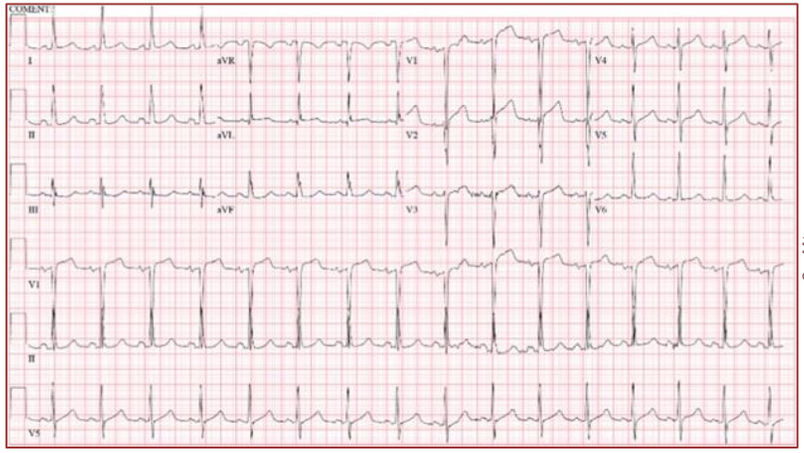
Kounis Syndrome

It is not a rare condition – it is a rarely recognized condition.

https://metro.co.uk/2020/05/16/child-hit-new-coronavirus-linked-disease-was-sick-heart-barely-squeeze-12714793/



ST elevations in leads V1 to V3.

Cesarz T, Ganti L. Kounis syndrome: ST elevations in the setting of anaphylaxis. J Allergy Clin Immunol Glob. 2023;2(4):100152. Published 2023 Jul 24. doi:10.1016/j.jacig.2023.100152

Acute Coronary Syndromes Triggered by Mast Cell Degranulation

Review and Update for Prehospital and Emergency Department Management

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LEARNING OBJECTIVES

1. Define Kounis Syndrome and its variants (Types I-IV).
2. Identify the five distinct pathways that trigger mast cell activation and coronary events, and the sixth direct path to KS.
3. Recognize the signs and symptoms in the field (prehospital) and in the ED
4. Recognize the need for better communications of observations of potential triggers by Prehospital to ED staff
5. Understand why management of an allergic coronary syndrome differs from a standard ACS — and how it differs by trigger mechanism.
6. Apply type-specific and trigger-specific treatment principles
7. Counsel recovered patients on prevention.

Disclosure

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HISTORICAL MILESTONES

The concept of allergic angina — coronary spasm caused by endothelial dysfunction or microvascular angina leading to allergic acute MI — was described ~ 70 years ago.
It took decades for the medical community to recognize it as a distinct clinical entity.

- **1950** — Pfister et al. reported the 1st known case description: a 49-year-old man who developed MI and urticaria after penicillin treatment.
- **1991** — Kounis and Zavras described the full pathophysiology of vasospastic angina linked to allergic reactions, establishing the syndrome's conceptual framework.
- **2005** — The condition was formally renamed "Kounis Syndrome."
- **2006** — Braunwald et al. classified allergic angina as a dynamic coronary occlusion mediated by vasospasm.
- **2006** — Kounis et al. published the first comprehensive review.
- **2009** — Biteker et al. published the first pediatric case series.

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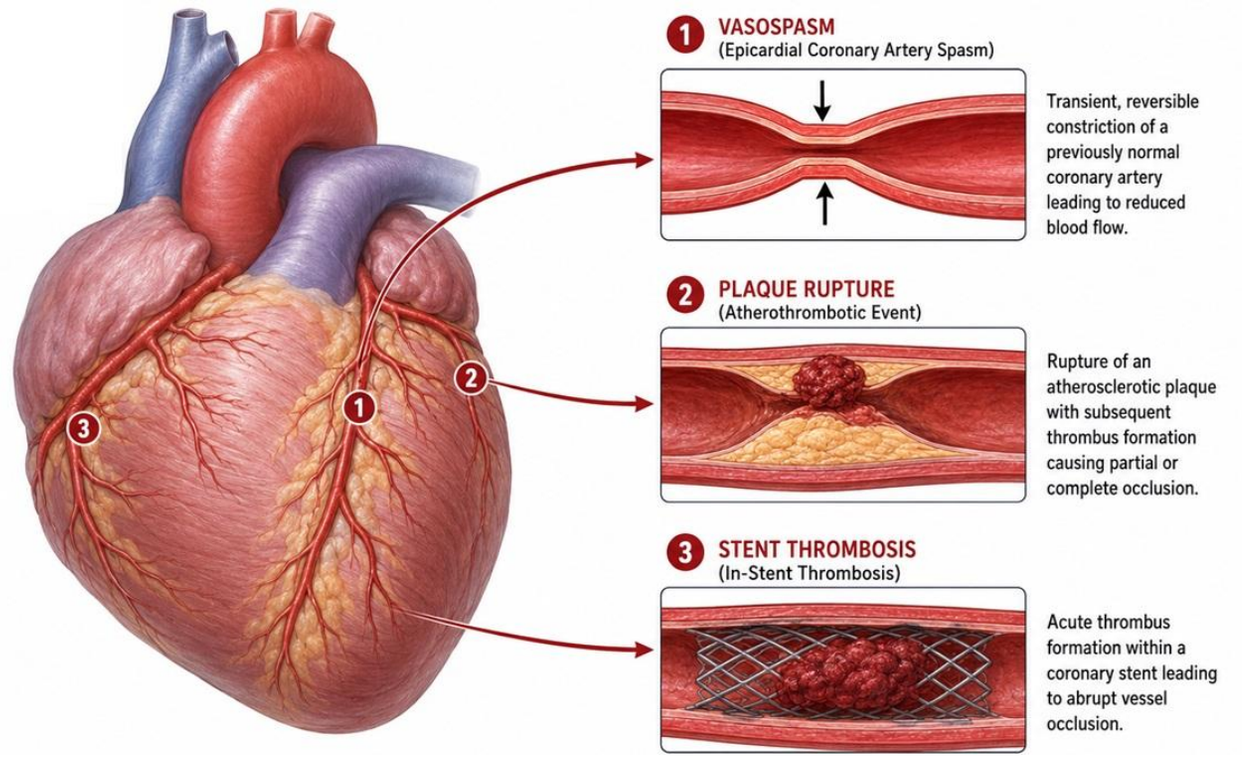
WHAT IS KOUNIS SYNDROME?

- **Kounis Syndrome**: Coronary hypersensitivity disorder: the association of an ACS (Acute Coronary Syndrome) with a hypersensitivity, allergic, anaphylactic, or anaphylactoid reaction. (Mesenteric, peripheral, and cerebral arteries can be involved in similar entities.)
  - Other names include:
    - **Allergic angina**
    - **Allergic myocardial infarction (MI)**
    - **Coronary hypersensitivity disorder**
- **Key concept**: an allergic or pseudo-allergic reaction does not just cause hives and wheezing — it can cause a heart attack.



There **are 5 distinct triggering mechanisms** for Kounis syndrome **and all lead** to 2 key **fundamental dilemmas** in treatment:

Epinephrine Delema: (epi, the cornerstone of anaphylaxis treatment) can cause coronary vasoconstriction, increase myocardial oxygen demand, and worsen ischemia

Coronary vasodilator Delema: (nitroglycerin, nicorandil, standard ACS treatment) can worsen anaphylactic hypotension.

❖*The optimal treatment balance shifts depending on which triggering pathway is active*

HOW MANY TYPES? THE CLASSIFICATION

3 types are well established; a 4th has been proposed:

Type I — Allergic Vasospastic Angina / MINOCA (Myocardial Infarction with Non-Obstructive Coronary Arteries)

- Patients with normal or near-normal coronary arteries.
- Allergic reaction causes endothelial dysfunction and coronary vasospasm.
- Troponin may be normal or mildly elevated.
- The most common variant, accounting for ~ 43–58% of reported cases.

Type II — Allergic Myocardial Infarction

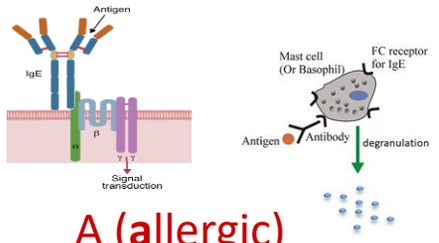
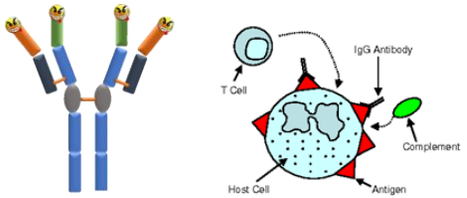
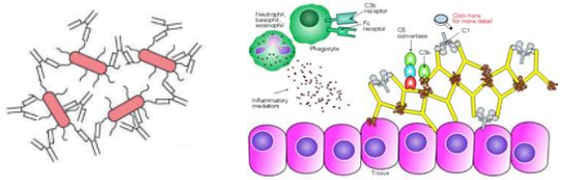
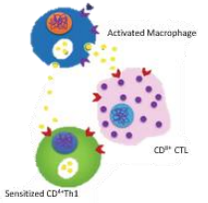
- Patients with pre-existing atherosclerotic CAD (Coronary Artery Disease), either previously quiescent or symptomatic.
- Allergic reaction causes plaque erosion or rupture, culminating in acute MI.
- Accounts for ~ 25% of cases.

- **Type III — Allergic Stent Thrombosis**
  - **Subtype IIIa**: Occluding thrombus infiltrated by eosinophils and/or mast cells.
  - **Subtype IIIb**: Stent restenosis.
  - Least variant (~7–9% of cases).

Type IV (Proposed) — Allergic Peri-Operative and Post-Intervention

- KS triggered in patients with coronary artery bypass grafts (CABG) or during or after other complex coronary interventions.
- Not yet universally accepted but described in recent case series.

