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Anomalous Coronary Arteries: When to Follow-up, Risk Stratify, and Plan Intervention

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Abstract

Purpose of Review Coronary artery anomalies are a diverse group of entities, ranging from benign variations of normal anatomy to life-threatening conditions. There is, however, no universal consensus in their classification, risk stratification, and management. The aim of this review is to develop a straightforward clinical approach for the assessment and care of patients with anomalous coronary arteries.

Recent Findings Autopsy series and population screening studies have recently provided useful clinical data on the prevalence and outcomes of coronary anomalies. Also, findings on coronary computed tomography angiography, magnetic resonance imaging, and invasive angiography, enriched with fractional flow reserve and intravascular ultrasound, have allowed identification of several high-risk features associated with specific coronary anomalies.

Summary Management of patients with anomalous coronary arteries requires an individualized approach based on clinical, physiological, and anatomic features. High-quality studies are paramount for further development of this fascinating field.

Keywords Coronary anomalies · AAOCA · ALCAPA · Congenital heart disease · Myocardial bridge · Coronary fistula

Introduction

Anomalous coronary arteries (ACA) are a broad group of conditions with different anatomic features, physiological consequences, and clinical presentations [1••]. Their clinical significance ranges from virtually nil, when a coronary anomaly known to be associated with a good outcome is incidentally found in an asymptomatic patient, to the most extreme presentation, when sudden cardiac death (SCD) occurs. Historically, the prevalence of ACA in large catheterization series is around 1.3%, but estimates vary widely depending on the definition of ACA, the method used for screening and evaluation, as well as the selection criteria of the population included in studies [2, 3].

Classification and Natural History

Although there is no universal consensus on the classification of ACA, they can be broadly divided as abnormalities in origin, course, termination, and size [4]. An abnormal origin of a coronary artery can be localized in the opposite sinus of Valsalva or, more rarely, in the pulmonary artery (PA). Primary abnormalities of coronary course are found in myocardial bridges (MBs), when a coronary segment leaves the epicardial space and dives into the myocardium for a variable depth and length, returning distally to the epicardial space. A termination anomaly is observed in coronary artery fistulas, communications between coronary arteries and vascular structures bypassing a capillary bed. Size anomalies include coronary stenosis and aneurysms.

There is currently a paucity of prospective information on the natural history of ACA, as most studies report the clinical

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presentation, imaging characteristics, and intervention outcomes [1••]. Importantly, autopsy studies of young athletes who experienced SCD show ACA as the second most common etiology after hypertrophic cardiomyopathy, although it is not always clear that the ACA is the direct cause of the event [5]. In the absence of randomized trials comparing watchful waiting, medical treatment, and percutaneous or surgical interventions, recommendations for management of ACA are mainly based on pathophysiology, incomplete clinical data, case series, and expert opinion.

Although ACA can be categorized based on various anatomical definitions, we propose here a classification based on anomaly severity and need for additional testing or risk stratification. We grouped the anomalies as low risk (no further evaluation necessary), unclear risk (additional risk stratification to be considered on an individual basis), and high risk (intervention is usually recommended). This proposed classification of ACA is shown in Fig. 1.

Low Risk

The majority of discovered coronary anomalies are not associated with symptoms or adverse clinical events and are considered benign variants of normal coronary anatomy. In most such instances, no treatment or follow-up is required. However, a minority of cases might present with symptoms or increased risk of complications. The need for additional testing is restricted to very select cases in this group.

Minimal Anatomical Variations Frequently, benign ACA are incidentally found in cardiac imaging studies. This category of anomalies includes variations of the normal coronary anatomy that are usually not associated with impairment of coronary flow or myocardial ischemia. They are not more prevalent in autopsy studies of young people having SCD than in the general population [6]. Separate ostia of the left anterior descending artery (LAD) and left circumflex artery from the aorta (without a left main stem), split right coronary artery (RCA), high origin of the RCA from the right sinus of Valsalva, and origin of the left circumflex artery from the RCA or from the right sinus of Valsalva taking a retroaortic path are all examples of benign ACA that have no clinical significance in the absence of associated atherosclerosis, and no additional follow-up or testing is required [2, 7].

