MINI-SENTINEL MEDICAL PRODUCT ASSESSMENT

SIGNAL REFINEMENT OF ANGIOEDEMA EVENTS IN ASSOCIATION WITH USE OF DRUGS THAT ACT ON THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM REPORT

Prepared by: Darren Toh, ScD,[1] Marsha E. Reichman, PhD,[2] Monika Houstoun, PharmD,[2] Mary Ross Southworth, PharmD,[3] Xiao Ding, PhD,[4] Adrian Hernandez, MD,[5] Mark Levenson, PhD,[4] Lingling Li, PhD,[1] Carolyn McCloskey,MD, MPH,[2] Azadeh Shoaibi, MS, MHS,[6] Eileen Wu, PharmD,[2] Gwen Zornberg, MD, MS, ScD,[2] and Sean Hennessy, PhD, PharmD[7]

Author Affiliations: 1. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA. 2. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), Silver Spring, MD. 3. Office of New Drugs, CDER, FDA, Silver Spring, MD. 4. Office of Translational Sciences, CDER, FDA, Silver Spring, MD. 5. Division of Cardiology, Duke University School of Medicine, Durham, NC. 6. Office of Medical Policy, CDER, FDA, Silver Spring, MD. 7. Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

October 15, 2012

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Mini-Sentinel Medical Product Assessment

Signal Refinement of Angioedema Events in Association with Use of Drugs that Act on the Renin-Angiotensin-Aldosterone System Report

Table of Contents

I. INTRODUCTION

Renin is secreted by the kidneys and cleaves angiotensinogen to form angiotensin I. Angiotensin I is converted to angiotensin II through the angiotensin-converting enzyme and non-angiotensin-converting enzyme pathways. Angiotensin II leads to the release of catecholamines and promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Angiotensin II also inhibits renin release, thus providing a negative feedback to the system. This cycle, from renin through angiotensin to aldosterone and its associated negative feedback loop, is known as the renin-angiotensin-aldosterone system (RAAS).

Antihypertensive medications that act on RAAS include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and aliskiren.[1] ACEIs inhibit the production of angiotensin II by blocking the angiotensin-converting enzyme pathway, whereas ARBs inhibit the vasoconstricting and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor. Aliskiren, approved for marketing by the U.S. Food and Drug Administration (FDA) in 2007 for the treatment of hypertension, is a direct renin inhibitor and acts by decreasing plasma renin activity and inhibiting the conversion of angiotensinogen to angiotensin I. Whether aliskiren affects other RAAS components is not fully known.

Angioedema is the rapid, localized swelling of the dermis and subcutis caused by vascular leakage.[2-5] This response is mediated by vasoactive mediators, such as histamine, serotonin, and kinins (e.g., bradykinins), which cause the arterioles to dilate while inducing a brief episode of vascular leakage in the venules. Angioedema can be hereditary or acquired. It usually presents as swelling of the lips, tongue, mouth, larynx, pharynx, or periorbital region, but can also occur in hands or intestines. Angioedema of the upper respiratory tract can lead to airway obstruction, which can be life-threatening.

ACEIs, of which there are ten marketed in the U.S. (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, perindopril, ramipril, and trandolapril), are known to increase the risk of angioedema.[4-7] It is generally believed that ACEIs precipitate angioedema by directly interfering with the degradation of bradykinin, thereby potentiating its biological effect.[4,5] The incidence rate of angioedema in ACEI users is estimated to be about 2 per 1,000 person-years,[8,9] compared with 0.4-0.8 per 1,000 person-years in users of non-ACEI, non-ARB antihypertensive medications.[9] Overall, 1-2 per 1,000 ACEI users may develop angioedema while being treated.[4-6,9] The risk is the greatest immediately following treatment initiation and gradually diminishes over time but remains higher than no use.[5,8-10] Some cases may become manifest only after a prolonged duration of therapy, sometimes after one year of treatment initiation.[8,9]

There are eight ARBs marketed in U.S. (azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan). Data on the incidence of ARB-induced angioedema are limited, especially for individual ARBs.[11] The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) found a lower incidence of angioedema in telmisartan users compared with ramipril users (1 vs. 3 per 1,000 persons).[12] One study found an incidence rate of 1 per 1,000 person-years of angioedema in the U.S. veterans who received ARBs.[9] Several ARBs list angioedema in the adverse event section of labeling.

Little information is available for the association between aliskiren and angioedema. In the pre-market development program, there were reports of angioedema associated with aliskiren, therefore its label

contains a warning about angioedema and is similar to ACEI class labeling. As of January 6, 2009, there were 54 reports of aliskiren-associated angioedema in the FDA's Adverse Event Reporting System. Some of the angioedema cases involved airway obstruction and required intubation. The aliskiren labeling was updated with this additional safety information in November 2009. Pooled analyses of randomized trials suggested that the risk of angioedema and urticaria as a combined outcome was similar or lower for aliskiren compared with ACEIs and ARBs.[13,14]

This Mini-Sentinel project addressed the following question: What is the risk of angioedema with ACEIs, ARBs or aliskiren compared with β-blockers? To address this question we examined ACEIs as a class, ARBs both as a class and as individual molecular entities, aliskiren, and β-blockers as a class (including acebutolol, atenolol, bisoprolol, carvedilol, labetalol, metoprolol, nebivolol, pindolol, propranolol, and timolol). A protocol that describes the analysis plan has been posted on the Mini-Sentinel website (www.mini-sentinel.org).[15]

II. METHODS

A. DATA SOURCE

The Mini-Sentinel program is part of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national system for monitoring the safety of medical products as mandated by the FDA Amendments Act of 2007.[16,17] The current assessment included 17 Data Partners contributing data to the Mini-Sentinel Distributed Database (MSDD), which was comprised of administrative and claims data formatted into a common data model at the time of the assessment.[18]

B. COHORT

The protocol called for the use of a "new-user" cohort design[19] to identify individuals aged 18 years or older with a first prescription of an oral formulation of a marketed ACEI, ARB, aliskiren, or β-blocker – as either single ingredient or combination products, except in combination with another study drug – between January 1, 2001 and December 31, 2010. Azilsartan, an ARB approved on February 25, 2011, was not included in this assessment. We refer to the dispensing date of the first prescription as the *index date*. To be eligible for the analyses, these individuals must also meet 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 of any other study drug; and 3) no diagnosis of angioedema. We further excluded individuals who initiated more than one study drug on the index date (e.g., a combination product that contains more than one study drug). Gaps of 45 days or less in enrollment, pharmacy or medical benefit were not considered to be disenrollment because they usually represent administrative gaps rather than actual disenrollment. If there were more than one eligible new-use episode for a given individual, only the first episode was included.

An alternate definition of new user, which allowed patients who were otherwise eligible to have prior use of another study drug, was considered in the posted protocol but not implemented because: 1) feasibility analysis suggested that the sample size would be sufficient using the primary new-use definition, and 2) patients who switched treatment might be very different from those who did not.

C. OUTCOME

The primary outcome of interest was angioedema, which was identified by an 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 to identify angioedema in claims data is high, ranging from 90%[8,20] to 95%.[9] The secondary outcome of interest was serious angioedema, defined as angioedema with airway obstruction requiring inpatient care. We identified possible serious angioedema events by an inpatient ICD-9-CM code 995.1 recorded at any position plus a code indicating intensive care unit admission, intubation, tracheostomy, or laryngoscopy occurring within two days of the date of hospital admission.[9,21,22] The codes used to identify these procedures can be found in Appendix C of the protocol.[15]

D. POTENTIAL CONFOUNDERS

We identified *a priori* a list of potential confounders that would be adjusted for in the analyses based on literature review[8-10,23-25] and subject-matter knowledge of the workgroup members (**Table 1**). Previous studies have suggested that African-American race may be a risk factor for angioedema,[8-10,23-25] but race was not included in the list as the information is sparse in the MSDD. Time trends in occurrence of angioedema were also considered but not included, as preliminary results did not indicate a clear trend (Appendix 1). Other covariates that are commonly used in pharmacoepidemiologic studies, such as the number of outpatient visits or unique medications dispensed (as proxies for general health status), were discussed but not included because there is no strong evidence to suggest an association between these measures and the risk of angioedema.

Table 1. Potential confounders ascertained during the 183-day period preceding the index date

Confounder	Categorization	Identified by
Age as of the index date	18-44, 45-54, 55-64, ≥65 yrs	
Sex	Male/Female	
Diagnosis of		Recorded at least once in an outpatient, inpatient, or emergency department setting
Allergic reactions[10]	Yes/No	ICD-9-CM codes 477.x, 518.6, 558.3, 691.x, 692.xx (excluding 692.75-692.77), 693.x, 708.x, 995.0, 995.27, 995.3, 995.6x, 995.7, V07.1, V13.81, V14.x, V15.0x, V72.7
Diabetes[9,26]	Yes/No	ICD-9-CM code 250
Heart failure[9]	Yes/No	ICD-9-CM codes 402.x1, 404.x1, 404.x3, 428.xx
Ischemic heart disease[9]	Yes/No	ICD-9-CM codes 410-414
Use of prescription non-steroidal anti-inflammatory drugs (NSAIDs)[2]	Yes/No	National Drug Codes obtained from the First DataBank

E. FOLLOW UP

We followed eligible patients from the index date until the earliest occurrence of the first angioedema diagnosis, 365 days of follow-up, initiation of another study drug, cessation of use of study drug, death, disenrollment from the health plan, end of medical benefit, or December 31, 2010. Cessation of use occurred when an individual's days supplied appeared to have been exhausted for at least 14 days. We chose a maximal follow-up of 365 days because we were interested in the immediate and intermediate risk of angioedema associated with these drugs.

We performed two parallel analyses based on the FDA approval date of aliskiren (March 5, 2007). The first analysis included all new users of study ARBs, ACEIs, and β-blockers from January 1, 2001 to December 31, 2010. The second analysis involved all new users of study ACEIs, ARBs, aliskiren, and β-blockers identified between March 5, 2007 and December 31, 2010.