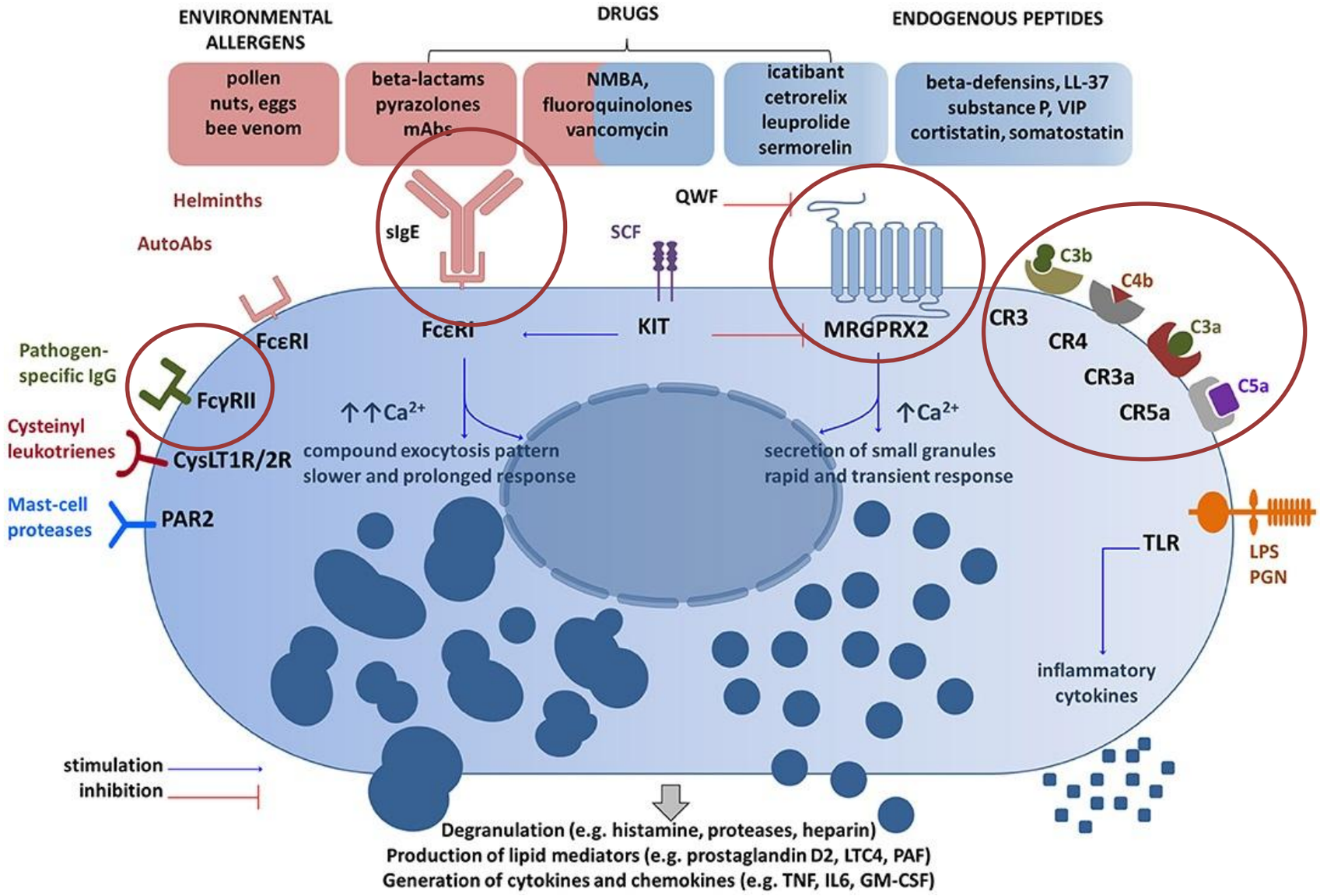
Classic Gell–Coombs: Four Types of Hypersensitivity *

	Type I: Allergy, Anaphylaxes, in Atopic persons	Type II: Antibody mediated Hypersensitivity	Type III: Immune complex-mediated Hypersensitivity	Type IV: Delayed-Type Hypersensitivity
	Classic Types I, II and III are all related to antibody functions			Mediated by T-cell subtypes (Th1, Th2, CTLs, or Th17
Who	IgE (mostly) & Granule products	IgG or IgM	Immune complexes	T-cells
How	Antigen induces cross linking of sensitized IgE bound to Mast cells and basophils. Mast cells and basophils **degranulate**	The Fab of an antibody attacks "friendly" cells, and the Fc portion of the same antibody interacts with Complement or other cells to mediate killing	Antigen-Antibody complexes are deposited in various tissue. Complexes induce complement activation generating an inflammatory response mediated by massive infiltration of neutrophils	Sensitized T cells Th1, Th2, CTLs, or Th17). Th cells release excess cytokines that activate macrophages or CTL ($CD8^+$) cells, which mediate direct cellular damage (no antibody involved)
What	**Massive release of bioactive mediators** causing Systemic anaphylaxis, or localized anaphylaxis (hay fever, asthma/bronchospasms, hives, food allergies, skin atopy)	**Antibody-induced damage to cells**, RBCs are common targets; Blood transfusion reactions, autoimmune hemolytic anemia, erythroblastosis fetalis, Goodpasture's syndrome	**Too many Insoluble complexes:** Generalized (serum sickness, necrotizing vasculitis, rheumatoid arthritis, SLE, or localized (glomerulonephritis, Arthus reaction), Subacute bacterial endocarditis	**Cytokine & Cytotoxic damage:** Graft-rejection, contact dermatitis, tubercular lesions, PPD reaction, contact dermatitis (e.g., Poison ivy)
	 A (allergic)	 B (antibody cytotoxic)	 C (immune complex)	 D (delayed)

*** European Academy of Allergy and Clinical Immunology** has added **3 more types** (**V, VI, and VII**) and created various subtypes [Jutel M, Agache I, Zemelka-Wiacek M, et al. Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper. Allergy. 2023;78(11):2851-2874. doi:10.1111/all.15889]

Receptor Systems involved in Mast Cell degranulation

- **Types 1 &2**: Fcε receptor
- **Type 3**: Fcγ receptors
- **Type 4:** Complement receptors (CRs)
- **Type 5:** MRGPRX2
  - Activated by basic secretagogues and neurokinins. Several commonly used small-molecule drugs (e.g., neuromuscular blocking agents, fluoroquinolones, vancomycin can activate these receptors under in vitro experimental conditions, producing mast cell degranulation.
- **Contributory to type 1 and 2**:
  - Tyrosine kinase c-Kit (a receptor Kinase)
  - Receptors for Cysteinyl leukotrienes
  - Protease-activated receptor 2 (PAR2)
- **Contributory to Epinephrine therapy**
  - Adrenergic receptors (α and β)
- Pattern Recognition Receptors (e.g., TLRs)

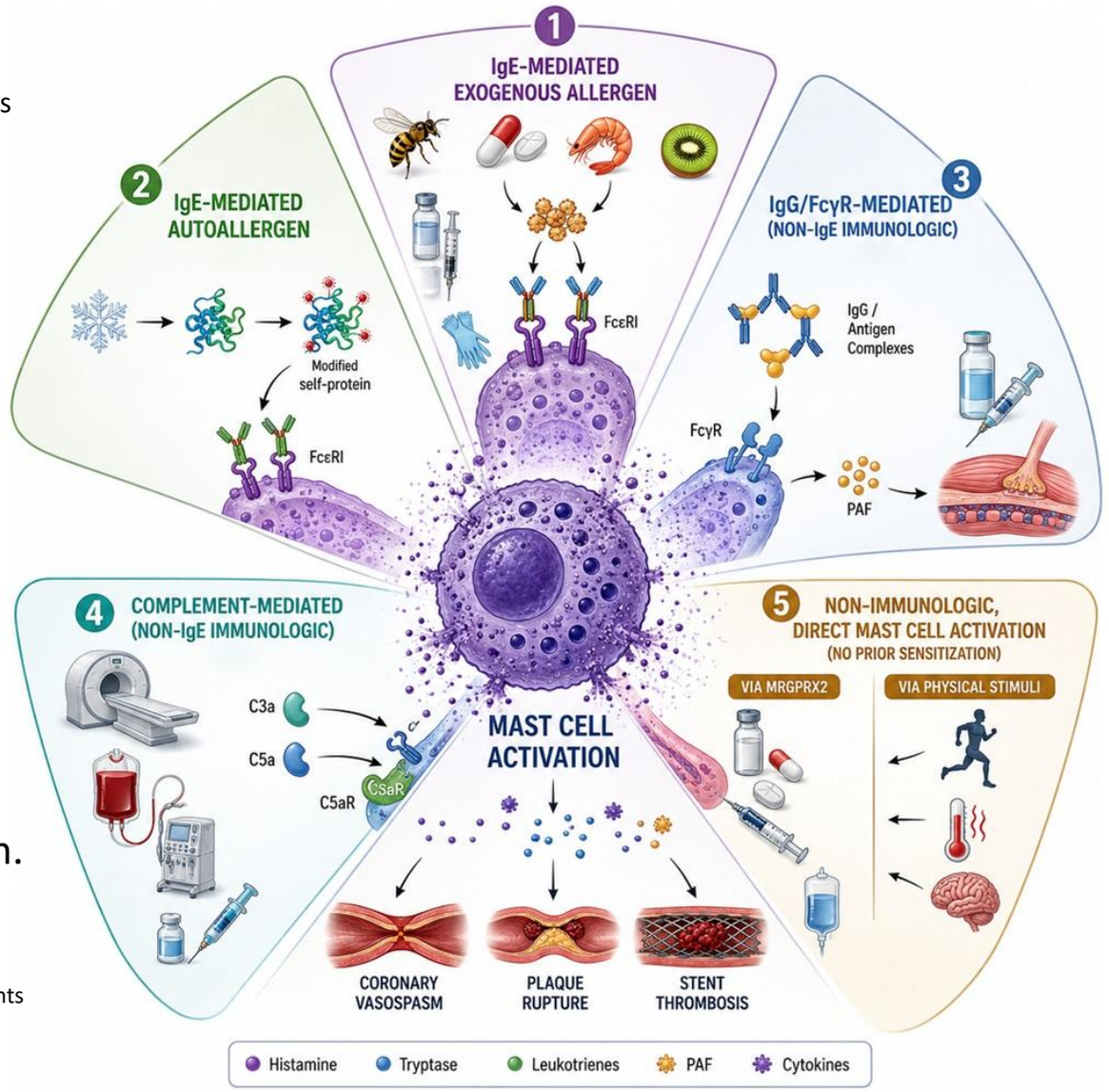


20;9:3027. doi: 10.3389/fimmu.2018.03027. https://www.frontiersin.org/articles/10.3389/fimmu.2018.03027/full

