Angioedema Incidence in US Veterans Initiating Angiotensin-Converting Enzyme Inhibitors

Donald R. Miller, Susan A. Oliveria, Dan R. Berlowitz, Benjamin G. Fincke, Paul Stang, David E. Lillienfeld

Abstract—Angioedema is a rare but potentially serious complication of angiotensin-converting enzyme inhibitor (ACE) use. We conducted a study to estimate incidence of ACE-related angioedema and explore its determinants in a large racially diverse patient population. We used linked medical and pharmacy records to identify all patients in the US Veterans Affairs Health Care System from April 1999 through December 2000 who received first prescriptions for antihypertensive medications. We studied 195 192 ACE initiators and 399 889 patients initiating other antihypertensive medications (OAH). New angioedema was identified by diagnosis codes using methods validated in a national sample of 869 angioedema cases with confirmation for over 95% of cases. Overall, 0.20% of ACE initiators developed angioedema while on the medication and the incidence rate was 1.97 (1.77 to 2.18) cases per 1000 person years. This compares with a rate of 0.51 (0.43 to 0.59) in OAH initiators and the adjusted relative risk estimate was 3.56 (2.82 to 4.44). Fifty five percent of cases occurred within 90 days of first ACE use but risk remained elevated with prolonged use, even beyond 1 year. We estimate that 58.3% of angioedema in patients starting antihypertensives was related to ACE. We also found that angioedema rates were nearly 4-fold higher in blacks, 50% higher in women, and 12% lower in those with diabetes. This study provides a reliable estimate of angioedema incidence associated with ACE use in a diverse nontrial patient population, confirming that the incidence is low, but finding substantial variation by race, sex, and diabetes status. (Hypertension. 2008;51:1624-1630.)

Key Words: angioedema ■ angiotensin-converting enzyme inhibitors ■ antihypertensive agents ■ adverse effects ■ pharmacoepidemiology ■ drug toxicity

Angiotensin-converting enzyme inhibitors (ACE) are commonly prescribed medications for patients with high blood pressure, diabetes, chronic heart failure, and coronary heart disease. Their use has been associated with lower risk of myocardial infarction, delay in symptoms of heart failure, diminished progression of kidney disease, and lower mortality risk.1–4 These medicines are used by millions of patients with few side effects.

One potentially serious complication of ACE is angioedema, a subcutaneous nonpitting edema typically of sudden onset and short duration.5–9 It can involve nearly any part of the body, although the larynx, tongue, lips, and face are most often involved. When the airways are affected it can be life-threatening.

Research conducted to date suggests that the incidence of angioedema associated with ACE use is low,9–16 on the order of 1 or 2 per 1000 patients, but both its incidence and determinants are not well understood. Previous estimates have come primarily from small observational studies in select patient populations or from clinical trials of relatively healthy people. The best of these is Omapatril Cardiovascular TreAtment Versus Enalapril (OCTAVE), a randomized double-blind clinical trial of 12 557 persons with hypertension treated with enalapril,11 in which an incidence rate of 6.8 per 1000 was found over 24 weeks of follow-up. Although this probably our best estimate, it remains uncertain how well it applies to the larger more diverse population of patients seen in clinical settings with comorbidities that may have made them ineligible for trials.

The current study was undertaken to assess the incidence of angioedema in ACE users and to explore its determinants in a large racially diverse patient population. To estimate the independent contribution of ACE use to angioedema risk, incidence of angioedema in new ACE users was compared to that among new users of other antihypertensive medications (OAH), and other factors were considered in the analysis. This study also includes detailed chart review of a large number of patients with angioedema to confirm the validity
of our methods for identifying angioedema, refining the analysis, and obtaining more accurate estimates of the incidence of ACE-associated angioedema.

