

Should β -blockers be given to patients with heart disease and peanut-induced anaphylaxis? A decision analysis

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Background: β -Blocker therapy postmyocardial infarction is generally recommended because it reduces mortality. However, β -blockers may increase anaphylaxis mortality in the growing population of patients with peanut-induced anaphylaxis.

Objective: We sought to assess the risks and benefits of β -blocker therapy among patients with peanut allergy and heart disease.

Methods: We created a Markov model for patients with heart disease at risk for peanut-induced anaphylaxis to compare life expectancy with the following strategies: (1) β -blocker and (2) no β -blocker. Meta-analysis and a literature review were used to estimate model parameters. We performed sensitivity analysis to explore parameter uncertainty.

Results: For peanut-allergic patients who are postmyocardial infarction or who have congestive heart failure, the heart disease benefit of β -blockers outweighs the increased likelihood of dying from anaphylaxis, increasing life expectancy by 9.4 and 17.4 months, respectively. β -Blocker was preferred unless (1) the annual rate of moderate to severe anaphylaxis exceeded 6.0% for postmyocardial infarction and 15% for congestive heart failure patients; (2) β -blocker therapy increased the incidence of moderate to severe anaphylaxis >2.5-fold for postmyocardial infarction and >5.8-fold for congestive heart failure patients; (3) anaphylaxis case fatality exceeded 6.5% postmyocardial infarction; or (4) β -blocker therapy increased anaphylaxis case fatality >25-fold postmyocardial infarction.

Conclusion: Our results suggest that for patients postmyocardial infarction or with congestive heart failure who are at risk for peanut-induced anaphylaxis, β -blocker use should still improve survival. However, the epidemiology of

anaphylaxis and effects of β -blocker therapy on anaphylaxis incidence and mortality require further study. (*J Allergy Clin Immunol* 2004;113:977-82.)

Key words: Anaphylaxis, peanut allergy, coronary artery disease, congestive heart failure, β -adrenergic receptor antagonists

An estimated 3 million persons in the United States are allergic to peanuts or tree nuts,¹ and recent medical literature and popular press reports have focused attention on the dangers of unintended exposures to these foods among patients who are susceptible.^{2,3} Exposures occur despite attempts at avoidance, and reactions range from mild and self-limited to fatal anaphylaxis, with an estimated 150 deaths per year.⁴ In the Western world, the incidence of peanut allergy appears to be increasing in children,⁵ and because this allergy infrequently resolves itself, an increasing number of adults are expected to be at risk for anaphylaxis in the future.⁶

At the same time, coronary heart disease continues to be a leading cause of morbidity and mortality. The American Heart Association 2003 estimates include 12.9 million persons in the United States with coronary heart disease and 1.1 million cases of myocardial infarction (MI) or fatal coronary heart disease.⁷ β -Blockers reduce mortality after MI,⁸ and several guidelines have endorsed their long-term use in patients post-MI^{9,10} and in patients with congestive heart failure (CHF).¹¹ Although these guidelines discuss common contraindications to use of β -blockers, none directly addresses food allergy and anaphylaxis risk.

Reports of severe and fatal anaphylaxis among patients receiving β -blockers have raised concerns about their use among patients who are at risk for anaphylaxis.¹² One author reported 5 cases of severe anaphylaxis during an 18-month period among patients taking propranolol.¹³ β -Blockade enhances both the generation of and end-organ response to mediators of anaphylaxis; as a result, epinephrine may be ineffective therapy for anaphylaxis in a patient taking a β -blocker.¹⁴ Prescribing information for β -blockers contains warnings regarding possible severe anaphylaxis among patients who are at risk.¹⁵

A 1989 guideline advises against β -blocker use among patients undergoing immunotherapy because of anaphylaxis risk¹⁶ but does not directly address β -blockers for patients with peanut allergy. When a patient with peanut allergy develops heart disease, clinicians must consider the evidence and weigh the risks and benefits of using a β -blocker. Because there are no randomized trials or

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*Abbreviations used*CHF: Congestive heart failure
MI: Myocardial infarction

even prospective cohort studies that examine the effect of β -blocker therapy on anaphylaxis incidence and mortality, we developed a decision-analytic model¹⁷ to help clinicians decide whether β -blocker therapy is beneficial for patients with peanut allergy and heart disease.

