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REVIEW ARTICLE

Comparing Pharmaceutical Therapies in the Treatment of Post-Kawasaki Disease Giant Coronary Artery Aneurysms: An Exploration of Sequelae in Pediatric Populations

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ABSTRACT: Kawasaki Disease (KD) is a pediatric vasculitis of an unknown but suspected infectious etiology that results in a marked inflammatory response. The generally effective standard of treatment is a combination of intravenous immunoglobulin (IVIG) and acetylsalicylic acid (ASA), the former to reduce the prevalence of coronary artery aneurysms and to lower fever, and the latter to prevent ensuing thrombosis. However, KD patients who develop persistent giant coronary artery aneurysms (CAAs) experience long-term symptoms, many pertaining to damage and restriction of the coronary arteries. This analysis explores prominent cardiovascular drugs' pharmacological mechanisms and compares their efficacy in relation to leading symptoms, with special attention given to vasodilation, myocardial oxygen demand, and smooth muscle proliferation. Ultimately, this review examines these pharmaceutical treatments as potential adapted therapeutic approaches for subacute pediatric KD survivors who have experienced severe CAAs, aiming to reduce the risk of coronary artery complications and promote informed decisions regarding cardiac outcomes overall.

KEYWORDS: Translational Medical Sciences, Disease Treatment and Therapies, Kawasaki Disease, Giant Coronary Artery Aneurysms, Calcium Channel Blockers, Beta-Blockers, Nitrates, ACE Inhibitors.

Introduction

Kawasaki Disease (KD) is an uncommon vasculitis that primarily affects children. To be diagnosed, it presents with a long-lasting fever (five days or more) and at least four of these symptoms: bacterial conjunctivitis, rash, erythema and edema of the extremities, changes surrounding the oral cavity (strawberry tongue, erythema, cracked lips), and cervical lymphadenopathy (1.5 cm or greater in diameter).[1] KD has been documented all around the world, with approximately 2,000-4,000 cases diagnosed annually in the United States; these numbers are over ten times greater in many east-Asian countries.[2] If KD goes undetected, 25% of its hosts develop coronary artery aneurysms– the swelling of a coronary artery to 1.5 times its standard size– with complications including coronary artery stenosis, arrhythmias, and increased risk of myocardial infarction in severe cases.[2] Even if treated after seven days of illness, there is a 66% increased risk of CAA development. If IVIG is delayed to 10 days after the acute phase, individuals are 5.3 times more likely to develop CAAs. And while 71% of CAAS treated with IVIG regress within two years, structural abnormalities remain. After two years, follow-up with CAA patients found that 14% had developed stenosis, more frequently in the right coronary artery, inlet, or outlet of aneurysms. As the damaged arterial walls heal, they not only stiffen but thicken, increasing the risks of thrombosis or heart attack.[3] CAAs with dilations that measured only 4 mm in the acute phase caused formational changes that increased the size of the intimal-medial wall over time.[4] The risk of CAA development increases from 25% to 37% for patients with incomplete KD, which is characterized by an extensive fever but a smaller number of the other symptoms commonly associated with the disease.[4] Other issues arise in the chronic phase, including stenosis and endothelial dysfunction that heighten the risk of ischemia. Two years after the acute phase, stenotic lesions were visible in 14% of CAA patients.

As such, treating the long-term cardiac effects of KD in the most severe cases is a priority. Calcium causes muscle (including the cardiac variety) to contract by binding with regulatory proteins that cover actin binding sites, thus allowing myosin proteins to pull actin filaments. As the two slide over one another, the sarcomere, or functional unit of muscle, contracts. CCBs prevent calcium molecules from entering the heart by blocking voltage-gated ion channels, thus preventing the cardiac muscle from contracting. The coronary blood vessels relax, and vasoconstriction is reduced. CCBs are approved by the US Food and Drug Administration (FDA) and are currently in use with cardiac conditions such as hypertension and coronary artery disease that involve constricted blood vessels, similar to KD.[5] Switching focus, when hormones, including epinephrine and norepinephrine, bind to β-1 adrenergic receptors, they trigger a release of calcium, increasing heart rate and contractile strength. Both of these are associated with increased arterial stiffness and a possible dysfunction of endothelial cells. Beta-blockers utilize competitive inhibition, preventing adrenaline from triggering cardiac contraction and reducing the heart's workload. Beta-blockers are also approved by the FDA for tachycardia, hypertension, coronary artery disease, and similar conditions.[6] Moreover, once in the body, nitrates are converted into nitric oxide, which activates the enzyme guanylyl cyclase within the smooth muscle cells of the blood vessels.

