

Original Article

Risk for Anaphylactic Reaction From Cardiac Catheterization in Patients Receiving β -Adrenergic Blockers or Angiotensin-Converting Enzyme-Inhibitors

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What is already known about this topic? Exposure to β -adrenergic blockers has been associated with a greater risk of more severe anaphylactic reactions, in patients exposed to intravenous high osmolar contrast media. Angiotensin-converting enzyme-inhibitors have also been implicated as a risk factor for more severe anaphylaxis.

What does this article add to our knowledge? In patients taking β -adrenergic blockers or angiotensin-converting enzyme-inhibitors, who are exposed to intra-arterial low osmolar contrast media, we found no statistically or clinically significant increase in risk for more frequent or severe anaphylactic reaction.

How does this study impact current management guidelines? Our findings do not support the contention that patients undergoing cardiac catheterization should have their β -adrenergic blocker or angiotensin-converting enzyme-inhibitor suspended. We find this practice unnecessary as a risk reduction measure.

BACKGROUND: β -Adrenergic blockers (BBs) have been associated with increased risk for severe anaphylactic reaction (AR) from contrast media; however, this was shown with intravenous contrast media, before widespread use of low osmolar contrast media, angiotensin-converting enzyme-inhibitors (ACE-Is), and cardioselective BBs.

OBJECTIVE: To assess the risk for AR during cardiac catheterization (CC) associated with BB or ACE-I exposure.

METHODS: Patients who experienced adverse reactions during CC from January 2004 to December 2013 were identified; 1 to 2 matched controls were assigned for each case. We analyzed AR rates in association with demographic variables, medication exposures (BBs, ACE-Is, angiotensin-receptor blockers, aspirin), and comorbidities: cardiovascular disorders, asthma, and atopy. **RESULTS:** We analyzed 71,782 CCs. Of these, severe 70 reactors were identified—46 (0.06%) fulfilled AR criteria. There were 35

cases of mild to moderate AR and 11 cases of severe AR (0.015%). There were no significant differences in age (61.3% vs 61.5%), sex (63% vs 64% males), cardiovascular disorder rate (78% vs 93%), and exposure to BBs (46% vs 51%; cardioselective: 77% vs 80%) and ACE-Is (37.0% vs 37.2%) in cases versus controls. Via multivariate logistic regression, BB exposure was not associated with greater AR frequency ($P = .35$) or severity ($P = .40$). Neither cardioselective BBs ($P = 0.2$) nor noncardioselective BBs ($P = .5$) influenced AR severity. ACE-Is had no effect on AR frequency ($P = .35$) or severity ($P = .14$). Lower AR frequency was associated with cardiovascular disorder ($P = .01$).

CONCLUSIONS: In this case-control study, severe AR was rarely observed. Exposure to BBs or ACE-Is did not significantly influence AR frequency or severity; however, most BBs were cardioselective. Our findings imply that cardioselective BB or ACE-I suspension is not warranted in association with CC. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: β -Adrenergic blockers; Angiotensin-converting enzyme-inhibitors; Anaphylactic reaction; Cardiac catheterization; Low osmolar contrast media

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication August 1, 2019; revised September 26, 2019; accepted for publication October 9, 2019.

Available online ■■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.10.020>

INTRODUCTION

There are more than 32 million contrast-enhanced studies performed in the United States each year.¹ There has been a marked increase in patients undergoing cardiac catheterization (CC), with a 350% increase in the number of CCs performed between 1979 and 2005, with more than a million CCs done

Abbreviations used

ACE-I- angiotensin-converting enzyme-inhibitor
 AR- anaphylactic reaction
 ARB- angiotensin-receptor blocker
 BB- β -adrenergic blocker
 CC- cardiac catheterization
 CVD- cardiovascular disease
 HOCM- hyperosmolar contrast media
 LOCM- low osmolar contrast media

annually.² The risk of anaphylactic reactions (ARs) in this population is complicated by the high frequency of cardiovascular disease (CVD) and concomitant treatment with β -adrenergic blockers (BBs), which has previously been associated with an increased risk of severe AR.³ These patients are frequently also taking angiotensin-converting enzyme-inhibitors (ACE-Is), which have also been implicated as a risk factor for more severe anaphylaxis and fatal perioperative anaphylaxis.^{4,5}

