Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System

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Background: Although certain drugs that target the renin-angiotensin-aldosterone system are linked to an increased risk for angioedema, data on their absolute and comparative risks are limited. We assessed the risk for angioedema associated with the use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and the direct renin inhibitor aliskiren.

Methods: We conducted a retrospective, observational, inception cohort study of patients 18 years or older from 17 health plans participating in the Mini-Sentinel program who had initiated the use of an ACEI (n=1 845 138), an ARB (n=467 313), aliskiren (n=4867), or a β-blocker (n=1 592 278) between January 1, 2001, and December 31, 2010. We calculated the cumulative incidence and incidence rate of angioedema during a maximal 365-day follow-up period. Using β-blockers as a reference and a propensity score approach, we estimated the hazard ratios of angioedema separately for ACEIs, ARBs, and aliskiren, adjusting for age, sex, history of allergic reactions, diabetes mellitus, heart failure, or ischemic heart disease, and the use of prescription nonsteroidal anti-inflammatory drugs.

Results: A total of 4511 angioedema events (3301 for ACEIs, 288 for ARBs, 7 for aliskiren, and 915 for β-blockers) were observed during the follow-up period. The cumulative incidences per 1000 persons were 1.79 (95% CI, 1.73-1.85) cases for ACEIs, 0.62 (95% CI, 0.55-0.69) cases for ARBs, 1.44 (95% CI, 0.58-2.96) cases for aliskiren, and 0.58 (95% CI, 0.54-0.61) cases for β-blockers. The incidence rates per 1000 person-years were 4.38 (95% CI, 4.24-4.54) cases for ACEIs, 1.66 (95% CI, 1.47-1.86) cases for ARBs, 4.67 (95% CI, 1.88-9.63) cases for aliskiren, and 1.67 (95% CI, 1.56-1.78) cases for β-blockers. Compared with the use of β-blockers, the adjusted hazard ratios were 3.04 (95% CI, 2.81-3.27) for ACEIs, 1.16 (95% CI, 1.00-1.34) for ARBs, and 2.85 (95% CI, 1.34-6.04) for aliskiren.

Conclusions: Compared with β-blockers, ACEIs or aliskiren was associated with an approximately 3-fold higher risk for angioedema, although the number of exposed events for aliskiren was small. The risk for angioedema was lower with ARBs than with ACEIs or aliskiren.

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DRUGS THAT TARGET THE renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are widely used in patients with hypertension or ischemic heart disease, especially those with other comorbidities such as congestive heart failure, diabetes mellitus, or chronic kidney disease.[1,2] Angioedema, a serious and sometimes life-threatening adverse event that usually manifests as swelling of the lips, tongue, mouth, larynx, pharynx, or periorbital region, has been linked to the use of these medications, particularly ACEIs.[3-6]

See Editor's Note at end of article

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However, limited information is available about the absolute and relative risks for angioedema associated with the use of these medications. Existing evidence is primarily based on investigations of specific cohorts (eg, predominantly male veterans or Medicaid beneficiaries), whose findings may not be generalizable to other populations, or based on investigations with few events, which provide unstable risk estimates.[5-10]

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This study was designed to assess the risk for angioedema associated with the use of ACEIs (as a class), ARBs (as a class and as individual agents), and aliskiren (a first-in-class direct renin inhibitor approved by the US Food and Drug Administration [FDA] in 2007). The study was performed among a large, diverse, population-based cohort who received these drugs in real-world clinical settings.

METHODS

DATA SOURCE

The Mini-Sentinel program is part of the Sentinel Initiative, a multifaceted effort by the FDA to develop a national system for monitoring the safety of medical products as mandated by the 2007 FDA Amendments Act.[11,12] This study included 17 health plans (listed in the Additional Contributions section at the end of this article) contributing data to the Mini-Sentinel Distributed Database, which is composed of administrative claims and clinical information formatted into a common data model.[13]

DESIGN

A study protocol was developed before the analysis and has been previously published.[14] We used an inception cohort design[15] to identify patients 18 years or older with an outpatient dispensing of an oral formulation of the following medications as a single ingredient or as combination products with nonstudy drugs between January 1, 2001, and December 31, 2010: (1) an ACEI (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, perindopril, ramipril, or trandolapril), (2) an ARB (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, or valsartan), (3) aliskiren, or (4) a β-blocker (acebutolol, atenolol, bisoprolol, carvedilol, labetalol, metoprolol, nebivolol, pindolol, propranolol, or timolol), used as a common reference group. We refer to the dispensing date of the first prescription of any of the study drug as the index date. To be eligible for the study, these patients must also have met each of the following criteria during the 183-day period preceding the index date: (1) continuous health plan enrollment with pharmacy and medical benefits, (2) no prescription for any other study drug, and (3) no diagnosis of angioedema in any care setting.

