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Review Article

Kounis Syndrome: An Updated Narrative Review of Pathophysiology, Clinical Manifestations, and Management

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Abstract

Kounis syndrome is an increasingly recognized clinical entity characterized by the coexistence of acute coronary syndrome and allergic or hypersensitivity reactions. The syndrome represents the interaction between inflammatory pathways activated during allergic responses and the coronary circulation, leading to coronary vasospasm, plaque rupture, or coronary thrombosis. Various mediators released during mast cell activation, including histamine, leukotrienes, tryptase, and platelet-activating factor, play a central role in the pathophysiology by promoting vasoconstriction, endothelial dysfunction, platelet activation, and plaque destabilization. Although the condition has been reported in a wide range of clinical settings, its true incidence remains uncertain because it is frequently underdiagnosed or misinterpreted as either isolated anaphylaxis or conventional acute coronary syndrome. Kounis syndrome may be triggered by numerous allergens, most commonly drugs, insect stings, foods, and contrast media. Three clinical variants have been described depending on the underlying coronary anatomy and mechanism of injury: type I involving coronary vasospasm in patients with normal coronary arteries, type II occurring in individuals with preexisting atherosclerotic disease, and type III associated with coronary stent thrombosis. Clinical presentation is heterogeneous and may include chest pain, electrocardiographic changes, elevated cardiac biomarkers, and signs of systemic allergic reactions. Diagnosis relies on the integration of clinical history, laboratory findings, electrocardiography, and coronary imaging. Management requires simultaneous treatment of the allergic reaction and the acute coronary event, which can create therapeutic challenges. Identification and avoidance of triggering allergens are important for preventing recurrence. Increased awareness among clinicians is essential for early recognition and appropriate management. This review summarizes current knowledge regarding the epidemiology, pathophysiology, clinical manifestations, diagnostic strategies, and treatment approaches of Kounis syndrome.

Key Words: kounis syndrome; allergic acute coronary syndrome; coronary vasospasm; hypersensitivity reactions; mast cell activation

Introduction

Kounis syndrome is defined as the occurrence of acute coronary syndrome in the setting of an allergic, hypersensitivity, anaphylactic, or anaphylactoid reaction. The syndrome represents a complex interaction between inflammatory pathways activated during allergic reactions and the coronary circulation. In this condition, the same mediators responsible for allergic manifestations, such as histamine, tryptase, leukotrienes, and platelet-activating factors, can induce coronary artery vasospasm, promote platelet activation, and trigger plaque destabilization, ultimately leading to myocardial ischemia or infarction (1,2). Because of this pathophysiological overlap, Kounis syndrome is often described as an "allergic acute coronary syndrome," reflecting the coexistence of immunologic and cardiovascular processes.

The syndrome was initially described as allergic angina and allergic myocardial infarction, highlighting the relationship between mast cell activation and coronary vasomotor abnormalities. Over time, accumulating clinical observations expanded the concept to include a broader spectrum of coronary involvement, ranging from transient vasospasm in angiographically normal coronary arteries to plaque rupture and coronary thrombosis in patients with underlying atherosclerotic disease (1,2). This broader conceptualization is important because it demonstrates that allergic inflammation can influence coronary pathology

through multiple mechanisms, including endothelial dysfunction, inflammatory mediator release, and platelet aggregation.

Although Kounis syndrome is increasingly recognized in the cardiology and emergency medicine literature, its true incidence remains uncertain. The condition is widely believed to be underdiagnosed due to the nonspecific nature of its presentation and the difficulty of simultaneously identifying both allergic and cardiac manifestations. Many cases may be misinterpreted as isolated anaphylaxis or conventional acute coronary syndrome, especially when allergic symptoms are mild or transient. Observational studies and systematic reviews suggest that drugs, insect stings, foods, and environmental allergens represent the most commonly reported triggers, with chest pain being the most frequent presenting symptom in affected patients (3,4). However, the diversity of triggers and clinical presentations complicates epidemiological assessment and contributes to the likely underreporting of the syndrome.

From a clinical perspective, Kounis syndrome presents a diagnostic and therapeutic challenge. Physicians are often required to manage two potentially life-threatening conditions simultaneously: myocardial ischemia and an acute allergic reaction. Standard therapies for acute coronary syndrome and anaphylaxis may interact in complex ways, which complicates treatment decisions. For example, drugs commonly used in anaphylaxis may influence coronary tone or myocardial oxygen demand, while certain cardiovascular therapies may interfere with allergic response management (5). Consequently, early recognition of the syndrome is crucial to guide appropriate therapeutic strategies and to prevent complications.

Beyond its immediate clinical implications, Kounis syndrome also represents an important pathophysiological model illustrating the relationship between inflammation and coronary artery disease. Increasing evidence suggests that mast cell activation and inflammatory mediator release may contribute to plaque destabilization and coronary events even outside the context of classical allergic reactions. In this regard, Kounis syndrome provides a unique framework for understanding how immunologic mechanisms can influence coronary vascular pathology. As awareness of the syndrome grows, improved recognition and reporting may help clarify its true incidence and clinical significance (1,2).