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Guanalyl cyclase causes increased levels of cyclic guanosine monophosphate (cGMP) and decreased calcium, thus relaxing the smooth muscle, similar to the result of CCBs. Nitrates, FDA-approved as well, are currently in use for angina pectoris, hypertension of the arteries, and heart failure.[7] Finally, ACE inhibitors are an FDA-approved medication often used to treat hypertension [130-139/80-89], systolic heart failure, or to reduce the risk of cardiovascular disease. ACE inhibitors block the angiotensin-converting enzyme from converting inactive angiotensin I to angiotensin II, a vasoconstrictor that increases blood pressure as well as aldosterone levels. ACE also breaks down bradykinin, a molecule involved in vasodilation and inflammation; thus, inhibitors allow for vessel relaxation and reduce levels of oxidative stress.[8] This analysis aims to examine the benefits and pitfalls of four classes of cardiovascular medications, in conjunction with present therapies, in improving severe long-term issues with coronary artery damage and lessening myocardial stress that can result from KD in pediatric populations.

Methods

A comprehensive literature review was conducted to examine pharmaceutical therapies for post-KD coronary artery complications. CCBs were selected for the review due to their direct effects on coronary artery vasodilation, relevant to the lack of vasoreactivity and arterial vasospasm observed in post-KD patients. Beta-blockers were selected due to their ability to reduce myocardial oxygen demands and increase coronary perfusion, which lowers the risk of ischemia. ACE inhibitors were selected for their vascular remodeling and endothelial repair capabilities, in addition to inhibiting certain inflammation, which are all common factors related to post-KD coronary abnormalities. Nitrates were selected for their fast-acting coronary vasodilatory abilities in adults. As they are not used chronically or routinely in pediatric populations, their selection is more conceptual, a comparison of mechanisms rather than a direct pedantic suggestion. Antiplatelet agents were not selected as their clinical application to KD has already been established. Statins were not selected as their main pathway, lowering lipid levels, is not directly relevant to coronary arterial recovery in post-KD patients. Relevant articles were identified through searches on PubMed, Google Scholar, and the NCBI Bookshelf using keywords including "Kawasaki Disease" (with a focus on subsequent "coronary artery aneurysm" keywords), "calcium channel blockers," "beta-blockers," "nitrates," and "ACE inhibitors." The review prioritized research published between 2000 and 2025 to include the most recent clinical findings and reviews. Criteria for inclusion centered on peer-reviewed journal articles and medical sources that discussed cardiovascular outcomes, medicinal mechanisms, and long-term management of KD patients' symptoms. Selected sources were synthesized to compare drug efficacy, mechanisms, and potential benefits for post-KD coronary health.

