# MINI-SENTINEL MEDICAL PRODUCT ASSESSMENT

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

## Version 2

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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.

## History of Modifications

| Version | Date | Modification | By |
|---|---|---|---|
| 2 | 10/10/2012 | • Updated list of codes for allergic reactions in Table 1<br>• Updated page numbers | Mini-Sentinel Angioedema Workgroup |

# MINI-SENTINEL MEDICAL PRODUCT ASSESSMENT

# Protocol for Signal Refinement of Angioedema Events in Association with Use of Drugs That Act on the Renin-Angiotensin-Aldosterone System

**Version 2**

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# I. BACKGROUND

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. 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.[1-4] 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. (Appendix 1), are known to increase the risk of angioedema.[3-6] It is generally believed that ACEIs precipitate angioedema by directly interfering with the degradation of bradykinin, thereby potentiating its biological effect.[3, 4] The incidence rate of angioedema in ACEI users is about 2 per 1,000 person-years, [7, 8] compared with 0.4-0.8 per 1,000 person-years for users of non-ACEI, non-ARB antihypertensive medications.[8] Overall, 1-2 per 1,000 ACEI users may develop angioedema while being treated.[3-5, 8] The risk is the greatest immediately following treatment initiation and gradually diminishes over time but remains higher than no use.[4, 7-9] Some cases become manifest only after a prolonged duration of therapy, sometimes after one year of treatment initiation.[7, 8]

ARBs, of which there are eight marketed in U.S. (Appendix 1), have also been associated with angioedema. Although it is perceived that ARBs are associated with a lower risk of angioedema than ACEIs, data on the true incidence of ARB-induced angioedema are limited, especially for individual ARBs.[10] 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).[11] One study found an incidence rate of 1 per 1,000 person-years of angioedema in the U.S. veterans who received ARBs.[8] The current ARB labeling for risk of angioedema is varied and not consistent in its placement (warnings vs. precautions vs. adverse reactions).

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 is consistent with 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. A recent pooled analysis of randomized trials suggests that the risk of angioedema and urticaria as a combined outcome is similar or lower for aliskiren compared with ACEIs and ARBs.[12]

# II. OVERARCHING GOALS

In keeping with the current goal that Mini-Sentinel (MS) be useful for signal refinement (in the continuum of signal generation, signal refinement, signal evaluation), the objective of this assessment is to explore the differential risks of angioedema by simultaneously assessing the risk associated with ACEIs, ARBs, and aliskiren using a common referent group, β-blockers. The results from this assessment will not be 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 will 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. Another goal of this activity is to build general strategies in Mini-Sentinel for signal refinement regarding medical products for which substantial post-market experience has accrued.

# III. QUESTION OF INTEREST

This assessment is interested in the following question: Are ACEIs, ARBs or aliskiren associated with a similar risk of angioedema when compared with a common referent group, β-blockers? To address the question this protocol examines ACEIs as a class, ARBs both as a class and as individual molecular entities, aliskiren, and β-blockers as a class.

# IV. ASSESSMENT PLAN

## A. DATA SOURCE

This assessment will include all Data Partners contributing data to the Mini-Sentinel Distributed Database (MSDD).

## B. IDENTIFICATION OF NEW-USERS OF DRUGS OF INTEREST

We propose to use a "new-user" cohort design.[13] We will identify health plan members aged 18 years or older with a first prescription of an oral formulation of ACEIs, ARBs (except azilsartan), aliskiren, or β-blockers (as either single ingredient or combination products, except in combination with another drug of interest). Azilsartan was approved on February 25, 2011 and is therefore not available in the MSDD at the time of this assessment. We refer to the dispensing date of the first prescription as the *index date*. We will require eligible individuals to meet all of the following criteria during the 183-day period prior to the index date: 1) continuous health plan enrollment, pharmacy and medical benefit; 2) no prescription of any of the drugs of interest; and 3) no diagnosis of angioedema. We will exclude individuals who initiated more than one drug of interest on the index date. Gaps of 45 days or less in enrollment,

pharmacy or medical benefit will be ignored because they usually represent administrative gaps rather than actual disenrollment. For each individual, if there is more than one new-use episode that meets the inclusion criteria, only the first episode will be used.

The first workplan (Appendix 2) will provide information on the use of drugs of interest by Data Partner. After examining results several decisions will be made as to whether there is:

1. A temporal trend in the incidence of angioedema in the referent group – new users of β-blockers; and

2. An 80% statistical power to detect a hazard ratio of 2.

If there is a temporal trend in the incidence of angioedema in new users of β-blockers, we will include calendar year in the list of potential confounders (see below). If the number of new users identified with the proposed definition does not result in sufficient power we will consider an alternate definition that allows patients to have a dispensing of another drug(s) of interest during the 183-day baseline period prior to the first dispensing of a drug of interest. If it is determined that we have to use this definition, prior use of other drugs of interest will be adjusted for in the analysis. A crude site-specific hazard ratio (HR) of 2 is reasonable because the incidence rate was estimated to be 0.5 per 1,000 person-years for β-blockers, 1 per 1,000 person-years for ARBs and 2 per 1,000 person-years for ACEIs in a large study.[8]

## C. IDENTIFICATION OF OUTCOMES OF INTEREST

The primary outcome of interest is angioedema, which will be 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 visit. The positive predictive value of this algorithm to identify angioedema in administrative claims data is high, ranging from 90%[7, 14] to 95%.[8] The secondary outcome of interest is serious angioedema, defined as angioedema with airway obstruction requiring inpatient care. We will identify 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.[8, 15, 16] A list of procedure codes to identify these events can be found in Appendix 3.

