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Etiology, clinical presentation, and management of left main coronary artery aneurysms

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Abstract

Background and Aim of the Study: The widespread use of noninvasive/invasive coronary imaging increased the probability of recognition of coronary aneurysms. Left main coronary aneurysms (LMCA), though rare, are potentially life-threatening but in the absence of controlled studies, guidelines do not provide any specific recommendation for their management. We, therefore, aimed to investigate the epidemiology, clinical presentation, therapeutic strategies, and prognostic implication of LMCA.

Methods: A systematic review of the literature was performed to retrieve all the reported cases of LMCA as of December 2021, which were summarized and classified according to their etiology, clinical presentation, and therapeutic management.

Results: Out of 1997 works retrieved, 180 studies were analyzed, describing 209 LMCA cases (aged 51 ± 19 years, 68% males). Atherosclerosis was the most common etiology (40%), followed by inflammatory (12%), congenital (9%), or degenerative (6%) conditions. Stable angina (43%) and acute coronary syndromes (32%) were more often the first clinical manifestations, while 29 (14%) LMCA were incidental findings. Most cases were treated surgically (53%), while percutaneous intervention was rarely adopted (7%). Data about antithrombotic therapies were scarce and heterogeneous. Finally, when longitudinal data were reported ($n = 81$), LMCA resulted associated with a severe prognosis, with a 15% mortality over an 8-month median follow-up.

Conclusions: LMCA are most frequently, but not exclusively, caused by advanced atherosclerosis. Irrespective of their etiology and clinical presentation, LMCA may be associated with high short-term mortality. In absence of controlled studies, a careful evaluation of each case is warranted to optimize therapeutic strategies.

KEYWORDS

acute coronary syndrome, aneurysm, ectasia, left main coronary artery, myocardial ischemia

Abbreviations: CAA, coronary artery aneurysms; CABG, coronary artery bypass graft; CAD, coronary artery disease; ICA, invasive coronary angiography; LAD, left anterior descending artery; LCx, left circumflex coronary artery; LMCA, left main coronary aneurysms; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Drs. Negro and Gentile equally contributed to this work.

1 | INTRODUCTION

A coronary artery aneurysms (CAA) is defined as a segment of a coronary epicardial artery exceeding the diameter of the adjacent vessel by 1.5-fold and involving less than one-third of its total length.[1–3] CAA may be saccular when the transverse diameter exceeds the longitudinal one, or fusiform when the longitudinal diameter exceeds the transverse one.[4] Coronary artery ectasia is defined when the dilated segment involves more than one-third of vessel length.[5]

After the first historical description of CAA by Morgagni,[6] several cases have been published,[7] and the International Coronary Artery Aneurysm Registry (CAAR) found a prevalence of 0.35% among 436,467 patients referred to invasive coronary angiography (ICA).[8]

Although heterogeneous systemic or cardiovascular conditions may underlie CAA development, the disarray of the components of vascular tunica media may be a common mechanism.[9] Atherosclerosis is the most frequent determinant of CAA, but they can also be associated with genetically-transmitted disease, inflammatory processes, or congenital abnormalities, or may be secondary to coronary interventions or traumas.[10]

Chest pain, secondary to either chronic or acute coronary syndrome (ACS),[9] may be the first clinical presentation of CAA, though they may be incidental findings at imaging[11] or postmortem examinations.[9] CAA dimensions, morphology, and etiology contribute to their prognostic significance but their location plays a major role. In this regard, the left anterior descending artery (LAD) is the most frequently involved vessel, followed by the right (RCA) and the left circumflex arteries (LCx).[8] Left main coronary aneurysms (LMCA), though very rare,[8] may yield life-threatening consequences.[8] However, the available knowledge on LMCA relies on case reports or small series, and their epidemiological and clinical features are poorly understood. Intending to expand the comprehension of LMCA, we systematically reviewed the literature to retrieve all the published cases. We hence summarized and described their epidemiological, anatomical, and etiological features, as well as their clinical presentation, treatments, and prognostic correlates.

2 | MATERIALS AND METHODS

At the end of December 2021, online databases (PubMed and MEDLINE) were systematically screened to retrieve all the reported cases of LMCA, by using the keywords "left main aneurysm" and "left main ectasia." Eligible publications were independently selected by 2 raters (F.N. and A.R.). First, the titles and abstracts of all citations were reviewed. Thereafter, the full text was obtained for potentially relevant cases. Non-English language works were translated through an open-source online tool (https://translate.google.com); if the translation was not clear, the articles were excluded. Both autoptic and in vivo reports were included, collecting data for individual patients within the case series. The lack of key features, such as patient's age at presentation, sex, clinical presentation, and adopted therapeutic strategy was considered an exclusion criterion and, after a careful quality check, the final decision to include each study was based upon the consensus of all the authors.

Beyond clinical data, details about LMCA morphology, dimensions, as well as concomitant CAA, or significant stenoses in different coronary segments were collected. As for LMCA etiology, if not specifically stated, an atherosclerotic origin was attributed in the case of diffuse coronary atherosclerosis, while an idiopathic origin was assigned otherwise. Although reported only in a minority of cases, data about antithrombotic therapies and outcomes were collected too, considering their clinical relevance.

Finally, extracted data were cross-checked and summarized through descriptive statistics, performed through SPSS (version 25.0, IBM Statistics). Quantitative variables were expressed as mean ± standard deviation or median (interquartile range) and compared by either independent *t* test or Mann–Whitney *U* test, as appropriate. Qualitative variables were expressed as numbers (percentages) and compared by Chi-square or Fisher's tests.

