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Coronary Artery Anomalies

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ABSTRACT: Coronary artery anomalies (CAAs) are a group of congenital conditions characterized by abnormal origin or course of any of the 3 main epicardial coronary arteries. Although CAAs have been identified as a common underlying condition in young athletes with sudden cardiac death, the widespread use of invasive and noninvasive coronary imaging has led to increased recognition of CAAs among adults. CAAS are often discovered as an incidental finding during the diagnostic workup for ischemic heart disease. The clinical correlates and prognostic implication of CAAs remain poorly understood in this context, and guideline-recommended therapeutic choices are supported by a low level of scientific evidence. Several studies have examined whether assessment of CAA-related myocardial ischemia can improve risk stratification in these patients, suggesting that multimodality imaging and functional tests may be key in the management of CAAs. The aim of this review is to outline definitions, classification, and epidemiology of the most relevant CAAs, highlighting recent advances and the potential impact of multimodality evaluation, and to discuss current therapeutic opportunities.

Key Words: coronary vessels ■ death, sudden, cardiac ■ heart defects, congenital ■ myocardial ischemia

Coronary artery anomalies (CAAs) include several congenital conditions characterized by abnormal origin or course of any of the 3 main epicardial coronary arteries. Because of the existence of many possible interindividual normal anatomic variants, the term CAA has historically been restricted to those occurring in <1% of the general population.[1]

A wider use of echocardiography in the pediatric population has led to a more frequent recognition of CAAs in children and adolescents. In parallel, the widespread use of invasive and noninvasive coronary imaging for the assessment of ischemic heart disease has increased the reported prevalence of CAAs in adults, often as incidental findings.[2,3] The prognostic implications of CAAs in this setting remain poorly understood,[2] and guideline-recommended therapeutic decisions are supported by a low level of scientific evidence.[4,5] Management of asymptomatic patients with CAAs may be challenging, particularly in younger individuals. CAAs have been associated with sudden cardiac death (SCD), especially in young individuals engaged in sports.[6] In one of the largest autopsy studies conducted to date, the anomalous aortic origin of a coronary artery was the second most common cause of SCD in young competitive athletes.[7]

The present review aimed to summarize the epidemiological, clinical, and prognostic features of the most relevant CAAs (as detailed in the Data Supplement), underscoring the current diagnostic and therapeutic pathways, as well as persisting uncertainties and perspectives.

CLASSIFICATION AND EPIDEMIOLOGY OF CAAS

Normally, there are 3 main epicardial coronary arteries: the right coronary artery, emerging from the right sinus of Valsalva, and the left anterior descending and left circumflex coronary arteries, characterized by an initial common tract (the left main coronary artery) that arises from the left sinus of Valsalva.[1] In the general population, both the course of each epicardial artery and the distribution of the collateral branches may show significant interindividual variability, so various phenotypes have been identified as normal variants, which are distinguished from CAAs by their higher prevalence (ie, >1% among unselected individuals) and not having been as-

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Nonstandard Abbreviations and Acronyms

CAA	coronary artery anomaly
CCTA	coronary computed tomography angiography
CMR	cardiac magnetic resonance
ICA	invasive coronary angiography
MACE	major adverse cardiac event
PCI	percutaneous coronary intervention
SCD	sudden cardiac death

sociated with major adverse events.[1,2,8] Among these, the origin of the posterior descending coronary artery from either the right (70%) or the left (10%) coronary artery defines the coronary dominance (codominance in 20% of cases), with the dominant artery usually providing blood supply to the sinoatrial and atrioventricular nodes, albeit with some exceptions. Further variants relate to the blood supply of the inferior myocardial wall, derived from posterolateral branches originating from either the right coronary artery or the circumflex coronary artery, whereas the left anterior descending coronary artery may supply a portion of the apical inferior wall in the case of a wraparound course (in up to 30% of people).[1,2,8] Other common possible findings include trifurcation of the left main artery, with a ramus intermedius (in ≈20% of the cases), distributing across a variable portion of the lateral wall of the left ventricle, and the presence of a conus branch directly emerging from the right sinus of Valsalva—and not from the right coronary artery—to supply the right ventricular outflow tract (with a prevalence ranging from 10%–50%).[8,9] The origin of the main epicardial arteries also may show some variability. An acute takeoff angle (ie, an angle between the proximal coronary artery and the aortic wall ≤45°), reported in ≈2% of people, or a high takeoff (ie, a coronary ostium ≥1 cm above the sinotubular junction) of either the left main or, more often, the right coronary artery is generally considered a benign variant but may complicate percutaneous coronary interventions (PCIs). Similarly, PCI of the right coronary artery may be more complex in the case of a shepherd's crook morphology, characterized by a tortuous and higher course of the proximal segment of the vessel and classified as a normal variant, found in ≈5% of people.[10,11]

CAAs were described in the 18th century, but the first scientific statement on their relevance and a comprehensive classification was published in 1969[12] and revised in 2000.[13] Use of a heterogeneous nomenclature in historical reports may have led to an underestimation of the true prevalence of CAAs, ranging from 1% to 5.6% in various angiographic or autopsy studies. At least 2 other potential biases may have contributed to such variability: Postmortem examination of coronary arteries is more often performed in young individuals with SCD; and patients with suspected or known CAAs have been referred more often to specialized angiographic centers.[14]

The widespread use of coronary computed tomography angiography (CCTA) has yielded further insight into the epidemiological boundaries of CAAs,[15,16] the prevalence of which appears to be even higher (≈7.9%, as reported in a cohort of 1759 patients).[15]

CAAs can be classified as CAAs of origin, of course, and of termination (Table 1 and Figure 1).

Anomalies of Origin

Anomalous origins of coronary arteries from the pulmonary trunk are rare. In a cohort of 126 595 patients undergoing invasive coronary angiography (ICA), such CAAs were found in 12 cases (0.01%), with pulmonary origin of the left main coronary artery being the most common (n=10), followed by pulmonary origin of the right coronary artery (n=2) and by a single case of pulmonary origin of the left anterior descending artery.[11] Notably, the pulmonary origin of both coronaries has been described in some reports.[17,18]

Although anomalous aortic origin of the coronaries is more common, affecting at least 1 in 1000 individuals, data from observational studies are extremely heterogeneous, so an accurate estimate of its burden is difficult to extrapolate.[8,11,19] The anomalous origin from the opposite sinus is the most clinically relevant, whereas the origin of an artery from the noncoronary sinus represents an unusual finding.[2,13,19] The presence of these CAAs is not associated with other congenital abnormalities,[20] whereas other rarer subtypes (eg, single or inverted coronary arteries) are usually observed in the context of complex congenital heart diseases.[12,13]