A structured literature search was performed to identify relevant studies on Kounis syndrome. Electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and Embase were searched for articles published until 2026. The search strategy used combinations of the following keywords and Medical Subject Headings: “Kounis syndrome”, “allergic angina”, “allergic myocardial infarction”, “allergic acute coronary syndrome”, “mast cell activation”, “anaphylaxis”, “coronary vasospasm”, and “hypersensitivity reactions”. Titles and abstracts were screened for relevance, followed by full-text evaluation of potentially eligible studies. Original articles, observational studies, systematic reviews, and clinically relevant case series focusing on the epidemiology, mechanisms, diagnosis, and management of Kounis syndrome were included. Reference lists of selected articles were also reviewed to identify additional relevant publications.

This narrative review aims to summarize the current understanding of Kounis syndrome, including its epidemiology, underlying mechanisms, clinical manifestations, diagnostic approaches, and management strategies. By integrating available clinical and experimental data, the review seeks to highlight key aspects of this complex syndrome and emphasize the importance of considering allergic mechanisms in the differential diagnosis of acute coronary events.

2. Epidemiology and Incidence

The true epidemiology of Kounis syndrome remains difficult to determine because the condition is widely believed to be underrecognized and underreported in routine clinical practice. Most available data originate from case reports, case series, and small observational studies rather than large prospective cohorts. Consequently, the real prevalence is likely higher than reported in the literature. The syndrome may occur across a broad age range and has been described in both sexes, although some reports suggest a slightly higher prevalence in middle-aged men, which may reflect the higher baseline prevalence of coronary artery disease in this population (6,7).

Several clinical registries and observational studies have attempted to estimate the frequency of Kounis syndrome in patients presenting with allergic reactions or acute coronary events. In emergency department settings, the coexistence of allergic reactions with myocardial ischemia appears to be uncommon but not negligible. Some analyses have suggested that a small proportion of patients presenting with anaphylaxis may develop electrocardiographic changes or biochemical evidence of myocardial injury, findings that are consistent with the spectrum of Kounis syndrome (6,8). However, these events may not always be recognized as part of the same pathophysiological entity, which contributes to the likely underestimation of the syndrome.

The diversity of triggers further complicates epidemiological assessment. Drugs are among the most frequently reported causes and include antibiotics, nonsteroidal anti-inflammatory drugs, anesthetic agents, and radiographic contrast media. In addition, food allergens and insect stings have been repeatedly documented as precipitating factors. Because these exposures are common in medical and community settings, clinicians may encounter Kounis syndrome in a variety of clinical contexts including emergency medicine, cardiology, anesthesiology, and interventional procedures (7–9).

Another important aspect influencing epidemiological data is the heterogeneous clinical presentation of the syndrome. In some patients, allergic symptoms dominate the clinical picture and cardiac manifestations may be subtle or transient. In others, the presentation resembles classical acute coronary syndrome, and the allergic component may be overlooked or considered incidental. This variability in clinical expression likely contributes to diagnostic delays and incomplete recognition of the condition in large clinical datasets (6,8).

In recent years, increasing awareness among cardiologists and allergists has led to a growing number of published cases and reviews describing the syndrome. Nevertheless, the absence of standardized diagnostic criteria and prospective epidemiological studies continues to limit precise estimates of its incidence and prevalence. Improved recognition and systematic reporting are therefore essential to better understand the epidemiological burden of Kounis syndrome and its impact on cardiovascular outcomes.

3. Pathophysiology

The pathophysiology of Kounis syndrome is primarily driven by the activation and degranulation of mast cells during an allergic or hypersensitivity reaction. Mast cells are abundant in the heart and in the adventitia of coronary arteries, where they play a central role in inflammatory and immune responses. When activated by immunoglobulin E–mediated or non–immunoglobulin E–mediated mechanisms, these cells release a wide range of vasoactive and proinflammatory mediators that can directly affect coronary vascular tone and myocardial perfusion (10,11).

Among the most important mediators released during mast cell activation are histamine, tryptase, chymase, leukotrienes, prostaglandins, thromboxane, and platelet-activating factor. These substances exert multiple effects on the coronary circulation. Histamine and leukotrienes can induce intense coronary vasoconstriction, while platelet-activating factor promotes platelet aggregation and thrombus formation. In addition, proteolytic enzymes such

as tryptase and chymase can activate matrix metalloproteinases, which may weaken the fibrous cap of atherosclerotic plaques and promote plaque rupture (10–12). The combined effects of vasospasm, platelet activation, and plaque destabilization create a pathophysiological environment that may lead to myocardial ischemia or infarction.

Inflammatory cells other than mast cells also contribute to the pathogenesis of the syndrome. Eosinophils, macrophages, and T lymphocytes may be recruited to the site of allergic inflammation and further amplify the inflammatory cascade. Eosinophils release cytotoxic proteins and inflammatory mediators that can damage endothelial cells and promote vascular dysfunction. This process enhances endothelial permeability and facilitates the interaction between circulating platelets and the vascular wall, increasing the likelihood of thrombus formation within the coronary arteries (11,13).

Another important mechanism involves the interaction between allergic mediators and the endothelium. Endothelial dysfunction plays a key role in the development of coronary vasospasm and thrombosis. During allergic reactions, inflammatory mediators impair endothelial nitric oxide production and increase oxidative stress within the vascular wall. These changes reduce the normal vasodilatory capacity of coronary arteries and favor vasoconstriction, platelet activation, and thrombogenesis. In patients with underlying atherosclerosis, these processes may accelerate plaque instability and precipitate an acute coronary event (10,12).