WHAT CAUSES KS? THE FIVE PATHWAYS TO MAST CELL ACTIVATION

Not all KS is "allergy." **Five distinct pathways** that can activate mast cells (and other effector cells) to produce coronary events:

1. **IgE-Mediated, Exogenous Allergen** (Classical Type I Hypersensitivity)
   - Prior sensitization required. Allergen cross-links IgE on mast cell FcεRI → degranulation.
   - Triggers: bee/wasp venom, antibiotics (penicillins, cephalosporins), foods (shellfish, kiwi), NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), latex, contrast media (some cases).
   - This is **the most common pathway**, (most reported KS cases.)
2. **IgE-Mediated, Autoallergen** (Type I Autoallergic, i.e., Type Ib Hypersensitivity)
   - Cold exposure alters conformation of self-proteins
     → autoreactive IgE recognizes these neoepitopes → FcεRI cross-linking → degranulation.
   - Same molecular machinery as #1, but the "allergen" is endogenous.
   - Relevant to cold urticaria (ColdU) — 37% of ColdU patients experience cold-induced anaphylaxis.
3. **IgG/FcγR-Mediated** (Non-IgE Immunologic)
   - IgG/antigen complexes → FcγR (Fc gamma Receptor) cross-linking on macrophages, neutrophils, basophils → PAF (Platelet-Activating Factor) release (not histamine).
   - Triggers: NMBAs (Neuromuscular-Blocking Agents), some drugs in perioperative setting.
   - Tryptase is often NORMAL despite severe reaction.
4. **Complement-Mediated** (Non-IgE Immunologic)
   - C3a/C5a anaphylatoxins → complement receptors on mast cells → degranulation.
   - No prior sensitization required. Triggers: contrast media, blood products, dialysis membranes, protamine.
5. **Non-Immunologic, Direct Mast Cell Activation:** No prior sensitization. Dose-dependent (unlike IgE, which is dose-independent)
   - **a) Via MRGPRX2**
     - (Mas-Related G Protein-Coupled Receptor X2): vancomycin, fluoroquinolones, opioids, Neuromuscular Blocking Agents (NMBAs).
   - **b) Via physical stimuli**:
     - exercise (increased plasma osmolarity), heat (cholinergic pathway), stress (CRH/neuropeptide pathway).



Most common Allergens causing KS

(systematic review of 214 patients):

- **Drugs** (38%):
  - **Antibiotics are the leading drug class (43% of drug-triggered cases),** especially amoxicillin, amoxicillin-clavulanate, and cephalosporins.
- **Animal stings or bites** (26%):
  - Bee stings, wasp stings, fly bites, jellyfish stings.
- **Foods**:
  - Shellfish, kiwifruit, and other allergens.
- **Environmental exposures**:
  - Latex, mold, pollen.

Nearly 70% of patients develop symptoms **within 30 minutes of exposure to the trigger.*

32-year-old woman presents with Anaphylaxis (cardiovascular-predominant) s/p lunch with Scombroid Fish

- Presentation
  - Orthostatic hypotension,
  - tachycardia, AND specifically: orthostatic tachycardia
  - migratory urticaria after fish ingestion
- Cutaneous involvement (urticaria) plus cardiovascular compromise (orthostatic hypotension) constitutes multi-organ involvement.
  - Anaphylaxis can be diagnosed even with isolated cardiovascular collapse after
    - Absence of respiratory symptoms does not exclude anaphylaxis: up to 10–20% of cases lack respiratory or cutaneous findings entirely.
    - Given the fish trigger, this could represent
      - Scombroid poisoning (histamine toxicity),
        - » Scombroid poisoning typically showing normal tryptase levels unlike Kounis syndrome (coronary vasospasm in normal arteries)
        - » should be actively considered, as it can present without chest pain in young women, with ST changes found only on ECG
      - IgE-mediated fish allergy (less likely)

THE SIXTH PATHWAY TO KS: SCOMBROID FISH POISONING — HISTAMINE WITHOUT MAST CELLS

Scombroid poisoning is a unique trigger for KS coronary events *without* mast cell degranulation.

What happens:

– Improperly stored fish (mackerel, tuna, bonito, bluefish, mahi-mahi, anchovies, sardines, herring) contain bacteria that convert histidine → histamine. The **patient ingests massive amounts of preformed histamine** directly.

Why it matters:

– The clinical presentation mimics anaphylaxis — flushing, urticaria, palpitations, hypotension, GI symptoms → Direct histamine-mediated coronary vasospasm ---> MI.

- A narrative review of 19 patients with scombroid-related acute coronary vasospasms found Non-ST-Elevation Myocardial Infarction-like patterns, most with normal coronary arteries.

Critical diagnostic distinction:

- **Scombroid: Tryptase is NORMAL** (no mast cell degranulation, histamine came from the fish, not from the patient's mast cells). Serum/urine histamine is elevated.
- **True fish allergy (IgE-mediated):** Tryptase is **ELEVATED** (mast cells degranulated). Histamine is also elevated.

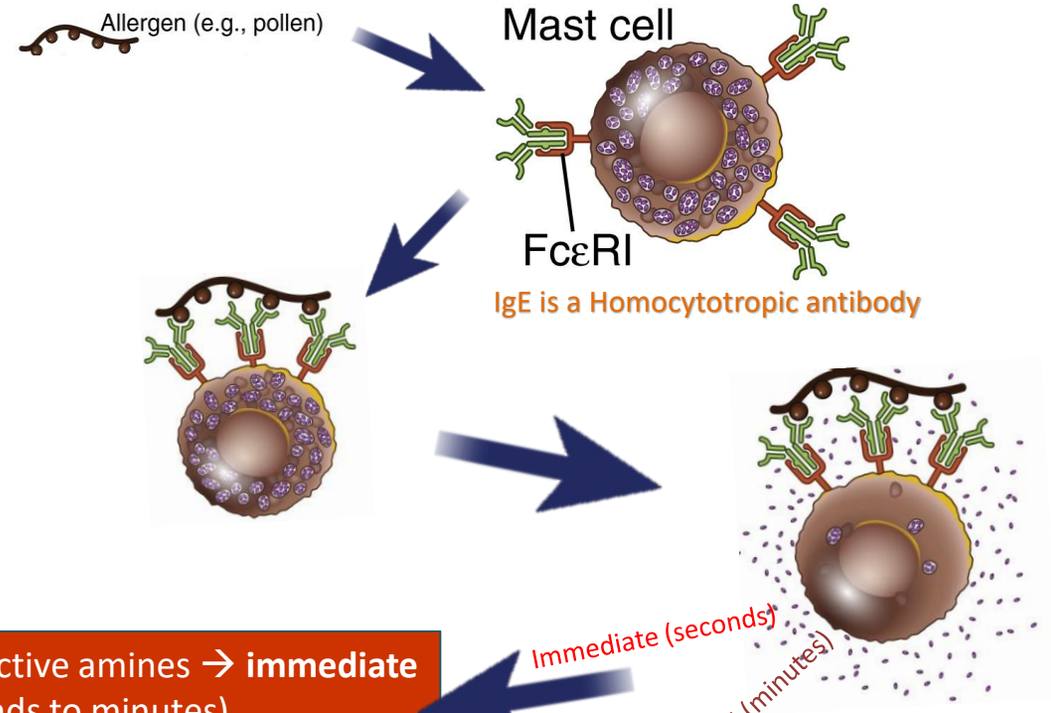
- **Distinction matters because**:

– Scombroid responds well to H1 + H2 antihistamines alone.
– No desensitization is needed — the patient is not allergic to fish.
– Prevention is food safety (proper refrigeration), not allergen avoidance.
– Clustering of cases (multiple diners affected) excludes true allergy

Scombroid accounts for ~5% of food toxicities in the USA and is the most common cause of fish-related illness worldwide.

HOW MAST CELL ACTIVATION PRODUCES THE MEDIATOR CASCADE THAT ATTACKS THE HEART AND BLOOD VESSELS:

- **Preformed mediators (released in seconds):**
  - **Histamine** → coronary vasospasm, increased vascular permeability, platelet activation, tachycardia
  - **Tryptase and chymase** (neutral proteases) → activate MMPs (Matrix Metalloproteinases) → degrade the fibrous cap of atherosclerotic plaques → plaque erosion/rupture
  - **Heparin/proteoglycans**
  - **TNF-α** (Tumor Necrosis Factor-alpha)
- **Newly synthesized mediators (a few minutes):**
  - Arachidonic acid products:
    - leukotrienes C4/D4/E4, prostaglandin D2, thromboxane A2 → potent coronary vasoconstrictors and platelet aggregators
  - Platelet-Activating Factor (alkyl- acyl - glycerophosphocholine) → platelet aggregation, further vasospasm, increased vascular permeability
- **Newly synthesized mediators (hours):**
  - Cytokines (IL-1, IL-4, IL-5, IL-6, IL-13) → amplify the inflammatory cascade



Vasoactive amines → **immediate** (seconds to minutes) hypersensitivity reaction

Lipid mediators synthesized from existing membrane lipids (e.g., Arachidonic acid, plasmanylcholine, etc.) enhance the **immediate** (2-3 minutes) hypersensitivity reaction

Cytokines (and lipid mediators) released by mast cells are responsible for the **late-phase** reactions (2- 4 hours after re-exposure to the allergen)

HOW RAPID MAST CELL ACTIVATION PRODUCES CORONARY CONSEQUENCES

Mast Cell mediators converge on three coronary targets

1. Coronary Vasospasm (→ Type I KS)

- Histamine (H1 receptors on vascular smooth muscle) + leukotrienes + thromboxane A2 → intense coronary artery **constriction**
- Endothelial dysfunction → reduced nitric oxide → **impaired vasodilation**
  - ➢ Can develop in completely normal coronary arteries!