The absence of the left main coronary artery with a separate origin of the left anterior descending and left circumflex arteries is found in up to 0.67% of subjects[2] and is considered a normal variant. It should be distinguished from congenital atresia of the left main coronary artery, in which a fibrous tract may hamper myocardial perfusion; in adults, this finding is limited to a few cases.[21] The absence of or severe hypoplasia of the right coronary or left circumflex arteries is another rare CAA.[8,11]

Anomalies of Course

The course of CAAs is of clinical importance especially when dealing with anomalous origin from the opposite sinus, which should be further classified, in order of frequency, as retroaortic, interarterial, subpulmonic (intraconal or intraseptal), prepulmonic, or retrocardiac.[19,22] It is noteworthy that the subpulmonic variant refers to the passage between the aorta, right ventricular outflow tract, pulmonary infundibulum, and interventricular septum (ie, below the pulmonary valve).[19,22]

Table 1. Simplified Nomenclature of CAAs

Type of anomaly	Variant	Subvariants
Anomalies of origin	Anomalous pulmonary origin of the coronaries	Origin of left main coronary artery from the pulmonary artery Origin of right coronary artery from the pulmonary artery Origin of circumflex coronary artery from the pulmonary artery Origin of left and right coronary arteries from the pulmonary artery
	Anomalous aortic origin of the coronaries	Origin of left main coronary artery from the right aortic sinus of Valsalva Origin of right coronary artery from the left aortic sinus of Valsalva Origin of left anterior descending coronary artery from the right aortic sinus of Valsalva Origin of left anterior descending coronary artery from the right coronary artery Origin of circumflex coronary artery from the right aortic sinus of Valsalva Origin of circumflex coronary artery from the right coronary artery Single coronary artery Inverted coronary arteries Others
	Congenital atresia of the left main artery	
Anomalies of course	Myocardial (or coronary) bridging	Symptomatic Asymptomatic
	Coronary aneurysm	Congenital Acquired
Anomalies of termination	Coronary arteriovenous fistula	Congenital Acquired
	Coronary stenosis	Congenital Acquired

CAA indicates coronary artery anomaly.

Coronary arteries with a normal origin also can show some peculiarity in their course. The presence of an intramural tract is defined as myocardial bridging. Although included in many CAAs classifications, it should not be considered as such from a strict epidemiological standpoint, being found in 0.5% to 12% of ICAs and in up to 86% of autopsy series, with an estimated prevalence of 1 in 4 individuals.[23]

A coronary aneurysm is a focal dilatation of a coronary artery of at least 1.5 times its lumen and involving

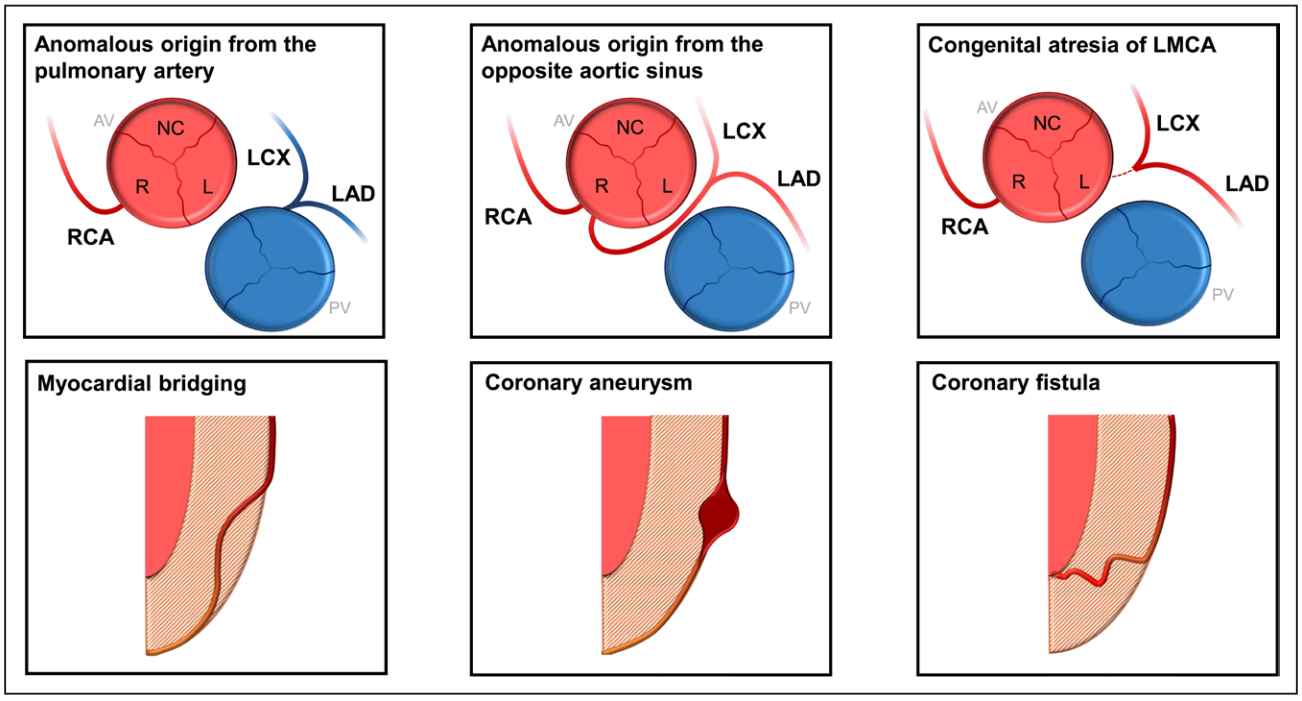

Figure 1. Schematic representation of the major types of coronary artery anomalies.
AV indicates aortic valve; L, left coronary sinus; LAD, left anterior descending coronary artery; LCX, circumflex coronary artery; LMCA, left main coronary artery; NC, noncoronary sinus; PV, pulmonary valve; R, right coronary sinus; and RCA, right coronary artery.

