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9-24-2021

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Elizabeth T. Mansi

Eric S. Johnson

Micah L. Thorp

Alan S. Go

Ming-Sum Lee

See next page for additional authors

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Authors

Elizabeth T. Mansi, Eric S. Johnson, Micah L. Thorp, Alan S. Go, Ming-Sum Lee, Albert Yuh-Jer Shen, Ken J. Park, Katarzyna Budzynska, Abraham Markin, Sue Hee Sung, Jamie H. Thompson, Matthew T. Slaughter, Tiffany Q. Luong, Jaejin An, Kristi Reynolds, Douglas W. Roblin, Andrea E. Cassidy-Bushrow, Jennifer L. Kuntz, Raymond G. Schlienger, Sigrid Behr, and David H. Smith

BRIEF REPORT

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Physician adjudication of angioedema diagnosis codes in a population of patients with heart failure prescribed angiotensin-converting enzyme inhibitor therapy

Elizabeth T. Mansi[1,2] 🔵 | Eric S. Johnson[2] | Micah L. Thorp[3] | Alan S. Go[4] | Ming-Sum Lee[5] | Albert Yuh-Jer Shen[5] | Ken J. Park[3] | Katarzyna Budzynska[6] | Abraham Markin[7] | Sue Hee Sung[4] | Jamie H. Thompson[2] | Matthew T. Slaughter[2] | Tiffany Q. Luong[8] | Jaejin An[8] | Kristi Reynolds[8] | Douglas W. Roblin[9] | Andrea E. Cassidy-Bushrow[10] | Jennifer L. Kuntz[2] | Raymond G. Schlienger[11] | Sigrid Behr[11] | David H. Smith[2] 🔵

[1]School of Public Health, University of Washington, Seattle, Washington, USA

[2]Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon, USA

[3]Department of Nephrology, Kaiser Permanente Northwest, Portland, Oregon, USA

[4]Division of Research, Kaiser Permanente Northern California, Oakland, California, USA

[5]Department of Cardiology, Los Angeles Medical Center, Kaiser Permanente Southern California, Los Angeles, California, USA

[6]Department of Family Medicine, Henry Ford Hospital, Detroit, Michigan, USA

[7]Department of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan, USA

[8]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California, USA

[9]Mid-Atlantic Permanente Research Institute, Rockville, Maryland, USA

[10]Department of Public Health Sciences, Henry Ford Health System, Detroit, Michigan, USA

[11]Quantitative Safety and Epidemiology, Novartis Pharma AG, Basel, Switzerland

Correspondence
David H. Smith, Kaiser Permanente Center for Health Research, Portland, OR, USA.
Email: david.h.smith@kpchr.org

Funding information
Novartis Pharma AG

Abstract

Purpose: Our objective was to calculate the positive predictive value (PPV) of the ICD-9 diagnosis code for angioedema when physicians adjudicate the events by electronic health record review. Our secondary objective was to evaluate the inter-rater reliability of physician adjudication.

Methods: Patients from the Cardiovascular Research Network previously diagnosed with heart failure who were started on angiotensin-converting enzyme inhibitors (ACEI) during the study period (July 1, 2006 through September 30, 2015) were included. A team of two physicians per participating site adjudicated possible events using electronic health records for all patients coded for angioedema for a total of five sites. The PPV was calculated as the number of physician-adjudicated cases divided by all cases with the diagnosis code of angioedema (ICD-9-CM code 995.1) meeting the inclusion criteria. The inter-rater reliability of physician teams, or kappa statistic, was also calculated.

Results: There were 38 061 adults with heart failure initiating ACEI in the study (21 489 patient-years). Of 114 coded events that were adjudicated by physicians, 98 angioedema events were confirmed for a PPV of 86% (95% CI: 80%, 92%). The kappa statistic based on physician inter-rater reliability was 0.65 (95% CI: 0.47, 0.82).

Conclusions: ICD-9 diagnosis code of 995.1 (angioneurotic edema, not elsewhere classified) is highly predictive of angioedema in adults with heart failure exposed to ACEI.