F. STATISTICAL ANALYSIS

1. Overview

Analyses were first done at individual Data Partner sites using the distributed SAS programs developed centrally by the Mini-Sentinel Operations Center (MSOC). Each program was tested by the MSOC and one to two Data Partners prior to full distribution. Summary-level outputs were transferred to the MSOC, who then analyzed data from all participating Data Partners to obtain overall estimates ("MS-wide estimates"). As described in greater detail below, none of the analyses required the Data Partners to transfer individual-level data. Whenever the sample size allowed, we further stratified the analyses by age group (18-44, 45-54, 55-64, and ≥65 years), sex, and follow-up period (0-30, 31-60, 61-90, 91-180, 181-270, and 271-365 days, as well as 0-30, 0-60, 0-90, 0-180, and 0-270 days following the index date).

2. Comparison of baseline characteristics

We compared the baseline characteristics of initiators of ARBs, ACEIs, and aliskiren separately with initiators of β-blockers. This was done both at individual sites and across Data Partners, by requesting summary-level counts from each Data Partner (to obtain the site-specific results), and by combining the summary-level counts (to obtain the MS-wide results). We examined the between-group imbalances using standardized differences, calculated as the difference in means or proportions between two groups divided by the pooled estimate of the standard deviation of the two groups.[27] We chose standardized difference because it is less sensitive to sample size and reflects the magnitude of relative differences. A standardized difference of greater than 0.1 is generally considered meaningful.

3. Calculation of cumulative incidence and incidence rate of angioedema and serious angioedema

We calculated the cumulative incidence per 1,000 persons and incidence rate per 1,000 person-years of angioedema and the 95% confidence intervals (CIs) separately for ACEIs (as a class), ARBs (individually and as a class), aliskiren, and β-blockers (as a class). Each Data Partner sent its site-specific summary results to the MSOC, who then summed up the number of angioedema cases and the persons or persons-times from all sites to obtain the MS-wide estimates.

4. Site-adjusted analysis

Site-specific estimates. Using a distributed SAS program developed by the MSOC, each site fit a Cox model separately for the ACEI–β-blocker pair, the ARB–β-blocker pair, the individual ARB–β-blocker pairs, and the aliskiren–β-blocker pair to estimate the crude HR and 95% CI of angioedema. The Cox model included an indicator variable for drug exposure (e.g., 1 for ACEIs and 0 for β-blockers) as the only independent variable. The time scale for the Cox model was time since the index date. Data Partners ran the distributed program, and sent the SAS output and log files, along with a pre-specified aggregate-level dataset, to the MSOC for further analyses. The aggregate-level dataset included one record per risk set, each was anchored by an angioedema case. The dataset was used in both the crude and adjusted analyses described below. The two SAS files and the analytic dataset did not contain any individual-level information.

MS-wide estimates. We used two methods to obtain the site-adjusted MS-wide estimates. In the first method, we used the aggregate-level dataset described above to fit a logistic model separately for each drug pair of interest. In the ACEI–ß-blocker pair analysis, for example, the outcome variable in the logistic model was whether the angioedema case was exposed to an ACEI, the independent variable – specified as an offset in the model – was the log odds of the site-specific proportion of individuals in the risk set who were ACEI users. The model also included Data Partner site as a stratification variable. The method was based on the case-centered logistic regression approach developed by Fireman *et al*, who have shown that such a model maximizes the same likelihood as a stratified Cox model, and both yield the same parameter estimates.[28]

In the second method, we performed a meta-analysis using both fixed-effect and random-effects models to pool the crude site-specific estimates obtained from the SAS output files. The MS-wide HR was calculated as a weighted average of the site-specific HRs using the inverse of the site-specific variance as the weight.[29-31] As a secondary analysis, we used the site-specific sample size as the weight.

5. Propensity score-adjusted analysis

Site-specific estimates. We used a propensity score (PS)-stratified approach and a multivariable-adjusted approach to obtain the adjusted site-specific estimates. The PS[32,33] was the probability of initiating a β-blocker, which was estimated by a logistic model fit separately for each drug pair at each site. The PS model included the variables listed in Table 1 and was common across all sites. This approach let each site fit the same PS model but allowed the coefficients to vary by site. Using a distributed program developed by the MSOC, each site fit 1) the PS model; 2) a PS-stratified Cox model that included an indicator variable for drug exposure as an independent variable and the estimated PS (in quintiles) as a stratification variable;[32,33] 3) a case-centered logistic model with the risk set identified from individuals with the same PS quintile as the case; and 4) a multivariable-adjusted Cox model that included as independent variables an indicator variable for drug exposure plus the variables listed in Table 1. In theory, models 2 and 3 should yield identical results if the same time unit was used. We compared the results from the case-centered approach and the two Cox models to verify the validity of the case-centered approach.

The adjusted analyses of individual ARBs used PSs estimated from the entire drug class because they were more stable. All pre-specified subgroup analyses used PSs estimated from the entire study cohort

for the same reason. The Data Partners ran the distributed program, and then sent the SAS output and log files free of any individual-level information to the MSOC.

MS-wide estimates. We used two methods to obtain the adjusted MS-wide estimates. In the first method, we used the pre-specified aggregate-level dataset sent by the Data Partners to fit a case-centered logistic model separately for each drug pair of interest. The model was identical to the one described in the site-adjusted MS-wide analysis, except that the log odds were calculated at each site among at-risk individuals in the same PS quintile as the case.

In the second method, we performed a meta-analysis using both fixed-effect and random-effects models to pool the site-specific estimates from the multivariable-adjusted analysis obtained from the SAS output files. The MS-wide HR was calculated as a weighted average of the site-specific HRs with the inverse of the site-specific variance as the weight.[29-31] As a secondary analysis, we used the site-specific sample size as the weight. In these PS-adjusted analyses, site was adjusted for either explicitly (as a stratification variable in the case-centered logistic model) or implicitly (in meta-analyses that pooled site-specific estimates).

6. Comparison of methods

To examine the relative performance of each approach, we compared 1) the site-specific estimates from the PS-stratified Cox model, the case-centered approach, and the multivariable-adjusted Cox model performed locally at each site; and 2) the MS-wide estimates from the case-centered approach and the meta-analyses performed centrally at the MSOC.

7. Sensitivity analysis

As a sensitivity analysis, we used a 365-day look-back period to define new use and to exclude prior angioedema. We also performed a separate analysis restricting to angioedema cases identified from an inpatient or emergency department encounter.

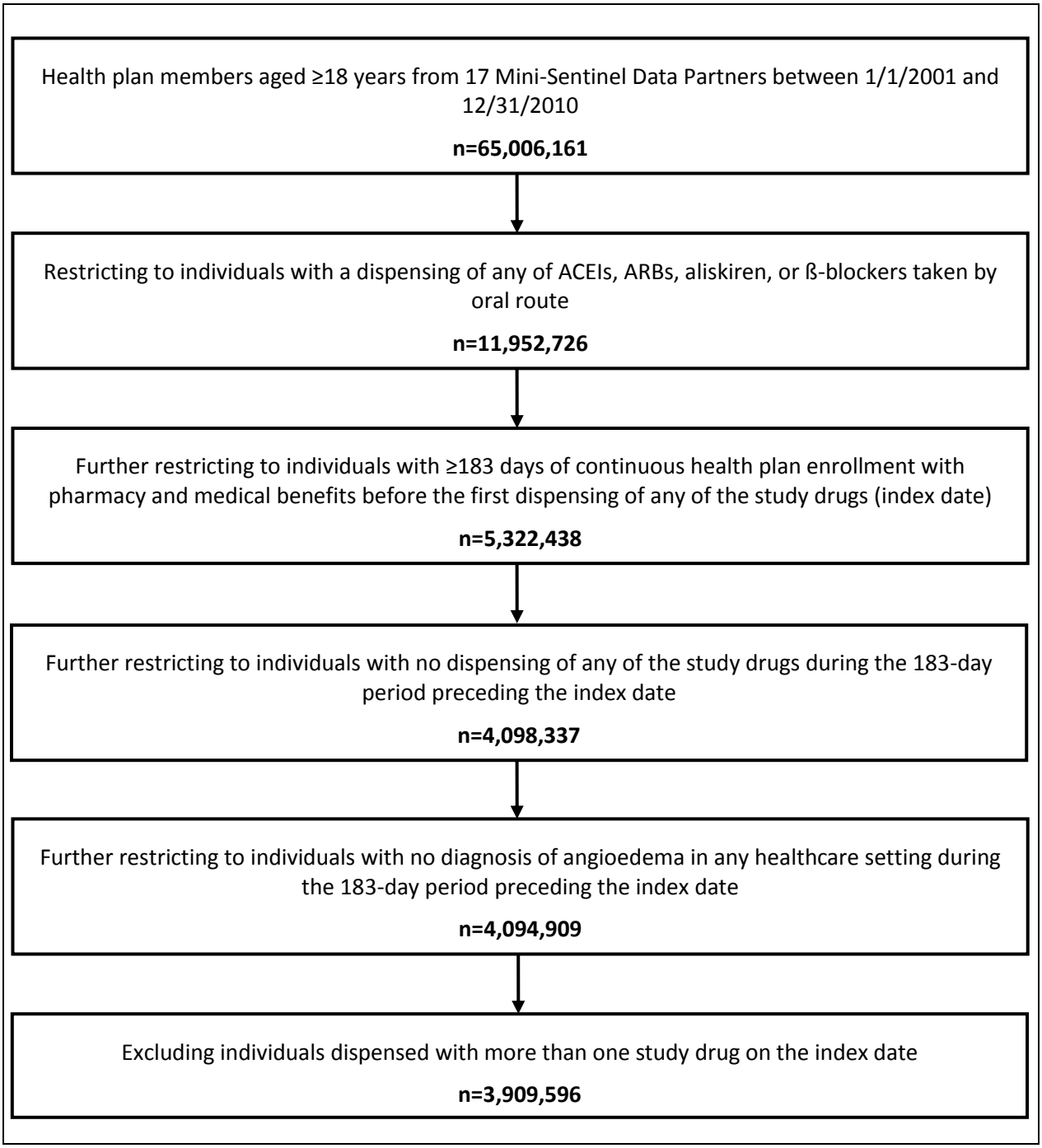
III. RESULTS

Although the protocol called for two co-primary assessments based on the availability of the study drugs, results from the two assessments were very similar. Thus, in the main text of this report we only present results that used data from 2001 to 2010; results that were based on data available after aliskiren approval are presented in Appendix 2. Note that in the aliskiren analyses shown below, ß-blocker initiators identified over the period of 2001-2010 were used as the referent group to be consistent with the analyses of ACEIs and ARBs.

