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# Icatibant is not an appropriate treatment option for ACE-inhibitor induced angioedema of the head and neck

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**ABSTRACT** A critical appraisal and clinical application of Sinert T, Levy P, Bernstein JA, et al. Randomized trial of icatibant for angiotensin-converting enzyme inhibitor-induced upper airway angioedema. *J Allergy Clin Immunol Pract.* 2017;5(5):1402-9. doi: [10.1016/j.jaip.2017.03.003](https://doi.org/10.1016/j.jaip.2017.03.003).

**Keywords:** *Icatibant, ACE-inhibitor induced angioedema, ACE-inhibitor, Angioedema*

## Clinical Context

Our patient is a 58-year-old African American gentleman who presented to the emergency department with lip and tongue swelling after starting lisinopril for blood pressure control. The patient was diagnosed with hypertension and began treatment with the lisinopril two days prior to the onset of angioedema. The patient had significant swelling of his tongue, lips, as well as the soft tissue in his neck. His airway was assessed and determined to not need intubation. He reported inability to eat but denied having difficulty breathing, and stated he has never had angioedema previously. His only other medication is famotidine for gastric reflux. Our patient is employed as a maintenance worker, he drinks about a pint of alcohol a day with no intention of cutting back, and has a 40 pack year history of smoking with some interest in cessation. At the time of admission, he was frustrated with his inability to eat and the slow progress of the swelling to decrease, and was concerned about being able to leave the hospital as soon as possible. Our patient had received a dose of steroids as well as antihistamines in the emergency department, and he wanted to know about treatment to hasten the reduction of the swelling as this was his barrier to being discharged. His question led us to evaluate icatibant.

## Clinical Question

Is icatibant (a bradykinin receptor antagonist) appropriate treatment for ACE-inhibitor induced angioedema?

## Research Article

Sinert T, Levy P, Bernstein JA, et al. Randomized trial of icatibant for angiotensin-converting enzyme inhibitor-induced upper airway angioedema. *J Allergy Clin Immunol Pract.* 2017;5(5):1402-9. doi: [10.1016/j.jaip.2017.03.003](https://doi.org/10.1016/j.jaip.2017.03.003)

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## Related Literature

A literature search of PubMed for keywords of "icatibant", "Angioedema", and "ACE Inhibitor" yielded many results pertaining to this possible treatment. In 2010, Cicardi et al. demonstrated with a randomized double blind clinical trial that icatibant provided significant improvement when used to treat hereditary angioedema.<sup>1</sup> Hereditary angioedema is most often a result of C1-inhibitor deficiency, which leads to excess bradykinin activity, contributing to angioedema through increased vasodilation and vascular permeability.<sup>2</sup> Icatibant is a bradykinin receptor antagonist that is specific for the B2 receptor, which blocks the activity of bradykinin.<sup>2</sup> The study by Cicardi et al. demonstrated the time to reach the clinical endpoint was significantly reduced in patients treated with icatibant compared to placebo.<sup>1</sup>

There are several cases looking at the use of this icatibant treatment in ACE-inhibitor induced angioedema rather than hereditary angioedema. Currently the mainstay of treatment for ACE-inhibitor induced angioedema is conservative management including discontinuing the ACE-inhibitor and maintaining the airway. Initial PubMed search identified eleven case reports that described the use of icatibant as a treatment for ACE-inhibitor induced angioedema of the head and neck, with mixed results among cases.<sup>3-13</sup> Three of the results from the literature search included clinical trials, which offered more robust study designs and results than the aforementioned case reports. Baş et al. first reported in 2015 that icatibant does offer potential benefits when used as a treatment for ACE-inhibitor induced angioedema of the head and neck.<sup>14</sup> The study was a double blind clinical trial that compared icatibant treatment with IV prednisolone and clemastine antihistamine therapy in 27 white patients. The results of this study indicated that patients treated with icatibant experienced a significant reduction in the time for resolution of their symptoms. One limitation of this study however was the alternative treatment of steroid and antihistamine, which are indicated for histamine induced angioedema rather than ACE-inhibitor induced angioedema. Therefore this initial trial was not the most ideal comparison to look at.

A more recent study by Straka et al. attempted to reanalyze this idea in a more diverse population.<sup>15</sup> This trial included 33 subjects composed of a mixture of men and women, two thirds of whom were African American. This study was a double blind randomized control trial that compared icatibant treatment to that of placebo. Overall the findings of this trial did not agree with the previous study by Baş et al. The new findings were that there was no significant difference in resolution time for those individuals treated with icatibant versus the placebo treatment.<sup>15</sup> The authors acknowledged that a potential reasoning for this difference could be the fact that there was a longer time between onset of symptoms and administration of treatment for the study compared to the original study by Baş et al.