AR from contrast media can be serious or potentially life-threatening; such reactions still occur despite the widespread use of low osmolar contrast media (LOCM). The old terminology of "anaphylactoid" is no longer favored, because these contrast-induced reactions are clinically indistinguishable from classical IgE-mediated ARs. They differ from IgE-mediated ARs though, in that they are due to activation of complement, fibrinolytic, and kinin systems, and the release of histamine, prostaglandins, bradykinins, and other inflammatory mediators.⁶ LOCM has been associated with a lower risk for AR and severe AR.⁷ This is thought to be due to the reduced viscosity and osmolality. Conventional or high osmolar contrast media (HOCM) have 5 to 8 times the osmolality of plasma; LOCM have 2 to 3 times the osmolality of plasma.³

BBs have previously been associated with elevated risk for severe AR to HOCM.⁸ Both the therapeutic actions and the greater risk associated with BB use are due to β -adrenergic receptor blockade. The latter likely stems from an indirect inhibition of adenylate cyclase, thus lowering intracellular cyclic adenosine-3',5'-monophosphate, leading to a decreased threshold for anaphylactogenic mediator release.⁹ Increase in wheal size was observed when skin test sites were infiltrated with BBs before allergen inoculation.¹⁰ Infusions of cyclic adenosine-3',5'-monophosphate have been shown to lower the susceptibility to anaphylaxis in mice who were being administered BB treatment. A blunted response to epinephrine and/or inhaled bronchodilators also can hamper the treatment of anaphylaxis; thus, higher doses of epinephrine may be needed to overcome beta blockade in refractory anaphylaxis.^{11,12} BBs that selectively block β -1 receptors, often referred to as cardioselective BBs, are less likely to predispose to bronchospasm, because they act solely on the β -1 receptors in the cardiovascular system, and not on the β -2 receptors found in the respiratory bronchioles. Whether cardioselective BBs also are associated with increased risk of severe AR has not been established.

Use of ACE-Is may also pose risk for more severe anaphylaxis. Two cases of anaphylaxis were reported in patients receiving venom immunotherapy while taking ACE-I therapy. When these drugs were withheld, anaphylaxis was not observed. Anaphylaxis then recurred with resumption of ACE-I treatment.¹³ More recently, 2 European registries have implicated

ACE-I as being a risk factor for severe and fatal anaphylaxis.^{14,15} Van der Linden et al¹⁶ observed that plasma levels of endogenous epinephrine, norepinephrine, and angiotensin II rose in relation to hypotension during insect sting anaphylaxis.¹⁷ Venom immunotherapy significantly increases angiotensin II levels in patients receiving maintenance immunotherapy injections for Hymenoptera sting anaphylaxis.¹⁸ Agents such as ACE-I, whose pharmacologic activity reduces angiotensin I and angiotensin II, may confer increased risk to patients with a history of anaphylaxis. ACE-Is are further thought to impact a patient's compensatory physiologic response to anaphylaxis, predisposing to more severe reactions.¹⁷ Hemodynamic changes during anaphylaxis include peripheral vasodilatation and decreased effective intravascular volume, which may be followed by coronary vasoconstriction and myocardial depression. Increased vascular permeability may rapidly lead to a shift, of up to half, of intravascular fluid volume to the extravascular space, thus prompting a release of compensatory catecholamines and activation of the renin-angiotensin-aldosterone system.¹⁹ Blocking the terminal end of this physiological cascade with an ACE-I may diminish circulatory compensation mechanisms, and theoretically lead to prolonged or more severe anaphylaxis. Furthermore, angiotensinamide, an angiotensin II analogue, has successfully been used in a case of intraoperative anaphylaxis refractory to epinephrine and norepinephrine.¹⁹

A recent study done in the United Kingdom implicated both BBs and ACE-Is as being contributing factors in perioperative anaphylaxis.¹⁵ The 6th National Audit Project investigated cases of life-threatening anaphylaxis that occurred in the National Health System hospital complex during 1 year. Roughly 3 million anesthetic cases were reviewed; 266 cases of life-threatening or fatal ARs were identified. In this study, patients at highest risk of cardiac arrest or death were the elderly, those with cardiac disease, and those taking BBs or ACE-Is. Exposure to BBs or ACE-Is was associated with greater severity of reaction; 6 of the 10 fatalities were either associated with BBs or ACE-Is, or both.

With the previously reported risks of BBs, and the mounting evidence implicating ACE-Is as a risk factor for severe anaphylaxis, we carried out this study to examine the risk of exposure to these drugs on the frequency and severity of AR in the setting of the administration of intra-arterial LOCM in a population with a high rate of CVD.