END POINTS

The primary outcome of interest was angioedema, identified by *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) code 995.1, recorded in any position during an outpatient, inpatient, or emergency department encounter. The positive predictive value of this algorithm in administrative claims data ranges from 90%[7,16] to 95%.[8] The secondary outcome of interest was serious angioedema, defined as angioedema with airway obstruction requiring inpatient care. We identified serious angioedema events by an inpatient *ICD-9-CM* code 995.1, plus a code indicating intensive care unit admission, intubation, tracheostomy, or laryngoscopy occurring within 2 days of the date of hospital admission.[8] The codes used to identify these events can be found in the published protocol.[14]

FOLLOW-UP PERIOD

The follow-up period began on the index date and ended at the earliest occurrence of the following: first angioedema diagnosis, death, disenrollment, 365 follow-up days, December 31, 2010, cessation of use of study drug, or initiation of another study drug of a different class (except for individual ARB analyses, for which censoring also occurred with initiation of a different ARB). Cessation of use occurred when the days' supplies were exhausted for longer than 14 days without a subsequent dispensing. We chose a maximal follow-up period of 365 days because we were interested in the immediate and intermediate risk for angioedema associated with the use of these drugs. Previous studies[6-8,17] have shown that the risk for angioedema is greatest immediately after treatment initiation and gradually diminishes over time but remains higher compared with no use of these drugs.

STATISTICAL ANALYSIS

We compared the baseline characteristics among initiators of ACEIs, ARBs, and aliskiren separately with those among initiators of β-blockers using standardized differences, of which a value exceeding 0.1 is generally considered meaningful.[18] For ACEIs, ARBs, individual ARBs, aliskiren, and β-blockers, we calculated the cumulative incidences and incidence rates of angioedema and serious angioedema, as well as their 95% CIs.

We estimated the site-adjusted hazard ratios (HRs) and 95% CIs separately for ACEIs, ARBs, individual ARBs, and aliskiren, with β-blockers as the common reference group, using the case-centered logistic regression approach developed by Fireman et al.[19] This approach used site-specific aggregate-level data sets to fit a logistic regression model separately for each drug pair of interest. The aggregate data sets included 1 record per risk set, each anchored by an angioedema event. For example, in the ACEI and β-blocker analysis, each record included (1) a binary variable indicating whether the case was exposed to an ACEI and (2) the log odds of the site-specific proportion of ACEI-exposed patients in the risk set. The case-centered logistic regression model included the binary indicator variable as the dependent variable, the log odds as the independent variable (specified as an offset), and the data partner site as a stratification variable. Such a model maximizes the same likelihood as a stratified Cox proportional hazards regression model fit using individual-level data, and both yield the same parameter estimates.[19] The major difference is that the case-centered approach does not require individual-level data to leave the data partners' firewalls, maintaining patient privacy and data security.[20]

We combined the case-centered approach with propensity scores (PS)[21,22] to adjust for the following covariates ascertained during the 183-day period preceding the index date[8,17,23,24]: age (18-44, 45-54, 55-64, and ≥65 years), sex, and history of allergic reactions, diabetes mellitus, heart failure, or ischemic heart disease, as well as the use of prescription nonsteroidal anti-inflammatory drugs. Propensity scores (the probabilities of initiating a β-blocker) were estimated by a logistic regression model fit separately at each site for each drug pair that included these covariates as independent variables. To obtain PS-adjusted HRs, we fit a case-centered logistic regression model separately for each drug pair identical to the one aforementioned, except that the log odds were calculated only among at-risk individuals in the same PS quintile as the case. The adjusted analyses of individual ARBs used PS estimated from the entire drug class because they were more stable. Race/ethnicity has been shown to be an important determinant of the ACEI-angioedema relationship,[7,8,17,25-27] but this information was unknown or missing in approximately 70% of our population and was not adjusted for.

