction	7 (5.0)	6 (6.7)	1 (2.0)	0.43
Palpitations	7 (5.0)	4 (4.4)	3 (6.1)	0.98
Presyncope	5 (3.6)	2 (2.2)	3 (6.1)	0.48
Aborted SCD	2 (1.4)	1 (1.1)	1 (2.0)	1.00
Fatigue	2 (1.4)	1 (1.1)	1 (2.0)	1.00
Arrhythmias	1 (0.7)	0 (0)	1 (2.0)	0.76
SCD	0 (0)	0 (0)	0 (0)	NA
Unspecified	4 (2.9)	4 (4.4)	0 (0)	0.33
Other	5 (3.6)	4 (4.4)	1 (2.0)	0.80
Recreational sport, *n* (%)	126 (48.1)	49 (36.6)	77 (60.2)	0.005
Competitive sport, *n* (%)	54 (20.6)	10 (7.5)	44 (34.4)	**<0.001**

BMI: body mass index; Cx-AAOCA: circumflex anomalous aortic origin of a coronary artery; LCA: left coronary artery; NA:not applicable; L-AAOCA: left anomalous aortic origin of a coronary artery; R-AAOCA: right anomalous aortic origin of a coronary artery; RCA: right coronary artery; SCD: sudden cardiac death.

reported, but not further defined. Surgical reintervention was required in 3 patients and non-surgical reintervention in 1. The median hospital stay was 9 days (Table 3).

In the logistic regression, the strongest predictors were a slit-like ostium with an OR of 5.5 ($P < 0.001$) followed by an intramural course with an OR of 4.66 ($P < 0.001$). Age was not a predictor for surgery, but paediatric centres had an OR <1 compared to adult centres >1 (OR 0.16 versus OR 6.26), which was also shown with patients <30 years of age having a lower OR for operation (OR 0.44, $P = 0.001$). Further, a positive exercise stress-testing electrocardiogram was a strong predictor for surgery with an OR of 5.67 ($P = 0.009$) (Table 4).

DISCUSSION

Main findings

This research presents the initial findings of the European prospective multicentre cohort study EURO-AAOCA. As there were paediatric and adult centres involved, a bimodal age distribution could be observed. Further, patients were treated significantly differently in different centres, reflecting the heterogeneity in the management of patients with an AAOCA in Europe.

Age distribution

Compared to other registries [i.e. Congenital Heart Surgeons Society (CHSS) [14], AAOCA registry, or Texas Heart Institute [8]], where only paediatric patients were included, the peculiarity of the EURO-AAOCA registry is that it includes patients across all ages from both paediatric and adult centres. Also, while other registries do include middle-aged patients, none are multicentre [12, 13, 15]. The bimodal pattern may serve as a representation of various centres contributing with differing weights to the final population. However, it could also indicate the potential for AAOCA to become symptomatic later in life through different mechanisms (e.g. age-related changes to the aorta), as suggested by Bigler *et al.* [17]. The higher proportion of men compared to