3 | RESULTS

3.1 | Characteristics of the selected cases

Out of 1997 initially retrieved, 180 manuscripts were selected, describing 209 LMCA cases (Figure S1 and Table S1). Most cases were published within last two decades, while a minority were published in the last century, since 1975 (Figure S2).

As reported in Table 1, the mean age of patients was 51 ± 19 years, and most individuals were males (68%). Hypertension was the most common risk factor (47%), followed by dyslipidemia, smoking, diabetes, and a family history of coronary artery disease (CAD). Only 16 patients had a prior myocardial infarction, while 6 and 4 individuals had previously undergone percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), respectively. Obstructive CAD was highly prevalent and involved LAD, LCx, and RCA in 84 (44%), 71 (37%), and 58 (30%) patients, while multivessel CAA involved LAD, LCx, and RCA in 59 (30%), 52 (26%), and 38 (19%) patients.

Atherosclerosis was the most common etiology (40%), followed by inflammatory (12%), congenital (9%), and degenerative (6%) conditions, while only 7 cases of secondary LMCA were reported. The specific causes of nonatherosclerotic LMCA are reported in Table S2. The etiology of LMCA was related to age (Figure 1): an atherosclerotic substrate prevailed in patients >55 years, while an inflammatory condition in those younger than 40 years. A different distribution of LMCA etiologies was also observed when distinguishing patients according to sex (Figure 1): atherosclerosis was the most common etiology among men (42% vs. 17% in women), while congenital cases were more prevalent among women (18% vs. 7%).

Saccular prevailed over fusiform LMCA (131 vs. 52 cases), with a median maximum diameter of 20 (13–30) mm. When comparing saccular versus fusiform LMCA (Table S3), no significant differences were observed, except for concomitant RCA aneurysms, which were more common in patients with fusiform LMCA ($p = .021$), and for

TABLE 1 Clinical and angiographic characteristics

	All cases ($n = 209$)
Clinical features	
Age, years ($n = 188$)	51 ± 19
Males, *n* (%) ($n = 185$)	125 (68)
Hypertension, *n* (%) ($n = 129$)	60 (47)
Diabetes, *n* (%) ($n = 129$)	18 (14)
Smoking, *n* (%) ($n = 126$)	25 (20)
Dyslipidemia, *n* (%) ($n = 123$)	35 (29)
Family history of CAD, *n* (%) ($n = 129$)	11 (9)
Prior myocardial infarction, *n* (%) ($n = 134$)	16 (12)
Previous PCI, *n* (%) ($n = 140$)	6 (4)
Previous CABG, *n* (%) ($n = 141$)	5 (2)
LMCA etiology and characteristics	
Atherosclerotic, *n* (%)	84 (40)
Degenerative, *n* (%)	12 (6)
Inflammatory, *n* (%)	26 (12)
Congenital, *n* (%)	19 (9)
Secondary, *n* (%)	7 (3)
Idiopathic, *n* (%)	61 (29)
Saccular/fusiform, *n* (%) ($n = 183$)	131/52 (72/28)
Maximum diameter, mm ($n = 141$)	20 (13–30)
Associated coronary disease	
LAD stenosis, *n* (%) ($n = 193$)	84 (44)
LAD aneurysm, *n* (%) ($n = 199$)	59 (30)
LCx stenosis, *n* (%) ($n = 194$)	71 (37)
LCx aneurysm, *n* (%) ($n = 197$)	52 (26)
RCA stenosis, *n* (%) ($n = 193$)	58 (30)
RCA aneurysm, *n* (%) ($n = 199$)	38 (19)
Clinical presentation	
Acute coronary syndrome, *n* (%)	68 (33)
STEMI, *n* (%)	39 (19)
NSTEMI, *n* (%)	5 (2)
Unstable angina, *n* (%)	24 (11)
Effort angina, *n* (%)	95 (45)
Incidental finding, *n* (%)	29 (14)
Other, *n* (%)[a]	17 (8)
Therapeutic management	
Surgical repair, *n* (%)	112 (53)
Percutaneous intervention, *n* (%)	13 (7)
Hybrid approach, *n* (%)	5 (2)
Antithrombotic therapy	
SAPT, *n* (%) ($n = 65$)	12 (19)
DAPT, *n* (%) ($n = 65$)	13 (20)
Oral anticoagulant, *n* (%) ($n = 65$)	35 (54)
Dual antithrombotic therapy, *n* (%) ($n = 65$)	4 (2)
Outcome	
Follow-up duration, months ($n = 81$)	8 (6–23)
Death, *n* (%) ($n = 81$)	12 (15)
Cardiovascular death, *n* (%) ($n = 81$)	9 (11)

Note: Data are presented as mean ± standard deviation, median (interquartile interval), or *n* (%), as appropriate.

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LMCA, left main coronary artery aneurysm; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SAPT, single antiplatelet therapy; STEMI, ST-elevation myocardial infarction.

[a]Heart failure ($n = 6$), cardiac tamponade ($n = 4$), unexplained syncope ($n = 3$), malignant arrhythmias ($n = 3$), respiratory infection ($n = 1$).

antithrombotic therapy, with a predominant prescription of oral anticoagulants (75% vs. 41%) in patients with fusiform LMCA, and of SAPT/DAPT in patients with saccular LMCA (27% and 25% vs. 13% and 0%).

Effort angina and ACS were the most common clinical presentations (45% and 32% of cases, respectively). Other possible manifestations included heart failure ($n = 6$), cardiac tamponade ($n = 4$), unexplained syncope ($n = 3$), malignant arrhythmias ($n = 3$), and one case of recurrent respiratory infection. LMCA was reported as an incidental finding in 29 (14%) patients: 20 cases during ICA and 9 cases at coronary computed tomography angiography (CCTA).

