

REVIEW

Anaphylaxis and cardiovascular disease: therapeutic dilemmas

P. Lieberman¹ and F. E. R. Simons²

¹Departments of Internal Medicine and Pediatrics (Divisions of Allergy and Immunology), University of Tennessee College of Medicine, Germantown, TN, USA and ²Department of Pediatrics and Child Health and Department of Immunology, Faculty of Medicine, University of Manitoba, Winnipeg, MB, Canada

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Summary

Cardiovascular disease (CVD) increases the risk of severe or fatal anaphylaxis, and some medications for CVD treatment can exacerbate anaphylaxis. The aim of this article is to review the effect of anaphylaxis on the heart, the potential impact of medications for CVD on anaphylaxis and anaphylaxis treatment, and the cardiovascular effects of epinephrine. The therapeutic dilemmas arising from these issues are also discussed and management strategies proposed. PubMed searches were performed for the years 1990–2014 inclusive, using terms such as angiotensin-converting enzyme (ACE) inhibitors, adrenaline, allergic myocardial infarction, anaphylaxis, angiotensin-receptor blockers (ARBs), beta-adrenergic blockers, epinephrine, and Kounis syndrome. Literature analysis indicated that: cardiac mast cells are key constituents of atherosclerotic plaques; mast cell mediators play an important role in acute coronary syndrome (ACS); patients with CVD are at increased risk of developing severe or fatal anaphylaxis; and medications for CVD treatment, including beta-adrenergic blockers and ACE inhibitors, potentially exacerbate anaphylaxis or make it more difficult to treat. Epinephrine increases myocardial contractility, decreases the duration of systole relative to diastole, and enhances coronary blood flow. Its transient adverse effects include pallor, tremor, anxiety, and palpitations. Serious adverse effects (including ventricular arrhythmias and hypertension) are rare, and are significantly more likely after intravenous injection than after intramuscular injection. Epinephrine is life-saving in anaphylaxis; second-line medications (including antihistamines and glucocorticoids) are not. In CVD patients (especially those with ACS), the decision to administer epinephrine for anaphylaxis can be difficult, and its benefits and potential harms need to be carefully considered. Concerns about potential adverse effects need to be weighed against concerns about possible death from untreated anaphylaxis, but there is no absolute contraindication to epinephrine injection in anaphylaxis.

Correspondence:

Dr P. Lieberman, Departments of Internal Medicine and Pediatrics (Divisions of Allergy and Immunology), University of Tennessee College of Medicine, Germantown, TN 38138, USA.

E-mail: phillieberman@hotmail.com

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Introduction

Anaphylaxis is a systemic allergic or hypersensitivity reaction that is rapid in onset and can result in death [1]. Risk factors for the development of severe or fatal anaphylaxis include advanced age, concomitant diseases such as cardiovascular disease (CVD) and some of the medications used to treat it, and chronic pulmonary diseases. Cofactors such as exercise, emotional stress, acute infection, and non-steroidal anti-inflammatory drugs potentially amplify anaphylaxis [2–6].

Target organ involvement and patterns of symptoms and signs observed during anaphylaxis can differ among patients and can differ from one episode to another in the same patient. Typically, symptoms are

sudden in onset (minutes to a few hours after exposure to a trigger) and occur in two or more body systems: skin and mucous membranes; upper and/or lower respiratory tract; cardiovascular system; gastrointestinal tract; and/or central nervous system [1–6].

The cardiovascular system is involved in up to 72% of patients with anaphylaxis [7]. Symptoms and signs can include chest pain, tachycardia, hypotension, dizziness, collapse, shock, loss of consciousness, and cardiac arrest. As previously noted, patients with CVD are potentially at increased risk of developing severe or fatal anaphylaxis, and beta-adrenergic blockers and angiotensin-converting enzyme (ACE) inhibitors potentially exacerbate anaphylaxis; additionally, beta-blockers can make it more difficult to treat [2–6].

However, the impact of CVD on the development of anaphylaxis symptoms and the contributory effects of medications used in CVD treatment to the severity of anaphylaxis have not been universally demonstrated [7–17].