<50% of the vessel length (as opposite to ectasia, which involves ≥50% of the vessel). Coronary aneurysms may be differentiated into saccular if the transverse diameter exceeds the longitudinal diameter and fusiform if the opposite is true.[24] Although coronary aneurysm may be attributable to various systemic diseases (eg, atherosclerosis, syphilis, Kawasaki disease), congenital coronary aneurysms are extremely rare.[24,25]

Congenital coronary stenosis is another rare anomaly, characterized by a significant tightening—up to complete occlusion or atresia—of a coronary ostium.[2]

Anomalies of Termination

Coronary arteriovenous fistulas are characterized by the direct termination of a coronary artery, which often may be enlarged and tortuous, into another cardiovascular lumen (ie, another vessel or a cardiac chamber). Although they may be a relatively common finding (reported prevalence, ≈0.9% at CCTA), in the context of complex malformations, they are rare in adults.[26]

CAAS AND OUTCOME: FROM INNOCENT BYSTANDERS TO LIFE-THREATENING CONDITIONS

The clinical and prognostic implications of CAAs are poorly understood because most of the current evidence derives from few retrospective studies. Nonetheless, some variants have historically been associated with an increased risk of cardiac events; thus, therapeutic choices are currently driven mainly by anatomic features.[4,5]

Anomalies of Origin

Anomalous pulmonary origin of coronaries is associated with ischemia in the supplied myocardial territories, the extension of which depends both on the vessel involved and on the development of collateral circulation. Although patients with anomalous pulmonary origin of the right coronary artery may be asymptomatic or complain of mild angina or dyspnea, some cases of severe symptoms and even SCD have been reported.[27,28] On the contrary, anomalous pulmonary origin of the left coronary artery may be rapidly lethal in >90% of cases,[29] defining the so-called infant type.[30] Notably, a later diagnosis, or adult type, should not be univocally associated with a good prognosis. In a comprehensive review of 151 cases with a mean age of 41 years, 66% had symptoms, 17% had ventricular arrhythmias or SCD, and only 14% were asymptomatic.[31]

The prognostic significance of the anomalous aortic origin of coronaries, especially those originating from the opposite sinus, is more nuanced.[2,19] According to historical reports, both the right and left coronary arteries originating from the opposite sinus may be associated with an increased risk of SCD.[32–34] Among 1866 sudden deaths that occurred in American athletes over a 27-year period, 119 (17%) were attributed to such CAAs,[7] and left coronary artery originating from the right sinus was the most frequently involved, particularly in the presence of high-risk features such as a slit-like ostium, an acute takeoff angle, and an interarterial course.[35] Nevertheless, the absolute risk of SCD attributable to these anomalies remains unclear; although it could have been overestimated because of referral bias in autopsy studies and small series, it seems exceedingly low in larger registries.[19,36] Furthermore, because most of the available studies have focused on young individuals practicing strenuous exertion, it remains unclear whether these anomalies should be considered dangerous when documented in nonathletes or in the elderly. Only 1 study attempted to address this question. In 68 subjects (mean age, 56±11 years) undergoing CCTA for the evaluation of atherosclerotic disease, the presence of anomalous coronary origin from the aorta was not associated with increased risk of major adverse cardiac events (MACEs) compared with matched control subjects, regardless of the presence of high-risk features.[37] Whereas an event-free survival up to adulthood could per se represent a selection bias with respect to more detrimental variants, with aging, the risk of MACEs secondary to atherosclerotic disease could progressively overcome that of the abnormal anatomy.[37]

Finally, the presence of a single coronary artery with an interarterial course may increase the risk of MACEs.[11,38] Congenital atresia of the left main coronary artery has been associated with congestive heart failure or malignant arrhythmias during infancy in most cases.[21]

Anomalies of Course

The course of the abnormal vessel is a risk modifier in patients with anomalous coronary artery origin from the aorta. Whereas subpulmonic, prepulmonic, retroaortic, and retrocardiac courses have not been associated with SCD, an interarterial course is considered malignant and is often associated with other high-risk anatomic features (eg, slit-like ostium, intramural tract).[19] The distinction between these subvariants may be difficult in some cases (eg, distinguishing subpulmonic from interarterial courses).[39]

Myocardial bridging may be associated with typical or atypical angina,[40] but its prognostic impact is debated. In a meta-analysis including 5486 subjects, myocardial bridging was associated with a higher risk of myocardial infarction but not of other MACEs.[41] Conversely, a report pooling 21 studies showed that, although MACEs and myocardial ischemia were more common in patients with myocardial bridging, no significant differences emerged when myocardial infarction and cardiovascular death were considered end points.[42] Some characteristics of myocardial bridging such as its length or depth or the degree of endothelial dysfunction could contribute differently to myocardial ischemia.[23]

Similarly, the prognostic significance of coronary aneurysms is unclear. Whereas the pathophysiologi-

cal substrate may play a major role, larger coronary artery diameter has been independently associated with increased risk of serious events.[43]

Finally, although the stenosis (or slit-like aspect) of a coronary ostium is a risk modifier for other CAAs, current evidence on the clinical significance of isolated congenital coronary stenosis or atresia is limited to a few reports.[44] In theory, such CAAs should be considered potentially fatal, increasing the risk of heart failure or neonatal death.[44]

Anomalies of Termination

Coronary arteriovenous fistulas can range from completely asymptomatic to potentially lethal, depending on left-to-right shunt or steal phenomena secondary to the low resistance of the anomalous connection. Although the most severe phenotypes usually manifest early during infancy, a few adult cases have been reported. Dyspnea and right ventricular involvement are landmark signs; other nonspecific manifestations (eg, chest pain, endocarditis, arrhythmias) have rarely been described.[26,45]

DIAGNOSTIC PRINCIPLES IN PATIENTS WITH CAAS

Although the presence of a CAA can be suspected in the case of a young individual with ischemia-like symptoms, CAAs are much more often incidental findings during workup for ischemic heart disease, causing clinical uncertainty for the cardiologist and anxiety for the patient (Figure 2). Various diagnostic techniques can be used to investigate coronary anatomy and to assess the presence of high-risk features. CCTA is currently considered the gold standard, and cardiac magnetic resonance (CMR) is becoming an alternative.[3] Furthermore, in uncertain cases, provocative tests can assess inducible myocardial ischemia, and electrocardiographic monitoring systems could detect arrhythmic events.

ICA: From Anatomic Evaluation to Invasive Functional Assessment

ICA was considered the most important and definite tool to identify and classify CAAs. However, because of its invasiveness, relatively low spatial resolution, and lack of 3-dimensional images, it has been progressively replaced by CCTA.[46–48] However, the possible utility of ICA in this setting has been reappraised through the implementation of intravascular imaging approaches, allowing a more precise evaluation of intraluminal geometry.[49] Intravascular ultrasound is an invasive tomographic technique with at least 10 times higher temporal and spatial discriminative accuracy compared with standard ICA; hence, it may be useful for better definition of the proximal portion of CAAs, especially anomalous aortic origin of coronaries. In a proof-of-concept study, Angelini et al[49] used intravascular ultrasound to determine the percentage of stenosis of the proximal intramural course in patients whose right coronary artery originated from the left sinus and to guide subsequent PCI in selected cases. Conversely, optical coherence tomography is a light-based modality of intravascular imaging with higher spatial resolution but lower penetrance compared with intravascular ultrasound. Hence, it is more useful to define the coronary luminal surface than the entire depth of vessel walls and anatomic relationships. The use of optical coherence tomography to study CAAs is limited to a few reports.[49]