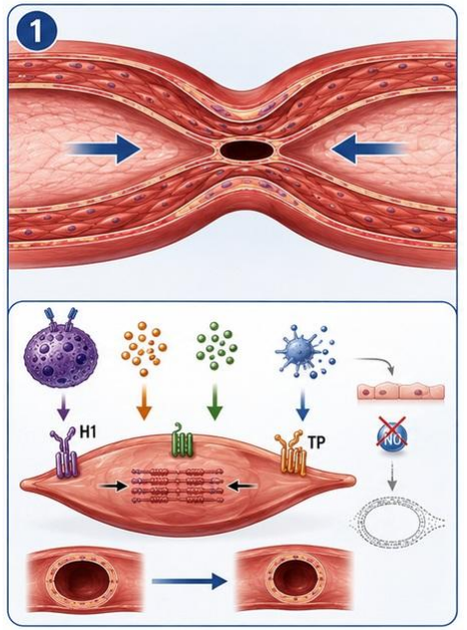
2. Plaque Destabilization (→ Type II KS)

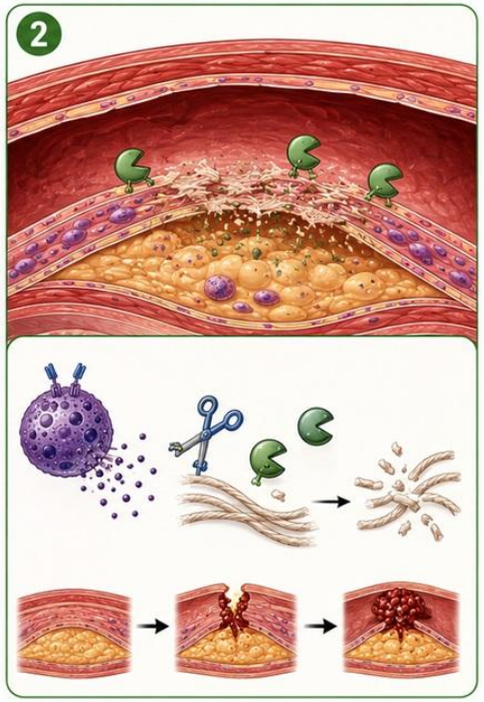
- Tryptase/chymase activate MMPs → degrade collagen in the fibrous cap
- Inflammatory mediators weaken the plaque shoulder
- Result: **plaque erosion or rupture** → thrombus formation → acute MI

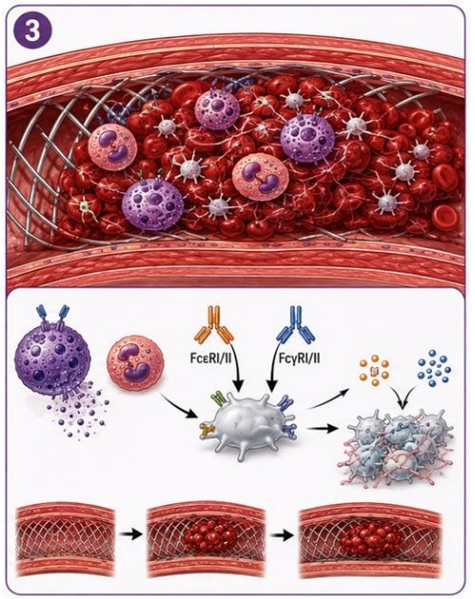
3. Platelet Activation and Thrombosis (→ Types II and III KS)

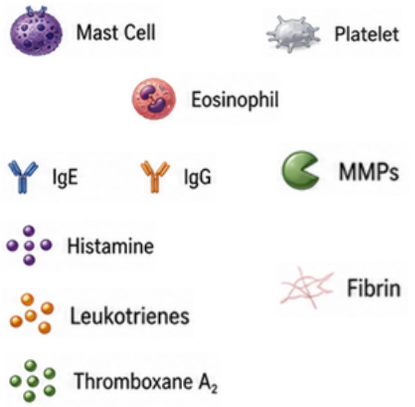
- Platelets have IgE receptors (FcεRI, FcεRII) and IgG receptors (FcγRI, FcγRII)
- Platelets are directly activated by the allergic cascade
- PAF + thromboxane A2 → platelet aggregation → coronary thrombosis
- (In Type III: thrombus forms on/in a coronary stent; producing eosinophil/mast cell infiltration)

Critical insight: mast cells are in affected area *before plaque rupture* even in non-allergic ACS. KS reveals that allergy and atherosclerosis share a common final pathway









MEDIATOR PROFILE DIFFERS BY WITH THE TRIGGER PATHWAY

Pathway	Primary Mediator	Tryptase	Histamine	PAF	Key Implication
IgE-mediated (Type I hypersensitivity)	Histamine + tryptase	ELEVATED (TDR/BT ≥1.66)*	Elevated	Present	Antihistamines highly effective
IgE autoallergic (cold)	Histamine + tryptase	May be elevated; total IgE higher in severe cases	Elevated	Present	Omalizumab effective; antihistamines effective
IgG/FcγR-mediated	PAF (**NOT** histamine)	Often NORMAL (only 4% elevated in one study)	May be normal	**DOMINANT** mediator	Antihistamines may be LESS effective; PAF is the key driver
Complement-mediated	Histamine + complement fragments	Variable	Elevated	Present	Complement levels (C3, C4) may be decreased
MRGPRX2/physical	Histamine (but less tryptase)	Variable, may be lower	Elevated	Present	Dose-dependent; slower infusion may prevent
Scombroid (exogenous histamine)	Exogenous histamine only	NORMAL (no Mast Cell degranulation)	Very high	Absent	Antihistamines alone usually sufficient; no allergy workup needed

** A Tryptase (During Reaction) /Tryptase (basal) ratio ≥1.66 discriminates IgE from non-IgE mechanisms significantly better (Area under the curve of 0.79) than absolute tryptase alone.*

WHO IS SUSCEPTIBLE?

Anyone who can have an allergic reaction can develop KS, but patients with both cardiovascular risk factors and atopic histories are at highest risk.

Demographics

- Male predominance: ~70–75% for most types
- Mean age: 54 years (range 2–99; pediatric cases reported)
- Age varies by trigger:
  - Contrast-related → older;
  - NSAID-related → younger

Comorbidities:

- Atopic history (asthma, eczema, allergic rhinitis): ~32%
- Hypertension (34%),
- Diabetes (17%),
- Dyslipidemia (16%)
- Smoking history

* A 2025 prospective ED study found that among 200 patients with allergic symptoms, 12% had elevated hs-cTnI (High-Sensitivity Cardiac Troponin I), with 6% diagnosed with KS. Myocardial injury was more prevalent in patients with diabetes, hypertension, dyslipidemia, and smoking.

Trigger-specific susceptibility:

1. **Classic IgE-mediated**:
   - Atopic individuals; occupational exposures (beekeepers, healthcare workers);
   - HLA-associations with specific drug allergies
2. **Cold-induced autoallergic**:
   - Female predominance (2:1 for ColdU);
   - Onset age 20–30;
   - PLAID (PLCγ2-Associated Antibody Deficiency) for familial forms
3. **Complement-mediated**:
   - Primed complement-heavy inflammatory environment (e.g., bacterial sepsis) that makes C3a/C5a-mediated coronary hypersensitivity more likely or more severe
4. **IgG/FcγR-mediated**:
   - In perioperative setting; FcγR polymorphisms may play a role
5. **MRGPRX2/physical**:
   - Athletes (Exercise-Induced Anaphylaxis); postprandial exercisers
   - Food-Dependent Exercise-Induced Anaphylaxis; MRGPRX2 V282M variant
6. **Scombroid**:
   - Anyone who eats improperly stored fish — no individual susceptibility required

HOW IS IT RECOGNIZED? SIGNS AND SYMPTOMS

Allergic manifestations (present in ~76% of cases):

- Urticaria (74%), angioedema, pruritus, flushing
- Dyspnea/wheezing/bronchospasm
- Hypotension/anaphylactic shock
- Nausea, vomiting, abdominal pain

Cardiac manifestations:

- Chest pain (67%) — the most common cardiac symptom
- Diaphoresis, palpitations
- Syncope or near-syncope
- Cardiac arrest (severe cases)
- Orthostatic Tachycardia

Also consider KS when:

- Patient collapses during exercise with urticaria
- Swimmer develops urticaria and cardiovascular collapse after cold water immersion
- Multiple diners develop flushing, palpitations, and chest tightness after eating fish (scombroid)
- A patient develops chest pain during or after a drug infusion (vancomycin, fluoroquinolone, opioid)

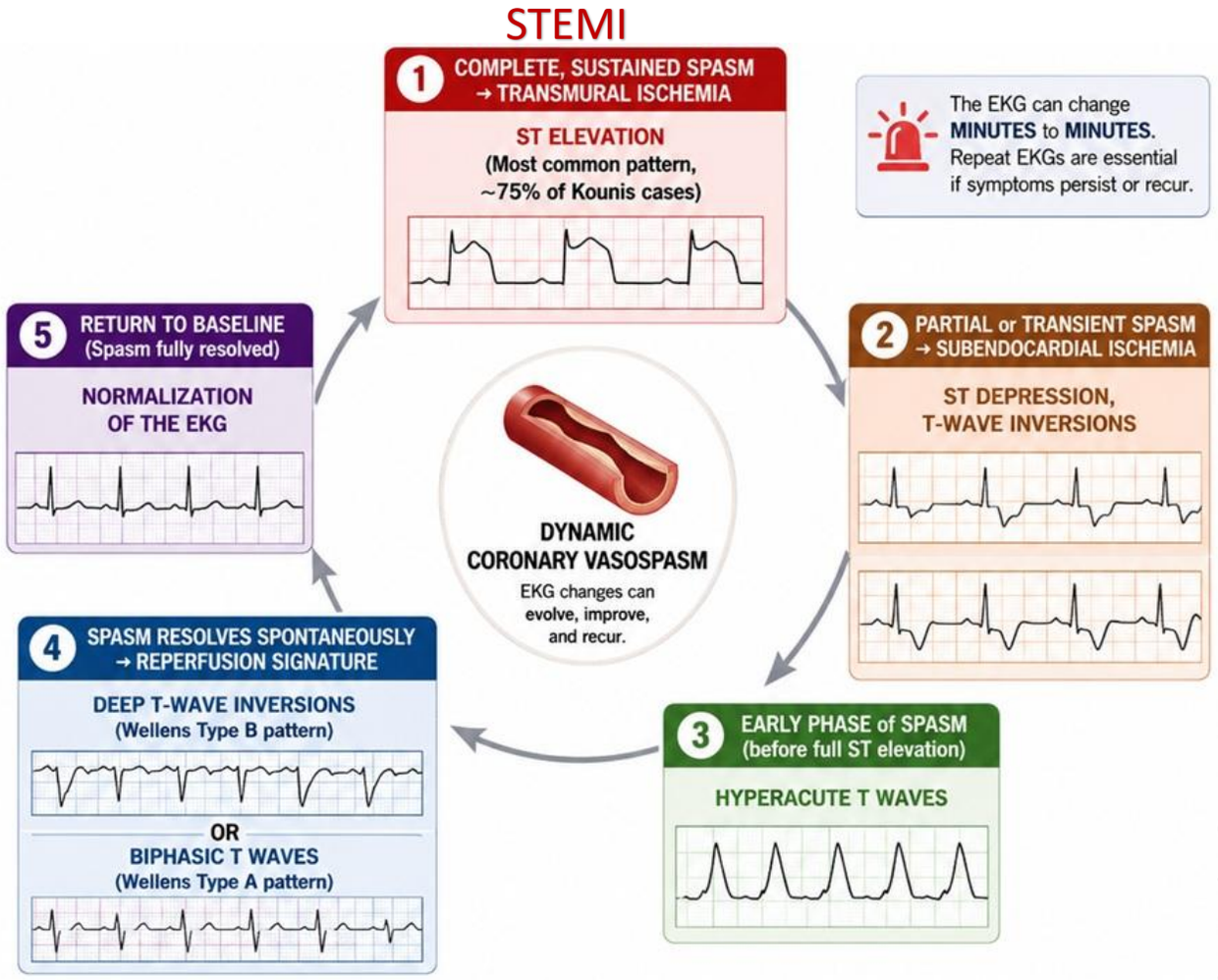
Type-specific presentations:

- **Type I:** Chest pain + allergic symptoms in a patient with NO known heart disease.
  - Often younger patients. Symptoms may resolve completely with anti-allergic treatment alone. Troponin may be normal or only mildly elevated.
- **Type II:** Chest pain + allergic symptoms in a patient WITH known or occult CAD.
  - Presents like a classic STEMI (ST-Elevation Myocardial Infarction) or NSTEMI (Non-ST-Elevation Myocardial Infarction). Troponin is typically elevated. Higher risk of complications.
- **Type III**: Acute stent thrombosis symptoms (sudden severe chest pain, hemodynamic collapse) in temporal association with an allergic reaction in a patient with a coronary stent.
  - Pathology shows eosinophil/mast cell infiltration of the thrombus.
- **Type IV** (proposed): ACS symptoms in a patient with prior CABG or complex coronary intervention during an allergic episode.

Red flag: "Hives + chest pain" *or* "Anaphylaxis + ECG changes

In Kounis syndrome, EKG pattern depends on Severity, Duration, and Completeness of Coronary Vasospasm *AND* Underlying Coronary Anatomy

Type I Kounis (vasospasm, no CAD): Vasospasm is **dynamic** and often **fluctuating**. Thus, the **EKG can cycle through the entire spectrum of ischemic patterns**:



CLINICAL PEARLS

- ST elevation is most common (~75%), but other patterns are frequent.
- Deep T-wave inversions or biphasic T waves can mimic Wellens patterns.
- Symptoms + EKG changes that come and go = think vasospasm.
- Remove trigger, relieve spasm, and monitor closely.

KEY TAKEAWAYS FOR FIRST RESPONDERS

- ✓ Type I Kounis = Vasospasm in normal coronary arteries.
- ✓ EKG findings are dynamic and can fluctuate over time.
- ✓ Repeat 12-lead EKGs if symptoms persist or change.
- ✓ Treat the allergic trigger and support the patient.
- ✓ Think Kounis in any allergic/anaphylactic patient with chest pain and EKG changes.

Critical difference from atherosclerotic ACS:

- Kounis vascular changes: typically rapidly reversible with antiallergic therapy (antihistamines, corticosteroids)
- EKG normalizes once the vasospasm resolves.
- Wellens-like pattern in Kounis is post-spasm reperfusion phase

HIGH CLINICAL SUSPICION + SERIAL EKGs = EARLY DIAGNOSIS AND BETTER OUTCOMES

DIAGNOSTIC WORKUP: EKG findings

The prehospital 12-lead ECG is critical. Transmit it with the clinical context: "*Patient with anaphylaxis **AND** ST elevation*."

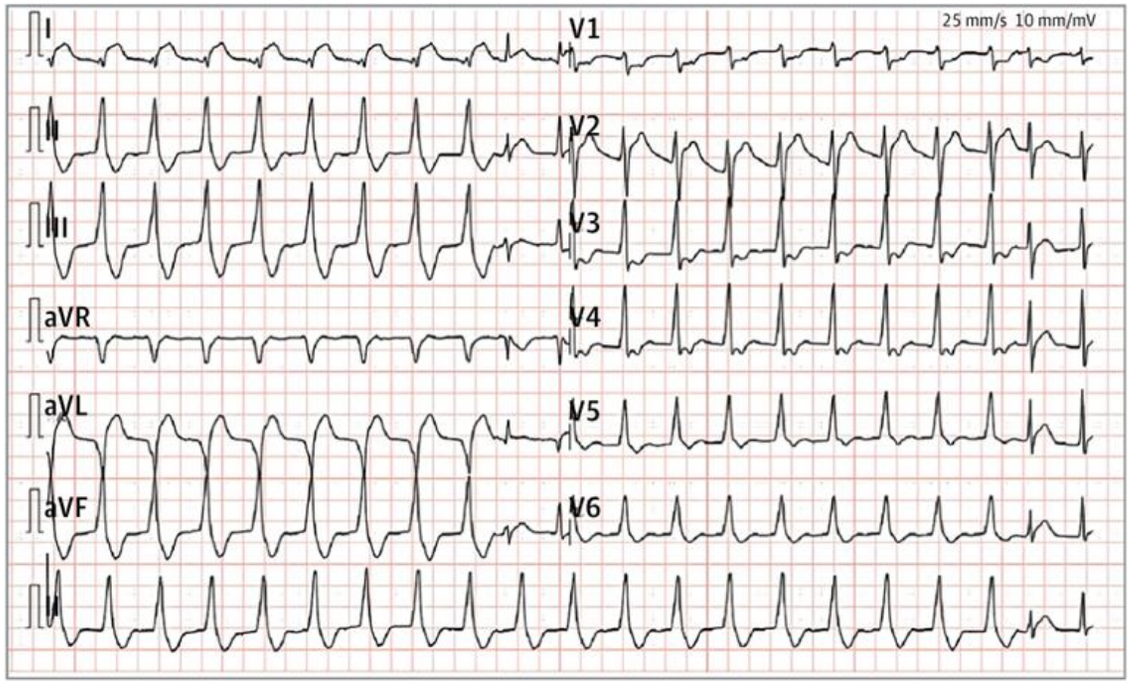
- General KS EKG Changes:
  - STE (ST-Segment Elevation): present in 71–81% of cases — the most common ECG finding.
  - ST-segment depression
  - T-wave inversion
  - New-onset arrhythmias: Atrial Fibrillation), Ventricular Tachycardia, VF (Ventricular Fibrillation)
- Conduction abnormalities
  - Only ~3% have a completely normal ECG

Type I (vasospasm): EKG changes are typically dynamic & reversible — ST elevation resolves promptly with anti-allergic therapy (antihistamines + corticosteroids). *This rapid resolution is a diagnostic clue*.

Type II (plaque rupture): EKG changes resemble classic STEMI (ST-Elevation Myocardial Infarction) or NSTEMI with persistent ST changes, evolving Q waves, reciprocal changes. Less likely to resolve with anti-allergic therapy alone.

Type III (stent thrombosis): Acute ST elevation in the territory of the stented vessel. Abrupt onset.

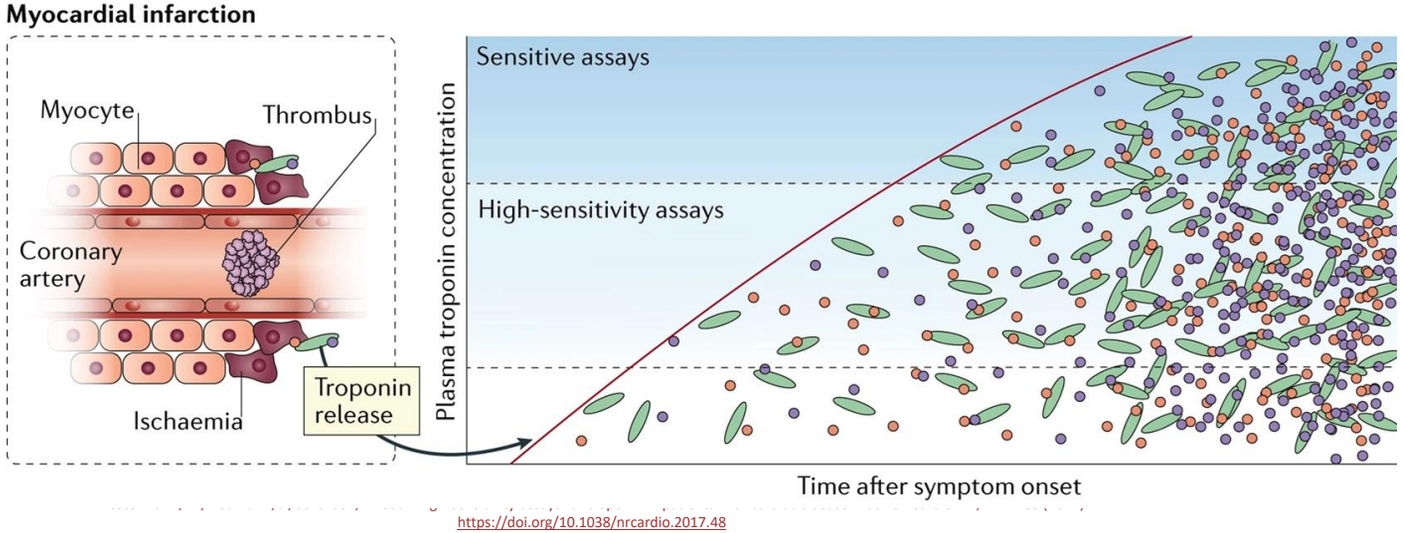
Scombroid-related ACS: Typically, NSTEMI-like pattern (ST depression, T-wave changes) rather than STEMI; resolves with antihistamines.