KEYWORDS
ACE inhibitor, adjudication, angioedema, angioneurotic edema, angiotensin-converting enzyme inhibitor

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Key Points

- The ICD-9 diagnosis code for angioedema has very good positive predictive value (86%) when adjudicated by physician review of electronic health records in patients with heart failure who initiate ACEI.
- Inter-rater reliability for physician adjudication of angioedema events is good (kappa = 0.65).
- Observational studies of [ICD-9 code for] angioedema in adults with heart failure taking ACEI may not require physician review of electronic health records to confirm the diagnosis of angioedema.

1 | INTRODUCTION

International Classification of Disease (ICD) diagnosis codes are subject to misclassification bias or measurement error, and validation studies should be performed to assess their use in observational studies. ICD-9 code 995.1 designates "Angioneurotic edema, not elsewhere specified" and is used to code angioedema for any etiology other than hereditary (e.g., allergic, idiopathic, or adverse event to medication). Angioedema itself is a potentially life-threatening condition characterized by sudden localized swelling of deep tissues caused by the vascular extravasation of fluid into the interstitium.[1] It can involve any part of the body, although the larynx, tongue, lips, and face are most often involved.[2] Angiotensin-converting enzyme inhibitor (ACEI)-associated angioedema is a well-documented adverse reaction that affects 0.1%–0.7% of ACEI users overall; with a twofold to fourfold higher risk of angioedema in Black patients compared to White patients.[2–6] Another risk factor for ACEI-associated angioedema is heart failure, with a nearly twofold higher incidence compared with those who do not have heart failure.[2,6] Approximately 35–40 million patients are prescribed ACEI worldwide[4] for treatment of high blood pressure and heart failure, as well as for its renal and cardioprotective effects.[2]

The gold standard adjudication process employs trained clinicians to confirm the accuracy of the codes based on the patient's paper or electronic health record (EHR). To date, the authors have found no previously published epidemiologic studies based exclusively on adjudication performed by physicians of ICD-9 diagnosis codes for angioedema in heart failure patients initiating ACEI. Our primary objective was to estimate the positive predictive value (PPV) of ACEI-associated angioedema in heart failure patients based on physician confirmation of ICD-9 codes by EHR review. Secondarily, we calculated the inter-rater reliability of concordance, with the kappa statistic.

2 | METHODS

2.1 | Setting and population

Our source population included patients from five US-based healthcare delivery systems that contribute to the Cardiovascular Research Network (CVRN): Kaiser Permanente (KP) Northern California, KP Southern California, KP Northwest, KP mid-Atlantic and the Henry Ford Health System (Detroit, MI, United States). All participating institutions are integrated healthcare delivery systems offering a continuum of care to their patients. Each partner institution recruited two study physicians: one physician to serve as the primary adjudicator, and the second physician to serve as the secondary adjudicator. This allowed calculation of inter-rater reliability in addition to PPV. One physician team reviewed cases from two institutions.

We assembled a cohort of adults with heart failure based on modified diagnostic criteria developed by the CVRN. This included at least three outpatient visits or one or more hospitalization(s) with a primary/principal discharge diagnosis code of heart failure. We identified new users of ACEI as those who did not have ACEI prescription fills in the preceding 12 months. The time frame for the analysis was between July 1, 2006 and September 30, 2015. All ACEI and dosing regimens, including fixed-dose combinations, were considered based on prescription fills. We followed patients until the first diagnosis of angioedema or censoring. Censoring was defined by (1) discontinuation of ACEI therapy; (2) initiation of a different class of renin-angiotensin-aldosterone system-blocking therapy; (3) 365 days of ACEI therapy; (4) disenrollment from the health plan; (5) death; or (6) end of data collection on September 30, 2015. The study design is depicted in Figure 1.

2.2 | Outcome

We identified angioedema events using ICD-9 diagnosis code 995.1 (Angioneurotic edema, not elsewhere classified) documented in the outpatient, emergency department, or inpatient setting (not limited to the primary coding field). Patients could only contribute the first coded angioedema event to the analysis. Primary and secondary physician adjudicators reviewed coded angioedema events against EHR notes within 7 days of the event. To confirm diagnosis of angioedema, we required documentation of signs or symptoms consistent with angioedema, such as "difficulty swallowing," or "edema" and its site (e.g., lips; see Supporting Information for details).