Experimental and clinical observations have demonstrated that mast cells are frequently located in close proximity to coronary atherosclerotic plaques. Their activation may therefore directly influence plaque behavior. Studies have shown that mast cell–derived enzymes can degrade extracellular matrix components within the fibrous cap of plaques, promoting structural weakening and increasing the risk of rupture. This mechanism provides a biological explanation for the occurrence of myocardial infarction during severe allergic reactions in patients with pre-existing coronary artery disease (11–13).

Taken together, these mechanisms illustrate that Kounis syndrome represents a complex interaction between allergic inflammation and coronary artery pathology. The syndrome cannot be explained by a single pathway but rather results from the combined effects of vasospasm, inflammatory mediator release, platelet activation, endothelial dysfunction, and plaque destabilization. Understanding these mechanisms is important because it provides insight into the clinical diversity of the syndrome and helps explain why allergic reactions may occasionally culminate in severe coronary events.

4. Triggers and Etiological Factors

Kounis syndrome may be precipitated by a wide variety of allergens and hypersensitivity-inducing agents. These triggers initiate mast cell activation and the subsequent release of inflammatory mediators that affect the coronary circulation. Reported precipitating factors include drugs, environmental allergens, insect stings, foods, and several medical interventions. Because allergic reactions can occur in many clinical settings, the syndrome has been described in emergency departments, intensive care units, operating rooms, and catheterization laboratories (14,15). The wide range of allergens capable of triggering this syndrome highlights the heterogeneous etiological background of Kounis syndrome. The most frequently reported triggers described in the literature are summarized in Table 1.

Category	Examples	Clinical Context
Drugs	Antibiotics (beta-lactams, vancomycin), NSAIDs, anesthetic agents, analgesics	Drug hypersensitivity reactions in emergency or perioperative settings
Contrast agents	Iodinated radiographic contrast media	Coronary angiography, CT imaging
Insect venom	Bee, wasp, hornet stings	Community exposure or outdoor activities
Foods	Shellfish, nuts, fish, fruits	Food-induced allergic reactions
Environmental allergens	Latex, pollen, animal dander	Medical procedures or environmental exposure
Medical materials	Coronary stents, polymer coatings, metal components (nickel, chromium)	Interventional cardiology procedures

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; CT: computed tomography.

Table 1: Major Triggers of Kounis Syndrome Reported in the Literature

Pharmacologic agents represent the most frequently reported triggers of Kounis syndrome. Numerous medications have been implicated, including antibiotics such as beta-lactams and vancomycin, nonsteroidal anti-inflammatory drugs, analgesics, anesthetic agents, and radiographic contrast media. In many of these cases, the allergic reaction occurs shortly after drug exposure and is accompanied by symptoms such as urticaria, hypotension, bronchospasm, or angioedema together with signs of myocardial ischemia. Contrast agents used during diagnostic imaging and coronary angiography are particularly relevant in cardiology practice because they may provoke hypersensitivity reactions capable of triggering coronary vasospasm or thrombosis (14–16).

Insect stings are another well-recognized cause of Kounis syndrome. Hymenoptera stings from bees, wasps, and hornets have been repeatedly associated with acute coronary events following severe allergic reactions. Venom components may activate mast cells and stimulate the release of vasoactive mediators that induce coronary vasospasm and platelet aggregation. In some reported cases, myocardial infarction has developed shortly after the sting in patients without previously known coronary artery disease, suggesting that allergic mediator–induced vasospasm alone may be sufficient to provoke ischemia (15,17).

Food allergens have also been described as potential triggers of the syndrome, although they appear less frequently than drug-related reactions. Foods such as shellfish, fish, nuts, fruits, and other allergenic products may provoke systemic allergic responses that subsequently involve the coronary circulation. In these situations, the clinical picture often begins with typical allergic manifestations followed by chest pain and electrocardiographic changes compatible with myocardial ischemia (14,18).

Environmental exposures represent another category of potential etiological factors. Latex, pollen, animal dander, and other environmental allergens have occasionally been associated with coronary manifestations during hypersensitivity reactions. In addition, medical devices and materials used in interventional procedures may induce allergic responses. Components of coronary stents, including metals such as nickel or chromium as well as polymer coatings and drug-eluting compounds, have been implicated in hypersensitivity reactions that may contribute to stent thrombosis in susceptible individuals (16,19).

The wide range of triggers highlights the heterogeneous nature of Kounis syndrome and underscores the importance of obtaining a detailed clinical history when evaluating patients presenting with acute coronary symptoms in the context of an allergic reaction. Identification of the causative allergen is clinically relevant because avoidance of the triggering agent is an important component of preventing recurrence.

5. Classification of Kounis Syndrome

Kounis syndrome has been categorized into three main variants based on the underlying coronary anatomy and the pathophysiological mechanisms involved. This classification helps clinicians understand the different clinical scenarios in which allergic reactions can precipitate myocardial ischemia and guides appropriate management strategies. The classification was developed following the accumulation of clinical observations demonstrating that allergic reactions may affect both normal and diseased coronary arteries as well as coronary stents (11,20).