Incidentally Discovered Myocardial Bridge This is a common coronary anomaly, usually found in patients referred for coronary computed tomography angiography (CCTA) or invasive coronary angiography (ICA) for other reasons. It is defined as the presence of a coronary artery that leaves the epicardial space along its course and penetrates the myocardium

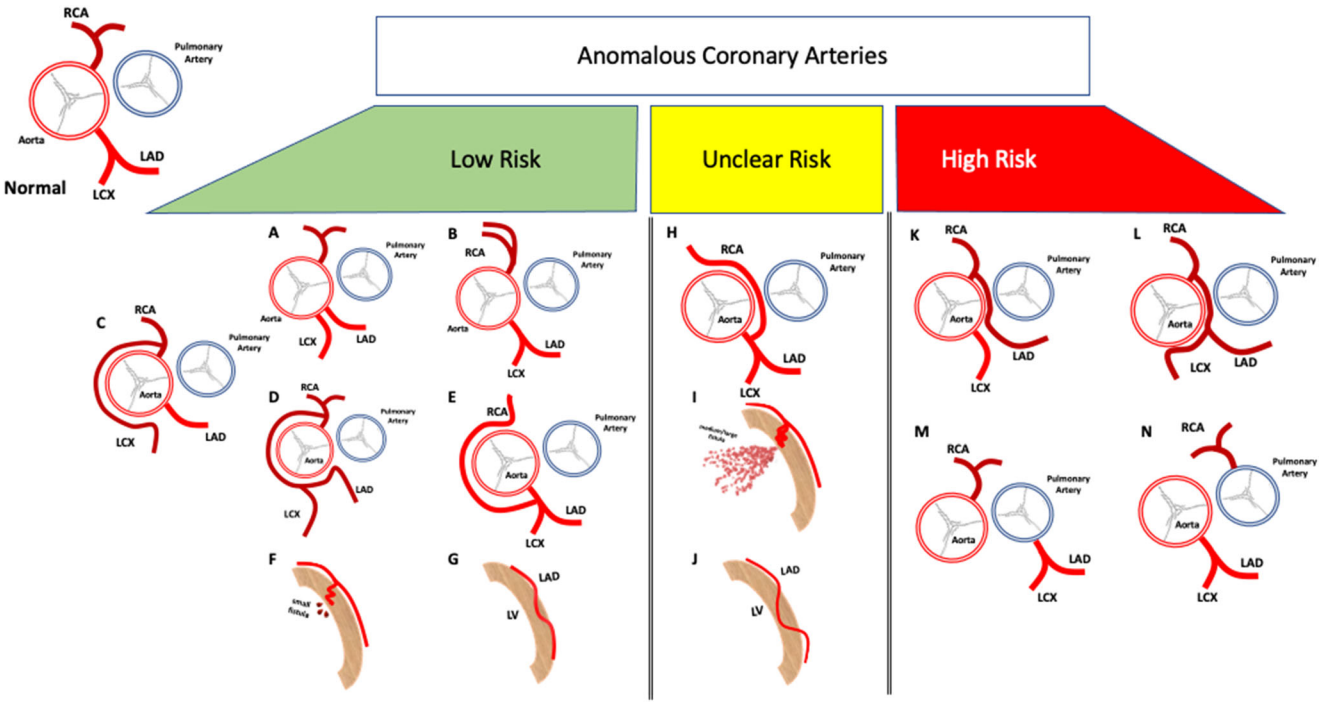

Fig. 1 Approach of the anomalous coronary artery according to anatomical diagnosis. (**A**) Separate ostia of the LAD and LCX; (**B**) split RCA; (**C**) LCX origin from RCA; (**D**) retroaortic LMCA from RCA; (**E**) retroaortic RCA from LMCA; (**F**) small coronary artery fistula; (**G**) shallow MB; (**H**) interarterial RCA from LMCA; (**I**) medium/large coronary artery fistula; (**J**) deep MB; (**K**) interarterial LAD from RCA; (**L**) interarterial LMCA from RCA; (**M**) ALCAPA; and (**N**) ARCAPA. LMCA means left main coronary artery. LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery; ALCAPA, anomalous left coronary artery from the pulmonary artery; ARCAPA, anomalous right coronary artery from the pulmonary artery; and MB, myocardial bridging