A. BASELINE PATIENT CHARACTERISTICS

Between January 1, 2001 and December 31, 2010, there were 65,006,161 individuals aged 18 years or older from the 17 participating Data Partners. After applying the eligibility criteria, we identified 1,845,138 ACEI initiators, 467,313 ARB initiators, 4,867 aliskiren initiators, and 1,592,278 ß-blocker initiators (**Figure 1**). In a parallel analysis restricted to data between March 5, 2007 and December 31, 2010, there were 1,083,869 ACEI initiators, 269,549 ARB initiators, 811,257 ß-blocker initiators, and 4,867 aliskiren initiators who met the eligibility criteria for the assessment (Appendix 2).

Figure 1. Flowchart to create the study cohort, 2001-2010



ACEI, ARB, and aliskiren initiators differed from ß-blocker initiators in a number of baseline characteristics, as indicated by a standardized difference of greater than 0.1 (**Table 2**). For example, they were more likely to be male and previously diagnosed with diabetes, but were less likely to have a prior diagnosis of ischemic heart disease. As expected, race information was missing in the majority of patients.

Table 2. Baseline patient characteristics by drug class, 2001-2010

Characteristics	ACEIs (n=1,845,138)		ARBs (n=467,313)		Aliskiren (n=4,867)		ß-blockers (n=1,592,278)
	N (%)	*Std. diff.**	*N (%)*	*Std. diff.**	*N (%)*	*Std. diff.**	*N (%)*
Age (years)							
18-44	452,058 (24.5)	0.15	106,413 (22.8)	0.19	1,093 (22.5)	0.19	497,043 (31.2)
45-54	529,986 (28.7)	0.11	137,402 (29.4)	0.13	1,449 (29.8)	0.14	378,090 (23.7)
55-64	465,406 (25.2)	0.10	126,259 (27.0)	0.14	1,321 (27.1)	0.15	336,843 (21.2)
≥65	397,688 (21.6)	0.06	97,239 (20.8)	0.07	1,004 (20.6)	0.08	380,303 (23.9)
Female sex	863,222 (46.8)	0.20	237,066 (50.7)	0.12	2,275 (46.7)	0.20	901,539 (56.6)
Diagnosis of							
Allergic reactions	147,611 (8.0)	0.04	45,329 (9.7)	0.02	569 (11.7)	0.09	144,897 (9.1)
Diabetes	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)
Ischemic heart disease	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)
Race †							
African American	94,928 (5.1)	0.05	19,787 (4.2)	0.00	219 (4.5)	0.02	66,842 (4.2)
American Indian or Alaska Native	3,967 (0.2)	0.00	472 (0.1)	0.03	8 (0.2)	0.01	3,318 (0.2)
Asian American	45,771 (2.5)	0.00	5,625 (1.2)	0.09	29 (0.6)	0.12	40,030 (2.5)
Native Hawaiian or other Islander	8,025 (0.4)	0.02	924 (0.2)	0.02	10 (0.2)	0.02	4,706 (0.3)
White	492,268 (26.7)	0.08	75,566 (16.2)	0.32	791 (16.3)	0.31	484,557 (30.4)
Unknown	1,200,179 (65.0)	0.06	364,939 (78.1)	0.33	3,810 (78.3)	0.33	992,826 (62.4)

* Standardized difference, compared with β-blockers.

† Race was not adjusted for in the analyses. It is included in the table to characterize the high percentage of unknown values

B. CUMULATIVE INCIDENCE AND INCIDENCE RATE OF ANGIOEDEMA AND SERIOUS ANGIOEDEMA

The average length of follow-up over a maximum of 365 days was 149 days for ACEI initiators, 136 days for ARB initiators, 112 days for aliskiren initiators, and 126 days for β-blocker initiators. During the follow-up period, we observed 3,301 cases of angioedema among ACEI initiators, 288 cases among ARB initiators, 7 cases among aliskiren initiators, and 915 cases among β-blocker initiators.

The risk of angioedema – as measured by cumulative incidence and incidence rate – was the highest for ACEIs, and similar between ARBs and β-blockers (**Table 3**). The risk in aliskiren initiators appeared to be similar to the risk in ACEI initiators, but it was based only on seven exposed cases. There was a moderate variation in the risk of angioedema across individual ARBs, with losartan appearing to have a higher risk than other ARBs. Information was sparse for a number of ARBs, especially candesartan and eprosartan.

The risk of serious angioedema was low across all drug classes. Consistent with what was observed with angioedema, the risk was higher among ACEI initiators. There was limited information on the risk of serious angioedema for initiators of individual ARBs and aliskiren; only one case of serious angioedema was observed among aliskiren initiators.

Table 3. Cumulative incidence and incidence rate of angioedema and serious angioedema, 2001-2010

Drug	Number of events	Persons	Person-years	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)
Angioedema					
ACEIs	3,301	1,845,138	753,105.4	1.79 (1.73, 1.85)	4.38 (4.24, 4.54)
ARBs	288	467,313	173,437.9	0.62 (0.55, 0.69)	1.66 (1.47, 1.86)
Candesartan	4	12,286	4,177.0	0.33 (0.09, 0.83)	0.96 (0.26, 2.45)
Eprosartan	0	1,165	392.3	--	--
Irbesartan	24	44,094	15,997.7	0.54 (0.35, 0.81)	1.50 (0.96, 2.23)
Losartan	94	106,522	41,230.2	0.88 (0.71, 1.08)	2.28 (1.84, 2.79)
Olmesartan	39	92,973	30,170.1	0.42 (0.30, 0.57)	1.29 (0.92, 1.77)
Telmisartan	11	26,530	8,177.9	0.42 (0.21, 0.74)	1.35 (0.67, 2.41)
Valsartan	110	183,743	69,397.0	0.60 (0.49, 0.72)	1.59 (1.30, 1.91)
Aliskiren	7	4,867	1,498.1	1.44 (0.58, 2.96)	4.67 (1.88, 9.63)
β-blockers	915	1,592,278	548,684.3	0.58 (0.54, 0.61)	1.67 (1.56, 1.78)
Serious angioedema					
ACEIs	326	1,845,138	753,581.4	0.18 (0.16, 0.20)	0.43 (0.39, 0.48)

Drug	Number of events	Persons	Person-years	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)
ARBs	10	467,313	173,511.8	0.02 (0.01, 0.04)	0.06 (0.03, 0.11)
Candesartan	0	12,286	4,178.5	--	--
Eprosartan	0	1,165	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)
Olmesartan	1	92,973	30,179.7	0.01 (0.00, 0.06)	0.03 (0.00, 0.19)
Telmisartan	0	26,530	8,180.2	--	--
Valsartan	6	183,743	69,425.1	0.03 (0.01, 0.07)	0.09 (0.03, 0.19)
Aliskiren	1	4,867	1,499.4	0.21 (0.01, 1.14)	0.67 (0.03, 3.72)
β-blockers	51	1,592,278	548,953.6	0.03 (0.02, 0.04)	0.09 (0.07, 0.12)

C. SITE-ADJUSTED AND PROPENSITY-SCORE ADJUSTED ANALYSES

Table 4 shows the MS-wide results from analyses that adjusted only for Data Partner site. ACEIs were associated with an approximately 2.7-fold increased risk of angioedema compared with β-blockers. Across different approaches, the risk was 11% to 36% higher among ARB initiators when compared with the same referent group. The site-adjusted HR for aliskiren ranged from 2.8 to 3.2. Overall, results from the case-centered approach and the meta-analyses were very similar, although the effect estimates varied moderately when the sample size was smaller, as in the analyses of individual ARBs, aliskiren and serious angioedema. At the site-level, the case-centered approach and two Cox models produced highly comparable results (not shown).

Table 4. Site-adjusted MS-wide HRs of angioedema and serious angioedema using β-blockers as the referent group, 2001-2010

Drug	The case-centered approach	Inverse variance-weighted fixed-effect meta-analysis	Random-effects meta-analysis	N-weighted fixed-effect meta-analysis
Angioedema				
ACEIs	2.77 (2.57, 2.98)	2.70 (2.50, 2.90)	2.74 (2.39, 3.14)	2.71 (2.51, 2.92)
ARBs	1.11 (0.97, 1.28)	1.15 (1.00, 1.32)	1.36 (1.03, 1.79)	1.17 (1.01, 1.36)
Candesartan	0.91 (0.34, 2.43)	1.03 (0.39, 2.77)	1.16 (0.31, 4.31)	0.90 (0.33, 2.48)
Eprosartan	--	--	--	--
Irbesartan	1.05 (0.70, 1.58)	1.17 (0.77, 1.75)	1.44 (0.69, 3.01)	1.96 (1.16, 3.32)
Losartan	1.48 (1.20, 1.84)	1.56 (1.26, 1.93)	1.60 (1.23, 2.09)	1.43 (1.14, 1.80)

Drug	The case-centered approach	Inverse variance-weighted fixed-effect meta-analysis	Random-effects meta-analysis	N-weighted fixed-effect meta-analysis
Olmesartan	0.84 (0.60, 1.16)	0.82 (0.59, 1.14)	0.82 (0.59, 1.14)	0.83 (0.60, 1.17)
Telmisartan	0.83 (0.45, 1.50)	0.99 (0.54, 1.80)	1.10 (0.53, 2.30)	0.81 (0.41, 1.58)
Valsartan	1.04 (0.85, 1.28)	1.07 (0.87, 1.32)	1.14 (0.81, 1.60)	1.09 (0.87, 1.37)
Aliskiren	2.75 (1.30, 5.81)	2.83 (1.34, 5.98)	2.83 (1.34, 5.98)	3.18 (1.41, 7.15)
Serious angioedema				
ACEIs	4.42 (3.29, 5.96)	4.04 (2.99, 5.46)	4.04 (2.99, 5.46)	5.45 (3.50, 8.50)
ARBs	0.52 (0.26, 1.05)	0.56 (0.28, 1.14)	0.57 (0.25, 1.31)	0.39 (0.17, 0.91)
Candesartan	--	--	--	--
Eprosartan	--	--	--	--
Irbesartan	--	--	--	--
Losartan	0.97 (0.30, 3.18)	1.08 (0.33, 3.54)	1.08 (0.33, 3.54)	0.75 (0.17, 3.20)
Olmesartan	0.80 (0.10, 6.20)	0.67 (0.09, 5.13)	0.67 (0.09, 5.13)	0.67 (0.09, 5.13)
Telmisartan	--	--	--	--
Valsartan	1.05 (0.43, 2.56)	1.23 (0.50, 3.03)	1.26 (0.43, 3.70)	0.70 (0.22, 2.190)
Aliskiren	8.67 (1.11, 67.62)	7.04 (0.92, 54.20)	7.04 (0.92, 54.02)	7.04 (0.92, 54.20)

In general, further adjusting for all pre-specified potential confounders did not change the HR estimates substantially (**Table 5**). Compared with β-blockers, the PS-adjusted risk was 3 times greater for ACEIs, 2.9 times greater for aliskiren, and 15-31% higher for ARBs. The HR for aliskiren is based on a small number of cases. The PS-adjusted HR was higher for losartan than for other ARBs, but still lower than ACEIs.