Type I Kounis syndrome occurs in patients with angiographically normal coronary arteries and without preexisting coronary artery disease. In this variant, the release of inflammatory mediators during an allergic reaction leads primarily to coronary artery vasospasm. Histamine, leukotrienes, and platelet-activating factor cause intense vasoconstriction of the coronary vessels, which may result in transient myocardial ischemia. Cardiac biomarkers may remain normal in some patients if the ischemia is brief, although myocardial infarction can occur if vasospasm is prolonged. Coronary angiography in these cases often reveals normal vessels once the vasospasm resolves (20,21).

Type II Kounis syndrome occurs in patients with underlying atherosclerotic coronary artery disease. In this situation, the inflammatory mediators released during an allergic reaction can induce plaque erosion or rupture in addition to causing coronary vasospasm. The combination of vasoconstriction, platelet activation, and plaque destabilization may lead to the formation of an intracoronary thrombus and the development of an acute myocardial infarction. This variant therefore resembles a conventional acute coronary syndrome but is triggered by an allergic inflammatory cascade (11,22).

Type III Kounis syndrome involves patients with coronary stents. In this variant, allergic reactions may provoke stent thrombosis through hypersensitivity mechanisms directed against stent components, including metal alloys, polymer coatings, or the drugs used in drug-eluting stents. Histological examination of aspirated thrombus material in some reported cases has demonstrated infiltration with eosinophils and mast cells, supporting the role of allergic inflammation in the pathogenesis of this form of the syndrome. Both early and late stent thrombosis have been described in association with hypersensitivity reactions (20,23).

This classification underscores that Kounis syndrome is not limited to coronary vasospasm but encompasses a spectrum of mechanisms linking allergic inflammation with coronary artery pathology. Recognition of these variants is clinically important because the therapeutic approach may differ depending on whether the patient has normal coronary arteries, underlying atherosclerotic disease, or a coronary stent. Understanding the classification also highlights the diverse ways in which allergic reactions can influence coronary physiology and precipitate acute cardiovascular events. The clinical variants of Kounis syndrome and their main pathophysiological characteristics are summarized in Table 2.

Type	Coronary Anatomy	Pathophysiological Mechanism	Clinical Features
Type I	Normal coronary arteries	Allergic mediator–induced coronary vasospasm	Transient ischemia, possible normal cardiac biomarkers
Type II	Pre-existing atherosclerotic disease	Plaque rupture or erosion triggered by inflammatory mediators	Acute myocardial infarction with elevated cardiac biomarkers
Type III	Coronary stent present	Hypersensitivity reaction leading to stent thrombosis	Acute stent thrombosis with myocardial ischemia

Abbreviations: MI: myocardial infarction.

Table 2: Classification and Main Characteristics of Kounis Syndrome

6. Clinical Presentation

The clinical presentation of Kounis syndrome is heterogeneous and reflects the simultaneous occurrence of allergic reactions and acute coronary events. Patients may present with symptoms characteristic of myocardial ischemia together with manifestations of hypersensitivity. The most commonly reported symptom is chest pain, which may resemble classical angina or acute myocardial infarction. This symptom often appears shortly after exposure to the triggering allergen and may be accompanied by typical allergic manifestations such as urticaria, flushing, pruritus, dyspnea, bronchospasm, angioedema, or hypotension (7,24).

The temporal relationship between allergen exposure and the onset of cardiac symptoms is an important diagnostic clue. In many cases, chest discomfort develops within minutes to hours after exposure to the precipitating factor, particularly in drug-induced reactions or insect stings. However, the sequence of symptoms may vary. In some patients, allergic manifestations dominate the early clinical picture and myocardial ischemia becomes evident later, whereas in others, chest pain may be the first symptom that leads to medical evaluation (7,25).

Electrocardiographic findings in Kounis syndrome are variable and depend on the underlying coronary mechanism. ST-segment elevation, ST-segment depression, and T-wave abnormalities have all been reported. These changes may be transient in cases dominated by coronary vasospasm, but persistent alterations may occur when plaque rupture or coronary thrombosis develops. In some patients, arrhythmias such as atrial fibrillation, ventricular tachycardia, or atrioventricular conduction disturbances may also occur during the acute event (24,26).

Cardiac biomarkers frequently demonstrate evidence of myocardial injury, particularly in patients with prolonged ischemia or myocardial infarction. Elevated troponin levels are commonly observed in type II and type III variants of the syndrome. In contrast, patients with transient vasospasm may show minimal or no biomarker elevation if ischemia resolves rapidly. Laboratory findings related to allergic activation, such as increased serum tryptase or immunoglobulin E levels, may also support the diagnosis when measured during the acute phase (25,27).

The severity of clinical presentation ranges from mild allergic symptoms associated with transient chest discomfort to life-threatening conditions such as cardiogenic shock, malignant arrhythmias, or severe anaphylaxis. Hypotension may occur as a result of systemic vasodilation during anaphylaxis or secondary to myocardial dysfunction caused by ischemia. In rare cases, cardiac arrest has been reported during severe allergic reactions involving the coronary circulation (24,26).