Results

There are several coronary arterial complications associated with KD, with coronary artery aneurysms (CAAs) being the most prominent among them. While the appearance of these cardiac difficulties and their mortality rates are fairly low, they can vary greatly depending on the severity and duration of the abnormality, from the broader dilation of coronary artery ectasia to the more extreme giant aneurysms. Such risks are most common in the acute phase, with giant CAAs budding in 0.18% of patients treated with IVIG (these tout a mortality rate of 6.28%).[4] Long-term pharmaceuticals could be necessary to manage damaging coronary symptoms. The four drug classes of interest for this subject are CCBs, beta-blockers, nitrates, and ACE inhibitors. CCBs, most commonly in use with coronary artery disease, reduce the amount of calcium ions flowing into muscle cells and thus promote vasodilation.[5] An oral dihydropyridine CCB, such as amlodipine, has a relatively long half-life of 30-50 hours.[9] Once-daily doses would be sufficient, and it is already in use treating chronic hypertension, vasospastic angina, and risk reduction with documented coronary artery disease. Amlodipine is generally considered safe for pediatric use, with appropriate dosages and monitoring.[7] When employed to treat hypertension for a prolonged period, amlodipine has been well-tolerated with minimal side effects. For children aged 6 years and below, amlodipine doses begin at 0.05-0.2 mg/kg/day, and can be increased to a maximum of 0.3-0.6 mg/kg/day.[7] CCBs would be useful in cases where there is significant vasospasm around the CAA, thus contingent on preserved smooth muscle, and as a preventive for associated angina and myocardial episodes. Beta-blockers decrease myocardial oxygen demand by decreasing heart rate and force of contraction. Selective beta-blockers, such as metoprolol, target beta-1 receptors, which are located within the heart. Non-selective versions target both beta-1 and beta-2 receptors, which are found throughout the body but primarily in the smooth muscle cells of the airway.[6] Non-selective beta-blockers are thus more dangerous for those with respiratory conditions. Contingent on careful monitoring and professional oversight, beta-blockers are already in use with pediatric patients. Beta-blockers could be employed to decrease general myocardial stress or aggravation of the CAA, simultaneously reducing symptoms like angina. Propranolol has become the standard of care to treat infantile hemangiomas, a benign tumor composed of blood vessels.[10] Nitrates, the most common forms being nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate, are generally used for immediate chest pain or other similarly emergent situations. They are less commonly used in pediatric patients, partially due to the rapid rate at which a tolerance can be developed (12-24 hours).[7] Nitrates could be used as a preventative measure to avoid worsening or developing further CAAs due to their vasodilatory capacities. The direct increase in blood flow and oxygen to the myocardium that they deliver would be an asset in immediate cardiac episodes, but not an appealing long-term option. ACE inhibitors lower angiotensin II levels and associated bradykinin levels, reducing preload and afterload, in addition to preventing platelet aggregation and allowing for endothelial

restoration. They are also often used for hypertension due to their vasodilatory capabilities. ACE inhibitors are commonly employed for pediatric patients; Enalapril, for example, is administered twice daily with doses from 0.05mg/kg/dose to 0.5mg/kg/dose. ACE inhibitors could have a double-sided advantage: reduction of cardiac stress while increasing blood flow through vasodilation and endothelial repair, as well as reduction of the inflammatory markers that so heavily contribute to CAAs. Their multifaceted benefits make them one of the more effective potential pharmaceutical applications out of the four.

Discussion

History & Evolution:

In 1967, Dr. Tomisaku Kawasaki noticed a pattern of ill infants, whose symptoms consisted of a fever, rash, convalescent desquamation, and lymphadenopathy, among others.[11] Despite Dr. Kawasaki's contrary hypothesis, pediatrician Takajiro Yamamoto and pathologist Noboru Tanaka believed that KD was not a self-limiting illness– a claim cemented by ten post-KD autopsies with sudden cardiac episodes listed as the cause of death.[11] Tracing the history of KD is difficult because its precise etiology remains unknown, but responsible factors are thought to be some combination of genetic predisposition, environment, and intensified immune response. KD tends to occur more frequently in children of Asian or Pacific Islander descent. While the average annual incidence in the San Diego region is 25 out of 100,000 in children under 5 years old, the rate doubled (50 out of 100,000) for Asian and Pacific Islander children.[12] Beyond ethnicity, certain immune system alleles have been hypothesized to increase genetic predisposition to KD. Several possible susceptibility genes have been identified, with links between variations in their sequences and higher rates of KD being explored. The ITPKC gene is responsible for making an enzyme that affects the Ca^{2+}/NFAT pathway, that negatively regulates T-cell activation and thus prevents excess inflammation. A single-nucleotide polymorphism (SNP) has been found to hinder the production of the ITPKC enzyme, allowing higher levels of calcium to be released and T-cells to become overly active.[13] The CASP3 gene codes for caspase-3, which plays a role in apoptosis of immune cells, mediating phagocytosis or cleaving signal proteins from the cell body to prevent autoimmune attack. Due to a SNP in CASP3, programmed cell death and cleavage do not occur properly, and the buildup of these damaged immune factors causes irregular inflammation.[14] The protein produced by the CD40 gene resides on B-cells and macrophages, and binds to CD40 ligands on T-cells and platelets. This binding not only activates the cells involved but also causes pro-inflammatory cytokines to be produced. In KD patients, overexpression of the CD40 ligand can cause excess inflammation that is specifically tied to the vascular endothelium, which can lead to coronary artery lesions.[15] This excess activation can bring on the inflammation that damages the coronary endothelial cells. Further, KD frequency is higher in winter and spring months, when respiratory viral infections are more prevalent.[16] No single virus has been pinpointed as a KD trigger, but they may cause an abnormal immune behavior in their host, which could be tied to the inflammation in KD. Bacterial infections, such as Streptococcus species infection, can cause the production of superantigens, molecules that trigger an immense immune response through mass T-cell activation. Another noteworthy possibility is the post-WWII industrialization of Japan. As the country revamped its production in the 1950s and 1960s, pollution followed. This environmental toxicity is a possible explanation for the rise of KD cases that began in the 1960s.[11]