Table 5. Propensity score-adjusted MS-wide HRs of angioedema and serious angioedema using β-blockers as the referent group, 2001-2010 *

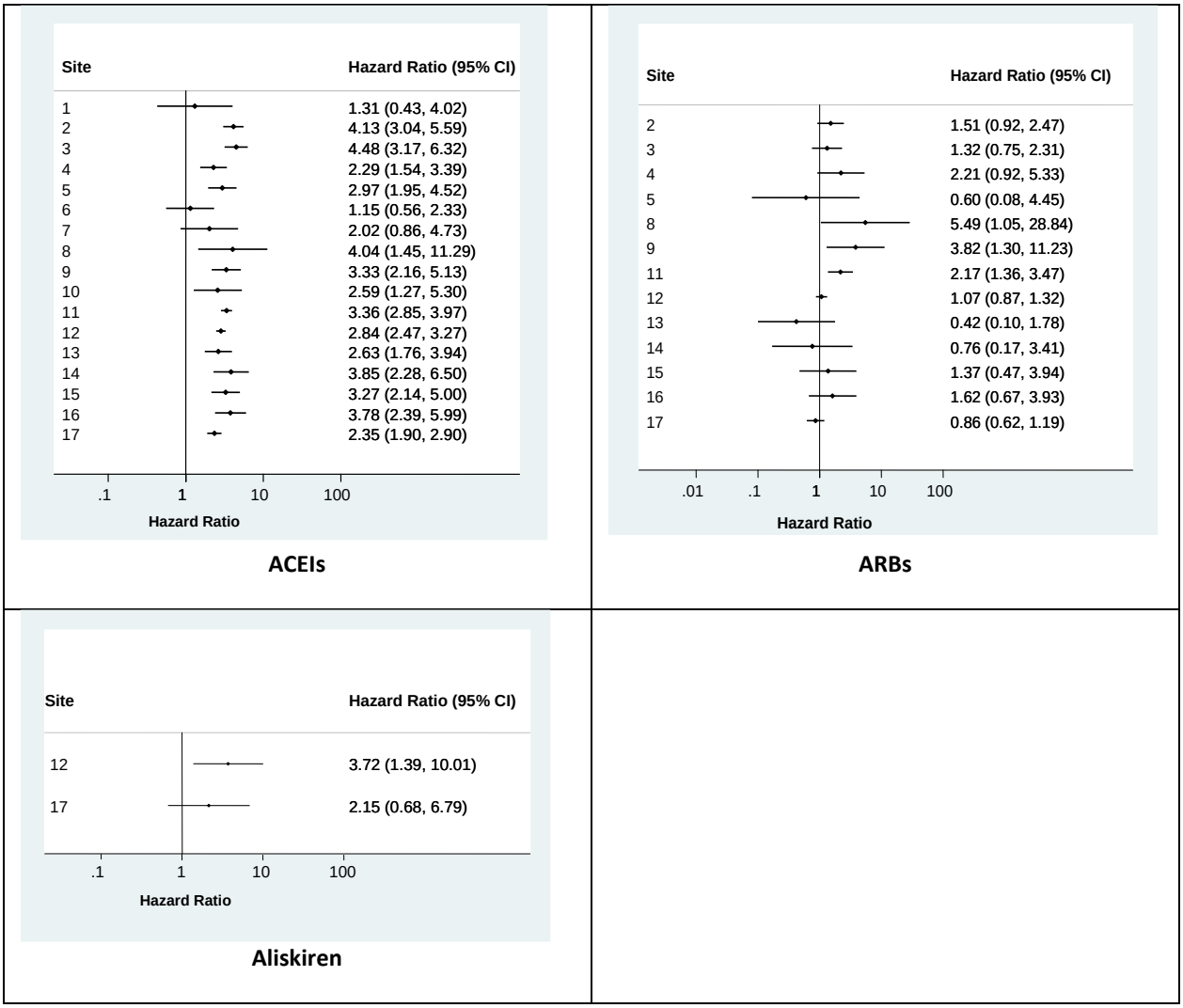
Drug	The case-centered approach	Inverse variance-weighted fixed-effect meta-analysis	Random-effects meta-analysis	N-weighted fixed-effect meta-analysis
Angioedema				
ACEIs	3.04 (2.81, 3.27)	2.98 (2.76, 3.21)	2.99 (2.63, 3.40)	2.97 (2.75, 3.22)
ARBs	1.16 (1.00, 1.34)	1.15 (1.00, 1.33)	1.31 (1.00, 1.70)	1.17 (1.01, 1.37)

Drug	The case-centered approach	Inverse variance-weighted fixed-effect meta-analysis	Random-effects meta-analysis	N-weighted fixed-effect meta-analysis
Candesartan	0.95 (0.35, 2.55)	1.08 (0.40, 2.89)	1.20 (0.33, 4.31)	0.94 (0.34, 2.59)
Eprosartan	--	--	--	--
Irbesartan	1.11 (0.73, 1.67)	1.18 (0.78, 1.78)	1.42 (0.66, 3.06)	2.00 (1.18, 3.38)
Losartan	1.53 (1.23, 1.90)	1.52 (1.22, 1.89)	1.53 (1.21, 1.93)	1.42 (1.12, 1.80)
Olmesartan	0.88 (0.63, 1.22)	0.86 (0.62, 1.19)	0.86 (0.62, 1.19)	0.87 (0.62, 1.22)
Telmisartan	0.86 (0.47, 1.56)	0.98 (0.54, 1.79)	1.00 (0.53, 1.89)	0.81 (0.41, 1.60)
Valsartan	1.08 (0.88, 1.34)	1.09 (0.89, 1.35)	1.16 (0.82, 1.65)	1.11 (0.88, 1.40)
Aliskiren	2.85 (1.34, 6.04)	2.86 (1.35, 6.04)	2.86 (1.35, 6.04)	3.19 (1.42, 7.18)
Serious angioedema				
ACEIs	4.91 (3.62, 6.65)	4.20 (3.08, 5.71)	4.20 (3.08, 5.71)	5.57 (3.55, 8.73)
ARBs	0.56 (0.28, 1.14)	0.59 (0.28, 1.22)	0.60 (0.26, 1.41)	0.40 (0.17, 0.94)
Candesartan	--	--	--	--
Eprosartan	--	--	--	--
Irbesartan	--	--	--	--
Losartan	1.01 (0.31, 3.34)	0.94 (0.28, 3.16)	0.94 (0.28, 3.16)	0.62 (0.14, 2.69)
Olmesartan	0.83 (0.11, 6.57)	0.80 (0.10, 6.36)	0.80 (0.10, 6.36)	0.80 (0.10, 6.36)
Telmisartan	--	--	--	--
Valsartan	1.14 (0.46, 2.82)	1.31 (0.52, 3.31)	1.35 (0.44, 4.19)	0.72 (0.22, 2.31)
Aliskiren	8.84 (1.13, 69.41)	8.53 (1.08, 67.41)	8.53 (1.08, 67.41)	8.53 (1.08, 67.41)

* Adjusted for age, sex, diagnosis of allergic reactions, diabetes, heart failure, and ischemic heart disease, use of prescription non-steroidal anti-inflammatory drugs, and Data Partner site.

Figure 2 shows the PS-adjusted HRs of angioedema for ACEIs, ARBs, and aliskiren obtained from the case-centered approach by site. Consistent with the MS-wide estimates, the site-specific point estimates for ACEIs and aliskiren were all greater than 1. Nine out of the 13 sites that contributed information to the ARB analysis had a point estimate that was in the same direction as the MS-wide estimate.

Figure 2. Propensity score-adjusted HR of angioedema from the case-centered approach by site



For serious angioedema, the risk among ACEIs initiators was 4-5 times the risk among β-blocker initiators. There was no indication that ARBs were associated with a higher risk of serious angioedema when compared with the same referent group. As there was only one case of serious angioedema among aliskiren initiators, the ability to compare its risk to β-blockers was limited.

D. PRE-SPECIFIED SUBGROUP ANALYSES

Table 6 shows the results from the pre-specified stratified analyses by age group, sex, and follow-up period. We only present the findings from the case-centered approach; results (not shown) from meta-analyses were similar. Analyses for aliskiren were not performed because of the small number of cases.

The risk of angioedema – as measured by cumulative incidence and incidence rate – among ACEI initiators was relatively similar across different age groups, although it seemed to be higher in patients aged ≥65 years. The risk among ARB and ß-blocker initiators was similar across age groups. When

compared with ß-blockers, the risk of angioedema associated with ACEIs appeared to vary by age (p-value for Wald test of homogeneity=0.047), with those aged ≥65 years having the highest PS-adjusted HR. There was no indication that age modified the effect of ARBs on angioedema.

The risk of angioedema was greater in female initiators of all three classes of drugs than their male counterparts. Although the difference in the PS-adjusted HR for ACEIs between female and male was statistically significant (p-value for Wald test of homogeneity=0.002), the difference in magnitude was not great (3.3 vs. 2.6). On the other hand, the association between ARBs and angioedema was similar between male and female.

The risk of angioedema was elevated immediately following treatment initiation across all three drug classes. The PS-adjusted HR for ACEIs was the greatest during the first 30 days of use, and remained significantly higher than β-blockers throughout the 1-year follow-up period. The PS-adjusted HR for ARBs was also the highest during the first 30 days following treatment initiation, but attenuated when we extended the follow-up period to the first 60, 90, 180, and 270 days of use. Sixty-six percent (2,173/3,301) of all angioedema cases among ACEI initiators occurred during the first 90 days of follow-up, compared with 65% (187/288) for ARBs, and 66% (602/915) for ß-blockers. By way of comparison, five out of the seven (71%) angioedema cases occurred during the first 90 days among aliskiren initiators.