ADDITIONAL ANALYSES

For comparison, we performed a meta-analysis to pool the site-specific adjusted HRs obtained from a multivariable Cox proportional hazards regression model that adjusted for the same

covariates in the PS model. The pooled HR was the weighted average of the site-specific HRs using the inverse of the site-specific variance as the weight.[28-30]

We also performed an analysis that (1) used a 365-day lookback period to define new use and to exclude prior angioedema, (2) was restricted to angioedema events identified from inpatient or emergency department encounters, and (3) was limited to the cohort identified after the FDA approval date of aliskiren (March 5, 2007). Whenever possible, we stratified the analyses by age, sex, and follow-up period.

All the analyses were performed using commercially available software (SAS; SAS Institute, Inc), were developed and tested centrally by the Mini-Sentinel Operations Center, and were executed concurrently by all 17 data partners. None of the analyses required data partners to transfer individual-level data. The Mini-Sentinel program is a public health activity under the auspices of the FDA and is not under the purview of institutional review boards.[31,32]

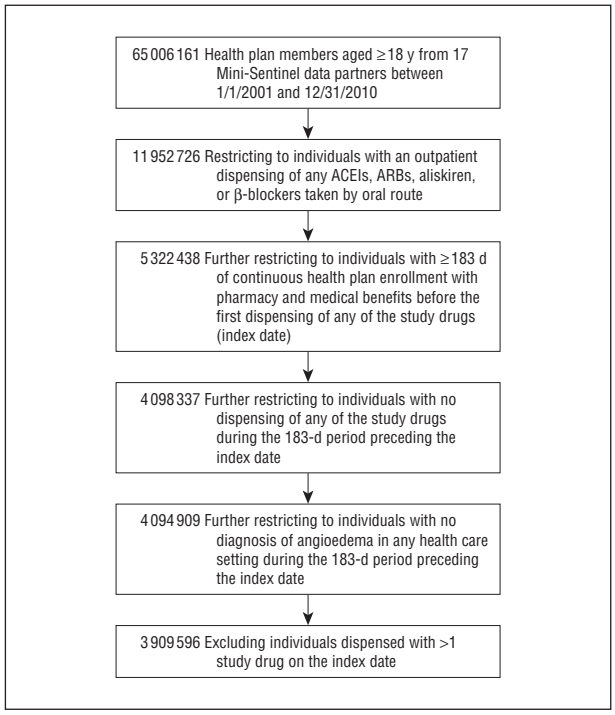

Figure. Flowchart to create the study cohort, 2001-2010. ACEIs indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

RESULTS

A total of 1 845 138 ACEI initiators, 467 313 ARB initiators, 4867 aliskiren initiators, and 1 592 278 initiators of β-blockers were eligible for the study (**Figure**). Initiators of ACEIs, ARBs, or aliskiren were more likely than β-blocker initiators to be male and to have a previous diagnosis of diabetes mellitus but were less likely to have a prior diagnosis of ischemic heart disease (**Table 1**).

The mean follow-up durations were 149 days for ACEI initiators, 136 days for ARB initiators, 112 days for aliskiren initiators, and 126 days for β-blocker initiators. eTable 1 (http://www.archinternmed.com) gives the numbers of patients censored for various reasons. During the follow-up period, we observed 3301 angioedema events associated with the use of ACEIs, 288 events with ARBs, 7 events with aliskiren, and 915 events with β-blockers (**Table 2**). The risk for angioedema (as measured by the cumulative incidence and incidence rate) was highest for ACEIs and was similar between ARBs and β-blockers (Table 2). The risk associated with the use of aliskiren seemed to be similar to that of the ACEIs but was based on only 7 exposed cases. There was moderate variation in risk across individual ARBs, with losartan having a greater risk than other ARBs. However, information was sparse for several ARBs, especially candesartan and eprosartan. The risk for serious angioedema was low across all drug classes but was also higher for ACEIs. Limited information was available on the risk for serious angioedema associated with the use of individual ARBs and aliskiren.

The HRs from the site-adjusted and PS-adjusted (which also adjusted for site) analyses were similar (Table 2). Compared with the use of β-blockers, the angioedema risk was approximately 3-fold higher for ACEIs and