Besides intravascular imaging, ICA can now be integrated with functional assessment of flow-limiting vessel narrowing through dedicated techniques such as fractional flow reserve and instantaneous wave-free ratio. These approaches are increasingly being used to determine coronary flow reserve in the setting of CAAs (especially with myocardial bridging and anomalous aortic origin of the coronaries with interarterial or subpulmonic course), where they may also drive therapeutic choices (eg, interventional versus conservative strategies).[23,50–52]

CCTA: The Current Gold Standard

Multidetector CCTA offers numerous advantages that have made it the gold standard technique for the study of CAAs.[15,46,47,53] CCTA offers a detailed characterization of the anatomic clues associated with high-risk CAAs, allows visualization of the surrounding cardiac and noncardiac structures and of their relative 3-dimensional relations,[54–56] and is more widely applicable for population studies. The introduction of ECG gating[57,58] and postprocessing rendering systems[59] has resulted in significant improvements in image quality, reduction in acquisition time, and reduction of radiation exposure.[57,60]

CMR: An Emerging Role

CMR has emerged as an alternative to CCTA in patients with CAAs.[61] Beside allowing similar anatomic definition of the origin and course of coronary arteries,[39] the evaluation of systolic and valvular function and the characterization of myocardial tissue can provide valuable information. Moreover, assessment of the presence and extension of late gadolinium enhancement can unveil the presence of fibrosis, suggesting a causal link between the anomaly and myocardial ischemia.[62] However, because of the slightly lower spatial resolution and the lower availability of specific instrumentation and expertise, only a secondary role is still ascribed to CMR in the investigation of CAAs.[3]

Echocardiography

Transthoracic echocardiography is considered a key examination in the diagnostic workup of CAAs in children, in

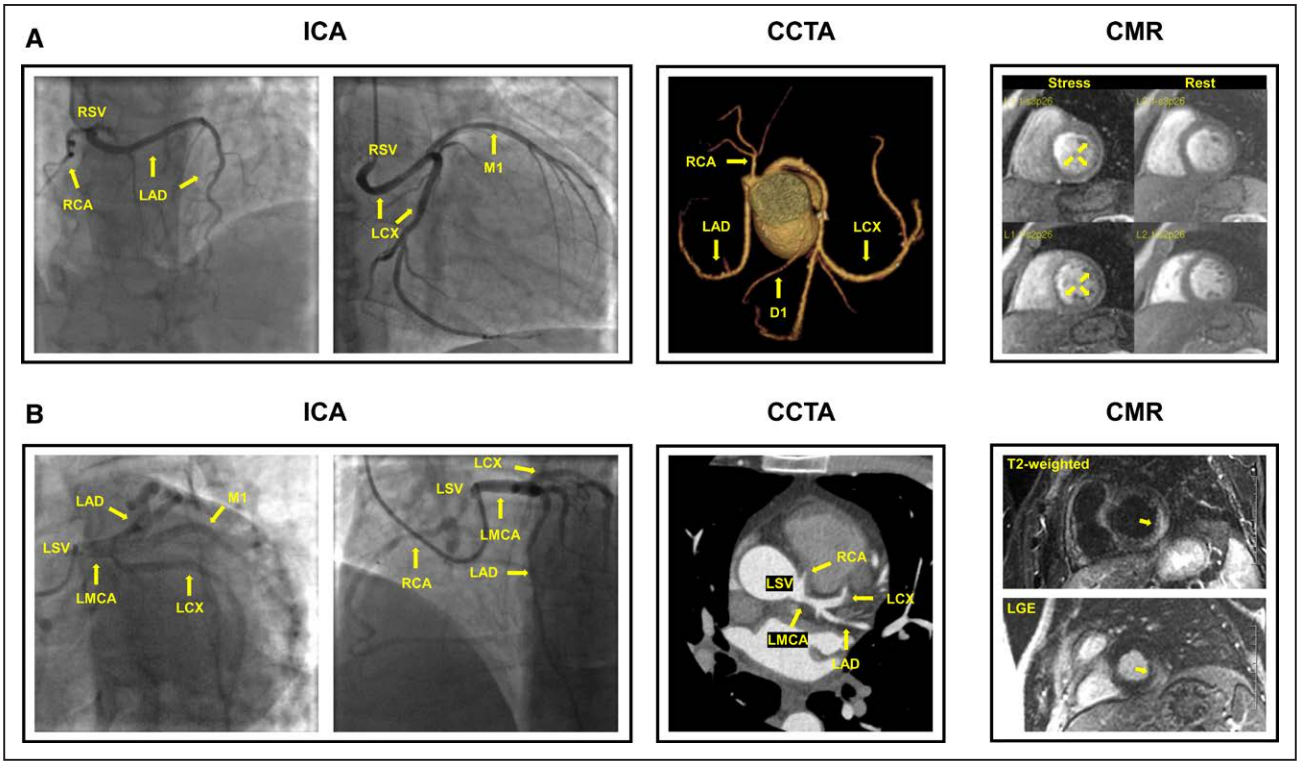

Figure 2. Real-life examples of coronary artery anomalies as unexpected findings.
A, A 44-year-old man presented to the emergency room for typical chest pain, with nonspecific electrocardiographic abnormalities and normal high-sensitivity troponin T levels. An exercise ECG was performed and was positive for ischemic electrocardiographic changes at peak exercise and during recovery. The invasive coronary angiography showed no significant coronary stenosis; instead, an unexpected abnormality was observed: The left anterior descending artery (LAD) originated from the right aortic sinus, sharing the same ostium with the right coronary artery (RCA), and the left circumflex artery (LCx) emerged from the right aortic sinus but from a separate and higher ostium. Coronary computed tomography angiography (CCTA) showed a subpulmonic and a retroaortic course of the LAD and LCx, respectively. A stress cardiac magnetic resonance (CMR) demonstrated diffuse subendocardial inducible ischemia not matching any specific coronary supplied territory. The patient was treated conservatively. **B**, A 42-year-old man with sudden onset of oppressive chest pain and an ECG pattern diagnostic for inferior ST-segment–elevation myocardial infarction (STEMI) was referred to our catheterization laboratory for emergency percutaneous coronary intervention. No coronary occlusion or stenoses were found, but the RCA had an abnormal origin from the left aortic sinus. At CCTA, the RCA had an initial interarterial course, with a slight lumen reduction that was more evident during systole. Over the next days, the patient remained stable, with complete resolution of symptoms and ECG abnormalities, whereas high-sensitivity troponin T progressively decreased to normal levels from a peak value of 1696 ng/L. Finally, CMR was performed to assess the presence and extent of myocardial necrosis but rather revealed morphological findings suggestive of acute myocarditis. D1 indicates first diagonal branch; LGE, late gadolinium enhancement; LMCA, left main coronary artery; LSV, left sinus of Valsalva; and RSV, right sinus of Valsalva.

whom optimal acoustic windows commonly allow the visualization of coronary ostia without radiation exposure.[63] The transesophageal approach is accurate for the identification of both the origin and the initial tract of coronary arteries.[64] Furthermore, the assessment of chamber volumes and contractility and valvular function provides fundamental complementary information.[3] However, considering the lower diagnostic accuracy in identifying coronary ostia and the inability to visualize their entire course and relations with the great vessels and other structures, echocardiography plays a minor role in adults with CAAs.