METHODS

We used a computer simulation model to capture the risks of death from heart disease and from anaphylaxis for a population of patients with heart disease and peanut allergy. In this Markov model, cohorts of 10,000 identical adults with peanut allergy and heart disease were assigned to 1 of 2 strategies: (1) β -blocker therapy or (2) no β -blocker. To capture prognostic uncertainty, patients might move among predefined states of health over time. Each month, patients might remain in a particular Markov health state or move to another health state after a health-related event such as death. The likelihoods of these events are termed *transition probabilities*. Base-case estimates are shown in Table I.^{8,12,14,18-23}

In our model, cohort members started in the baseline health state, and during each monthly cycle, patients could die from a fatal cardiovascular event or age-related mortality, as occurs within the general population. Alternatively, patients might have anaphylaxis that might be fatal. Persons who remained alive returned to the baseline health state and were given credit for having lived that month. Monthly cycles were repeated until all members of the cohorts had died. By tracking the outcome for all cohort members, the model estimated the average life expectancy associated with each strategy. We did not apply discounting, nor did we adjust for quality of life. Data for annual mortality rates with increasing age were obtained from US life tables.²⁴

Sensitivity analysis

We performed sensitivity analysis to test model assumptions. In 1-way sensitivity analysis, we varied model parameters 1 at a time to find the threshold value at which the life expectancy would be equal for both strategies. We also performed 2-way sensitivity analysis by plotting the threshold values produced when model parameters were varied simultaneously. All analyses were performed by using Decision Maker (WinDM Beta 2002.5; Pratt Medical Group, Boston, Mass).

Postmyocardial infarction model

We used published meta-analyses of randomized, controlled trials comparing β -blocker versus placebo^{8,18,25} to estimate annual heart disease-specific mortality and efficacy of β -blockers for reducing mortality. By using actuarial techniques, we calculated the excess annual mortality rate caused by heart disease.^{8,18,25} We calculated the relative risk of death and 95% CI associated with β -blocker therapy by performing a DerSimonian and Laird random effects meta-analysis²⁶ of these trials with Microsoft Excel97 (Microsoft Corp, Redmond, Wash). The efficacy of β -blocker therapy equalled 1 minus relative risk.

Congestive heart failure model

Similarly, we calculated an excess mortality rate from heart disease and relative risk of mortality with β -blocker therapy for patients with CHF on the basis of a meta-analysis of trials from a systematic review.¹⁹

Anaphylaxis incidence

In questionnaire studies, as many as 50% of peanut-allergic respondents reported an adverse reaction in the previous year, but most reactions were mild (not anaphylaxis), and most were in children.²⁷ Pumphrey²⁸ reported that 16% of patients prescribed epinephrine kits for a period of 7 years had subsequent reactions that might have benefited from the epinephrine injection. In a prospective study by Ewan and Clark,²⁹ ~16% of children and adults with peanut and nut allergy had a reaction during an average of 2 years. However, only 26% of the reactions were moderate, and 3% were severe, so a 2.3% annual rate of moderate or severe reaction was used as the base-case estimate. We tested a range of values in sensitivity analysis (Table I).

Anaphylaxis mortality

Observational studies have reported case fatality rates from anaphylaxis with any cause of 0.65% and 0.7%.^{20,21} When fatal anaphylaxis occurs, it is often caused by peanut or tree nut allergy^{30,31}; a Swedish registry of fatal and near-fatal reactions to foods found 4 deaths in 45 severe reactions to peanut, tree nut, or soy, for a case fatality rate of 8.9%.²² However, all deaths occurred among patients younger than 19 years, so this rate may not apply to an older population. After reviewing the literature and consulting an expert allergist (L. J. R.), we used a case fatality rate of 2.5% for moderate or severe anaphylaxis (Table I).

Effect of β -blocker on anaphylaxis incidence

Case series of fatal and nonfatal anaphylaxis have noted β -blocker use in several instances,^{30,32,33} but the number of patients at risk is uncertain. One prospective study of patients receiving immunotherapy showed no increased incidence of adverse reactions among patients receiving β -blocker therapy compared with those not receiving β -blockers.²³ In the base-case estimate, we assumed that β -blocker therapy did not increase the incidence of anaphylaxis (Table I).