## D. POTENTIAL CONFOUNDERS

Table 1 lists the baseline variables ascertained during the 183-day period preceding the index date that will be adjusted for in the analyses. Age on the index date and sex will be determined from the MSDD's demographic file. Conditions listed in Table 1 will be identified by ICD-9-CM diagnosis codes recorded during an outpatient, inpatient, or emergency department visit from the MSDD's diagnosis file. Use of prescription non-steroidal anti-inflammatory drugs will be ascertained from MSDD's outpatient pharmacy dispensing file using National Drug Codes; over-the-counter use will not be captured.

Previous studies have suggested that African-American race may be a strong risk factor for angioedema.[7-9, 17-19] Race information is not uniformly collected in all the Data Partners, with large percentages of "unknown" race at most sites. Analyses focused on race were considered seriously by the workgroup, but race will not be adjusted for due to the sparsity of race data across Data Partners, and the likelihood that results of such analyses would be biased and misleading. Other potential

confounders that are commonly used in pharmacoepidemiologic studies, such as the number of outpatient visits or medications used (as proxies for general health status), were discussed but not included in this assessment because existing literature does not show an association with angioedema.

If there is a temporal trend in the incidence of angioedema, the analyses will further adjust for calendar year. Should calendar year be included in the list of confounders, we will examine the temporal trend and determine the functional form of calendar year in the regression models (e.g., linear, categorical).

**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 years | |
| Sex | Male/Female | |
| Diagnosis of | | Recorded at least once in an outpatient, inpatient, or emergency department visit |
| Allergic reactions[9] | Yes/No | ICD-9-CM codes 477.x, 518.6, 558.3, 691.x, 692.xx (except 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[8, 20] | Yes/No | ICD-9-CM code 250 |
| Heart failure[8] | Yes/No | ICD-9-CM code 402.x1, 404.x1, 404.x3, 428.xx |
| Ischemic heart disease[8] | Yes/No | ICD-9-CM codes 410-414 |
| Use of non-steroidal anti-inflammatory drugs[1] | Yes/No | National drug codes obtained from the FirstDataBank |

## E. FOLLOW-UP

We will follow the new users from the index date until the earliest occurrence of the first angioedema diagnosis, 365 days of follow-up, initiation of another drug of interest, cessation of use of drug of interest, death, disenrollment from the health plan, end of medical benefit, or December 31, 2010. Cessation of use occurs when a patient's days supplied appears to have been exhausted for at least 14 days. We chose a maximal follow-up of 365 days because we are interested in the immediate and intermediate risk of angioedema associated with these medications.

## F. STATISTICAL ANALYSIS

### 1. Overview

There are two co-primary assessments in this project. The first assessment will include all new users of ACEIs, ARBs, and β-blockers from January 1, 2001 to December 31, 2010. The second assessment will include all new users of ACEIs, ARBs, aliskiren, and β-blockers between March 5, 2007 (FDA approval

date of aliskiren) and December 31, 2010 to allow comparable temporal drug use and outcome to be examined.

Analyses will first be performed at individual Data Partner sites. Site-specific estimates or aggregate data from each site will then be transferred to the Mini-Sentinel Operations Center (MSOC) for further analyses to create MS-wide estimates. The workgroup will work closely with the MSOC to develop distributed SAS programs (Appendix 2) that will enable the Data Partners to send to the MSOC 1) summary counts for descriptive analyses; and 2) SAS output and log files; and 3) a pre-specified aggregate-level dataset for additional statistical analyses. As described below, none of the analyses will require the Data Partners to transfer individual-level data.

We will perform the analyses for all eligible patients, and by age group (18-44, 45-54, 55-64, and ≥65 years), sex, and follow-up period. We will estimate the average HRs for 0-30, 31-60, 61-90, 91-180, 181-270, and 271-365 days after the index date. Although dividing follow-up into distinct periods is commonly done, this approach may be subject to "depletion of susceptibles" or selection bias.[21] Therefore, we will also estimate the average HRs for 0-30, 0-60, 0-90, 0-180, and 0-270 days following the index date.

### 2. Comparison of baseline characteristics

We will compare the baseline characteristics of new users of ARBs, ACEIs, and aliskiren separately with new users of β-blockers. We will do this, both at the individual-site level and across Data Partners, by requesting summary counts from each Data Partner (to obtain the site-specific results), and by combining these summary counts (to obtain the MS-wide results). At each site and for all sites combined, we will examine 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 (Table 2, using ACEI initiators as an example).[22] We chose standardized difference because it is less sensitive to sample size and reflects the magnitude of relative differences. In looking at data combined across Data Partners, differences in health care environments and in relative numbers of members will guide interpretation of results.