Table 1. Baseline Characteristics of Patients by Drug Class Use, 2001-2010

	ACEIs (n = 1 845 138)		ARBs (n = 467 313)		Aliskiren (n = 4867)		β-Blockers (n = 1 592 278)
Characteristic	No. (%)	SDP[a]	No. (%)	SDP[a]	No. (%)	SDP[a]	No. (%)
Age group, y							
18-44	452 058 (24.5)	0.15	106 413 (22.8)	0.19	1093 (22.5)	0.19	497 043 (31.2)
45-54	529 986 (28.7)	0.11	137 402 (29.4)	0.13	1449 (29.8)	0.14	378 090 (23.7)
55-64	465 406 (25.2)	0.10	126 259 (27.0)	0.14	1321 (27.1)	0.15	336 843 (21.2)
≥65	397 688 (21.6)	0.06	97 239 (20.8)	0.07	1004 (20.6)	0.08	380 303 (23.9)
Female sex	863 222 (46.8)	0.20	237 066 (50.7)	0.12	2275 (46.7)	0.20	901 539 (56.6)
Diagnosis							
Allergic reaction	147 611 (8.0)	0.04	45 329 (9.7)	0.02	569 (11.7)	0.09	144 897 (9.1)
Diabetes mellitus	346 155 (18.8)	0.33	74 801 (16.0)	0.30	861 (17.7)	0.39	117 449 (7.4)
Heart failure	40 650 (2.2)	0.07	10 168 (2.2)	0.07	123 (2.5)	0.05	53 738 (3.4)
IHD	87 236 (4.7)	0.24	27 333 (5.8)	0.18	403 (8.3)	0.09	178 590 (11.2)
Use of prescription NSAIDs	281 333 (15.2)	0.01	68 386 (14.6)	0.03	683 (14.0)	0.04	248 850 (15.6)

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; IHD, ischemic heart disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SDP, standardized difference in proportion.

[a]Compared with the use of β-blockers.

Table 2. Angioedema and Serious Angioedema Events by Study Drug Use During a Maximal Follow-up Period of 365 Days, 2001-2010

Drug	No. of Events	No. of Exposed Persons	No. of Exposed Person-Years	Value (95% CI)		HR (95% CI)	
				Cumulative Incidence per 1000 Persons	Incidence Rate per 1000 Person-Years	Site Adjusted	Propensity Score Adjusted
Angioedema							
ACEIs	3301	1 845 138	753 105.4	1.79 (1.73-1.85)	4.38 (4.24-4.54)	2.77 (2.57-2.98)	3.04 (2.81-3.27)
ARBs	288	467 313	173 437.9	0.62 (0.55-0.69)	1.66 (1.47-1.86)	1.11 (0.97-1.28)	1.16 (1.00-1.34)
Candesartan	4	12 286	4177.0	0.33 (0.09-0.83)	0.96 (0.26-2.45)	0.91 (0.34-2.43)	0.95 (0.35-2.55)
Eprosartan	0	1165	392.3				
Irbesartan	24	44 094	15 997.7	0.54 (0.35-0.81)	1.50 (0.96-2.23)	1.05 (0.70-1.58)	1.11 (0.73-1.67)
Losartan potassium	94	106 522	41 230.2	0.88 (0.71-1.08)	2.28 (1.84-2.79)	1.48 (1.20-1.84)	1.53 (1.23-1.90)
Olmesartan	39	92 973	30 170.1	0.42 (0.30-0.57)	1.29 (0.92-1.77)	0.84 (0.60-1.16)	0.88 (0.63-1.22)
Telmisartan	11	26 530	8177.9	0.42 (0.21-0.74)	1.35 (0.67-2.41)	0.83 (0.45-1.50)	0.86 (0.47-1.56)
Valsartan	110	183 743	69 397.0	0.60 (0.49-0.72)	1.59 (1.30-1.91)	1.04 (0.85-1.28)	1.08 (0.88-1.34)
Aliskiren	7	4867	1498.1	1.44 (0.58-2.96)	4.67 (1.88-9.63)	2.75 (1.30-5.81)	2.85 (1.34-6.04)
β-Blockers	915	1 592 278	548 684.3	0.58 (0.54-0.61)	1.67 (1.56-1.78)	1 [Reference]	1 [Reference]
Serious Angioedema							
ACEIs	326	1 845 138	753 581.4	0.18 (0.16-0.20)	0.43 (0.39-0.48)	4.42 (3.29-5.96)	4.91 (3.62-6.65)
ARBs	10	467 313	173 511.8	0.02 (0.01-0.04)	0.06 (0.03-0.11)	0.52 (0.26-1.05)	0.56 (0.28-1.14)
Candesartan	0	12 286	4178.5				
Eprosartan	0	1165	392.3				
Irbesartan	0	44 094	16 002.4				
Losartan	3	106 522	41 255.2	0.03 (0.01-0.08)	0.07 (0.02-0.21)	0.97 (0.30-3.18)	1.01 (0.31-3.34)
Olmesartan	1	92 973	30 179.7	0.01 (0.00-0.06)	0.03 (0.00-0.19)	0.80 (0.10-6.20)	0.83 (0.11-6.57)
Telmisartan	0	26 530	8180.2				
Valsartan	6	183 743	69 425.1	0.03 (0.01-0.07)	0.09 (0.03-0.19)	1.05 (0.43-2.56)	1.14 (0.46-2.82)
Aliskiren	1	4867	1499.4	0.21 (0.01-1.14)	0.67 (0.03-3.72)	8.67 (1.11-67.62)	8.84 (1.13-69.41)
β-Blockers	51	1 592 278	548 953.6	0.03 (0.02-0.04)	0.09 (0.07-0.12)	1 [Reference]	1 [Reference]