Effect of β -blocker on anaphylaxis mortality

There have been several reports of treatment-refractory anaphylaxis among patients receiving β -blockers,^{34,35} and many experts list β -blockers as a risk factor for severe anaphylaxis.¹⁶ To bias our result against β -blocker therapy, we chose a 10-fold increase in case fatality (25% or 10 times the base-case 2.5%) and evaluated a range of 1 to 40 in sensitivity analysis (Table I).

Effect of anti-IgE therapy

We also examined the effect of potential new therapies for peanut allergy in sensitivity analysis. In a recent dose-ranging study, Leung et al⁴ found that anti-IgE therapy decreases susceptibility to reactions in patients with peanut allergy. More than 20% of patients given the higher doses of TNX-901 raised their threshold susceptibility to the equivalent of 24 peanuts, which is thought to be well above the usual amount in an accidental exposure. We therefore considered the effect of anti-IgE therapy that lowered the likelihood of moderate to severe anaphylaxis and death from anaphylaxis by 20% to 80%.

RESULTS

Postmyocardial infarction model

Under the baseline assumptions, patients treated with β -blockers had a higher lifetime risk for anaphylaxis mortality but a much lower lifetime risk of cardiac mortality. As a result, the average life expectancy for 58-year-old patients allergic to peanut post-MI was about 9.4 months longer with β -blocker therapy than without

TABLE I. Base-case data and assumptions

Variable	Post-MI model			CHF model		
	Baseline	Range	Reference	Baseline	Range	Reference
Age	58	30-90	(8,18)	59	30-90	(19)
Excess annual cardiac mortality						
Without β -blocker	7.0%	3.3% to 8.3%	(8,18)	12%	6% to 15%	(19)
Relative risk on β -blocker	0.807	0.74-0.88	(8,18)	0.729	0.62-0.86	(19)
Annual rate of anaphylaxis*						
Without β -blocker	2.3%	1% to 30%	(20-22)	2.3%	1% to 30%	(20-22)
Relative risk on β -blocker	1.0	0.9-5	(23)	1.0	0.9-5	(23)
Anaphylaxis* case fatality rate						
Without β -blocker	2.5%	1% to 9%	(20-22)	2.5%	1% to 9%	(20-22)
Relative risk on β -blocker	10	1-40	(12,14)	10	1-40	(12,14)

*Moderate to severe anaphylaxis.

TABLE II. Results

Variable	Post-MI model		CHF model	
	β -Blocker	No β -blocker	β -Blocker	No β -blocker
Lifetime risk of				
Moderate to severe anaphylaxis	25%	24%	19%	16%
Anaphylaxis mortality	6%	0.6%	5%	0.4%
Cardiac mortality	63%	72%	74%	84%
Life expectancy, y	11.1	10.3	8.4	7.0

β -blocker (Table II). This is about 60% of the benefit of β -blocker therapy seen in the model when risk of anaphylaxis was removed.

Congestive heart failure model

Both baseline annual mortality and efficacy of β -blocker therapy were higher in CHF trials than in the post-MI trials, so β -blocker therapy had an even greater benefit. For 59-year-old patients with peanut allergy and CHF, β -blocker therapy increased life expectancy by ~17 months (Table II). This is ~78% of the benefit of β -blocker therapy seen in the model when risk of anaphylaxis was removed.

Sensitivity analysis

We performed sensitivity analysis to assess the robustness of the result favoring β -blocker therapy by varying model parameters over clinically plausible ranges to determine whether the optimal choice of therapy changed with alternative assumptions (Table III). If a threshold value at which the 2 strategies were equal fell within the plausible range, the decision was sensitive to that parameter. Estimated data values above the threshold favored one strategy, and values below it favored the other.

In the post-MI model, the decision was sensitive to the 4 parameters related to anaphylaxis risk (Tables I and III). No β -blocker was preferred if β -blocker treatment increased the incidence of moderate to severe anaphylaxis by >2.5-fold or increased the case fatality rate of anaphylaxis by >25-fold. Similarly, no β -blocker was

TABLE III. Threshold analysis

Variable	Threshold	
	Post-MI	CHF
Age	None	None
Excess annual cardiac mortality		
Without β -blocker	2.7%	1.9%
Relative risk on β -blocker	0.93	0.96
Annual rate of anaphylaxis*		
Without β -blocker	6.0%	15%
Relative risk on β -blocker	2.5	5.8
Case fatality for anaphylaxis*		
Without β -blocker	6.5%	None
Relative risk on β -blocker	25	None

*Moderate to severe anaphylaxis.

preferred if the baseline annual risk of moderate to severe anaphylaxis exceeded 6.0% or the baseline case fatality from anaphylaxis exceeded 6.5% (Table III).