Because the clinical manifestations overlap with both anaphylaxis and conventional acute coronary syndrome, Kounis syndrome may remain unrecognized during the initial evaluation. A careful clinical history focusing on recent allergen exposure and the simultaneous presence of allergic symptoms is therefore essential. Recognition of this association allows clinicians to consider Kounis syndrome in the differential diagnosis of acute coronary events occurring in the context of hypersensitivity reactions.

7. Diagnostic Approach

The diagnosis of Kounis syndrome relies primarily on clinical suspicion supported by laboratory and imaging findings. Because the syndrome represents the coexistence of an acute allergic reaction and myocardial ischemia, recognition requires careful evaluation of both components. The presence of chest pain or electrocardiographic abnormalities occurring in temporal association with allergic manifestations should raise suspicion for this condition. A detailed history regarding recent exposure to potential allergens such as medications, contrast agents, foods, or insect stings is essential in establishing the diagnosis (3,14).

Electrocardiography is usually the first diagnostic test performed in patients presenting with chest pain. Electrocardiographic findings in Kounis syndrome are variable and may include ST-segment elevation, ST-segment depression, or nonspecific T-wave changes depending on the underlying coronary mechanism. In cases dominated by coronary vasospasm, these changes may be transient and resolve after treatment of the allergic reaction. However, persistent abnormalities may be observed when plaque rupture or coronary thrombosis occurs (3,28).

Measurement of cardiac biomarkers plays an important role in confirming myocardial injury. Elevated troponin levels indicate myocardial necrosis and are commonly detected in patients with type II and type III variants of Kounis syndrome. In contrast, patients with transient coronary vasospasm may show minimal or no elevation in cardiac biomarkers if ischemia resolves rapidly. Serial measurement of troponin is therefore recommended in patients with suspected myocardial involvement during allergic reactions (14,29).

Laboratory markers related to allergic activation may also assist in the diagnostic evaluation. Serum tryptase is considered one of the most useful biomarkers of mast cell activation and may be elevated during acute allergic reactions. Measurement of tryptase levels within the first few hours after symptom onset may provide evidence supporting the presence of an allergic mechanism. Elevated immunoglobulin E levels and eosinophilia may also be observed, although these findings are less specific (3,30).

Coronary angiography remains the definitive diagnostic modality for evaluating coronary anatomy in patients with suspected Kounis syndrome presenting with features of acute coronary syndrome. Angiographic findings may vary depending on the type of the syndrome. Patients with type I variant may demonstrate transient coronary vasospasm without significant atherosclerotic lesions, whereas those with type II variant often show evidence of plaque rupture or thrombosis. In type III variant, angiography may reveal coronary stent thrombosis. In selected cases, intravascular imaging techniques such as intravascular ultrasound or optical coherence tomography can provide additional information regarding plaque morphology and thrombus formation (14,31).

Because the syndrome can mimic several cardiovascular conditions, a comprehensive diagnostic approach is required. Integration of clinical history, electrocardiographic findings, biomarker evaluation, and coronary imaging allows clinicians to distinguish Kounis syndrome from other causes of myocardial ischemia. Early identification is clinically important because it influences therapeutic decisions and highlights the need to address both the allergic and cardiovascular components of the condition. The key diagnostic tools and therapeutic considerations in patients with suspected Kounis syndrome are summarized in Table 3.

Domain	Key Components	Clinical Role
Clinical evaluation	History of allergen exposure, allergic manifestations, chest pain	Establish temporal association between allergy and cardiac symptoms
Laboratory tests	Troponin, serum tryptase, IgE levels	Detection of myocardial injury and mast cell activation
Electrocardiography	ST-segment elevation or depression, T-wave abnormalities	Identification of myocardial ischemia
Coronary imaging	Coronary angiography, IVUS, OCT	Assessment of vasospasm, plaque rupture, or stent thrombosis
Medical treatment	Antihistamines, corticosteroids, nitrates, calcium channel blockers	Control of allergic reaction and coronary vasospasm
ACS therapy	Antiplatelet agents, anticoagulation, PCI when indicated	Management of myocardial infarction or coronary thrombosis

Abbreviations: IgE: immunoglobulin E; IVUS: intravascular ultrasound; OCT: optical coherence tomography; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention.

Table 3. Diagnostic and Therapeutic Approach in Kounis Syndrome

8. Differential Diagnosis

The differential diagnosis of Kounis syndrome includes several cardiovascular and non-cardiovascular conditions that may present with chest pain, electrocardiographic abnormalities, or myocardial injury during systemic inflammatory or stress responses. Because the syndrome combines features of acute coronary syndrome and allergic reactions, distinguishing it from other causes of myocardial ischemia requires careful evaluation of clinical history, laboratory findings, and imaging results. Recognition of concurrent allergic manifestations remains a key element in differentiating Kounis syndrome from other cardiac conditions (32,33).

Vasospastic angina, also known as Prinzmetal angina, represents one of the most important differential diagnoses. This condition is characterized by transient coronary vasospasm leading to episodic chest pain and reversible ST-segment elevation. Although the mechanism involves coronary vasoconstriction similar to type I Kounis syndrome, vasospastic angina typically occurs without an accompanying allergic reaction or systemic inflammatory response. The absence of hypersensitivity symptoms such as urticaria, bronchospasm, or hypotension can therefore help distinguish classic vasospastic angina from allergic coronary vasospasm (32,34).