for a variable depth and extension, usually returning to the epicardium before its termination [8]. The vast majority of MB is seen in the LAD artery. The myocardial tissue overlying the tunneled coronary artery is the MB. This anatomic feature predisposes to systolic compression of the coronary artery, which may be more or less prominent. Because most of the coronary flow occurs in diastole, systolic compression is usually not associated with symptoms or myocardial ischemia.

The prevalence of MB varies depending on the method used for detection. Autopsy series and CCTA studies describe MB to be present in about 30% of patients [9]. On the other hand, the prevalence of MB on ICA varies from 0.5 to 12% [10]. This discrepancy shows that the presence of the bridge itself, as detected by CCTA, may not lead to systolic compression (the "milking effect" on ICA) at rest in most patients. In the setting of an incidentally found MB in a patient that is asymptomatic or presents with atypical symptoms, no treatment is required. These incidental MBs are classified as type A in the Schwarz proposed nomenclature of MBs and have excellent long-term outcomes [11]. On the other hand, Schwarz types B (objective signs of ischemia) and C (altered intracoronary hemodynamics) may be associated with clinical events, and will be discussed in the section of ACA with unclear risk.

Anomalous Aortic Origin of a Coronary Artery Without an Interarterial Course Ectopic origin of the left main or the RCA, usually from the opposite sinus of Valsalva, may follow several different paths to its normal destination. Prepulmonic, retroaortic, retrocardiac, and subpulmonic are considered benign courses, since they are not more prevalent in patients with SCD, and there is no pathophysiological basis for myocardial ischemia, except in the presence of concomitant atherosclerosis [12]. A review of studies addressing the prevalence of anomalous aortic origin of the coronary artery (AAOCA) found retroaortic course to be the most common subtype, present in approximately 0.26% of the population [13]. Patients discovered to have an AAOCA without an interarterial course should be reassured about the benign nature of this condition, and no specific treatment or follow-up is required.

Small Coronary Fistulas Coronary artery fistulas (CAF) may be congenital or acquired, secondary to chest trauma or invasive cardiac procedures. Congenital CAF are rare anomalies, found in approximately 0.1 to 0.2% of patients referred for ICA [2, 4]. They originate from a coronary artery, usually the RCA, and drain into a cardiac chamber or another vascular structure. The most common termination sites are the right ventricle, right atrium, superior vena cava, coronary sinus, and pulmonary artery (PA) [14]. CAF drainage into left cardiac chambers is found in only about 10% of cases [15]. However, in young children, small fistulas detected by Doppler echocardiography more frequently originate from the left coronary artery system [16].

It is estimated that up to 75% of CAF are small and incidentally discovered in patients undergoing investigation of unrelated symptoms or treatment of other heart conditions [17]. Although current guidelines do not establish a threshold for the definition of a small CAF, simple fistulas (1 origin, 1 vessel, single termination) that are smaller than the reference distal coronary artery are usually considered to be small [18]. These incidental, small, and asymptomatic fistulas usually lead to no volume overload or myocardial ischemia and do not require any medical or interventional treatment, except usual clinical follow-up, since CAF may enlarge over time [19].

Unclear Risk

There are ACA in which the association with symptoms, myocardial ischemia, and clinical events is variable, warranting proper risk stratification for defining adequate treatment. In these circumstances, the risks and benefits of intervention should be carefully weighed using both noninvasive and invasive methods on an individual basis. Although ICA has been traditionally the method of choice for evaluating coronary artery disease, when it comes to ACA, CCTA and magnetic resonance imaging allow better characterization of the vessel course and relation to other cardiac and vascular structures [1••]. Recently, CCTA has been the preferred imaging modality for most patients, whereas magnetic resonance has been considered and alternative test for younger individuals to whom radiation exposure might be a concern. Advantages and disadvantages of different imaging tools in the risk assessment of ACA are summarized in Table 1.