Antithrombotic therapy was rarely reported (65/209), and most patients received oral anticoagulants ($n = 35$, 60% warfarin, 9% rivaroxaban, 6% heparin, 25% unspecified), while SAPT or DAPT were less commonly prescribed (20% and 19%, respectively). Only 4 patients received a dual antithrombotic therapy (i.e., including both anticoagulant and antiplatelet drugs).

Longitudinal data were reported in 81 cases, with an 8-month median follow-up (interquartile range: 6–23 months). A high mortality rate was observed (15%) in this subset, mostly related to cardiovascular causes (75%), including ACS (5 cases), cardiac tamponade secondary to aneurysm rupture (2 cases), or heart failure (2 cases).

3.2 | Invasive and noninvasive imaging

ICA was performed in almost all the cases of LMCA ($n = 195$, 94%), mainly as the initial investigation, complemented by intracoronary

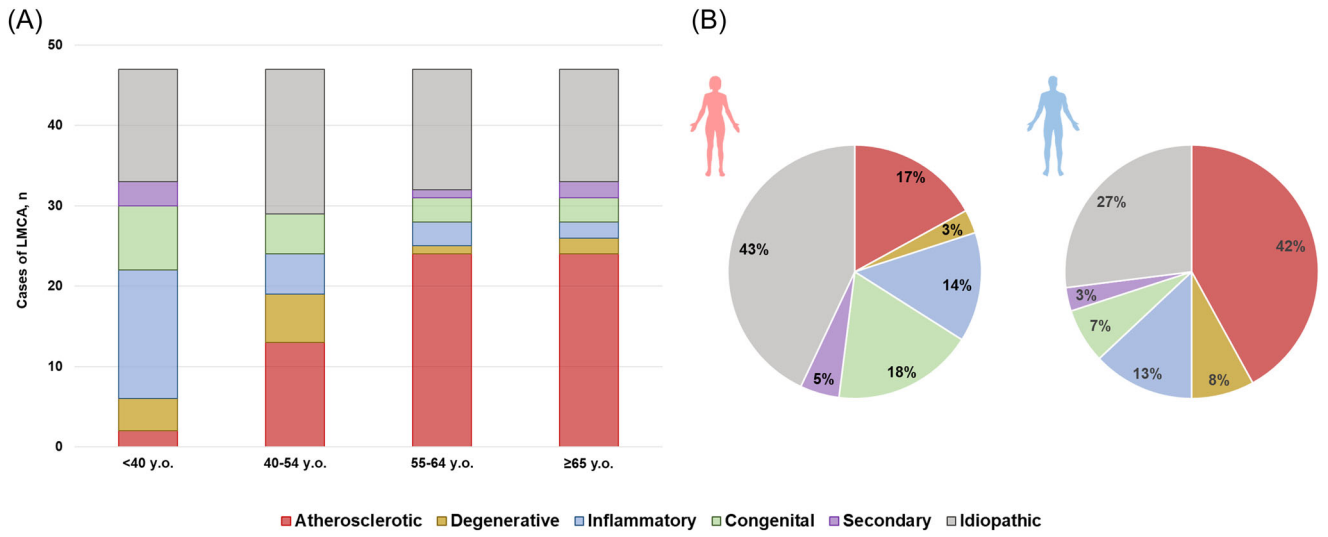

FIGURE 1 Etiology of left main coronary aneurysms (LMCA) according to age and sex. (A) While an atherosclerotic substrate prevailed in patients >55 years, inflammatory conditions were more common in younger individuals. (B) Atherosclerosis was the most common etiology among men, while congenital cases prevailed among women

imaging in a few cases, involving either intravascular ultrasound (IVUS, $n = 10$) or optical coherence tomography (OCT, $n = 1$). CCTA was performed in 125 cases (60%). While it represented the initial investigation in a minority of cases ($n = 15$, 7%), CCTA was mainly used as a second-level test to confirm LMCA diagnosis, characterize coronary anatomy, and plan surgical intervention ($n = 50$) as well as reevaluate patients during follow-up ($n = 19$). Other tests such as echocardiography ($n = 21$) or magnetic resonance ($n = 7$) were rarely employed.

3.3 | Atherosclerotic versus nonatherosclerotic LMCA

Many differences were observed when comparing atherosclerotic versus nonatherosclerotic LMCA (Table 2). Patients with atherosclerotic LMCA showed higher prevalence of hypertension (73% vs. 30%, $p < .001$), smoking habit (33% vs. 12%, $p = .006$), dyslipidemia (47% vs. 17%, $p = .001$), and family history of CAD (22% vs. 0%, $p < .001$). No significant difference in previous ACS, PCI, CABG, or LMCA morphology was observed, while concomitant CAA on LAD, but not on other coronary arteries, were more common in patients with atherosclerotic LMCA (39% vs. 23%, $p = .012$).

Effort angina was more frequent in patients with atherosclerotic LMCA (64% vs. 34%, $p < .001$), while nonatherosclerotic LMCA represented more often incidental findings (22% vs. 2%, $p = .018$). A similar incidence of ACS was observed between the two groups (32%), with more frequent unstable angina in patients with atherosclerotic LMCA (18% vs. 7%, $p = .017$), and ST-elevation myocardial infarction (STEMI, 23% vs. 12%, $p = .027$) in those with nonatherosclerotic LMCA. Most patients with atherosclerotic LMCA underwent surgical intervention (74% vs. 56%, $p = .023$), with no differences in antithrombotic therapies and outcomes.