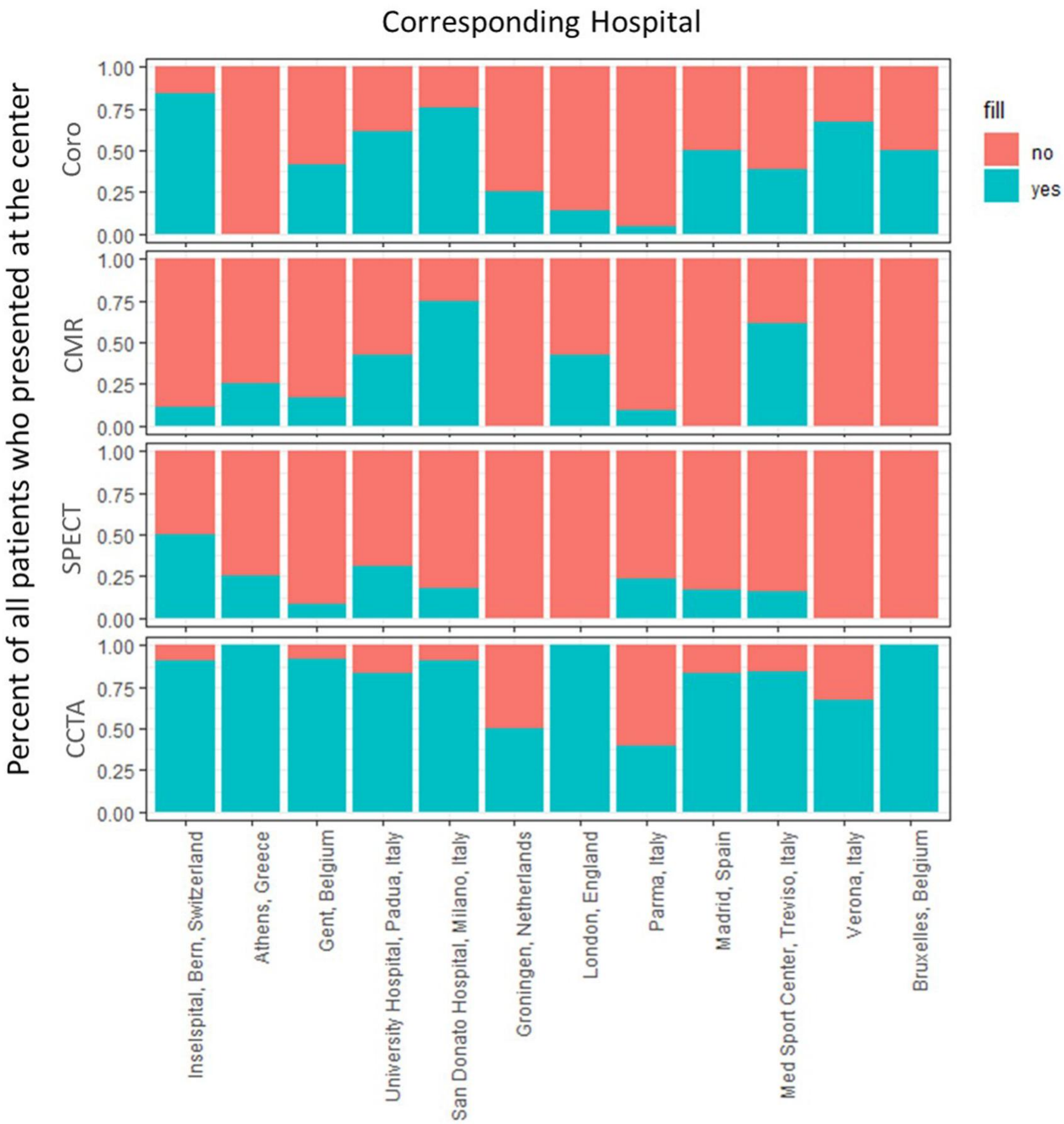


Figure 3: Different diagnostic tests done at different centres. On the left in blue are the paediatric centres and on the right in red are the adult or mixed centres. CCTA: coronary computed tomography angiography; CMR: cardiovascular magnetic resonance imaging; SPECT: single-positron emission computer tomography.

women could be explained by a greater rate of screening for CAD especially in middle-aged patients, consequently resulting in a higher rate of incidental findings.

Current guidelines recommend CCTA or functional non-invasive imaging tests as the preferred modality for the exclusion of CAD in symptomatic middle-aged patients [16]. Thus, it is expected that an increasing number of AAOCA are going to be discovered in this particular age group, in which the question usually is whether it is incidental or the true underlying cause of the patient's symptoms. In the current registries, it is unclear how this middle-aged population differs from the paediatric population and if the same diagnostic and therapeutic approaches are applicable. The risk of AAOCA-related ischaemia has been reported to be less relevant in patients older than 30 years [17]. In our cohort, there was no difference in severe initial presentations for age groups. However, it has to be noted that in this research, we have not analysed follow-up data, which are still being collected.

Demographic data showed that R-AAOCA was 3 times more common than L-AAOCA and about half of the patients were symptomatic at baseline, which is consistent with what published in the CHSS registry [14]. There was a clear difference in the type of symptoms reported between the different age groups. Patients <30 years were 4 times more likely to have syncope at 1st presentation, while chest pain was comparable between the 2 groups. Patients <30 years were found to be more frequently engaged in competitive sports activities. Considering that ischaemia in AAOCA represents a dynamic process involving lateral compression during exercise [17], this finding could imply an increased reliability of symptoms in this cohort, potentially elucidating the increased incidence of syncope. However, the existing literature denotes that the dependability of symptoms is, in reality, limited. A study by Basso *et al.*, which included 27 athletes who experienced SCD during or after exertion, showed that almost 50% of these cases did not show symptoms [2].