Yu S, Lv H, Liu M. Sequential Electrocardiography Changes. JAMA Intern Med. 2026;186(2):264–265. doi:10.1001/jamainternmed.2025.6138

DIAGNOSTIC WORKUP: Laboratory studies

- **Cardiac troponin (cTn) or high-sensitivity cardiac troponin (hs-cTn):**
  - Elevated in ~73% of cases. May be normal or mildly elevated in Type I.



https://doi.org/10.1038/nrcardio.2017.48

Serum tryptase: A mast cell degranulation marker.

Elevated levels support the diagnosis. Draw within 1–2 hours of symptom onset (peaks at 1 hour, returns to baseline by 6 hours). A normal tryptase does not exclude KS.

Histamine (Serum and Urine):

Elevated in allergic ACS. Very short half-life (~minutes); difficult to capture clinically. (Urine N-methylhistamine is more practical)

IgE levels:

May be elevated, supporting an allergic etiology.

Eosinophil count:

Peripheral eosinophilia may be present.

Creatine Kinase-MB (CK-MB):

May be normal in Type I (vasospasm without necrosis) or
May be levated in Types II/III.

B-type Natriuretic Peptide /N-terminal pro-B-type Natriuretic Peptide (BNP/ NT-pro BNP):

If heart failure is suspected.

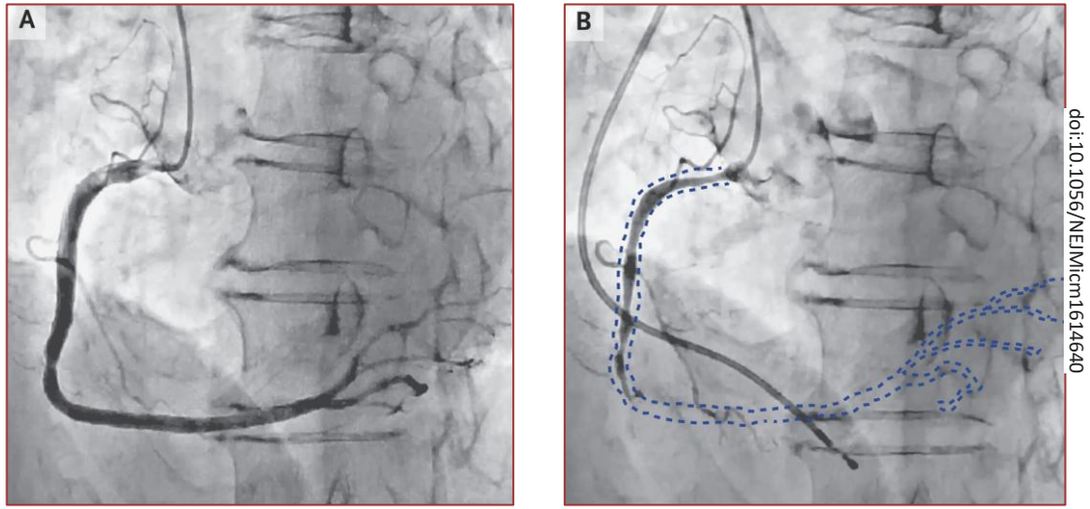
Prospective ED study: 12% of patients presenting with allergic symptoms had elevated hs-cTn, and 6% were diagnosed with KS — reinforcing the importance of obtaining an ECG and troponin in patients with significant allergic reactions.

Anastasopoulou M, et al. Incidence of Elevated Cardiac Biomarkers in Patients Presenting to the Emergency Department With Allergic Symptoms: Implications for the Diagnosis of Kounis Syndrome. Am J Cardiol. 2026;258:1-8. doi:10.1016/j.amjcard.2025.08.036

Pattern	Interpretation of Likely Pathway
↑ Tryptase + ↑ Troponin + ↑ IgE	IgE-mediated (classical or autoallergic)
Normal tryptase + ↑ Troponin + severe reaction	IgG/FcγR or MRGPRX2 pathway
Normal tryptase + ↑ Histamine + normal troponin + fish meal	Scombroid
↑ Tryptase + ↑ Troponin + ↓ C3/C4	Complement-mediated

DIAGNOSTIC WORKUP: Imaging

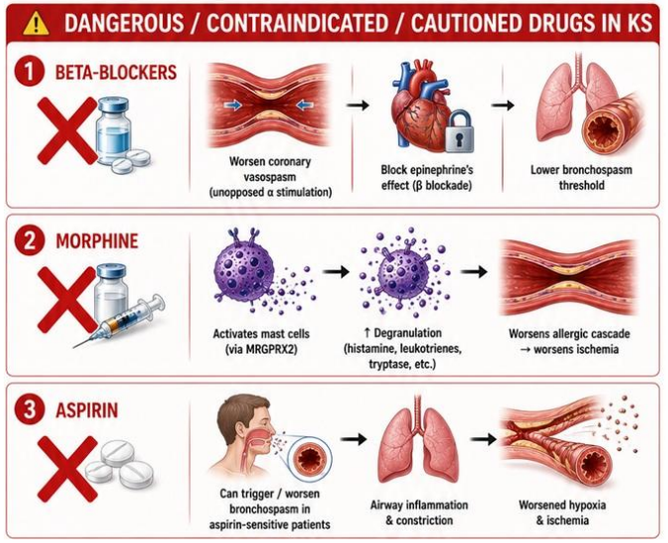
- Coronary angiography: Gold standard for classification.
  - **Type I**: Normal coronary arteries or vasospasm that resolves with nitrates (51% of cases show normal coronaries)
  - **Type II:** Occlusive lesions, plaque rupture/erosion. (33%)
  - **Type III**: Stent thrombosis or restenosis; aspirated thrombus showing eosinophil/mast cell infiltration is pathognomonic.
- Echocardiography:
  - Assess wall motion abnormalities, LV (Left Ventricular) function
  - May show regional wall motion abnormalities corresponding to the affected coronary territory
  - Helps differentiate from takotsubo cardiomyopathy (apical ballooning pattern).
- Cardiac MRI:
  - Can differentiate myocarditis from MI;
  - Useful in ambiguous cases, especially when MINOCA is suspected
  - Late gadolinium enhancement pattern differs: subendocardial (ischemic) vs. subepicardial/mid-wall (myocarditis)

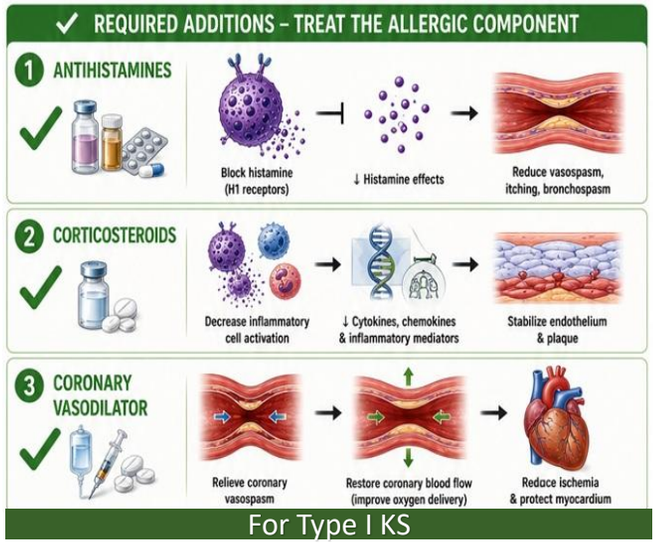


Acetylcholine injection into the right coronary artery provoked a vasospasm that led to total occlusion of the proximal right coronary artery (the dashed lines in Panel B outline the area in which the contrast agent shown in Panel A was absent);

Kondo T, Terada K. Coronary-Artery Vasospasm. *N Engl J Med*. 2017;376(25):e52. doi:10.1056/NEJMicm1614640

Recognizing KS Changes Management in Critical Ways:





Standard ACS drugs can be harmful:

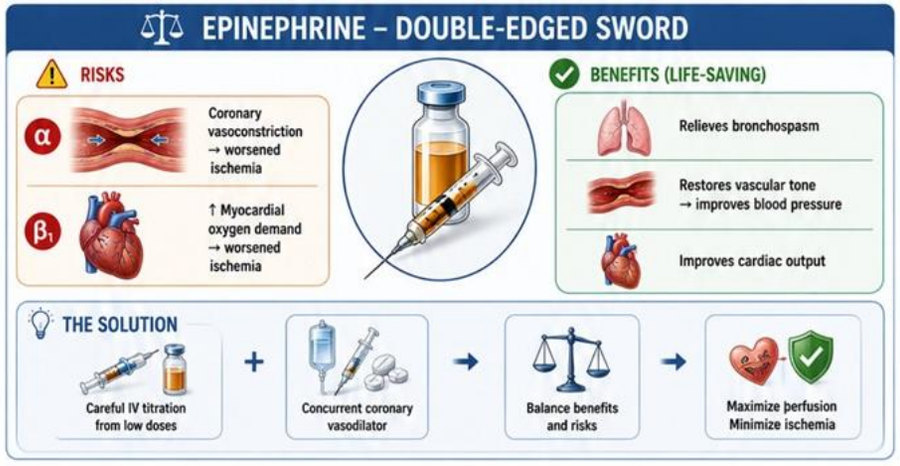
- Beta-blockers: CONTRAINDICATED. Worsen coronary vasospasm (unopposed alpha-receptor stimulation) AND block epinephrine's effect AND lower bronchospasm threshold
- Morphine: AVOID. Activates mast cells via MRGPRX2 → more degranulation → worsens the allergic cascade.
- Aspirin: CAUTION — can worsen bronchospasm in aspirin-sensitive patients.

Must Treat the allergic component simultaneously:

- **In Type I**, treating the allergy alone may resolve the cardiac event entirely.
- Failing to treat the allergy means the inflammatory cascade continues to drive coronary damage.