METHODS

We reviewed charts of patients who underwent a left heart catheterization at the Cleveland Clinic Foundation Main Campus, between January 2004 and December 2013. Adverse reactions and the treatment administered were reviewed. Based on clinical presentation, adverse reactions were classified as being compatible with AR, or vasovagal/hemodynamic reactions. ARs were classified as the presence of 1 or more of the following, within 20 minutes of contrast media infusion: urticaria, angioedema, chest tightness or wheezing with shortness of breath, throat constriction or change in voice with or without stridor, hypotension (≥ 30 mm Hg drop in systolic blood pressure), syncope while in the supine position, and cardiac dysrhythmia or arrest associated with urticaria and/or angioedema.

ARs were further divided into mild/moderate (limited to urticaria and/or angioedema, with/without the need for treatment), severe (throat constriction or stridor, bronchospasm, or transient

hypotension), or life-threatening (persistent hypotension or respiratory compromise with the need of subsequent hospitalization). Vasovagal reactions were those not consistent with anaphylaxis, and characterized by symptoms such as nausea, emesis, flushing, or generalized warmth. Other reactions consisted of hemodynamic (pulmonary edema or angina) or nephrotoxic events, pain at site of contrast injection, anxiety, confusion, and various other nonspecific complaints.

We identified 1 to 2 matched controls for each reactor. Controls were matched by sex, age, and date of CC. Controls were excluded if they had pretreatment with antihistamine and/or corticosteroid. Medical records were initially reviewed by fellows in the Department of Allergy and Clinical Immunology, who were blinded to case-control status and study aims. A second round of data validation was also performed. All paper charts were requested from the Medical Records Department, and compared with the electronic medical record, because before 2006 the electronic medical record lacked institution-wide implementation. Information obtained from medical records included further details of adverse reactions, comorbid conditions, and medications listed at the time of catheterization. A subject was deemed to have CVD if a diagnosis of angina, coronary artery disease, arrhythmia, cardiomyopathy, congestive heart failure, pulmonary hypertension, past myocardial infarction, valvular heart disease, or hypertension was present, or based on exposure to 1 or more of the following medications: nitrate, antiarrhythmic, digitalis, BBs, ACE-Is, angiotensin-receptor blocker (ARB), or calcium channel blocker (excluding patients receiving the latter 4 agents for migraine, ocular hypertension, proteinuria, or other noncardiovascular disorder). We focused our attention on the medication list to identify all patients who received BBs, ACE-Is, ARBs, and aspirin before their CC. We further classified BBs into cardioselective (eg, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, or nebivolol) or noncardioselective (eg, nadolol, penbutolol, propranolol, sotalol, or timolol).

Statistical analysis

Although not explicitly depicted in this article, our statisticians described data obtained using means and SDs for all continuous variables, and counts and percentages for all categorical variables. The study group was divided into 2 groups (case/control). ANOVA test was used to compare continuous variables, and the chi-square test was used for categorical variables. Fisher exact test was conducted when 1 or more of the cells had an expected frequency of 5 or less. To build a multivariate logistic regression model, univariate logistic regression was first performed. The variables significant at $P < .15$ on univariate analysis were identified as potential predictor variables and entered into a multivariate logistic regression model. Correlation analysis of the predictors was conducted to avoid the multicollinearity in a regression model. Backward method was used for variable selections. Receiver-operator characteristics curves were generated. All analyses were performed by using the SAS 9.4 for Linux (SAS, Cary, NC). The level of statistical significance was set at $P < .05$ (2 tailed).

RESULTS

A total of 71,782 patient records were reviewed. As illustrated in Figure 1, we identified 70 cases (0.1%) of possible AR; 24 did not meet inclusion criteria (ie, reactions were deemed to be vasovagal or hemodynamic). We thus included 46 cases/reactors (0.064% rate of AR) in our analysis. A total of 86 matched controls were identified, who also had CC performed using the

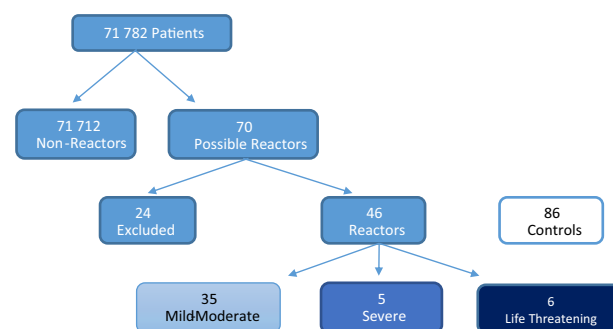


FIGURE 1. Flowchart of patient selection.