Epinephrine (adrenaline) is the life-saving medication of first choice in anaphylaxis treatment [2–6]; yet its use in patients with CVD, especially those with acute coronary syndrome (ACS), can present a dilemma for physicians because concerns about its potential cardiac adverse effects need to be weighed against concerns about death from untreated anaphylaxis [18].

Here, we review anaphylaxis and the heart, the potential impact of CVD medications on anaphylaxis and anaphylaxis treatment, the cardiovascular effects of epinephrine, and the therapeutic dilemmas that consequently arise.

Methods

PubMed searches were performed for the years 1990–2014 inclusive, using relevant terms including ‘ACE inhibitor’, ‘adrenaline’, ‘allergic myocardial infarction’, ‘anaphylaxis’, ‘angiotensin-receptor blocker’, ‘beta-adrenergic blocker’, ‘epinephrine’, and ‘Kounis syndrome’.

Results and discussion

Anaphylaxis and the heart

In the healthy human heart, mast cells are numerous. They are located predominantly between myocardial fibres, around blood vessels, and in the arterial intima. They are often detected in close contact with the small intramural coronary arteries, as well as in the walls of the large epicardial vessels [19, 20]. In patients with CVD, including those with ACS and cardiomyopathies, the number and density of cardiac mast cells are increased in these areas. In ACS, mast cells are key constituents in atherosclerotic plaques and accumulate at sites of plaque erosion and rupture [20, 21].

In anaphylaxis, the heart is both a source of mediators of inflammation and a target for these mediators [19–21]. Histamine, leukotriene C₄, prostaglandin D₂, tryptase, platelet-activating factor, chymase, and renin released locally from cardiac mast cells potentially cause coronary artery spasm, induce hypotension, and influence the contractile function of the heart, thereby contributing directly to the cardiovascular manifestations of anaphylaxis [20]. Elevated levels of beta-tryptase can be found in post-mortem serum in some patients with fatal coronary artery disease (CAD) and no history of anaphylaxis [22]. Additionally, chymase, along with angiotensin-converting enzyme, participates

in conversion of angiotensin I to angiotensin II, leading to cardiac dysfunction [23].

In an epidemiologic study of anaphylaxis admissions and fatalities in Australia from January 1997 through December 2005, major risk factors associated with death from drug-induced anaphylaxis included advanced age (55–85 years) and the presence of cardiovascular and respiratory comorbidities [24]. In these older patients, during the 9 years studied, anaphylaxis admissions increased by 150% and anaphylaxis fatalities increased by 300% [24].

In a retrospective consecutive cohort study of 220 patients with anaphylaxis presenting to an emergency department (ED), cardiovascular symptoms were more likely to occur in patients aged 50 years or older (55.6% vs. 30.1%; $P < 0.001$), especially in those older than 65 years (64.3% vs. 32.3%; $P = 0.002$) as compared with patients younger than 50 years or 65 years, respectively [25]. In addition, those aged 50 years or older (40.7% vs. 63.3%; $P = 0.004$), or aged 60 years or older (32.1% vs. 61.5%; $P = 0.003$) were less likely to be prescribed self-injectable epinephrine, as compared with younger patients [25].

In a retrospective case review of 25 elderly people (mean age 59 years) with fatal anaphylaxis, 19 of the 23 patients undergoing autopsy had CVD confirmed at autopsy; indeed, CVD was the most common pathologic finding identified [26].

Patients undergoing cardiac surgery not only have impaired cardiovascular function because of their underlying heart disease, but are also at risk of perioperative anaphylaxis from agents such as antibiotics, neuromuscular blockers, blood products, heparin, polypeptides (aprotinin, natural rubber latex, protamine), and colloid intravascular volume expanders (albumin, dextrans, gelatins, and hydroxyethyl starch) [27]. Detecting anaphylaxis can be challenging in these patients because most anaesthetic drugs can cause vasodilation, hypotension, and cardiopulmonary dysfunction due to direct and indirect effects on adrenergic responses [27].

