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INTEGRATED STUDY MASTER'S THESIS

Treatment Methods of Coronary Artery Aneurysms. Literature review

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Abbreviations

CAA- Coronary artery aneurysm
CAE- Coronary artery ectasia
CASS- Coronary Art Surgery Study
MMPs- Matrix Metalloproteinases
TIMP- Tissue Inhibitors of Metalloproteinases
DES- Drug-Eluting Stent
BMS- Bare-Metal Stent
FBN1- Fibrillin-1 gene
TGF- β - Transforming Growth Factor beta
CCTA- Coronary Computed Tomography Angiography
PTFE- Polytetrafluoroethylene
PCI- Percutaneous Coronary Intervention
CABG- Coronary Artery Bypass Grafting
CAP- Coronary Artery Perforation
SVGA- Saphenous vein graft aneurysms
ACS- Acute Coronary Syndrome
SAPT- Single Antiplatelet Therapy
Hs-CRP- High sensitivity CRP
TTE- Transthoracic Echocardiography
IVUS- Intravascular Ultrasound
LAD- Left Anterior Descending coronary artery
OCT- Optical Coherence Tomography
MACE- Major Adverse Cardiovascular Events
DAPT- Dual Antiplatelet Therapy
SUCRA- Surface Under the Cumulative Ranking Curve
AMI- Acute Myocardial Infarction
TTR- Time-in-Therapeutic Range
CAAR- Coronary Artery Aneurysm Registry
OAT- Oral Anticoagulant Therapy
AHA- American Heart Association
LMWH- Low-Molecular-Weight Heparin
INR- International Normalized Ratio
DOAC- Direct Oral Anticoagulant
RAAS- Renin–Angiotensin–Aldosterone System
MBG- Myocardial Blush Grade
TIMI- Thrombolysis in Myocardial Infarction
TFC- TIMI Frame Count
MACCE- Major Adverse Cardiac and Cerebrovascular Event

Abstract

Objective: Coronary artery aneurysms (CAAs) are rare vascular abnormalities that present with various clinical features. Currently, no standardized treatment guideline has been defined. All conducted treatment methods are oriented toward the patient's individual profile. This literature review intends to give an overview of current treatment modalities and identify the safety as well as effectiveness of the treatment options.

Methods: A literature search was conducted using platforms such as PubMed, Scopus and Google Scholar. Studies from the past 10–20 years were included that addressed the etiology, pathophysiology, diagnosis and treatment of CAAs.

Results: The leading cause of CAAs is atherosclerosis, but other congenital and inflammatory conditions also contribute to it. Treatment options include pharmacological treatment, percutaneous interventions and surgery. The decision regarding which option to proceed with depends on the patient's characteristics.

Conclusion: CAA management remains individualized due to limited clinical trials. Further research in this field is necessary to establish clear treatment guidelines.

Keywords: Coronary artery aneurysms, Treatment methods of Coronary artery aneurysms, Pharmacological therapy for Coronary artery aneurysms, Percutaneous interventions, Surgical management of Coronary artery aneurysms, Short- and long-term effects of percutaneous interventions, Short- and long-term effects of surgical procedures

Abstract in Lithuanian:

Tikslas: Koronarinės arterijos aneurizmos (KAA) yra retos kraujagyslių anomalijos, pasireiškiančios įvairiais klinikiniais požymiais. Šiuo metu nėra nustatytų standartizuotų gydymo gairių. Gydymo metodas yra parenkamas individualiai. Šio literatūros apžvalgos tikslas – pateikti dabartinių gydymo būdų apžvalgą, bei įvertinti jų saugumą ir veiksmingumą.

Metodai: Literatūros paieška buvo atlikta naudojant „PubMed“, „Scopus“ ir „Google Scholar“ platformas. Įtraukti pastarųjų 10–20 metų tyrimai, kuriuose nagrinėjama KAA etiologija, patofiziologija, diagnostika ir gydymas.

Rezultatai: Pagrindinė KAA priežastis yra aterosklerozė, taip pat įgimtos ligos, bei Uždegiminės būklės. Galimi gydymo būdai: medikamentinis gydymas, perkutaninės intervencijos ir chirurginis gydymas. Sprendimas, kurį gydymo būdą pasirinkti, priklauso nuo paciento charakteristikų.

Išvada: Dėl ribotų klinikinių tyrimų KAA gydymas išlieka individualizuotas. Norint nustatyti aiškias gydymo gaires, būtini tolesni tyrimai šioje srityje.

Raktažodžiai: Koronarinės arterijos aneurizmos, Koronarinės arterijos aneurizmų gydymo metodai, Farmakologinis koronarinės arterijos aneurizmų gydymas, Perkutaninės Intervencijos koronarinės arterijos aneurizmų gydyme, Chirurginis koronarinės arterijos aneurizmų gydymas, Perkutaninių intervencijų trumpalaikiai ir ilgalaikiai padariniai, Chirurginių procedūrų trumpalaikiai ir ilgalaikiai padariniai.

(Translated using DeepL and with the assistance of Prof. Andrius Berūkštis)

1.0 Introduction:

1.1 Background

Coronary artery aneurysms (CAA) are described as dilations that involve confined segments of the coronary arteries. They are typically defined as an enlargement of the vessel diameter, reaching at least 1.5 times the diameter of the surrounding normal arterial segment.(1–3) CAAs were first described by the French doctor C. Bougon in 1812. They are generally considered rare,(1,4) however coronary angiography studies indicate an incidence ranging from 0.3% to 5.3%.(4) Despite the fact that many CAA cases are discovered by accident, CAAs can cause serious complications such as thromboembolism, rupture of the coronary artery, vascular spasm and in some cases even sudden cardiac arrest.(2,4) Even though, the identification of CAAs has improved due to developing imaging tools, it is still challenging to find the appropriate treatment strategy.(1,2) Because of the scarcity of conducted randomized controlled trials and established treatment guidelines, no definite treatment approach has been formulated yet.(4)

The clinical manifestation of CAAs differs greatly, ranging from asymptomatic cases to life-threatening incidents.(4) Although, the exact pathophysiology is still unknown, it is believed to be related to various etiologies including atherosclerosis, congenital abnormalities such as Kawasaki disease, vasculitis and iatrogenic causes.(1,3,4) The complex presentation of CAAs further complicates the treatment strategy, since variations in size, shape, location and associated risks strongly affect the treatment decisions.(3,4) Different treatment approaches are established, including pharmacological therapy with anticoagulants and antiplatelets, percutaneous coronary interventions using covered stents or stent-assisted coil embolization and surgical procedures such as coronary artery bypass grafting or aneurysm excision. (1,3,4) However, due to the lack of established recommendations and guidelines, the treatment approaches are most commonly tailored individually depending on the features of the aneurysm and patients' circumstances.(3)

1.2 Objectives

Due to the absence of significant randomized controlled studies or clinical protocols regarding the treatment of CAAs, a broad assessment of different treatment options is needed. This thesis will evaluate the effectiveness and safety of pharmacological, percutaneous and surgical interventions in treating CAAs. Reviewing existing treatment techniques and comparing their short- and long-term clinical results is the primary objective of this thesis. Patient-specific factors that affect the treatment selection such as the aneurysm size, location and the underlying etiology, will also be examined. To

accomplish these objectives, the following research question is established: “What are the most effective and safe treatment methods for managing coronary artery aneurysms in terms of short- and long-term clinical outcomes?”. In order to identify the most effective methods for managing CAAs, this thesis will conduct a thorough literature review, assessing the latest clinical findings.

1.3 Structure of the thesis

The thesis is divided into five main parts, with the first providing an introduction to the topic. The next chapter describes the methodology utilized to carry out the literature review as well as the search approach, inclusion and exclusion criteria and data collection. The third chapter is a detailed literature review on CAAs, discussing the definition, epidemiology, pathophysiology, diagnostic methods, available treatment methods and their outcomes. The focus of this thesis is to assess the treatment results and possible side effects, as well as to highlight both short- and long-term outcomes of different treatment modalities. The fourth chapter will be a discussion that analyzes the clinical significance of various treatment options and compares the results with previous research data. At the end, a short summary will be provided with suggestions for further research and clinical practice.

2.0 Methods:

2.1 Source collection

This thesis presents a literature review that summarizes and evaluates current treatment approaches for coronary artery aneurysms. It discusses the efficacy, safety and associated consequences of pharmacological, percutaneous and surgical treatments. For the literature search, different platforms were used such as PubMed (Medline), Scopus and Google scholar, as these databases offer access to a wide selection of reviewed cardiology articles. In order to provide reliable and accurate information, search keywords were carefully chosen and included phrases like “coronary artery aneurysm treatment,” “pharmacological therapy for coronary artery aneurysms,” “surgical management of coronary artery aneurysms” and “percutaneous coronary intervention AND coronary artery aneurysm”. The search results were refined using Boolean operators (AND, OR). By manually searching the bibliographies of research papers, further references were found.

2.2 Criteria

Different selection criteria were developed to ensure that only relevant material was included. Studies were eligible if they investigated CAA therapy options, described clinical results or offered

contrasting data on different management strategies. Since some authors use the medical terms coronary artery aneurysm (CAA) and coronary artery ectasia (CAE) equivalently and consider their exact differentiation difficult, (4) this literature review included studies that addressed both entities. This also included studies that focused on CAAs etiology, pathophysiology, diagnostics methods or associated conditions such as Kawasaki disease. Studies only addressing coronary intervention methods were also included because they provided a broader understanding of the approach itself. Different study types were used such as meta-analyses, cohort studies, comparative studies, systematic reviews as well as observational studies, published within the last 10-20 years. The publication period was extended to 20 years due to the scarcity of available data. Only studies in the English language were included. Case reports with less than ten patients were excluded. In order to facilitate a comparison of various therapy techniques, the focus was placed on effectiveness, safety and both short- and long-term outcomes.

2.3 Ethics

For this thesis no ethical approval was needed because this thesis only used pre-reviewed scientific material. Only academic publication was used to assure reliability. A comparative review was made to evaluate the advantages and disadvantages of each treatment option.