Table 6. Pre-specified subgroup analysis of angioedema, 2001-2010

Subgroup	Number of events	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)	Site-adjusted HR * (95% CI)	Propensity score-adjusted HR * (95% CI)
Aged 18-44 yrs					
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)	Referent	Referent
Aged 45-54 yrs					
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)	Referent	Referent
Aged 55-64 yrs					
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)	Referent	Referent

Subgroup	Number of events	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)	Site-adjusted HR * (95% CI)	Propensity score-adjusted HR * (95% CI)
Aged ≥65 yrs					
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)	Referent	Referent
Male					
ACEIs	1,337	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)	Referent	Referent
Female					
ACEIs	1,962	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)	Referent	Referent
0-30 days					
ACEIs	1,420	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)	Referent	Referent
31-60 days					
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)	Referent	Referent
61-90 days					
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)

Subgroup	Number of events	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)	Site-adjusted HR * (95% CI)	Propensity score-adjusted HR * (95% CI)
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)	Referent	Referent
91-180 days					
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)	Referent	Referent
181-270 days					
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)	Referent	Referent
271-365 days					
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)	Referent	Referent
0-60 days					
ACEIs	1,873	1.02 (0.97, 1.06)	7.05 (6.74, 7.38)	3.03 (2.75, 3.34)	3.30 (2.98, 3.64)
ARBs	169	0.36 (0.31, 0.42)	2.58 (2.20, 3.00)	1.23 (1.02, 1.47)	1.29 (1.06, 1.55)
β-blockers	522	0.33 (0.30, 0.36)	2.40 (2.20, 2.62)	Referent	Referent
0-90 days					
ACEIs	2,173	1.18 (1.13, 1.23)	6.08 (5.83, 6.34)	2.98 (2.72, 3.26)	3.25 (2.96, 3.57)
ARBs	187	0.40 (0.35, 0.46)	2.18 (1.87, 2.51)	1.13 (0.95, 1.35)	1.20 (1.00, 1.43)
β-blockers	602	0.38 (0.35, 0.41)	2.14 (1.97, 2.32)	Referent	Referent

Subgroup	Number of events	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)	Site-adjusted HR * (95% CI)	Propensity score-adjusted HR * (95% CI)
0-180 days					
ACEIs	2,744	1.49 (1.43, 1.54)	5.08 (4.89, 5.28)	2.88 (2.66, 3.12)	3.16 (2.91, 3.43)
ARBs	235	0.50 (0.44, 0.57)	1.86 (1.63, 2.11)	1.10 (0.95, 1.29)	1.16 (0.99, 1.36)
β-blockers	753	0.47 (0.44, 0.51)	1.86 (1.73, 2.00)	Referent	Referent
0-270 days					
ACEIs	3,060	1.66 (1.60, 1.72)	4.64 (4.47, 4.80)	2.82 (2.61, 3.05)	3.10 (2.87, 3.35)
ARBs	262	0.56 (0.50, 0.63)	1.71 (1.51, 1.93)	1.09 (0.94, 1.26)	1.14 (0.98, 1.32)
β-blockers	842	0.53 (0.49, 0.57)	1.74 (1.62, 1.86)	Referent	Referent

* From the case-centered logistic regression approach.

E. SENSITIVITY ANALYSIS

When we extended the look-back period from 183 days to 365 days preceding the index date, the number of eligible initiators (and angioedema cases) was 1,392,602 (2,623) for ACEIs, 312,826 (181) for ARBs, 3,260 (3) for aliskiren, and 1,185,727 (655) for β-blockers. Compared with β-blockers, the PS-adjusted HR from the case-centered approach was 3.36 (95% CI: 3.07, 3.67) for ACEIs, 1.21 (1.01, 1.45) for ARBs, and 4.01 (1.28, 12.57) for aliskiren. Results (not shown) from the meta-analyses were also similar to the analyses with a 183-day look-back period.

Fifty-four percent (1,782/3,301) of the angioedema cases among ACEI initiators were identified from an inpatient or emergency department encounter; this proportion was 29% (83/288) for ARBs, 29% (2/7) for aliskiren, and 31% (282/915) for β-blockers. In an analysis restricted to these angioedema cases, the adjust HR from the case-centered approach was 5.34 (4.69, 6.07) for ACEIs, 1.09 (0.83, 1.42) for ARBs, and 2.72 (0.67, 11.07) for aliskiren.

IV. DISCUSSION

A. SUMMARY OF FINDINGS

In this Mini-Sentinel project, we found that ACEIs were associated with a 3-fold increased risk of angioedema compared with β-blockers, a drug class not thought to be linked to angioedema. This finding demonstrates Mini-Sentinel's ability to reproduce known associations.[4-7] There was indication that the risk might be greater for ARBs when compared with β-blockers – ranging from 15% to 31% higher from various methods – although the lower bound of the 95% CIs were all very close to one. Aliskiren was associated with a nearly 3-fold higher risk of angioedema when compared with the same referent group. However, this was based on only seven exposed cases. There was a suggestion that losartan had a greater risk of angioedema compared with other individual ARBs.

In keeping with the current goal that Mini-Sentinel be useful for signal refinement (in the continuum of signal generation, signal refinement, signal evaluation), the results summarized in this report are not expected to provide definitive evidence of a causal association between these drugs and angioedema, elucidate the association with regard to factors such as dose-response and duration-response relations, or identify subgroups at the highest risk. Findings should be interpreted in the larger context of all that is known about these drugs from various sources, such as randomized controlled trials and post-market reports, and other observational studies.

B. COMPARISON WITH PRIOR STUDIES

1. ACEIs

Table 7 includes a list of selected studies that have examined the associations between the study drugs and angioedema. The largest study on this topic to date was done using data from the Veteran Affairs Health Care System.[9] In that study, Miller *et al* found that the incidence rate per 1,000 person-years was about 2 among 195,192 ACEI initiators and 0.5 among 94,020 β-blocker initiators.[9] In our study, the incidence rates in these two cohorts were both higher, but the cumulative incidence – calculated using exposed persons as the denominator – among ACEI initiators was similar in both studies (1.8 vs. 1.8 per 1,000 ACEI-exposed persons; cumulative incidence information was not available for β-blockers in the Miller study). In addition, the cumulative incidence of serious angioedema associated with ACEIs was comparable between the Miller study and ours (0.14 vs. 0.18 per 1,000 ACEI-exposed persons). Consistent with previous studies,[5,8-10] we observed that the risk was the greatest immediately following ACEI initiation. In the Miller study, 55% of the angioedema cases occurred within 90 days following ACEI initiation, compared with 66% in our study.

Differences in the study population might have led to higher incidence rates in our study. For example, the proportion of female users, who seemed to have a higher risk of angioedema, was more than 50% in our study compared with 3% in the Miller study. However, it is unlikely that differences in the study population only impacted incidence rate, and not cumulative incidence.

A more plausible explanation might be differences in the study design, more specifically, in how person-time was counted. In our study, we calculated exposed person-times from treatment initiation until the earliest occurrence of angioedema diagnosis, 365 days of follow-up, initiation of another study drug, cessation of use of study drug, death, disenrollment from the health plan, end of medical benefit, or December 31, 2010. Cessation of use occurred when an individual's days supplied appeared to have been exhausted for at least 14 days. That is, even if patients subsequently resumed their initial treatment, we would not count the person-times if the resumption occurred more than 14 days later. The description of Miller *et al* paper suggested that the authors estimated the incidence rate using all exposed person-times (including person-times that accumulated after resumption) over a maximal follow-up of 21 months, or allowed a more generous gap between dispensings when creating the exposure period. This could explain why the average length of follow-up was 0.4 year in our study and 0.9 year in the Miller study. As the risk of angioedema gradually diminished over time, the Miller study might have included more person-times with a lower risk of angioedema. A study done by Brown *et al* using Tennessee Medicaid study used a similar follow-up approach to the Miller study, and found a similar incidence rate.[8]

Despite these potential differences, our adjusted HR of 3.04 (95% CI: 2.81, 3.27) for ACEIs (from the case-centered approach) was similar to the relative risk of 3.56 (2.82, 4.44) in the Miller study obtained from a Poisson regression analysis using all other anti-hypertensive medications as the referent group.

Randomized trials generally observed a higher cumulative incidence of angioedema associated with ACEIs than observational studies (Table 7). This may be due to differences in the study population, or a more careful ascertainment of milder cases in the trials, especially those that resolve quickly and did not require medical attention.

2. ARBs

Compared with what is known about ACEIs, the relation between ARBs and angioedema is not as well-understood. Miller *et al* found that the incidence rate of angioedema was 1 per 1,000 person-years among 9,816 ARB initiators.[9] Our incidence rate was higher, which could be attributed to the differences in study design or study population as described above. In the Miller study, the crude incidence rate in ARB users was twice as high as the rate in β-blocker users, but it is unclear how similar or different our adjusted HR would be compared with Miller's, as this information was not available. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) found a lower cumulative incidence of angioedema in telmisartan users compared with ramipril users (1 vs. 3 per 1,000 persons).[12] The cumulative incidence of angioedema for telmisartan was lower in our study, possibly due to differences in the study population and the ability to capture milder cases.

3. Aliskiren

Little is known about the association between aliskiren and angioedema. Pooled analyses of randomized trials with 4,578 patients who received aliskiren monotherapy suggests that the risk of angioedema and urticaria as a combined outcome was similar or lower for aliskiren compared with ACEIs and ARBs.[13,14] Unfortunately, the analyses did not examine angioedema separately and individual trials were too small to provide reliable estimates. With seven exposed cases, we observed that the risk of angioedema among aliskiren initiators is similar to ACEIs. Further investigations are warranted to better understand the relation between aliskiren and angioedema.