Takotsubo cardiomyopathy should also be considered in patients presenting with acute chest pain and electrocardiographic changes after severe emotional or physical stress. This condition is characterized by transient left ventricular systolic dysfunction that often mimics acute myocardial infarction but occurs in the absence of obstructive coronary artery disease. Although stress-related catecholamine surges are considered the primary mechanism, allergic reactions may occasionally act as triggering stressors. Imaging studies demonstrating characteristic patterns of left ventricular wall motion abnormalities can help differentiate Takotsubo cardiomyopathy from Kounis syndrome (33,35).

Acute myocarditis represents another condition that may resemble Kounis syndrome. Myocarditis can present with chest pain, elevated cardiac biomarkers, and electrocardiographic abnormalities similar to acute coronary syndrome. However, myocarditis is typically associated with viral infections or autoimmune inflammation rather than allergic

hypersensitivity. Cardiac magnetic resonance imaging may help identify myocardial inflammation and edema, which support the diagnosis of myocarditis rather than coronary ischemia (32,36).

Hypersensitivity myocarditis should also be considered in the differential diagnosis. This condition is often drug-induced and involves eosinophilic infiltration of the myocardium. Although hypersensitivity myocarditis is also associated with allergic reactions, the primary pathology occurs within the myocardial tissue rather than the coronary arteries. Endomyocardial biopsy may demonstrate eosinophilic inflammation and confirm the diagnosis in selected cases (32,37).

Because these conditions share overlapping clinical features, accurate diagnosis requires integration of clinical presentation, allergic history, laboratory markers, and imaging findings. Identifying the temporal relationship between allergen exposure and cardiac symptoms remains particularly important. Careful consideration of alternative diagnoses ensures appropriate management and helps avoid misclassification of Kounis syndrome as another form of myocardial injury.

9. Management Strategies

The management of Kounis syndrome is based on a central principle: both the allergic reaction and the acute coronary event must be treated simultaneously. This dual therapeutic requirement is what makes the syndrome clinically difficult. In contrast to conventional acute coronary syndrome or isolated anaphylaxis, treatment decisions in Kounis syndrome must account for the possibility that drugs beneficial for one component may aggravate the other. Current evidence is derived mainly from reviews, case series, and case reports rather than randomized studies, so treatment is largely individualized according to the clinical presentation and the suspected variant of the syndrome (38–40).

In patients with type I Kounis syndrome, where coronary vasospasm predominates in the absence of underlying obstructive coronary disease, treatment is generally directed toward controlling the allergic reaction and relieving vasospasm. Corticosteroids and H1 and H2 antihistamines are commonly used to suppress the hypersensitivity response, while nitrates and calcium channel blockers may help reverse coronary spasm when blood pressure is adequate. In this setting, vasospasm may resolve once the allergic cascade is controlled. Care is required in hypotensive patients, because vasodilator therapy may worsen hemodynamic instability (38–40).

In type II Kounis syndrome, management must also address plaque disruption or thrombotic acute coronary syndrome superimposed on allergic activation. These patients are usually treated according to standard acute coronary syndrome principles, including antiplatelet therapy, anticoagulation, and coronary angiography when indicated, while also receiving anti-allergic treatment. In type III Kounis syndrome, urgent management of stent thrombosis becomes the priority, usually with immediate coronary intervention and standard antithrombotic therapy, alongside treatment of the allergic reaction. This approach reflects the fact that allergic inflammation may trigger a true coronary occlusive event rather than isolated vasospasm (38–40).

The most controversial aspect of treatment is the use of epinephrine in patients with anaphylaxis and suspected myocardial ischemia. Epinephrine remains the first-line and life-saving therapy for anaphylaxis, but in Kounis syndrome it may theoretically aggravate coronary vasospasm, increase myocardial oxygen demand, and worsen ischemia. Published case reports and reviews describe rare episodes of myocardial ischemia after therapeutic epinephrine administration, which is why close monitoring is necessary in patients with chest pain, electrocardiographic changes, or known coronary disease. This does not mean that epinephrine is contraindicated in true anaphylaxis, but it should be administered with caution and with awareness of the potential cardiac consequences (38,41,42).

Additional practical concerns have also been emphasized in the literature. Morphine may promote histamine release and is therefore generally avoided when possible in this setting. Beta-blockers may complicate the treatment of anaphylaxis by reducing responsiveness to epinephrine and may leave alpha-adrenergic vasoconstriction unopposed. For these reasons, management should be individualized according to hemodynamic status, severity of allergic manifestations, electrocardiographic findings, and the presence or absence of obstructive coronary disease. Overall, early recognition of the syndrome is critical because timely, balanced treatment may prevent progression to extensive myocardial injury, cardiogenic shock, or fatal arrhythmias (38–40).

10. Special Clinical Situations

Kounis syndrome has been reported in several specific clinical contexts where exposure to allergens or hypersensitivity-inducing agents is common. These situations include diagnostic and interventional cardiology procedures, perioperative drug administration, and exposure to medical devices. Recognition of these clinical settings is important because allergic reactions occurring in these environments may rapidly evolve into coronary events and may initially be misinterpreted as procedure-related complications.