3.0 Literature Review

3.1 Definition, Epidemiology and Etiology of CAA

In the literature, coronary artery aneurysms are often described as enlargements of a confined arterial segment that can reach over 1.5 times the size of the neighboring non-dilated coronary artery segment.(1–3) Variants of CAAs are giant coronary aneurysms and coronary ectasias. Giant aneurysms are a type of aneurysm that either reach more than four times the normal vessel diameter or measuring more than 20 mm in diameter in adults and more than 8 mm in diameter in children.(4–6) Coronary ectasias (CAE) are diffuse enlargements of the coronary segment, with a diameter that is larger than that of the reference normal coronary segment by more than 50%. Precisely differentiating CAE from CAAs is difficult due to overlapping features, which complicates diagnosis and classification.(2,4)

The morphological classification of CAAs encompasses different measures including the shape, size and the number of the arterial segments that are involved.(5) In order to adequately distinguish aneurysm subtypes such as true and false aneurysms, it is necessary to assess the extent of

involvement of the vessel wall layers.(1,2) False aneurysms are defined as enlargements that only affect one or two layers of the vessel wall. They typically occur due to loss of vessel wall integrity between the medial muscular layer and the outer elastic layer. The most common etiologies of false aneurysms are traumas or complications of interventional coronary procedures.(1,2) Conversely, true aneurysms involve every structural layer of the entire vessel wall and according to their morphological characteristics they can present as fusiform or saccular aneurysms.(1,2,5) Due to the involvement of all three vessel layers, true aneurysms have a relatively better stability. However, a continuous surveillance is necessary in order to avoid fatal complications.(2) An aneurysm is defined as saccular if the width of the affected segment is greater than its length and for fusiform aneurysms it is vice versa.(3)

The occurrence of CAAs extends from 0.3-5,3%. In comparison, the prevalence of giant CAAs accounts for only 0.02%.(1) The use of various imaging modalities such as coronary CT or MR angiography as well as invasive procedures like coronary angiography, improves the detection of coronary pathologies including CAAs or coronary ectasias.(1,7) Nevertheless there is a distinct variability in the overall reported CAA cases, which makes the published values unreliable for accurately representing the general population. The reason for this is the lack of a consensus on diagnostic criteria for CAAs. Accordingly, different clinical institutions use various diagnostic criteria for CAAs and might therefore include other coronary pathologies in their clinical trials. An additional contributing factor is that the angiographic diagnosis is dependent on the experience and subjective judgement of the clinician.(1)

It must also be considered that the incidence varies in different geographical regions.(1,2) A study among patients from different ethnic groups with Kawasaki disease was carried out to assess the incidence of CAAs. The study revealed that African American patients have a significantly lower incidence of CAAs (1.2%, $p=0.007$), whereas Asian patients showed the highest incidence (10.3%). However, the p-value for the Asian patients is not statistically significant. This may be due to the smaller sample size ($n=29$). Other ethnic groups such as Caucasian, Hispanic and Mediterranean showed moderate rates extending from 6.9% to 8.7%. These results underline a potential ethnical difference in the development of CAAs, which might be correlated to genetic or environmental factors.(8) In addition to the ethnic differences, the gender is also an important factor, with men being more commonly affected than women.(1,9) A German diagnostic angiography study demonstrated CAEs in 1.79% of the 4970 male patients and 0.56% of the 2131 female patients. In this conducted study the patients were diagnosed by angiography at an average age of $63.5 \text{ years} \pm 10.5$. (10) Regarding the vessel involvement, the right coronary artery was predominately involved and

accounted for 40% of cases. Subsequently, the left anterior descending artery was also demonstrating involvement, with 32% of cases. In contrast, the left main coronary artery only involved in 3.5% of cases, was the least frequently affected artery. The pattern of vessel involvement is dependent on the etiology of CAAs. Atherosclerotic or vasculitic CAAs affect typically multiple arteries, whereas congenital or traumatic associated aneurysms usually affect one vessel. (1,11)

CAAs mainly arise due to atherosclerosis, which accounts for approximately half of CAAs in the adult population.(1,2,4,5) The formation of CAAs is closely connected to atherosclerotic disease because they have overlapping histopathological features such as hyaline degeneration, buildup of lipids, destruction of vessel layers and fibrosis.(3) The Coronary Artery Surgery Study (CASS), cited by Abou et al., reported an occurrence of CAAs of 4.9%, which is higher than the rates of CAAs noted in other angiographic studies. This study reviewed about 20,000 angiographic images and found that male patients with CAAs and coronary artery disease generally had a higher occurrence of prior myocardial infarction and multivessel coronary disease, compared to those with only coronary artery stenosis. Coronary artery stenosis was detected in 957 out of 978 patients.(1,2)

While atherosclerosis is the leading pathology behind CAAs in adults, Kawasaki disease is the leading etiology of CAAs in pediatric patients. It is an acute systemic vasculitis of vessels with a relatively small to medium diameter that usually affects children under five years. The inflammation of arteries can possibly lead to aneurysmal changes, especially in the coronary arteries.(1,2,12,13) A study in Sweden recorded the rates of CAAs in 77 children with Kawasaki disease. The study revealed that CAAs were found in 31% of patients (n=24) and that the affected children were generally younger with an average age of 20 months compared to children that did not have CAAs (median age 34 months). This study uncovered that the most vulnerable group were infants with incomplete Kawasaki disease, where 73% developed CAAs, while only 11% of infants with complete Kawasaki disease developed CAAs. The overall prevalence of CAAs was higher in incomplete Kawasaki disease, affecting 47% of patients, whereas only 21% of children with the complete form were affected.(14)

The increased use of percutaneous coronary interventions also represents a contributor to the formation for CAAs. Procedures like balloon angioplasty or the implantation of stents for the treatment of acute coronary syndrome pose a risk for the development of CAAs.(1) Drug-eluting stents (DES) might predispose to the formation of aneurysms because they have antiproliferative properties that prolong vascular healing, reduce smooth muscle cell growth and cause hypersensitivity reactions.(1,2,15) A comparative study assessed the connection of drug-eluting-stent use and the incidence of CAAs in 3,612 patients. Around 4,419 lesions were detected in these patients, who

received angiographic assessment in order to monitor changes after the DES implantation. Overall, 34 CAAs were detected in 29 patients (0.8% per patient). The study concluded that the formation of CAAs after DES implantation is generally rare and that the length of the affected coronary segment is the main determinant for their development.(16) While DES implantation carries some risks of vessel wall changes, the actual incidence of CAA formation remains low.(15,16)

It has been noted that connective tissue diseases such as Marfan syndrome and Ehlers-Danlos syndrome also tend to be connected to the formation of CAAs. These congenital diseases result from mutations that interfere with the synthesis of essential extracellular matrix proteins, which ensure the structural stability of the vessel wall.(1,2,6) Additionally, several pathogens such as mycobacteria, bacteria and fungi, as well as infections like Lyme disease or HIV, can predispose patients to the formation of CAAs. Pathogens can infiltrate the arterial wall, and the immune response can lead to the formation antigen-antibody complexes. Some infections could even lead to an obstruction of the coronary lumen by formation of a thrombus.(1,2,6)

3.2 Pathophysiology of CAA

The pathophysiology behind the development of CAAs is still unsettled and remains under investigation. Nevertheless, there are several studies that suggest a correlation between various risk factors and the formation of CAAs.(5,11) Recognized risk factors are the “male sex, hypertension, smoking, atherosclerosis, hyperhomocysteinemia and conditions such as chronic Epstein-Barr virus infection.”(5) Furthermore, the presence of specific genotypes can pose an additional risk, for example the detection of “HLA-DR B1813, DR16, DQ2 and DQ5 alleles as well as the presence of the 5A allele of the MMP-3 gene and the ACE gene deletion-insertion polymorphism”.(5,17)

As already mentioned, atherosclerosis is the leading pathology that may be implicated in the formation of coronary artery aneurysms.(1,3,5) Both conditions share histopathological characteristics such as tissue degeneration and accumulation of lipids within the tunica intima and media of the vessel wall. These pathological modifications are associated with a loss of vessel wall stability, as well as degradation of muscular and elastic elements within the vessel.(1–3,18) Additionally, remodeling processes such as calcifications or fibrosis lead to fragility of the vessel wall, thereby reducing its ability to withstand hemodynamic stress. Together these factors can contribute to the formation of CAAs.(1,18) Key drivers of these processes are matrix metalloproteinases (MMPs), enzymes that contribute to structural vessel wall changes by causing degradation of extracellular matrix proteins, such as collagen. The destruction of these essential

elements can therefore lead to a compromise in vessel wall integrity and further promote aneurysmal formation.(1–3) The activity of these enzymes is mediated by inhibitor proteins called tissue-specific inhibitors (TIMP-1/-2/-3 and -4).(1,5) Different types of cells such as macrophages and smooth muscle cells release these inhibitory proteins. A reduction in TIMP activity alongside an elevated concentration of MMP-2/-3/-9/-12 is linked to a higher susceptibility to CAAs.(17)

Furthermore, inflammation is closely involved in the pathogenesis of CAAs. Studies revealed that patients presenting with CAAs, but without coexisting obstructive coronary artery disease have relatively higher values of inflammatory markers including C-reactive protein and interleukin 6 levels.(5)

Besides atherosclerosis, CAAs can also arise from diseases such as Kawasaki disease or Takayasu arteritis, which are both types of systemic vasculitis.(1) Kawasaki disease represents the most common congenital etiology for CAAs.(4) The exact pathological mechanisms behind the development of CAAs in Kawasaki disease are not fully understood yet. However, researchers suggest that an abnormal immune reaction of both the innate and adaptive immunity causes inflammation within the vessel. There are different phases of inflammatory changes, including the acute, subacute and chronic phases. Each phase is distinct for its structural alterations within the arterial wall.(19) The acute phase is known to resolve spontaneously and is mainly characterized by a necrotizing inflammation of the arterial wall, which is caused by neutrophilic migration into the vessel layers. (19) Subsequently, this cellular invasion leads to progressive breakdown of the inner and middle arterial layers, which further interferes with vascular integrity (2,19) Regulatory proteins such as MMP-3 and MMP-9 are also upregulated in Kawasaki disease and involved in structural vascular remodeling. The translocation of smooth muscle cells from the medial layer to the inner intimal layer plays a key role in the accumulation of myofibroblasts inside the vessel lumen and contributes to CAA formation.(20) A study referenced by Rivas et al. revealed that peripheral blood mononuclear cells of affected patients release high levels of IL-1 β and IL-18. These cytokines are secreted following activation of the NLRP3-inflammasome pathway, which triggers inflammation and vessel wall changes in Kawasaki disease.(20) Conversely, the subacute and chronic phases mainly show an infiltration of plasma cells, lymphocytes and eosinophils, which contribute to inflammation. This process can take several months or even years. During the subacute and chronic phases, smooth muscle cells transform to myofibroblasts. These myofibroblasts remain active and may cause a stenosis of the lumen of the affected vessel.(19)

Another type of vasculitis is Takayasu arteritis, which is considered a large-vessel vasculitis targeting the aorta. While CAAs are generally an uncommon manifestation of Takayasu arteritis, studies have

demonstrated that some patients acquire CAAs. The reported incidence of CAAs is 10-12% among affected patients.(2) In contrast to Kawasaki disease, Takayasu arteritis mainly affects females from Asian countries.(2,21) The exact pathomechanism underlying Takayasu arteritis is still unknown and under investigation. However, it is believed that CAAs in Takayasu arteritis develop due to hypertension, which diminishes the strength of the vessel wall and leads to increased degradation of the elastic fibers within the medial vessel layer. (2,21)

In addition to acquired and congenital conditions, iatrogenic causes such as percutaneous interventions (PCI) are also linked to the formation of CAAs. These aneurysms are mainly caused by mechanical and pressure-induced injury, which result from procedures like balloon angioplasty, stent implantation or atherectomy.(2) Generally, the occurrence of CAAs after interventional procedures is relatively low, accounting for 0.3-6.0% of cases. The reported coronary abnormalities were rather pseudoaneurysms than true aneurysms.(15)The pathophysiology of CAA after PCI includes various mechanisms. Mechanical trauma can lead to vascular wall damage, such as dissection of the arterial wall. Additionally, barotrauma caused by high-pressure balloon inflations can result in arterial tearing, which may subsequently contribute to the development of CAAs.(1,2)