Disease Mechanisms:

Although various bacteria have been proposed as infectious triggers, the exact agent that triggers KD is unknown. When the body encounters an infection, components from the bacterial cell wall called pathogen-associated molecular patterns (PAMPs) will be released. Cellular damage can also act as a trigger, with injured or dying cells releasing damage-associated molecular patterns (DAMPs).[17] This is detected by pattern recognition receptors (PRRs) such as Toll-like receptors (TLR2 and TLR4) that become activated by binding to the PAMPs and DAMPs. These PRRs activate immune pathways that produce proinflammatory cytokines, including TNF-α, IL-1β, and IL-6. In addition to causing a fever and inflammation, these cytokines cause neutrophils to enter blood vessel walls, including those of the coronary arteries. They release reactive oxygen species and S100 alarmins that act as DAMPs, stimulating IL-1β production. Macrophages enter the vessel walls as well and activate the NLRP3 inflammasome, which releases more IL-1β, building up a cytokine storm. Due to the aforementioned susceptibility genes, an additional influx of Ca^{2+} causes hyperactivity in T-cells as they produce cytokines like IL-2 and IL-17. Vascular damage accrues here, with immune cells and cytokines weakening the coronary artery walls and promoting thrombosis in the endothelial cells. Impaired endothelial function has been noted in those who previously had KD, even without CAA development in the acute phase.[4] Additionally, matrix metalloproteinases are upregulated by the excess amounts of IL-1β and begin to break down collagen and elastin in the arterial walls, causing CAAs. If IVIG is employed, it binds to receptors on macrophages that reduce cytokine production, and TNF-α, IL-1β, IL-18, and IL-6 levels drop as the IL-1 pathway is suppressed. The CD40 pathway is downregulated, reducing the persistent T and B-cell stimulation, and in the majority of cases, the excess release of cytokines stops.[18]

Comparative Drug Analysis:

The current most commonly employed treatment for KD is a combination of intravenous immunoglobulin (IVIG) and aspirin; the former is administered within the first 10 days, with a recommended 2 g/kg dose. IVIG decreases inflammation and reduces the incidence of CAAs by 5% to 25%.[19] High-dose aspirin (ASA) is given at a dosage of 80-100 mg/kg/day during the acute phase of KD in the United States, with moderate dose (30-50 mg/kg/day) administered in Japan and areas of Western Europe.[19] Patients are subsequently weaned to low-dose ASA (3-5 mg/kg/day), which is continued for