Methods

Data Sources
This was a national study of veterans receiving health care from the United States Veterans Affairs Health Care System (VA) from October 1, 1998 through December 31, 2000. Data sources included national VA pharmacy records obtained from the Pharmacy Benefits Management Strategic Health Group (PBM),22 computerized health encounter records from the Austin Automation Center,18,19 and Medicare claims obtained from the Centers for Medicare and Medicaid Services for VA patients receiving part of their care outside of the VA that was covered by Medicare.20,21 This research was part of the Diabetes Epidemiology Cohorts Program.22 The Institutional Review Board at the Edith Nourse Memorial VA Hospital in Bedford, Massachusetts reviewed and approved the study protocol and a waiver of informed consent. All study procedures were in accordance with institutional guidelines.

National Cohort Study Sample
We identified all VA patients who received VA prescriptions for antihypertensive medications from October 1998 through December 2000. Each patient’s prescriptions were processed to assess timing and duration of use and multiple prescriptions for a given medication were summarized into episodes of use. To study only new users of antihypertensive medications, we restricted the sample to those patients who did not receive an antihypertensive prescription in the first 6 months of the study (October 1998 through March 1999) and then subsequently received a first prescription (from April 1999 through December 2000). Prior analyses indicated that this 6-month “clean” period excludes more than 90% of past users of a class of medications. The remaining sample was split into the 2 study groups, those who first initiated ACE and those who initiated a different class of antihypertensive medication (OAH). Patients in the latter group, initiating OAH, who subsequently were prescribed ACE up through December 2000 also were excluded.

Identification of Angioedema
First episodes of angioedema were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (995.1)3 recorded during inpatient stays or outpatient visits and contained in either national VA patient records or Medicare claims. We evaluated this method in a large medical chart review study described below. The date of the first code was taken as the day of onset of the angioedema. All episodes of angioedema occurring during the study period were included and analyzed in relation to the time of antihypertensive prescriptions.

Other Patient Information
Patient records from national computerized data files also provided information to assign demographic (sex, age, race) and comorbidity status (chronic heart failure [CHF; ICD-9-CM=428], coronary artery disease [CAD; 410–414], diabetes mellitus [DM; 250], and high blood pressure [HBP; 401–405]). Deaths were identified from the VA Beneficiary Identification and Record Location file (a registry of all veterans whose families have applied for death benefits that has been shown to reasonably reliable and complete24, supplemented by searches of VA inpatient files, Medicare claims, and Social Security files.

Statistical Analysis
All analyses were conducted using Statistical Analysis Software (SAS) version 8.0.23 We counted the numbers of new angioedema cases and the total numbers of patients in each medication group in each month before, during, and after medication initiation. Counts were combined across months and case counts were divided by total patient counts to calculate unadjusted incidence rates for the time periods before the first prescription, after the first prescription, and after use had ended in each medication group. Incidence rates are presented as cases of angioedema per 1000 person-years and exact Poisson 95% confidence intervals were calculated for rates.26 Additional analyses were performed for cases with angioedema codes from inpatient stays or intensive care units and for cases dying within 90 days of their angioedema. Multivariate Poisson regression models were used to estimate adjusted relative risk of angioedema for ACE use, relative to use of OAH.27,28 Models included terms for calendar year, age, sex, race, and diagnoses of congestive heart failure, coronary artery disease, and diabetes. Unfortunately, we did not have sufficient information on other potentially important correlates of angioedema risk, including smoking and allergies.11 In separate models, we evaluated risk of angioedema associated with initiation of specific ACE medications and modification of the risk using interaction terms as a test of homogeneity across strata of covariates. Population attributable risk percentages were calculated using relative risk estimates for angioedema obtained from the regression models.29,30