3.4 | Clinical presentation of LMCA

The characteristics of patients according to the clinical presentation of LMCA are reported in Table 3. Patients in whom LMCA was an incidental finding were younger and had a lower prevalence of dyslipidemia compared to those presenting with stable angina (both $p < .05$). The etiology of LMCA was less frequently atherosclerotic in this subset, showing a lower prevalence of coronary stenosis compared to patients presenting with either stable angina or ACS (all $p < .05$). No significant differences were observed in therapeutic management and outcomes across these subgroups.

3.5 | Therapeutic management and outcome of LMCA

In most cases of LMCA, patients underwent surgical repair (53%), while a percutaneous intervention or a hybrid approach was rarely performed (7% and 2% of cases), as detailed in Table 4. When comparing surgically versus nonsurgically managed patients (Table 5), a conservative approach was more common in the case of previous CABG ($p = .009$), while a surgical intervention was preferred in case of atherosclerotic or degenerative etiology, and of larger LMCA (all $p < .05$). The presence of associated CAD prevailed in surgically treated patients, which received more commonly antiplatelets over anticoagulants ($p = .008$). During follow-up, the incidence of all-cause death—but not of cardiovascular death—was higher in non-surgically treated cases (23 vs. 5%, $p = .029$).

TABLE 2 Comparison of atherosclerotic versus nonatherosclerotic left main coronary aneurysms

	Atherosclerotic (n = 84)	Nonatherosclerotic (n = 125)	p
Clinical features			
Age, years (n = 188)	61 ± 11	46 ± 20	**<.001**
Males, n (%) (n = 185)	52 (84)	73 (59)	**.001**
Hypertension, n (%) (n = 129)	36 (72)	24 (30)	**<.001**
Diabetes, n (%) (n = 129)	11 (22)	7 (9)	.066
Smoking, n (%) (n = 126)	16 (33)	9 (12)	**.006**
Dyslipidemia, n (%) (n = 123)	22 (47)	13 (17)	**.001**
Family history of CAD, n (%) (n = 129)	11 (22)	0 (0)	**<.001**
Prior myocardial infarction, n (%) (n = 134)	8 (17)	8 (9)	.263
Previous PCI, n (%) (n = 140)	3 (6)	3 (3)	.666
Previous CABG, n (%) (n = 141)	4 (8)	1 (1)	.053
LMCA characteristics			
Saccular/fusiform, n (%) (n = 183)	53/24 (69/31)	78/28 (74/26)	.510
Maximum diameter, mm (n = 141)	18 (13–30)	20 (14–30)	.251
Associated coronary disease			
LAD stenosis, n (%) (n = 193)	58 (74)	26 (23)	**<.001**
LAD aneurysm, n (%) (n = 199)	33 (39)	26 (23)	**.012**
LCx stenosis, n (%) (n = 194)	54 (69)	17 (15)	**<.001**
LCx aneurysm, n (%) (n = 197)	25 (30)	27 (24)	.330
RCA stenosis, n (%) (n = 193)	48 (62)	10 (9)	**<.001**
RCA aneurysm, n (%) (n = 199)	21 (25)	17 (15)	.099
Clinical presentation			
Acute coronary syndrome, n (%)	27 (32)	41 (32)	**.033**
STEMI, n (%)	10 (12)	29 (23)	–
NSTEMI, n (%)	2 (2)	3 (2)	–
Unstable angina, n (%)	15 (18)	9 (7)	–
Effort angina, n (%)	53 (64)	42 (34)	**<.001**
Incidental finding, n (%)	2 (2)	27 (22)	**<.001**
Other, n (%)	2 (2)	15 (12)	**.018**
Therapeutic management			
Surgical repair, n (%)	46 (74)	66 (56)	**.023**
Percutaneous intervention, n (%)	6 (10)	8 (7)	.563
Hybrid approach, n (%)	2 (3)	3 (3)	1.000

(Continues)

TABLE 2 (Continued)

	Atherosclerotic (*n* = 84)	Nonatherosclerotic (*n* = 125)	*p*
Antithrombotic therapy			.608
SAPT, *n* (%) (*n* = 65)	5 (28)	7 (15)	–
DAPT, *n* (%) (*n* = 65)	4 (22)	9 (19)	–
Oral anticoagulant, *n* (%) (*n* = 65)	9 (50)	26 (55)	–
Dual antithrombotic therapy, *n* (%) (*n* = 65)	0 (0)	1 (2)	–
Outcome			
Follow-up duration, months (*n* = 81)	6 (5–12)	11 (6–24)	.115
Death, *n* (%) (*n* = 81)	2 (8)	10 (18)	.325
Cardiovascular death, *n* (%) (*n* = 81)	1 (4)	8 (14)	.262

Note: Data are presented as mean ± standard deviation, median (interquartile interval), or *n* (%), as appropriate. Bold means statistically significant ($p < .05$).

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LMCA, left main coronary artery aneurysm; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SAPT, single antiplatelet therapy; STEMI, ST-elevation myocardial infarction.

4 | DISCUSSION

To the best of our knowledge, this is the first systematic review of LMCA. Although considered extremely rare, the number of LMCA reported has increased in the last decades and may continue to grow with the widespread use of invasive and noninvasive coronary imaging (Figure 2). Considering the lack of controlled studies, the current guidelines do not report any specific recommendation for LMCA. The comprehensive description of their epidemiological and clinical features provided in the present study may therefore help to optimize the related diagnostic and therapeutic algorithms (Figure 3).