Provocative Tests and Electrocardiographic Monitoring

Current guidelines on the management of adults with congenital heart disease suggest the use of a provocative test either when CAAs are an incidental finding or when their clinical significance cannot be completely extrapolated from anatomic studies (Table 2).[4,5] However, no standardized protocols have been proposed so far to stratify CAA-related ischemia because only a few studies have addressed this topic.

Physical exercise stress protocols mimic physiological conditions; therefore, they are empirically considered the first choice to assess inducible ischemia. Exercise ECG is often the first test performed in individuals able to run or cycle because of its cost-effectiveness and wide availability.[65] Although the interpretation of ECG changes is often limited by the presence of abnormalities at baseline, the implementation of more advanced measurements (eg, the ST-segment depression/heart rate hysteresis) may improve its diagnostic accuracy.[66] Although the occurrence of life-threating events in patients with CAAs

Table 2. Comparison of Current International Guidelines for the Assessment of CAAs

2018 AHA/ACC guideline for the management of adults with congenital heart disease			2020 ESC guidelines for the management of adult congenital heart disease		
COR	LOE	Recommendations	COR	LOE	Recommendations
I	C	Coronary angiography with catheterization, CCTA, or CMR is recommended for the evaluation of an anomalous coronary artery.			
I	C	Anatomic and physiological evaluation should be performed in patients with anomalous aortic origin of the left coronary from the right sinus or right coronary from the left sinus.	I	C	Nonpharmacological functional imaging (eg, nuclear study, echocardiography, or CMR with physical stress) is recommended in patients with coronary anomalies to confirm/exclude myocardial ischemia.

Adapted from Baumgartner et al[4] and Stout et al.[5] AHA/ACC indicates American Heart Association/American College of Cardiology; CAA, coronary artery anomaly; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; COR, Class of Recommendation; ESC, European Society of Cardiology; and LOE, Level of Evidence.

has been linked to strenuous effort,[2,7,35] the sensitivity of stress testing in identifying patients at risk of myocardial ischemia secondary to CAAs is low, and no studies have validated specific and reliable predictive targets to be achieved in this context.[67]

Exercise or pharmacological stress imaging with dobutamine or vasodilators is another option deserving further investigation. Stress echocardiography is widely available but may be limited by poor acoustic windows, wide interoperator variability in interpretation, and the lack of standardized protocols.[68] Stress CMR is an attractive alternative considering its higher diagnostic accuracy and lower operator dependency.[69] Indeed, the feasibility of dobutamine stress CMR in a large pediatric cohort with anomalous aortic origin of a coronary artery (n=182 patients with 221 stress CMR scans available for evaluation) has been demonstrated, showing inducible hypoperfusion in 14% of cases, with a high interobserver agreement and in the absence of significant procedure-related adverse events.[70]

Single-photon emission computed tomography has been proposed as a first choice to detect CAA-related ischemia.[3,71,72] Exercise positron emission tomography may be another alternative, having been tested in a single study (27 adults with right coronary artery originating from the left sinus) to assess the burden of myocardial ischemia in patients symptomatic for typical angina or exertional dyspnea.[73]

The coexistence of a CAA and ischemic symptoms does not automatically imply a causative role of the former, particularly in the absence of high-risk anatomic clues and in older individuals in whom atherosclerotic disease should always be excluded.[72,74] Moreover, other possible causes of myocardial ischemia (eg, coronary spasm, microvascular disease) can be more difficult to rule out.[75] In such cases, matching between myocardial territories supplied by the CAA and ischemic areas is important. Hybrid imaging (eg, combining CCTA and nuclear imaging) has been proposed for this purpose,[72,74,76] but a wider use of CMR, combining perfusion sequences, anatomic information, and tissue characterization, should be encouraged and will likely be a preferred subject of future studies (Figure 3).[69]

Last, because arrhythmias can represent the first manifestation of CAA-related ischemia, electrocardiographic monitoring (eg, Holter monitoring, loop recorders) may be proposed in patients with known CAAs and suspicious symptoms (eg, palpitations, presyncope, syncope).[4,13]

ROLE AND DETECTION OF ISCHEMIA IN PATIENTS WITH CAAS

Myocardial ischemia is considered the primary cause of life-threatening events in patients with CAAs. Although some CAAs (pulmonary origin of coronary arteries, coronary atresia, etc) are invariably associated with severe impairment of myocardial perfusion,[2,14] such a relationship is much more nuanced for other anomalies (eg, anomalous aortic origin of coronaries), the clinical significance of which may be harder to prove. Although the use of provocative tests is advised in uncertain cases, mechanisms linking some CAAs to myocardial ischemia are still debated. Moreover, even in the case of myocardial ischemia, it remains unclear whether it is associated with an increased risk of life-threatening events.[37]

As discussed, an interarterial course, ostial tightness, and an acute takeoff angle are considered high-risk anatomic features because they are consistently associated with SCD in young athletes.[7,14,35] From a pathophysiological standpoint, the possible compression of the anomalous coronary between the great vessels was first proposed as a causative mechanism of ischemia and hence SCD. However, such a compressive effect from a low-pressure vessel such as the pulmonary artery seems unlikely in the absence of significant pulmonary hypertension.[2] Conversely, the vigorous systolic expansion of the aorta may cause a kinking (mainly in the presence of an acute or high takeoff angle) or precipitate a coronary spasm, and the presence of a slit-like ostium may facilitate intermittent vessel occlusion.[48] However, isolated coronary spasm has rarely been reported in patients with CAAs; it may be transient or rapidly reversed or may affect the entire coronary tree rather than being the sole

