The angiotensin-converting enzyme (ACE) inhibitors are now widely prescribed for the treatment of hypertension as well as for providing cardiovascular and renal protection in patients with heart failure, chronic kidney disease, and at high risk of cardiovascular events. Worldwide, it is estimated that tens of millions of patients are now taking these agents. Given this widespread exposure to ACE inhibitors, it is evident that even rare events can multiply and affect significant numbers of patients. This certainly applies to angioedema, a serious side effect of the ACE inhibitors that has been known about since these drugs were first introduced. The article by Miller et al in this issue of Hypertension represents a careful effort to estimate the frequency of this event in contemporary clinical practice.

One of the chief attributes of the ACE inhibitors has been their overall tolerability. By far the most commonly encountered complaint with these agents is a dry, nonproductive cough. The cause of this cough has never been established, but bradykinin—which exists in increased concentrations as a direct result of the action of the ACE inhibitors—is the most commonly cited culprit. This cough is generally not of medical significance, but can sometimes lead to increased doctor visits and costs when the explanation for a newly evident cough is being sought. This symptom is sufficiently intrusive to cause discontinuation of ACE inhibitor therapy in up to 20% of patients.

Angioedema is potentially far more troubling. As with cough, bradykinin seems to be the cause of this event. Angioedema varies in severity. In its mildest form, it may be manifested by a transient swelling of the lips, tongue, or mouth. More serious cases, however, can cause acute respiratory distress by affecting the upper airway and larynx. Obviously, patients with these drastic manifestations of angioedema typically are hospitalized and may require intubation or even tracheostomy. These episodes can be fatal. Although most instances of angioedema are localized to the head and neck, it has been surmised that the epigastric discomfort that has been associated with ACE inhibitors may, in fact, reflect an angioedema-like effect in the gastrointestinal tract.

ACE inhibitor–induced angioedema is more prevalent in black patients than in white. The current report by Miller and colleagues provides further confirmation of the heightened risk in blacks. It is possible, too, that angioedema in black people can be particularly severe. One coroner’s office actually observed, within a 3-year period, 6 fatal cases of angioedema in black patients exposed to ACE inhibitors. This concern has led to extraordinary labeling in the FDA-approved package inserts of all the ACE inhibitors. The labeling points out that because black patients, when treated for hypertension, tend to get lesser antihypertensive effects with ACE inhibitors than other ethnic groups, but at the same time be exposed to a higher probability of angioedema, their treatment with ACE inhibitors provides a diminished benefit risk ratio. This brings up the question as to whether ACE inhibitors should still be considered first-line therapy in black patients. When pondering this issue, however, we should remember that in hypertensive black patients with nondiabetic kidney disease, treatment based on an ACE inhibitor was superior to that with either β blocker or calcium channel blocker treatments in protecting against progression of kidney disease.

Soon after the ACE inhibitors were introduced into clinical practice, there was a wide misconception that almost all angioedema events took place within the first few days or weeks of therapy. Sadly, this reassuring statement has not turned out to be true. Reports during the past 3 years, including that of Miller et al, have emphasized that although a relatively high proportion of angioedema episodes occur during the early part of treatment, these serious events can be observed after months or even years of ACE inhibitor therapy. In fact, in a large clinical survey by Zingale et al the average ACE inhibitor exposure before the occurrence of angioedema was a full 12 months; remarkably, it took an additional 12 months from the occurrence of the angioedema until the ACE inhibitor therapy was discontinued.

ACE inhibitors are by no means the only cause of angioedema. Many cases have been attributed to different foods, for example, and for many patients the stimulus for their angioedema is not evident. Clinical trials also have revealed that angioedema can occur during treatment with drug classes other than ACE inhibitors. In the Valsartan Antihypertensive Long-term Use Evaluation trial, in which the effects on major clinical end points of the angiotensin receptor blocker, valsartan, were compared with those of the calcium channel blocker, amlodipine, there was a 0.13% incidence of angioedema reported for each drug across the 5 years of the study. Similarly, another clinical outcomes study, the Lo-
sartan Intervention For Endpoint reduction in hypertension (LIFE) trial, which compared the angiotensin receptor blocker, losartan, with the β blocker, atenolol, over a 5-year period, reported angioedema incidence rates of 0.1% and 0.2%, respectively. Whether the event rates of angioedema reported in these trials reflected effects of the drugs being tested, or whether they simply demonstrated the background reported in these trials, is not clear.

**Estimating the Incidence of Angioedema With ACE Inhibitors**

There are a variety of ways to measure the frequency of these events. The most simple is to await the submission of reports by physicians in the community who observe episodes of angioedema in their own patients. In reality, though, this approach grossly underestimates the incidence of serious drug side effects. For a start, many such episodes, particularly if they are of short duration, may go unrecognized by the patient. Even when recognized, the patient may not connect the angioedema to the ACE inhibitor therapy and therefore not report it to the physician. When physicians eventually diagnose angioedema, particularly if it is not sufficiently severe to warrant admission to a hospital, there may be a reluctance to file a report for fear of then being inundated with requests from the manufacturer of the drug or from regulatory agencies to provide additional clinical information. Many physicians in such situations may satisfy themselves by making a notation in the patient’s chart and resolving the issue by switching the patient to another drug class.