Different conducted studies reported the development of CAAs after drug-eluting stent implantation and bare-metal stenting. Even though, it is known that the implantation of DES is supposed to prevent restenosis by inhibiting neointimal proliferation, it has been noted that they can still lead to CAAs through different processes such as prolonged healing of the endothelium, inflammation of the medial vessel layer as well as hypersensitivity reactions. The reason for this is that certain drugs within the DES have cytotoxic features. Additionally, hypersensitivity reactions were observed in both stenting methods. In BMS implantation, mainly allergic reactions to the metal components were reported, whereas in DES implantation, it is often the polymer within the stent that causes immune-mediated inflammation through infiltration of lymphocytes and granulocytes such as eosinophils.(2,15)

A conducted study by Joner et al. analyzed 40 autopsies of patients with drug-eluting stents to assess the outcomes after DES implantation and the coronary artery healing process, including a comparison with BMS. Among 23 patients with DES implanted for more than 30 days, 14 patients had a late stent thrombosis. Histological results revealed a prolonged healing process, increased deposition of fibrin as well as impaired endothelial regeneration. Other histological findings were consistent with hypersensitivity reactions.(22)

Randomized trials with an angiographic follow-up reported similar occurrence rates of CAAs in both DES and BMS (1.1%; 0.8%), with no statistically significant difference between both groups. (15) A study performed in Korea analyzed the long-term results of CAAs after DES implantation. Around 3,612 patients with 4,419 lesions were followed up with coronary angiography. Among these patients, 34 CAAs were reported in 29 patients on approximately 414 ± 213 days after DES implantation.(23) According to the existing data the formation of CAAs after stenting may occur in 1.25-3.9% of cases. Nevertheless, these numbers should be interpreted with caution because of the inconsistent follow-ups and different measures after PCI evaluation.(2)

Besides acquired conditions, genetic connective tissue disorders have been noted to be related to the development of CAAs. In Marfan syndrome, mutations affect the FBN1 gene, which encodes the protein fibrillin-1. Under physiological conditions, this protein contributes to the assembly of elastic fibers, which ensure resistance to mechanical vascular stress. Usually, the regulator protein TGF- β is inactive when bound to latent TGF- β -binding proteins (LTBPs), which are attached to fibrillin-1. Due to the mutation in Marfan syndrome, there is a low level of fibrillin-1 and thus an increased activity of TGF- β , which damages components of the vessel wall and can lead to aneurysmal formation.(1,2) Clinical studies also underline the association between connective tissue conditions and the formation of CAAs. A cohort study revealed that, in 109 patients with Marfan syndrome carrying the FBN1 gene mutation, CAAs were diagnosed in 46% of patients. The prevalence was notably increased in patients who underwent aortic root replacement. These results emphasize the significance of fibrillin-1 deficiency on vessel wall integrity.(24)

3.3 Clinical manifestations

Many CAAs present without distinctive clinical features. As a result, they are only recognized through different diagnostic studies such as coronary angiography, CT scan or MRI. (18) In some cases, CAAs were only found during postmortem examinations.(4) As already mentioned, affected patients are usually asymptomatic. Nevertheless, certain patients may show specific clinical features but they are usually related to pre-existing coronary artery diseases or might develop from complications associated with the aneurysm.(18) There are various reported clinical manifestations. The most common cardiac-related features include symptoms such as dyspnea or angina pectoris as well as manifestations related to myocardial infarction, arrhythmias or signs of heart failure.(4,11) The development of clinical symptoms is associated with various pathological processes.(25) Turbulent blood flow or even stasis of blood can promote the formation of thrombus within the aneurysm, which can subsequently lead to thromboembolic events. Conversely, angina pectoris is

most commonly associated with reduced myocardial perfusion due to atherosclerotic plaques within the aneurysmal segment.(1,18)

Furthermore, giant aneurysms tend to increase in size overtime. As they enlarge, they can reach dimensions that could lead to interference with nearby anatomical structures. In severe cases that could lead to conditions such as superior vena cava syndrome due to compression of the Vena cava superior. If the size of the giant aneurysm is excessively large, it may even be misinterpreted as a cardiac tumor on imaging.(1) Even though the rupture of CAAs is usually uncommon, it is a lethal complication that could result in cardiac tamponade or hemopericardium. This is most commonly observed in giant aneurysms because their arterial wall is severely fragile due to the persistent inflammation.(3,4,11,18)

Aneurysms that result after aortocoronary saphenous vein grafting are able to expand largely and are therefore more susceptible to rupture.(4) CAAs were frequently detected alongside other vascular conditions such as arterial hypertension or abdominal aortic aneurysms.(18,25) There is a larger range of possible clinical manifestations, from asymptomatic cases to life-threatening events. Early recognitions are essential in order to evaluate associated risks and establish an appropriate treatment.(18)

3.4 Diagnostic approaches

Different imaging modalities, including non-invasive and invasive techniques, can be used for the diagnosis of coronary artery aneurysms. These modalities allow assessment of the aneurysmal features such as location, diameter, extent and associated complications of CAAs. A combination of both non-invasive and invasive diagnostic approaches is used to ensure an exact diagnosis and evaluation.(1,4) One of the non-invasive diagnostic tools that is being used more frequently is coronary computed tomography angiography (CCTA). This modality enables a three-dimensional and detailed visualization of the coronary arteries.(1) It allows a concise measurement of size, morphology, shape and the presence of thrombi and stenosis.(1,5,18) Even though, the main tool is invasive coronary angiography, its accuracy can be limited due to co-existing pathologies such as intraluminal thrombi, which can obscure the vessel wall and thereby causing an inaccurate measurement of the actual aneurysm dimension.(4,5) In contrast, CCTA is much more sensitive and can measure the exact diameter of the coronary artery, while also detecting if intraluminal thrombi are present.(1,4) The use of CCTA becomes more valuable particularly in patients where a detailed visualization of the coronary arteries is necessary. A conducted study by Forte et al. further

accentuated the importance of CCTA in enabling precise measurements of coronary pathologies. In this study, around 390 CCTA were analyzed, with 15 CAAs detected in nine different patients. Most of the CAAs were predominately in the right coronary artery. Through CCTA the researchers were able to precisely visualize the coronary aneurysms. In some patients' thrombi were detected, while others showed a narrowing of the coronary lumen. Additionally, measurements revealed a significant difference in vessel diameter between those with and without aneurysms.(26) Although CCTA is an essential tool for diagnosing CAAs as well as for further follow-up, it still poses some risks related to the administration of contrast agents along with radiation exposure. Therefore, it is often not used in vulnerable patients, including young patients and patients with impaired renal function.(1)

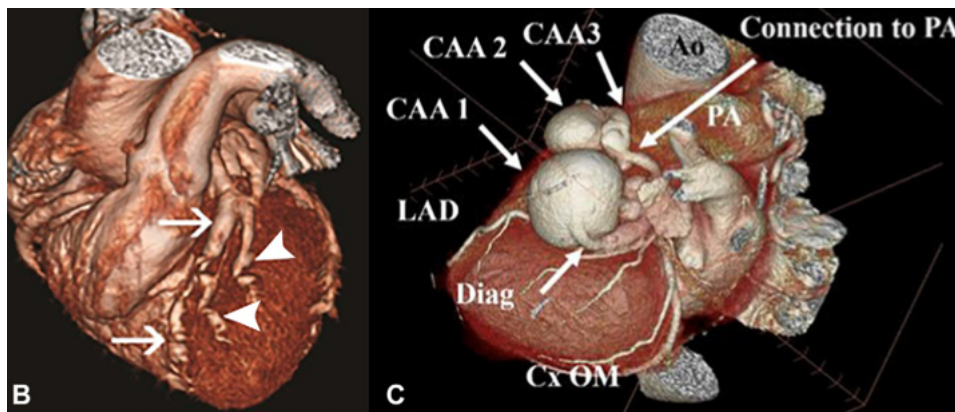


Fig. 1: CCTA 3D images showing coronary artery aneurysms

(B) LAD and diagonal aneurysms in a young woman with lupus vasculitis

(C) Three giant aneurysms in the diagonal branch with fistula to the pulmonary artery

(Source: Thangathurai et al., Radiol Cardiothoracic Imaging 2021) (19)

Another non-invasive diagnostic option, without any risks of radiation or iodinated contrast media, is magnetic resonance angiography (MRA).(1,18) MRA is able to visualize aneurysms within the proximal main branches of the coronary artery and assess the flow characteristics within the vessel. Even though the spatial resolution of MRA is generally poorer when contrasted with CCTA, it can be an alternative option in patients with comorbidities who are not eligible for CCTA.(1) Especially in Kawasaki disease patients with CAAs, MRA is used to detect aneurysmal dilation and stenoses in the proximal segments of the vessel. However, its accuracy is still limited when visualizing the distal parts of the coronary arteries. (1)

A further non-invasive tool is the echocardiography including transthoracic and transesophageal echocardiography. Echocardiography enables a picture of the proximal vessel segments of the left

and right coronary arteries as well as measurement of the aneurysm diameter.(1) TTE is most commonly used in pediatric Kawasaki patients because it is a non-invasive imaging tool. It allows repeated assessment of the coronary artery size and helps to detect increases in vessel diameter, especially in incomplete Kawasaki cases.(27) Echocardiography is also important among the adult population who experienced Kawasaki disease in the past because it is a useful tool to monitor for complications.(1)

Invasive diagnostic methods such as coronary angiography remain key diagnostic tools because they enable a detailed assessment of CAAs. Coronary angiography allows clinicians to characterize the aneurysms features and detect coexisting complications such as coronary stenosis, atherosclerosis and thrombus formation.(1,18) Even though coronary angiography has a diagnostic value, it still has certain restrictions. It only produces a two-dimensional image of the vessel lumen, which does not give reliable and accurate information about the structure of the arterial wall and might therefore misinterpret the size of the aneurysm, especially in cases of coexisting thrombi or plaques that partially obstruct the vessel.(1,28) Furthermore, it is unable to precisely distinguish true aneurysms from pseudoaneurysm.(1) These limitations underline the importance of selective use of coronary angiography, especially for younger patients such as those with Kawasaki disease, where an assessment of potential advantages and risks is needed before an invasive procedure.(1,29) Coronary angiography offers a possibility in diagnosing and managing CAAs. However, as already mentioned it has several limitations and therefore needs complementary diagnostic methods such as IVUS to provide a detailed view of the vessel.(28)

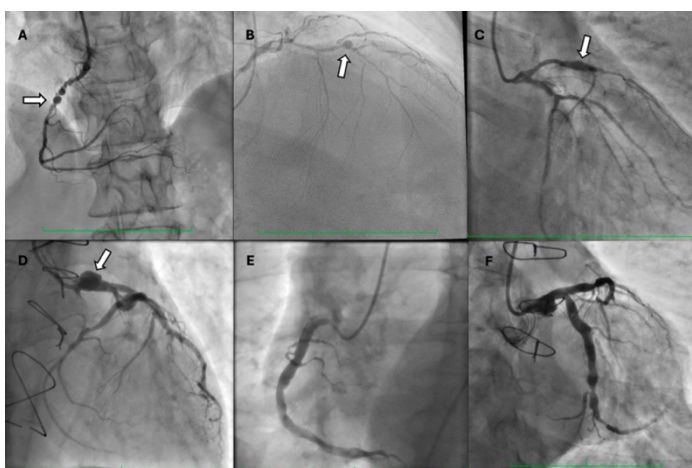


Fig. 2: Coronary angiography images reproduced from Woźniak et al., 2024, showing abnormalities such as saccular aneurysms of the right coronary artery (A) as well as LAD (B), fusiform aneurysm

in the LAD (C), saccular aneurysm of the left main coronary artery (D) and coronary ectasias in both the right coronary (E) and left circumflex arteries (F)
(Source: Woźniak et al., 2024) (5)