One of the most frequently reported scenarios is contrast-induced Kounis syndrome during diagnostic angiography or percutaneous coronary intervention. Radiographic contrast media are well known triggers of hypersensitivity reactions and may induce mast cell activation and release of inflammatory mediators. In susceptible individuals this cascade may provoke coronary vasospasm or even plaque rupture, leading to acute myocardial ischemia during or shortly after the procedure (43,44). In such cases the temporal relationship between contrast administration and the onset of chest pain or electrocardiographic changes is a critical diagnostic clue.

Drug-related Kounis syndrome is also commonly observed in perioperative and emergency medicine settings. Antibiotics, anesthetic agents, analgesics, and anti-inflammatory medications have all been implicated as triggers. Because these medications are frequently administered in hospitalized patients, allergic reactions may occur in individuals with underlying cardiovascular risk factors. The resulting inflammatory response may therefore precipitate myocardial ischemia through vasospasm, thrombosis, or plaque destabilization. Careful documentation of drug exposure and allergic history is essential for identifying the causative agent and preventing recurrence (44,45).

Another clinically important setting involves coronary stent implantation. Hypersensitivity reactions to stent components such as metal alloys, polymer coatings, or drug-eluting compounds have been associated with coronary stent thrombosis. In these cases, inflammatory cell infiltration including eosinophils and mast cells has been identified within thrombotic material aspirated during coronary intervention. These findings support the hypothesis that allergic inflammation may contribute to both early and late stent thrombosis in susceptible patients (19,46).

Kounis syndrome has also been described in association with environmental exposures and occupational allergens, although these cases appear less frequently in the literature. Latex exposure during medical procedures, insect venom, and other environmental allergens may provoke systemic hypersensitivity reactions capable of affecting coronary circulation. In some individuals the cardiovascular manifestations may dominate the clinical picture, making recognition of the allergic trigger more difficult.

These special clinical situations emphasize that Kounis syndrome may occur in diverse healthcare settings and may involve a wide spectrum of triggers. Awareness of these contexts can facilitate early recognition of the syndrome and prompt initiation of appropriate treatment strategies aimed at controlling both the allergic reaction and the associated coronary event.

11. Prognosis and Outcomes

The prognosis of Kounis syndrome varies widely depending on the severity of the allergic reaction, the extent of coronary involvement, and the presence of underlying cardiovascular disease. In many reported cases, particularly those involving transient coronary vasospasm without structural coronary artery disease, the clinical course is favorable once the allergic reaction is treated and coronary perfusion is restored. However, in patients with preexisting atherosclerosis or coronary stents, the syndrome may result in myocardial infarction, arrhythmias, or hemodynamic instability, which significantly influences short-term outcomes (47,48).

Short-term prognosis is closely related to the type of Kounis syndrome and the promptness of diagnosis and treatment. Patients with type I variant generally experience reversible coronary vasospasm and may recover completely without permanent myocardial damage if treatment is initiated early. In contrast, type II and type III variants may involve plaque rupture, intracoronary thrombosis, or stent thrombosis, which are associated with higher rates of myocardial injury and potential complications such as heart failure or malignant arrhythmias (47,49).

The severity of the allergic reaction also plays an important role in determining clinical outcomes. Severe systemic reactions such as anaphylaxis may lead to profound hypotension, reduced coronary perfusion, and cardiogenic shock. These hemodynamic disturbances can exacerbate myocardial ischemia and worsen cardiac outcomes. In rare cases, cardiac arrest has been reported during severe allergic reactions involving the coronary circulation, emphasizing the potential life-threatening nature of the syndrome (48,50).

Long-term outcomes are less well characterized because most published data are derived from isolated case reports or small case series with limited follow-up. Nevertheless, recurrence of Kounis syndrome has been documented in some patients who were re-exposed to the same allergen or a cross-reactive agent. This highlights the importance of identifying the causative trigger and implementing preventive strategies to avoid future exposure (47,49).

Another important consideration is the potential relationship between allergic inflammation and atherosclerotic disease progression. Experimental and clinical evidence suggests that mast cell activation and inflammatory mediator release may contribute to endothelial dysfunction and plaque instability. Therefore, recurrent allergic reactions could theoretically influence the long-term course of coronary artery disease, although this relationship remains an area of ongoing investigation (48,50).

Overall, the prognosis of Kounis syndrome is generally favorable when the condition is recognized early and treated appropriately. Nevertheless, the syndrome may lead to serious complications when coronary thrombosis, severe anaphylaxis, or delayed diagnosis occurs. Increased awareness among clinicians and careful identification of triggering allergens remain key factors in improving patient outcomes.

12. Prevention Strategies

Prevention of Kounis syndrome primarily focuses on the identification and avoidance of triggering allergens. Because the syndrome develops in the context of hypersensitivity reactions, careful evaluation of the patient's allergy history is an essential component of preventive care. Patients with previously documented allergic reactions to drugs, foods, insect venom, or medical materials should be carefully assessed before exposure to potential triggers, particularly in clinical settings where medications or contrast agents are frequently administered (7,30).

In patients undergoing diagnostic or interventional procedures, special attention should be given to known allergies to radiographic contrast media or medications commonly used during cardiovascular interventions. Premedication protocols including antihistamines and corticosteroids have been used in selected high-risk patients with a history of contrast reactions, although these strategies may not completely eliminate the risk of hypersensitivity. Careful monitoring during and after contrast administration remains important, especially in individuals with previous allergic events (30,51).