**Table 2. Baseline characteristics of ACEI initiators and β-blockers initiators**

| Characteristics | ACEI initiators | β-blockers initiators | Standardized differences |
|---|---|---|---|
| Age (years) | | | |
| 18-44 | | | |
| 45-54 | | | |
| 55-64 | | | |
| ≥65 | | | |
| Female sex | | | |
| Race * | | | |
| African American | | | |

| Characteristics | ACEI initiators | β-blockers initiators | Standardized differences |
|---|---|---|---|
| American Indian or Alaska Native | | | |
| Asian American | | | |
| Native Hawaiian or other Islander | | | |
| White | | | |
| Unknown | | | |
| Diagnosis of † | | | |
| Allergic reactions | | | |
| Diabetes | | | |
| Heart failure | | | |
| Ischemic heart disease | | | |
| Use of prescription non-steroidal anti-inflammatory drugs | | | |
| Prior use of ‡<br>ACEIs<br>ARBs<br>Aliskiren<br>ß-blockers | | | |

* Race will not be adjusted for in the analyses due to the high percentage of unknown entries at many sites. It is included in the table to characterize the extent of missingness.

† Recorded at least once in an outpatient, inpatient, or emergency department visit during the 183-day period preceding the index date.

‡ Determined during the 183-day period preceding the index date. This row only applies to "alternative new users" (i.e., patients who met all the eligibility criteria except that they had one or more dispensings of another drug(s) of interest during the 183-day period prior to the first dispensing of a drug of interest).

Note: Each drug-pair (ACEIs as a class–β-blockers, ARBs as a class–β-blockers, and aliskiren–β-blockers) will have a separate table. We will create a separate set of tables for each of the two co-primary assessments. Each site will create each of these tables separately. The MSOC will combine site-specific summary counts to obtain MS-wide estimates.

## 3. Calculation of incidence and incidence rate of angioedema

We will calculate the 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) (Table 3). Each Data Partner will send its site-specific summary counts to the MSOC, who will then sum up the number of angioedema cases and the persons or persons-years from all sites to obtain the MS-wide estimates.

**Table 3. Overall incidence and incidence rate of angioedema and serious angioedema by drug class and individual ARB**

| Drugs | Number of events | Persons | Person-years | Incidence per 1,000 persons (95% CI) | Incidence rate per 1,000 person-years (95% CI) |
|---|---|---|---|---|---|
| **Angioedema** | | | | | |
| ACEIs | | | | | |
| ARBs | | | | | |
| Candesartan | | | | | |
| Eprosartan | | | | | |
| Irbesartan | | | | | |
| Losartan | | | | | |
| Olmesartan | | | | | |
| Telmisartan | | | | | |
| Valsartan | | | | | |
| Aliskiren | | | | | |
| β-blockers | | | | | |
| **Serious angioedema** | | | | | |
| ACEIs | | | | | |
| ARBs | | | | | |
| Candesartan | | | | | |
| Eprosartan | | | | | |
| Irbesartan | | | | | |
| Losartan | | | | | |
| Olmesartan | | | | | |
| Telmisartan | | | | | |
| Valsartan | | | | | |
| Aliskiren | | | | | |
| β-blockers | | | | | |

Whenever possible, we will create a table for 1) all patients, 2) each age group (18-44, 45-54, 55-64, and ≥65 years), 3) each sex, 4) each calendar year (2001 to 2010), and 5) each follow-up period (0-30, 31-60, 61-90, 91-180, 181-270, and 271-365 days; and 0-30, 0-60, 0-90, 0-180, and 0-270 days). We will create a separate set of tables for each of the two co-primary assessments, and for both new users and "alternative" new users. Each site will create these tables separately. The MSOC will combine site-specific summary counts to obtain MS-wide estimates.

### 4. Crude analysis comparing the risk of angioedema of each drug/drug class with β-blockers

**Site-specific estimates.** We will work with the MSOC to develop a distributed SAS program that will allow each site to estimate the crude HR and 95% CI of angioedema using β-blockers as the referent group (Table 4). Specifically, each site will 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. The Cox model will include an indicator variable for drug exposure (e.g., 1 for ACEIs and 0 for β-blockers) as the only independent variable. In both the crude and adjusted analyses, as well as both the site-specific and MS-wide analyses, the time scale for the Cox models will be time since the index date. The Data Partners will run the distributed program, and then send the SAS output and log files, and a pre-specified aggregate-level dataset to the MSOC for further analyses. The aggregate-level dataset will include one record per risk set, each is anchored by an angioedema case, and will be used in both the crude and adjusted analyses described below (Appendix 2).

