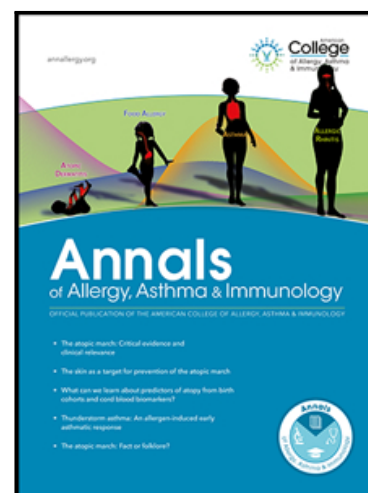


Incidence and Risk Factors of Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema: A Large Case-Control Study

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Title: Incidence and Risk Factors of Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema: A Large Case-Control Study

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The prevalence of angiotensin converting enzyme inhibitor-induced angioedema (ACEI-IA) ranges from 0.2% to 0.7%¹⁻⁵. Risk factors include being African American, a woman, or an adult over 65 years old¹⁻⁶. Previous studies are limited to epidemiologic data from single-center studies or risk factors collected from large clinical trials. The objective for this study was to evaluate the incidence of ACEI-IA in a sample of patients from three distinct geographic regions of the US, analyzing patients' characteristics, and comparing possible associated risk factors.

We performed a case-control study using electronic medical records (EMRs) from an integrated tertiary health-care system across three regions in the US (Minnesota, Arizona, and Florida). We included patients prescribed an ACEI from January 1st, 2008 to December 31st, 2018. We identified patients with angioedema using the International Classification of Diseases Clinical Modification (ICD-CM) revision 9 and 10 codes 995.1 and T78.3 (angioneurotic edema), respectively. Controls were identified as patients who received ACEI and did not develop angioedema during the study period. We categorized our variables based on age groups, sex, race, and comorbidities (renal disease [ICD-CM 581.9; 791.0; N04.9], congestive heart failure [ICD-CM 428.0; I50], coronary artery disease [ICD-CM 414.0; I25.10], hypertension [ICD-CM 401.1; I10]), and other comorbidities. Additionally, the use of non-steroidal anti-inflammatory drugs (NSAID), patients' listed allergies, type of ACEI, and the US region where the evaluation occurred were compared. We only included patients diagnosed with angioedema after being prescribed an ACEI. Multivariable logistic regression models adjusted by age, gender, race, and site were fit to further evaluate which characteristics are significantly associated with ACEI-IA. Odds ratios in each comparison with 95% confidence intervals were estimated using Wald

evaluation. All tests were two-sided and p-values less than 0.05 were considered statistically significant. R-Studio with R version 3.6.2. was used for data analysis.

Among the 145,101 patients prescribed an ACEI, 716 patients (0.49%;95% CI 0.46%, 0.53%) developed ACEI-IA. Of the patients with ACEI-IA, the median age was 66 (Range: 21.0, 99.0), 54.4% were older than 65 years old, 50.4% women, 88.5% Caucasian, and 84.8% were on lisinopril. Women (OR 1.44;95% CI 1.24, 1.67;P <.001), African Americans (OR 2.88;95% CI 2.14, 3.89;P < .001), NSAID users (OR 2.28;95% CI 1.85, 2.80;P < .001), patients with a drug allergy label other than ACE allergy label (OR 4.86;95% CI 3.82, 6.17;P .01), patients with NSAID allergy label (OR 2.43;95% CI 1.38, 4.29;P <.01), patients with registered allergy other than drug allergy (OR 2.54;95% CI 1.97, 3.29;P <.01), and patients diagnosed in the US upper Midwest region (OR 1.57;95% CI 1.24, 1.99;P <.01) had an increased risk of ACEI-IA on multivariable analysis (Table 1). Patients aged 80 or older had a lower risk of ACEI-IA. Eleven percent of patients with ACEI-IA presented with the index reaction within the first month. A cumulative 75% of patients developed ACEI-IA within 4 years, and 25% in the subsequent 7 years of therapy. We were not able to follow up on patients who did not continue care at our institution.

In this case-control study, we found an overall ACEI-IA incidence of 0.49% which is comparable to prior studies (0.2-0.7%)^{1, 2, 4}. African Americans, women, NSAID users, patients with a listed allergy in their medical chart, and patients in the US Upper Midwest region were identified as risk factors of ACEI-IA. The risk of ACEI-IA is increased among African Americans. This risk can be up to five times higher when compared to Caucasians⁷. In our study,

African Americans had a three-fold risk of ACEI-IA compared to Caucasians. Genetic variations have been linked to the risk difference among races and gender⁸. Age greater than 65 and women have also been identified as risk factors for ACEI-IA^{4,6}. In previous reports, patients older than 65 had 60% more risk of ACEI-IA than younger patients^{4,6}. In our study, the risk of ACEI-IA was higher in women but not in the elderly. Moreover, elderly (≥ 80 years) patients' risk was lower than the risk of patients between 20 and 39 years of age. A similar finding was reported by Banerji et al.¹ However, we consider this finding can be secondary to a progressive decline in bradykinin levels expected with aging⁹.