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; HR, hazard ratio.

aliskiren and was 16% higher for ARBs. Within ARBs, the PS-adjusted HR was highest for losartan. For serious angioedema, the risk with ACEIs was 5 times the risk with β-blockers. There was no indication that ARB use increased the risk for serious angioedema compared with β-blocker use. Because there was only one case of serious angioedema among aliskiren initiators, the ability to assess this association was limited.

Results from the case-centered approach and meta-analysis were comparable (eTable 2), although the effect estimates varied moderately when the sample size was smaller. Using a 365-day look-back period, the numbers of eligible initiators and angioedema events were smaller, but the HRs were similar (eTable 3). Fifty-four percent (1782 of 3301) of angioedema events among ACEI initiators were identified from inpatient or emergency department encounters; these proportions were 29% (83 of 288) for ARBs, 29% (2 of 7) for aliskiren, and 31% (282 of 915) for β-blockers. Results were qualitatively similar when restricting the analysis to these angioedema events (eTable 4) or when restricting to the cohort identified after the FDA approval date of aliskiren (eTable 5).

The PS-adjusted HR for ACEIs was higher in patients 65 years or older than in patients of other age groups ($P = .047$, Wald test of homogeneity) and was higher in women than in men ($P = .002$), but the differences in magnitude were moderate (**Table 3**). Neither age nor sex seemed to modify the ARB-angioedema association. The PS-adjusted HR for ACEIs was greatest during the first 30 days of use (**Table 4**); the magnitude diminished but remained significantly higher compared with β-blockers during the remainder of the follow-up period. Sixty-six percent of all the angioedema events among ACEI initiators observed during the follow-up period occurred during the first 90 days compared with 65% for ARBs and 66% for β-blockers. Subgroup analyses were not performed for individual ARBs, aliskiren, or serious angioedema because of the few cases.

COMMENT

In this study, the risk for angioedema associated with the use of ACEIs or aliskiren was 3 times the risk with β-blockers, a drug class not thought to be linked to angioedema. However, results for aliskiren were based on only 7 exposed cases. The risk seemed to be 16% greater for ARBs compared with that for β-blockers, with a lower 95% CI bound of 1.00. Among individual ARBs, losartan appeared to be associated with the greatest risk, but information on several individual ARBs was limited. To our knowledge, this study is the largest of its kind and the first to examine the aliskiren-angioedema association using routinely collected clinical data.

Table 5 lists selected studies that examined associations between the use of the study drugs and angioedema. Miller et al[8] found in US veterans that the angioedema incidence rates per 1000 person-years were 2 cases among ACEI initiators (n = 195 192) and 0.5 cases among β-blocker initiators (n = 94 020). Both of these incidence rates in our

Table 3. Drug Class Use Results by Age and Sex Group During a Maximal Follow-up Period of 365 Days, 2001-2010