Table 2: Diagnostics

	All ($n = 262$)	≥30 years ($n = 134$)	<30 years ($n = 128$)	*P*- value
ECG performed, *n* (%)	239 (91.2)	118 (88.1)	121 (94.5)	0.10
Pathologic ECG, *n* (%)	55 (21)	38 (28.4)	17 (13.3)	**0.001**
Holter ECG performed, *n* (%)	50 (19.1)	22 (16.4)	28 (21.9)	0.33
Echocardiography performed, *n* (%)	223 (85.1)	107 (79.9)	116 (90.6)	0.023
LVEF (%)median (interquartile range)	64 (59.4–67.5)	60 (55–65)	66 (62–70)	**<0.001**
LV wall motion abnormalities Echo, *n* (%)	27 (10.3)	23 (17.2)	4 (3.1)	**<0.001**
Echocardiography stress performed, *n* (%)	22 (8.4)	11 (8.2)	11 (8.6)	1.00
Echo stress positive, *n* (%)	1 (0.4)	1 (0.7)	0 (0)	1.00
CMR performed, *n* (%)	100 (38.2)	53 (39.6)	47 (36.7)	0.73
LGE, *n* (%)	24 (9.2)	19 (14.2)	5 (3.9)	0.015
LGE ischaemic pattern, *n* (%)	11 (4.2)	8 (6)	3 (2.3)	0.83
Coronary angiography performed, *n* (%)	145 (55.3)	108 (80.6)	37 (28.9)	**<0.001**
Critical coronary artery disease, *n* (%)	21 (8)	21 (15.7)	0 (0)	0.81
IVUS performed, *n* (%)	71 (27.1)	48 (35.8)	23 (18)	0.012
FFR ($n = 49$) median (interquartile range)	0.91 (0.87–0.94)	0.91 (0.87–0.94)	0.83 ± 0.11	0.12
FFR <0.8, *n* (%)	7 (2.7)	3 (2.2)	4 (3.1)	0.045
SPECT performed, *n* (%)	64 (24.4)	39 (29.1)	25 (19.5)	0.097
SPECT maximum heartrate predicted (%)	92 (%)	99 (%)	88.2 ± 7.9 (%)	0.055
SPECT result positive, *n* (%)	12 (4.6)	8 (6)	4 (3.1)	0.25
Exercise stress-testing ECG performed, *n* (%)	106 (40.5)	53 (39.6)	53 (41.4)	0.86
Exercise stress-testing ECG positive, *n* (%)	17 (6.5)	16 (11.9)	1 (0.8)	**<0.001**
Exercise stress-testing ECG maximum heartrate predicted (%), median (interquartile range)	90 (85–96)	91 (85–99)	90 (85–93)	0.24
CCTA performed, *n* (%)	210 (80.2)	122 (91)	88 (68.8%)	**<0.001**

CCTA: coronary computed tomography angiography; CMR: cardiovascular magnetic resonance imaging; ECG: electrocardiogram; FFR: fractional flow reserve; IVUS: intravascular ultrasound; LGE: late gadolinium enhancement; LV: Left ventricle; LVEF: left ventricular ejection fraction; SPECT: single-positron emission computer tomography.