Drug hypersensitivity is another major contributor to the development of Kounis syndrome. Antibiotics, nonsteroidal anti-inflammatory drugs, and anesthetic agents have frequently been implicated as triggers. For patients with documented drug allergies, alternative medications should be selected whenever possible. Detailed documentation of allergic reactions in medical records is important to prevent accidental re-exposure, which has been reported as a cause of recurrent episodes of the syndrome (3,7).

Patients who have experienced Kounis syndrome should also receive counseling regarding avoidance of the identified trigger. In cases related to insect venom or environmental allergens, referral to an allergy specialist may be appropriate for further evaluation and consideration of immunotherapy. Education about recognizing early symptoms of allergic reactions may allow patients to seek medical care promptly if similar events occur in the future (3,30).

In addition to allergen avoidance, optimization of cardiovascular risk factors may contribute to reducing the severity of potential coronary complications. Control of hypertension, dyslipidemia, diabetes mellitus, and smoking cessation are standard measures for preventing coronary artery disease progression and may reduce the likelihood that allergic inflammation will precipitate plaque instability or thrombosis (7,51).

Although no standardized preventive guidelines exist specifically for Kounis syndrome, awareness of the condition among clinicians plays a critical role in reducing recurrence and improving patient safety. Early recognition of hypersensitivity reactions, careful selection of medications, and thorough documentation of allergic history remain the most practical strategies for preventing future episodes.

13. Future Perspectives

Despite increasing recognition of Kounis syndrome over the past two decades, many aspects of the condition remain incompletely understood. One of the major limitations in the current literature is the lack of large prospective studies. Most available data derive from case reports and small observational series, which limits the ability to accurately estimate the true incidence of the syndrome and to define standardized diagnostic and therapeutic approaches. Establishing multicenter registries may help clarify the epidemiological characteristics and clinical outcomes associated with this condition (6,7).

Another important area for future research involves the development of more specific diagnostic criteria. At present, the diagnosis is largely based on clinical suspicion and the temporal association between allergic reactions and acute coronary events. Although biomarkers such as serum tryptase, immunoglobulin E levels, and cardiac troponins can provide supportive evidence, no single laboratory test can definitively confirm the diagnosis. Future studies exploring additional biomarkers of mast cell activation and vascular inflammation may improve diagnostic accuracy and facilitate earlier recognition of the syndrome (6,52).

Advances in cardiovascular imaging may also contribute to a better understanding of the mechanisms involved in Kounis syndrome. Intravascular imaging modalities such as optical coherence tomography and intravascular ultrasound have already demonstrated their value in identifying plaque rupture, thrombus formation, and coronary vasospasm. Further application of these techniques may provide insights into how allergic inflammation influences coronary plaque stability and vascular function (7,53).

The relationship between allergic inflammation and atherosclerosis is another important research direction. Experimental studies have suggested that mast cells and other inflammatory cells may play a role in

plaque development and destabilization. Understanding the molecular pathways linking hypersensitivity reactions with coronary artery disease may help identify novel therapeutic targets that could prevent coronary complications in susceptible individuals (6,52).

Finally, greater awareness among clinicians remains essential for improving recognition and management of Kounis syndrome. Educational initiatives aimed at cardiologists, allergists, emergency physicians, and anesthesiologists may help ensure that the syndrome is considered in the differential diagnosis of acute coronary events occurring in the context of allergic reactions. Improved awareness, combined with systematic research efforts, will likely enhance the understanding of this complex interaction between immunology and cardiovascular disease.

14. Conclusion

Kounis syndrome represents a unique clinical entity in which allergic or hypersensitivity reactions trigger acute coronary events through complex inflammatory mechanisms. The syndrome illustrates the close interaction between immunologic activation and the coronary circulation, demonstrating how the release of mediators from mast cells and other inflammatory cells can provoke coronary vasospasm, plaque destabilization, or intracoronary thrombosis. Although awareness of the condition has increased in recent years, it remains underrecognized in clinical practice because its presentation often overlaps with both classical acute coronary syndrome and systemic allergic reactions.

The clinical manifestations of Kounis syndrome are heterogeneous and may range from transient coronary vasospasm with minimal myocardial injury to severe myocardial infarction or stent thrombosis accompanied by systemic anaphylaxis. Early recognition of the syndrome requires careful attention to the temporal relationship between allergen exposure and cardiac symptoms. Identification of allergic manifestations occurring simultaneously with myocardial ischemia is a key element in establishing the diagnosis and differentiating the syndrome from other cardiovascular conditions.

Management of Kounis syndrome requires a balanced therapeutic approach that addresses both the allergic reaction and the coronary event. Treatment strategies must be individualized according to the clinical presentation, underlying coronary anatomy, and severity of the hypersensitivity response. In addition, identification and avoidance of the triggering allergen are essential components of long-term management in order to prevent recurrence.

Increasing awareness among clinicians is essential to improve recognition and appropriate treatment of this condition. Greater attention to allergic mechanisms in patients presenting with acute coronary symptoms may help identify cases that would otherwise remain unrecognized. Further research focusing on the epidemiology, pathophysiology, and optimal management of Kounis syndrome will be necessary to clarify its true clinical significance and to guide evidence-based therapeutic strategies.

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