Epinephrine is a double-edged sword:

- Alpha-receptor stimulation → coronary vasoconstriction, → worsen ischemia.
- Beta-1 stimulation → increased myocardial oxygen demand → worsen ischemia
- *But* in life-threatening anaphylaxis, it remains essential.
- **Solution**: **careful IV titration** from low doses rather than bolus IM injection when KS is suspected *with* **concurrent coronary vasodilator.**



Prognosis is generally favorable when recognized:

Overall recovery rate: 87–94%; Mortality rate: 4–7%.

But delayed diagnosis and inappropriate treatment increase morbidity and mortality.

Epinephrine and Allergic Reactions

- Epinephrine rescues patients with anaphylaxis through multiple pharmacological effects, including binding to
  - α1 adrenergic receptors
    - peripheral vasoconstriction effects
  - β1 adrenergic receptors,
    - rate and force increases in cardiac contractions
      - increased heart rate, myocardial contractility,
    - renin release
  - β2 adrenergic receptors
    - **inhibition** of release of histamine and other preformed molecules from mast cells
    - **Reduces the release** of newly synthesized mediators such as prostaglandin D2 from mast cells.
    - Bronchodilation

Epinephrine: vascular smooth muscle contraction, increases cardiac output, inhibits bronchoconstriction.

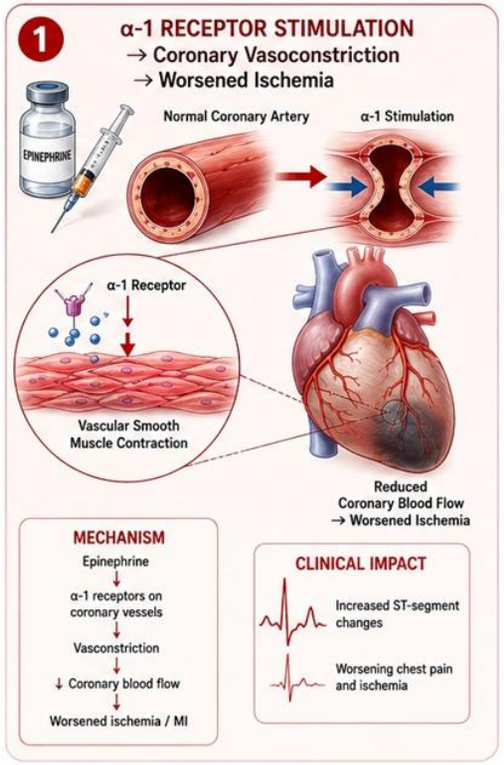
THE EPINEPHRINE DILEMMA

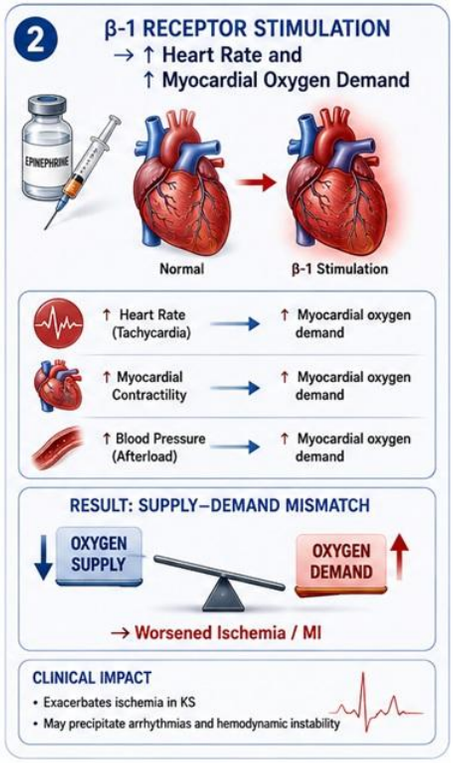
Epinephrine's **unique risks in KS**:

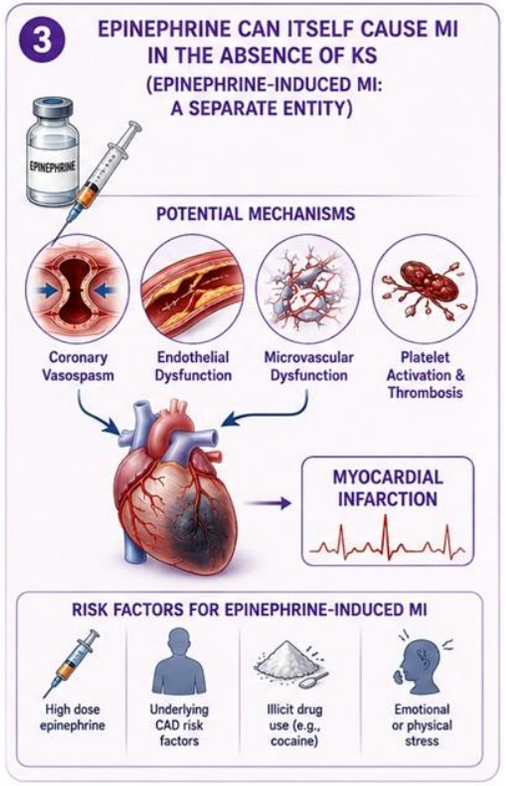
α-1 receptor stimulation → coronary vasoconstriction → **worsened ischemia**.

β-1 receptor stimulation → ↑heart rate and ↑ **myocardial oxygen demand**.

Epinephrine itself *can cause MI* in the absence of KS (epinephrine-induced MI is a separate entity).







Practical approach to Epinephrine use:

- In life-threatening anaphylaxis with suspected KS: epinephrine remains indicated because benefit of treating anaphylaxis outweighs cardiac risk.
- Prefer IV infusion starting at low doses (0.05–0.1 µg/kg/min) with careful upward titration over IM bolus.
- Simultaneously administer a coronary vasodilator (nitroglycerin or nicorandil) to counteract coronary vasoconstriction.
- Monitor ECG continuously.
- In mild-to-moderate allergic reactions without hemodynamic compromise: antihistamines and corticosteroids may suffice; epinephrine may not be needed

TREATMENT: UNIVERSAL PRINCIPLES ACROSS ALL TRIGGERS

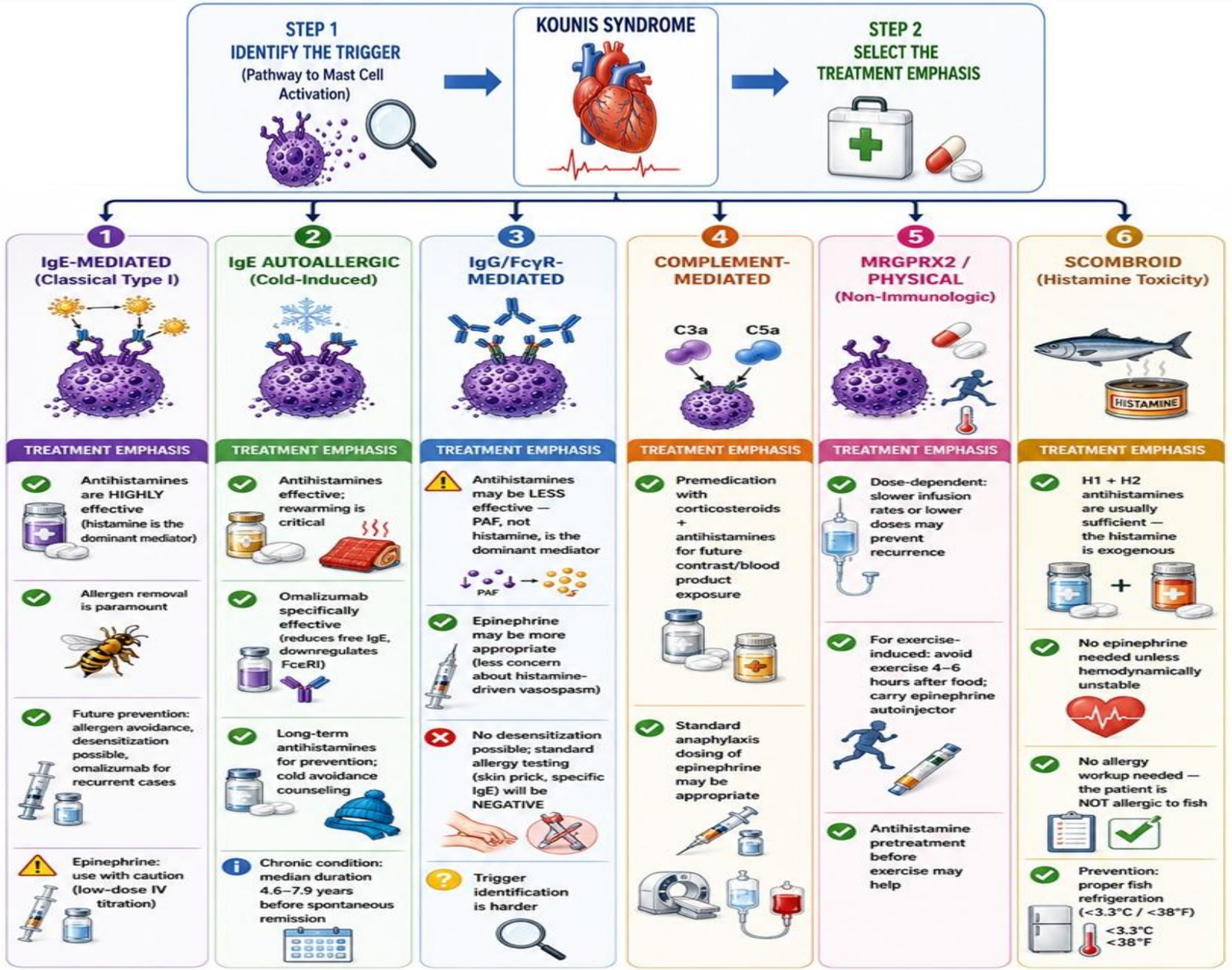
What is Different?

- For "allergic Type I KS" TREAT THE ALLERGY FIRST!
  - **REMOVE ALLERGEN**/STOP THE TRIGGER: Single most important intervention
  - ADD H1-antihistamine (diphenhydramine 25–50 mg IV)
  - ADD H2-antihistamine (famotidine 20 mg IV)
  - ADD IV corticosteroids (hydrocortisone 200 mg or methylprednisolone 1–2 mg/kg)
  - ADD coronary vasodilator: NTG (Nitroglycerin) sublingual/IV or nicorandil
  - **AVOID** beta-blockers → use CCBs (Calcium Channel Blockers) instead
  - **AVOID** morphine → use fentanyl if analgesia needed (lower MRGPRX2 activation)
  - **USE CAUTION** with aspirin
  - **USE CAUTION** with epinephrine (see previous slide)
- For patients on beta-blockers who develop KS:
  - Glucagon 1–5 mg IV (adults) has inotropic and chronotropic effects NOT mediated through beta-receptors
  - May be needed to overcome beta-blocker-induced epinephrine resistance

What is The Same?