4.1 | Clinical correlates and etiological substrate of LMCA

The age of presentation of LMCA was almost 15 years younger than that reported for all CAA. Although the involvement of the left main stem may be associated with an earlier onset of symptoms,[12] the higher prevalence of congenital and inflammatory origins may suggest a unique epidemiological profile for LMCA. Most cases of LMCA regarded male individuals.[8] Although the higher prevalence of cardiovascular risk factors and advanced atherosclerosis may explain such finding,[13] a possible influence of sex hormones on vessel frailty could not be excluded.[14] Accordingly, while atherosclerotic and degenerative etiology were more common in men, congenital LMCA prevailed among women. Future studies are expected to shed light on these observations. Of note, no sex difference was observed in the relative prevalence of inflammatory LMCA. Though systemic inflammatory disorders may be more frequent in adult women, the incidence of some vasculitis, such as Kawasaki's disease, is usually higher in male children.[15]

Only a minority (12%) of patients with LMCA had a previous history of myocardial infarction, while diffuse CAD, characterized by the presence of either obstructive lesions or heterotopic CAA, was common in patients with atherosclerotic LMCA. Such finding is not surprising considering the progressive nature of atherosclerosis.[16] Nevertheless, concomitant lesions were also observed in about one-fourth of patients with nonatherosclerotic etiology. In these cases, LMCA may hence represent an epiphenomenon of a diffuse arterial frailty.[9,17] An accurate evaluation of the whole coronary tree and, potentially, of other vascular districts may therefore be warranted.[18]

4.2 | Clinical presentation, diagnosis, and management of LMCA

Stable angina was the most common clinical presentation of LMCA. Notably, the prevalence of such symptom was significantly higher than that reported for all CAA (43% vs. 17%).[8] Whereas reduced coronary flow reserve secondary to concomitant coronary stenoses may be implicated, aneurysm-related blood stasis may predispose to thromboembolic events, coronary spasm, and microvascular dysfunction which could participate in transient myocardial ischemia.[2,19] In line with this hypothesis, the larger myocardial territory supplied by the left main may explain the higher prevalence of ischemic

TABLE 3 Comparison of left main coronary aneurysms according to their clinical presentation

	ACS (n = 68)	Stable angina (n = 95)	Incidental finding (n = 29)
Clinical features			
Age, years (n = 188)	49 ± 18	56 ± 15	45 ± 24[a]
Males, n (%) (n = 185)	53 (80)	44 (64)	19 (65)
Hypertension, n (%) (n = 129)	23 (44)	21 (48)	9 (43)
Diabetes, n (%) (n = 129)	7 (14)	9 (21)	1 (5)
Smoking, n (%) (n = 126)	16 (31)	8 (19)	1 (5)
Dyslipidemia, n (%) (n = 123)	13 (29)	17 (40)	1 (5)[a]
Family history of CAD, n (%) (n = 129)	4 (8)	7 (16)	0 (0)
Prior myocardial infarction, n (%) (n = 134)	9 (18)	3 (6)	2 (9)
Previous PCI, n (%) (n = 140)	2 (4)	4 (8)	0 (0)
Previous CABG, n (%) (n = 141)	1 (2)	3 (6)	1 (4)
LMCA etiology and characteristics			
Atherosclerotic, n (%)	27 (40)	52 (57)	2 (7)[b,a]
Degenerative, n (%)	2 (3)	4 (4)	6 (21)[b,a]
Inflammatory, n (%)	11 (16)	8 (9)	3 (10)
Congenital, n (%)	1 (2)	7 (8)	7 (24)
Iatrogenic, n (%)	1 (2)	3 (3)	3 (10)
Idiopathic, n (%)	26 (38)	17 (19)	8 (28)
Saccular/fusiform, n (%) (n = 183)	43/17 (72/28)	53/27 (66/34)	19/6 (76/24)
Maximum diameter, mm (n = 141)	20 (15–30)	18 (12–28)	20 (14–32)
Associated coronary disease			
LAD stenosis, n (%) (n = 193)	32 (49)	45 (55)	4 (15)[b,a]
LAD aneurysm, n (%) (n = 199)	18 (28)	30 (35)	5 (19)
LCx stenosis, n (%) (n = 194)	25 (39)	42 (51)	2 (8)[b,a]
LCx aneurysm, n (%) (n = 197)	14 (22)	25 (29)	6 (22)
RCA stenosis, n (%) (n = 193)	17 (26)	37 (46)[b]	2 (7)[a]
RCA aneurysm, n (%) (n = 199)	8 (12)	22 (25)	2 (7)
Therapeutic management			
Surgical repair, n (%)	43 (65)	35 (67)	14 (52)
Percutaneous intervention, n (%)	7 (11)	4 (6)	2 (7)
Hybrid approach, n (%)	1 (2)	2 (3)	1 (4)
Antithrombotic therapy			
SAPT, n (%) (n = 65)	8 (25)	1 (6)	2 (29)
DAPT, n (%) (n = 65)	7 (22)	2 (12)	2 (29)
Oral anticoagulant, n (%) (n = 65)	17 (53)	11 (65)	3 (43)
Dual antithrombotic therapy, n (%) (n = 65)	0 (0)	1 (6)	0 (0)

(Continues)

TABLE 3 (Continued)

	ACS (*n* = 68)	Stable angina (*n* = 95)	Incidental finding (*n* = 29)
Outcome			
Follow-up duration, months (*n* = 81)	7 (5–16)	12 (6–18)	12 (6–18)
Death, *n* (%) (*n* = 81)	3 (9)	3 (10)	1 (9)
Cardiovascular death, *n* (%) (*n* = 81)	2 (6)	1 (3)	1 (9)

Note: Data are presented as mean ± standard deviation, median (interquartile interval), or *n* (%), as appropriate.

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LMCA, left main coronary artery aneurysm; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SAPT, single antiplatelet therapy; STEMI, ST-elevation myocardial infarction.