**Table 4. Site-specific crude and adjusted HRs (95% Cls) of angioedema and serious angioedema using β-blockers as the referent group**

| Drugs | Crude HR (95% CI) | Adjusted HR (95% CI) | | |
|---|---|---|---|---|
| | | PS-stratified Cox model | The Fireman case-centered logistic model | Multivariable-adjusted Cox model |
| **Angioedema** | | | | |
| ACEIs | | | | |
| ARBs | | | | |
| Candesartan | | | | |
| Eprosartan | | | | |
| Irbesartan | | | | |
| Losartan | | | | |
| Olmesartan | | | | |
| Telmisartan | | | | |
| Valsartan | | | | |
| Aliskiren | | | | |
| **Serious angioedema** | | | | |
| ACEIs | | | | |
| ARBs | | | | |
| Candesartan | | | | |
| Eprosartan | | | | |
| Irbesartan | | | | |

| Drugs | Crude HR (95% CI) | Adjusted HR (95% CI) | | |
|---|---|---|---|---|
| | | PS-stratified Cox model | The Fireman case-centered logistic model | Multivariable-adjusted Cox model |
| Losartan | | | | |
| Olmesartan | | | | |
| Telmisartan | | | | |
| Valsartan | | | | |
| Aliskiren | | | | |

Whenever possible, we will create a table for: (1) all patients; (2) each age group (18-44, 45-54, 55-64, and ≥65 years); (3) each sex; (4) each calendar year (2001 to 2010); and (5) each follow-up period (0-30, 31-60, 61-90, 91-180, 181-270, and 271-365 days; and 0-30, 0-60, 0-90, 0-180, and 0-270 days). We will create a separate set of tables for each of the two co-primary assessments. Each site will create these tables separately. The MSOC will combine site-specific results to obtain MS-wide estimates.

**MS-wide estimates.** We will use two methods to obtain the "crude" MS-wide estimates. (Note: The MS-wide analysis will adjust for Data Partner site, therefore the estimates are not strictly "crude".) The first method is based on the case-centered logistic regression approach developed by Fireman et al.[23] In this approach, we will use the pre-specified summary-level dataset sent by the Data Partners to fit a logistic model, separately for each drug pair of interest. In the ACEI–ß-blocker pair, for example, the outcome variable in the logistic model will be whether the angioedema case was exposed to an ACEI, the independent variable – to be specified as an offset in the model – will be the log odds of the site-specific proportion of individuals in the risk set who were ACEI users. The model will also include Data Partner site as a stratification variable. As shown by Fireman et al, such model maximizes the same likelihood as a stratified Cox regression model, and both yield the same parameter estimates.[23]

In the second method, we will perform a meta-analysis using both fixed-effect and random-effects model to pool the crude site-specific estimates obtained from the SAS output files. The MS-wide HR will be calculated as a weighted average of the site-specific HRs using the inverse of the site-specific variance as the weight.[24-26] As a secondary analysis, we will use the site-specific sample size as the weight.

### 5. Adjusted analysis comparing the risk of angioedema of each drug/drug class with β-blockers

**Site-specific estimates.** We will use a propensity score (PS)-stratified approach and a multivariable-adjusted approach to obtain the adjusted site-specific estimates. The PS[27, 28] will be the probability of initiating a β-blocker, which will be estimated by a logistic regression model fit separately for the ACEI–β-blocker pair, the ARB–β-blocker pair, and the aliskiren–β-blocker pair at each site. The PS model will include the variables listed in Table 1 and will be common across all Data Partners. This approach lets each site fit the same PS model but allows the coefficients to vary by site. We will work with the MSOC to develop a distributed SAS program that will allow each site to fit 1) the PS model; 2) a PS-stratified Cox model that will include an indicator variable for drug exposure as an independent variable and the PS (in quintiles) as a stratification variable; 3) a case-centered logistic model with the risk set of each angioedema case identified from individuals with the same PS quintile as the case; and 4) a multivariable-adjusted Cox model that will include an indicator variable for drug exposure plus the

variables listed in Table 1 as the independent variables. In theory, models 2 and 3 should yield identical results. We will use this comparison to verify the validity of the Fireman approach.

The adjusted analyses of individual ARBs will use the PS estimated from the entire drug class because this PS will be more stable than the PS estimated with individual ARBs. All pre-specified subgroup analyses will use the PS estimated from the entire study cohort. The Data Partners will run the distributed program, and then send the SAS output and log files from these models to the MSOC.

**MS-wide estimates.** We will use two methods to obtain the adjusted MS-wide estimates. In the first method, we will use the pre-specified aggregate-level dataset described above to fit a case-centered logistic regression model (which is equivalent to a stratified Cox model), separately for each drug pair of interest. The model will be identical to the one described in the "crude" MS-wide analysis, except that the log odds will be calculated at each site among individuals in the same PS quintile as the case who were at risk of angioedema at the time the case occurred.

In the second method, we will perform a meta-analysis using both fixed-effect and random-effects model to pool the site-specific HRs from the multivariable-adjusted analysis obtained from the SAS output files. The MS-wide HR will be calculated as a weighted average of the site-specific HRs using the inverse of the site-specific variance as the weight.[24-26] As a secondary analysis, we will use the site-specific sample size as the weight.

### 6. Comparison of methods

We will compare 1) the adjusted site-specific estimates from the PS-stratified Cox model, the Fireman approach, and the multivariable-adjusted Cox model performed locally at each site; and 2) the adjusted MS-wide estimates from the Fireman approach and the meta-analysis performed at the MSOC.