Medical Chart Review Study
To evaluate methods used in the national cohort study and to inform the analysis, we conducted a national medical chart abstraction study with a subset of the angioedema cases. To maximize its applicability to our national study, we selected and recruited VA facilities from across the country. After receiving human studies approval at each hospital, we obtained medical charts for patients from 20 VA facilities throughout the United States (see acknowledgments), representing over 20% of the entire VA patient population. Complete medical charts for patients with a diagnosis code of angioedema were abstracted by trained VA health care providers (internists, residents, nurses, doctors of pharmacy) using standardized forms and methods. Confirmation of the angioedema in the medical chart was based on explicit notation of the diagnosis and description of the relevant symptoms in notes near the time of the code assignment. Additional information from earlier and later notes in the record indicating corrected or alternative diagnoses was applied to reclassify confirmation status. We assigned the likelihood of angioedema as (1) current firm (diagnosis noted with description of specific symptoms of edema of the tongue or lips, or asymmetrical facial swelling at the time of the medical visit or stay), (2) current probable (either diagnosis or symptoms at the current visit), (3) past firm (both diagnosis and symptoms but with reference made to an episode of angioedema in the recent past), (4) past probable (either diagnosis or symptoms referring to the recent past), or (5) none (neither). Confirmation assignments were evaluated by a panel of 3 VA physicians who independently reviewed 10% of the charts and assigned likelihood of angioedema to each case. In addition to confirmation of the diagnosis, medical chart data were used to confirm antihypertensive medication use and the timing of use in relation to the angioedema episode.

Results
There were 1 715 858 veteran VA patients who were prescribed antihypertensive medications from April 1999 through December 2000 (Table 1), representing 49.4% of the entire VA population at that time. These patients were predominantly male (98%), older (64% over 65 years of age), and of white race (78%), and associated chronic medical conditions were relatively common. More than 50% of those taking antihypertensive medications (888 124) were prescribed an ACE.

For the follow-up study, the sample was limited to the 595 881 patients who initiated antihypertensive medications during that period, with 195 192 starting ACE and 399 889 starting another agent (Table 1). The predominant ACE was lisinopril (72%), followed by fosinopril (22%) and captopril...
In terms of other antihypertensive medications initiated, most were diuretics (32.6%), β-adrenergic blockers (23.5%), calcium channel blockers (21.1%), and peripherally acting antiadrenergic agents (16.6%). ACE initiators were similar to other patients starting antihypertensive medications in terms of demographic characteristics but they more often had chronic heart failure and especially diabetes.

A total of 5901 VA patients were identified with new angioedema during that period (Table 1). Of these patients, 704 (11.9%) were diagnosed as inpatients, 337 (5.7%) were subsequently admitted to intensive care, and 302 (5.1%) died sometime after the episode—9 within 1 week and 33 within 1 month. The demographic and morbidity profile of these patients was similar to the overall VA patient population, except for older age (70% over 65 years) and a preponderance of blacks (25%).

With the sample restricted to those newly prescribed antihypertensive medications, there were a total of 833 new angioedema cases, 434 in ACE initiators and 399 in OAH initiators (Table 2). In the new ACE users, most (352 or 81.1%) of the cases occurred after the new prescription and while still using the drug. Overall, 0.20% of patients initiating ACE developed angioedema while on the medication and the angioedema rate was calculated to be 1.97 cases per 1000
person years with a 95% confidence interval of 1.77 to 2.18. Rates were highest in the 30 days after the new prescription (7.38 [6.12 to 8.82]). Fifty-five percent of cases occurred within 90 days of first ACE use and the rate in that period was 4.13 (3.57 to 4.75). Rates declined gradually over the following year but remained elevated, even in those with more than 1 year of ACE use (0.93 [0.64 to 1.31]). These rates compare with a rate of 0.47 (0.34 to 0.63) in this group before ACE initiation and a rate of 0.51 (0.43 to 0.59) in the comparison group of OAH initiators while using the drug. Angioedema incidence was elevated after OAH initiation but the increase was slight (0.99 [0.68 to 1.39]) and it dropped in the next time period with no apparent trend in rates by time. When the OAH initiation group was broken out by class of antihypertensive medication, there was little variation among the other classes: calcium channel blockers (0.52/1000), beta adrenergic blockers (0.46/1000), thiazide diuretics (0.66/1000), peripherally acting antiadrenergic agents (0.42/1000), loop diuretics (0.50/1000), other diuretics (0.60/1000), centrally acting antiadrenergic agents (0.76/1000), angiotensin II receptor blockers (0.99/1000), alpha- and alpha-betaadrenergic blockers (0.28/1000), and vasodilators (0.40/1000). Evaluation of angioedema risk associated with other specific classes of antihypertensive medications is beyond the scope of this report.