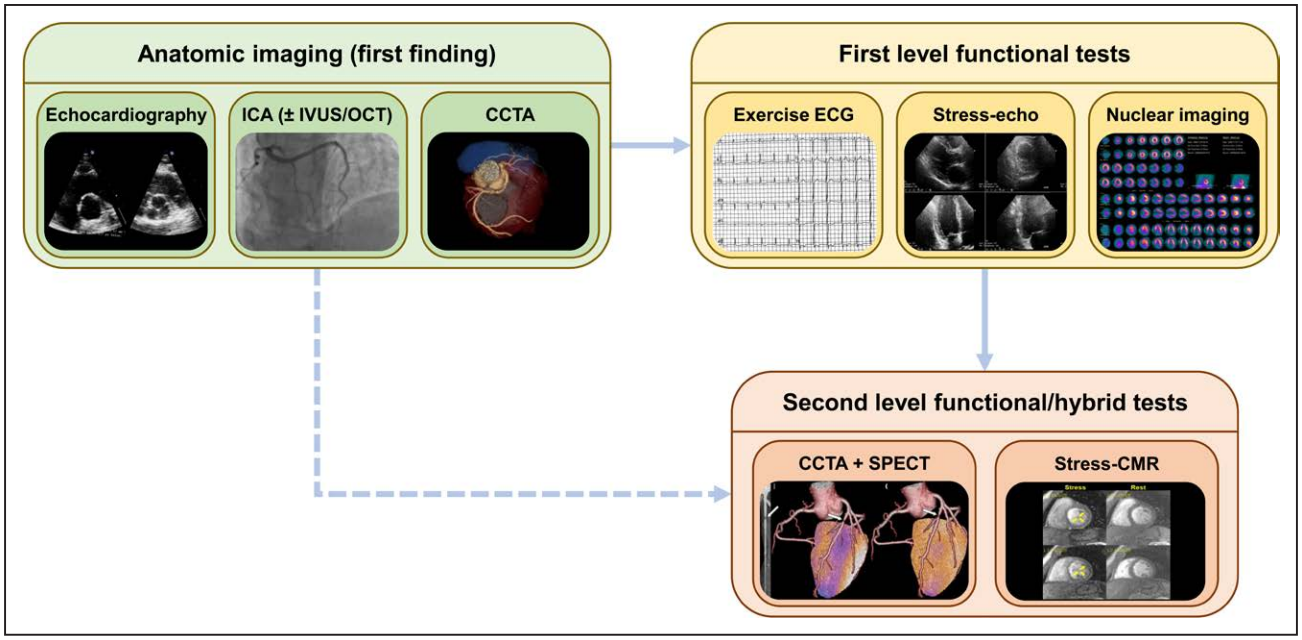

Figure 3. Imaging and functional tests to diagnose coronary artery anomalies (CAAs) and assess myocardial ischemia. CAAs are most often identified as unexpected findings at echocardiography or at invasive coronary angiography (ICA) or coronary computed tomography angiography (CCTA) during the diagnostic workup of ischemic heart disease. First-level functional tests (ie, exercise ECG, stress echocardiography, or nuclear imaging) may then be proposed to assess the presence of CAA-related myocardial ischemia. However, second-level tests (such as hybrid imaging, including CCTA and single-photon emission computed tomography [SPECT], or stress cardiac magnetic resonance [CMR]) may be more accurate in this clinical context by establishing the potential matching between the CAA and the ischemic territories. Example image of cardiac SPECT/CCTA hybrid imaging adapted with permission from Pazhenkottil et al.[76] IVUS indicates intravascular ultrasound; and OCT, optical coherence tomography.

anomalous vessel.[77,78] Because most of the evidence linking CAAs to SCD derives from studies in young individuals doing strenuous effort, the reproducibility of such mechanisms is unlikely in daily life and impracticable during a provocative test, questioning the real causal nature of such conditions in nonathletes SCD victims.

Angelini and coworkers[79] proposed an alternative explanation: The existence and specific features of an initial intramural course may be pivotal in the pathogenesis of myocardial ischemia in patients with malignant CAAs. Indeed, although such tracts may often be hypoplastic compared with the distal vessel, various degrees of lateral compression secondary to the shear stress exerted by the aortic walls may precipitate ischemia during systole and the initial diastole, particularly in the presence of increased aortic stiffness. Other observational studies[67,80] seem to support this hypothesis, but further research is needed to establish definitive conclusions.

In summary, when current knowledge and persisting uncertainties are balanced, myocardial ischemia remains the most likely mechanism of SCD in patients with CAAs. Although the real impact of ischemia on the absolute risk of cardiovascular events remains to be clarified, it seems reasonable to consider the presence of inducible ischemia as a potential predictor of life-threatening events. Conversely, whether the absence of inducible myocardial ischemia could be considered a reassuring sign in this context is unknown and requires further study.

THERAPEUTIC OPPORTUNITIES

Anomalies of Origin

The indications for surgical management of CAAs are summarized in Table 3. An anomalous pulmonary origin of coronary arteries is generally considered malignant. The aim of surgery is to restore a dual coronary system through the reimplantation of the anomalous vessel in the ascending aorta.[81] Direct translocation of the anomalous artery is the technique of choice.[81] When the anomalous ostium is too distant from the aorta, the Takeuchi procedure can be performed by creating an intrapulmonary tunnel by means of a parietal flap from the pulmonary artery connecting the anomalous ostium to the aorta.[82] Alternatively, the anomalous coronary artery can be detached from the pulmonary artery and prolonged to reach the aorta through either a tube created joining flaps from the aorta and the pulmonary artery[83,84] or oblique coronary prolongation techniques.[85] Finally, coronary artery bypass graft surgery may be an alternative.[4,5] Postoperative outcome depends mostly on the degree of left ventricular disfunction at baseline. In the largest study published so far (n=65), operative mortality was 6.2%,[86] and data on long-term follow-up are lacking.

The prognostic consequences of anomalous aortic origins of coronaries are extremely variable, and each therapeutic choice should be tailored to the patient's characteristics (Table 3).[36,56] Surgery appears to be a safe

Table 3. Comparison of Current International Guidelines for the Management of CAAs