Anomalous Aortic Origin of the Right Coronary Artery Anomalous origin of the RCA from the opposite sinus may be associated with symptoms and adverse outcomes in a minority of patients. AAOCA with an interarterial course, notably the left coronary artery arising from the right sinus (L-AAOCA), is the most frequently found coronary anomaly in young athletes and military recruits experiencing SCD [5, 12, 20]. On the other hand, R-AAOCA is a more frequent condition in clinical practice. An MRI screening study of high school students showed interarterial R-AAOCA to be almost three times more frequent than L-AAOCA [21]. This underrepresentation of R-AAOCA in studies of patients with SCD suggests that many patients with this pattern of ACA may have a more benign outcome and deserve risk stratification instead of proceeding directly to intervention.

In R-AAOCA, several clinical and imaging features can provide useful information to assess the possible risks and

Table 1 Imaging tools in the diagnosis and stratification of anomalous coronary artery

Imaging tool	Advantages	Disadvantages
Coronary computed tomography angiography (CCTA)	Noninvasive technique High diagnostic accuracy Good image quality Shorter scanning time Widely available	Radiation exposure Use of iodine-contrast media Absence of functional information Less accuracy in high and/or irregular heart rate
Cardiac magnetic resonance imaging (MRI)	Noninvasive technique High spatial resolution Cardiac anatomy and function No ionizing radiation No iodine-contrast media	Risk of gadolinium contrast in kidney disease Claustrophobia Longer scanning time No smaller vessels analysis Less accessible Metallic implants
Invasive coronary angiography (ICA)	Therapy possible Highest accuracy Use of other analysis methods (as IVUS an FFR/iFR)	Radiation exposure Use of iodine-contrast media Invasive method
Intravascular ultrasound (IVUS)	Complete arterial wall visualization Measurement of lumen dimensions	Invasive method Catheter cost Less accessible Limited axial resolution No physiological information
Fractional flow reserve (FFR)	Independent of heart rate or rhythm Physiologic assessment High reproducibility Low intra-individual variability	Invasive method Catheter cost Less accessible No morphology information

benefits of conservative management versus surgical intervention. Clinical data including patient age and symptoms are part of the risk assessment in ACA [13]. Most episodes of SCD occur in patients younger than 35 years old, usually during or shortly after strenuous exercise, but arrhythmic events related to ACA can occur at any age. Exertional syncope and chest pain are also risk factors for adverse outcomes, since they are suggestive of coronary insufficiency; nevertheless, SCD may occur in previously asymptomatic individuals, being the first manifestation of ACA [12].

Resting electrocardiogram, transthoracic echocardiogram, and stress tests are frequently part of the risk assessment in patients with structural cardiac abnormalities. However, patients with normal exercise tests are still at risk of subsequent SCD, demonstrating the inaccuracy of these methods for risk stratification of R-AAOCA [22].

Anatomic features of R-AAOCA, best evaluated by CCTA or magnetic resonance imaging, are considered possible mechanisms of myocardial ischemia and adverse clinical outcomes. AAOCA with an interarterial course, between the aorta and the pulmonary trunk, is one of the features most commonly associated with myocardial ischemia [23]. The main mechanism of flow limitation is still a matter of debate, but compression of the intramural component of the coronary artery (i.e., within the aortic wall), frequently observed in patients with interarterial AAOCA, is the most likely pathophysiological basis for myocardial ischemia and subsequent clinical events [24, 25]. Risk stratification by CCTA also includes evaluating other high-risk characteristics of R-AAOCA, such as an acute take-off angle from the aorta of less than 45°, a slit-like ostium, and a long narrowed segment [26–31]. Proximal vessel narrowing of ≥ 50% and a length of narrowing > 5.4 mm have been associated with symptoms and subsequent myocardial revascularization in patients with AAOCA [32]. Noninvasive measurement of fractional flow reserve (FFR) by computed tomography is being investigated in the assessment of AAOCA, but data is still limited [33].