Results from Poisson regression are presented in Table 3. The adjusted relative risk for new ACE users relative to new OAH users was 3.56 (95% confidence intervals of 2.82 to 4.44). The risk was elevated for all 3 ACE agents individually. Although the risk appeared to be somewhat lower for captopril, as has been reported from a previous study,15 the differences were not statistically significant. These models also confirm that, independent of other factors considered, the risk of angioedema was increased substantially for blacks (3.88 [2.99 to 4.95]), females (1.45 [1.15 to 1.88]), and those with chronic heart failure (1.22 [1.08 to 1.38]) or coronary artery disease (1.31 [1.16 to 1.48]), and decreased significantly for those with diabetes (0.88 [0.82 to 0.95]). We also ran an additional series of models with interaction terms to test for differences in risk of ACE-associated angioedema by demographic factors and comorbidity. None of the terms were significant in these models, and they are not presented.

To study the more severe cases, we repeated the analysis with restriction to angioedema cases diagnosed in hospital, admitted to intensive care, or dead within 90 days of the angioedema. The results were comparable to those obtained with all cases. The incidence of inpatient angioedema was 0.136 per 1000 for new ACE users compared with 0.031 for OAH initiators; 90 day postangioedema mortality was 0.010 per 1000 for new ACE users as compared to 0.006 for new OAH users. The adjusted relative risks of severe angioedema from Poisson regression were nearly 4.0 for ACE initiation

<table>
<thead>
<tr>
<th>Table 2. Angioedema Rates Among Patients Initiating ACE or Other Antihypertensives (OAH)—April 1999 to December 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of Angioedema</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Before drug use</td>
</tr>
<tr>
<td>During drug use</td>
</tr>
<tr>
<td>Duration</td>
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<tr>
<td>&lt; 30 days</td>
</tr>
<tr>
<td>31 to 60 days</td>
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<tr>
<td>61 to 90 days</td>
</tr>
<tr>
<td>91 to 180 days</td>
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<tr>
<td>181 to 270 days</td>
</tr>
<tr>
<td>271 to 360 days</td>
</tr>
<tr>
<td>&gt; 360 days</td>
</tr>
<tr>
<td>After discontinuing use</td>
</tr>
</tbody>
</table>

*Estimated from multivariate Poisson regression models.

Table 3. Relative Risk Estimates* for Angioedema in VA Patients Prescribed ACE or Other Antihypertensives

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Category</th>
<th>Relative Risk*</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiating ACE</td>
<td>other AH</td>
<td>3.56</td>
<td>2.82 to 4.44</td>
</tr>
<tr>
<td>Black</td>
<td>white</td>
<td>3.88</td>
<td>2.99 to 4.95</td>
</tr>
<tr>
<td>Other race</td>
<td>white</td>
<td>0.91</td>
<td>0.77 to 1.13</td>
</tr>
<tr>
<td>Female</td>
<td>male</td>
<td>1.45</td>
<td>1.15 to 1.88</td>
</tr>
<tr>
<td>Age &lt;45 years</td>
<td>75+ years</td>
<td>1.17</td>
<td>0.78 to 1.77</td>
</tr>
<tr>
<td>Age 45 to 54 years</td>
<td>75+ years</td>
<td>0.90</td>
<td>0.80 to 1.04</td>
</tr>
<tr>
<td>Age 55 to 64 years</td>
<td>75+ years</td>
<td>1.17</td>
<td>0.91 to 1.51</td>
</tr>
<tr>
<td>Age 65 to 74 years</td>
<td>75+ years</td>
<td>1.42</td>
<td>1.15 to 1.74</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>No CHF</td>
<td>1.22</td>
<td>1.08 to 1.38</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>No CAD</td>
<td>1.31</td>
<td>1.16 to 1.48</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>No DM</td>
<td>0.88</td>
<td>0.82 to 0.95</td>
</tr>
<tr>
<td>ACE initiated: in separate model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>other AH</td>
<td>3.63</td>
<td>2.34 to 5.48</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>other AH</td>
<td>3.45</td>
<td>2.06 to 5.46</td>
</tr>
<tr>
<td>Captopril</td>
<td>other AH</td>
<td>2.20</td>
<td>1.08 to 3.95</td>
</tr>
</tbody>
</table>

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References: 1, 15

*Estimated from multivariate Poisson regression models.
and for black race; risk estimates for other factors were not significantly different from 1.0.