Table 3: Surgery

	All ($n = 262$)	≥30 years ($n = 134$)	<30 years ($n = 128$)	*P*-value
Surgery performed, *n* (%)	74 (28.2)	43 (32.1)	31 (24.2)	0.097
Unroofing	55 (21)	30 (22.4)	25 (19.5)	0.43
Reimplantation	7 (2.7)	4 (3)	3 (2.3)	1.00
Coronary Artery Bypass Graft	5 (1.9)	5 (3.7)	0 (0)	0.13
Pulmonary artery translocation	0 (0)	0 (0)	0 (0)	NA
Vouhe's procedure	2 (0.8)	0 (0)	2 (1.6)	0.34
Ostioplasty	4 (1.5)	3 (2.2)	1 (0.8)	0.86
Other	1 (0.4)	1 (0.7)	0 (0)	1.00
Aortic cross-clamp time (min), median (interquartile range)	54.5 (46–69.2)	54 (48–67)	57.9 ± 21.7	0.86
Intraoperative complications, *n* (%)	7 (2.7)	6 (4.5)	1 (0.8)	**<0.001**
Coronary lesion	3 (1.1)	3 (2.2)	0 (0)	0.26
Bleeding	2 (0.8)	1 (0.7)	1 (0.8)	1.00
Change of surgical strategy	1 (0.4)	1 (0.7)	0 (0)	1.00
Perioperative ischaemia	1 (0.4)	1 (0.7)	0 (0)	1.00
Commissure reimplantation after unroofing, *n* (%)	7 (2.7)	2 (1.5)	5 (3.9)	0.19
Intimal tacking down, *n* (%)	39 (14.9)	25 (18.7)	14 (10.9)	0.42
Trapdoor reimplantation technique, *n* (%)	2 (0.8)	1 (0.7)	1 (0.8)	1.00
Aortic valve repair, *n* (%)	4 (1.5)	2 (1.5)	2 (1.6)	1.00
Postoperative complications, *n* (%)	10 (3.8)	7 (5.2)	3 (2.3)	0.65
Pericardial effusion requiring drainage	2 (0.8)	1 (0.7)	1 (0.8)	1.00
Pleural effusion requiring drainage	1 (0.4)	0 (0)	1 (0.8)	0.98
Postoperative arrhythmia	3 (1.1)	3 (2.2)	0 (0)	0.26
Postoperative neurological deficit persisting at discharge	1 (0.4)	1 (0.7)	0 (0)	1.00
Other	9 (3.4)	6 (4.5)	3 (2.3)	0.54
Death after surgery, *n* (%)	0 (0)	0 (0)	0 (0)	NA
Non-surgical reintervention after surgery, *n* (%)	3 (1.1)	2 (1.5)	1 (0.8)	1.00
Surgical reintervention after surgery, *n* (%)	1 (0.4)	1 (0.7)	0 (0)	1.00
Hospital stay after surgery, median (interquartile range)	9 (6–14)	10 (7–15)	8 (6–10.2)	0.072

CABG: coronary artery bypass graft.

Table 4: Univariable logistic regression for referral to surgery

	n	OR	*P*-value adjusted (FDR)
R-AAOCA	150	2.0 (1.14–3.57)	**0.040**
L-AAOCA	51	1.56 (0.81–2.94)	0.23
Intramural course	142	4.66 (2.55–8.93)	**<0.001**
Slit-like ostium	112	5.50 (2.96–10.65)	**<0.001**
Acute take-off angle	129	1.57 (0.87–2.89)	0.19
R-AAOCA with all high-risk features	71	2.15 (1.2–3.84)	**0.028**
Symptomatic	146	3.7 (2.04–6.67)	**<0.001**
Age at diagnosis	262	1.01 (1.00–1.02)	0.14
Paediatric centres	70	0.16 (0.06–0.36)	**<0.001**
Adult centres	192	6.26 (2.77–16.83)	**<0.001**
Age <30 years	128	0.61 (0.35–1.04)	0.12
Recreational sport	126	1.84 (1.05–3.28)	0.069
Competitive sport	54	1.52 (0.79–2.85)	0.23
LGE	93	1.20 (0.44–3.13	0.71
SPECT positive	55	1.45 (0.33–5.74)	0.65
Exercise stress-testing ECG	102	5.67 (1.87–19.65)	**0.009**
Pathologic ECG	239	1.02 (0.52–1.94)	0.95

ECG: electrocardiogram; FDR: false discovery rate; L-AAOCA: left anomalous aortic origin of a coronary artery; LGE: late gadolinium enhancement; OR: odds ratio; R-AAOCA: right anomalous aortic origin of a coronary artery; SPECT: single-positron emission computer tomography.