The results were not sensitive to patient age or to the efficacy of β -blockers for reducing mortality after MI. In our meta-analysis of post-MI trials comparing long-term β -blocker with placebo, we found a relative risk of death of 0.81 with a 95% CI of 0.74 to 0.88. The threshold of 0.93 is outside this range, so β -blocker therapy was preferred even with the most conservative estimate of efficacy. Similarly, the result did not change when we varied excess annual mortality from heart disease from 3.3% to 8.3%. No β -blocker therapy was preferred only if the annual mortality from heart disease fell below 2.7% (Table III).

Threshold values for the CHF model are also shown in Table III. The decision was sensitive to the annual rate of anaphylaxis but not to the 3 other parameters related to anaphylaxis risk (Tables I and III). As in the post-MI model, the decision was not sensitive to age, annual cardiac mortality, or the effect of β -blockers on heart disease.

Fig 2 depicts a 2-way sensitivity analysis for post-MI patients examining the effect of simultaneously varying (1) the relative risk of death from an episode of anaphylaxis with β -blocker therapy and (2) the annual rate of moderate to severe anaphylaxis. For the base-case

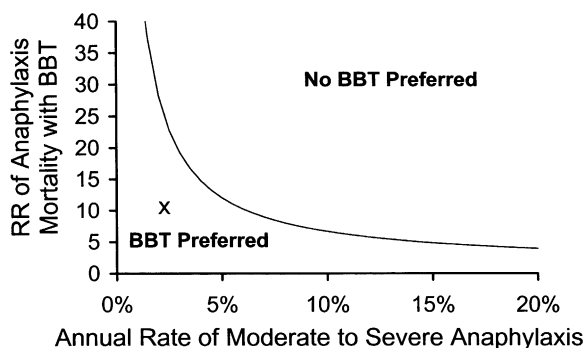


FIG 1. Sensitivity analysis for patients after myocardial infarction. β -Blocker therapy (BBT) is preferred for all combinations of the 2 model parameters in the region below and to the left of the line. An x depicts the baseline estimates. RR, Relative risk.

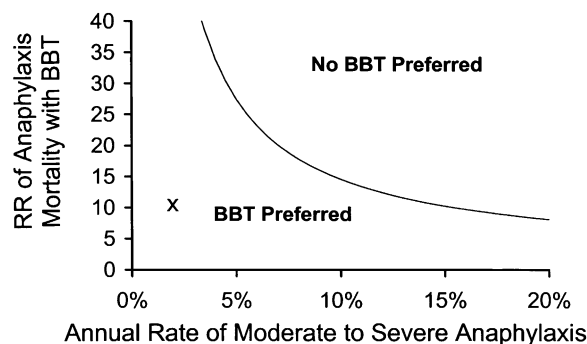


FIG 2. Sensitivity analysis for patients with CHF. BBT is preferred for all combinations of the 2 model parameters in the region below and to the left of the line. An x depicts the baseline estimates. RR, Relative risk.

estimates, β -blocker therapy was preferred, but for sufficiently high combinations of these risks, no β -blocker treatment was preferred. Fig 2 depicts the same analysis for patients with CHF.

In a separate analysis, anti-IgE therapy would extend life by only ½ to 3 weeks for patients not treated with β -blockers because of shortened life expectancy from heart disease. For patients treated with β -blockers, however, anti-IgE therapy would extend life by 1.5 to 6.6 months by mitigating the increased risk of anaphylaxis. When compared with patients given neither treatment, patients treated with both anti-IgE therapy and β -blockers would gain 12 months (post-MI) to 22 months (CHF).

DISCUSSION

Our analysis suggests that patients with heart disease and peanut allergy, who may be at increased risk for anaphylaxis mortality with β -blocker therapy, should benefit from β -blocker therapy because of reduced heart disease mortality. The average life expectancy gains range from 9.4 to ~17 months, with greater benefits for patients with CHF. For comparison, 35-year-old cigarette smokers who stops smoking increase their life expectancy by 8 to 10 months, and prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in patients with advanced HIV disease is thought to increase life expectancy by 5.3 months.³⁶

Although our model is based on average patient characteristics and treatment effects, some patients with different risk profiles may receive less benefit from β -blocker therapy. The beneficial effect of β -blockers is thought to be additive with other medical therapies for patients with heart disease, so most patients would be expected to benefit with regard to cardiac disease. For example, β -blocker therapy is usually considered to be a contraindication for patients with asthma and patients at risk for anaphylaxis from other causes (eg, venom or drugs). The risks for fatal anaphylaxis may be even higher among patients with food allergy and asthma, as seen in observational studies.³⁷ Conversely, patients without

asthma may be at much lower risk of fatal anaphylaxis and so may benefit more from β -blocker therapy. A patient with a history of particularly severe or frequent reactions may not want to risk taking a β -blocker. The added anxiety about potential anaphylaxis must be weighed against the benefits of β -blockers for reducing morbidity and mortality from heart disease. The beneficial effect of β -blockers is thought to be independent of other therapies for patients with heart disease,³⁸ so alternative medications that do not carry an increased risk for anaphylaxis could not supplant β -blockers. When assessing the risks and benefits for an individual patient, clinicians can use the thresholds and sensitivity analysis developed here to help guide the decision.

In contrast with the substantial evidence supporting the long-term benefit of β -blocker therapy for heart disease, data regarding the epidemiology and risk of anaphylaxis are limited. Our results were sensitive to anaphylaxis incidence and mortality and the effect of β -blocker therapy, but these were the most uncertain model parameters. We chose a 10-fold increase in anaphylaxis mortality for patients with peanut allergy treated with β -blockers, which may be higher than the true value, deliberately to bias our results against β -blocker therapy. Also, not all patients with peanut allergy are susceptible to anaphylaxis,³⁹ and some may outgrow their peanut allergy,^{40,41} but the fraction of patients in whom peanut allergy resolves is controversial. If susceptibility wanes over time or can be reduced with new therapies,⁴ then β -blockers would have an even more beneficial effect.

Our model was based on several other assumptions. We considered life expectancy only and did not adjust for β -blocker effects on quality of life. In addition, we modeled mortality from cardiac disease but not the reduced risk of MI among patients taking β -blockers. We assumed a class effect of β -blockers for both cardiac disease and anaphylaxis, though data regarding the latter are limited. Most reports of anaphylaxis and β -blocker use have involved the noncardioselective agent propranolol, but cardioselective agents have also been associated with anaphylactic and anaphylactoid reactions.¹⁴ We also chose not to consider long-term effects of anaphylaxis episodes, because most

resolve without sequelae, but some patients who survive a prolonged hospital course may develop long-term morbidity.

The care of patients with both peanut allergy and heart disease presents several challenges. As with any patient with food allergy, establishing the diagnosis is important, as is strict avoidance of the allergenic foods. Patients with significant peanut allergy should be given an epinephrine injection kit and an oral antihistamine and instructions on their appropriate use.² When a patient presents with an acute event, a careful history is important to distinguish acute coronary syndrome from anaphylaxis, because treatments for the 2 conditions are pharmacologic opposites. In the case of anaphylaxis, the usual dose of epinephrine for some patients is inadequate because of β -blockade, but for others, unopposed α -adrenergic effects may raise blood pressure and promote coronary vasospasm.¹² Emergency providers should consider the use of glucagon, which may be effective in the treatment of epinephrine-resistant shock.⁴² Finally, fluid resuscitation should be vigorous, because patients may lose 1/2 of their intravascular volume to extravascular spaces within 10 minutes.⁴³

Our results suggest that for patients with peanut allergy who are post-MI or who have CHF, β -blocker use should still reduce mortality. As peanut allergy incidence increases in the Western world, more patients may be faced with this choice, and our model provides a framework to aid clinicians and patients in the decision-making process. However, our results depend on a few key assumptions, and the epidemiology of anaphylaxis and the effects of β -blocker therapy on anaphylaxis incidence and mortality require further study.

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