- Oxygen supplementation
- Continuous cardiac monitoring
- IV access
- 12-lead ECG
- Serial troponin measurements
- Coronary angiography when indicated
- Percutaneous Coronary Intervention) / stenting for occlusive lesions (Types II and III)
- Antiplatelet therapy (with caveats — see below)
- Nitrates for vasospasm (with caveats)

HOW TREATMENT OF KS DIFFERS BY TRIGGER MECHANISM



The trigger mechanism for KS changes the treatment emphasis, guides what will likely work and what won't and what may cause more harm than good.

Kounis Syndrome: Type Specific Treatment

Identify the type→ Follow the Algorithm → Treat the Allergy and Heart

TYPE I
Allergic Vasospastic Angina (Normal Coronaries)

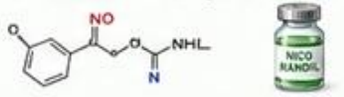
PRIMARY GOAL
Treat the allergy; the cardiac event will follow.

1 ALLERGY MANAGEMENT
- Remove allergen
- Antihistamines (H1 + H2)

- IV corticosteroids

2 TREAT VASOSPASM
- NTG sublingual/IV or CCBs for persistent vasospasm (monitor BP — avoid if hypotensive)

- Nicorandil for refractory cases



3 EPINEPHRINE (USE WITH CAUTION)
Only if anaphylaxis is life-threatening: IV infusion starting at 0.05–0.1 µg/kg/min with careful titration

PROGNOSIS
Excellent.
ECG changes and symptoms often resolve promptly with anti-allergic therapy alone.

TYPE II
Allergic MI (Pre-existing CAD)

PRIMARY GOAL
Treat BOTH the allergy AND the ACS simultaneously.

1 ALLERGY MANAGEMENT
All anti-allergic measures as in Type I

2 REVASCULARIZATION
Coronary angiography + PCI / stenting as indicated

3 ACS MANAGEMENT
- DAPT: aspirin (if tolerated) + $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor)

- Anticoagulation: heparin per standard ACS protocols

AVOID beta-blockers (use CCBs for rate/spasm control)

AVOID morphine (use fentanyl)

PROGNOSIS
Good with combined treatment; may require PCI.

TYPE III
Allergic Stent Thrombosis

PRIMARY GOAL
Urgent revascularization + intensive allergy control.

1 EMERGENCY INTERVENTION
Emergency angiography + thrombectomy / PCI

2 ALLERGY MANAGEMENT
All anti-allergic measures as in Type I

3 INTENSIVE ANTIPLATELET & ANTICOAGULATION
- DAPT: intennification

- Anticoagulation: heparin per standard ACS protocols

4 ADDITIONAL CONSIDERATIONS
- Consider stent material as potential allergen (nickel, polymer coatings)

- Histopathology of aspirated thrombus showing eosinophil / mast cell infiltration confirms diagnosis

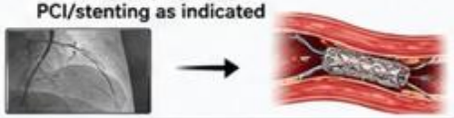
PROGNOSIS
Higher morbidity; requires aggressive intervention.

TYPE IV (PROPOSED)
Allergic Post-Intervention

PRIMARY GOAL
Treat as Type II with attention to graft-specific anatomy.

1 ALLERGY & ACS MANAGEMENT
All anti-allergic measures as in Type I

2 INTERVENTION STRATEGY
Treat as Type II: Coronary angiography + PCI/stenting as indicated



3 ADDITIONAL CONSIDERATIONS
- Attention to graft-specific anatomy

- DAPT + anticoagulation as indicated
- Avoid beta-blockers; avoid morphine

4 MULTIDISCIPLINARY CARE
Cardiology + Allergology co-management

PROGNOSIS
Variable; depends on underlying disease and intervention.

WHY KS MATTERS TO PREHOSPITAL RESPONDERS

First responders are often the 1st to encounter KS and the 1st to make treatment decisions that can help or harm:

- Will **see the allergic reaction** first.
  - The patient stung by a bee, the patient who just took an antibiotic, the patient eating shellfish .
  - If they develop chest pain, Think KS.
- **Field ECG is critical**.
  - A 12-lead ECG showing ST changes in a patient with an allergic reaction should trigger a KS alert. Transmit the ECG to the receiving facility with the clinical context: "Patient with anaphylaxis AND ST elevation."
- **Rapid transport** to a PCI-capable facility is essential for Types II and III.
- Document the timeline:
  - What was the exposure?
  - When did symptoms start?
  - What allergic signs appeared first?

KS Medication decisions in the field matter:

- DO give epinephrine *for life-threatening* anaphylaxis but *be aware* it may worsen cardiac ischemia.
- DO obtain IV access and give fluids for hypotension.
- DO give antihistamines (diphenhydramine) if available in your protocols.
- DO apply continuous cardiac monitoring.
- **DO NOT** give beta-blockers.
- DO communicate the allergic context to the receiving ED — this changes their management.

WHY KS MATTERS TO ED PERSONNEL

- Think KS whenever ACS and allergy coexist.
  - A prospective ED study found that 6% of patients presenting with allergic symptoms had KS — it is not rare.
- What to do:
  - Obtain an EKG and troponin on every patient with a significant allergic reaction, especially those with cardiovascular risk factors.
  - Draw a serum tryptase level early (within 1–2 hours of symptom onset) as it supports the diagnosis and may be the only way to confirm mast cell activation retrospectively.

  - Modify your ACS protocol:
    - Hold beta-blockers.
    - Avoid morphine; use fentanyl if analgesia is needed.
    - Use aspirin cautiously (risk of bronchospasm).
    - Treat the allergy aggressively with corticosteroids and antihistamines.
    - Consult both cardiology and allergology/immunology early.
    - Be prepared for the epinephrine dilemma: if the patient needs epinephrine for anaphylaxis but has active ischemia, use IV titration from low doses with concurrent nitroglycerin.

Consider KS in the differential for MINOCA — especially in younger patients with no traditional risk factors.

CONSIDERATIONS FOR RECOVERED KS PATIENTS

- **Allergen identification is essential for Type I KS**
  - Referral to an allergist/immunologist for comprehensive testing (skin prick testing, specific IgE panels, provocation testing when safe) withing 4–6 weeks after the acute event.
  - Strict allergen avoidance is the most effective prevention strategy. Once the trigger is identified, the patient must avoid it completely.
  - Carry an epinephrine auto-injector if at risk for anaphylaxis — but understand the cardiac implications. Patients should inform all healthcare providers about their KS history.
  - Wear a medical alert bracelet/necklace listing the specific allergen and "Kounis Syndrome — avoid beta-blockers."
- **Cardiac follow-up**: Stress testing, echocardiography, and ongoing cardiology follow-up as appropriate for the type of KS.
- **Medication review**: Avoid known triggers.
  - If the patient requires antibiotics, NSAIDs, or contrast agents in the future, premedication protocols (antihistamines + corticosteroids) and close monitoring in a medical setting are recommended.
  - Mast cell stabilizers (e.g., cromolyn sodium, ketotifen) may be considered for patients with recurrent episodes or underlying mast cell disorders.
- **Manage cardiovascular risk factors aggressively** (hypertension, diabetes, dyslipidemia, smoking cessation) — especially for Types II and III.

MINIMIZING RISKS

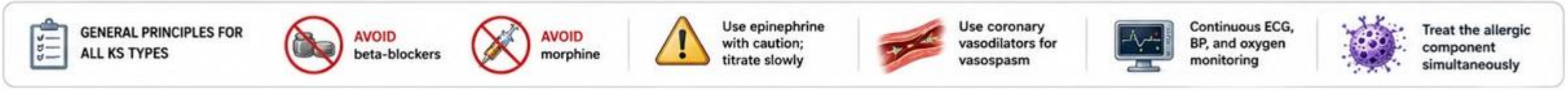
For healthcare systems:

- Educate all emergency personnel (prehospital and ED) about KS.
- Include KS in ACS differential diagnosis protocols.
- Ensure tryptase levels can be drawn and processed in the ED.
- Develop institutional protocols for "allergic ACS" that modify standard ACS pathways.

For clinicians:

- Always ask about allergies AND cardiac history simultaneously.
- Monitor for cardiac symptoms during any allergic reaction treatment.
- Consider biocompatible stent materials in patients with known metal allergies

- For patients:
  - Comprehensive allergy history before administering any medication.
  - Pre-medication protocols for patients with known drug allergies requiring high-risk medications or contrast.
  - Allergy testing and documentation after any significant allergic reaction.
  - Awareness that even "mild" allergies can have cardiac consequences.



SUMMARY: TAKE-AWAY MESSAGES

For First Responders:

- "Hives + chest pain = think Kounis." If a patient having an allergic reaction develops chest pain, ECG changes, or hemodynamic instability — suspect KS.
- Get a 12-lead ECG. Transmit it with the allergic context.
- Treat anaphylaxis with epinephrine when life-threatening but know it can worsen cardiac ischemia.
- Do NOT give beta-blockers.
- Communicate the allergic context to the receiving facility.
- Rapid transport to a PCI-capable center.

For ED Clinicians:

- KS is not rare — it is rarely recognized. Think of it whenever allergy and ACS coexist.
- Modify your ACS protocol: no beta-blockers, no morphine, cautious aspirin, aggressive anti-allergic therapy.
- Draw tryptase early.
- The epinephrine dilemma is real: titrate IV from low doses when both anaphylaxis and ischemia are present.
- Involve cardiology AND allergology.
- Ensure recovered patients get allergen identification and long-term prevention planning.

Recognizing that a heart attack is allergic in origin changes everything about how it is treated. Awareness saves lives.

QUESTIONS?

Kounis Syndrome

It is not a rare condition – it is a rarely recognized condition.