TABLE I. Characteristics of the study population

Characteristic	Cases/reactors	Controls	P value
Age (y), mean $\pm$ SD	61.3 $\pm$ 13.2	61.5 $\pm$ 12.6	.92
Sex: female, n (%)	17 (37)	31 (36)	.92
Race			.23
White	40 (87)	66 (77)	
Black	3 (6.5)	15 (17)	
Other	3 (6.5)	5 (6)	
CVD, n (%)	44 (97)	81 (94)	.99
CVD, n (%) mild-moderate reactors	33 (94)		
CVD, n (%) severe reactors	5 (100)		
CVD, n (%) life-threatening reactors	6 (100)		
Aspirin use, n (%)	34 (74)	63 (73)	0.94

same procedural technique, in the same catheterization laboratories. Reactors and controls had similar dates of procedure. There were 35 mild to moderate, 5 severe, and 6 life-threatening reactions (0.015 rate of severe AR) observed.

CVD was a common characteristic among reactors, as shown in Table I, with all severe and life-threatening reactors meeting at least 1 of our criteria of CVD.

Medication exposures in reactors and controls are displayed in Figure 2. BBs were used more frequently than ACE-Is or ARBs. Of the control subjects, 64% were using BB medication, compared with 56.5% of reactors ($P = .40$). In both control and reactor subjects, approximately 80% were taking cardioselective BBs, with metoprolol being the most frequently prescribed. The specific BBs that patients were receiving are presented in Table II. ACE-I usage was identical, whereas ARB usage was more frequent in the reactor group (18% vs 8%; $P = .11$).

Medication exposures were similar in subjects with severe/life-threatening AR when compared with subjects with mild to moderate AR, except for ACE-I exposure, which was more frequent in the mild to moderate AR group. As shown in Figure 3, there was no remarkable difference comparing subjects with severe/life-threatening with those who had mild to moderate AR for BBs (45% vs 60%), ACE-Is (18% vs 43%), or ARBs (18% vs 17%). Medication exposures, including types of BB (presented in Table II), in our reactors were similar to those in matched controls. Considered separately, neither cardioselective BBs nor noncardioselective BBs had an influence on rate of AR ($P = .2$ for cardioselective, $P = .5$ for

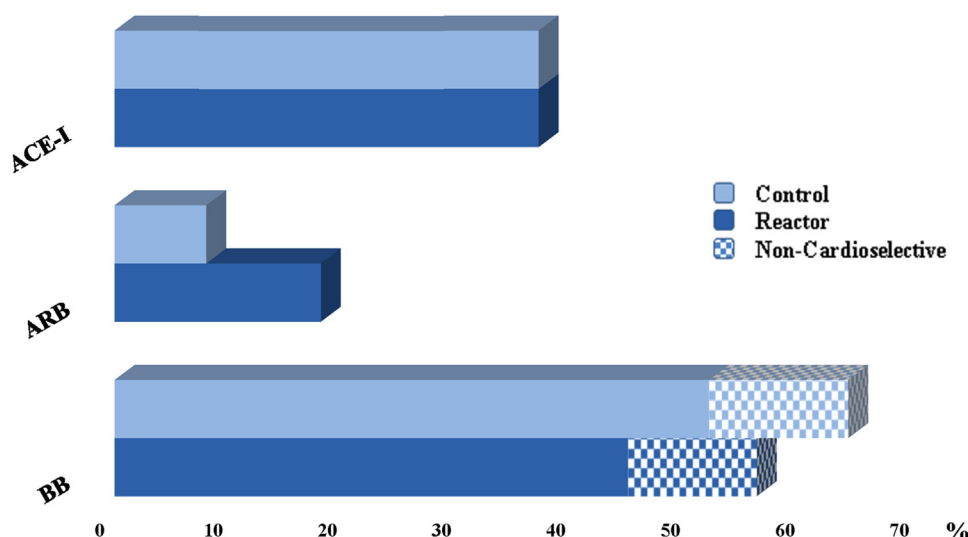


FIGURE 2. Medication exposures in reactors and controls.