While both of these original studies produced contradicting results, they each were limited by their small sample size. In an attempt to expand on these findings, Sinert et al. designed their larger clinical trial to answer the question of whether icatibant is an effective treatment in patients with moderately severe ACE-inhibitor induced angioedema of the head and neck.<sup>16</sup> This study was chosen for critical appraisal because it better fits our interests for our patient. The sample size is much larger and more diverse, and the patients in this study were primarily taking lisinopril, and the patient met all of the inclusion criteria.

## Critical Appraisal

The study by Sinert et al. was a phase 3 clinical trial that was randomized and double blinded. It included patients from 59 treatment centers from the United States, UK, Canada, and Israel. The study participants included subjects who were above the age of 18 who were being treated with an ACE-inhibitor and presented with angioedema of the head and/or neck for the first time after treatment and not attributed to any other cause. The study also excluded any subjects who required immediate intubation due to the severity of the angioedema. Participants had to meet at least moderately severe classification of angioedema based on characteristics such as difficulty breathing, swallowing, speaking, and tongue swelling, and had to be within the initial 12 hours of onset of the angioedema. Patients who received other treatments including corticosteroids, antihistamines, or epinephrine were not excluded from the study unless they demonstrated a clear response to one of those treatments.

Participants were randomly assigned to treatment group with 30mg of icatibant or a placebo, and stratification also occurred based on severity of angioedema as well as race of the participants. A physician blinded to treatment was responsible for performing the initial assessment for a patient, as well as all follow up assessments, to determine effectiveness of the treatment based on a rating scale. The rating scale was developed through quantitative analysis of physician interviews to establish criteria which were clinically relevant, valid, and reliable. The criteria were clearly outlined and presented to raters and demonstrated good reliability between



the different physicians performing the evaluations, with an intraclass correlation coefficient greater than 0.80.<sup>17</sup> The primary efficacy outcome that was analyzed was the amount of time from administration of treatment until the patient was no longer having breathing or swallowing symptoms and met discharge criteria. Secondary outcomes included time to onset of symptom relief based on the standardized rating scale, airway intervention, hospital admission, and supplemental treatment with steroids, antihistamines, or epinephrine after initial clinical trial treatment. Intention to treat analysis was completed on the icatibant treatment population of 61 participants and the placebo treatment population of 60 participants.

Results of this study indicated that there was no significant difference in the treatment of ACE-inhibitor induced angioedema with icatibant compared to placebo treatment in regards to the primary outcome of time to meeting discharge criteria (P=0.63) or secondary outcome of time to onset of symptom relief (P=0.57). The two treatment groups were comparable in numbers of participants meeting other secondary outcomes such as admission to hospital. Other subgroup analyses based on gender, race, age, and BMI all showed no difference between the two treatment groups. These results correspond to those found by Straka et al. and go against the findings of Baş et al.

## Clinical Application

As mentioned previously, our patient was interested in treatment to hasten his recovery, by reducing swelling so he could be discharged. His concern aligns with the criteria that were used for the Sinert et al. study, which used improvement of symptoms and meeting discharge criteria as their primary outcome. The patient also met all of the inclusion criteria for the study, and the details corresponded well to his personal details. The study had a majority of African Americans above 75kg who were treated with lisinopril, just as our patient had been treated. The angioedema of the head and neck was attributed solely to the administration of an ACE-inhibitor based on timing and clinical correlation. The only area of this study that does not correlate to our patient was the fact that our patient had onset of symptoms within just a few days of initiation of treatment, whereas the majority of those in the study started their ACE-inhibitor more than 90 days before onset of symptoms. This however is not likely to impact the application of the results to our patient, because in the study they were still confident that participants had angioedema attributable to the ACE-inhibitor. The more important timeline would be the time between onset of symptoms and initiation of treatment. Additional support for application of these study findings is that the majority of patients in the study received steroids as well as antihistamines before treatment, and our patient had already been started on both of these therapies in the emergency department.

In applying the results of this clinical trial to our own patient, it is not recommended to treat with icatibant as it would not provide any added benefit over conservative treatment for him. We did not add on any additional therapeutic treatment to our patient. There was no added harm by applying these results to our patient, as the current standard of care for patients with ACE-inhibitor induced angioedema of the head and neck is normal conservative management until symptoms improve. In the placebo arm of the study, this did not result in any added harm to those patients either. As all of these studies have come out within just the past few years, it will be interesting to see the development of icatibant and other medications as potential treatment options for ACE-inhibitor induced angioedema in the future.

Learning points:

1. Currently there is no accepted treatment for ACE-inhibitor induced angioedema of the head and neck beyond conservative management including discontinuation of ACE-inhibitor and maintenance of the airway and ability to swallow.
2. ACE-inhibitor induced angioedema, although rare, is a serious and potentially life threatening condition. It should be noted that African Americans should not be initially started on ACE-inhibitors for hypertension control due to their increased risk. It is unclear why our patient was started on this sole treatment regimen.



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