Although CCTA may precisely identify several anatomic features of ACA, the dynamic component of intramural systolic compression is missed, since computed tomography usually assesses coronary arteries in diastole. In this context, the use of intravascular ultrasound (IVUS) during ICA has been incorporated to the evaluation of ACA, allowing quantification of coronary stenosis secondary to intramural compression during both systole and diastole [34]. Importantly, optimal catheterization of ACA can be technically difficult in the absence of a dedicated catheter and may lead to complications such as dissection and spasm [35]. Although promising, there is still a lack of prospective outcome data to define the optimal threshold of IVUS-calculated stenosis that is associated with symptoms, clinical events, and improvement after intervention.

Lee et al. performed FFR measurements in 37 adult patients with interarterial R-AAOCA and observed values < 0.80 in only 3 (8.1%) cases [36]. Although median follow-up was of only 2 years, the authors observed no clinical events

in those with FFR ≥ 0.80 managed conservatively. Other reports have also demonstrated that the majority of adult patients with R-AAOCA have FFR values higher than 0.80, although this cutoff value, which is used for atherosclerotic disease, has not been validated for AAOCA [37, 38].

In summary, risk stratification for patients diagnosed with R-AAOCA still requires further validation. Currently, surgery should be selectively considered for patients with symptoms, evidence of myocardial ischemia, or high-risk features on either CTA, IVUS, or FFR (Table 2) [39].

Myocardial Bridges Although infrequent, some patients may develop chest pain and myocardial ischemia related to MB, and there are several proposed mechanisms that might impair coronary flow in this setting: prolonged coronary compression into early diastole, septal branch steal, spasm, dissection, and associated atherosclerosis related to abnormal shear stress in the coronary segment proximal to the MB [8].

In symptomatic patients, evidence of myocardial ischemia related to the MB territory, usually the LAD, should be sought with noninvasive imaging stress studies. The presence of ischemia is associated with the degree of coronary systolic narrowing [40, 41]. Although exercise stress tests are usually preferred, dipyridamole stress has shown good agreement in patients with MB undergoing nuclear perfusion imaging [42].

Invasive assessment may be considered in symptomatic patients. The classic finding on ICA is the phasic compression of the coronary artery during systole, also called "milking effect," ranging from mild to severe. The use of IVUS allows precise visualization of MB as the "half-moon" phenomenon, an echo lucent halo surrounding the bridged segment [43]. Importantly, IVUS increases the sensitivity of ICA for the detection of MB. In a series of 331 patients undergoing IVUS assessment of the LAD, MBs were observed in only 3% by angiography, whereas IVUS detected MB in 23% [44]. IVUS may also demonstrate MB characteristics associated with impaired coronary flow. The MB muscle index, a product of bridge length and halo thickness, has recently been shown to be predictive of reduced coronary flow during dobutamine stress, although this finding requires further validation [45].

FFR measurements during ICA are increasingly being considered in the evaluation of MB. It is important to note, however, that FFR uses *mean* coronary and aortic pressures, which may be problematic in the setting of an MB. Systolic pressure overshooting in the coronary artery distal to the MB and generation of a negative systolic pressure gradient (coronary pressure after the MB higher than aortic pressure due to compression of blood against the high resistance microcirculation during systole) may lead to an elevation in mean coronary pressure calculated by FFR and underestimation of flow impairment by MB [46]. Flow indices that are independent of systolic pressures, like diastolic FFR and instantaneous wave-free ratio (iFR), both at rest and after dobutamine challenge, are considered physiologically more sound in the invasive assessment of MB, but this is still an unresolved issue [46–48].

If symptoms or ischemia are considered to be related to the MB after noninvasive or invasive risk stratification, betablockers are the treatment of choice, and non-dihydropyridine calcium-channel blockers are also considered an option [49]. Nitrates should be avoided, since they have been associated with increased systolic compression of the tunneled arteries and worsening of angina [50]. Percutaneous coronary intervention (PCI) is usually discouraged for MB due to elevated rates of stent thrombosis, restenosis, and vessel perforation, but may be considered along with surgery (bypass or myotomy) on an individual basis for the very unusual patient with refractory symptoms [8].