2.3 | Statistical analysis

We calculated the PPV as the number of cases adjudicated by the primary physician divided by all cases with a diagnosis code of 995.1

FIGURE 1 Study design. Censoring was defined by (1) discontinuation of angiotensin-converting enzyme inhibitor (ACEI) therapy; (2) initiation of a different class of renin-angiotensin-aldosterone system-blocking therapy; (3) 365 days of ACEI therapy; (4) disenrollment from the health plan; (5) death; or (6) end of data collection on September 30, 2015. CVRN, Cardiovascular Research Network [Colour figure can be viewed at wileyonlinelibrary.com]
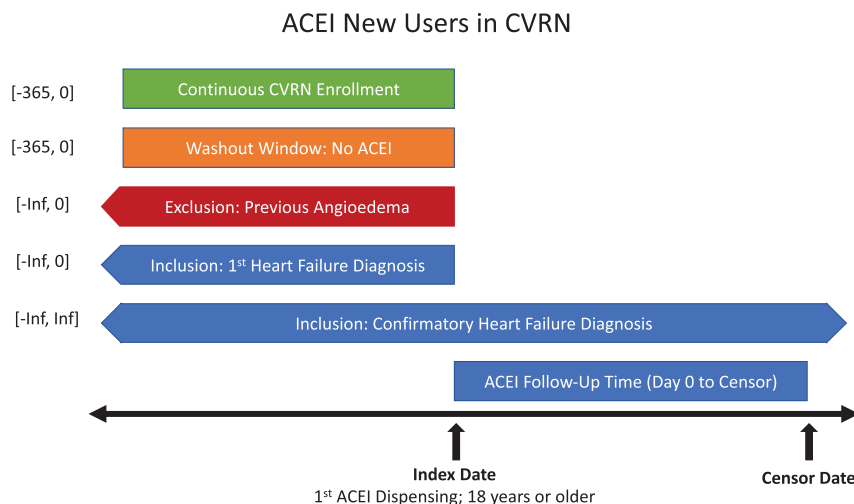
meeting the inclusion criteria. When an event could not be confirmed because of incomplete documentation, the physician classified the event as "unconfirmed." To meet our secondary aim, we calculated the kappa statistic to evaluate inter-rater reliability of the two physicians. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, United States).

3 | RESULTS

We observed 116 coded angioedema events among 38 061 new ACEI users (21 489 patient-years). Two patients had no EHR notes related to the event and were excluded from analysis. Of the remaining 114 events, the first physician adjudicator confirmed 98 events and could not confirm 16 events: seven events had clear documentation that the patient did *not* experience angioedema and nine events had unclear documentation of the occurrence of angioedema. Among the 38 061 new ACEI users, prescriptions were: lisinopril (94.24%), lisinopril/hydrochlorothiazide combination (3.57%), captopril (1.16%), enalapril (0.4%), benazepril (0.37%), ramipril (0.21%), and fosinopril (0.03%).

Table 1 shows patient characteristics according to whether the event was confirmed by the primary physician adjudicator and includes the incidence of confirmed cases of angioedema by racial

subgroup. In all 114 coded events, the PPV based on the primary adjudicator was 86% (95% CI: 80%, 92%). The PPV for Black and White patients appeared similar with a PPV of 90% for Black patients (95% CI: 82%, 97%) and 84% for White patients (95% CI: 74%, 94%). The settings of care for the 114 coded events were: 27 outpatient care (23.7%), 68 emergency/urgent care (59.6%), and 19 inpatient/ICU (16.7%). The PPV for each care setting was as follows: 85% for outpatient care (95% CI: 71%, 98%), 90% for emergency/urgent care (95% CI: 82%, 97%), and 83% for inpatient/ICU (95% CI: 66%, 100%).

All 98 confirmed events had documentation of the site of edema (neck or head) and 97 confirmed cases also had documentation of a symptom associated with angioedema (e.g., difficulty swallowing or speaking). To calculate the inter-rater reliability, the second physician adjudicator reviewed the EHR. This resulted in a kappa statistic of 0.65 (95% CI: 0.47, 0.82). We did not attempt to reconcile the adjudication between physicians. Two of the 114 events were not adjudicated by a second physician (an oversight), so the kappa was based on 112 events.