Intravascular ultrasound is an invasive modality that has become very useful and is considered a key diagnostic tool for a detailed view of the structural composition of the coronary arteries. It is an addition to invasive modalities, when a precise assessment of the vessel is needed. IVUS generates a cross-sectional view and enables a picture of the entire vessel wall of the coronary artery, which allows a clear view of the aneurysm morphology. By clearly visualizing the vessel layers, differentiation between true and pseudoaneurysms is possible.(1,4,11) A performed study showed the importance of IVUS in diagnosing true CAAs and also evaluating its physiological impact. IVUS confirmed in 19 patients with bilateral fusiform CAAs, large true aneurysms with mild atherosclerosis. The Doppler measurements showed an impaired coronary blood flow and higher arterial resistance within the vessels during stress, even though no vessel obstruction was detected.(30) Additionally, IVUS, especially Virtual Histology-IVUS, can also be used in patients who previously had manifestations of Kawasaki disease in order to detect vascular changes such as “intimal thickening” and features resembling atherosclerosis. It reveals these changes in the initial phase of the disease and allows detailed assessment of coronary artery remodeling.(31)

Another invasive procedure is optical coherence tomography (OCT), which is a diagnostic imaging technique that uses infrared light within the vessel to generate cross-sectional vessel views with an enhanced visualization.(32) It enables a detailed view of the coronary artery, allowing a concise view of atherosclerotic characteristics or present complications such as thrombosis within the vessel.(5) Compared to IVUS, which uses ultrasound waves, OCT provides about ten times higher spatial resolution but has a limited imaging depth of about 1-2 mm. OCT is ideal for detailed visualization of the vessel lumen but if a “red thrombus” is present, its imaging quality is degraded due to light interaction.(32) OCT is frequently used to assess CAAs in Kawasaki patients.(33) In a cohort study involving pediatric patients with Kawasaki disease, OCT revealed detailed structural changes such as hyperplasia of the intima and fibrosis, even in segments that were normal on coronary angiography.(34) While OCT could underestimate the vessel dimension compared to IVUS due to its difficulty in visualizing the full external elastic membrane, it is still a valuable technique for precise imaging in percutaneous interventions. A comparison of both techniques reveals that OCT provides an enhanced imaging resolution and is especially indicated for assessing complications after stent implantation as well as evaluating calcified lesions. Its limitations are the reduced depth penetration and the necessity to clear the vessel lumen prior to the procedure. In contrast, IVUS has a greater

tissue penetration and is able to visualize all vessel layers and determine if any remodeling is present. IVUS is especially preferred when a full vessel assessment is required. The choice between these two diagnostic techniques is mainly dependent on the investigation goal.(32)

3.5 Indications for treatment

Coronary artery aneurysms are often accidentally detected and usually do not produce distinct clinical features until associated complication arise.(3,4) Due to the absence of standardized management protocols of coronary artery aneurysms, the treatment is often adapted to the patient based on the aneurysm features as well as clinical manifestations.(1,4,18) Important considerations include the patient's symptoms, the underlying cause of the CAA, the morphological characteristics and whether it is expanding over time. Other factors such as the presence of an infection or concurrent atherosclerosis also play a significant role.(1,4) In symptomatic patients such as those presenting with angina pectoris or acute coronary syndrome, percutaneous or surgical approaches are often indicated. In certain patients without acute coronary syndrome, PCI can be an option but only if the patients' coronary anatomical features permit the procedure. The aim of the pharmacological treatment is to minimize adverse outcomes and slow disease progression.(18) The aneurysm size has an impact on deciding the treatment approach, with giant aneurysms being recognized as a justification for operative intervention.(1,4) Aneurysms meet the criteria of giant if they are ≥ 8 mm in diameter in children, ≥ 20 mm in diameter in adults or $\geq 4\times$ the reference diameter of the vessel.(4) Especially giant aneurysms are prone to thrombosis or rupture. It is suggested that patients with suspected giant aneurysms receive medical therapy and undergo invasive exclusion in order to prevent serious complications.(6) Generally, the treatment of CAAs is oriented on clinical manifestations and risk factors.(1,4)

In contrast, in pediatric Kawasaki patients the goal is to lower the likelihood of developing CAAs by early administration of intravenous immunoglobulin therapy.(5) In case of already developed CAAs, a combined therapy of aspirin and warfarin is used in order to prevent lethal cardiovascular complications such as myocardial infarction and death.(35)

3.6 Pharmacological therapy of CAAs

The conservative treatment of CAAs, particularly pharmacological therapy, is typically considered to minimize the likelihood of cardiovascular adverse events.(18) As already noted, the aneurysm features are the main determinants to guide the therapy. Features such as the aneurysm diameter, etiology (congenital vs. acquired), presence of thrombi or the patient's risk factor for obstruction or

bleeding, play a crucial role in determining the treatment choice.(1,4,18) As there is limited research and a lack of randomized controlled trials or general consensus regarding the treatment of CAA, individualized management is often indicated. (1,4,5)

One of the essential goals of pharmacological therapy is the reduction of adverse cardiovascular events such as thromboembolism.(25) Although, there is existing data on CAAs, the rarity of this disease reduced the number of conducted studies. Current accessible data on therapy options is mainly based on observational data.(3,4) The indicated therapy follows a patient-oriented approach in order to decrease the likelihood of complications such as thromboembolism. This underlines the necessity for individualized management where potential risk factors are considered. (4,18,25)

3.6.1 Antiplatelet therapy

Antiplatelet therapy is often employed in the treatment plan of coronary artery aneurysms, in order to reduce the occurrence of adverse events such as thromboembolism.(4,25) However, the indication of antiplatelet agents in accidentally detected aneurysms is still under investigation, as there is limited data. There is no definitive agreement to confirm the benefit of dual- antiplatelet therapy or anticoagulation in patients without coexisting coronary artery disease. (4,5)

While some retrospective studies indicated comparable outcomes between patients with or without CAAs, there is still a debate whether a high-intensity antithrombotic treatment strategy is justified.(11) In contrast, other studies proposed a strong connection between CAAs and adverse cardiovascular events.(36) An observational study by Warisawa et al. using coronary CT revealed that half of the patients (53.6%) with incidentally found CAAs had major adverse cardiovascular outcomes during the post-interventional monitoring period. The reported events included cases of revascularization, myocardial infarction and non-coronary vascular events. These outcomes underline that the presence of CAAs can be linked to a higher risk of MACE, thus emphasizing that preventive measures should focus on both treating the aneurysm itself and considering other vascular comorbidities.(36)

Given the absence of evidence from randomized clinical trials, treatment strategies for CAAs vary and are mainly guided by the data from small case series.(11) As cited in Zhu et al., Sheikh et al. suggested that some patients with CAAs would benefit from extended dual-antiplatelet therapy, especially those who underwent invasive coronary procedures or those with an increased susceptibility to thrombotic complications.(4) Given the lack of sufficient evidence regarding the antiplatelet treatment of CAAs, treatment decisions often focus on potential complications and patients' specific risk factors. Overall, antiplatelet agents may be beneficial in the management of

CAAs but there are no guidelines that propose an ideal treatment strategy. Therefore, the treatment should be adapted for each patient, until further studies and data become available.(4,11,18)

The systemic review by Azarboo et al. analyzed the effectiveness of different antithrombotic treatment methods in patients who exhibited coronary ectasia (CAE). The primary focus was mainly on the reduction of MACE. Out of 589 initial studies, a full-text assessment of 48 studies was done, of which only eight fulfilled the inclusion criteria, involving in total 5,039 patients with CAE. Most of the patients were adult men. This systematic review compared the clinical outcomes of patients who received aspirin, dual-antiplatelet therapy or anticoagulation therapy with those patients who did not receive pharmacological treatment. Most studies used MACE as the primary outcome. This review revealed that both aspirin and DAPT were associated with less major cardiovascular events compared to patients with no treatment. In this case, DAPT was most effective based on the SUCRA values. Conversely, the indication of anticoagulants did not reveal a significant advantage over no treatment in preventing MACE. (37)

Another study conducted in Taiwan from 2005 to 2011 analyzed around 1,397 patients diagnosed with CAA, in which age-related differences in etiology, comorbidities and treatment methods were demonstrated. The pediatric population, mainly patients under 20 years old, made up 41.9% of the study and was predominately diagnosed with Kawasaki disease (95.7%). After an established diagnosis, aspirin and intravenous gamma globulin were prescribed. Aspirin was administered in 82.9% and gamma globulins in 53.6 % of cases. Other antithrombotic agents such as heparin, warfarin and dipyridamole were less often indicated but were also prescribed especially after the diagnosis. In contrast to that, adult patients who comprised approximately 58.1% of the study population, commonly had cardiovascular comorbidities. Among these patients, 63.4% had hypertension, 39.6% had hyperlipidemia and 26.1 % had diabetes mellitus. After the diagnosis of CAA, around 72.5% of the patients were diagnosed with atherosclerosis. The increased cardiovascular comorbidities led to an increased prescription of antithrombotic agents such as aspirin, clopidogrel and heparin after the diagnosis was made. Aspirin was most commonly given in 75.8% of cases followed by beta-blockers, nitrates and statins.(38)

This study not only revealed differences in the pathophysiology of CAA across the pediatric and adults' population, but it also emphasized different management approaches. Aspirin was most often administered across both age groups, emphasizing its role in preventing of thromboembolic events.(38)

3.6.2 Anticoagulation

Anticoagulation therapy for CAA/CAE is still under debate because various retrospective studies report contrasting results.(4,11) In patients that present with acute myocardial infarction, CAE tends to be correlated with less favorable long-term outcomes, as demonstrated in a follow-up period of around four years. Zhu et al. referenced an observational study where 1698 patients had an acute myocardial infarction. Out of those, 51 patients had concomitant coronary artery ectasia. Results showed that AMI patients who also have coronary ectasia tend to have a comparatively greater risk of experiencing cardiac complications. No major adverse cardiac events (MACE) were noted in patients who received warfarin with adequate anticoagulation control ($TTR \geq 60\%$). In contrast, patients who either received no anticoagulation or received warfarin treatment with a $TTR < 60\%$ had a 33% rate of MACE. The p-value was 0.03, which indicates that the difference between both groups was statistically significant.(4)

Expanding on these results, the CAAR study provided more insights into whether oral anticoagulation (OAT) therapy benefits patients with coronary artery aneurysms. The obtained data showed that oral anticoagulation could reduce ischemic events such as unstable angina and thrombosis, without significantly increasing the bleeding risk.