Finally, we estimated the attributable risk percentages for ACE and angioedema. Among new ACE users, the proportion of angioedema related to ACE exposure was estimated at 71.9%, and the proportion of angioedema attributable to ACE among all patients newly prescribed antihypertensive medications was 58.3%.

**Medical Chart Review**

Medical records for 1043 of the angioedema cases were obtained, and a total of 869 were judged to be complete. Evidence confirming angioedema was found in all but 41 of the charts (95.3%), with 487 (56.0%) assigned as “current firm,” 146 (16.2%) as “current probable,” 16 (1.8%) as “past firm,” and 179 (20.6%) as “past probable.” There was consensus on the assignments for 94% of cases by the 3 reviewing clinicians.

We also used the medical chart abstraction data to verify the use and timing of medications. Out of the 384 cases indicating recent ACE use in the charts, all but 20 (5.2%) had VA prescription records for ACE. For cases with notation of OAH, only 7 of 415 were without VA prescriptions. However, OAH were infrequently recorded in the charts at the time of the angioedema (36% of those with OAH prescriptions) as compared to chart recording of ACE use for 77% of those with VA prescriptions. Verification of the dates of angioedema onset and prescription dispensation confirmed the temporal relationship between the condition and previous exposure to the ACE in all but 7 cases. Most of these exceptions were for patients who responded rapidly to first exposure and had the angioedema diagnosis on the same day as the first prescription, which we conservatively considered as being before first use. Overall, these discrepancies suggest that missed medications and date errors could have only a minimal effect on the rates and associations estimated in our analysis.

Although the relatively high confirmation rate of the diagnosis in the chart review analysis was reassuring, as a further check, we repeated the Poisson regression modeling of risk in a sample restricted to patients from facilities with chart review and to those angioedema cases with confirmed diagnosis. The results were broadly similar to those observed and presented for the national sample.

**Discussion**

This is the largest observational study of medication-related angioedema published to date. It provides important information on the risks of this condition across the spectrum of patients seen in clinics, including many patients who would not have been included in trials because of comorbidities. It is derived from a population of about 2 million VA patients prescribed antihypertensive prescriptions, focusing on a sample of nearly 600,000 patients first initiating this treatment with 833 new angioedema cases identified over a 21-month period. Furthermore, an extensive medical record review of a 14% sample indicated confirmation for over 95% of cases. From these data, we estimate an angioedema incidence in patients newly prescribed ACE of 1.97 per 1000 person years of use with relatively narrow confidence intervals (1.71 to 2.18). We project that about 1 of every 2600 new ACE users experiences angioedema within 30 days and about one of every 1000 experiences it within a year after first use. It also is evident that risk remains elevated with continued ACE use, even more than 1 year after initiation. The majority (71.9%) of angioedema occurring in new ACE users is attributable to the drug, and more than half (58.3%) of the adverse condition occurring in the population of patients newly prescribed antihypertensive medications is attributable to ACE.

Our estimated incidence of ACE-associated angioedema agrees well with those reported from other studies.9–13 Even though there are a number of reasons why some variance might be expected. Compared to other study populations,7,11,12,31,32 VA patients are older and are predominantly male, with relatively high prevalence of comorbidities such as diabetes.22–33 We found lower risk of angioedema in men and patients with diabetes, and the later findings agree with those reported from the OCTAVE Study.11 Unfortunately, we did not have information on smoking or allergies so we could not evaluate the higher angioedema risks associated with these conditions in the OCTAVE Study. In agreement with other recent studies,12,13,15,16 we found that the most important demographic factor modifying angioedema risk is race, with blacks having 4-fold higher risk of angioedema. In the VA, 15.2% of ACE users are blacks; this is less than the 26.3% from the Medicaid recipient population studies12,15 but not lower than most other populations studied, including OCTAVE,11 and it is similar to the general population of the United States.34 If we standardize our incidence rate30 by sex, age, and race to the general population reporting hyperten-

sion,34 our overall estimate of ACE-associated angioedema is 2.7 per 1000 person years of ACE use.