Table 7. Selected published studies on the associations of ACEIs, ARBs, and aliskiren with angioedema

Study	Design	Drug	Exposed persons	Exposed person-years	Number of events	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)
ACEIs							
Kostis et al[10]	Trial	Enalapril	12,557	-- *	86	6.8 (5.5, 8.4)	--
Pfeffer et al[34]	Trial	Captopril	4,879	--	35	7.2 (5.2, 10.0)	--
Piller et al[26]	Trial	Lisinopril	9,054	--	37	4.1 (3.0, 5.2)	--
Yusuf et al[12]	Trial	Ramipril	8,576	--	25	2.9 (2.0, 4.3)	--
Brown et al[8]	Observational	All	27,834	52,734	82	2.9 (2.4, 3.7)	1.6 (1.2, 1.9)

Study	Design	Drug	Exposed persons	Exposed person-years	Number of events	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)
Miller et al[9]	Observational	All	195,192	179,088	352	1.8 (1.6, 2.0)	2.0 (1.8, 2.2)
ARBs							
Pfeffer et al[34]	Trial	Valsartan	4,885	--	21	4.3 (2.8, 6.6)	--
Yusuf et al[12]	Trial	Telmisartan	8,542	--	10	1.2 (0.6, 2.2)	--
Miller et al[9]	Observational	All	9,816	--	--	--	1.0†
Aliskiren							
White et al[13]	Pooled analysis of trials	Aliskiren	4,203	--	13§	3.1 (1.8, 5.3)	--
White et al[14]	Pooled analysis of trials	Aliskiren	4,578	--	15§	3.3 (2.0, 5.4)	--

* Information not provided.
† Only point estimate was provided, information needed to estimate the 95% CI was not available in the paper.
§ Angioedema and urticaria as a combined outcome.

C. METHODS CONSIDERATION

1. Discussion of analytic approaches

We used two methods that do not require sharing of individual-level information to combine data from 17 Data Partners. The first method, which is based on the Fireman's case-centered logistic regression approach, needs only aggregate-level data to obtain the same effect estimates that would have been observed through a stratified Cox model fit using individual-level information.[28] The second method combines site-specific effect estimates via meta-analysis, obviating the need to transfer either individual-level or aggregate-level dataset across sites. Both methods allow investigators to adjust for a large number of potential confounders without the need to share individual-level information. They can also accommodate pre-specified subgroup analyses by generating subgroup-specific aggregate-level dataset (for the case-centered approach) or subgroup-specific effect estimates at each site (for the meta-analyses). In this project, the MS-wide point estimates and 95% CIs from the two methods were similar, especially in analyses with large sample size, suggesting that both methods achieved similar level of confounding adjustment, and can both be considered in future Mini-Sentinel signal refinement activities.

We performed three meta-analyses, two done with a fixed-effect model, one done with a random-effects model. The fixed-effect model assumes that all "studies" (i.e., analyses done at Data Partner

sites) share a common true effect estimate, and all observed differences are due to sampling error. The random-effects model assumes that all studies are randomly drawn from a population of effect estimates, i.e., each study can have its own effect estimates. The choice of appropriate model depends on what investigators know or hypothesize about the variation across sites. It is not uncommon to use both models in studies. Within the fixed-effect model, the inverse-variance weighted method is among the most commonly used approaches.[30] We observed that using the total sample size as the weight produced results similar to the inverse-variance weighted approach, but the two approaches could yield different results when the sample size was small. A major difference between the two approaches is that the inverse variance approach incorporates information on the number of outcomes, which is a major driving force of statistical efficiency. Although total sample size is correlated with the number of outcomes, using the former as the weight does not fully reflect the precision of a site-specific effect estimates.

2. Estimation of PSs

There were at least two possible ways to estimate PSs in this study. The first approach would have each Data Partner fit the same PS model. The advantage of this approach is consistency. Operationally, having one model allows for a single, centralized development of the analytic program, which reduces the programming burden and chance for errors across sites. On the other hand, the approach does not fully utilize the information available at each site. In Mini-Sentinel, certain Data Partners have access to clinical data like vital signs and laboratory results, but such information would not be used when one uses a common PS model across all Data Partners. We chose to use this approach because there was no evidence to suggest that measured variables other than the ones considered would be strong confounders.

An alternative would be to have each Data Partner fit its own PS model, which could include additional confounders available only at certain sites. One could also combine the two approaches, i.e., have each site fit a common PS model, and allow sites with richer data to fit a separate model with additional variables.[35,36] This will introduce additional operational complexities but may be preferred for certain assessments in the future. A variant to the site-specific PS method is the high-dimensional PS approach, which allows investigators to pre-specify a set of confounders and use an automated approach to identify additional potential confounders.[37-39] The approach will more fully utilize the information available at each site. A freely available SAS macro (http://www.drugepi.org/dope-downloads/) facilitates implementation of the approach. A challenge will be to understand the PS model created by the approach, as hundreds of additional variables, presented in coding systems like ICD-9-CM, NDC, or CPT-4, may not be immediately interpretable to the investigators.

3. Alternative approaches considered

One of the objectives of this activity was to build general strategies in Mini-Sentinel for signal refinement regarding medical products for which substantial post-market experience has accrued. We discussed several alternative approaches but determined that these approaches were not ideal for the project. However, these approaches may be appropriate for certain Mini-Sentinel signal refinement activities in the future.

Centralized analysis of individual-level data with individual confounders. Using this approach, we would request the Data Partners to send an individual-level dataset with individual confounder information for

centralized analyses. Of all available approaches, this would provide the workgroup with the most analytic flexibility,[36] but it would require transferring of potentially identifiable individual-level information.

Centralized analysis of individual-level data with confounder summary scores. An alternative approach to the centralized analysis above would be to have each site estimate PSs, and then send an individual-level dataset with information on the exposure, outcome, time-to-event, PSs, and pre-specified subgroup status.[36] Methods that use confounder summary scores (e.g., PSs, disease risk scores) are appealing in distributed data systems like Mini-Sentinel because they obscure individual-level characteristics into non-identifiable measures while achieving a similar degree of confounding control.[36] Another advantage of these confounder summary scores is the reduction of data dimensionality. For rare outcomes like angioedema, conventional multivariable-adjusted analysis may lead to unstable effect estimates. A PS analysis may minimize such risk because it models the relation between the confounders and the exposure, which is often more common than the outcome of interest, especially when the medical products being studied have been approved for a number of years. In principle, all information would be considered de-identified. However, the possibility of re-identification could not be fully ruled out through unique combinations of exposure, outcome, and pre-specified subgroup status, especially at smaller Data Partner sites.

Instead of using PSs, we could use disease risk scores, which offer a number of advantages when there are multiple exposure categories and one outcome of interest.[40] A single score is sufficient to examine multiple comparators, as opposed to a need for multiple PSs. However, as the number of angioedema events was expected to be low in many Data Partner sites, constructing disease risk scores would be a challenge.

PS matching. This approach has several advantages when the exposure is binary.[36,41] For example, both absolute and relative risk estimates can be computed easily in the matched cohort if balance is achieved for all baseline covariates. The matching process can also serve as an important step to identify patients who may have contraindications or other characteristics that preclude them from being “eligible” to receive both treatments. Removing these patients, for whom the PS is usually extremely low or high, creates clinical equipoise and may improve the internal validity of the study. A similar aggregate-data structure used in the case-centered approach can be used for a PS-matched analysis, obviating the need to transfer individual-level data.[42] However, when there are multiple exposures, as in this project, a pairwise PS matching using a common referent group may result in different subsets of matched referent population in each pair, making direct comparisons difficult. Using a 1:1:1:1 matching scheme would ensure the same referent population is used for all analyses, but it might substantially reduce the number of patients in our analyses given the expected low number of aliskiren initiators.

Distributed regression analysis.[43-45] Distributed regression analysis fits regression models on distributed databases, and produces identical results to those from centralized conventional multivariable-adjusted regression analysis. In distributed regression analysis, Data Partners transfer only summary or intermediate statistics to a centralized location for model fitting. For instance, in distributed linear regression with horizontally partitioned database, the required summary statistics include the sums of the covariates, the sums of covariate squares, and the sum of products between covariates. Currently, there are a number of technical requirements that need to be overcome to perform such analysis in a distributed data system. In addition, the approach has not been extended to time-to-event outcomes.

D. LIMITATIONS

The results of this assessment should be interpreted in the context of the following limitations. Residual confounding may be a threat to the validity of our findings. Most notably, previous studies have suggested that African-American race may be a risk factor for angioedema and a potential effect modifier for the effect of ACEIs on angioedema.[8-10,23-25] Race information is sparse across the vast majority of Data Partners and was therefore not adjusted for in this assessment. However, our results are consistent with previous studies that adjusted for race.[8,9] Smoking was another covariate not available to us that has also been suggested to be a confounder for the effect of ACEIs on angioedema.[24-26]

A 183-day baseline look-back period might not be sufficient to identify all previous angioedema, which may predict both the risk of subsequent angioedema and the choice of antihypertensive treatment. It might also not be long enough to identify prior use of the study drugs. We chose 183 days because it was considered sufficient to identify a majority of recently occurred angioedema that were mostly likely to affect prescribing, while ensuring that not too many otherwise eligible individuals would be excluded as a result of longer enrollment requirement. The number of eligible patients was lower in a sensitivity analysis that used a 365-day look-back period, but the results remained similar.

Although the positive predictive value of the diagnosis code for angioedema is high, some cases, especially those that are milder and resolved quickly – therefore do not require medical attention – might not have been captured in electronic healthcare databases. This might lead to an underestimation of the true cumulative incidence and incidence rate of angioedema. As the association between ACEIs and angioedema 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. On the other hand, this could potentially lead to an overestimation of the relative risk of angioedema when comparing ACEIs with ß-blockers because there would be a differential case ascertainment and diagnosis. The proportion of angioedema cases diagnosed during an outpatient visit was much lower in ACEI initiators compared with initiators of other study drugs, which suggests that milder cases were no more likely to be captured among ACEI initiators, or that ACEIs might be associated with more severe cases.

E. STRENGTHS

With more than 1,845,000 ACEI initiators, 467,000 ARB initiators, and 4,800 aliskiren initiators, this study, to our knowledge, is the largest assessment of the relations between these medications and angioedema. The validity of the findings is strengthened by the consistent results from various analyses. Validity is further improved 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. A distributed approach, with programs developed and tested centrally and executed concurrently by all 17 Data Partners, coupled with methods that do not require individual-level data to leave Data Partners' firewalls, ensure that all analyses were done efficiently and securely.

V. CONCLUSION

In conclusion, this Mini-Sentinel assessment replicated the known association between ACEIs and angioedema. The assessment also provided new information on the risk of angioedema for ARBs (both

as a class and as individual molecular entities) and the direct renin inhibitor, aliskiren. There was no strong evidence to suggest that ARBs as a group substantially increased the risk of angioedema; an elevated risk, if any, would be much lower for ARBs than for ACEIs. The risk of angioedema varied moderately across individual ARBs, with losartan appearing to be associated with a higher risk than others. Based on seven exposed cases our analyses suggested that aliskiren might be associated with an approximately 2.9-fold higher risk of angioedema compared with ß-blockers.