2018 AHA/ACC guideline for the management of adults with congenital heart disease			2020 ESC guidelines for the management of adult congenital heart disease		
COR	LOE	Recommendations	COR	LOE	Recommendations
I	B	Surgery is recommended for AAOC from the left sinus or AAOC from the right sinus for symptoms or diagnostic evidence consistent with coronary ischemia attributable to the anomalous coronary artery.	I	C	Surgery is recommended for AAOC in patients with typical angina symptoms who present with evidence of stress-induced myocardial ischemia in a matching territory or high-risk anatomy.*
			IIa	C	Surgery should be considered in asymptomatic patients with AAOC (right or left) and evidence of myocardial ischemia.
IIa	C	Surgery is reasonable for anomalous aortic origin of the left coronary artery from the right sinus in the absence of symptoms or ischemia.	IIa	C	Surgery should be considered in asymptomatic patients with AAOLCA and no evidence of myocardial ischemia but a high-risk anatomy.*
IIa	C	Surgery for AAOC is reasonable in the setting of ventricular arrhythmias.			
			IIb	C	Surgery may be considered for symptomatic patients with AAOC even if there is no evidence of myocardial ischemia or high-risk anatomy.*
IIb	B	Surgery or continued observation may be reasonable for asymptomatic patients with an anomalous left coronary artery arising from the right sinus or right coronary artery arising from the left sinus without ischemia or anatomic or physiological evaluation suggesting potential for compromise of coronary perfusion (eg, intramural course, fish mouth–shaped orifice, acute angle).	IIb	C	Surgery may be considered for asymptomatic patients with AAOLCA without myocardial ischemia and without high-risk anatomy* when they present at a young age (<35 y).
			III	C	Surgery is not recommended for AAORCA in asymptomatic patients without myocardial ischemia and without high-risk anatomy.*
I	B	Surgery is recommended for anomalous ALCAPA.	I	C	Surgery is recommended in patients with ALCAPA.
I	C	In a symptomatic adult with anomalous ARCAPA with symptoms attributed to the anomalous coronary, surgery is recommended.	I	C	Surgery is recommended in patients with ARCAPA and symptoms attributable to anomalous coronary artery.
IIa	C	Surgery for anomalous ARCAPA is reasonable in an asymptomatic adult with ventricular dysfunction or with myocardial ischemia attributed to the anomaly.	IIa	C	Surgery should be considered for ARCAPA in asymptomatic patients with ventricular dysfunction or myocardial ischemia attributable to coronary anomaly.

Adapted from Baumgartner et al[4] and Stout et al.[5] AAOC indicates anomalous aortic origin of the coronaries; AAOLCA, anomalous aortic origin of the left coronary artery; AAORCA, anomalous aortic origin of the right coronary artery; AHA/ACC, American Heart Association/American College of Cardiology; ALCAPA, anomalous left coronary from the pulmonary artery; ARCAPA, anomalous right coronary from the pulmonary artery; CAA, coronary artery anomaly; COR, Class of Recommendation; ESC, European Society of Cardiology; and LOE, Level of Evidence.

*High-risk anatomy includes features like an intramural course and orifice anomalies (slit-like orifice, acute take-off angle, orifice >1 cm above the sinotubular junction).

and effective approach to relieve CAA-related symptoms. In a single-center study (n=115), 97% of subjects were symptom-free during follow-up, and no deaths were documented either perioperatively or postoperatively.[87] In a systematic review of surgically corrected left coronary artery originating from the right aortic sinus (n=325), mortality was low (0.9%), and only 2.2% of the patients were symptomatic at the last follow-up.[88] However, there is no demonstration that surgery reduces SCD in these patients, and because of the lack of controlled studies and long-term follow-up data, the real risk-to-benefit ratio of surgery is unknown. Moreover, although anatomic clues historically associated with SCD should not be overlooked, the demonstration of a causal link between CAAs and myocardial ischemia appears mandatory before surgery is indicated. Indeed, in 1 study including 24 patients with such CAAs, subclinical signs of inducible ischemia persisted even after surgical correction,[89] cautioning against unwarranted surgical attempts.

Once surgery has been chosen, multiple techniques are available. In the presence of a short or absent intramural course, the most indicated options are either direct reimplantation of the anomalous vessel in the correct aortic sinus or osteoplasty, which consists of creating a larger neo-ostium by extending the preexisting anomalous orifice toward the correct aortic sinus through a pericardial patch.[36,81] In cases with a long intramural course, the technique of choice is unroofing, in which the common wall between the anomalous vessel and the aorta is resected and a neo-ostium is opened in the anatomically correct sinus. Such techniques are not without risk because incision of the aortic valve commissure can lead to aortic insufficiency or damage the coronary wall. In the case of interarterial course, pulmonary translocation may be an alternative.[36,81] Finally, coronary artery bypass graft surgery should be restricted to patients in whom there is significant atherosclerosis or when an alternative approach is not feasible because coronary flow along the anomalous vessel is usually impaired only during stress or intense exercise. Hence, significant competitive flow has to be expected for most of the time, undermining the long-term patency of the bypass conduit.[36,81,90]

The use of PCI in patients with such CAAs has been proposed as a possible alternative but is supported by weak evidence. In 1 study including 42 predominantly adults with the right coronary artery originating from the left aortic sinus and an intramural proximal course, PCI relieved symptoms in 71% of subjects, but the rate of in-stent restenosis was 13% at a mean follow-up of 5 years.[49]

As to medical treatments, few case reports[91,92] and only 2 large series[93,94] have been published. Whereas Kaku et al[93] described a cohort of 56 adults managed conservatively with exercise restriction or medical therapy (namely β-blockers, calcium channel blockers, nitrates, and antiarrhythmic drugs) and reported no SCD at a mean follow-up of 5.6 years, Opolski et al[94] showed that 19 of 70 (27%) medically managed patients reported a worsening in chest pain or diminished exercise tolerance at a mean follow-up of 1.3 years, particularly in those with interarterial course.

Congenital atresia of the left main coronary artery is often highly symptomatic and presents at a young age. Therefore, surgical correction is indicated in almost all cases, usually with coronary artery bypass graft surgery.[21]

Anomalies of Course

The interarterial course is considered the most malignant anomaly of coronary artery course, and surgical correction is usually indicated. The choice of surgical technique depends mostly on the origin of the anomalous vessel and the extent of the intramural tract.[81]

In cases of symptomatic myocardial bridging, treatment aims at modifying the hemodynamic triggers that may aggravate myocardial ischemia such as increased heart rate, reduced diastolic filling time, hypertension, myocardial hypertrophy, and vasospasm.[23] Medical therapy is considered the first choice, and β-blockers are the mainstay of therapy thanks to their negative chronotropic and inotropic effects.[23,95] Calcium channel blockers may be complementary to β-blockers by further reducing inappropriate coronary contractility, with ivabradine, an agent with pure heart rate–lowering properties, being a valid alternative.[23] Conversely, vasodilators are not indicated because they may increase systolic vessel squeezing, heart rate, and proximal vessel dilation, thus reducing downstream coronary flow.[23,96] PCI should be restricted to cases refractory to medical therapy because of the high rates of stent failure.[23,95] In these cases, coronary artery bypass graft surgery or supra-arterial myotomy can be done instead.[23]

Coronary aneurysms are rare, and most data on their management derive from case series including different pathogeneses.[24] Some studies have reported a higher incidence of MACEs,[97] whereas others have not[98]; therefore, there is ongoing debate on whether to treat these patients with prophylactic antiplatelet or anticoagulant therapy.[24] Whereas vasodilators are contraindicated because they may exacerbate myocardial ischemia,[99] invasive management of a coronary aneurysm is appropriate when it is considered the culprit of an acute coronary syndrome or responsible for ischemic symptoms or when it shows high-risk features of rupture. Percutaneous treatment is usually the first choice and consists of the deployment of covered stents or balloon- or stent-assisted coil embolization.[24] On the contrary, the most common surgical approach involves resecting the proximal and distal extremities of the aneurysm and interposing a graft if necessary; alternative surgical procedures include ligation, resection, or marsupialization.[24]