[a]$p < .05$ vs. stable angina.

[b]$p < .05$ vs. ACS.

TABLE 4 Surgical, percutaneous, and hybrid techniques adopted in patients with a left main coronary aneurysm

Surgical intervention (*n* = 112) **Technique**	***N***
❖ CABG + aneurysm ligation	28
❖ Isolated CABG	27
❖ Unspecified surgery	17
❖ CABG + aneurysm resection	10
❖ CABG + aneurysm repair	10
❖ Unspecified repair	9
❖ Aneurysmectomy + fistula ligation/repair	8
❖ Aneurysmectomy + graft repair	3
Percutaneous (*n* = 13) **Technique**	***N***
❖ PCI	8
❖ PCI + aneurysm coiling	3
❖ PCI + thromboaspiration	2
❖ PCI + pericardiocentesis	1
❖ Septal occluder + aneurysm coiling	1
Hybrid (*n* = 5) **Technique**	***N***
❖ CABG + PCI	5

Abbreviations: LCx, left circumflex coronary artery; PCI, percutaneous coronary intervention.

symptoms. Conversely, ACS was less frequently the first manifestation of LMCA compared with other CAA (32% vs. 62%). Although the prevalence of ACS did not differ across LMCA etiologies, STEMI was more common in nonatherosclerotic cases (23% vs. 12%). In these cases, acute thrombosis secondary to blood stasis or flow turbulence may prevail, while plaque ulceration or erosion may be responsible for non-STEMI in presence of diffuse atherosclerosis.[19,20] Finally, LMCA were incidental findings in 29 cases, mostly of congenital or degenerative etiology, while other presentations such as heart failure, cardiac tamponade, syncope, or malignant arrhythmias were uncommon. Although an underreporting of these cases cannot be excluded, such findings correspond to those reported in the CAAR.[8]

In most cases of LMCA, ICA represented the initial investigation. Although ICA may be limited in the morphological characterization of LMCA, a more extensive use of IVUS and/or OCT may provide useful details about LMCA structure and etiology, improving percutaneous interventions.[21] CCTA was used in many cases of LMCA, particularly in the last two decades. Considering its higher spatial resolution, CCTA was often chosen as a second-level technique to confirm LMCA location and morphology, and it may provide unique information about LMCA etiology (e.g., atherosclerotic vs. non-atherosclerotic) and the tridimensional relations with the surrounding structures.[11] Therefore, it may be warranted to optimize surgical planning and during follow-up.

In absence of dedicated studies, both the interventional and the pharmacological management of patients with LMCA are challenging. Among the studied cases, various surgical approaches were adopted, the choice of which was based on both LMCA morphology and the presence of concomitant CAD. Aneurysm repair and simultaneous CABG was the most common strategy, followed by CABG. Isolated aneurysm repair was less frequently performed but may be a plausible option in nonatherosclerotic cases.[22] Compared with the CAAR, percutaneous approaches were less frequently utilized in the present study (7% vs. 53%). Anatomical, technical, and safety reasons may limit such techniques in patients with LMCA. However, when surgery is prohibitive or contraindicated, covered stents may be positioned to restore the native vessel profile, excluding an aneurysmal sac to prevent its growth, while aneurysm coil embolization is another alternative.[22]

Although rarely reported, oral anticoagulation was the most adopted antithrombotic strategy, while either SAPT or DAPT were

TABLE 5 Comparison of surgically versus nonsurgically treated left main coronary aneurysm

	Surgical treatment (*n* = 112)	Nonsurgical treatment (*n* = 97)	*p*
Clinical features			
Age, years (*n* = 188)	52 ± 16	52 ± 20	.830
Males, *n* (%) (*n* = 185)	80 (71)	53 (62)	.186
Hypertension, *n* (%) (*n* = 129)	33 (46)	37 (51)	.588
Diabetes, *n* (%) (*n* = 129)	8 (11)	15 (20)	.200
Smoking, *n* (%) (*n* = 126)	11 (16)	19 (29)	.110
Dyslipidemia, *n* (%) (*n* = 123)	17 (25)	23 (35)	.304
Family history of CAD, *n* (%) (*n* = 129)	7 (10)	5 (8)	1.000
Prior myocardial infarction, *n* (%) (*n* = 134)	11 (15)	6 (9)	.426
Previous PCI, *n* (%) (*n* = 140)	3 (4)	4 (6)	.682
Previous CABG, *n* (%) (*n* = 141)	0 (0)	6 (9)	**.009**
LMCA etiology and characteristics			
Atherosclerotic, *n* (%)	46 (41)	23 (24)	**.023**
Degenerative, *n* (%)	11 (10)	2 (2)	**.033**
Inflammatory, *n* (%)	11 (10)	18 (19)	.075
Congenital, *n* (%)	12 (11)	8 (8)	.148
Secondary, *n* (%)	3 (3)	5 (5)	.673
Idiopathic, *n* (%)	29 (26)	41 (43)	**.021**
Saccular/fusiform, *n* (%) (*n* = 183)	73/24 (75/25)	65/24 (71/29)	.575
Maximum diameter, mm (*n* = 141)	24 (15–32)	20 (11–27)	**.032**
Associated coronary disease			
LAD stenosis, *n* (%) (*n* = 193)	49 (45)	26 (30)	.075
LAD aneurysm, *n* (%) (*n* = 199)	27 (25)	21 (23)	.856
LCx stenosis, *n* (%) (*n* = 194)	41 (38)	19 (22)	**.042**
LCx aneurysm, *n* (%) (*n* = 197)	20 (19)	24 (28)	.183
RCA stenosis, *n* (%) (*n* = 193)	32 (29)	12 (14)	**.027**
RCA aneurysm, *n* (%) (*n* = 199)	12 (11)	21 (25)	**.020**
Clinical presentation			
Acute coronary syndrome, *n* (%)	43 (38)	33 (34)	.938
STEMI, *n* (%)	24 (21)	19 (19)	–
NSTEMI, *n* (%)	3 (3)	3 (3)	–
Unstable angina, *n* (%)	16 (14)	12 (12)	–
Effort angina, *n* (%)	48 (43)	31 (33)	.343
Incidental finding, *n* (%)	14 (13)	19 (19)	.280
Other, *n* (%)	7 (6)	13 (13)	.175
Antithrombotic therapy			**.008**
SAPT, *n* (%) (*n* = 65)	8 (38)	2 (9)	–
DAPT, *n* (%) (*n* = 65)	5 (24)	4 (18)	–