Patients with anaphylaxis can present with ACS (angina, myocardial infarction) or arrhythmias in the absence of any exogenous epinephrine administration. Allergic myocardial infarction was first described by Pfister and Plice in 1950 [28]. Allergic angina and allergic myocardial infarction in anaphylaxis are now commonly known as Kounis syndrome [29–35], which can occur in patients with diagnosed CAD, those with subclinical CAD, and in young healthy people, even children, with no history of CAD [30, 31]. In patients who experience chest pain and ST-segment elevation during anaphylaxis and have normal electrocardiograms, echocardiograms, and coronary angiograms after resolution of anaphylaxis, the syndrome is attributed to transient coronary artery vasospasm [31].

Published case reports, small case series, and reviews of patients with Kounis syndrome are increasing in number year on year. Use of the term Kounis syndrome has now broadened beyond vasospastic allergic angina and allergic myocardial infarction to include cardiac symptoms caused by stent thrombosis with occlusion. Kounis syndrome should be considered in anyone who develops ACS or an arrhythmia during an anaphylactic episode [29–35].

Medications used for the treatment of CVD and their potential impact in anaphylaxis

Beta-blockers, ACE inhibitors, and other medications play a critically important role in reducing mortality and preventing complications in patients with CVD [36, 37]. Some [8, 9, 13–15, 17], although not all [10–12], reports suggest that these medications can exacerbate anaphylaxis and make it more difficult to treat.

In an ED study with a retrospective observational cohort design, 302 adults (median age 44.3 years [range 32–58]) were treated for severe anaphylaxis triggered by food, medication, venom, and other agents. Of the 302 patients, 29% were taking at least one antihypertensive medication: beta-blockers were taken by 16%, ACE inhibitors by 11%, calcium channel blockers by 7%, angiotensin-receptor blockers (ARBs) by 3%, and diuretics by 15%. Of the 302 patients, 18% had syncope, hypoxia, or hypotension; 19% required hospitalization; and 46% had involvement of three or more body organ systems. After appropriate adjustments for age, sex, triggers, and pre-existing lung disease, the association between antihypertensive medication use in aggregate and involvement of three or more organ systems during their anaphylactic episode yielded an odds ratio (OR) of 2.8 (95% confidence interval [CI], 1.5–5.2; $P = 0.0008$), and the association between antihypertensive use and hospitalization yielded an OR of 4.0 (95% CI, 1.9–8.4; $P = 0.0001$) [13].

Most clinical and epidemiological data on the impact of CVD medications in anaphylaxis pertain to beta-adrenergic blockers and ACE inhibitors. Case reports suggest that when anaphylaxis occurs in a patient using a beta-blocker, it can be more severe or protracted and difficult to treat [8]. Administered concomitantly with epinephrine, beta-blockers are associated with unopposed alpha-agonism, an enhanced vasoconstrictor response, and an increase in blood pressure. This effect may be more prominent with non-selective beta-blockers such as propranolol than with selective beta-1 blockers such as metoprolol [8, 9].

In a retrospective observational study of 1389 patients with a history of anaphylaxis to insect stings who were treated with venom immunotherapy (VIT), 11.2% of the patients (mean age 53.4 ± 10.6 years) had CVD. In

these patients, the incidence and severity of systemic allergic symptoms from field stings or from sting challenges did not differ significantly between those with CVD who were taking beta-blockers (1 of 7 patients, 14.3%) and those with CVD who were not taking beta-blockers (4 of 29 patients, 13.8%) [10]. The authors concluded that use of beta-blockers during VIT may be indicated in heavily exposed patients with severe CVD and described a fatal case that highlighted the need for extreme caution when substituting medications from another class for a beta-blocker in a cardiac patient [10].

Another retrospective observational study reported 657 consecutive patients (mean age 44 years [range 6–84 years]) with a history of venom-induced anaphylaxis after *Hymenoptera* field stings. In the 26.2% of patients with severe anaphylaxis, 4 of 12 risk factors were significantly associated with severe anaphylaxis: elevation of baseline serum tryptase, absence of urticaria or angio-oedema, time interval of less than 5 min from sting to symptom onset, and advanced age (all $P < 0.001$). However, in the 19.8% of 657 patients who had CVD, no relationship could be established between the severity of anaphylaxis and risk factors such as comorbidities and concurrent cardiovascular medications, including beta-blockers (9% of the 657 patients; $P = 1.0$), ACE inhibitors (4.9%; $P = 1.0$), and both (4.1%; $P = 0.78$). The investigators noted the need for careful reflection if cardiovascular medications were to be changed or discontinued [11].