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several weeks. High ASA doses have been shown to reduce fever and inflammation. Low doses are used to prevent platelets from aggregating and forming blood clots. Switching focus, other classes of medicines, such as nitrates and CCBs, which are used for vasodilation, may appear promising for treating long-term KD cardiac dysfunctions, but struggle, as ACE inhibitors do, to overcome the issue of coronary artery smooth muscle necrosis that lingers in 25% of untreated children as a result of CAAs.[20] Application is more likely to be successful with a considerable amount of preserved smooth muscle, on which CCBs, ACE inhibitors, and nitrates could act to induce vasodilation. In these cases, CCBs are geared towards vasodilation, especially effective in coronary arteries, and they reduce the afterload, allowing the heart to pump out blood more easily. By blocking angiotensin II, which increases afterload, ACE inhibitors also allow the left ventricle of the heart to pump blood more easily, reducing oxygen demands. With lowered levels of aldosterone, blood volume lowers, and venous return decreases as well, reducing strained blood pressure and oxygen requirements. Nitrates are focused on venodilation, so their efficacy on coronary arteries is present but lessened compared to CCBs– they reduce preload, so less blood fills the heart directly.[21] Because of this, CCBs are more suited for preventing vasospasm or stenosis, as they allow blood to flow more smoothly through arteries rather than simply reducing cardiac workload. Both CCBs and ACE inhibitors can also be used long-term without a tolerance developing, compared to nitrates, which can lose efficacy within 12-24 hours.[22] This can happen when reduced sulfhydryl (SH) groups are depleted in numbers due to their frequent usage in the transformation of nitrates to nitric oxide– SH groups are oxidized in this process. Without the active SH forms available, vasodilation cannot occur because nitric oxide cannot be made.[23] Many routes cause nitrate tolerance to develop rapidly, another being oxidative stress from nitrates, causing increased production of reactive oxygen species (superoxide). Superoxide combines with nitric oxide to create the harmful compound, peroxynitrite, while simultaneously damaging the enzyme that creates nitric oxide (ALDH2) and inhibiting guanylyl cyclase, which aids in vasodilation.[24] Additionally, CCBs have demonstrated possible anti-proliferative effects. CCBs block calcium channels and thus reduce the amount of intracellular calcium, a major signaling molecule in the cell growth cycle. Less calcium influx results in less cell proliferation.[25] They also have the potential to induce autophagy, which can reduce the thickening and remodeling of the arterial wall often seen in KD.[26] As angiotensin and aldosterone stimulate the proliferation of vascular smooth muscle, ACE inhibitors can prevent chronic dilation or remodeling of the left ventricle.[27] ACE inhibitors also prevent bradykinin, a vasodilatory peptide that increases nitric oxide release, from being broken down by ACE, relaxing vascular smooth muscle and thus reducing the oxidative stress that damages endothelial cells. It also prevents thrombin-induced platelet aggregation– reducing the risk of arterial thrombosis.[28] Nitrates, while effective for angina symptoms, do not display prominent anti-proliferative effects that would be beneficial for the management of chronic KD symptoms. Beta-blockers, used for a variety of cardiac conditions from hypertension to heart failure, have anti-proliferative qualities as well, as they activate nitric oxide synthase and thus increase the amount of nitric oxide available. Such cellular reductive potential has been observed in vascular smooth muscle and endothelial cells.[29] They are, in general, less targeted in comparison to CCBs, though, reducing heart rate and blood pressure, thus reducing oxygen demands but not improving oxygen supply the way CCBs, ACE inhibitors, and nitrates do. They appear helpful in managing symptoms, but don't address the issue of thickened or restricted arteries. However, as beta-blockers do not rely on a smooth muscle mechanism for effectiveness, they would skirt the smooth muscle destruction issue that the other three classes face. Beta-blockers also share CCBs' and ACE inhibitors' resilience, but their usage cannot be terminated abruptly. This would cause the body to endure the effects of a sudden influx of adrenaline without competition, placing stress on the heart and its vessels.

Potential Side Effects

CCBs can have various side effects, which must be considered in depth when administering them to pediatric patients. There are two classes of CCBs, each with different effects: dihydropyridines, which function as previously mentioned to widen blood vessels, and non-dihydropyridines, which can have the same vascular functions but also act on the conduction system of the heart itself. Dihydropyridines can cause headaches and flushing from vasodilation of blood vessels in the skin and brain.They can also cause peripheral edema, as the increased pressure in the capillaries allows fluid to leak out into the interstitial space. Non-dihydropyridines can cause constipation, as the smooth muscles in the GI tract are relaxed and peristalsis is impaired. Both types can cause nausea, dizziness, and fatigue. The more severe side effects tend to belong to non-dihydropyridines, including bradycardia due to CCBs acting on the SA and AV nodes, and heart block from an interruption of the heart's electrical signals.[30] Both types can cause hypotension due to excessive vasodilation. CCBs, like many drugs, are metabolized in the liver by CYP450 enzymes, primarily CYP3A.[31] Certain CCBs, like Verapamil and Diltiazem, can inhibit CYP3A function, ensuring that their breakdown and that of other drugs is slowed. These two non-dihydropyridines often disrupt the breakdown of ciclosporin, statins, benzodiazepines, buspirone, and sildenafil. Other substances can inhibit CYP3A and amplify the effects of CCBs in the body, such as cimetidine, erythromycin, grapefruit juice, azole antifungals, and HIV medications (protease inhibitors).[5] On the opposite side of the spectrum, other drugs can induce the CYP3A enzyme, reducing CCBs' time in the body and strength. Anti-seizure medications, rifampicin, and phenobarbital can act as CYP3A inducers.3 With this in mind, amlodipine displays potential for post-KD cardiac health management– contingent, of course, on the presence of functional smooth muscle cells. Beta-blockers, again, also have two classes: selective and non-selective. The main side effects of selective beta-blockers are hypotension and bradycardia, with things like fatigue and dizziness in addition. Non-selective drugs can, along with the