(Continues)

TABLE 5 (Continued)

	Surgical treatment (*n* = 112)	Nonsurgical treatment (*n* = 97)	*p*
Oral anticoagulant, *n* (%) (*n* = 65)	7 (33)	14 (64)	–
Dual antithrombotic therapy, *n* (%) (*n* = 65)	1 (5)	0 (0)	–
Outcome			
Follow-up duration, months (*n* = 81)	7 (6–16)	10 (6–24)	.484
Death, *n* (%) (*n* = 81)	2 (5)	10 (23)	**.029**
Cardiovascular death, *n* (%) (*n* = 81)	2 (5)	7 (16)	.162

Note: Data are presented as mean ± standard deviation, median (interquartile interval), or *n* (%), as appropriate. Bold means statistically significant ($p < .05$).

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LMCA, left main coronary artery aneurysm; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SAPT, single antiplatelet therapy; STEMI, ST-elevation myocardial infarction.

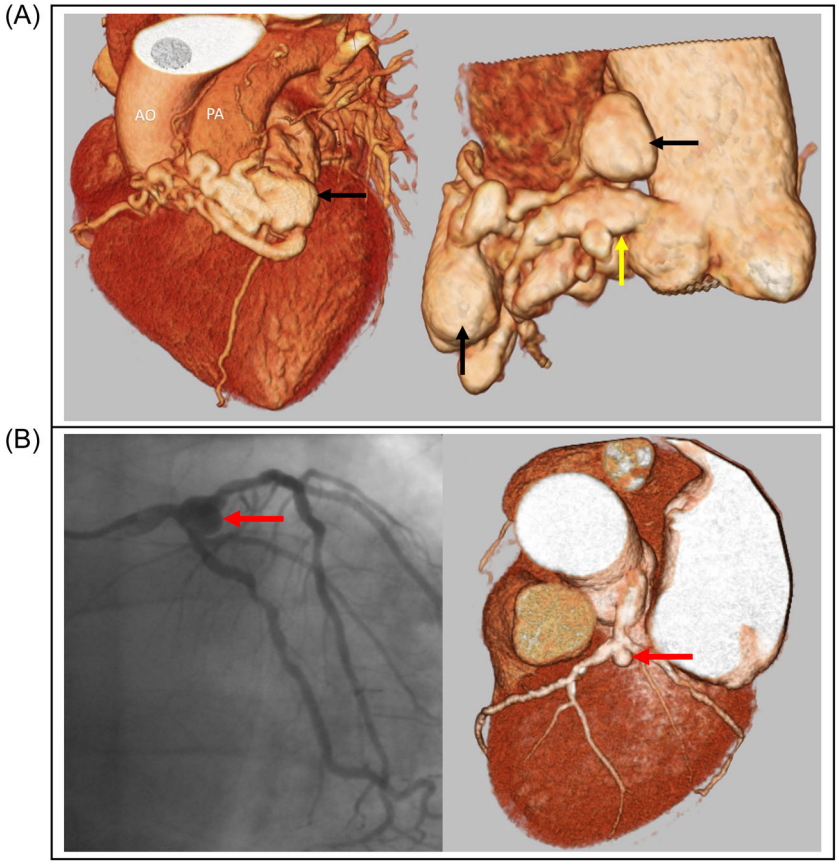

FIGURE 2 Real-life examples of left main coronary aneurysms (LMCA). (A) A 76-year-old hypertensive woman with no history of cardiac disease or symptoms underwent a coronary computed tomography angiography (CCTA) because of an echocardiographic suspect of periaortic mass. CCTA images showed an LMCA (yellow arrow), connected through a fistulous tract to the pulmonary artery (black arrows). Considering the lack of symptoms and the mild entity of the shunt, the patient was managed conservatively. (B) A 72-year-old man with multiple cardiovascular risk factors and complaining of atypical chest pain underwent an invasive coronary angiography (left panel) which showed a saccular LMCA (red arrows), in absence of significant obstructive CAD. Considering the surgical risk, the patient was managed conservatively. After a 2-year follow-up, the patient was asymptomatic and the CCTA (right panel) showed substantial stability of coronary anatomy. CAD, coronary artery disease.