In a subsequent clinical practice-based study, the same group reported the relationship between 12 risk factors (including cardiovascular medications) and systemic reactions during VIT build-up using a rush protocol in 743 patients (mean age 46 ± 21 years). Of these patients, 25.2% had a history of CVD and 24.5% were on cardiovascular medication(s), including ACE inhibitors (11.6%, mainly ramipril and enalapril), beta-blockers (3%, as alternatives were substituted in some patients before VIT initiation), and a combination of ACE inhibitors and beta-blockers (1.5%). Of the patients on cardiovascular medication(s), 11.7% had a history of systemic reactions and 3% had anaphylaxis diagnosed using objective criteria. Concomitant CVD, asthma, or chronic obstructive pulmonary disease, and treatment with ACE inhibitors ($P = 0.097$), beta-blockers ($P = 1.0$), or both at the time of the anaphylactic episode were not significantly related to the incidence of systemic reactions [12].

Contrasting findings were reported in a retrospective/prospective observational study of 6 risk factors associated with anaphylaxis after *Hymenoptera* field stings, conducted in 962 patients (mean age 38.2 ± 16.9 years) who were not yet protected by VIT. Of these, 21.4% had a severe anaphylactic reaction to a field sting. Severe

reactions were associated with an elevated baseline serum tryptase level (non-linear association), older age ($P < 0.001$), male sex ($P < 0.001$), preceding milder reactions to field stings ($P < 0.001$), and vespid venom allergy ($P < 0.008$). The 4.4% of patients taking ACE inhibitors were more likely to experience severe anaphylaxis after a field sting, defined as shock, loss of consciousness, or cardiac arrest, as compared with those not taking ACE inhibitors (42.9% vs. 20.4%, respectively; $P = 0.019$). No association with the use of beta-blockers (70% cardioselective), taken by 5.4% of patients, was found, although their role could not be entirely excluded [14].

In a subsequent retrospective observational study of the clinical effectiveness of VIT, the most important of 15 risk factors associated with a systemic reaction ('therapy failure') during in-hospital *Hymenoptera* sting challenges was ACE inhibitor medication (based on OR 5.24 [95% CI, 1.83–13]; $P < 0.001$) [15]. The investigators noted that theoretical considerations in support of a detrimental effect of ACE inhibitors in anaphylaxis included impaired degradation of bradykinin and imbalances in the renin-angiotensin system [15].

In studies to date, the number of patients taking ARBs has been too small to allow an ARB-specific analysis of associated risks. One group of investigators noted that although the potentially harmful role of ARBs could not be excluded in their study, they might be associated with a lower anaphylaxis risk because they selectively block the type 1 receptor for angiotensin II and, unlike ACE inhibitors, do not interfere directly with kinin catabolism [14, 16].

In a computer simulation model designed to capture the risk of death from heart disease and from anaphylaxis in 10 000 theoretical patients with peanut allergy who were post-myocardial infarction or had congestive heart failure, the cardiac benefits of beta-blockers were found to outweigh the increased risk of fatal anaphylaxis [17].

In an anaphylaxis registry study involving 4783 patients (all ages, all triggers), the increased risk of severe anaphylaxis after monotherapy with beta-blockers or ACE inhibitors was found to be modestly but significantly increased when a beta-blocker and an ACE inhibitor were taken concurrently [38]. The investigators confirmed this finding in a murine model in which, given alone, drugs from these classes had either no significant effects (ramipril) or modest augmenting effects (metoprolol), but when given concurrently, they exacerbated anaphylaxis severity and significantly increased the release of mast cell mediators [38]. Using bone marrow-derived cultured mast cells, they also provided some evidence that the synergistic effect was due at least in part to decreasing the threshold for mast cell activation [38].