aforementioned symptoms, result in bronchospasm or asthma attacks by preventing epinephrine from dilating the bronchioles.[32] Beta-blockers amplify several other drugs, such as antihypertensives and antiarrhythmics, and bring about immense bradycardia and possible heart block. CCBs (especially non-dihydropyridines), for example, slow AV node conduction and lower heart rate, just like beta-blockers. By blocking the visible effects of epinephrine and norepinephrine in cases of low blood sugar, beta-blockers can exacerbate hypoglycemia, especially when paired with insulin. As the sympathetic nervous system can trigger glycogenolysis, or the breakdown of glycogen into glucose, but without the effects of key hormones (epinephrine and norepinephrine), the process is inhibited considerably.[33] Conversely, H2-receptor antagonist, cimetidine, can amplify the effects of beta-blockers by interfering with the CYP450 enzymes (CYP1A2, CYP2C9, CYP2D6) in the liver, responsible for metabolizing propranolol and metoprolol.[34] Further, NSAIDs– utilized to manage pain and inflammation, as well as fevers– inhibit renal prostaglandin synthesis and cause water and sodium retention and vasoconstriction, effectively counteracting the effects of beta-blockers by raising heart rate and blood pressure.[35] Medications like rifampin and phenobarbital induce hepatic CYP450 enzymes, processing beta-blockers more quickly and reducing their efficacy.[36] Switching focus, the most common forms of nitrate medications are nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate. Isosorbide dinitrate is a prodrug; thus, it requires conversion in the liver to be activated in the form of isosorbide mononitrate and nitric oxide, giving it a lengthier onset of action and duration. This medication is utilized for both prevention and longer-term treatment.[37] Isosorbide mononitrate does not rely on a hepatic aspect, giving it a longer half-life (5-6 hours) and consistent release, a reliable option for the treatment of chronic angina.[38] Similar to CCBs, nitrates would rely on the presence of functional smooth muscle in the coronary arteries to be effective. Associated side effects are hypotension, headaches (which over 10% of users experience), dizziness, cutaneous flushing, or a tingling under the tongue. More severe reactions can result in syncope, methemoglobinemia, reflex tachycardia, or Monday disease.[7] The effects of nitrates can be severely amplified when paired with PDE5 inhibitors (such as tadalafil [Cialis] or sildenafil [Viagra]), medications that block the enzyme PDE5 to allow for the presence of vasodilatory cGMP.[39] This pairing can decrease blood pressure dangerously, as can the grouping of nitrates with other antihypertensives like beta-blockers. Nitrates are also intensified by diuretic medications, which increase urinary output, reducing the levels of water and sodium within the body. Thus, the liquid available to contribute to the pressure of the blood vessels is decreased, and nitrates induce vasodilation, creating a serious risk of hypotension.[5] Nitrates would not be optimal in terms of chronic usage due to the speed with which a tolerance can be developed. Additionally, in the context of KD, nitrates are not used widely in pediatric patients, aside from severe cardiovascular emergencies. ACE inhibitors are utilized to prevent heart failure and hypertension, and are commonly classified by chemical structure: sulfhydryl-containing, dicarboxylate-containing, and phosphonate-coating. Sulfhydryl-containing ACE inhibitors, such as captopril and zofenopril, have an -SH group and tend to be short-acting. These are often used in acute settings for treatment of heart failure, and as such, they require repeated daily dosages (beginning at 6.25 mg TID for heart failure, and 25 mg BID or TID for hypertension). Taste disturbances and a variety of skin reactions, from rashes to blisters, are common reactions. Dicarboxylic-containing inhibitors, such as benazepril or lisinopril, are frequently employed for long-term use. Phosphonate-containing ACE inhibitors are long-acting prodrugs activated in the liver and can be beneficial for renally impaired patients. A dry cough is a common side effect of all forms of ACE inhibitors, as the inhibition of bradykinin metabolization can result in irritation of the bronchi, with an increased risk of bronchospasm accompanying this. Dizziness and hypotension are also common side effects. Angioedema, swelling of the face and upper airway caused by bradykinin buildup, is a rare yet deadly possibility. ACE inhibitors reduce the rate of blood filtration through the kidneys, reducing the amount of lithium that is cleared from the bloodstream, creating the potential for lithium toxicity. The combination of ACE inhibitors and Allopurinol can increase cutaneous hypersensitivity, manifesting in rashes or systemic allergic reactions. Combining ACE inhibitors with diuretics can lead to intensified hypotensive effects due to reduced blood volume as a result of frequent urination. ACE inhibitors should not be paired with angiotensin receptor blockers (ARBs) as their combined hypotensive effects can be drastic– kidney dysfunction and hyperkalemia are also serious results of the combination.[40] ACE inhibitors are the most frequently prescribed hypertensive medications for pediatric populations (around age 6 and older), with captopril, lisinopril, and enalapril among the most popular.[8]