Table 5: Symptoms and surgery by anomalous type

	n	Symptoms	Surgery
R-AAOCA	150 (58%)	54 (36%)	53 (35%)
R-AAOCA with all high-risk features	84 (32%)	65 (77%)	41 (49%)
L-AAOCA	51 (20%)	26 (51%)	19 (37%)
L-AAOCA with all high-risk features	10 (4%)	5 (50%)	9 (90%)
LCA from RCA	7 (3%)	5 (71%)	0 (0%)
RCA from LCA	2 (1%)	1 (50%)	0 (0%)
High origin LCA	5 (2%)	4 (80%)	0 (0%)
High origin RCA	16 (6%)	10 (63%)	1 (6%)
Cx-AAOCA	20 (8%)	9 (45%)	0 (0%)
Other	10 (4%)	6 (60%)	4 (40%)

Cx-AAOCA: circumflex anomalous aortic origin of a coronary artery; L-AAOCA: left anomalous aortic origin of a coronary artery; LCA: left coronary artery; R-AAOCA: right anomalous aortic origin of a coronary artery; RCA: right coronary artery.

Diagnostics

Diagnostic approaches may vary between paediatric and adult patients. For middle-aged patients, the presence of concomitant CAD poses a further challenge, and diagnosing a haemodynamically significant AAOCA becomes a diagnosis of exclusion. Significant differences in the use of advanced diagnostic tests were observed between different centres and age groups (Fig. 3). CCTA was performed more frequently in adult centres, while paediatric centres conducted fewer CCTA scans, preferring usually CMR. This discrepancy is due to persistent concerns about radiation exposure in children and young adults. However in this series, the utilization of the radiation-free alternative (i.e. CMR) did not differ between the 2 age groups. Although CMR may have limited spatial resolution [18], it can provide additional information, such as the detection of scar tissue, which serves as a substrate for ventricular tachycardia [2], as well as stress tests and evaluation of myocardial perfusion. Among patients who underwent CMR, one-quarter presented with LGE, half of them exhibited an ischaemic pattern. This finding suggests the presence of scar tissue in some of these patients, which may contribute to the risk of ventricular tachycardia. Compared to an autopsy study with cases of SCD and AAOCCA, fibrosis was reported in a third of cases and there mainly subendocardial [19]. The higher ratio of deceased patients with subendocardial LGE may suggest the malignancy of this finding in AAOCA patients.

It should be noted that advanced invasive evaluations (i.e. IVUS and FFR assessment) were only performed in a relatively small proportion of patients, although it is the recommended gold standard for haemodynamic evaluation [17]. However, due to the invasive nature of FFR and IVUS, its application in the paediatric population has to be considered more carefully and is probably less suitable.

The differences between the centres in approaching diagnosis of AAOCA patients is challenging for comparing the results. Especially the lack of stress tests does not allow for a differentiation between haemodynamically relevant and non-relevant AAOCA. Another problem is that the anatomical high-risk features have been reported but not quantified (e.g. minimal lumen area of the intramural course, angle of the take-off or the intramural length).

Surgery

According to the guidelines published by ESC in 2020 [6], when AAOCA patients present with symptoms, or evidence of stress-induced myocardial ischaemia in matching territory, the gold standard treatment is surgical repair. Among the available techniques, the unroofing of the intramural segment is the most frequent technique reported [20]. However, there is no operation that can fit all anatomical variants of AAOCA. Other techniques (such as coronary ostioplasty or translocation of the anomalous coronary) may be selected to treat at best the anatomy of the anomalous coronary artery [20]. In our population, surgery was performed in a third of all patients, and coronary unroofing was used in most of them (Table 3). These findings are in accordance with current literature and guidelines, which recommend unroofing as the preferred surgical technique in AAOCA with intramural course [20]. In particular, no pulmonary artery translocations were performed, indicating a change in views on the pathological mechanism underlying the malignancy of AAOCA. This more extensive surgery was previously employed to address the historically suspected scissor-like mechanism. However, since this mechanism could not be demonstrated, the current consensus attributes ischaemia to lateral compression of the intramural segment, making that technique obsolete. Unroofing was performed more frequently in patients <30, while CABG was only performed in patients ≥30 years. This can be explained by the higher rate of concomitant CAD in patients ≥30 years, which has been described in other studies [21, 22].