We found that 11% of patient on ACEI-IA present within the first month of therapy which is similar contemporary report where ACEI-IA developed between 10% of the first month of therapy; contrary to prior reports where most patients with ACEI-IA present within the first month of therapy^{3,6}. Banerji et al also found that around 80% of patients with ACEI-IA present after 4 years¹ which is comparable to 75% that was found in our cohort.

In our study, patients in the Upper-Midwest had a higher risk of ACEI-IA than patients in the Southeast. Environmental factors may have an impact on the susceptibility to develop angioedema secondary to ACEI therapy. For instance, lower levels of vitamin D -as seen in people from areas with longer winters- have been observed in patients with chronic spontaneous urticaria¹⁰; and even though the role of vitamin D in the pathophysiology of angioedema is unknown, it may play a role in bradykinin-mediated reactions as well. The risk of ACEI-IA was also higher in patients with any allergy listed (drug allergy label or other allergies such as food allergy) in their charts. Similar findings were observed in previous reports⁶. In addition to NSAIDs, we found that the risk of ACEI-IA was up to four times higher in patients with a drug

allergy history. In our cohort, a history of drug allergy label, NSAID allergy label, or other types of allergies (i.e., food allergy) increases the risk of ACEI-IA.

Our study had some limitations. Our institution is a large referral center and provides care to high complexity patients. Hence, our population may be limited to healthcare access bias and may not represent the US normal demographic distribution. There was an association between NSAID use and ACEI-IA, but we cannot differentiate between NSAID-induced angioedema, the time when the NSAID was taken, or if the medication was taken over the counter, which could have led to the underestimation of NSAID use in our study. Additionally, cases with ACEI-IA might have been underestimated since it is a clinical diagnosis without a specific ICD-CM code and no retrospective review for each individual was performed; some cases may have been recorded as allergic reactions of non-bradykinin induced angioedema or documented with another disease code and we were not able to include cases with ICD-10 code T46.4X1A (ACEI inhibitor aggravated angioedema or poisoning by ACE-I). Furthermore, the time-to-onset of ACEI-IA after ACEI prescription and overall ACEI-IA incidence might have also been affected by patients who were lost to follow-up or deceased after ACEI prescription.

In conclusion, the overall incidence of ACEI-IA in our cohort was similar to previous reports. We found a higher risk of ACEI-IA among African Americans, women, NSAID use, other drug allergy label, and patients in the Upper Midwest. Most cases of ACEI-IA occur within the first 4 years therapy with less than 12% occurring during the first month of therapy. Additional information is needed to determine the relationship with NSAID-induced angioedema.

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Table 1. Multivariable analysis of patients with angiotensin converting enzyme induced angioedema

<i>Categories</i>	<i>Adjusted OR (95% CI)</i>	<i>P value</i>
Age		
20 - 39	Reference	
40 - 59	1.02 (0.69,1.5)	.98
60 - 79	1.06 (0.73,1.55)	.75
≥ 80	0.64 (0.43,0.98)	.04
Sex		
Female	1.44 (1.24,1.67)	<.01
Race		
Caucasian	Reference	
Asian	1.25 (0.62,2.53)	.53
African American	2.88 (2.14,3.89)	<.01
Other	0.77 (0.5,1.2)	.25
Site		
Southeast	Reference	
Southwest	0.93 (0.68,1.29)	.69
Upper Midwest	1.57 (1.24,1.99)	<.01
Medication		
Benazepril	Reference	
Captopril	1.38 (0.65,2.95)	.40
Enalapril	1.21 (0.66,2.19)	.54
Fosinopril	0.65 (0.15,2.87)	.57
Lisinopril	1.52 (0.9,2.59)	.12
Moexipril	3.1 (0.7,13.76)	.14
Quinapril	1.73 (0.78,3.83)	.17
Ramipril	1.16 (0.57,2.36)	.68
Comorbidities		
Renal Disease	Reference	
Congestive Heart Failure	0.88 (0.21,3.59)	.86
Coronary Artery Disease	1.6 (0.4,6.5)	.51
Hypertension	1.22 (0.3,4.92)	.78
NSAID Use		
Yes	2.28 (1.85,2.8)	<.001
Listed allergy in Chart		
No Known Allergy	Reference	
Drug allergy label other than ACEI	4.86 (3.82, 6.17)	.01
NSAID allergy label	2.43 (1.38, 4.29)	<.01
Registered allergy other than drug allergy	2.54 (1.97, 3.29)	<.01

Notes: OR: Odds ratio; ACEI: Angiotensin converting enzyme inhibitor; NSAID: Non-steroidal anti-inflammatory drugs; Age (0-20): 0%, Medication (Perindopril): 0%, Medication (Trandolapril): 0%, Comorbidities (Other): 0%, so they are not involved in the model; multivariable logistic regression model adjusted by age, gender, race, and site.