Applications of Various Treatments for Coronary Dysfunction:

CCBs could vasodilate the smooth muscle of the coronary arteries, allowing for better blood flow and reduced hypertension. Improving coronary blood flow would also result in more oxygen reaching the cardiac muscle. This could relieve the angina caused by narrowed or scarred arteries. Additionally, stenotic arteries mean the heart must pump blood with more force, leading to a greater demand for myocardial oxygen with the excessive workload. Employing CCBs would simultaneously allow more blood oxygen to reach the cardiac muscle while reducing the demand for it. Widening coronary arteries with CCBs would also decrease the risk of vasospasms that suddenly restrict blood flow, which would, in conjunction with lessened myocardial oxygen demands, decrease the risk and rate of myocardial infarctions. Certain CCBs, like amlodipine, have also been shown to increase the production of nitric oxide, which could aid in endothelial recovery and reduce inflammation.[41] If utilized for symptomatic relief with giant CAAs, CCBs must be used with caution, as their vasodilatory nature could stress an already weakened arterial wall– putting the patient at risk of dissection.[42] Beta-blockers, most commonly used with hypertension, prevent hormones from

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binding with β-adrenergic receptors, causing a lessened heart rate and decreased contraction. This results in lowered blood pressure and reduced cardiac oxygen demand with the reduced workload. The period of diastole is lengthened, and coronary perfusion, the delivery of oxygenated blood to the myocardium, improves. Beta-blockers, in a similar vein to CCBs, improve coronary perfusion and reduce oxygen demands, lowering the risk of ischemia, and thus can reduce the risk and severity of myocardial infarctions. Certain third-generation beta-blockers, such as nebivolol and carvedilol, also possess anti-proliferative effects beneficial to the endothelium and smooth muscle.[29] Beta-blockers are incredibly versatile in terms of range, but the majority are ingested at least two times per day. However, if one were employed for long-term post-KD symptom management, the selection would be based on patient history. For those susceptible to coronary vasospasm, non-selective beta-blockers would be a poor choice as beta-2 receptors play a role in vasoconstriction. Selective beta-1 blockers would also be a favorable choice in those with conditions concerning the airway, such as asthma, as non-selective blockers can increase the risk of bronchospasm. Prospective studies that evaluate how beta-blockers impact long-term intellectual development in adolescent and pediatric patients would be highly relevant as well.[43] Often employed for cases of angina, nitrates increase the amount of nitric oxide present, causing smooth muscle to relax, leading to vasodilation within coronary arteries. As both are lessening cardiac contraction, nitrates would have similar advantages to CCBs, improving the amount of nutrient-rich blood directed toward the heart while reducing the demand for it. Spontaneous occurrences of vasospasm with significant consequences, such as ischemia or myocardial infarction, are less likely to occur with nitrates. However, nitrates are employed in selective acute cardiac cases, and not for chronic pediatric use, as the safety data in children is extremely limited. They also ease symptoms of angina that come from a lack of oxygen and associated overworking of the cardiac muscle in an attempt to compensate for the loss. ACE inhibitors reduce blood volume for both afterload and preload, placing less stress on the left ventricle, which could already be facing post-inflammatory strain. The stimulation of nitric oxide by bradykinin would reduce the risk of inflammation and thrombosis, promoting endothelial cell health and elasticity of coronary arteries that are damaged or in proximity to CAAs. Matrix metalloproteinase activity has also been shown to decrease in the presence of ACE inhibitors, which indicates reduced destruction of the arterial walls.[44] Currently, the employment of ACE inhibitors for medium post-KD CAAs (≥4 mm) has not produced definitive results concerning CAA regression, with 67% regression using ACE inhibitors and 65% without. However, in giant CAAs (≥8 mm), regression rates were higher by a factor of 1.6 (36% vs 23%), suggesting a possible path for more severe cases, although further research is needed.[45] Future research could evaluate the potential of a synergistic approach with CCBs and ACE inhibitors, the CCB studies targeting coronary vasoreactivity and potential ischemia, and the ACE inhibitor studies focusing on coronary remodeling, inflammation, and endothelial dysfunction. Comprehensively, CCBs could be employed for symptomatic relief or in conjunction with other therapies involving spastic areas near aneurysms, treating related ischemia. Acting on functional smooth muscle, they'd prevent vasospasm and dilate stenotic coronary arteries. ACE inhibitors have considerable myocardial and vascular protective effects by reducing the risk of remodeling and left ventricular stress. These inhibitors could also improve arterial flexibility and possibly play a role in giant CAA regression. Nitrates are useful for immediate management of symptoms like angina, but utilize less direct mechanisms and are not well-tolerated long-term in pediatric populations– making them a fairly mechanistic hypothetical treatment. Beta-blockers can lower heart rate and myocardial oxygen demand without relying on smooth muscle, making them an appealing long-term option– although supportive, not curative– for blood pressure and myocardial strain reduction if muscle cells are compromised.

