

# Assessment of the US Food and Drug Administration's Sentinel analysis tools: angiotensin-converting enzyme inhibitors and angioedema

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5. Food and Drug Administration, Silver Spring, MD



# Disclosure

- The Mini-Sentinel program was funded by the U.S. Food and Drug Administration through the Department of Health and Human Services contract number HHSF223200910006I
- The views expressed in this paper are those of the authors and are not intended to convey official U.S. Food and Drug Administration (FDA) policy or guidance
- All authors have been involved with the development and operation of the Sentinel System
- Drs. Gagne, Wang, and Schneeweiss are consultant to Aetion, Inc., and Dr. Schneeweiss reports owning shares of Aetion, Inc.
- Dr. Gagne is a consultant to Optum, Inc.
- Dr. Schneeweiss is a consultant to WHISCON
- Dr. Hennessy has research funding from AstraZeneca Pharmaceuticals and Bristol-Myers Squibb, and has done consulting for AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, AbbVie Inc., Merck Sharp & Dohme Corp, none of which is related to ACE inhibitors or beta-blockers

# Background

- Sentinel (formerly Mini-Sentinel) enables FDA to conduct active safety monitoring of medical products
- A key component of the Sentinel analytic framework is a set of customizable modular programs that:
  - Enable rapid analyses of associations between medical products and pre-specified outcomes
  - Use complex design and analysis strategies to implement self-controlled and cohort-based assessments
- Sentinel has undertaken an effort to evaluate the performance of these modular program tools

# Objective

- To assess the extent to which the Sentinel Propensity Score Matching (PSM) tool could produce the same results as a more traditional customized protocol-based assessment comparing angioedema in patients initiating angiotensin-converting enzyme (ACE) inhibitors versus beta-blockers

# Sentinel protocol-based assessment

## ORIGINAL INVESTIGATION

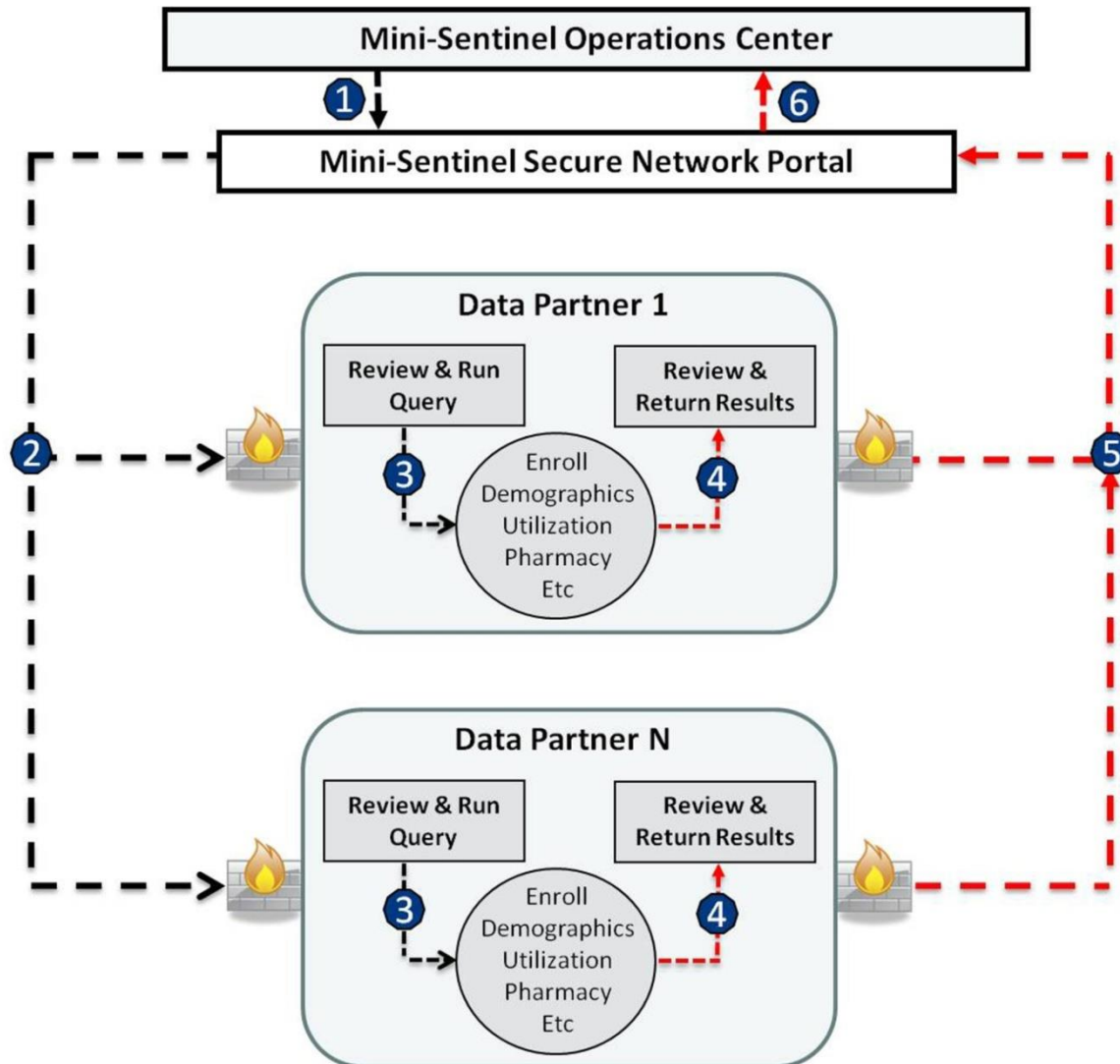
### Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System