VI. ACKNOWLEDGEMENTS

The authors would like to thank the following Data Partners for participating in the project: Aetna, HealthCore, Inc., the HMO Research Network (Group Health Research Institute, Harvard Pilgrim Health Care Institute, HealthPartners Research Foundation, Henry Ford Health System, Lovelace Clinic Foundation, Marshfield Clinic Research Foundation, and Meyers Primary Care Institute), Humana, the Kaiser Permanente Center for Effectiveness and Safety Research (Kaiser Permanente Colorado, Kaiser Permanente Georgia, Kaiser Permanente Hawaii, Kaiser Permanente Mid-Atlantic, Kaiser Permanente Northern California, and Kaiser Permanente Northwest), and Vanderbilt University/Tennessee Medicaid. The authors also thank the following individuals: Aarthi Iyer and Jillian Lauer of Harvard Pilgrim Health Care Institute for their administrative support; Nicolas Beaulieu, James Marshall, and Lisa Trebino of Harvard Pilgrim Health Care Institute, and Erick Moyneur and Eric Gravel of Statlog Consulting Services, Inc. for their programming support; and Bruce Fireman of Kaiser Permanente Northern California for his guidance on the application of the case-centered logistic regression approach.

VII. REFERENCES

1. Zaman MA, Oparil S, Calhoun DA. Drugs targeting the renin-angiotensin-aldosterone system. Nat Rev Drug Discov 2002;1:621-36.

2. Greaves M, Lawlor F. Angioedema: manifestations and management. J Am Acad Dermatol 1991;25:155-61; discussion 61-5.

3. Temino VM, Peebles RS, Jr. The spectrum and treatment of angioedema. Am J Med 2008;121:282-6.

4. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med 1992;117:234-42.

5. Vleeming W, van Amsterdam JG, Stricker BH, de Wildt DJ. ACE inhibitor-induced angioedema. Incidence, prevention and management. Drug Saf 1998;18:171-88.

6. Slater EE, Merrill DD, Guess HA, et al. Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. JAMA 1988;260:967-70.

7. Sabroe RA, Black AK. Angiotensin-converting enzyme (ACE) inhibitors and angio-oedema. Br J Dermatol 1997;136:153-8.

8. Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther 1996;60:8-13.

9. Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. Hypertension 2008;51:1624-30.

10. Kostis JB, Kim HJ, Rusnak J, et al. Incidence and characteristics of angioedema associated with enalapril. Arch Intern Med 2005;165:1637-42.

11. Howes LG, Tran D. Can angiotensin receptor antagonists be used safely in patients with previous ACE inhibitor-induced angioedema? Drug Saf 2002;25:73-6.

12. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547-59.

13. White WB, Bresalier R, Kaplan AP, et al. Safety and tolerability of the direct renin inhibitor aliskiren: a pooled analysis of clinical experience in more than 12,000 patients with hypertension. J Clin Hypertens (Greenwich) 2010;12:765-75.

14. White WB, Bresalier R, Kaplan AP, et al. Safety and tolerability of the direct renin inhibitor aliskiren in combination with angiotensin receptor blockers and thiazide diuretics: a pooled analysis of clinical experience of 12,942 patients. J Clin Hypertens (Greenwich) 2011;13:506-16.

15. Toh D, Reichman ME, Houstoun M, et al. Protocol for signal refinement of angioedema events in association with use of drugs that act on the renin-angiotensin-aldosterone system 2011. (Accessed January 17, 2012, at http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_Angioedema-and-RAAS_Protocol.pdf)

16. Behrman RE, Benner JS, Brown JS, McClellan M, Woodcock J, Platt R. Developing the Sentinel System--a national resource for evidence development. N Engl J Med 2011;364:498-9.

17. Platt R, Carnahan RM, Brown JS, et al. The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:1-8.

18. Curtis LH, Weiner MG, Boudreau DM, et al. Design considerations, architecture, and use of the Mini-Sentinel distributed data system. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:23-31.

19. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915-20.

20. Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor--associated angioedema. JAMA 1997;278:232-3.

21. Kachroo S, Jones N, Reynolds MW. Systematic literature review for evaluation of angioedema. Final report prepared for the Foundation for the National Institutes of Health via the Observational Medical Outcomes Partnership (OMOP). Lexington, MA: United Biosource Corporation; 2009.

22. Jarrett N, Lux L, West S. Systematic evaluation of health outcome of interest definitions in observational studies and clinical definitions for the Observational Medical Outcomes Partnership: Angioedema. Research Triangle Park, NC: RTI International; 2009.

23. Gibbs CR, Lip GY, Beevers DG. Angioedema due to ACE inhibitors: increased risk in patients of African origin. Br J Clin Pharmacol 1999;48:861-5.

24. Morimoto T, Gandhi TK, Fiskio JM, et al. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. J Eval Clin Pract 2004;10:499-509.

25. Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. Immunol Allergy Clin North Am 2006;26:725-37.

26. Piller LB, Ford CE, Davis BR, et al. Incidence and predictors of angioedema in elderly hypertensive patients at high risk for cardiovascular disease: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Clin Hypertens (Greenwich) 2006;8:649-56; quiz 57-8.

27. Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. BMJ 2005;330:960-2.

28. Fireman B, Lee J, Lewis N, Bembom O, van der Laan M, Baxter R. Influenza vaccination and mortality: differentiating vaccine effects from bias. Am J Epidemiol 2009;170:650-6.

29. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

30. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 501 [updated September 2008]: The Cochrane Collaboration; 2008.

31. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

32. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41-55.

33. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984;79:516-24.

34. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893-906.

35. Rassen JA, Avorn J, Schneeweiss S. Multivariate-adjusted pharmacoepidemiologic analyses of confidential information pooled from multiple health care utilization databases. Pharmacoepidemiol Drug Saf 2010;19:848-57.

36. Rassen JA, Solomon DH, Curtis JR, Herrinton L, Schneeweiss S. Privacy-maintaining propensity score-based pooling of multiple databases applied to a study of biologics. Med Care 2010;48:S83-9.

37. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512-22.

38. Toh S, García Rodríguez LA, Hernán MA. Confounding adjustment via a semi-automated high-dimensional propensity score algorithm: an application to electronic medical records. Pharmacoepidemiol Drug Saf 2011;20:849-57.

39. Rassen JA, Schneeweiss S. Using high-dimensional propensity scores to automate confounding control in a distributed medical product safety surveillance system. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:41-9.

40. Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. Stat Methods Med Res 2009;18:67-80.

41. Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. Pharmacoepidemiol Drug Saf 2010;19:858-68.

42. Fireman B, Toh S, Butler MG, et al. A protocol for active surveillance of acute myocardial infarction in association with the use of a new antidiabetic pharmaceutical agent. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:282-90.

43. Karr AF, Lin X, Sanil AP, Reiter JP. Secure regression on distributed databases. J Comput Graph Stat 2005;14:263-79.

44. Fienberg SE, Fulp WJ, Slavkovic AB, Wrobel TA. "Secure" log-linear and logistic regression analysis of distributed databases. Lect Notes Comput Sci 2006;2006:277-90.

45. Lin X, Karr AF. Privacy-preserving maximum likelihood estimation for distributed data. Journal of Privacy and Confidentiality 2009;1:213-22.

VIII. APPENDIX 1: INCIDENCE RATE OF ANGIOEDEMA BY YEAR, 2001-2010

Table A1. Incidence Rate of Angioedema by Year, 2001-2010

Year	ACEIs	ARBs	Aliskiren	β-blockers
2001	4.02 (3.20, 4.99)	0.46 (0.01, 2.55)	--	1.58 (1.11, 2.19)
2002	5.08 (4.41, 5.83)	2.67 (1.46, 4.47)	--	1.12 (0.83, 1.48)
2003	4.22 (3.57, 4.94)	2.12 (1.06, 3.80)	--	1.55 (1.19, 1.99)
2004	3.90 (3.42, 4.42)	1.03 (0.60, 1.65)	--	1.62 (1.31, 1.99)
2005	3.37 (2.98, 3.80)	1.36 (0.92, 1.93)	--	1.45 (1.17, 1.77)
2006	3.59 (3.21, 3.99)	1.19 (0.80, 1.70)	--	1.55 (1.26, 1.89)
2007	3.93 (3.54, 4.35)	1.36 (0.93, 1.92)	13.72 (2.83, 40.09)	1.53 (1.23, 1.87)
2008	4.71 (4.33, 5.12)	1.63 (1.20, 2.16)	6.57 (1.36, 19.20)	1.71 (1.42, 2.03)
2009	4.78 (4.41, 5.17)	2.24 (1.71, 2.88)	--	2.23 (1.90, 2.59)
2010	5.92 (5.39, 6.49)	2.69 (1.95, 3.61)	3.78 (0.10, 21.06)	2.07 (1.68, 2.52)

A 183-day look-back period was used. In 2001 there was 1 ARB event among 4,802 persons and 2,188.98 person years. These data include cases diagnosed in all settings. Not all Data Partners contributed data in each year.