A more systematic approach, and one we have tended to depend on, uses data provided from the registration studies carried out by sponsors to get approval to market their drugs from the FDA or other such agencies. Indeed, much of what we have known about angioedema caused by ACE inhibitors has come from such studies. In general, investigators participating in such trials are diligent in reporting adverse events, so there are reasonably reliable data concerning such findings as angioedema. The shortcoming of using on registration studies for antihypertensive drugs to estimate the incidence of adverse events is that these trials typically have drug exposures of only 4 to 8 weeks, which clearly would underestimate the extent of the problem.

Longer term clinical trials with large patient cohorts have provided valuable prospective information about angioedema during the treatment of hypertension. Perhaps the definitive trial in this regard is Omapatril Cardiovascular TreAtment Versus Enalapril (OCTAVE), for it was designed to focus specifically on establishing the incidence and clinical features of angioedema. These events were the primary end points of this trial, and the investigators were carefully trained in the recognition of angioedema events, either mild or serious. A total of 12,557 patients were treated with the ACE inhibitor, enalapril, in its full dosage range of 5 to 40 mg daily. During the 6 months of the study, 0.68% of patients (6.8 per 1000) were diagnosed with angioedema. Events were more common in the early months of the study than later on. Still, it is likely that even more events would have occurred had the study been extended to the same length as other experiences. Analysis of the factors that predicted angioedema events in OCTAVE confirmed that black patients were almost 3 times as likely as others to experience an episode. Previous histories indicative of allergic reactions, including rashes during treatment with other types of drugs, or episodes of seasonal allergy, were also predictive of angioedema. Interestingly, being over the age of 65 also increased the likelihood of an episode. An approximation of the severity of the angioedema events can be gauged by the types of treatment that were utilized: about half of the patients received no treatment at all; and either antihistamines or corticosteroids were given in 64% of patients. Only 1 patient received epinephrine and only 2 patients required hospitalization, though neither had acute airway symptoms.

The current report by Miller et al, although observational in design, provides a valuable perspective in understanding ACE inhibitor-induced angioedema. By studying all patients started on ACE inhibitors during a particular time period in the Veterans Affairs medical system, these investigators were able to count angioedema outcomes in a cohort numbering almost 200,000. This type of observation has the virtue of being carried out entirely within a closed healthcare system, so that all individuals presenting with angioedema—either as outpatients or inpatients—would have retrievable documentation of their diagnosis. A further strength of the report is the careful validation of diagnostic accuracy performed by this team of investigators and their colleagues.

The incidence rates of angioedema, as would be expected, were lower in this veterans study than reported in OCTAVE. After all, this was a retrospective look at the practice experience of large numbers of physicians, both primary care and specialist, who had no particular reason to be searching for angioedema. Thus, as Miller and colleagues acknowledge, it is likely that a meaningful number of angioedema events were either undiagnosed or not reported. Importantly, however, this experience was of sufficient magnitude to allow useful analysis of major clinical associations with angioedema. Once again, the susceptibility of black patients to experience angioedema was confirmed. Of interest, though, women in this particular population appeared to be more vulnerable to angioedema than men. The investigators also noted that patients with diabetes mellitus were less likely that those without diabetes to have episodes of angioedema. There is no obvious explanation for this interesting finding.

Therapy of life threatening angioedema is supportive and consists in maintaining patency of airways, if necessary by intubation or tracheostomy, and the use of corticosteroids, antihistamines, and epinephrine. Icatibant, a bradykinin inhibitor currently in development, has been shown to reduce the severity and duration of episodes of hereditary angioedema and could be promising for the treatment of ACE inhibitor-associated angioedema as well.

Angioedema, although rare, still affects many patients treated with ACE inhibitors. The frequency of these episodes is relative greater in the days after the start of therapy, but serious and even fatal events have been reported in patients after months or even years of treatment. Clearly, when considering the use of ACE inhibitor therapy in black patients, the increased risk of angioedema should be taken into account.
into account and discussed with the patients. There is still a great deal we do not know about this condition. Even so, ACE inhibitors have been valuable in preventing fatal and nonfatal cardiovascular and renal events in patients at risk, and it is likely that they will continue to be prescribed in the foreseeable future.

Disclosures
None.

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Angiotensin-Converting Enzyme Inhibitors and Angioedema: Estimating the Risk
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_Hypertension_. 2008;51:1465-1467; originally published online April 14, 2008;
doi: 10.1161/HYPERTENSIONAHA.108.111393

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
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