## V. RATIONALE FOR USING THE PROPOSED ANALYTIC STRATEGIES AND ALTERNATIVE APPROACHES CONSIDERED

One of the goals of this activity is to build general strategies for signal refinement regarding medical products for which substantial post-market experience has accrued. Performing a centralized, conventional multivariable-adjusted analysis to obtain MS-wide estimates may not be the preferred approach because it requires transferring of potentially identifiable individual-level information. On the other hand, methods that obscure individual-level characteristics into summary measures (e.g., PS, disease risk score) are viable alternatives because they reduce or eliminate the need for transferring potentially identifiable information while achieving a similar degree of confounding adjustment.[29] As shown by Fireman et al.,[23] a PS-stratified Cox regression analysis can be performed with only aggregate-level data using a case-centered logistic regression approach.

Additionally, multivariable-adjusted analysis may lead to unstable estimates if the outcome is rare. PS analysis avoids this problem by modeling the relation between the confounders and the exposure, which is often more "common" than the outcome for medical products that have been on the market for a number of years.

To obtain MS-wide estimates, site-specific results may also be combined by meta-analysis,[30] which obviates the need to share either individual-level or aggregate-level dataset. The current assessment will

compare the results from meta-analysis and an analysis that uses the site-specific aggregate-level dataset to inform future signal refinement activities.

The workgroup discussed the following approaches but determined that these approaches were less preferable than the proposed analytic strategy for the purpose of this assessment:

1. PS matching. This approach has several advantages for binary exposures.[29, 31] When there are multiple exposures, as in this assessment, 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 will ensure the same referent population is used for all analyses, but this may substantially reduce the number of patients in the final analyses, as users of aliskiren is expected to be much lower than others.
2. Disease risk score. The risk factors for angioedema are not well-known, therefore constructing a disease risk score would be difficult.

## VI. POWER CALCULATION

To calculate the statistical power, we assume α=0.05 and a two-sided significance level. We assume an incidence rate of 0.5 per 1,000 person-years among β-blockers users, an estimate obtained from a study by Miller et al, the largest study published to date,[8] and an exponential hazard of 0.105 for loss-to-follow-up (i.e., 10% loss-to-follow-up rate by the end of one year). If we have the same number of β-blockers users and comparator users, we will need a sample size of about 49,000 to have an 80% statistical power to detect a HR of 2 (Table 5). A HR of 2 is considered reasonable because the incidence rate was estimated to be 1 per 1,000 person-years in ARB users and 2 per 1,000 person-years in ACEI users in the Miller study.[8]

**Table 5. Number of users (x1,000) required to have a statistical power of 80% to detect a given hazard ratio**

| Ratio (Comparator:β-blocker) | Hazard ratio | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1.1 | 1.2 | 1.3 | 1.4 | 1.5 | 1.6 | 1.7 | 1.8 | 1.9 | 2.0 |
| 1:1 | 3,459 | 906 | 421 | 247 | 165 | 119 | 91 | 72 | 59 | 49 |
| 2:1 | 2,636 | 700 | 329 | 196 | 132 | 96 | 74 | 59 | 49 | 41 |
| 1:2 | 5,107 | 1,318 | 604 | 350 | 231 | 165 | 124 | 98 | 79 | 66 |

## VII. LIMITATIONS

1. Residual confounding may be a threat to the validity of our analysis. Most notably, previous studies have suggested that African-American race may be a strong risk factor for angioedema.[7-9, 17-19] Race information is extremely sparse across the vast majority of Data Partners and is therefore not adjusted for in this assessment. Smoking is another variable not available to us that has also been suggested to be a confounder.[18-20]

2. The sample size may be limited in the analyses of individual drugs or at certain Data Partner sites.

3. A 183-day look-back period may not be sufficient to identify all previous angioedema, which may predict both the risk of subsequent angioedema and the choice of antihypertensive medication. The workgroup chose 183 days because it is sufficient to identify a majority of recently occurred angioedema that are mostly likely to affect prescribing, while ensuring that not too many individuals will be excluded as a result of longer enrollment requirement.

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# IX. APPENDICES

## A. APPENDIX A: LIST OF ANTIHYPERTENSIVE MEDICATIONS OF INTEREST (AND THEIR FDA APPROVAL DATE)

| Angiotensin converting enzyme inhibitors | Angiotensin receptor blockers | Direct renin inhibitors | B-blockers |
|---|---|---|---|
| Benazepril (6/25/91) | Candesartan (6/4/98) | Aliskiren (3/5/07) | Acebutolol (12/28/84) |
| Captopril (4/6/81) | Eprosartan (12/22/97) | | Atenolol (8/19/81) |
| Enalapril (12/24/85) | Irbesartan (9/30/97) | | Bisoprolol (7/31/92) |
| Fosinopril (5/16/91) | Losartan (4/14/95) | | Carvedilol (9/14/95) |
| Lisinopril (12/29/87) | Olmesartan (4/25/02) | | Labetalol (8/1/84) |
| Moexipril (4/19/95) | Telmisartan (11/10/98) | | Metoprolol (8/7/78) |
| Quinapril (11/19/91) | Valsartan (12/23/96) | | Nebivolol (12/17/07) |
| Perindopril (12/30/93) | Azilsartan (2/25/11)* | | Pindolol (9/3/82) |
| Ramipril (1/28/91) | | | Propranolol (11/13/67) |
| Trandolapril (4/26/96) | | | Timolol (11/25/81) |

* Will not be included in this assessment

## B. APPENDIX B: SCOPE OF PROGRAMMING WORK FOR DATA PARTNERS

The Data Partners will run up to three workplans. All programs will be written in SAS using the Mini-Sentinel Common Data Model. Each program will be written and tested at the MSOC and 1-2 Data Partners prior to full distribution. The Data Partners are expected to implement the distributed SAS programs, review results of each program in consultation with the MSOC and the workgroup, and help trouble-shoot site-specific problems that may arise. **No individual-level information** will be transferred from the Data Partners to the MSOC.