The study used data from 1,542 patients, of whom 211 patients received OAT and 1,331 did not receive it. In order to reduce the possibility of bias, the researchers used a propensity-matched sample, which was divided into two main groups. The anticoagulation group consisted of 195 patients, while around 390 patients were assigned to the non-OAT group. Both groups were monitored for a period of three years. They investigated how often patients with CAA were affected by myocardial infarction, unstable angina or thrombosis and whether these cardiac events could be prevented by OAT. These outcomes were termed as “coronary ischemic events”(39). OAT was associated with significantly fewer ischemic events compared to non-OAT. The OAT group was affected in 8.7% of cases, whereas the non-OAT group in 17.2% with a p-value of 0.01. These results were mostly caused by a lower incidence of unstable angina in 4.6% of individuals in the OAT cohort compared with 10% of patients in the non-OAT group, with a p-value of <0.01 . There were no reported cases of aneurysmal thrombosis formation within the OAT group, while 3.1% of patients were affected in the non-OAT group, with a p-value of 0.03. The number of experienced myocardial infarctions was relatively lower in the oral anticoagulation group (4.1%) when contrasting it to the non-OAT group (7.7%). However, this result is not statistically significant ($p=0.13$). Furthermore, bleeding rates in the OAT group were higher (10.3%) compared to the non-OAT group (6.2%), but the results did not reach statistical significance ($p=0.08$). (39)

While these studies only report on adults with CAA, anticoagulation is also crucial in pediatric Kawasaki patients. In Kawasaki disease, CAAs have a risk of progressive enlargement of the aneurysm, especially when the maximal Z-score (measure of aneurysm size relative to the body surface area) exceeds ten. In such cases, anticoagulant agents such as warfarin or low-molecular-weight heparin (LMWH) may be considered, in order to prevent complications.(18) These findings correspond to the Class IIa guidelines that support antithrombotic therapy in pediatric patients with giant CAAs.(4) Smaller investigations indicate that direct oral anticoagulants may be an alternative option for the treatment of CAAs in Kawasaki patients. (18)

Observational data demonstrated that patients with large or giant CAAs have an overall higher risk for the development of thrombosis during the acute and chronic phases of Kawasaki disease. The standard therapy includes antiplatelet medications and anticoagulants. Updated recommendations underline the role of anticoagulation especially in patients with a decrease in CAA size from giant to medium, because this size reduction can be associated with the development of a thrombus inside the vessel lumen.(33) In Kawasaki disease, antithrombotic therapy is often determined by the degree of coronary artery involvement. A low-dose therapy of aspirin is often sufficient in patients exhibiting relatively small-sized CAAs, while patients with moderate-sized CAAs may benefit from a dual-antiplatelet therapy. In cases of large-sized aneurysms or when the maximal Z score exceeds 10, anticoagulation therapy including warfarin or LMWH is added to aspirin. Patients who have large or giant aneurysms with a higher susceptibility for thrombosis, a combination of two antiplatelet agents with warfarin or LMWH is indicated.(40)

Although both anticoagulants, warfarin and LMWH are effective, their use in children carries some practical challenges. The administration of warfarin requires continuous monitoring of the international normalized ratio (INR) to maintain therapeutic levels and LMWH involves frequent subcutaneous administration. Due to these difficulties in pediatric patients, direct oral anticoagulants may be a safe alternative. Data represented a generally low incidence of cardiovascular complications. Even in cases of bleeding, these agents have effective antidotes.(33)

A randomized controlled trial evaluated apixaban for thromboprophylaxis in children that suffer from congenital and acquired heart disease, including Kawasaki disease. Apixaban's pharmacokinetic profile in pediatric patients was similar to that observed in adults. Even though the rates of minor bleeding were higher, apixaban was not associated with clinically significant bleeding events when compared to the conventional therapy of warfarin or LMWH. Therefore, apixaban may represent a potential alternative to the standard anticoagulation in pediatric patients.(41)

3.6.3 Blood pressure control and role of ACE inhibitors

Blood pressure control is an essential step in the management of CAAs because it might decrease hemodynamic stress on the vessel wall and thereby decrease the overall risk of associated cardiovascular complications.(18) The administration of ACEI in combination with statins might have a potential therapeutic benefit because of their anti-inflammatory features.(4,18) These properties encompass the regulation of inflammatory cytokine release and the inhibition of the renin-angiotensin-aldosterone system (RAAS).(1) Nevertheless, the exact mechanism and efficacy of ACEI in the context of CAAs management, requires further investigations. It is noted that the combination of ACEI with statin agents shows a reduction in inflammation. However, these results were only demonstrated in studies with a general small sample size.(1,18)

Some studies suggested a potential link between the ACE gene polymorphism and the development of CAAs, proposing ACE inhibitors as a possible treatment option. However, large-scale studies confirming their ability in preventing the development or progression of CAAs are still absent.(5,6)

While antihypertensive therapy is a necessary step in the clinical management of CAAs, agents such as calcium-channel antagonists are not routinely indicated. They are prescribed in patients who have been diagnosed with “vasospastic angina”.(5) Furthermore, the role of beta-blockers in CAA patients has not yet been sufficiently explored.(18) Some experts suggest that the administration of nitroglycerin is contraindicated because it might cause myocardial ischemia due to systemic vasodilation that can reduce the coronary blood flow.(4,5,18) Due to limited data on the pharmacological management strategies for CAAs, additional evidence is needed.(18) Generally, patients diagnosed with CAAs need monitoring in order to detect potential complications. The type of monitoring strategy is usually adapted to the level of coronary artery involvement and the patients’ clinical profile.(4)

3.6.4 Statin therapy in CAA patients

Statins are used in clinical practice because they are able to lower the cholesterol levels in the blood. Beyond the lipid-lowering effect, studies have shown their anti-inflammatory features as well as their ability to stabilize atherosclerotic plaques. In patients with CAAs secondary to atherosclerosis, statins can help in stabilizing the plaque and reducing inflammation.(4,6,18) A therapy with a high dose of statins reduces LDL-cholesterol levels by at least 50% and is associated with a reduced occurrence of cardiac events.(42)

It is assumed that statins may inhibit inflammation contributors such as matrix metalloproteinases, especially MMP-2 and MMP-9.(5) As previously noted, increased expression of these enzymes can result in destruction of extracellular matrix structures, which may ultimately result in structural alterations of the vessel wall.(2) Experimental studies have demonstrated that statins such as simvastatin and atorvastatin are able to reduce the activity of MMP-9, whereas MMP-2 activity may be decreased by atorvastatin and pravastatin.(5) Furthermore some studies pointed to the “pleiotropic anti-inflammatory effect” of statins (4), emphasizing their potential application in CAAs, especially in cases secondary to Kawasaki disease.(4)

In Kawasaki patients with CAAs, statins are typically indicated for long-term treatment.(4) The guidelines have proposed a Class IIb recommendation for statin use because of their anti-inflammatory properties. A study investigated the tolerability and biological effects of atorvastatin in pediatric Kawasaki patients with CAA over a period of six weeks. Additional gene studies revealed a decreased expression of inflammatory markers as well as a better endothelial cell viability, compared to patients who only received the traditional treatment regimen of IVIG and infliximab.(33)

Even though, there are preliminary results from small-scale studies that demonstrate promising findings, it has not been confirmed whether the integration of statin therapy into the treatment regimen of adult or pediatric patients improves the overall outcomes. This is mainly because randomized controlled trials in this field have not yet been performed. However, the presented data about the advantages of statin therapy support the potential and benefit of these agents, particularly in selected patients with CAAs secondary to atherosclerosis or Kawasaki disease. (18,33,43)

3.6.5 Kawasaki-related CAA treatment

The following paragraph provides a concise summary of the pharmacological treatment of Kawasaki-related CAAs in pediatric patients. Even though this thesis primarily focuses on adult patients with CAAs, pediatric patients in the context of Kawasaki disease are included because this condition is a key contributing factor for the formation of CAAs.(18) This section is intended to give a brief overview about the treatment management in order to prevent or treat the formation of aneurysms related to Kawasaki disease.

The intention of pharmacological treatment in Kawasaki disease patients aims to suppress inflammatory processes and thereby decrease the overall risk of coronary associated complications.(44) The first-line treatment recommended in the latest guidelines, consists of a high dose of intravenous immunoglobulin (IVIg) together with aspirin.(33,44) The IVIg infusion is given

as a single infusion (2 g/kg) over 8-12 hours. Patients are considered IVIg resistant if they continue to have fever 36 hours or more after the IVIg infusion. In this case, additional therapy might be considered.(33) Without treatment, there is a 25% chance of developing CAAs. However, early administration of high-dose IVIg may lead to a substantial reduction to around 5%. (44)

Aspirin is often administered with IVIG infusion. The dosing of aspirin varies between different countries. While Europe and Japan prescribe a moderate-dose therapy of aspirin (30–50 mg/kg/day), the United States usually employs a high-dose treatment regimen with 80–100 mg/kg/day. If the patient does not have fever for 48-72 hours, an adjustment of the dose can be made by lowering it to 3–5 mg/kg/day and then continuing it for 6 to 8 weeks if no coronary artery aneurysms develop. No evidence confirms whether the 30–50 mg/kg/day or 80–100 mg/kg/day dosing strategy provides better outcomes. (33,44)

In patients with a markedly elevated risk of IVIg resistance, corticosteroids can be added to the treatment regimen. Japanese studies using risk scores such as Egami and Kobayashi demonstrated reduced IVIg resistance. However, the accuracy of these risk scores tends to be limited in non-Japanese populations.(33,44) Biologic agents such as infliximab (TNF-alpha inhibitor), can be considered as adjunctive therapy in Kawasaki disease. Trial results demonstrated a potential effect of infliximab in terms of reduction of inflammatory markers and in the progression of CAAs. However, the administration of infliximab did not affect IVIg resistance or prevent the development of CAAs. Other TNF-alpha inhibitors, such as etanercept, did not significantly decrease the occurrence of IVIg resistance but additional evaluations showed some benefits in patients older than one year.(44)

Cyclophosphamide might be used in cases of giant CAAs that continue to progress, especially when the standard treatment regimen failed to achieve disease control. Halyabar et al. evaluated the status of ten patients with severe Kawasaki disease who received intravenous cyclophosphamide after the standard regimen did not show satisfactory results. In all cases, the progression of CAA was stopped, and the patients had no severe side effects, except for one patient who had an episode of neutropenia. These results highlight the potential of cyclophosphamide in case of severe or treatment resistant cases of Kawasaki disease.(45)

Summarizing the provided information about the pharmacological treatment, it is evident that the treatment is guided by individual features such as aneurysm size, etiology and patients risk factors.(1,11) Antiplatelet and anticoagulation therapy are essential components of the treatment approach, especially in patients that are at risk of adverse cardiovascular events such as

thromboembolism.(25) Anticoagulation in patients with CAAs is increasingly considered because observational studies revealed a potential benefit in reducing ischemic events.(4,39) Especially, in pediatric Kawasaki patients with giant CAAs, anticoagulants are commonly used and direct oral anticoagulants are being studied as an alternative option.(18,33) Blood pressure control, is a crucial step in the management of CAAs.(18) ACE inhibitors combined with statins may help to reduce inflammation but more investigations are needed in order to confirm their benefits.(4,18) Furthermore, calcium-channel blockers are only indicated for selected patients who present with “vasospastic angina”.(5) Due to limited data on the pharmacological treatment for CAAs, further research is needed. Current treatment approaches are mainly adapted to the individual patient.(1,11)