However, paediatric centres seemed to be more conservative with referral to surgery (Supplementary Material, Table S1). Most of the centres included in this registry were surgical centres, which could represent a possible selection bias, with mainly potential surgical candidates being referred to surgical centres instead of the full spectrum of AAOCA. Furthermore, the higher number of high-risk anatomical features in the older population could be a reflection of this selection bias, as aforementioned.

In general, surgical repair was safe, as no operative or early deaths were reported. However, it is noticeable that there still exists a certain degree of surgical risk and occurrence of complications. Intraoperative complications occurred in 7 patients (2.7%), including coronary lesions, bleeding and perioperative ischaemia. Additionally, postoperative complications were observed in 10 patients (3.8%), encompassing pericardial and pleural effusion requiring drainage, postoperative arrhythmia and persisting neurological deficits. Surgical reintervention was necessary in 1 patient only, while non-surgical reintervention was required in 3 patients. These events are in line with recent literature [20], and demonstrate the compelling need of clarity in surgical indications when diagnosis of AAOCA is made (as shown in Table 5). In fact, the biggest challenge that surgical repair of AAOCA currently faces is the selection of appropriate patients. The decision to undergo surgery appeared to primarily depend on anatomical characteristics rather than relevant functional testing results, since functional tests were performed only in a small proportion of patients (Supplementary Material, Table S2).

Limitations

A limitation of these 1st results from the EURO-AAOCA registry is that only baseline and no subsequent follow-up data have been examined at this stage of analysis. Therefore, we cannot draw any conclusions regarding the long-term outcome in patients who were operated or treated conservatively. Surgical centres mainly contributed to the registry, which could lead to possible selection bias. Importantly, since paediatric as well as adult centres contributed to the final population and mostly surgical facilities were included, it is possible that not the entire spectrum of presentations is represented in this cohort. The image data itself was not available for analysis, but only the reports of the individual centres. Differences in interpretation of the scans could therefor lead to differing results between centres, which holds especially true for anatomical high-risk features.

CONCLUSION

R-AAOCA confirmed to be the most commonly diagnosed anomaly in this multicentre registry. Currently, no uniform agreement exists among centres with regard to diagnostic protocols and clinical management for AAOCA variants. Although surgery is a safe procedure in AAOCA, future longitudinal outcome data will hopefully shed light on how to best decide towards optimal selection of patients undergoing revascularization versus conservative treatment.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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DATA AVAILABILITY

Data are available upon request.

Author contributions

Christoph Gräni: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review and editing. **Anselm W. Stark:** Data curation; Formal analysis; Methodology; Validation; Writing—original draft; Writing—review and editing. **Mauro Lo Rito:** Conceptualization; Data curation; Investigation; Supervision; Validation; Writing—review and editing; **Alessandro Frigiola:** Investigation; Validation; Writing—review and editing. **Matthias Siepe:** Supervision; Writing—review and editing. **Bertrand Tchana:** Data curation; Investigation; Writing—review and editing. **Alberto Cipriani:** Data curation; Investigation; Writing—review and editing. **Alessandro Zorzi:** Investigation; Validation; Writing—review and editing. **Valeria Pergola:** Conceptualization; Investigation; Writing—review and editing. **Domenico Crea:** Data curation; Validation; Writing—review and editing. **George Sarris:** Investigation; Writing—review and editing. **Elephterios Protopapas:** Data curation; Investigation; Validation; Writing—review and editing. **Domenico Sirico:** Data curation; Writing—review and editing. **Giovanni Di Salvo:** Conceptualization; Writing—review and editing. **Cinzia Pegoraro:** Data curation; Writing—review and editing. **Patrizio Sarto:** Data curation; Supervision; Writing—review and editing. **Katrien Francois:** Data curation; Investigation; Methodology; Writing—review and editing. **Alessandra Frigiola:** Data curation; Investigation; Writing—review and editing. **Alessandra Cristofaletti:** Data curation; Investigation; Writing—review and editing. **Ryan E. Accord:** Data curation; Investigation; Writing—review and editing. **Alvaro Gonzalez Rocafort:** Data curation; Investigation. **Geoffroy Debeco:** Data curation; Investigation. **Massimo Padalino:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Validation; Visualization; Writing—review and editing.

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