Errors in case ascertainment are a possible reason for inaccuracy in our estimated incidence rates. The high proportion of cases confirmed in our medical chart review was reassuring with respect to possible overcounting of angioedema.35,36 On the other hand, undercounting may have occurred if angioedema cases failed to receive a diagnosis, particularly in cases with atypical presentation or those that resolved quickly. To the extent that this was present, it would most likely affect the least severe cases. This may be the reason why a higher incidence was reported from OCTAVE (6.8 per 1000) which conducted prospective adjudication of cases and probably included many milder cases that we might have missed.11 Given that most physicians are aware of the risk of angioedema associated with ACE use and that notation of use and discontinuation after an episode were much more likely for ACE than for the other drugs in our medical chart review, a missed diagnosis was probably more likely in patients using drugs other than ACE; this may have led to greater underestimation of angioedema risk associated with antihypertensive medications other than ACE. Some episodes of angioedema also may have been missed if patients were diagnosed and treated outside of the VA system with care not covered by Medicare, but this is unlikely to represent more than a small fraction of cases.21

Errors in the medication information are another potential source of bias. We may have missed some drug exposures if
patients received prescriptions from pharmacies outside of the VA. However, prior studies indicate that this is unlikely to have been common given that most patients take advantage of the low prescription copay and obtain most of their medicines from the VA.\textsuperscript{37,38} In the chart abstraction analysis, VA prescription data were found for all but a few percentages of cases with notation of ACE or OAH use. Errors in dates of medications or diagnoses also could have led to misattribution of the angioedema given the rapid onset of the condition. There was little evidence for this in the abstracted chart data with the exception of a small number of cases with diagnosis within days of first prescription but onset of symptoms several days before the diagnosis. While these cases may have had their angioedema mistakenly classified as occurring after the first prescription, it appears that this was not common enough to substantially bias the estimates given the low rates of angioedema in the group classified as “before use.”

There are a number of isolated reports of angioedema after OAH use in the literature,\textsuperscript{39–42} but we found little evidence for increased risk associated with antihypertensives other than ACE. There were only small increases in incidence after new OAH use, and trends in the rates were not consistent. Some of the OAH, such as calcium channel blockers, are commonly used to treat patients with congestive heart failure or coronary artery disease, and these patients may be at increased risk of angioedema from the disease or from other medications that they are taking for these diseases (eg, aspirin, beta adrenergic blockers). Nevertheless, the estimates did not change with adjustment for these conditions or for other antihypertensive medications. Finally, for this analysis, we did not have sufficient numbers of users of angiotensin II receptor blockers so evaluation of angioedema risks associated with use of these agents is reserved for future studies with more recent data.

Perspectives
This study represents the largest observational study to date examining the association between antihypertensive drug therapy and incidence of angioedema. It is remarkably consistent with clinical trials in showing a similarly modest increase in incidence associated with use of angiotensin-converting enzyme inhibitors when compared with other antihypertensive medications. This increased risk extends beyond the initial period of ACE use and does not appear to be shared with other antihypertensive medications. The strength of this study is that it demonstrates that this increased risk extends across a broad spectrum of patients, including the elderly and those with multiple comorbidities, who typically may not be included in clinical trials. Yet, specific subgroups exist with different risks of ACE-associated angioedema including increased risk in blacks and decreased risk in patients with diabetes. The challenge for future research will be to better identify those subgroups at the highest risk for angioedema in whom the risks of ACE therapy may outweigh the benefits. This information is essential in making appropriate clinical decisions about medical therapy for hypertensive patients and patients with congestive heart failure.

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Disclosures
D.R.B. has served as a consultant for Bristol-Myers Squibb, a manufacturer of antihypertensive medications. The remaining authors report no conflicts.

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