IX. APPENDIX 2: RESULTS THAT ANALYZED DATA FOLLOWING FDA APPROVAL DATE OF ALISKIREN

Table A2. Baseline patient characteristics by drug class, 3/5/2001–12/31/2010

Characteristics	ACEIs (n=1,083,869)		ARBs (n=269,549)		Aliskiren (n=4,867)		ß-blockers (n=811,257)
	N (%)	*Std. diff.**	*N (%)*	*Std. diff.**	*N (%)*	*Std. diff.**	*N (%)*
Age (years)							
18-44	271,667 (25.1)	0.16	58,190 (21.6)	0.24	1,093 (22.5)	0.21	262,618 (32.4)
45-54	316,827 (29.2)	0.14	79,834 (29.6)	0.15	1,449 (29.8)	0.16	187,624 (23.1)
55-64	273,145 (25.2)	0.10	74,504 (27.6)	0.15	1,321 (27.1)	0.15	171,670 (21.2)
≥65	222,230 (20.5)	0.07	57,021 (21.2)	0.05	1,004 (20.6)	0.06	189,345 (23.3)
Female sex	497,331 (45.9)	0.21	133,777 (49.6)	0.14	2,275 (46.7)	0.19	457,415 (56.4)
Race †							
African American	46,942 (4.3)	0.03	10,960 (4.1)	0.02	219 (4.5)	0.04	29,746 (3.7)
American Indian or Alaska Native	2,143 (0.2)	0.00	326 (0.1)	0.02	8 (0.2)	0.00	1,465 (0.2)
Asian American	19,801 (1.8)	0.00	3,334 (1.2)	0.04	29 (0.6)	0.09	14,284 (1.8)
Native Hawaiian or other Islander	4,279 (0.4)	0.02	731 (0.3)	0.00	10 (0.2)	0.02	2,387 (0.3)
White	268,298 (24.8)	0.05	47,887 (17.8)	0.21	791 (16.3)	0.24	219,149 (27.0)
Unknown	742,406 (68.5)	0.03	206,311 (76.5)	0.21	3,810 (78.3)	0.24	544,226 (67.1)
Diagnosis of							
Allergic reactions	91,045 (8.4)	0.06	28,033 (10.4)	0.01	569 (11.7)	0.06	81,126 (10.0)
Diabetes	193,435 (17.8)	0.27	45,195 (16.8)	0.27	861 (17.7)	0.33	69,001 (8.5)
Heart failure	18,206 (1.7)	0.13	5,343 (2.0)	0.10	123 (2.5)	0.07	30,619 (3.8)
Ischemic heart disease	47,738 (4.4)	0.29	16,061 (6.0)	0.20	403 (8.3)	0.12	98,338 (12.1)
Use of prescription NSAIDs	146,413 (13.5)	0.00	34,677 (12.9)	0.02	683 (14.0)	0.01	110,707 (13.6)

* Standardized difference, compared with β-blockers.
† Race was not adjusted for in the analyses. It is included in the table to characterize the high percentage of unknown values.

Table A3. Cumulative incidence and incidence rate of angioedema and serious angioedema, 3/5/2001–12/31/2010

Drug	Number of events	Persons	Person-years	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)
Angioedema					
ACEIs	1,951	1,083,869	406,277.5	1.80 (1.72, 1.88)	4.80 (4.59, 5.02)
ARBs	175	269,549	91,542.0	0.65 (0.56, 0.75)	1.91 (1.64, 2.23)
Candesartan	2	5,178	1,693.0	0.39 (0.05, 1.40)	1.18 (0.14, 4.27)
Eprosartan	0	135	47.8	--	--
Irbesartan	11	22,228	7,445.7	0.50 (0.25, 0.89)	1.48 (0.74, 2.64)
Losartan	61	57,130	19,760.5	1.07 (0.82, 1.37)	3.09 (2.36, 3.97)
Olmesartan	28	63,351	19,420.3	0.44 (0.29, 0.64)	1.44 (0.96, 2.08)
Telmisartan	6	17,643	5,179.8	0.34 (0.13, 0.74)	1.16 (0.43, 2.52)
Valsartan	65	103,884	36,441.7	0.63 (0.48, 0.80)	1.78 (1.38, 2.27)
Aliskiren	7	4,867	1,498.1	1.44 (0.58, 2.96)	4.67 (1.88, 9.63)
β-blockers	467	811,257	245,173.7	0.58 (0.53, 0.63)	1.91 (1.74, 2.09)
Serious angioedema					
ACEIs	224	1,083,869	406,539.2	0.21 (0.18, 0.24)	0.55 (0.48, 0.63)
ARBs	7	269,549	91,583.7	0.03 (0.01, 0.05)	0.08 (0.03, 0.16)
Candesartan	0	5,178	1,694.0	--	--
Eprosartan	0	135	47.8	--	--
Irbesartan	0	22,228	7,447.5	--	--
Losartan	3	57,130	19,776.0	0.05 (0.01, 0.15)	0.15 (0.03, 0.44)
Olmesartan	1	63,351	19,426.6	0.03 (0.00, 0.09)	0.05 (0.00, 0.29)
Telmisartan	0	17,643	5,180.5	--	--
Valsartan	3	103,884	36,456.5	0.03 (0.01, 0.08)	0.08 (0.03, 0.24)
Aliskiren	1	4,867	1,499.4	0.21 (0.01, 1.14)	0.67 (0.03, 3.72)
β-blockers	35	811,257	245,297.4	0.04 (0.03, 0.06)	0.14 (0.20, 0.20)

Table A4. Site-adjusted MS-wide HRs of angioedema and serious angioedema using β-blockers as the referent group, 3/5/2001–12/31/2010

Drug	The case-centered approach	Inverse variance-weighted fixed-effect meta-analysis	N-weighted fixed-effect meta-analysis	Random-effects meta-analysis
Angioedema				
ACEIs	2.70 (2.44, 2.98)	2.58 (2.33, 2.86)	2.68 (2.41, 2.98)	2.58 (2.13, 3.12)
ARBs	1.09 (0.91, 1.31)	1.12 (0.94, 1.34)	1.15 (0.95, 1.39)	1.21 (0.95, 1.55)
Candesartan	1.14 (0.28, 4.60)	1.44 (0.36, 5.82)	1.01 (0.22, 4.77)	1.44 (0.35, 6.02)
Eprosartan	--	--	--	--
Irbesartan	0.92 (0.50, 1.67)	0.93 (0.51, 1.70)	0.86 (0.45, 1.62)	0.93 (0.51, 1.70)
Losartan	1.66 (1.27, 2.18)	1.70 (1.30, 2.22)	1.67 (1.25, 2.22)	1.70 (1.30, 2.22)
Olmesartan	0.82 (0.56, 1.20)	0.81 (0.55, 1.19)	0.82 (0.55, 1.22)	0.81 (0.55, 1.19)
Telmisartan	0.64 (0.29, 1.44)	0.77 (0.34, 1.72)	0.46 (0.15, 1.46)	0.77 (0.34, 1.72)
Valsartan	1.00 (0.76, 1.31)	1.07 (0.82, 1.40)	1.12 (0.85, 1.48)	1.39 (0.77, 2.49)
Aliskiren	2.68 (1.26, 5.68)	2.74 (1.30, 5.81)	2.87 (1.34, 6.14)	2.74 (1.30, 5.81)
Serious angioedema				
ACEIs	3.93 (2.74, 5.63)	3.69 (2.56, 5.30)	3.87 (2.64, 5.69)	3.69 (2.56, 5.30)
ARBs	0.55 (0.24, 1.28)	0.59 (0.26, 1.38)	0.46 (0.18, 1.19)	0.58 (0.21, 1.60)
Candesartan	--	--	--	--
Eprosartan	--	--	--	--
Irbesartan	--	--	--	--
Losartan	1.37 (0.41, 4.55)	1.36 (0.41, 4.50)	1.21 (0.33, 4.42)	1.36 (0.41, 4.50)
Olmesartan	0.80 (0.10, 6.20)	0.67 (0.09, 5.13)	0.67 (0.09, 5.13)	0.67 (0.09, 5.13)
Telmisartan	--	--	--	--
Valsartan	1.15 (0.33, 4.00)	1.49 (0.42, 5.27)	0.75 (0.15, 3.69)	1.34 (0.22, 8.03)
Aliskiren	8.67 (1.11, 67.62)	7.04 (0.92, 54.20)	7.04 (0.92, 54.20)	7.04 (0.92, 54.20)

Table A5. Propensity score-adjusted MS-wide HRs of angioedema and serious angioedema using β-blockers as the referent group, 3/5/2001–12/31/2010 *

Drug	The case-centered approach	Inverse variance-weighted fixed-effect meta-analysis	N-weighted fixed-effect meta-analysis	Random-effects meta-analysis
Angioedema				
ACEIs	2.94 (2.65, 3.27)	2.84 (2.55, 3.15)	2.92 (2.62, 3.263)	2.81 (2.33, 3.38)
ARBs	1.17 (0.97, 1.41)	1.17 (0.97, 1.41)	1.21 (1.00, 1.472)	1.26 (0.98, 1.63)
Candesartan	1.24 (0.31, 4.99)	1.51 (0.37, 6.09)	1.07 (0.23, 5.045)	1.51 (0.37, 6.09)
Eprosartan	--	--	--	--
Irbesartan	0.97 (0.53, 1.78)	0.96 (0.52, 1.76)	0.90 (0.47, 1.70)	0.96 (0.52, 1.76)
Losartan	1.76 (1.33, 2.32)	1.78 (1.35, 2.35)	1.77 (1.32, 2.37)	1.78 (1.35, 2.35)
Olmesartan	0.87 (0.59, 1.29)	0.86 (0.58, 1.27)	0.88 (0.59, 1.31)	0.86 (0.58, 1.27)
Telmisartan	0.68 (0.30, 1.52)	0.80 (0.35, 1.80)	0.49 (0.16, 1.55)	0.80 (0.35, 1.80)
Valsartan	1.07 (0.81, 1.41)	1.12 (0.85, 1.47)	1.17 (0.89, 1.55)	1.42 (0.77, 2.61)
Aliskiren	2.83 (1.33, 6.00)	2.83 (1.33, 6.01)	2.96 (1.38, 6.37)	2.83 (1.33, 6.01)
Serious angioedema				
ACEIs	4.40 (2.74, 5.63)	3.93 (2.70, 5.71)	4.21 (2.84, 6.25)	3.93 (2.70, 5.71)
ARBs	0.55 (0.24, 1.28)	0.60 (0.25, 1.43)	0.46 (0.17, 1.21)	0.59 (0.22, 1.60)
Candesartan	--	--	--	--
Eprosartan	--	--	--	--
Irbesartan	--	--	--	--
Losartan	1.37 (0.41, 4.55)	1.17 (0.34, 3.97)	0.99 (0.26, 3.75)	1.17 (0.34, 3.97)
Olmesartan	0.80 (0.10, 6.20)	0.80 (0.10, 6.36)	0.80 (0.10, 6.36)	0.80 (0.10, 6.36)
Telmisartan	--	--	--	--
Valsartan	1.15 (0.33, 4.00)	1.50 (0.41, 5.48)	0.75 (0.15, 3.79)	1.35 (0.21, 8.54)
Aliskiren	8.67 (1.11, 67.62)	8.53 (1.08, 67.41)	4.21 (2.84, 6.25)	8.53 (1.08, 67.41)

* Adjusted for age, sex, diagnosis of allergic reactions, diabetes, heart failure, and ischemic heart disease, use of prescription non-steroidal anti-inflammatory drugs, and Data Partner site.