### 1. Workplan 1

The distributed program for workplan 1 will ask the Data Partners to

1. **Identify new-user cohorts and document the number of individuals excluded at each step**:
    a. Identify health plans members aged ≥18 years between Jan 1, 2001 and Dec 31, 2010.
    b. Further restrict to those who had a dispensing of any of the drugs of interest.
    c. Further restrict to those who had at least 183 days of continuous enrollment, pharmacy and medical benefit prior to the first dispensing of any of the drug of interest (index date).
    d. Further restrict to those who had no dispensing of any drug of interest during the 183-day period preceding the index date.
    e. Further restrict to those who had no diagnosis of angioedema during the 183-day period preceding the index date.
    f. Exclude those who initiated more than one drug of interest on the index date.
    g. If there are more than one new-use episode that meets the inclusion criteria, use only the first one.
2. **Identify "alternative new-user" cohorts**, which comprise patients who met all the eligibility criteria above, except that they had one or more dispensings of another drug(s) of interest during the 183-day period prior to the first dispensing of a particular drug of interest.
3. **Describe the new-user and "alternative new-user" cohorts** with respect to the distributions of potential confounders. Refer to Table 2 in the text. Note that for the alternative new users, Table 2 will include an additional row for prior use of ACEIs, ARBs, aliskiren, or ß-blockers.
4. **Calculate the total qualifying persons, person-years, incidence (per 1,000 persons) and incidence rate (per 1,000 person-years) of angioedema and serious angioedema and their 95% confidence intervals** during the follow-up period for both new users and alternative new users of each drug or drug class of interest. The program will also calculate, for each individual site, the incidence rates by age group, sex, calendar year, and follow-up period.
5. **Prepare summary outputs from steps #3 and #4 to be sent to the MSOC.**

## 2. Workplan 2

The distributed program for workplan 2 will ask the Data Partners to

1. **Run a PS model and prepare the SAS output and log files to be sent to the MSOC**. Fit a logistic model to estimate the PS (i.e., the probability of initiating a β-blocker, separately for the ACEI–β-blocker pair, the ARB–β-blocker pair, and the aliskiren–β-blocker pair). The PS model will be common to all Data Partners (see Table 1 in the text for the variables to be included in the PS model).

2. **Run a site-specific PS-stratified Cox model, a case-centered logistic model, and a multivariable-adjusted Cox model. Prepare the SAS output and log files of each model to be sent to the MSOC.**

3. **Prepare an aggregate-level dataset** to be sent to the MSOC. An indicator variable for site will be created by the MSOC upon receiving the data.

**Variables requested:**

| Variable | Definition | Comment |
|---|---|---|
| **Flag** | An indicator for the type of pre-specified analyses | **0**:All; **1**:18-44 years; **2**:45-54 years; **3**: 55-64 years; **4**: ≥65 years; **5**:Male; **6**: Female; **7:** March 2007 and after |
| **Case_Exp** | Exposure status of the angioedema case | **0**:β-blocker; **1**:ACEI; **2**:ARB; **3**:Aliskiren |
| **Ind_ARB** | The specific ARB being compared with β-blockers | **1**:Candesartan; **2**:Eprosartan; **3**:Irbesartan; **4**:Losartan; **5**:Olmesartan; **6**:Telmisartan; **7**:Valsartan; missing if Case_Exp=1 or 3 |
| **Period** | Follow-up in months when angioedema occurred | Range from 1 to 12 |
| **INPT_ED** | Angioedema diagnosed in an inpatient or ED visit | **1**:Yes; **0**:No |
| **Serious** | Serious angioedema | **1**:Yes; **0**:No |
| **P1-P3** | Proportion in risk set who used ACEI (P1), ARB (P2) or aliskiren (P3) | If the angioedema case was exposed to β-blockers, then P1-P3 will be non-missing. If the case was exposed to Drug *x*, then only P*x* will be non-missing |

**Sample summary-level dataset:**[23]

| Flag | Case_Exp | Ind_ARB | INP_ED | Period | Serious | P1 | P2 | P3 |
|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 1 | 0 | 1 | 0 | .53 | .25 | .11 |
| 1 | 2 | 6 | 0 | 1 | 0 | . | .33 | . |
| 1 | 1 | . | 1 | 1 | 1 | .45 | . | . |

Each row represents an angioedema case. The risk set includes all individuals in the same PS quintile who were at risk of angioedema at the time the case occurred.