Cardiovascular and other pharmacologic effects of epinephrine

Epinephrine exerts its pharmacologic effects through alpha- and beta-adrenergic receptors [39–43]. Through alpha-1 adrenergic receptor stimulation, it increases vasoconstriction, peripheral vascular resistance, and blood pressure, thereby preventing and relieving life-threatening hypotension, shock, laryngeal oedema, and upper airway obstruction [39]. Through beta-1 adrenergic receptor stimulation, it has inotropic and chronotropic effects. By increasing myocardial contractility and decreasing the duration of systole relative to diastole, it leads to enhanced coronary artery blood flow [39]. It also leads to bronchodilation through beta-2 adrenergic receptors [39], and when used promptly, it suppresses the release of mediators from mast cells and basophils [43].

Epinephrine is available in a variety of formulations, doses, and concentrations for administration by different routes [40] (Table 1). As recommended in all anaphylaxis guidelines, for the initial treatment of anaphylaxis, it should be given in a timely manner by i.m. injection in the mid-outer aspect of the thigh. In practical terms, the maximum i.m. dose in adults is 0.3–0.5 mg. If the response to the initial i.m. dose is not optimal, the dose can be repeated at 5- to 15-min intervals [2–6].

The rationale for administration of epinephrine by i.m. injection vs. s.c. injection is described in Table 1 [40]. In skeletal muscle, epinephrine has a vasodilator effect that facilitates rapid absorption into the central circulation and concomitant rapid onset of pharmacologic effects [39]. After s.c. injection, the vasoconstrictor effect of epinephrine in the subcutaneous tissue potentially delays its absorption and the onset of its pharmacologic effects [39]. The main reasons for initial administration of epinephrine by i.m. injection vs. i.v. injection are the significantly *higher* benefit-to-harm ratio and the significantly *lower* risk of overdose with i.m. injection as compared with i.v. injection [40, 44] (Table 1).

In patients who are unresponsive to the initial i.m. dose(s) of epinephrine and i.v. fluid resuscitation, epinephrine should be administered by the i.v. route, preferably by a physician who is trained and experienced in giving a vasopressor by infusion pump, with dose titrations based on the clinical information obtained through continuous electronic monitoring of blood pressure, of cardiac rate and function, and of oxygenation by pulse oximetry [2–4].

Transient pharmacologic effects of epinephrine such as pallor, tremor, anxiety, and palpitations potentially occur after the administration by any route and cannot be dissociated from its beneficial pharmacologic effects [39, 40]. Serious adverse effects including hypertension,

Table 1. Epinephrine: pros and cons of different routes of administration in anaphylaxis* (adapted from reference 40, with additional information from reference 44)**Intramuscular epinephrine****Pros**

Epinephrine has a vasodilator effect in skeletal muscle (in contrast to its vasoconstrictor effect in smooth muscle).[†]

Skeletal muscle is highly vascular, leading to rapid absorption.

Medication injected into the vastus lateralis muscle reaches the central circulation promptly.

Peak pharmacologic effects are achieved promptly.

i.m. epinephrine has a significantly higher benefit-to-harm ratio versus i.v. epinephrine.

i.m. epinephrine has a significantly lower risk of overdose versus i.v. epinephrine.

The i.m. route is the most commonly recommended route for initial treatment.

Cons

The i.m. route is not optimal if muscle perfusion is poor or absent due to shock or cardiorespiratory arrest.

Needle length and needle gauge of some auto-injectors might not be optimal for i.m. injection in some patients, although the force of injection carries epinephrine distal to the needle tip.

Subcutaneous epinephrine**Pros**

Readily accessible sites of injection.

Cons

Epinephrine leads to vasoconstriction and blanching of s.c. tissue, even in a 0.001 mg/mL (1 : 100 000) dilution.[‡]

Epinephrine delays its own absorption from s.c. tissue.[‡]

Compared with skeletal muscle, s.c. tissue is poorly vascularized.[§]

Rapid epinephrine absorption is even more critical in anaphylaxis than in asthma, for which the s.c. route was used in the past.[§]

Intravenous epinephrine**Pros**

Optimal route of administration for patients with severe anaphylaxis who have not responded to i.m. epinephrine and/or are experiencing profound hypotension or shock, or in whom cardiorespiratory arrest is imminent or has already occurred.