Anomalies of Termination

Small coronary arteriovenous fistulas are usually asymptomatic and managed with observational follow-up through serial echocardiography. An invasive approach is indicated only in cases of significant left-to-right shunt or coronary steal phenomena resulting in myocardial ischemia and ventricular overload.[100] The choice of technique for fistula closure depends on the fistula morphology, course, and tortuosity and the presence of an aneurysmal dilatation of the afferent vessel.[100] Surgical ligation at the drainage site is indicated for more complex fistulas, showing an overall operative mortality of ≈2%.[86] Conversely, percutaneous closure (eg, coil embolization, covered stents, vascular plugs, dedicated umbrella devices) is preferable in cases of a single nontortuous fistula.[100] Last, such CAAs are at high risk for developing bacterial endocarditis; hence, antibiotic prophylaxis is recommended in all patients undergoing invasive procedures.[100]

EXERCISE RESTRICTION

The majority of deaths associated with CAAs occur during exercise.[101] Moreover, although the occurrence of symptoms such as exertional dyspnea and chest discomfort may be the first clinical manifestations of CAAs, it has been shown that CAA-related SCDs may occur, in ≈50% of cases, in previously asymptomatic individuals.[101,102] Hence, eligibility for sport competitions should be carefully evaluated in subjects with CAAs, taking into consideration both the coronary anatomy and the presence of inducible ischemia. Although current guidelines on sport activity in patients with cardiovascular diseases provide specific recommendations for patients with CAAs, they are generally based on expert consensus opinions, given the absence of reliable clinical or epidemiological data, especially for subjects >40 years of age[103,104] (Table 4).

CONCLUSIONS

CAAs are increasingly found among adults because of the increasing use of invasive and noninvasive cardiovascular imaging. Although some anomalies should neces-

Table 4. Comparison of Current International Guidelines for Exercise Restrictions in Patients With CAAs

2015 ACC/AHA scientific statement for competitive athletes with cardiovascular abnormalities			2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease		
COR	LOE	Recommendations	COR	LOE	Recommendations
			IIa	C	When considering sports activities, evaluation with imaging tests to identify high-risk patterns and an exercise stress test to check for ischemia should be considered in individuals with AAOC.
			IIb	C	In asymptomatic individuals with an anomalous coronary artery that does not course between the large vessels or does not have a slit-like orifice with reduced lumen or intramural course, competition may be considered after adequate counseling on the risks provided that there is an absence of inducible ischemia.
			III	C	Participation in most competitive sports with a moderate or high cardiovascular demand among individuals with AAOC with an acutely angled takeoff or an anomalous course between the large vessels is not recommended.*
IIa	C	Athletes with AAORCA should be evaluated by an exercise stress test. For those without either symptoms or a positive exercise stress test, permission to compete can be considered after adequate counseling of the athlete or the athlete's parents (in the case of a minor) about the risk and benefit, taking into consideration the uncertainty of the accuracy of a negative stress test.			
III	B	Athletes with AAOLCA, especially when the artery passes between the pulmonary artery and aorta, should be restricted from participation in all competitive sports, with the possible exception of class IA sports, before surgical repair. This recommendation applies whether the anomaly is identified as a consequence of symptoms or discovered incidentally.			
III	C	Nonoperated athletes with AAORCA who exhibit symptoms, arrhythmias, or signs of ischemia on exercise stress test should be restricted from participation in all competitive sports, with the possible exception of class IA sports, before a surgical repair.			
IIb	C	After successful surgical repair of AAOC, athletes may consider participation in all sports 3 mo after surgery if the patient remains free of symptoms and an exercise stress test shows no evidence of ischemia or cardiac arrhythmias.	IIb	C	After surgical repair of an AAOC, participation in all sports may be considered, at the earliest 3 mo after surgery, if the athletes are asymptomatic and there is no evidence of inducible myocardial ischemia or complex cardiac arrhythmias during maximal exercise stress test.
I	C	Athletes with APOC artery can participate only in low-intensity class IA sports, regardless of whether they have had a prior myocardial infarction, and pending repair of the anomaly.			
IIb	C	After repair of APOC, decisions about exercise restriction may be based on presence of sequelae such as myocardial infarction or ventricular dysfunction.			
IIa	C	It is reasonable for athletes with myocardial bridging and no evidence of myocardial ischemia during adequate stress testing to participate in all competitive sports.	IIa	C	Participation in competitive and leisure-time sports should be considered in asymptomatic individuals with myocardial bridging and without inducible ischemia or ventricular arrhythmia during maximal exercise testing.
IIa	C	It is reasonable to restrict athletes with myocardial bridging of an epicardial coronary artery and objective evidence of myocardial ischemia or prior myocardial infarction to sports with low to moderate dynamic and low to moderate static demands.	III	C	Competitive sports are not recommended in individuals with myocardial bridging and persistent ischemia or complex cardiac arrhythmias during maximal exercise stress testing.
IIa	C	It is reasonable to restrict athletes who have undergone surgical resection of the myocardial bridge or stenting of the bridge to low-intensity sports for 6 mo after the procedure. If such athletes have no subsequent evidence of ischemia, they may participate in all competitive sports.			

Adapted from and Pelliccia et al[103] and Maron et al.[104] AAOC indicates anomalous aortic origin of the coronaries; AAOLCA, anomalous aortic origin of the left coronary artery; AAORCA, anomalous aortic origin of the right coronary artery; AHA/ACC, American Heart Association/American College of Cardiology; APOC, anomalous pulmonary origin of the coronaries; CAA, coronary artery anomaly; COR, Class of Recommendation; ESC, European Society of Cardiology; and LOE, Level of Evidence.

*This recommendation applies whether the anomaly is identified as a consequence of symptoms or discovered incidentally and in individuals <40 years of age.

sarily be considered malignant and need correction, the prognostic relevance of more common forms such as coronary arteries originating from the opposite aortic sinus remains uncertain. Diagnostic and therapeutic pathways based only on anatomic clues are overly simplistic, whereas the evaluation of the corresponding ischemic burden might be crucial to implement patient-tailored approaches. Future research should aim to clarify the pathophysiological determinants linking each type of CAAs to myocardial ischemia and how to assess its real impact on the individual risk of life-threatening events. Unfortunately, the relative rarity of such conditions, their clinical and phenotypic variability, and ethical considerations may hamper the design of large prospective studies in this context. International collaborations and multicenter registries could help resolve some of the current uncertainties.

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Data Supplement Figure I

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