## 3. Workplan 3

To be determined. This workplan will be informed by the findings from Workplan 2. We expect Workplan 3, if needed, to include modified analysis from Workplan 2 and/or sensitivity analysis.

## C. APPENDIX C: PROCEDURE CODES FOR EVENTS INDICATING SERIOUS ANGIOEDEMA

| Event | Code type | Code | Short description | Full description |
|---|---|---|---|---|
| ICU Admission | CPT-4 | 99220 | INITIAL OBSERVATION CARE | Initial observation care, per day, for the evaluation and management of a patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the problem(s) requiring admission to "observation status" are of high severity. |
| ICU Admission | CPT-4 | 99224 | SUBSEQUENT OBSERVATION CARE | Subsequent observation care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: Problem focused interval history; Problem focused examination; Medical decision making that is straightforward or of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the patient is stable, recovering, or improving. Physicians typically spend 15 minutes at the bedside and on the patient's hospital floor or unit. |
| ICU Admission | CPT-4 | 99225 | SUBSEQUENT OBSERVATION CARE | Subsequent observation care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the patient is responding inadequately to therapy or has developed a minor complication. Physicians typically spend 25 minutes at the bedside and on the patient's hospital floor or unit. |
| ICU Admission | CPT-4 | 99226 | SUBSEQUENT OBSERVATION CARE | Subsequent observation care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: A detailed interval history; A detailed examination; Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the patient is unstable or has developed a significant complication or a significant new problem. Physicians typically spend 35 minutes at the bedside and on the patient's hospital floor or unit. |

| Event | Code type | Code | Short description | Full description |
|---|---|---|---|---|
| ICU Admission | CPT-4 | 99221 | INITIAL HOSPITAL CARE | Initial hospital care, per day, for the evaluation and management of a patient, which requires these 3 key components: A detailed or comprehensive history; A detailed or comprehensive examination; and Medical decision making that is straightforward or of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the problem(s) requiring admission are of low severity. Physicians typically spend 30 minutes at the bedside and on the patient's hospital floor or unit. |
| ICU Admission | CPT-4 | 99222 | INITIAL HOSPITAL CARE | Initial hospital care, per day, for the evaluation and management of a patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the problem(s) requiring admission are of moderate severity. Physicians typically spend 50 minutes at the bedside and on the patient's hospital floor or unit. |
| ICU Admission | CPT-4 | 99223 | INITIAL HOSPITAL CARE | Initial hospital care, per day, for the evaluation and management of a patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the problem(s) requiring admission are of high severity. Physicians typically spend 70 minutes at the bedside and on the patient's hospital floor or unit. |
| ICU Admission | CPT-4 | 99291 | CRITICAL CARE FIRST HOUR | Critical care, evaluation and management of the critically ill or critically injured patient; first 30-74 minutes |
| ICU Admission | CPT-4 | 99292 | CRITICAL CARE ADDL 30 MIN | Critical care, evaluation and management of the critically ill or critically injured patient; each additional 30 minutes (List separately in addition to code for primary service) |
| Intubation | CPT-4 | 31502 | CHANGE OF WINDPIPE AIRWAY | Tracheotomy tube change prior to establishment of fistula tract |
| Intubation | CPT-4 | 31500 | INSERT EMERGENCY AIRWAY | Intubation, endotracheal, emergency procedure |
| Intubation | CPT-4 | 91000 | ESOPHAGEAL INTUBATION | Esophageal intubation and collection of washings for cytology, including preparation of specimens |