Cons

Establishing a peripheral i.v. route for epinephrine administration might be difficult in some patients.

i.v. injection of an epinephrine bolus is significantly more likely to cause harm[¶] (serious adverse effects) than i.m. injection of epinephrine.

Iatrogenic errors, including overdose, are significantly more common with i.v. bolus administration than with i.m. administration.

For safe administration in hypotension or shock, epinephrine is optimally given through an infusion pump and central line by physicians trained and experienced in continuous dose titration of vasopressors against continuously monitored cardiac rate, cardiac function, and blood pressure, and oxygenation monitored by using pulse oximetry. Errors in epinephrine dosing and/or intermittent monitoring of vital signs can be catastrophic for the patient.[¶]

*Other routes of epinephrine administration include inhalation through a metered-dose inhaler or a nebulizer and face mask; however, this route is not optimal for relief of systemic anaphylaxis symptoms.

[†]Endogenous epinephrine is a vasodilator in skeletal muscle in the 'fight or flight' response.

[‡]Epinephrine in a 0.001 mg/mL (1 : 100 000) dilution is widely used in surgery and dentistry to provide haemostasis and slow absorption of local anaesthetics from skin, s.c. tissue, mucosa, and submucosal tissue.

[§]After i.m. injection, median time to peak epinephrine levels is 8 min. After s.c. injection, median time to peak epinephrine levels is 34 min.

[¶]Serious systemic adverse effects include angina, myocardial infarction, cardiac arrhythmias, and cerebrovascular haemorrhage. Serious local side effects involve epinephrine extravasation, vasoconstriction, and tissue necrosis.

ventricular arrhythmias, myocardial infarction, and pulmonary oedema are most commonly reported when epinephrine is given by the i.v. route [44–46], particularly after bolus (push) i.v. administration, rapid i.v. infusion, or failure to guide dose titration using continuous electronic monitoring of blood pressure and cardiac rate and function [2–4, 40, 44]. Other errors during i.v. dosing involve erroneous administration of epinephrine 1 mg/mL solution by the i.v. route (i.e. failure to dilute it 10-fold or 100-fold for i.v. use) [47], or expression of epinephrine doses using ratios (e.g. epinephrine 1 : 1000) instead of mass concentrations (e.g. epinephrine 1 mg/mL) [48].

In an observational cohort study of 573 patients with anaphylaxis, of whom 57.6% received at least one dose of epinephrine, adverse cardiovascular events were associated with 3 of 30 doses of i.v. bolus epinephrine compared with 4 of 316 doses of i.m. epinephrine (10% vs. 1.3%; OR 8.7 [95% CI, 1.8–40.7]; $P = 0.006$). Moreover, overdose occurred with 4 of 30 doses of i.v. bolus epinephrine compared with 0 of 316 doses of i.m. epinephrine (13.3% vs. 0; OR 61.3 [95% CI, 7.5 to infinity]; $P < 0.001$) [44]. The authors concluded that their data support the safety of i.m. epinephrine and suggest a need for extreme caution and further education about i.v. bolus treatment with epinephrine in anaphylaxis.

Therapeutic dilemmas in the acute and long-term management of anaphylaxis in patients with CVD, and a way forward

For the acute management of all patients with anaphylaxis, although published guidelines recommend prompt i.m. injection of epinephrine [2–6], in many ED studies, epinephrine has been administered to as few as 7% or 12% of patients regardless of their anaphylaxis triggers, age, comorbidities, concurrent medications, or amplifying cofactors [49, 50]. In contrast, second-line medications such as H₁-antihistamines, H₂-antihistamines, and glucocorticoids are commonly administered [49, 50]. Implementation of a protocol or management plan for anaphylaxis treatment significantly improved the rate of epinephrine injection in initial management [51].

H₁-antihistamines relieve itching, flushing, and urticaria. H₂-antihistamines given concurrently with H₁-antihistamines provide some additional relief of urticaria but do not relieve itching. Glucocorticoids theoretically prevent biphasic or protracted anaphylaxis, although this effect awaits confirmation in randomized controlled trials. Selective beta-2 adrenergic agonists such as salbutamol (albuterol) have important bronchodilator effects. However, none of these second-line medications is life-saving in anaphylaxis because none of them has alpha-1 agonist vasoconstrictor effects, and none of them relieves shock or upper airway obstruction due to laryngeal oedema [2–6, 52–54].