Sengwee Toh, ScD; Marsha E. Reichman, PhD; Monika Houstoun, PharmD; Mary Ross Southworth, PharmD; Xiao Ding, PhD; Adrian F. Hernandez, MD; Mark Levenson, PhD; Lingling Li, PhD; Carolyn McCloskey, MD, MPH; Azadeh Shoaibi, MS, MHS; Eileen Wu, PharmD; Gwen Zornberg, MD, MS, ScD; Sean Hennessy, PharmD, PhD

| Drug  | No. of Events | No. of Exposed Persons | No. of Exposed Person-Years | Value (95% CI)                        |                                      | HR (95% CI)      |                           |
|-------|---------------|------------------------|-----------------------------|---------------------------------------|--------------------------------------|------------------|---------------------------|
|       |               |                        |                             | Cumulative Incidence per 1000 Persons | Incidence Rate per 1000 Person-Years | Site Adjusted    | Propensity Score Adjusted |
| ACEIs | 3301          | 1 845 138              | 753 105.4                   | Angioedema<br>1.79 (1.73-1.85)        | 4.38 (4.24-4.54)                     | 2.77 (2.57-2.98) | 3.04 (2.81-3.27)          |

Source: Toh S et al. *Arch Intern Med* 2012;172:1582-9.

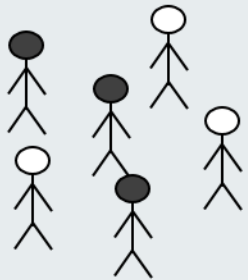
# Sentinel Distributed Database



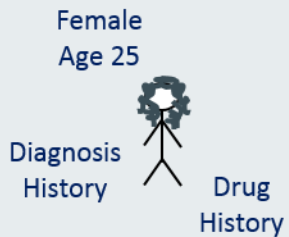
- 1- User creates and submits query (a computer program)
- 2- Data Partners retrieve query
- 3- Data Partners review and run query against their local data
- 4- Data Partners review results
- 5- Data Partners return results via secure network
- 6 Results are aggregated and returned

# Sentinel PSM tool

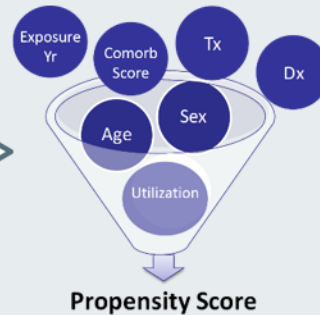
Identify treatment exposure and comparator exposure cohorts