| Event | Code type | Code | Short description | Full description |
|---|---|---|---|---|
| | | | | (separate procedure) |
| Intubation | ICD-9-CM_PX | 31.99 | OTHER OPERATIONS ON TRACHEA | Other operations on trachea |
| Intubation | ICD-9-CM_PX | 96 | NONOPERATIVE INTUBATION&IRRIGATION | Nonoperative intubation and irrigation |
| Intubation | ICD-9-CM_PX | 96.0 | NONOP INTUBAT GI&RESPIRATORY TRACTS | Nonoperative intubation of gastrointestinal and respiratory tracts |
| Intubation | ICD-9-CM_PX | 96.01 | INSERTION OF NASOPHARYNGEAL AIRWAY | Insertion of nasopharyngeal airway |
| Intubation | ICD-9-CM_PX | 96.02 | INSERTION OF OROPHARYNGEAL AIRWAY | Insertion of oropharyngeal airway |
| Intubation | ICD-9-CM_PX | 96.03 | INSERTION ESOPH OBTURATOR ARWAY | Insertion of esophageal obturator airway |
| Intubation | ICD-9-CM_PX | 96.04 | INSERTION OF ENDOTRACHEAL TUBE | Insertion of endotracheal tube |
| Intubation | ICD-9-CM_PX | 96.05 | OTHER INTUBATION RESPIRATORY TRACT | Other intubation of respiratory tract |
| Intubation | ICD-9-CM_PX | 96.06 | INSERTION OF SENGSTAAKEN TUBE | Insertion of Sengstaken tube |
| Intubation | ICD-9-CM_PX | 96.56 | OTHER LAVAGE OF BRONCHUS&TRACHEA | Other lavage of bronchus and trachea |
| Intubation | ICD-9-CM_PX | 96.7 | OTHER CONT INVASIVE MECHANICAL VENT | Other continuous invasive mechanical ventilation |
| Intubation | ICD-9-CM_PX | 96.70 | CONT INVASIVE MECH VENT UNSP DUR | Continuous invasive mechanical ventilation of unspecified duration |
| Intubation | ICD-9-CM_PX | 96.71 | CONT INVASV MECH VENT <96 CONSEC HR | Continuous invasive mechanical ventilation for less than 96 consecutive hours |
| Intubation | ICD-9-CM_PX | 96.72 | CONT INVASV MECH VENT 96 CONSEC HR> | Continuous invasive mechanical ventilation for 96 consecutive hours or more |
| Intubation | HCPCS | A0396 | ALS SPCLIZD SRVC DISPBL SPL;INTUBAT | ALS specialized service disposable supplies; esophageal intubation |
| Laryngoscopy | CPT-4 | 31231 | NASAL ENDOSCOPY DX | Nasal endoscopy, diagnostic, unilateral or bilateral (separate procedure) |
| Laryngoscopy | CPT-4 | 31505 | DIAGNOSTIC LARYNGOSCOPY | Laryngoscopy, indirect; diagnostic (separate procedure) |
| Laryngoscopy | CPT-4 | 31525 | DX LARYNGOSCOPY EXCL NB | Laryngoscopy direct, with or without tracheoscopy; diagnostic, except newborn |
| Laryngoscopy | CPT-4 | 31526 | DX LARYNGOSCOPY | Laryngoscopy direct, with or without tracheoscopy; |

| Event | Code type | Code | Short description | Full description |
|---|---|---|---|---|
| | | | W/OPER SCOPE | diagnostic, with operating microscope or telescope |
| Laryngoscopy | CPT-4 | 31527 | LARYNGOSCOPY FOR TREATMENT | Laryngoscopy direct, with or without tracheoscopy; with insertion of obturator |
| Laryngoscopy | CPT-4 | 31528 | LARYNGOSCOPY AND DILATION | Laryngoscopy direct, with or without tracheoscopy; with dilation, initial |
| Laryngoscopy | CPT-4 | 31529 | LARYNGOSCOPY AND DILATION | Laryngoscopy direct, with or without tracheoscopy; with dilation, subsequent |
| Laryngoscopy | CPT-4 | 31560 | LARYNGOSCOP W/ARYTENOIDECTOM | Laryngoscopy, direct, operative, with arytenoidectomy; |
| Laryngoscopy | CPT-4 | 31561 | LARYNSCOP REMVE CART + SCOP | Laryngoscopy, direct, operative, with arytenoidectomy; with operating microscope or telescope |
| Laryngoscopy | ICD-9-CM_PX | 31.42 | LARYNGOSCOPY AND OTHER TRACHEOSCOPY | Laryngoscopy and other tracheoscopy |
| Tracheostomy | CPT-4 | 31615 | VISUALIZATION OF WINDPIPE | Tracheobronchoscopy through established tracheostomy incision |
| Tracheostomy | CPT-4 | 31603 | INCISION OF WINDPIPE | Tracheostomy, emergency procedure; transtracheal |
| Tracheostomy | CPT-4 | 31605 | INCISION OF WINDPIPE | Tracheostomy, emergency procedure; cricothyroid membrane |
| Tracheostomy | CPT-4 | 31610 | INCISION OF WINDPIPE | Tracheostomy, fenestration procedure with skin flaps |
| Tracheostomy | CPT-4 | 31612 | PUNCTURE/CLEAR WINDPIPE | Tracheal puncture, percutaneous with transtracheal aspiration and/or injection |
| Tracheostomy | ICD-9-CM_PX | 31.1 | TEMPORARY TRACHEOSTOMY | Temporary tracheostomy |
| Tracheostomy | ICD-9-CM_PX | 31.2 | PERMANENT TRACHEOSTOMY | Permanent tracheostomy |
| Tracheostomy | ICD-9-CM_PX | 31.21 | MEDIASTINAL TRACHEOSTOMY | Mediastinal tracheostomy |
| Tracheostomy | ICD-9-CM_PX | 31.29 | OTHER PERMANENT TRACHEOSTOMY | Other permanent tracheostomy |
| Tracheostomy | ICD-9-CM_DX | V44.0 | TRACHEOSTOMY STATUS | Tracheostomy status |
| Tracheostomy | ICD-9-CM_DX | V55.0 | ATTENTION TO TRACHEOSTOMY | Attention to tracheostomy |

Serious angioedema, defined as angioedema with airway obstruction requiring inpatient care, will be identified by an inpatient ICD-9-CM code 995.1 recorded at any position plus a code indicating intensive care unit (ICU) admission, intubation, tracheostomy, or laryngoscopy occurring within two days of the date of hospital admission.

CPT-4: Current Procedural Terminology, 4th Edition

ICD-9-CM PX: International Classification of Diseases, 9th Revision, Clinical Modification procedure codes

ICD-9-CM DX: International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes