Pharmacotherapy for Angiotensin-Converting Enzyme Inhibitor–Induced Angioedema: A Systematic Review

Claire M. Lawlor, MD1, Ashwin Ananth, MD, MBA1, Blair M. Barton, MD1, Thomas C. Flowers1, and Edward D. McCoul, MD, MPH1,2,3

Abstract
Objective. Angioedema is a potentially life-threatening complication of angiotensin-converting enzyme inhibitor (ACEI) use, occurring in up to 0.5% of users. Although the pathophysiology of ACEI-induced angioedema is attributable to elevated serum bradykinin, standard management typically includes corticosteroids and antihistamines. We sought to summarize the evidence supporting pharmacotherapy for ACEI-induced angioedema.

Data Sources. PubMed, MEDLINE, and Embase portals.

Methods. A systematic literature review was conducted according to the PRISMA guidelines. Databases were queried by 3 independent reviewers for English-language studies published between 1980 and 2017. The initial search screened for all occurrences of “angioedema” and then was further refined to include studies of ACEI-related cases and exclude hereditary angioedema.

Results. Five articles representing 218 cases were identified, including 3 randomized controlled trials and 2 prospective case series with historical controls. One of 2 studies of icatibant (bradykinin B2 receptor antagonist) found more rapid symptom improvement than that with a control group of corticosteroids and antihistamines. Two studies of ecallantide (plasma kallikrein inhibitor) and 1 study of C1 inhibitor replacement found no significant benefit over control. No studies were identified that compared the efficacy of corticosteroids with antihistamines, of one dose with another, of fresh frozen plasma, or of combination therapy.

Conclusion. The efficacy of treatment of ACEI-induced angioedema with bradykinin antagonists, kallikrein inhibitor, and C1 inhibitor warrants further study. Although consistent benefit of these medications has not been demonstrated, their use has not caused harm. One study examining off-label use of icatibant has demonstrated efficacy over control. In addition, further study is needed to establish the efficacy and mechanism of action of standard pharmacotherapy such as corticosteroids and antihistamines in treatment of this condition.

Keywords
angioedema, angioneurotic edema, ACE inhibitor, pharmacotherapy

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Angiotensin-converting enzyme inhibitors (ACEIs) are among the most commonly prescribed antihypertensives worldwide, with 60 million prescriptions given or renewed yearly.1 ACEI-induced angioedema (ACEI-IA) affects approximately 0.5% of patients taking an ACEI, but reports demonstrate that up to 30% of cases of adults presenting to the emergency room with angioedema of the head and neck have been attributed to ACEI use.2,3 ACEI-IA most often presents as localized swelling of the head and neck that can range from mild lip or tongue edema to life-threatening laryngeal or pharyngeal edema.4 ACEI-IA can present soon after beginning ACEI therapy or up to a decade later.5 The risk of ACEI-IA seems to increase with duration of ACEI treatment and with African American race.6 Cough is the most frequently reported side
effect of ACEI use and may be predictive of angioedema.\textsuperscript{7,8} The pathophysiology of ACEI-IA is believed to be related to decreased degradation of bradykinin and resultant binding of bradykinin to endothelial receptors, which causes increased vessel permeability and edema.\textsuperscript{9}

Treatment options described in the literature for ACEI-IA include corticosteroids, antihistamines, H2 blockers, alpha agonists, fresh frozen plasma, C1 inhibitor concentrate, ecallantide (a kallikrein inhibitor), and icatibant (a bradykinin B2 receptor blocker).\textsuperscript{10-14} However, there are few clinical trials evaluating the effectiveness of any therapies for ACEI-IA, and much of the treatment of acute ACEI-IA may be conducted without a strong evidence base. This study aims to systematically review the published clinical evidence related to pharmacologic treatment of acute-onset ACEI-IA.

Materials and Methods

A comprehensive review of the English-language literature was performed with the PubMed, Ovid/MEDLINE, and Embase portals through December 18, 2016. Search criteria included all occurrences in the title or abstract of the terms “angioedema” and “angioneurotic edema.” Article format included all occurrences in the title or abstract of the terms “angioedema” and “angioneurotic edema.” Article format was limited to clinical trials, clinical studies, randomized controlled trials, controlled trials, validation studies, observational studies, and multicenter studies. Inclusion criteria for the literature search were defined with the PICOS approach (population, intervention, control, outcome, study design) and are detailed in Table 1. A flowchart of the systematic search performed via PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) is given in Figure 1.

Two reviewers (C.M.L., A.A.) separately performed the search to confirm standardization. Three authors (C.M.L., A.A., B.M.B.) performed standardized eligibility assessment of the resultant articles, and duplicate publications were excluded. Each abstract was then screened for relevance to the assessment of pharmacotherapy for ACEI-IA. Irrelevant citations and case reports were excluded. The full text of the eligible citations was obtained with additional records from the reference lists of the published articles. The full-text articles were reviewed, and noneligible studies were excluded. Studies that examined hereditary angioedema (HAE), nonsteroidal anti-inflammatory drug-induced angioedema, and allergic angioedema were discarded.

Articles that met criteria for inclusion were then used for data collection. Data on study design, patient selection and inclusion criteria, controls, treatment regimens, ACEI exposures, sample size, additional therapies given to patients during the study period, outcome measures, response to treatment, and adverse events were collected. Quantitative analysis of pooled data was not performed due to the lack of uniformity on reporting of the primary outcomes, adequate control group, or route of treatment drug administered.

Results

The initial database search identified 905 articles, including 349 from PubMed, 293 from Ovid/Medline, and 263 from Embase. These results were screened for relevance to the acute management of ACEI-IA. After screening eligibility and removal of duplicates, 63 articles underwent full-text review by 3 authors (C.M.L., A.A., B.M.B.). Fifty-five articles were then excluded from quantitative analysis on the grounds of insufficient data and lack of relevance. Manual searching of reference lists of the 63 full-text articles yielded no additional eligible studies. An additional 3 articles were excluded due to inclusion of cases of non-ACEI-IA. In total, 5 articles were included for qualitative analysis.

Quality of evidence for each included manuscript is presented in Table 2. Three studies were multicenter, phase 2, double-blinded randomized controlled trials. Two studies were prospective case series with historical controls. The data source was patients presenting to the emergency room in Germany and the United States.

Five articles with 218 cases were included and are summarized in Tables 3 and 4. All 5 studies employed similar inclusion criteria: male and female patients >18 years old (although Bas et al\textsuperscript{15} specified “adults” without defining age) who presented to an emergency department with angioedema of the head and neck of acute onset within 10 to 12 hours of presentation. All patients included in the studies were taking an ACEI, and other causes of angioedema, including allergy and infection, were excluded. Two studies were proof-of-concept prospective case-control series that enrolled patients presenting to emergency rooms in Germany with acute-onset ACEI-IA.\textsuperscript{14,15} Both studies share the same 47-patient historical control group. Bas et al compared icatibant (30 mg, subcutaneous [SQ]) with methylprednisolone and clemastine. Greve et al\textsuperscript{14} compared

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**Table 1. PICOS Inclusion Criteria.**

<table>
<thead>
<tr>
<th>PICOS</th>
<th>Description</th>
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<tr>
<td>Population</td>
<td>Male and female adults &gt;18 y of age with acute-onset ACEI-induced angioedema</td>
</tr>
<tr>
<td>Intervention</td>
<td>Bradykinin B2 receptor inhibitor (icatibant), kallikrein inhibitor (ecallantide), C1-INH</td>
</tr>
<tr>
<td>Control</td>
<td>Antihistamines, corticosteroids, adrenergic agonists, H2 blockers, placebo</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Time to symptom or edema relief, time to meet discharge criteria from hospital</td>
</tr>
<tr>
<td>Study design</td>
<td>Case-control, randomized controlled trials</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; C1-INH, C1 esterase inhibitor.
C1 inhibitor concentrate with methylprednisolone and clemastine. While both studies concluded that the treatment arm was an effective treatment of acute ACEI-IA, neither study performed hypothesis testing due to the small sample size.

Of the 3 randomized controlled trials, 2 examined the efficacy of ecallantide, and 1 examined icatibant therapy. Lewis et al compared varying doses of ecallantide with placebo, but all groups were permitted to receive corticosteroids, antihistamines, H2 blockers, and/or adrenergic agonists. Bernstein et al enrolled patients for randomization only after they failed “standard therapy,” defined as treatment with H1 or H2 antagonists (oral, intramuscular, or intravenous), corticosteroids (oral or intravenous), and epinephrine. They were then assigned to receive ecallantide or placebo. If participants in either treatment arm demonstrated worsening of their symptoms or no improvement after 2 and 4 hours, they could receive a dose of ecallantide (30 mg, SQ). Only 1 article, Bas et al demonstrated statistical significance between the
### Table 3. Characteristics of Included Studies: Patients, Inclusion, ACEI Exposure, Arms, and Additional Therapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Controls; Patients Treated</th>
<th>Inclusion Criteria</th>
<th>ACEI Exposure</th>
<th>Arms</th>
<th>Additional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bas (2010)¹⁵</td>
<td>47; 8</td>
<td>Adults presenting to ED with acute angioedema of the head and neck &lt; 10 h, use of ACEI, evaluated by ENT</td>
<td>Enalapril, ramipril</td>
<td>Control: Historical, methylprednisolone, and clemastine</td>
<td>Treatment: Icatibant (30 mg, SQ)</td>
</tr>
<tr>
<td>Lewis (2015)¹⁶</td>
<td>18; 58a</td>
<td>Adults &gt; 18 y, ACEI dose within 36 h, presenting to ED with ACEI-induced angioedema within 12-h onset</td>
<td>80% of subjects on lisinopril, others not specifically listed</td>
<td>Control: Placebo SQ Treatment: Ecallantide (10, 30, 60 mg)</td>
<td>Subjects from any group could receive corticosteroids, H1 blockers, H2 blockers, and adrenergic agonists (use did not differ between groups)</td>
</tr>
<tr>
<td>Bas (2015)¹⁸</td>
<td>14; 13</td>
<td>Patients 18 to 95 y of age who were receiving ACEI and who presented to the ED with ACEI-induced angioedema affecting the upper aerodigestive tract &lt; 10-h duration</td>
<td>Benazepril, captopril, enalapril, lisinopril, ramipril</td>
<td>Control: Prednisone (500 mg, IV), clemastine (2 mg, IV) Treatment: Icatibant (30 mg, SQ)</td>
<td>Patients were treated with a combination of oral, IV, or IM H1 or H2 antagonists; oral or IV corticosteroids; and epinephrine prior to randomization. Ecallantide (30 mg, SQ) could be administered to any patient at any time after the blinded dose had been given. Ecallantide (30 mg, SQ) was also given at 2 and 4 h after blinded treatment if no improvement was noted.</td>
</tr>
<tr>
<td>Bernstein (2015)¹⁷</td>
<td>24; 26</td>
<td>Persons &gt; 18 y presenting within 12 h of symptom onset and currently taking an ACEI with angioedema of the head and neck that remained symptomatic 2 h after treatment with &quot;standard therapy&quot;</td>
<td>Not described</td>
<td>Control: Placebo SQ Treatment: Ecallantide (30 mg, SQ)</td>
<td></td>
</tr>
<tr>
<td>Greve (2015)¹⁴</td>
<td>47; 10</td>
<td>Patients &gt; 18 with acute ACEI-induced angioedema presenting to the ED</td>
<td>Enalapril, ramipril, lisinopril</td>
<td>Control: Historical, methylprednisolone, and clemastine Treatment: C1-INH (1000 IU, IV)</td>
<td>None</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACEI, angiotensin-converting enzyme inhibitor; C1-INH, C1 inhibitor; ED, emergency department; ENT, ear, nose, and throat; IM, intramuscular; IV, intravenous; SQ, subcutaneous.

¹ Three arms: 20, 19, 19.
<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcomes</th>
<th>Results: Control vs Treatment Arms</th>
<th>Adverse Events: Control vs Treatment Arms</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bas (2010)</td>
<td>Time to complete symptom relief</td>
<td>Mean time to complete symptom relief: control arm, 33 h (SD, 19.4 h); treatment arm, 4.4 h (SD, 0.8 h)</td>
<td>Control arm: Tracheotomy (3 of 47), intubation (2 of 47), received a second administration of corticosteroids (250-500 mg, methylprednisolone) because of symptom persistence or symptom worsening (12 of 47)</td>
<td>Treatment arm: None; Proof of concept, no statistical tests performed</td>
</tr>
<tr>
<td>Lewis (2015)</td>
<td>Meeting 6 discharge criteria within 6 h of treatment: improvement in edema, stable vital signs, absence of stridor, absence of dyspnea or drooling, no use of accessory muscles during respiration, and ability to drink without difficulty</td>
<td>Met 6 discharge criteria within 6 h: control arm, 72%; treatment arm, 88% (P &gt; .05)</td>
<td>Control arm: 17% ICU admission rate, 1 death from respiratory compromise; Treatment arm: 9% ICU admission rate, zero deaths</td>
<td>No statistical difference between any of the ecallantide groups and placebo (difference vs placebo, 16%; 95% CI –11% to 41%). There were no significant differences among any treatment groups in the proportion of subjects meeting the discharge eligibility criteria (P &gt; .05). Icatibant demonstrated increased efficacy over placebo in resolution of edema in &lt;4 h (P = .02) and median time to resolution of symptoms (P = .002)</td>
</tr>
<tr>
<td>Bas (2015)</td>
<td>Resolution of edema &lt;4 h after treatment administration; time to the complete resolution of edema after administration of the study treatment, as evaluated on the basis of investigator-assessed and patient-assessed symptom scores, as well as the investigator’s assessment of the severity of angioedema on the basis of the physical examination</td>
<td>Control arm: 0 of 14 patients had complete resolution of edema in &lt;4 h; median time to complete resolution of edema: 27.1 h (interquartile range: 20.3-48 h); Treatment arm: 5 of 13 patients receiving icatibant had complete resolution of edema &lt;4 h, median time to complete resolution of edema: 8 h (interquartile range: 3-16 h)</td>
<td>Control arm: Tracheotomy, 1 of 14; Treatment arm: None</td>
<td>Icatibant demonstrated increased efficacy over placebo in resolution of edema in &lt;4 h (P = .02) and median time to resolution of symptoms (P = .002)</td>
</tr>
<tr>
<td>Bernstein (2015)</td>
<td>Meeting discharge criteria within 4 h of treatment: stable vital signs; no evidence of stridor, dysphagia, dyspnea, or drooling; edema at or below Ishoo class I at the time of evaluation for discharge</td>
<td>Met discharge criteria within 4 h: control arm, 21%; treatment arm, 31%</td>
<td>Control arm: 6 patients required hospitalization &gt;24 h because of worsening of angioedema, chest pain, recurrence of angioedema, and supraventricular tachycardia; Treatment arm: 4 patients required hospitalization &gt;24 h because of angioedema, gastric pain, and chest pain</td>
<td>No statistical difference between ecallantide and placebo (difference in proportions, 10%; 95% CI, –14% to 34%)</td>
</tr>
<tr>
<td>Greve (2015)</td>
<td>Time to complete symptom relief</td>
<td>Mean time to complete symptom relief: control arm, 33 h (SD, 19.4 h); treatment arm, 10.1 h (SD, 3 h)</td>
<td>Control arm: Tracheotomy (3 of 47), intubation (2 of 47), received a second administration of corticosteroids (250-500 mg methylprednisolone) because of symptom persistence or symptom worsening (12 of 47); Treatment arm: None</td>
<td>Proof of concept, no statistical tests performed</td>
</tr>
</tbody>
</table>

Abbreviation: ICU, intensive care unit.
experimental and control groups. In that study, icatibant (30 mg, SQ) was compared with a control of methylprednisolone (500 mg, intravenous) and clemastine (2 mg), with the icatibant group demonstrating more frequent resolution of edema in <4 hours (P = .02) and a shorter time to complete resolution of edema (P = .002).

Notably, all 5 of the articles included in this review referenced a combination of corticosteroids, antihistamines, H2 blockers, and/or alpha agonists as “standard therapy.” In our systematic review, no studies were identified that tested the efficacy of corticosteroids, antihistamines, or alpha agonists against one another or against observation. Fresh frozen plasma (FFP) has also been utilized in the management of ACEI-IA but was similarly absent from our search results in any study meeting eligibility criteria. The efficacy of these treatment methods for the management of acute ACEI-IA is therefore not substantiated by our review of the existing literature.

**Discussion**

ACEI-IA is an uncommon but potentially fatal side effect of a class of medications prescribed to 35 to 40 million people worldwide. It has been proposed that the mechanism of ACEI-IA is similar to that of HAE. ACEIs block conversion of angiotensin I to angiotensin II and prevent the inactivation of bradykinin, leading to increased serum bradykinin levels. Bradykinin activates vascular bradykinin B2 receptors, increases vascular permeability, and causes angioedema. HAE types I and II, acquired angioedema with C1 inhibitor deficiency, and ACEI-IA are all attributed to serum bradykinin elevations, although the definitive data with C1 inhibitor deficiency, and ACEI-IA are all attributed to histamine. In contrast to histamine-mediated angioedema, such as HAE and ACEI-IA, has been shown to be poorly responsive to these conventional therapies, though high-quality evidence is lacking. Nonetheless, this proposed common mechanism has motivated the study of efficacy of the 3 Food and Drug Administration (FDA)-approved treatments for HAE (ecallantide, icatibant, and C1 inhibitor) in patients with acute onset of ACEI-IA.

Icatibant (Firazyr; Shire, Lexington, Massachusetts), a bradykinin B2 receptor antagonist, does not decrease serum bradykinin but inhibits its mechanism of action. It is FDA approved for the treatment of HAE. Off-label use of icatibant to treat ACEI-IA did demonstrate increased efficacy as compared with methylprednisolone and clemastine. Although this is promising, increased efficacy must be weighed against increased costs and adverse drug effects. Corticosteroids and antihistamines are available at generic pricing, while icatibant is an orphan drug that costs approximately $10,000 for a 30-mg dose. In initial clinical trials, up to 97% of patients reported injection site reactions to icatibant administration; however, newer reports show a more tolerable adverse effect profile with no difference between on- and off-label use.

C1 esterase inhibitor concentrate (Berinert, CSL Behring, Marburg, Germany; Cinryze, Shire ViroPharma Incorporated, Lexington, Massachusetts) is also FDA approved for the treatment of HAE. Its proposed mechanism is inhibition of C1 esterase, an important mediator in the bradykinin pathway, thus inhibiting the formation of bradykinin and limiting angioedema. However, the 1 study in our review that examined C1 inhibitor concentrate did not demonstrate increased efficacy over corticosteroids and antihistamines. Ecallantide (Kalbitor; Dyax Corp, Burlington, Massachusetts) is a kallikrein inhibitor that prevents the breakdown of high molecular weight kininogen to bradykinin. This therapy also failed to demonstrate statistical improvement over placebo in patients with acute onset of ACEI-IA who had already received a combination of corticosteroids, antihistamines, H2 blockers, and epinephrine.

Angioedema can be classified into histamine- and bradykinin-mediated responses to facilitate management. Histamine-mediated angioedema is a type I hypersensitivity reaction mediated by IgE and mast cell degranulation. Angioedema of this type led to development of “standard pharmacotherapy” for anaphylaxis and angioedema, consisting of corticosteroids, antihistamines, H2 blockers, and alpha agonists. Histamine-mediated angioedema is often of more rapid onset and shorter duration when compared with bradykinin-mediated presentations. Antihistamines inhibit binding of histamine to the histamine receptor on target cells. The endothelial cell is a key target of histamine that promotes increased vascular permeability and resultant edema. The mechanism of action of antihistamines in ACEI-IA remains poorly studied; however, it may prevent the effects of histamine released by mast cells in a non-IgE-related mechanism.

ACEI-IA occurs most frequently within the first month of therapy but can present after the patient has been exposed to the medication for months to years; additionally, it may remit and recur. This presentation precludes type I hypersensitivity and typical allergic reactions, the etiology of which is attributed to histamine. In contrast to histamine-mediated angioedema, bradykinin-mediated angioedema, such as HAE and ACEI-IA, has been shown to be poorly responsive to these conventional therapies, though high-quality evidence is lacking. However, studies that utilize these therapies as a control show no increased benefit of the treatment arm over the control and do demonstrate improvements in both groups, demonstrating at least some efficacy.

Corticosteroids are potent anti-inflammatory drugs that mimic the glucocorticoid actions of endogenous cortisol. The mechanism of action of corticosteroids involves regulation in gene expression on leukocytes as well as endothelial cells that promote changes in surface adhesion molecules, cytokine release, and intracellular junctions. Specifically, glucocorticoids promote increased endothelial barrier integrity through upregulation of junctional proteins and downregulation of matrix-cleaving proteases. The benefit of glucocorticoids in ACEI-IA is likely related to this counteraction of the increased vessel permeability seen in bradykinin-induced angioedema. However, studies are lacking that show the distinct mechanism(s) of corticosteroid action in ACEI-IA.
FFP has been administered for ACEI-IA refractory to corticosteroids, antihistamines, H2 blockers, and alpha agonists.\textsuperscript{11,21,28} The proposed benefit is that FFP contains kininase II, which degrades bradykinin and thus may worsen angioedema.\textsuperscript{11} Others propose that the risk of worsening angioedema with FFP administration is applicable only in cases of HAE, mediated by the addition of complement in the plasma; thus, this risk is negligible in ACEI-IA.\textsuperscript{28} At the time of this review, there were no observational or randomized controlled trials demonstrating the efficacy of FFP in the literature.

A limitation of this review is the relatively small number of studies captured by the search. The number of patients included is also small. Three of the 5 studies included were randomized controlled trials, which does elevate the aggregate level of evidence. However, some of the methods make the results difficult to generalize. In all 3 randomized controlled trials, patients in either treatment arm could receive additional therapy. In the Lewis et al study,\textsuperscript{16} subjects in either treatment arm could receive H1 blockers, H2 blockers, and adrenergic agonists. The authors comment that use of adjunctive medications did not differ between groups. In the Bernstein et al trial,\textsuperscript{17} ecallantide (30 mg, SQ) could be administered to any patient at any time after the blinded dose had been given. Ecallantide (30 mg, SQ) was also given at 2 and 4 hours after blinded treatment if no improvement was noted; this significantly affects the ability to compare ecallantide with the placebo. Finally, in the Bas et al study,\textsuperscript{18} 30 mg of icatibant with 500 mg of prednisolone was given to patients of either treatment arm if there had been no improvement after 6 hours. The authors comment that this was done for only 3 control group patients. Many challenges oppose the successful design of an effective, high-quality study to evaluate the efficacy of different treatment strategies in ACEI-IA. Foremost, the diagnosis of ACEI-IA is one of exclusion. While blood tests exist to diagnose HAE, no serum markers have been identified for ACEI-IA. Urticaria and other signs suggestive of histamine-induced edema must be ruled out. Early identification of ACEI-IA, discontinuation of ACEI therapy, and airway management are the primary therapies.\textsuperscript{18} The natural course of ACEI-IA is resolution of angioedema 24 to 72 hours after cessation of ACEI therapy.\textsuperscript{19} However, when patients present to the emergency department with acute upper airway swelling, treatment for histaminergic angioedema is often initiated prior to determination of the underlying etiology of the swelling. Ethically, it is difficult to recommend observation alone of any degree of airway swelling, especially when corticosteroids, antihistamines, H2 blockers, and alpha agonists are not contraindicated in angioedema secondary to bradykinin elevations. Finally, unless patients and examiners are blinded to treatment, assessment of improvement of the angioedema can be subject to observer bias. Two studies examined in this review used the Ishoo classification of edema (Bernstein,\textsuperscript{17} Lewis\textsuperscript{16}), but this is not standardized.\textsuperscript{29} Among the 5 studies reviewed in this text, a variety of means were used to assess for improvement in angioedema, including nonvalidated subjective symptom scores, nonvalidated physical examination criteria for examiners, airway evaluation by an otolaryngologist, and vital signs.

This review highlights a need for high-quality studies examining the efficacy of the so-called standard therapy, or corticosteroids, antihistamines, H2 blockers, and alpha agonists in the treatment of ACEI-IA. FFP remains poorly studied as well. Finally, more effective treatment strategies often follow a deeper understanding of underlying pathophysiology; therefore, further investigation into the mechanisms of ACEI-IA may elucidate new therapeutic options.

### Conclusions

The efficacy of treatment of ACEI-induced angioedema with bradykinin antagonists, kallikrein inhibitor, and C1 inhibitor warrants further study. Although consistent benefit of these medications has not been demonstrated, their use has not caused harm. One study examining off-label use of icatibant has demonstrated efficacy over control. In addition, further study is needed to establish the efficacy and mechanism of action of standard pharmacotherapy such as corticosteroids and antihistamines in treatment of this condition.

### Author Contributions

Claire M. Lawlor, conception, data acquisition, drafting, final approval, accountable; Ashwin Ananth, data acquisition, drafting, final approval, accountable; Blair M. Barton, data acquisition, drafting, final approval, accountable; Thomas C. Flowers, data acquisition, drafting, final approval, accountable; Edward D. McCoul, conception, drafting, final approval, accountable.

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