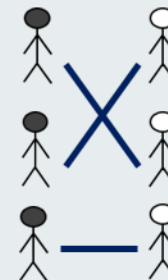
Extract covariate information



Estimate an exposure propensity score



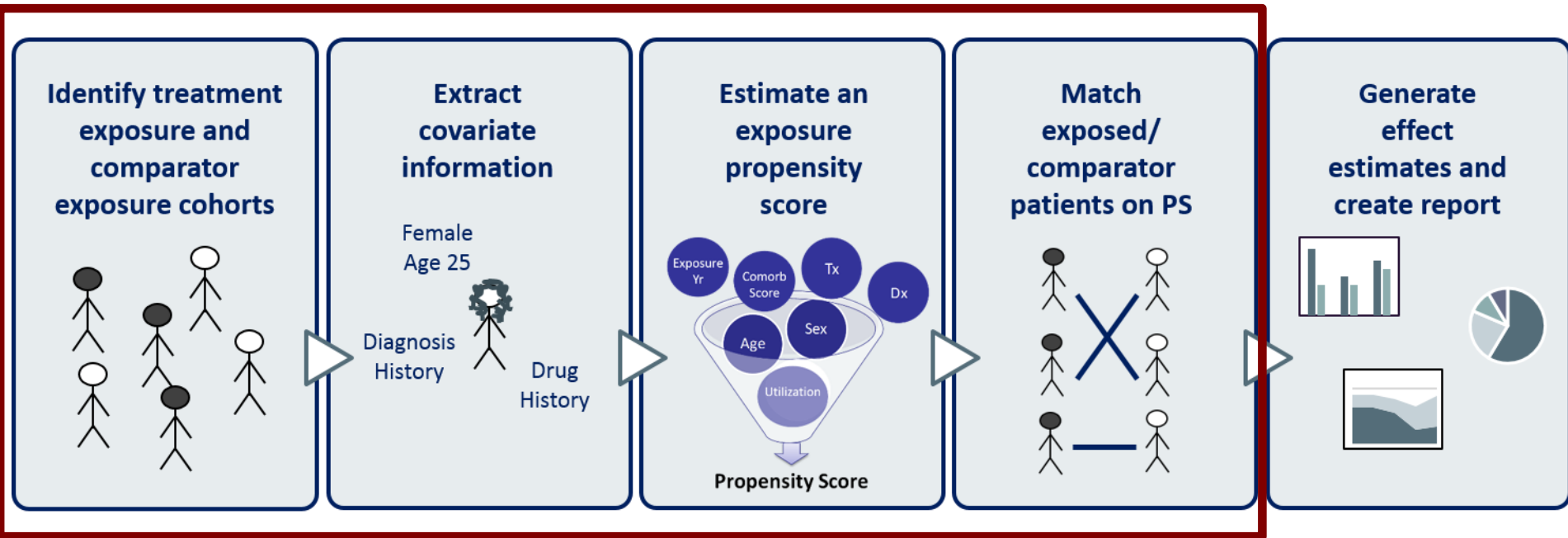
Match exposed/comparator patients on PS



Generate effect estimates and create report



# Sentinel PSM tool



Occur separately at each Data Partner



## Comparison of protocol-based and propensity score matching tool analyses

|   | <b><i>Protocol-based analysis</i></b>  | <b><i>PSM tool analysis</i></b>  |
|---|--|--|
| Number of Data Partners                               | 17   | 13   |
| Data date range                                       | January 1, 2001 to December 31, 2010   | January 1, 2008 to September 30, 2013  |
| Design  | New user cohort design   | New user cohort design   |
| Exposure of interest                                  | ACE inhibitors   | ACE inhibitors   |
| Comparator  | Beta-blockers  | Beta-blockers  |
| New-use wash-out period                               | 183 days   | 183 days   |
| Outcome of interest                                   | Angioedema   | Angioedema   |
| Outcome definition                                    | ICD-9-CM code 995.1, any care setting  | ICD-9-CM code 995.1, any care setting  |
| Confounders (assessed during 183-day baseline period) | Age; sex; recorded history of allergic reaction, diabetes, heart failure, ischemic heart disease, non-steroidal anti-inflammatory drug use | Same as protocol-based analysis plus # unique generic drugs dispensed; # prescriptions filled; # inpatient hospital encounters; # non-acute institutional encounters; # emergency room encounters; # ambulatory encounters |
| Confounding adjustment                                | Propensity score stratification (quintiles)  | Propensity score matching  |
| Start of follow-up                                    | Day after drug initiation date   | Day after drug initiation date   |
| End of follow-up                                      | First of end of continuous exposure, outcome, or prescription for a drug in the other class, angiotensin II receptor blocker, or aliskiren | First of end of continuous exposure, outcome, or prescription for a drug in the other class, angiotensin II receptor blocker, or aliskiren   |
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**Table 1. Cohort of new Initiators of angiotensin-converting enzyme inhibitors and beta-blockers (unmatched)**

| Characteristic                               | Primary Analysis                         |                           |               |                           | Covariate Balance   |                         |
|--|--|---------------------------|---------------|---------------------------|---------------------|-------------------------|
|  | Angiotensin-converting enzyme Inhibitors |                           | Beta-blockers |                           | Absolute Difference | Standardized Difference |
|  | N  | %                         | N             | %                         |                     |                         |
| Patients                                     | 2,211,215                                | 100%                      | 1,673,682     | 100%                      |                     |                         |
| Events while on therapy                      | 5,158                                    | 0.2%                      | 1,292         | 0.1%                      |                     |                         |
| Person-time at risk (days)                   | 186.9                                    | 266.6                     | 149.2         | 235.1                     |                     |                         |
| <b>Patient Characteristics</b>               |  |                           |               |                           |                     |                         |
| Gender (F)                                   | 997,962                                  | 45.10%                    | 946,344       | 56.50%                    | -11.4               | -0.2                    |
| Mean age (standard deviation)                | 54.6                                     | 12.7                      | 53.7          | 15.6                      | 0.9                 | 0.1                     |
| <b>Recorded History of:</b>                  |  |                           |               |                           |                     |                         |
| Allergic reactions                           | 207,344                                  | 9.4%                      | 190,387       | 11.4%                     | -2.0                | -0.1                    |
| Diabetes                                     | 471,661                                  | 21.3%                     | 173,083       | 10.3%                     | 11.0                | 0.3                     |
| Heart failure                                | 41,060                                   | 1.9%                      | 74,897        | 4.5%                      | -2.6                | -0.1                    |
| Ischemic heart diseases                      | 109,948                                  | 5.0%                      | 224,681       | 13.4%                     | -8.4                | -0.3                    |
| NSAID use                                    | 318,298                                  | 14.4%                     | 250,697       | 15.0%                     | -0.6                | 0.0                     |
| <b>Health Service Utilization Intensity:</b> |  |                           |               |                           |                     |                         |
|  | <b>Mean</b>                              | <b>Standard deviation</b> | <b>Mean</b>   | <b>Standard deviation</b> |                     |                         |
| Number of generics                           | 3.4                                      | 3.5                       | 4.1           | 4.0                       | -0.7                | -0.2                    |
| Number of filled prescriptions               | 7.5                                      | 9.6                       | 8.9           | 10.8                      | -1.4                | -0.1                    |
| Number of inpatient hospital encounters      | 0.1                                      | 0.4                       | 0.2           | 0.6                       | -0.1                | -0.3                    |
| Number of non-acute institutional encounters | 0.0                                      | 0.6                       | 0.1           | 0.9                       | -0.1                | -0.1                    |
| Number of emergency room encounters          | 0.2                                      | 0.7                       | 0.4           | 1.0                       | -0.2                | -0.2                    |
| Number of ambulatory encounters              | 4.8                                      | 6.3                       | 6.9           | 8.4                       | -2.1                | -0.3                    |
| Number of other ambulatory encounters        | 1.1                                      | 2.6                       | 1.5           | 3.6                       | -0.4                | -0.1                    |

**Table 1. Cohort of new Initiators of angiotensin-converting enzyme inhibitors and beta-blockers (unmatched)**

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|  | <b>Mean</b>                              | <b>Standard deviation</b> | <b>Mean</b>   | <b>Standard deviation</b> |                     |                         |
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| Number of inpatient hospital encounters      | 0.1                                      | 0.4                       | 0.2           | 0.6                       | -0.1                | -0.3                    |
| Number of non-acute institutional encounters | 0.0                                      | 0.6                       | 0.1           | 0.9                       | -0.1                | -0.1                    |
| Number of emergency room encounters          | 0.2                                      | 0.7                       | 0.4           | 1.0                       | -0.2                | -0.2                    |
| Number of ambulatory encounters              | 4.8                                      | 6.3                       | 6.9           | 8.4                       | -2.1                | -0.3                    |
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| Patients                                     | 2,211,215                                | 100%                      | 1,673,682     | 100%                      |                     |                         |
| Events while on therapy                      | 5,158                                    | 0.2%                      | 1,292         | 0.1%                      |                     |                         |
| Person-time at risk (days)                   | 186.9                                    | 266.6                     | 149.2         | 235.1                     |                     |                         |
| <b>Patient Characteristics</b>               |  |                           |               |                           |                     |                         |
| Gender (F)                                   | 997,962                                  | 45.10%                    | 946,344       | 56.50%                    | -11.4               | -0.2                    |
| Mean age (standard deviation)                | 54.6                                     | 12.7                      | 53.7          | 15.6                      | 0.9                 | 0.1                     |
| <b>Recorded History of:</b>                  |  |                           |               |                           |                     |                         |
| Allergic reactions                           | 207,344                                  | 9.4%                      | 190,387       | 11.4%                     | -2.0                | -0.1                    |
| Diabetes                                     | 471,661                                  | 21.3%                     | 173,083       | 10.3%                     | 11.0                | 0.3                     |
| Heart failure                                | 41,060                                   | 1.9%                      | 74,897        | 4.5%                      | -2.6                | -0.1                    |
| Ischemic heart diseases                      | 109,948                                  | 5.0%                      | 224,681       | 13.4%                     | -8.4                | -0.3                    |
| NSAID use                                    | 318,298                                  | 14.4%                     | 250,697       | 15.0%                     | -0.6                | 0.0                     |
| <b>Health Service Utilization Intensity:</b> |  |                           |               |                           |                     |                         |
|  | <b>Mean</b>                              | <b>Standard deviation</b> | <b>Mean</b>   | <b>Standard deviation</b> |                     |                         |
| Number of generics                           | 3.4                                      | 3.5                       | 4.1           | 4.0                       | -0.7                | -0.2                    |
| Number of filled prescriptions               | 7.5                                      | 9.6                       | 8.9           | 10.8                      | -1.4                | -0.1                    |
| Number of inpatient hospital encounters      | 0.1                                      | 0.4                       | 0.2           | 0.6                       | -0.1                | -0.3                    |
| Number of non-acute institutional encounters | 0.0                                      | 0.6                       | 0.1           | 0.9                       | -0.1                | -0.1                    |
| Number of emergency room encounters          | 0.2                                      | 0.7                       | 0.4           | 1.0                       | -0.2                | -0.2                    |
| Number of ambulatory encounters              | 4.8                                      | 6.3                       | 6.9           | 8.4                       | -2.1                | -0.3                    |
| Number of other ambulatory encounters        | 1.1                                      | 2.6                       | 1.5           | 3.6                       | -0.4                | -0.1                    |

**Table 2. Cohort of new Initiators of angiotensin-converting enzyme inhibitors and beta-blockers (matched)**

| Characteristic                               | Primary Analysis                         |                    |               |                    | Covariate Balance   |                         |
|--|--|--------------------|---------------|--------------------|---------------------|-------------------------|
|  | Angiotensin-converting enzyme Inhibitors |                    | Beta-blockers |                    | Absolute Difference | Standardized Difference |
|  | N  | %                  | N             | %                  |                     |                         |
| Patients                                     | 1,309,104                                | 59.2%              | 1,309,104     | 78.2%              |                     |                         |
| Events while on therapy                      | 3,311                                    | 0.3%               | 988           | 0.1%               |                     |                         |
| Person-time at risk (days)                   | 183.8                                    | 263.7              | 151.8         | 238.9              |                     |                         |
| <b>Patient Characteristics</b>               |  |                    |               |                    |                     |                         |
| Gender (F)                                   | 723,955                                  | 55.3%              | 689,617       | 52.7%              | 2.6                 | 0.1                     |
| Mean age (standard deviation)                | 54.1                                     | 13.1               | 54.4          | 14.9               | -0.3                | 0.0                     |
| <b>Recorded History of:</b>                  |  |                    |               |                    |                     |                         |
| Allergic reactions                           | 137,920                                  | 10.5%              | 134,933       | 10.3%              | 0.2                 | 0.0                     |
| Diabetes                                     | 150,036                                  | 11.5%              | 150,551       | 11.5%              | 0.0                 | 0.0                     |
| Heart failure                                | 35,302                                   | 2.7%               | 38,966        | 3.0%               | -0.3                | 0.0                     |
| Ischemic heart diseases                      | 102,200                                  | 7.8%               | 106,786       | 8.2%               | -0.4                | 0.0                     |
| NSAID use                                    | 191,798                                  | 14.7%              | 189,612       | 14.5%              | 0.2                 | 0.0                     |
| <b>Health Service Utilization Intensity:</b> |  |                    |               |                    |                     |                         |
|  | Mean                                     | Standard deviation | Mean          | Standard deviation |                     |                         |
| Number of generics                           | 3.7                                      | 3.7%               | 3.6           | 3.6%               | 0.0                 | 0.0                     |
| Number of filled prescriptions               | 8.1                                      | 10.2%              | 8.0           | 9.9%               | 0.1                 | 0.0                     |
| Number of inpatient hospital encounters      | 0.1                                      | 0.5%               | 0.1           | 0.5%               | 0.0                 | 0.0                     |
| Number of non-acute institutional encounters | 0.1                                      | 0.7%               | 0.1           | 0.7%               | 0.0                 | 0.0                     |
| Number of emergency room encounters          | 0.3                                      | 0.8%               | 0.3           | 0.8%               | 0.0                 | 0.0                     |
| Number of ambulatory encounters              | 5.6                                      | 7.3%               | 5.6           | 6.6%               | 0.0                 | 0.0                     |
| Number of other ambulatory encounters        | 1.2                                      | 2.9%               | 1.3           | 3.0%               | 0.0                 | 0.0                     |

**Table 2. Cohort of new Initiators of angiotensin-converting enzyme inhibitors and beta-blockers (matched)**

| Characteristic                               | Primary Analysis                         |                    |               |                    | Covariate Balance   |                         |
|--|--|--------------------|---------------|--------------------|---------------------|-------------------------|
|  | Angiotensin-converting enzyme Inhibitors |                    | Beta-blockers |                    | Absolute Difference | Standardized Difference |
|  | N  | %                  | N             | %                  |                     |                         |
| Patients                                     | 1,309,104                                | 59.2%              | 1,309,104     | 78.2%              |                     |                         |
| Events while on therapy                      | 3,311                                    | 0.3%               | 988           | 0.1%               |                     |                         |
| Person-time at risk (days)                   | 183.8                                    | 263.7              | 151.8         | 238.9              |                     |                         |
| <b>Patient Characteristics</b>               |  |                    |               |                    |                     |                         |
| Gender (F)                                   | 723,955                                  | 55.3%              | 689,617       | 52.7%              | 2.6                 | 0.1                     |
| Mean age (standard deviation)                | 54.1                                     | 13.1               | 54.4          | 14.9               | -0.3                | 0.0                     |
| <b>Recorded History of:</b>                  |  |                    |               |                    |                     |                         |
| Allergic reactions                           | 137,920                                  | 10.5%              | 134,933       | 10.3%              | 0.2                 | 0.0                     |
| Diabetes                                     | 150,036                                  | 11.5%              | 150,551       | 11.5%              | 0.0                 | 0.0                     |
| Heart failure                                | 35,302                                   | 2.7%               | 38,966        | 3.0%               | -0.3                | 0.0                     |
| Ischemic heart diseases                      | 102,200                                  | 7.8%               | 106,786       | 8.2%               | -0.4                | 0.0                     |
| NSAID use                                    | 191,798                                  | 14.7%              | 189,612       | 14.5%              | 0.2                 | 0.0                     |
| <b>Health Service Utilization Intensity:</b> |  |                    |               |                    |                     |                         |
|  | Mean                                     | Standard deviation | Mean          | Standard deviation |                     |                         |
| Number of generics                           | 3.7                                      | 3.7%               | 3.6           | 3.6%               | 0.0                 | 0.0                     |
| Number of filled prescriptions               | 8.1                                      | 10.2%              | 8.0           | 9.9%               | 0.1                 | 0.0                     |
| Number of inpatient hospital encounters      | 0.1                                      | 0.5%               | 0.1           | 0.5%               | 0.0                 | 0.0                     |
| Number of non-acute institutional encounters | 0.1                                      | 0.7%               | 0.1           | 0.7%               | 0.0                 | 0.0                     |
| Number of emergency room encounters          | 0.3                                      | 0.8%               | 0.3           | 0.8%               | 0.0                 | 0.0                     |
| Number of ambulatory encounters              | 5.6                                      | 7.3%               | 5.6           | 6.6%               | 0.0                 | 0.0                     |
| Number of other ambulatory encounters        | 1.2                                      | 2.9%               | 1.3           | 3.0%               | 0.0                 | 0.0                     |