Age or Sex Group	No. of Angioedema Events	Value (95% CI)		HR (95% CI)	
		Cumulative Incidence per 1000 Persons	Incidence Rate per 1000 Person-Years	Site Adjusted	Propensity Score Adjusted
18-44 y					
ACEIs	668	1.48 (1.37-1.59)	4.23 (3.91-4.56)	2.45 (2.12-2.83)	2.91 (2.51-3.38)
ARBs	61	0.57 (0.44-0.74)	1.81 (1.38-2.32)	1.19 (0.88-1.60)	1.25 (0.93-1.70)
β-Blockers	260	0.52 (0.46-0.59)	1.90 (1.68-2.15)	1 [Reference]	1 [Reference]
45-54 y					
ACEIs	972	1.83 (1.72-1.95)	4.47 (4.20-4.76)	2.76 (2.39-3.19)	3.05 (2.63-3.52)
ARBs	86	0.63 (0.50-0.77)	1.67 (1.34-2.07)	1.12 (0.85-1.47)	1.14 (0.87-1.50)
β-Blockers	233	0.62 (0.54-0.70)	1.73 (1.51-1.97)	1 [Reference]	1 [Reference]
55-64 y					
ACEIs	800	1.72 (1.60-1.84)	3.94 (3.68-4.23)	2.51 (2.15-2.92)	2.65 (2.27-3.09)
ARBs	82	0.65 (0.52-0.81)	1.62 (1.29-2.01)	1.18 (0.89-1.55)	1.20 (0.90-1.59)
β-Blockers	208	0.62 (0.54-0.71)	1.63 (1.42-1.87)	1 [Reference]	1 [Reference]
≥65 y					
ACEIs	861	2.17 (2.02-2.31)	4.92 (4.60-5.26)	3.51 (3.02-4.09)	3.69 (3.17-4.31)
ARBs	59	0.61 (0.46-0.78)	1.57 (1.19-2.02)	1.14 (0.84-1.55)	1.17 (0.86-1.59)
β-Blockers	214	0.56 (0.49-0.64)	1.43 (1.25-1.64)	1 [Reference]	1 [Reference]
Male sex					
ACEIs	1337	1.36 (1.29-1.44)	3.30 (3.13-3.48)	2.56 (2.27-2.90)	2.59 (2.29-2.93)
ARBs	126	0.55 (0.46-0.65)	1.49 (1.24-1.78)	1.22 (0.98-1.53)	1.29 (1.03-1.63)
β-Blockers	328	0.48 (0.43-0.53)	1.37 (1.23-1.53)	1 [Reference]	1 [Reference]
Female sex					
ACEIs	1962	2.27 (2.17-2.38)	5.64 (5.40-5.90)	3.09 (2.82-3.40)	3.29 (2.99-3.61)
ARBs	162	0.68 (0.58-0.80)	1.82 (1.55-2.13)	1.10 (0.91-1.32)	1.13 (0.94-1.37)
β-Blockers	586	0.65 (0.60-0.71)	1.89 (1.74-2.05)	1 [Reference]	1 [Reference]

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; HR, hazard ratio.

Table 4. Drug Class Use Results by Follow-up Period, 2001-2010

Follow-up Period	No. of Angioedema Events	Value (95% CI)		HR (95% CI)	
		Cumulative Incidence per 1000 Persons	Incidence Rate per 1000 Person-Years	Site Adjusted	Propensity Score Adjusted
0-30 d					
ACEIs	1420	0.77 (0.73-0.81)	9.68 (9.19-10.20)	3.25 (3.00-3.52)	3.57 (3.28-3.88)
ARBs	128	0.27 (0.23-0.33)	3.45 (2.88-4.10)	1.37 (1.17-1.59)	1.46 (1.25-1.71)
β-Blockers	373	0.23 (0.21-0.26)	2.98 (2.69-3.30)	1 [Reference]	1 [Reference]
31-60 d					
ACEIs	453	0.27 (0.24-0.29)	3.81 (3.47-4.18)	2.47 (2.05-2.98)	2.62 (2.16-3.17)
ARBs	41	0.10 (0.07-0.13)	1.44 (1.03-1.96)	1.12 (0.77-1.63)	1.11 (0.76-1.64)
β-Blockers	149	0.11 (0.09-0.12)	1.62 (1.37-1.90)	1 [Reference]	1 [Reference]
61-90 d					
ACEIs	300	0.25 (0.22-0.28)	3.27 (2.91-3.66)	2.52 (1.97-3.24)	2.79 (2.16-3.60)
ARBs	18	0.07 (0.04-0.11)	0.88 (0.52-1.39)	0.64 (0.37-1.11)	0.70 (0.40-1.23)
β-Blockers	80	0.09 (0.07-0.11)	1.25 (0.99-1.56)	1 [Reference]	1 [Reference]
91-180 d					
ACEIs	571	0.57 (0.52-0.62)	3.13 (2.88-3.39)	2.51 (2.10-3.01)	2.77 (2.31-3.34)
ARBs	48	0.22 (0.16-0.29)	1.18 (0.87-1.57)	1.05 (0.74-1.49)	1.02 (0.71-1.46)
β-Blockers	151	0.22 (0.19-0.26)	1.23 (1.04-1.44)	1 [Reference]	1 [Reference]
181-270 d					
ACEIs	316	0.54 (0.49-0.61)	2.63 (2.35-2.94)	2.39 (1.89-3.03)	2.60 (2.04-3.31)
ARBs	27	0.21 (0.14-0.30)	1.02 (0.67-1.48)	1.09 (0.67-1.78)	1.07 (0.65-1.78)
β-Blockers	89	0.23 (0.18-0.28)	1.10 (0.88-1.35)	1 [Reference]	1 [Reference]
271-365 d					
ACEIs	241	0.58 (0.51-0.66)	2.59 (2.27-2.94)	2.00 (1.53-2.61)	2.10 (1.60-2.76)
ARBs	26	0.29 (0.19-0.42)	1.28 (0.84-1.88)	1.65 (0.98-2.78)	1.61 (0.95-2.72)
β-Blockers	73	0.26 (0.21-0.33)	1.15 (0.90-1.45)	1 [Reference]	1 [Reference]