Table 2 Noninvasive and invasive imaging features of AAOCA associated with lower and higher risk of clinical events. Abbreviations: *AAOCA*, anomalous aortic origin of a coronary artery; *FFR*, fractionated flow reserve; *IVUS*, intravascular ultrasound; *LMCA*, left main coronary artery; *LAD*, left anterior descending artery; *LCX*, left circumflex artery; *RCA*, right coronary artery

AAOCA features	Lower risk	Higher risk
Ectopic vessel	RCA, LCx	LMCA, LAD
Course	Prepulmonic	Interarterial
	Retroaortic	
	Retrocardiac	
	Subpulmonic	
Intramural component	Absent	Present
Intramural length	Short	Long
Take-off angle from the aorta	Not acute (≥ 45°)	Acute (< 45°)
Ostium	Normal or oval	Slit-like
Degree of cross-sectional area stenosis (IVUS)	≤ 45–55%	> 45–55%
	*Optimal threshold not clear	*Optimal threshold not clear
FFR	≥ 0.80	< 0.80
	*Optimal threshold not clear	*Optimal threshold not clear

Medium and Large Coronary Artery Fistulas

Communications between coronary arteries and cardiac chambers or major intrathoracic vessels may lead to hemodynamic disturbances and symptoms. They usually present with heart failure due to left-to-right shunting (fistulas to right cardiac chambers or PA) or left ventricular volume overload (fistulas to left cardiac chambers) [17]. Anginal chest pain may also be a manifestation of CAF, as they offer a low resistance path to blood flow, deviating it from the distal coronary circulation. The proximal coronary artery becomes enlarged due to the high flow through the fistula [18]. Other rare manifestations include fistula thrombosis, endarteritis, arrhythmias, and fistula rupture with cardiac tamponade.

Considering the adverse outcomes related to some CAF, selected patients may require percutaneous or surgical intervention. The presence of medium-sized (1 to 2 times the distal coronary diameter), large (more than twice the distal coronary diameter), or complex CAF are associated with symptoms in approximately 50% of patients [14, 18]. Risk stratification begins with symptom assessment, including exercise intolerance, heart failure, or chest pain, all of which may be clues to the hemodynamic significance of the CAF.

Noninvasive imaging, including echocardiography, stress tests, and coronary CTA provide useful information in this setting [51]. Coronary artery ectasia and aneurysm proximal to fistula origin, ventricular dilation, or dysfunction secondary to volume overload, pulmonary hypertension, and evidence of ischemia in the myocardial territory supplied by the fistulous coronary artery are all indicative of abnormal physiology and considered indications for surgical or transcatheter intervention [15, 18].

Large CAF should also be considered for correction regardless of symptoms or risk stratification, since they are frequently associated with adverse outcomes [52, 53]. Nevertheless, acute myocardial ischemia and infarction have been described as a complication of both percutaneous and surgical intervention in 7 to 15% of cases [54–56]. A heart team–based approach, considering patient's age, symptoms, overall health status, and fistula characteristics is therefore recommended for optimal management decisions regarding congenital CAF [1]. Additionally, if an intervention is planned, a highly experienced operator should be considered due to the complexity of the procedure.

High Risk

Clinical presentation may be a strong factor in the decision-making process for intervention. Patients recovered from cardiac arrest are at the highest risk of subsequent events, though other severe symptoms might belong in this group. Therefore, the finding of a coronary anomaly known to be associated with SCD in this context is a compelling indication for intervention. Also, in those patients with related symptoms, myocardial ischemia, ventricular arrhythmias, or dysfunction, intervention should be strongly considered for symptomatic relief and prevention of SCD, particularly at younger ages.

Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery and Anomalous Origin of the Right Coronary Artery from the Pulmonary Artery Abnormal origin of a coronary artery from the PA is a rare anomaly, present in 1 in every 10,000 patients undergoing ICA [2]. In anomalous origin of the left coronary artery (ALCAPA), the left coronary artery originating from the PA delivers low-pressure and deoxygenated blood to the myocardium, leading to ischemia, mitral regurgitation, left ventricular dysfunction, and heart failure [57, 58]. This form of ALCAPA, called the infant-type, is associated with a poor prognosis, with a mortality of 90% in the first year of life if the anomaly is not corrected [59].