TABLE II. Class of BB used

BB Class	Cases/reactors	Controls
No. of subjects	46	86
BB usage, n (%)	26 (56.5)	55 (64)
Cardioselective	20 (43.5)	44 (51)
Atenolol	4 (7)	10 (12)
Metoprolol	16 (35)	34 (40)
Noncardioselective	6 (13)	11 (13)
Carvedilol	2 (4)	4 (7)
Labetalol	1 (2)	1 (1)
Nadolol	1 (2)	1 (1)
Propranolol	2 (4)	3 (3.5)
Sotalol	0	2 (2)

noncardioselective) or AR severity ($P = .65$ for cardioselective, $P = .29$ for noncardioselective). Similarly, ACE-Is and ARBs did not influence AR incidence ($P = .11$ and $P = .94$, respectively) or severity ($P = .14$ and $P = .94$, respectively). Aspirin use was similar in reactors versus controls, likely due to a similar CVD incidence, consistent with guidelines for cardioprotection during the period of this study.

DISCUSSION

Our findings imply that patients taking BB, ACE-I, or ARB therapy who receive intra-arterial LOCM are not at statistically or clinically increased risk for AR or more severe AR. Previous studies have reported an increased risk for more severe AR with intravenous HOCM exposure, which has been in use since the 1950s.^{3,8} HOCM has been supplanted by LOCM, which were introduced in the mid-1980s, and are now universally used for CC.²⁰ The widespread use of LOCM has markedly reduced the rate of all adverse reactions, from the 4% to 12% range with HOCM, to 1% to 3% with LOCM.²¹ The risk of severe reaction is 0.03% for LOCM compared with 0.16% for HOCM, but these reactions can still be serious and in some cases life-threatening.⁵

Predisposing factors to AR include a history of AR to contrast media, asthma, and CVD (independent of asthma and BBs).⁸ Regardless of contrast osmolarity, intra-arterial injection of contrast has a lower rate of AR compared with the intravenous route, but is more likely to provoke severe reaction.²² BB exposure (independent of underlying CVD) has been associated with increased risk of severe AR, specifically bronchospasm, in the context of intravenously injected HOCM. Patients receiving BBs were also 8 times more likely to be hospitalized after AR.⁹ Based on these findings, risk reduction measures have been recommended for such patients, with BB suspension considered on an individual risk-benefit basis, with the understanding that this would not be advisable for patients for whom BB suspension may lead to deleterious cardiac events and BB withdrawal symptoms.^{9,23-25}

Greenberger et al²⁶ examined the incidence of AR to intra-arterial conventional HOCM use in 952 patients during cardiac angiography, and found a trend for greater overall frequency of AR in patients receiving BBs.²⁶ The reactions were predominantly mild, and few severe reactions were observed.²⁶ This trend was only found in patients chronically taking non-cardioselective BBs, specifically propranolol. The type II error was calculated at a probability of 0.75. Recently, Aggarwal et al²⁷ reported that BB premedication was not associated with an increase in frequency of AR from coronary computed tomography angiography, using intravenous LOCM. The indication for BB premedication in coronary computed tomography angiography is to reduce the resting heart rate, which is required for optimal image quality. Patients in this study with a resting heart rate of more than 50/min received 50 to 100 mg of metoprolol, a cardioselective BB. It is reasonable to assume that a significant proportion of patients in this study had only a single BB exposure, because the number of patients chronically taking a BB versus only taking a single dose of BB was not disclosed. The physiology of patients on chronic BB therapy differs from that of patients exposed to a single dose, because chronic BB exposure has been associated with structural and functional myocardial changes. These changes include reduced interstitial fibrosis, regression of cardiomyocyte hypertrophy, improved