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; HR, hazard ratio.

Corrected on November 26, 2012

Table 5. Selected Published Studies on Associations Between the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System and the Risk for Angioedema

Source	Study Design	Study Drug	No. of Exposed Persons	No. of Exposed Person-Years	Length of Follow-up Period	No. of Angioedema Events	Value (95% CI)	
							Cumulative Incidence per 1000 Persons	Incidence Rate per 1000 Person-Years
ACEIs								
Kostis et al,[17] 2005	RCT	Enalapril	12 557	NA	Maximal 5 mo	86	6.85 (5.52-8.41)	. . .
Pfeffer et al,[33] 2003	RCT	Captopril	4879	NA	Median 25 mo	35	7.17 (5.08-9.85)	. . .
Piller et al,[23] 2006	RCT	Lisinopril	9054	NA	Maximal 48 mo	37	4.09 (2.92-5.57)	. . .
Yusuf et al,[34] 2008	RCT	Ramipril	8576	NA	Median 56 mo	25	2.92 (1.93-4.24)	. . .
Brown et al,[7] 1996	OS	All	27 834	52 734	Mean 23 mo	82	2.95 (2.36-3.64)	1.55 (1.24- 1.93)
Miller et al,[8] 2008	OS	All	195 192	179 088	Mean 11 mo	352	1.80 (1.62-2.00)	1.97 (1.77-2.18)
ARBs								
Pfeffer et al,[33] 2003	RCT	Valsartan	4885	NA	Median 25 mo	21	4.30 (2.73-6.45)	. . .
Yusuf et al,[34] 2008	RCT	Telmisartan	8542	NA	Median 56 mo	10	1.17 (0.59-2.09)	. . .
Miller et al,[8] 2008	OS	All	9816	NA	Maximal 21 mo	. . .	. . .	0.99[a]
Aliskiren								
White et al,[35] 2011	Pooled analysis of RCT	Aliskiren	4578	NA	Maximal 8-52 wk	15[b]	3.28 (1.91-5.28)	. . .

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ellipsis, not applicable; NA, not available; OS, observational study; RCT, randomized controlled trial.

[a] Only the point estimate was provided; information needed to estimate 95% CI was unavailable.

[b] Angioedema and urticaria as a combined outcome.

study were higher, but the cumulative incidence for ACEIs was similar (1.8 cases per 1000 ACEI-exposed persons; the cumulative incidence for β-blockers was unavailable in the study by Miller et al).

Differences in the study population might have led to our higher incidence rates. For example, the proportion of women, whose study drug-associated angioedema risk was greater, exceeded 50% in our study compared with 3% in the study by Miller et al.[8] However, it is unlikely that such differences would only influence the incidence rate and not the cumulative incidence. A more plausible explanation might be the difference in how the follow-up periods were constructed. Follow-up periods ceased completely in our study when patients stopped their treatment for at least 14 days. Miller et al seemed to have estimated the incidence rate using all exposed person-times (including person-times that accrued after resumption) during their maximal 21-month follow-up period, or they allowed a more generous gap between dispensings. This could explain why the mean follow-up period was 0.4 years in our study and 0.9 years in the study by Miller et al. Because the risk for angioedema gradually diminished over time,[6,7,17] the study by Miller and colleagues[8] might have included more follow-up times with a lower risk. Despite these potential differences, our PS-adjusted HR of 3.04 (95% CI, 2.81-3.27) for ACEIs was similar to the relative risk of 3.56 (95% CI, 2.82-4.44) obtained by Miller et al from a Poisson regression analysis using all other antihypertensive medications as a reference.