Of the 98 patients with a confirmed angioedema event, there was documentation of a permanent or temporary discontinuation of the ACEI in 81 patients (82.7%). The ACEI was not discontinued in 15 patients (15.3%) and discontinuation of the ACEI could not be determined in two patients (2.0%). Most confirmed events ($n = 61$, 62.2%) were managed in urgent care or the emergency department.

TABLE 1 Patient characteristics and positive predictive value overall and by racial subgroup

	Total new users *n* (%)	Confirmed angioedema[a]	Coded angioedema	PPV (95% confidence interval)
All patients	38 061 (100%)	98	114	86% (80%, 92%)
White	28 615 (75.18%)	43	51	84% (74%, 94%)
Black	6002 (15.77%)	52	58	90% (82%, 97%)
Asian	2798 (7.35%)	3	4	75% (32%, 100%)
Other race	646 (1.70%)	0	1	0

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; PPV, positive predictive value.
[a]Confirmed first angioedema event by physician adjudication in new ACEI users.

Eight events (8.2%) resulted in hospital admission and six patients required care in the intensive care unit (6.1%). No deaths occurred.

4 | DISCUSSION

To our knowledge, our study is the first to use physician adjudication exclusively to calculate PPV for coded angioedema events in heart failure patients initiating ACEI. Validation studies that estimate high PPV are useful for epidemiologic studies. In a comparative study, if the true hazard ratio is 2.0 then the observed (apparent) hazard ratio would only decline to 1.80 when the PPV is 85%, assuming non-differential misclassification.[7] The PPV in our study was 86% (95% CI: 80%, 92%) and did not appear to vary by the race of the patient. The latter was of particular interest as a previously published study showed a significant difference in PPV for angioedema between Black and White patients (we calculated a Fisher's exact *p* value of 0.003 based on the published data),[3] but the population was not limited to patients with heart failure. Our study is also consistent with previous publications[2–6] noting a higher relative number of angioedema observed in Black patients exposed to ACEI compared to other races.

Our study's estimate of the PPV is consistent with other retrospective cohort studies conducted with administrative databases that found PPV for coded angioedema events between 90% and 95.3%.[2,3,8,9] Those studies were not restricted to heart failure patients, may have included past events, and adjudication was not performed exclusively by physicians. Our study also included coded diagnoses beyond the primary condition; we cannot determine if this was done in the other studies.

The inter-rater reliability scale for kappa interpretation is 0–1, with "0" signifying agreement consistent with chance, and "1" signifying total agreement. Kappa is dependent on the frequency of the outcome and is constrained toward lower values for high probabilities (such as 0.86). We interpreted kappa according to Altman's definitions: moderate agreement (0.41–0.60); good agreement (0.61–0.80); and very good agreement (0.81–1.0).[10] As such, physician inter-rater reliability, measured in our study with a kappa statistic of 0.65, shows good agreement.

The main limitation of our study was the retrospective design and use of secondary data collected during routine clinical practice. As such, healthcare providers were not required to document their diagnosis of angioedema according to a study protocol with uniform diagnostic criteria. Consequently, ~14% of the events coded for angioedema lacked sufficient documentation of signs and symptoms to determine whether the diagnosis code was correct. An additional limitation is our generalizability. Because our population was restricted to US adults with heart failure initiating ACEI and managed in an integrated healthcare delivery system, the estimated PPV may be higher compared to the PPV in a population with a lower incidence of angioedema.[8] Accordingly, our estimated PPV may not fully generalize to other populations or other medications associated with angioedema. We plan to continue this study of physician adjudication of angioedema-coded events using ICD-10 codes in the future.

In summary, the ICD-9 diagnosis code of 995.1 (Angioneurotic edema, not elsewhere classified) is highly predictive of confirmed angioedema in adults with heart failure exposed to ACEI. However, it is noteworthy that studies using unadjudicated angioedema diagnosis codes may result in at most, a moderate overestimate of the actual incidence of angioedema based on ICD-9 coded findings.

ORCID

Elizabeth T. Mansi https://orcid.org/0000-0002-9625-3752
David H. Smith https://orcid.org/0000-0001-5296-6462

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