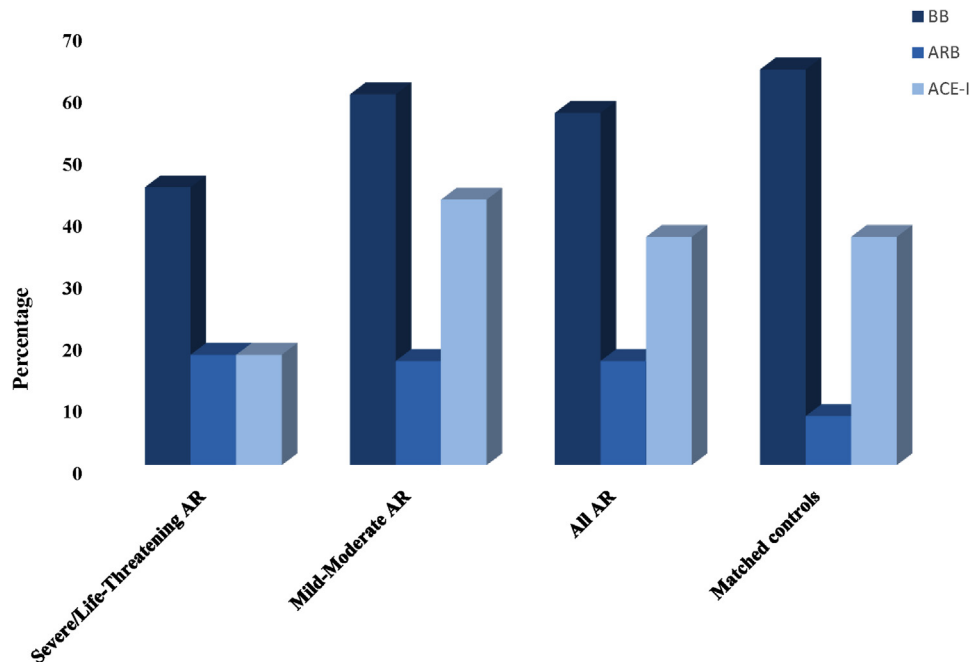


FIGURE 3. Exposures to BBs, ACE-Is, and ARBs in reactors and controls.

cardiomyocyte contractile performance, and increased cardiac β -receptor density.²⁸ A patient receiving 1 dose of metoprolol before coronary CTA may not be comparable to a patient who has had chronic BB exposure.

For the above reasons, we carried out this study to determine whether in a patient population with a high prevalence of CVD, and high rates of exposures to BBs, ACE-Is, and ARBs, greater risk for more severe AR could be identified in association with LOCM administration.

Our study has several limitations. Because this was a retrospective review, there is a possibility that not all data were considered, or that uncontrollable covariates could have led to bias. When reactions were screened and classified, as being either compatible with AR or vasovagal/hemodynamic, 24 reactors were excluded, because they did not meet the criteria to be classified as AR. Because of the retrospective nature of this study, we cannot confirm whether in fact these “vasovagal/hemodynamic” reactions were not indeed compatible with AR, but because of poor documentation of symptoms, they were not classified as such. As previously mentioned, a predisposing factor to AR is the presence of asthma. In several of the charts reviewed, it was not possible to reliably include or exclude asthma, because most patients did not have pulmonary function tests documented. Some patients had albuterol and other controller medications listed in their medication lists, but we did not deem this sufficient to include or exclude the diagnosis. We thus opted not to include this diagnosis in the patient characteristics, though this is a significant factor to consider. We did not find sufficient evidence to include or exclude atopy in several patients, so this was not included in patient characteristics. Although recent corticosteroid use could impact reactions to contrast media, we could not definitively determine whether some patients received steroids before their elective CC, so corticosteroid use was not listed under patient characteristics. Although we did not find BBs

to predispose to AR incidence or severity, we performed a power calculation to determine whether our sample size was sufficiently large to demonstrate such an effect. We calculated that to sufficiently power a “definitive” study, to determine whether AR was influenced by BBs as a class, or specifically cardioselective versus noncardioselective BBs, we would need a sample size of 777,118 and 2,808,252 subjects, respectively. The magnitude of the latter number is likely explained by the lower number of subjects currently receiving noncardioselective BBs. In the charts we reviewed, there was a bias toward prescribing cardioselective BBs, especially metoprolol. An explanation for this bias is that metoprolol is the preferred agent prescribed by cardiologists at Cleveland Clinic. We cannot determine whether this prescription pattern mirrors the rest of the United States. We thus cannot rule out risk related to noncardioselective BB use. Knowing that roughly 1,000,000 CCs are done in the United States annually,²⁹ we would need to review data from all CCs done in the United States, for 2 to 3 years, to achieve a sufficient sample size to adequately power a “definitive” study. The feasibility of such a study is uncertain. In the hypothetical situation where a nationwide study can be performed, analyzing all CCs done in the United States, and then demonstrate an increased risk of AR associated with BB use, it is unlikely this risk, although statistically significant, would also be clinically significant.

CONCLUSIONS

BB exposure has been associated with a greater risk of more severe AR in past studies in which intravenous HOCM was the anaphylactogenic stimulus. In this study, in which subjects receiving BBs underwent contrast studies using intraarterial LOCM, we found no statistically or clinically significant increase in risk for more frequent or severe AR. ACE-Is have also been

implicated as a risk factor for more severe anaphylaxis, but no increased risk of AR or severe AR was found in our study in association with procedures involving LOCM administration. Our findings do not support the contention that patients undergoing CCs are candidates for risk reduction measures for BB or ACE-I exposure before receiving LOCM.

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