In a minority of patients, rich collateralization from the RCA originating from the aorta delivers oxygenated and high-pressure blood to the left system in a retrograde fashion, with the blood flowing in the following direction: aorta, RCA, collateral vessels, anomalous left coronary artery, and finally shunting into the PA. These patients are usually spared from clinical manifestations in childhood and correspond to the adult-type of ALCAPA, presenting with angina, heart failure, arrhythmias, or SCD [60]. Myocardial ischemia secondary to flow deviation into the PA and left ventricular volume overload due to left-to-right shunting are the mechanisms involved in the pathophysiology of the adult form of ALCAPA.

The diagnosis of ALCAPA is an indication for intervention [1, 19]. The dismal prognosis of infants diagnosed with ALCAPA in the first months of life has consolidated surgical correction as the only acceptable therapy. Patients diagnosed after the first year of life are also at risk of serious events, including sudden cardiac arrest, and should be referred for surgical correction as well [61]. After 50 years of age, life-threatening clinical presentations are less common, but surgical correction should still be considered on an individual basis [60]. Coronary reimplantation is the preferred surgical approach, while interposition of a bypass graft with ligation of the abnormal pulmonary origin of the left coronary artery is also an option [62–64].

Anomalous origin of the right coronary artery from the pulmonary artery (ARCAPA) is an even less frequently encountered anomaly. The RCA originating from the PA delivers low-pressure and deoxygenated blood to a minor part of the myocardium when compared to ALCAPA, rendering the former a less critical condition. In a recent review of 223 cases of ARCAPA, the median age at diagnosis was 14 years, and 38% of patients were asymptomatic [65]. When symptoms were present, angina and dyspnea were the most common. Surgical correction is currently indicated for patients

with ARCAPA and associated symptoms, myocardial ischemia or left ventricular dysfunction [1, 19]. The management of those with incidentally discovered ARCAPA without the previously listed surgical indications is debated, but correction should still be considered in younger patients because of the risk of SCD [66, 67]. In any case of ALCAPA or ARCAPA, when surgical intervention is planned, an experienced operator is recommended due to the risks associated with the procedure.

Anomalous Aortic Origin of the Left Coronary Artery There is currently a lack of prospective data to describe the natural history of this ACA, nor are there randomized trials to define the role of intervention or medical treatment. However, as previously noted, L-AAOCA with an interarterial course is overrepresented in autopsy studies and is considered an important cause of SCD during or following vigorous exertion, especially in the young [5, 12, 20]. Noninvasive tests to investigate ischemia have not been shown to be accurate in this scenario, and a negative test should not be reassuring of a favorable prognosis [12, 39, 68]. The use of IVUS and FFR for the assessment of the intramural component, degree of stenosis, and coronary flow reduction in the setting of L-AAOCA is an area of active research, but there are still no studies relating findings on invasive evaluation and patient outcomes [69, 70]. Therefore, the identification of interarterial L-AAOCA is usually considered an indication for surgical correction, irrespective of symptoms or evidence of ischemia [1, 19, 71]. Unroofing is the surgical procedure recommended for most patients with L-AAOCA, while coronary reimplantation, PA translocation, and bypass are considered alternatives for selected cases [72, 73].

Conclusion

The field of coronary anomalies has evolved considerably in the past few years. Novel diagnostic techniques, both noninvasive and invasive, have significantly contributed to the current understanding of these conditions. However, major knowledge gaps persist, as evidence-based risk stratification tools and clinical trials comparing treatment options are still lacking. The pursuit of high-quality data is an important step in the development of standardized approaches to the management of patients with coronary anomalies.

Declarations

Conflict of Interest Eduardo Leal Adam reports personal fees from Bayer SA. Giuliano Generoso declares no competing interests. Marcio Sommer Bittencourt reports personal fees from Bayer SA, Boston Scientific, EMS, and NovoNordisk, and grants from Sanofi.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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