Angioedema is mediated by vasoactive mediators, such as bradykinins. It is generally believed that ACEIs precipitate angioedema by directly interfering with the degradation of bradykinin, potentiating its biological effect.[5,6] Although some ACEI-induced cases may manifest only after a prolonged duration of therapy, sometimes exceeding 1 year since treatment initiation,[7,8] the period immediately after treatment initiation is of greatest interest. Consistent with previous studies,[6-8,17] we observed that the risk was greatest immediately following ACEI initiation. Miller et al[8] found that 55% of angioedema events occurred within 90 days following ACEI initiation, while the percentage was 66% in our study.

Compared with what is known about ACEIs, the relationship between ARB use and angioedema is not as well understood. We found that the risk may be slightly elevated for the use of ARBs. In the study by Miller et al,[8] the incidence rate of angioedema was 1 case per 1000 person-years among 9816 ARB initiators, or 2 times the rate among β-blocker initiators, but information on the adjusted HR was unavailable. Our results also suggest that the risk might vary across individual ARBs; these findings need to be examined further.

The association between aliskiren use and angioedema is not well quantified. In the premarket development program, there were reports of aliskiren-associated angioedema; therefore, its label contains a warning about this risk and is similar to ACEI class labeling. Postmarket reports of serious angioedema events associated with the use of aliskiren in which patients required intubation were also received. Results of pooled analyses among randomized trials comprising 4578 patients who received aliskiren monotherapy suggest that the risk for angioedema and urticaria as a combined outcome was similar or lower for aliskiren compared with that for ACEIs or ARBs.[35,36] Unfortunately, the analyses did not examine angioedema separately, and individual trials were too small to provide reliable estimates. We observed that the risk for angioedema associated with the use of aliskiren is similar to that of ACEI use; further investigations are needed to better characterize the association.

Corrected on November 26, 2012

Our results should be interpreted in the context of several limitations. African American race may be a risk factor for angioedema and a potential effect modifier for the effect of ACEI use on angioedema.[7,8,17,25-27] Race/ethnicity information was missing in approximately 70% of our cohort and was not adjusted for in our analysis. An analysis that included only those with nonmissing race/ethnicity may introduce bias if missingness depends on the risk for angioedema and treatment choice.[37,38] If African Americans are less likely to receive ACEIs owing to this suspected risk, our HR would underestimate the actual relative risk (eTable 6).[39,40] The estimated absolute risks might also not be directly generalizable to populations with a different race/ethnicity distribution than ours. Smoking was another variable unavailable to us that has also been suggested to be a confounder for the effect of ACEI use on angioedema.[23,26,27]

Some angioedema cases (especially those that were milder, resolved quickly, and did not require medical attention) might not have been captured in our databases. This might lead to an underestimation of the true risk for angioedema and might partly explain why randomized trials generally observed higher cumulative incidences associated with the use of ACEIs and ARBs than observational studies (Table 5). Because the ACEI-angioedema association is well recognized, underestimation of risk may be less severe for these drugs as patients and physicians may be more attentive to any clinical manifestation of angioedema. But, this could potentially lead to biased HRs when comparing ACEIs with β-blockers because there would be a differential case identification. However, the proportion of angioedema events diagnosed during an outpatient visit (rather than an inpatient or emergency department setting) was much lower in ACEI initiators compared with initiators of other study drugs, suggesting that milder cases were no more likely to be captured among ACEI initiators or that ACEI use might be associated with more severe cases.

Although our use of an as-treated approach captured angioedema events while patients were receiving treatment, censoring patients when they stopped treatment might introduce bias if treatment cessation depended on the risk for angioedema and varied by study drug.[41,42] We attempted to account for this potential bias by extending the follow-up period for up to 14 days to capture events that might be diagnosed after treatment discontinuation.

The validity of our findings is strengthened by the consistent results from various analyses and by the high positive predictive value of the diagnosis code of angioedema. The large sample size and the demographic and geographic diversity of our population increase the generalizability of our findings.

In conclusion, this study characterized the relationships between the use of drugs targeting the renin-angiotensin-aldosterone system and the incidence of angioedema in a large, diverse cohort. The risk for angioedema associated with ACEI or aliskiren use was approximately 3 times the risk with β-blocker use, although results for aliskiren were based on only 7 exposed cases. The angioedema risk was lower with ARBs than with ACEIs or aliskiren.

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