3.7 Percutaneous interventions

Percutaneous interventions have a significant role in the management of CAAs, especially in cases when concomitant coronary artery stenosis can result in cardiovascular complications such as acute coronary syndrome.(18) It is often indicated in patients presenting with small CAAs (<10mm in diameter) or in selected patients with appropriate anatomical features.(4) The selection of the treatment modalities depends on the patient’s characteristics such as aneurysm size and shape.(5) The use of IVUS, micro-mesh stents or temporary anticoagulation may be helpful in order to prevent complications that might be linked to the stent such as thrombosis or stent malposition.(4)

The most used percutaneous treatment options of CAAs include the placement of covered stents or stent-assisted coil embolization. PTFE- covered stents are suitable for small CAAs (<10mm). In case of saccular or pseudoaneurysms, covered stents can be indicated to exclude the aneurysm from blood flow but only if they do not compromise major coronary bifurcations. Nevertheless, the indication of covered stents carries several risks and can be associated with thrombosis, difficulty navigating through twisted arteries and possible luminal obstruction of coronary side branches. (1,3,4) In case of CAAs with a wide neck, a suitable treatment option could be stent-assisted coil embolization. Covered stents are usually not indicated in these cases because they carry a risk of occluding coronary side branches.(1,4) Coil embolization requires an interventional cardiologist with expertise because this technique can cause coil herniation which might occlude the originating vessel or even lead to rupture of the aneurysm. To minimize these risks, stent-assisted coil embolization techniques are preferred.(1,3) When acute coronary syndrome is present, PCI is most commonly employed. When PCI is performed in CAAs complicated by ACS, there is a higher occurrence of interventional failures and complications such as no-reflow and embolization. To minimize the risk of thrombus formation

within aneurysmal vessels, intracoronary glycoprotein IIb/IIIa inhibitors and thrombectomy can be used to reduce thrombus formation and ensure adequate blood flow.(4,11,18)

Data on the use of PCI in patients with asymptomatic CAAs is still insufficient and yet no randomized trials exist that compare PCI with surgical approaches such as coronary artery bypass grafting (CABG) in these patients.(4) Currently the international guidelines differ in some aspects regarding PCI in Kawasaki patients. The Japanese guidelines advocate PCI in case of presence of myocardial ischemia and advise against it in cases with unfavorable coronary anatomy for minimally invasive procedures. Meanwhile, the American guidelines suggest PCI only for single-vessel lesions or for multiple localized lesions that are technically accessible.(4)

Studies revealed that PCI is a well-tolerated long-term treatment option, especially in symptomatic patients. However, surgical interventions are still preferred in patients presenting with a complex anatomy. Evidence regarding patients with CAAs but without distinct clinical features is still limited.(6)

3.7.1 Types and indications of percutaneous interventions

The interventional treatment of CAAs is complex due to variability in clinical presentation and limited clinical trial data. The heterogeneous clinical presentation guides the therapeutic decision.(11,46) There is no specific guideline for invasive interventions focusing on patients with CAAs without associated acute coronary syndrome. Therefore, individual management is indicated adapted to anatomical and clinical risk factors.(5,11)

Considering the different interventional procedure options, covered stents, especially those made of polytetrafluoroethylene (PTFE) have become more valuable in selected patients. The indication of covered stent exclusion is often preferred in cases of saccular aneurysms or pseudoaneurysms that do not affect the bifurcation point.(4,5) Nevertheless, the use of them is challenging due to limited navigability, especially in calcified or twisted vessel and could be associated with major complications such as thrombosis, stenosis within the stent or unintentional occlusion of coronary side branches. (1,5,11)

However, some studies revealed promising results regarding the treatment of CAAs with PTFE-covered stents. The retrospective study by Parikh et al. evaluated the utilization of PTFE-covered stents in 32 patients treated for coronary artery perforation (CAP) or coronary artery aneurysm (CAA) between 2003 and 2017. Overall, two patients from the CAP group died during hospitalization. Patients who were treated for CAP had relatively more complications in the long-term such as restenosis or the need for reintervention. In contrast, patients in the CAA group had favorable

intermediate-term outcomes with no need for revascularization during the follow-up. The results demonstrated the potential of PTFE-covered stents for both patient groups, with long-term results depending on the severity of underlying condition.(47) Covered stents for CAAs have been used off-label in selected patients. Currently no stents are designed exclusively for the management of coronary aneurysms.(5,11)

Notable advancements showed the application of self-expanding stents such as the Viabahn stent and polyurethane-covered stents like the Biotronik Papyrus.(46) Different stent systems have been used off-label. For medium-sized vessels measuring between 2.75 and 5mm in diameter, a specific stent type such as the Graftmaster coronary stent graft (Abbott Vascular) is frequently employed. This device contains a PTFE-membrane between two stent layers, which is based on a balloon catheter. In contrast, for large vessel sizes (5-10mm), the Atrium iCAST stent (MAQUET) has been frequently used. Recent innovations introduced the Papyrus stent (Biotronik), which is a flexible single stent with a reduced profile size compared to the Graftmaster stent graft.(11) It has been suggested to place a covered stent beneath a drug-eluting stent in order to avoid intimal proliferation.(46)

In case of involvement of coronary bifurcations or complex anatomy, coil embolization represents an alternative treatment option. During this procedure platinum coils are inserted into the CAA sac to cause thrombosis and prevent further involvement of the aneurysm with the circulation. This procedure was adapted from neuroradiological procedures and is particularly indicated in aneurysms with a broad neck.(1,4,5,46) This alternative technique also carries some risks such as rupture of the vessel during deliverability or herniation of the coil into the originating artery, which can lead to vessel occlusion.(1) In order to avoid these complications, coil embolization assisted by stents can be used in selected cases, whereby the stent is placed across the aneurysm segment to confine the coils and prevent thrombosis formation.(46)

While the indication of covered stents and coil embolization are frequently used techniques to exclude CAAs (3), drug-eluting stents (DES) might be associated with the formation of CAAs. The mechanism behind DES is the release of drugs that inhibit the excessive intimal proliferation and thereby decreasing the risk of restenosis.(48) The international Coronary Artery Aneurysm Registry (CAAR) conducted an observational study regarding the use and long-term effects of stent grafts in comparison to drug-eluting stents in the management of CAAs. Among 347 interventions in aneurysmal vessels, 196 involved the use of a DES in the aneurysmal segment, while 17 received stent grafts. Some variations were noted in the risk profiles of these patient groups. The patients in the stent graft group had greater cardiovascular risks such as a history of coronary artery disease, dyslipidemia or presented with giant aneurysms. Despite these differences, the long-term outcomes between both patient groups showed no disparities. The median follow-up was 38 months, where

MACE occurred in 29.6% of DES patients and 23.5% in patients who were treated with covered stents with a p-value of 0.598, which highlights a comparable long-term safety between these groups. During the follow-up, coronary angiographies showed aneurysmal changes in 15% of DES patients and a thrombosis incidence of 9.8%.(49) The review by Aoki et al. emphasized the implantation of DES can prolong vascular healing and that their use may be associated with the development of CAAs ranging from several days to years after the placement. However, the occurrence rate of CAAs after DES is relatively low ranging from 0.2% to 2.3% within 9 months, which is comparable to rates seen with bare-metal stents.(48) Even though, stent grafts seem to be a safe long-term option for CAAs, further clinical trials are required to determine the optimal management. (49)

The treatment of CAAs with bare-metal stents (BMS) and Amplatzer occluder devices cannot be included in this thesis. The available data on these treatment options is limited and mainly consists of single-case reports or small case series that involve less than 10 patients. They were not included because they did not meet the defined inclusion criteria for this literature.

In summary, the interventional treatment of CAAs is difficult due to the lack of guidelines and various clinical presentations as well as complex anatomy. Similar to the pharmacological treatment, the interventional management is tailored to each patient.(5) Covered stents, such as PTFE-covered stents are indicated but they carry several risks such as thrombosis or the occlusion of coronary side branches.(1) Latest devices, such as the PK Papyrus stent, offer a better flexibility.(6,11) However, Papyrus stents are not yet commercially available in some countries. Especially in cases where larger stents are necessary, the iCAST has shown promising results.(11) In anatomically difficult cases, coil embolization is an alternative treatment option, especially in wide-neck aneurysms. In selected cases, stent-assisted embolization can be indicated.(46) Although, DES have been implanted in aneurysmal segments of coronary arteries, their function in the treatment of CAAs is not well established yet. This is mainly due to the concern that they prolong the vascular healing and might even be associated with the formation of CAAs.(48,49) The CAAR registry noted no major differences in long-term outcomes comparing DES with covered stents.(49) The use of treatment devices such as BMS or Amplatzer occluders was excluded from this literature review due to scarcity of data.

3.8 Surgical treatment of CAAs

Another treatment possibility besides the pharmacological therapy and percutaneous intervention, is the surgical approach. The decision whether to continue with the surgical treatment for CAAs is complex and dependent on anatomical and clinical factors. Even though clear criteria for pursuing surgery are still absent, some expert opinions and retrospective studies have formulated reasonable

indications, especially when there is diffuse coronary involvement or left main stem involvement.(4,6) In these scenarios the surgical approach of coronary artery bypass grafting allows a total restoration of coronary blood flow, especially if the aneurysmal lesions coexist with significant coronary artery disease. This surgery can restore the blood flow in several regions by bypassing the affected segments, which is beneficial in cases with diffuse coronary artery disease.(6,18) Furthermore, surgical procedures are mostly indicated in cases of complications such as compression of neighboring structures, development of fistulas, high rupture risk or when the aneurysm is growing rapidly. (4,6) Surgery is considered a first-line approach in patients presenting with giant aneurysms. These giant aneurysms are generally described as having a diameter that is larger than 20mm or more than four times that of the normal vessel.(4,5) Additionally, the location of the aneurysm is an important factor in deciding whether to proceed with surgery. The surgical treatment is often indicated when the aneurysm is located in areas such as the bifurcation of coronary branches or directly within the left main coronary artery.(4–6)

In case of complications such as saphenous vein graft aneurysms (SVGA) that are greater than 10 mm in diameter, surgery is usually the more preferred treatment modality. Similarly, in pediatric Kawasaki patients with aneurysms involving the coronary ostia or associated with stenosis, surgical treatment is often recommended.(4,5) In many scenarios, open-heart surgery is performed not only to address the coronary aneurysm but also because most patients have coexisting cardiac diseases such as multivessel coronary disease.(50)

Although percutaneous interventions are increasingly considered for the treatment of CAAs, surgery remains the preferred option for complex or high-risk cases.(4,18) As with any other treatment option, surgical decisions are also based on patient specific characteristics including anatomical and clinical factors. All these criteria must be considered and an individualized approach should be established because surgical guidelines for CAAs are still lacking.(4)

3.8.1 Surgical techniques

As already noted surgical treatment is often indicated in high-risk cases or in cases of coexisting cardiac conditions that require open-heart surgery.(4,50) Indications for surgery include advanced coronary artery disease, aneurysms within the left main coronary artery or near bifurcations, giant aneurysms or in case of structural complications such as formation of fistulas, compression of neighboring structures or increased rupture risk.(3,4)

The most commonly used surgical techniques include ligation, resection or exclusion of the aneurysm combined with bypass grafting. Additionally, reconstruction or patch repair may also be done depending on the patient's anatomy.(3,4,18) Coronary bypass grafting involves the preparation of utilized arteries, such as the internal thoracic artery and the radial artery as well as veins such as the saphenous vein.(51) When concomitant multivessel coronary disease or involvement left main artery is present, CABG is often performed due to its ability to ensure restoration of coronary blood flow.(6) Sometimes reconstructions are necessary, depending on the aneurysm features. Resection of the aneurysms requires a distal bypass for example using a saphenous vein graft. In other cases, ligation of both the proximal and distal ends is made, followed by establishment of a bypass to the intact vessel segment. In some cases, CAAs are opened in order to close the fistulas, which is followed by revascularization. Collateral vessels from the aneurysm should be maintained in order to ensure adequate blood supply of the myocardium.(51)

A retrospective study conducted by Beckmann et al. analyzed the surgical treatment of CAAs between 2000 and 2016, where 15 patients received surgical treatment. Coronary artery bypass grafting with cardiopulmonary support was performed in 93% of patients. The authors reported that isolated CABG procedure is appropriate for small aneurysms, whereas giant CAAs mostly require a combination including ligation, resection, reconstruction or CABG. In case of fistulas, a closure should be performed, while maintaining relevant collateral vessels.(51)

Regarding the graft selection, arterial grafting was performed in 53% of cases, the remaining patients received venous grafts with or without the internal thoracic artery. Surgical exclusion was performed in 27% of patients through ligation or resection of the CAA. The cohort had an average age of 60 years (± 16) with men accounting for 47% of the cohort. There were 13% of patients who suffered from Kawasaki disease and 7% of patients who had Marfan syndrome. Most patients (73%) had aneurysms affecting a single artery, whereas 27% of patients had aneurysms affecting several vessels. In terms of the anatomical location, CAAs were commonly identified in the left anterior descending artery (33%), followed by the right coronary artery (33%). The left main stem was implicated in 19% of cases and the left circumflex artery in 14%. There were no reported deaths during hospitalization, and the long-term outcomes were overall favorable with only one patient (7%) requiring additional intervention.(51)

Even though surgical management is dependent on the patients' anatomy and clinical features, CABG remains the most frequently performed procedure.(4,11) The available options are reconstruction, resection, ligation or exclusion of the aneurysm. These techniques can be performed alone or

combined with CABG. In case of large aneurysms, exclusion or resection is necessary because of the increased rupture risk.(4,18) Regardless of the difficulty of this operation, the long-term outcomes of this procedure are satisfactory and the in-hospital mortality is generally low.(51)

In summary, the surgical intervention of CAAs is mainly indicated in complex cases such as large and symptomatic aneurysms, those that involve major branches, risk for complications or in coexisting coronary artery disease.(3,4) Among all techniques, CABG is the most frequently used procedure.(4) Various techniques such as ligation or resection can be performed alone or in combination with CABG, depending on the clinical situation.(3) Surgical intervention enables total revascularization. However, the choice between percutaneous interventions and surgery depends on several factors.(6) Although, surgical procedures are complex and carry some risks, short- and long-term outcomes are generally favorable and associated with low mortality rates.(51) Overall, the treatment choices should follow a multidisciplinary approach which is guided by the clinical features of the patient.(4)

3.9 Outcomes of different treatment options

3.9.1 Outcomes of pharmacological treatment

The principal goal of pharmacological management is to reduce the overall incidence of adverse cardiac events.(4,18) Currently, there still a debate regarding the most suitable antithrombotic strategy for treating CAAs.(18) Treatment options include aspirin, dual antiplatelet therapy and anticoagulation.(18) Studies have highlighted potential benefit of anticoagulation therapy.(4,18,39,52)

The CAAR registry analyzed patients with CAAs who were discharged from the hospital either with oral anticoagulation therapy (OAT) or without. Around 195 patients were discharged with OAT and 390 patients without OAT. The endpoints of this study included unstable angina, myocardial infarction and aneurysmal thrombosis. These complications occurred less often in patients with OAT (8.7%) compared to those without OAT (17.2%, $p=0.01$), mainly due to fewer cases of unstable angina and aneurysmal thrombosis. The reduction of myocardial infarction events was not statistically significant ($p=0.13$). The bleeding incidences were mildly higher in the OAT group but did not reach statistical significance. These findings suggest, that OAT may reduce ischemic complications in CAA patients. (39)

A systematic review analyzed the anticoagulation strategy in coronary artery ectasia (CAE). The analysis of studies revealed that patients who were treated with antiplatelet and anticoagulant agents had favorable outcomes with few MACEs, compared to patients who only received DAPT. The adverse cardiac events included STEMI, NSTEMI, unstable angina, bleeding and thrombosis. Several cases showed improvement after switching from DAPT to SAPT with anticoagulation. The follow-up period in some case reports was around four years, with low rates of new MACE or mortality. Analyzed case series showed similar results. In a South African study of 20 CAE patients, all received aspirin and 75% also received warfarin. There were no reported deaths. In a larger cohort of 317 patients, DAPT was linked to reduced acute coronary syndrome (ACS) incidence from 34% to 17% ($p=0.03$). Similarly, OAT was linked to reduced ACS from 42% to 29% ($p=0.02$). Another study of 51 patients demonstrated that those prescribed warfarin and with a time in therapeutic range (TTR) $\geq 60\%$ had no MACE, whereas 33% of patients with a TTR more than 60% or without warfarin had MACE ($p=0.03$). The authors concluded that a combined antiplatelet and anticoagulation therapy was connected to fewer cardiac complications and overall lower mortality.(52)

An observational study investigated the connection between coronary artery ectasia and inflammation by measuring the concentration of inflammation-associated markers in serum such as interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP). This study included 217 CAE patients, which were divided into three main age groups, consisting of patient younger than or equal to 50 years, patients between 51–70 years and patients older than 70 years. Additionally, 73 controls without coronary pathologies were included. The baseline measurements revealed that the levels hs-CRP and IL-6 levels were notably elevated in patients with coronary ectasia ($p < 0.05$), especially in the youngest CAE group. After a comparison of hs-CRP and IL-6 levels between the youngest (CAE-A) and the oldest group (CAE-C), a significant difference was seen ($p = 0.048$ for hs-CRP; $p = 0.025$ for IL-6). After 6 months of administration of rosuvastatin (10mg daily), there was a notable reduction of these inflammatory markers, which was greatest in the youngest cohort. The analysis of logistic regression confirmed that higher hs-CRP concentrations independently predict the presence of CAE, with an odds ratio of 1.782 (95% CI: 1.124–2.014, $p = 0.021$). Similarly, IL-6 concentrations are also independent determinants of CAE, with an odds ratio of 1.584 (95% CI: 1.112–1.986, $p = 0.030$). This study concluded that early administration of statins can be beneficial especially in younger individuals with CAE in order to reduce inflammation.(53)

A randomized study analyzed the impact of intracoronary diltiazem on coronary circulation in 60 patients with CAE. The patients either received 5mg of diltiazem or saline and the coronary flow was measured by using different tools such as myocardial blush grade (MBG), TIMI flow grading, as well

as TIMI frame count (TFC). After the administration of diltiazem, the parameters showed statistically significant changes. The MBG value improved from 2.4 to 2.6 and the TIMI flow grade increased from 2.4 to 2.8, while TFC decreased from 35 to 26 frames. There was no significant change noted in the saline group. These findings suggest that the administration of diltiazem improves both epicardial and microvascular coronary flow in CAE. It reduces vasospasm in the coronary arteries, which helps to substantially decrease the risk of myocardial ischemia.(54)

Pharmacological treatment of CAAs and CAEs aims to reduce thrombotic complications and adverse cardiac events.(4,18) The data from registries, case reports and case series highlighted that antiplatelet and anticoagulation therapy, can reduce the incidence of ischemic events.(39,52) Furthermore, statin therapy has been shown to significantly lower inflammatory markers, especially in younger patients.(53) Intracoronary diltiazem improves both epicardial and microvascular coronary flow.(54)

3.9.2 Outcomes of percutaneous treatment

Percutaneous coronary intervention can be a suitable treatment option for selected patients with CAAs. However, the exact indications remain debated and the evidence is still limited.(3,4) Favorable short-term results were reported in patients who underwent PCI for CAAs compared to those without stent implantation. Nevertheless, the follow-up studies revealed comparable rates of complications such as unstable angina and myocardial infarction.(18) The handling of CAAs strongly depends on the size as well as etiology of CAAs. Surgical procedures are commonly applied in giant aneurysms (>20 mm) that are susceptible to complications or aneurysms that are related to Kawasaki disease. PCI is often considered in small aneurysms or in cases where the anatomical conditions are favorable.(4,18) Percutaneous interventions in CAAs with concomitant acute coronary syndrome demonstrated less satisfactory outcomes due to increased risk of “procedural failure, mortality, no-reflow, stent thrombosis, distal embolization and target vessel revascularization”.(3) These adverse effects emphasize the procedural difficulties of PCI. Different factors have to be considered in order to prevent complications, including the selection of suitable stent sizes and optimal implantation sites as well as the management of thrombus formation.(3) In patients with CAAs without any symptoms the decision to perform PCI is still under debate because currently there is limited data that compares the outcomes.(4) The CAAR study accentuated that there are no notable differences in outcomes between CABG and PCI, highlighting that PCI is a viable option. However, the indication of bare-metal stents showed a high incidence of major adverse effects and mortality. It is necessary to emphasize that the CAAR study is based on observational data and lacks randomized clinical trial results. (4,55)

Out of 51,555 coronary angiograms (2002-2013), CAAs were identified in 414 patients. This study indicated that CAAs are usually uncommon in acute presentations, but they are indicative of atherosclerotic disease. Among these, 256 presented with acute events. Typically, the aneurysms were solitary and frequently involved the left anterior descending artery. The population consisted mainly of male patients (86%) with an average age of 65.5 years and had significant coronary stenosis (94%) as well as atherosclerotic risk factors. Over a follow-up period of 52 months, 42% of the cohort experienced cardiovascular events and 53 died. However, aneurysm associated complications were generally rare (n=4). The findings suggest that patients with CAAs in acute presentations have a generally higher risk for complications. However, most of the events are not directly caused by the aneurysm itself. Furthermore, antithrombotic therapy might improve the overall long-term outcomes.(56)

The short- and long-term effects of PCI for CAAs using different devices such as covered stents or DES, have been analyzed throughout different studies, focusing on procedural risks, effectiveness and complication incidences. The observational study by CAAR evaluated the long-term results of covered stents compared to DES in CAA patients. Covered stents were more commonly used in male patients and in those with prior coronary artery disease, elevated cholesterol levels or giant aneurysms. After a monitoring period of approximately three years, comparable rates in terms of major cardiovascular events were observed between stent-grafts and DES. The main predictors for adverse outcomes were rather HFrEF or connective tissue diseases. The conclusion of this study is that covered stents show safe long-term results, while emphasizing that the patient-associated risk factors have a bigger impact on the outcomes than the stent type. Randomized trials are still needed to confirm the optimal treatment, especially in complex cases.(49)

The systematic review by Will et al. used data from 81 patients to establish the safety as well as the effectiveness of covered stents for the elective treatment of CAAs. The findings highlighted that stents such as covered stents are generally effective, however they are still linked to a higher rate of reintervention, mainly at the stent site. The reported success rate was high with 95.1%. Although the immediate procedural outcomes were satisfactory, after a follow-up period of 13.4 months, around 26.2% of patients had adverse cardiac events, including 18.5% of patients who needed repeated intervention at the stent site and 7.6% of patients who experienced myocardial infarction. In this study, no deaths or strokes were reported. Most aneurysms were located in the native artery and in some cases in the saphenous vein graft. The most commonly indicated stents were PTFE-covered or Papyrus type stents and in some cases drug-eluting stents were implanted.(57)

Another observational study analyzed the results of Papyrus covered stent implantation in patients presenting with either CAA or coronary artery perforation. In 108 patients, 127 Papyrus covered stents were indicated. These patients were monitored for approximately 22 months. Overall, the outcomes were acceptable, with a MACE rate of 7.1%. No relevant difference in MACE was noted between both groups ($p=0.9$). The most common cardiovascular complications were myocardial infarction and repeated vessel revascularization, each occurring in 5 % of patients. However, stent thrombosis was more observed in patients with CAA (7.1%) compared to those with coronary artery perforation (0%). The clinical outcomes after hospital discharge were comparable in both groups, except for the higher stent thrombosis rate in the CAA group.(58)

In summary, PCI is frequently indicated in patients presenting with small aneurysms or those with optimal anatomical structures.(4) Despite favorable short-term outcomes of PCI, the long-term, outcomes do not significantly differ from patients managed without intervention.(18) The outcomes between CABG and PCI are generally similar, but the use of bare-metal stents was linked to higher incidences of adverse cardiovascular events.(4,55) Covered stents show favorable long-term outcomes in CAAs, while complications were more commonly linked to patient-specific risk factors.(49) In CAA patients with coexisting acute coronary syndrome, PCI is generally linked to a higher risk of thrombosis and other adverse effects.(4) Elective PCI, using covered stents has a generally high success rate but reintervention remains common.(57)

3.9.3 Outcomes of surgical procedures

For patients with CAAs who cannot be managed with percutaneous interventions due to high procedural risks, surgical treatment can be a viable alternative.(1) Surgical indications include giant aneurysms, involvement of the left main coronary artery or major coronary branches, coronary obstructive disease or if complications occur such as compression of neighboring structures or fistula formation.(4) The most indicated surgical procedures are the exclusion or resection of the aneurysm, reconstruction, aneurysmal thrombectomy or ligation combined with bypass grafting (CABG).(1,18) In case of smaller aneurysms, CABG can be performed solitary. However, giant aneurysms require a more extensive surgical intervention.(51)

In a single-centered series of 15 patients who were treated surgically for CAAs, no in-hospital deaths were reported in a follow-up period of 5.3 years. All patients received CABG and 27% received aneurysmal resection or ligation. The long-term outcomes were satisfactory, with only one patient who needed an additional intervention. This case-series concluded that surgery is a safe treatment

option, with satisfactory short-and long-term outcomes. Isolated CABG is sufficient for small CAAs, while combined approaches are frequently indicated for giant CAAs. (51)

The Coronary Artery Aneurysm Registry (CAAR) analyzed the results of patients who either underwent surgical or percutaneous revascularization. After a monitoring period of 37.2 months, outcomes did not differ significantly between CABG and PCI in terms of MACE or reported mortality (MACE: 31.6% vs. 31.4%; mortality: 15.6% vs 15.9%). The incidences of aneurysm progression or formation of new aneurysms were similar between both groups. Nevertheless, heart failure occurred more often in CABG patients compared to PCI patients (10.8% vs. 5.9%). However, these results are from a univariate analysis.(55)

A retrospective study from 2000 to 2005 compared the various treatment approaches in CAA patients. The follow-up period was approximately 5 years. It has been reported that CABG patients had less major cardiovascular and cerebrovascular events (MACCE) compared with the medical management group (26.1% vs. 39.6%) and generally showed better MACCE-free survival on the Kaplan-Meier analysis ($p=0.03$). Nevertheless, the advantage of CABG was not statistically significant after a multivariate adjustment was done ($p=0.19$). This indicated that the results might have been influenced by the patient selection or other relevant factors. PCI patients had intermediate MACCE rates (34.6%). After a multivariate analysis, the treatment modalities did not differ significantly.(59)

In summary, the available data shows that surgical treatment is a safe treatment option that offers good outcomes in selected patients.(51) CABG might be beneficial for selected patients but current data does not demonstrate consistent superiority over PCI in all cases.(55,59) All treatment decisions should be based on aneurysm size ,location, associated coronary disease and the patients clinical profile.(4,18)

4.0 Discussion

The therapeutic approach of coronary artery aneurysms is complex due to their variable underlying etiology, clinical presentations, anatomical abnormalities and the lack of a generalized treatment consensus. Current data suggest an individualized treatment approach that considers aneurysm features such as size, location, expansion, concomitant coronary diseases, as well as associated complications.(1,3,4,18) A comprehensive treatment strategy is used, including pharmacological treatment, percutaneous interventions and surgical management. Each intervention has its own clinical significance and outcomes.(1,18)

Pharmacological treatment has a significant role in the management of CAAs, especially in patients with cardiovascular risk factors.(1,18) The aim is to reduce thrombus formation and associated cardiovascular complications.(18,25) Aspirin is the most frequently indicated antiplatelet agent across both adult and pediatric populations.(4) Observational data from the CAAR registry have demonstrated that oral anticoagulation therapy is connected to lower rates of ischemic events such as unstable angina and aneurysmal thrombosis without evidence of an increase in bleeding risk. However, randomized controlled trials are still absent.(39) Furthermore, a systematic review supported the use of combined antiplatelet and anticoagulation therapy in patients with CAE because it may be associated with fewer MACE. However, the evidence is mainly derived from isolated case reports or small clinical series.(52) In Kawasaki-related CAAs, a combination of aspirin with anticoagulants is often indicated, especially for giant aneurysms. Conducted studies illustrated favorable safety results for the use of direct oral anticoagulants in Kawasaki patients.(33) Other pharmacological strategies include the indication of statins and ACE inhibitors, which have shown anti-inflammatory and plaque -stabilizing effects. To prevent further expansion of the aneurysm and associated complications, it is necessary to strongly control the blood pressure.(4,6,18) Even though observational studies have shown favorable results, the lack of randomized controlled trials prevent the formulation of a standardized treatment regimen.(4)

Percutaneous interventions are mainly indicated in patients presenting with small CAAs or favorable anatomy, especially in case of concomitant obstructive coronary artery disease or acute coronary syndrome. Covered stents, especially polytetrafluoroethylene-covered stents, are often employed to exclude aneurysms. Coil embolization is used in cases that involve major coronary bifurcations or wide-neck aneurysms.(1,4,6,11) Observational data from the CAAR registry indicated no apparent difference in long-term outcomes between covered-stents and drug-eluting stents. However, complications were more related to patient-specific risk factors.(49) When covered stents are used in elective PCI, there are associated with favorable procedural outcomes. However, reintervention remains frequent and long-term complications such as stent thrombosis are more commonly seen in aneurysmal vessels.(57) In acute coronary syndrome-associated CAAs, PCI is linked to higher incidence of procedural adverse events, including impaired coronary flow, thrombosis and embolization.(3) The data from the registry indicated that the long-term outcomes between PCI and surgical coronary artery bypass grafting are largely comparable. This highlights that PCI is a viable option, although only indicated in selected patients.(55)

Surgical interventions are generally reserved for high-risk cases, including giant aneurysms, involvement of the left main coronary artery, multiple aneurysms or in the case of mechanical complications.(1,4,18) Coronary artery bypass grafting (CABG) is the most frequently applied surgical procedure and most often combined with aneurysm resection, ligation or reconstruction.(1,4,18) Conducted case series have revealed that CABG is associated with satisfactory short-and long-term results with low in-hospital mortality.(51) Comparative analyses show no clear superiority of CABG over PCI with regard to MACE and mortality. (55,59)

When comparing these treatment modalities it becomes evident that the treatment choice is guided by the aneurysm features as well as the individual risk profile.(4) Pharmacological treatment is a non-invasive option and remains the treatment of choice for patients with CAAs at increased risk for cardiovascular complications.(3,18) PCI provides a less invasive revascularization method, particularly for small aneurysms.(4) However, the rates of reintervention are still high because of adverse cardiovascular events in the long-term.(57) Surgery is a more invasive option, with favorable outcomes in complex and high-risk cases.(1,4,51) The existing literature emphasizes that all three treatment options can be effective and safe when applied to the appropriate patients. Because most studies are observational with small sample sizes and diverse patient groups, a direct comparison to generate universal treatment guidelines is not possible. These factors make it difficult to decide which treatment strategy is superior. Further research in this field is necessary to identify the most important treatment method and to determine which modality offers the most favorable short- and long-term outcomes.

Throughout this literature review, it became evident that outcomes are not only dependent on the superiority of each treatment modality but more on how and when different treatment approaches can be integrated into a patient's treatment plan. Pharmacological treatment is mainly the basis and integrated across the different treatment pathways because it allows stabilization of disease progression and decreases the occurrence of complications.(1,18) In contrast, interventional and surgical procedures offer more of a targeted solution and are strongly dependent on the anatomical characteristics, clinical features and complication risks.(1,3,4,18) PCI is generally linked to favorable short-term outcomes, but its effectiveness may be decreased due procedural limitations and the need for reintervention.(57) Surgical interventions are associated with higher perioperative risk but are generally stable in the long-term in selected patients.(4,18,51) Comparative analysis of various studies revealed that long-term outcomes such as MACE and mortality are largely comparable between PCI and surgical interventions.(55,59)

5.0. Conclusion

Coronary artery aneurysms are relatively uncommon clinical entities caused by various etiologies such as atherosclerosis, Kawasaki disease, connective tissue disorders and other procedure-related causes.(1,4) The pathophysiological mechanisms differ according to the underlying cause.(4,18) While some patients are asymptomatic, others may present with life-threatening complications. The variability in clinical presentation emphasizes the importance of precise diagnostic evaluation.(18) Therefore both non-invasive and invasive modalities should be used.(1)

This literature review analyzed available data about therapeutic strategies of coronary artery aneurysms, focusing on both short- and long-term clinical outcomes. The findings revealed that there is no universal optimal treatment method. Currently, the treatment is based on the aneurysm features such as size, location and associated complications.(3)

Conservative pharmacological treatment remains a viable option to prevent cardiovascular complications.(18) Percutaneous interventions, including covered stents and coil embolization are methods that are effective in excluding CAAs. However, they also carry some procedural risks and may not be suitable in patients with complex anatomical features.(1,3,4,6) Surgical procedures, most commonly CABG, are typically indicated in patients presenting with large, symptomatic or high-risk aneurysms.(4) Studies showed that CABG is linked to favorable long-term clinical results.(51)

In conclusion, the data demonstrated that no single treatment modality is a definitive option. The most effective treatment strategy for CAAs is oriented toward the patient's clinical picture and integrates etiology, clinical features and diagnostic evaluation. The absence of large-scale trials hinders the formulation of a generalized treatment algorithm.(3,18)

Future research in this field should focus on multicenter, large-scale studies that compare pharmacological, percutaneous and surgical treatment strategies in different patient populations. Until then, the treatment of coronary artery aneurysms should be tailored to the patient's individual features. Generally, a multidisciplinary team involving cardiologists and cardiothoracic surgeons is recommended in order to ensure optimal patient outcomes

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