# Results

**Table 3: Results by analysis type**

| Exposure   | New Users | Person-Years at Risk | Average Person-Years at Risk | Number of Events | Incidence Rate per 1,000 Person-Years | Risk per 1000 New Users | Incidence Rate Difference per 1,000 Person-Years | Difference in Risk per 1000 New Users | Hazard Ratio (95% CI) | Wald P-Value |
|--|-----------|----------------------|------------------------------|------------------|---------------------------------------|-------------------------|--|---------------------------------------|-----------------------|--------------|
| <b>Unmatched Analysis (Data Partner-adjusted only)</b>                 |           |                      |                              |                  |                                       |                         |  |                                       |                       |              |
| ACE inhibitors   | 2,211,215 | 1,131,526            | 0.51                         | 5,158            | 4.56                                  | 2.33                    | 2.67   | 1.56                                  | 2.55 (2.40, 2.71)     | <0.0001      |
| Beta-blockers  | 1,673,682 | 683,614              | 0.41                         | 1,292            | 1.89                                  | 0.77                    |  |                                       |                       |              |
| <b>1:1 Matched Analysis, stratified on matched pair; Caliper=0.025</b> |           |                      |                              |                  |                                       |                         |  |                                       |                       |              |
| ACE inhibitors   | 1,309,104 | 248,697              | 0.19                         | 1,819            | 7.31                                  | 1.39                    | 4.98   | 0.95                                  | 3.14 (2.86, 3.44)     | <0.0001      |
| Beta-blockers  | 1,309,104 | 248,697              | 0.19                         | 580              | 2.33                                  | 0.44                    |  |                                       |                       |              |

ACE, angiotensin-converting enzyme

# Results

**Table 3: Results by analysis type**

| Exposure   | New Users | Person-Years at Risk | Average Person-Years at Risk | Number of Events | Incidence Rate per 1,000 Person-Years | Risk per 1000 New Users | Incidence Rate Difference per 1,000 Person-Years | Difference in Risk per 1000 New Users | Hazard Ratio (95% CI) | Wald P-Value |
|--|-----------|----------------------|------------------------------|------------------|---------------------------------------|-------------------------|--|---------------------------------------|-----------------------|--------------|
| <b>Unmatched Analysis (Data Partner-adjusted only)</b>                 |           |                      |                              |                  |                                       |                         |  |                                       |                       |              |
| ACE inhibitors   | 2,211,215 | 1,131,526            | 0.51                         | 5,158            | 4.56                                  | 2.33                    | 2.67   | 1.56                                  | 2.55 (2.40, 2.71)     | <0.0001      |
| Beta-blockers  | 1,673,682 | 683,614              | 0.41                         | 1,292            | 1.89                                  | 0.77                    |  |                                       |                       |              |
| <b>1:1 Matched Analysis, stratified on matched pair; Caliper=0.025</b> |           |                      |                              |                  |                                       |                         |  |                                       |                       |              |
| ACE inhibitors   | 1,309,104 | 248,697              | 0.19                         | 1,819            | 7.31                                  | 1.39                    | 4.98   | 0.95                                  | 3.14 (2.86, 3.44)     | <0.0001      |
| Beta-blockers  | 1,309,104 | 248,697              | 0.19                         | 580              | 2.33                                  | 0.44                    |  |                                       |                       |              |

ACE, angiotensin-converting enzyme

# Limitations

- Single drug-outcome pair, with little confounding
- Slight differences in Data Partners, data years, and confounding adjustment strategies between PSM and protocol-based analyses
- Both analyses limited by under-capture of potentially important confounders (e.g., race, genetic data)
- More evaluation needed for both retrospective and prospective assessments

## Conclusions

- Despite small differences in data and methods, the Sentinel PSM tool was able to produce an estimate that was very consistent with that produced by a highly customized protocol-based assessment
  - 3.14 (2.86 to 3.44) vs. 3.04 (2.81 to 3.27)
- This comparison provides initial evidence that Sentinel program tools can produce findings similar to those produced by a highly customized protocol-driven assessment
- Additional evaluations underway

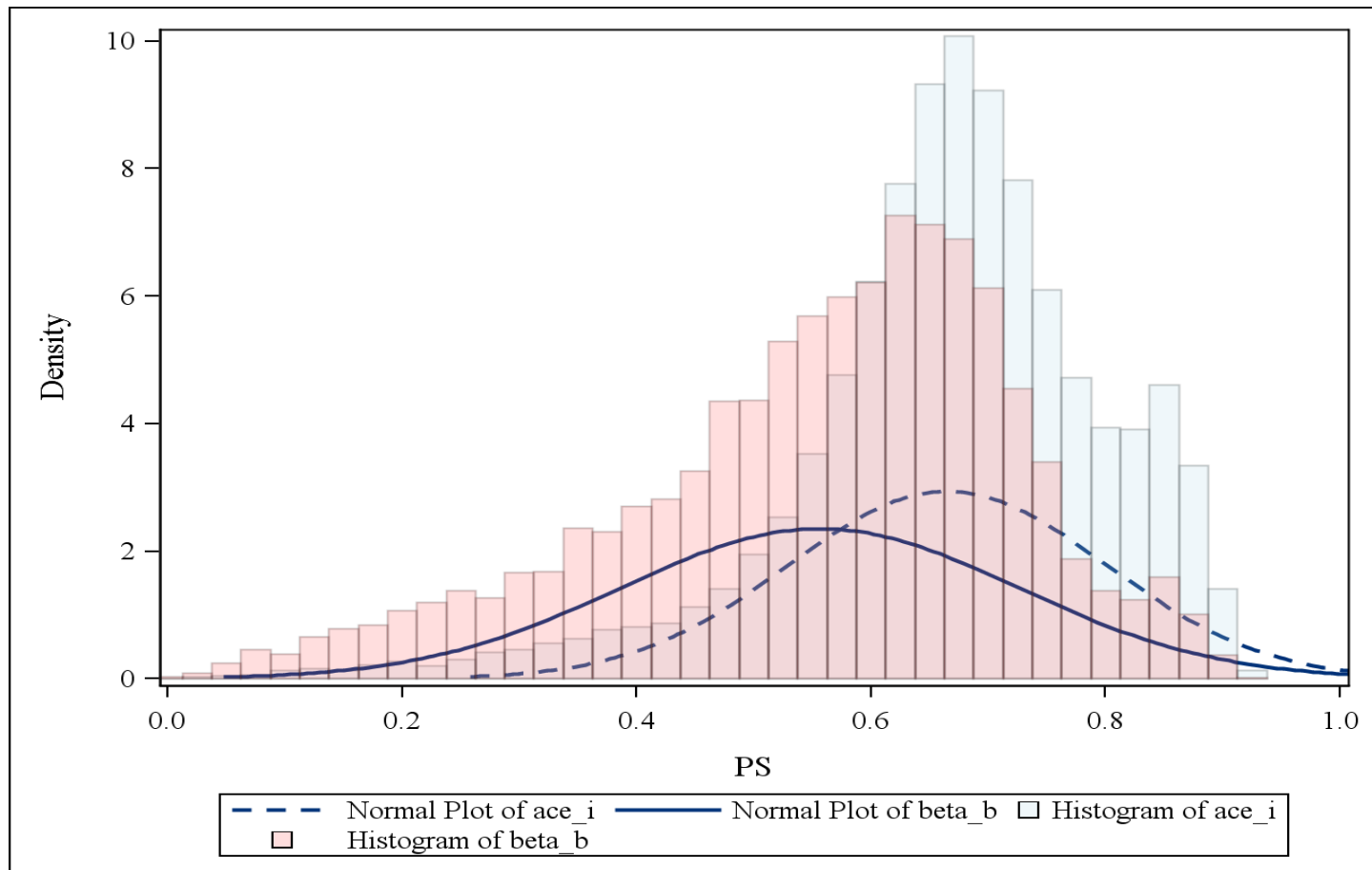


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# Additional slides

# PS distributions at 1 Data Partner (before matching)



# PS distributions at 1 Data Partner (after matching)