Systematic reviews of H₁-antihistamines, H₂-antihistamines, and glucocorticoids have failed to identify studies that satisfied the inclusion criteria and provide evidence from randomized controlled trials to confirm their effectiveness in anaphylaxis [52–54]. No anaphylaxis guidelines recommend the use of these medications as *initial* treatment in anaphylaxis or as a *substitute* for epinephrine treatment in anaphylaxis [2–6].

In patients with CVD, including ACS, the rate of epinephrine administration in anaphylaxis is largely unknown.

In a review of anaphylaxis treatment in 17 published case reports of Kounis syndrome in patients aged 13–72 years with ACS during beta-lactam antibiotic-induced anaphylaxis, epinephrine was given to only 23.5% of the patients. H₁-antihistamines were given to 70.6%, H₂-antihistamines to 35.3%, and glucocorticoids to 76.5%. Although epinephrine administration was apparently avoided by many clinicians, when it *was* given, the response was excellent and no deaths were reported [35].

In an individual patient with CVD and an acute anaphylactic episode, deciding whether to administer epinephrine, even in the relatively low, safe dose of 0.3 mg i.m., often presents a critical therapeutic dilemma, and the potential benefits vs. the harms of

epinephrine injection need to be weighed carefully. However, contrary to some interpretations [18], the presence of CVD does not ‘forbid’ the use of epinephrine in anaphylaxis, because no other medications have the life-saving effects of epinephrine in this medical emergency.

Long-term management of patients with CVD who are at increased risk of anaphylaxis also presents therapeutic dilemmas, as anaphylaxis can potentially be complicated by concurrent use of beta-blockers, ACE inhibitors, and other medications for CVD, and by advanced age, limited cardiovascular reserves, and chronic pulmonary disease. The relative importance of CVD, CVD medications, and other risk factors awaits further clarification [7–17].

A patient with CVD and a history of anaphylaxis can benefit from an allergy/immunology specialist’s evaluation of the risk of anaphylaxis recurrences and how to reduce that risk, in addition to a cardiologist’s evaluation of optimal long-term pharmacotherapy for CVD.

To date, the evidence for using or not using medications such as beta-blockers and ACE inhibitors in patients with CVD who are also at risk of anaphylaxis consists largely of case reports and retrospective observational studies [8–17]. Additional high-quality observational studies and prospective studies, designed to focus on CVD, the medications used to treat it, and related risk factors such as advanced age and chronic pulmonary disease, are urgently needed.

Specialists in allergy/immunology, cardiology, and emergency medicine should consider the possibility of collaborating in the development of evidence-based guidelines for optimal anaphylaxis management in patients with CVD. Such guidelines should address not only the management of acute anaphylactic episodes, but also the long-term management of patients at increased risk of anaphylaxis.

Conclusions

There is no absolute contraindication to epinephrine injection in anaphylaxis. Concerns about the potential adverse cardiovascular effects of epinephrine in patients with CVD need to be weighed against concerns about untreated or under-treated anaphylaxis and death.

The long-term pharmacologic management of patients at risk of anaphylaxis who have concomitant CVD remains a challenge for clinicians because some of the medications used to treat CVD potentially increase anaphylaxis severity and the difficulty of treating an anaphylactic episode. In such patients, the relative importance of CVD and CVD treatment as risk factors, compared with the importance of advanced age, chronic pulmonary disease, and limited cardiovascular reserves, needs to be further elucidated in observational and prospective studies.

Consideration should be given to the development of evidence-based guidelines by specialists in allergy/immunology, cardiology, and emergency medicine for the acute management of anaphylaxis in patients with CVD and the long-term pharmacologic management of patients with CVD who are also at risk of anaphylaxis.

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Conflict of interest

PL has served as a medical consultant for Mylan and Sanofi and as a speaker for Mylan. FERS has served on the Medical Advisory Boards for ALK, Mylan, and Sanofi.

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