Limitations:

Various limitations of this review must be acknowledged. Although information concerning the safety of all included medications for pediatric populations was included, post-KD pharmacological management research is generally limited to adult populations, suggesting data gaps for the unique coronary makeup of children. There is also a lack of long-term, larger-scale studies, as case and small cohort studies are so prevalent, limiting predictions of long-term outcomes on these medications, later complications from them, and the reasonable duration of therapy. Additionally, post-KD patients are incredibly diverse, varying in the exact sizes of aneurysms (even giant CAAs leave room for interpretation), amount of lingering dilation, and degree of coronary impairment, making these analyses difficult to broadly generalize. This review is also dependent on the synthesis of existing literature rather than clinical trials, which makes definitive recommendations difficult. Thus, addressing such limitations is vital to truly exploring long-term pharmaceutical care options for this population and their circumstances.

■ Conclusion

Overall, ACE inhibitors have the most direct relevance to post-KD coronary artery dysfunction, as endothelial dysfunction, lasting inflammation, and abnormal remodeling are common sequelae. ACE inhibitors can target these complications specifically: allowing for endothelial repair by increasing nitric oxide availability, decreasing vascular inflammation by reducing the release of pro-inflammatory cytokines, and preventing remodeling by lessening certain smooth muscle proliferation. CCBs hold potential to aid in the mechanistic management of specific post-KD symptoms, such as coronary vasospasm or proliferative changes in coronary smooth muscle that lead to ischemia. Beta-blockers are another option, especially because they can function with damaged vascular muscle, but are more of a strictly symptomatic approach, focused on reducing oxygen demand and improving general myocardial workload, which reduces ischemic risks. Of the quad, nitrates appear the least significant in terms of long-term KD man-

agement, as they are reliant on undamaged muscle, are easy to develop a tolerance to, and are used quite minimally in pediatric cases. They display strong coronary vasodilation through nitric oxide relaxation, and thus act as a conceptual comparison. Bringing any hypothetical drug into a relatively experimental context, especially one that concerns pediatric patients, is a risk that should not be taken lightly, and the same standard applies to all aforementioned medication classes. Yet, a carefully-monitored dosage and precise selection of ACE inhibitors, which are commonly used in pediatric cases, CCBs, or beta-blockers, may offer various context-dependent benefits, both for the patient and the pattern of treatment for severe long-term CAA-related consequences of KD.

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