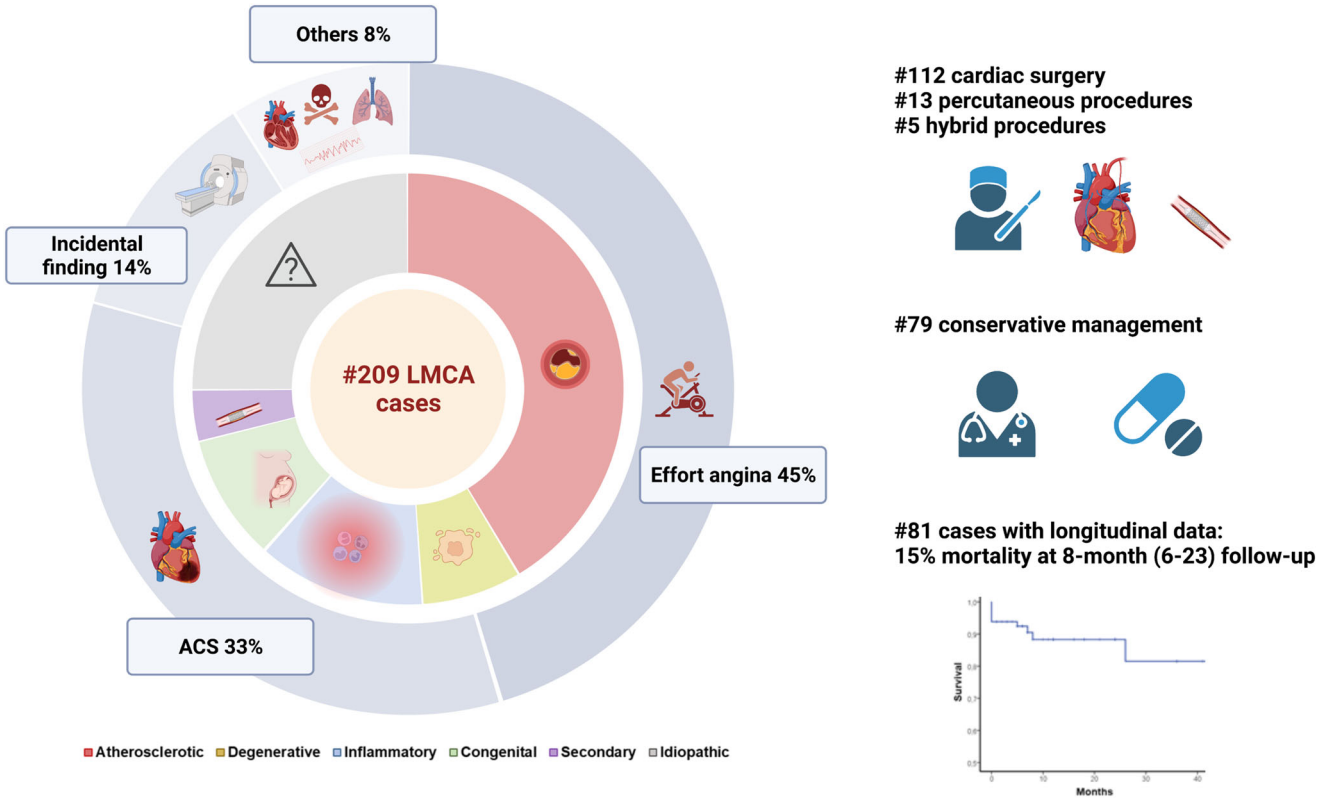

FIGURE 3 Epidemiology, clinical presentation, and management of left main coronary aneurysms (LMCA). ACS, acute coronary syndromes.

rarely prescribed.[8] The optimal antithrombotic therapy of CAA is debated. Previous studies suggested that anticoagulant therapies may be unnecessary,[8,22] though well-controlled anticoagulation was associated with a lower risk of adverse events in patients with coronary ectasia and ACS.[23] Future studies are therefore needed to outline the risk-to-benefit ratio of antithrombotic therapies in these patients.

Finally, follow-up details were available only in 81 cases, reporting a 15% mortality over a median 8-month follow-up. Acknowledging that no definitive conclusion could be derived from these data, patients with LMCA may suffer a dramatically higher risk of mortality in the short-term.[8] In absence of stronger evidence, a closer follow-up of these patients may hence be crucial.

4.3 | Study limitations

Considering the rarity of LMCA, the data reported in this review derives from case reports or small series, and not from controlled studies. Therefore, as in all the studies of this kind, publication bias could not be excluded, since the most challenging cases are more likely to be published. Considering the anatomic feature of the left main stem, compared with the other coronary arteries, a morphological distinction between aneurysm and ectasia may be difficult. To avoid confusion, only the term aneurysm was therefore used throughout the review. Although antithrombotic therapies were reported only in a minority of cases, considering the lack of recommendations, such data were collected whenever available, underling the heterogeneity of the adopted strategies. Finally, it should be acknowledged that our findings could not establish robust associations or causative relations, though they may generate hypotheses to be confirmed in future controlled studies.

5 | CONCLUSIONS

LMCA are rare but treacherous conditions, the incidence of which is expected to increase with the widespread use of noninvasive coronary imaging. Atherosclerosis is the most common etiology but inflammatory, degenerative, or congenital origins should be considered, particularly among younger individuals and women. Irrespective of etiology and clinical presentation, LMCA may be associated with high short-term mortality. Therefore, in absence of controlled studies, a careful evaluation of each case is warranted to optimize their management.

AUTHOR CONTRIBUTIONS

Francesco Negro: concept/design, data collection, drafting article. **Francesco Gentile**: concept/design, data analysis/interpretation, drafting article. **Antonio Rizza**: concept/design, data collection, critical revision of article. **Alberto Giannoni**: critical revision of article, supervision. **Giacomo Bianchi**: critical revision of article, supervision.

Alberto Clemente: critical revision of article, supervision. **Michele Emdin**: critical revision of article, supervision. **Cataldo Palmieri**: critical revision of article, supervision.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

The research protocol was approved by the locally appointed ethics committee, according to the Declaration of Helsinki and privacy rules, while no consent statement and clinical trial registration were required for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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