ENGELBERG CENTER for Health Care Reform at BROOKINGS

Brookings Roundtable on Active Medical Product Surveillance:

Findings from a Mini-Sentinel Medical Product Assessment

Marsha Reichman, U.S. Food and Drug Administration

Darren Toh, Harvard Medical School and Harvard Pilgrim Health Care Institute

October 16, 2012

Welcome and Overview

Housekeeping:

•To minimize feedback, please confirm that the microphone on your telephone is muted.

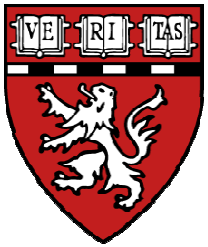
•To mute your phone, press the mute button or '*6'. (To un-mute, press '*7')

•There will be several opportunities for questions and discussion throughout today's session. **Please use the Q & A tab on the top of your screen to submit your questions into the queue at any point** and we will call upon you to state your question.

•Call the Level 3 Conferencing at 1-888-447-1119 with technical problems.

Angioedema events and drugs that target the renin-angiotensin-aldosterone system

A Mini-Sentinel protocol-based assessment



Darren Toh, ScD
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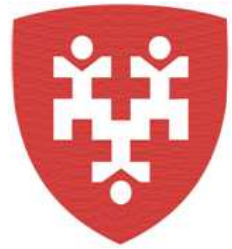

On behalf of the Mini-Sentinel angioedema workgroup

Mini-Sentinel angioedema workgroup

Name	Affiliation	Role
Marsha Reichman	OSE/CDER/FDA	Co-Lead
Monika Houstoun	OSE/CDER/FDA	Co-Lead
Sean Hennessy	University of Pennsylvania	Co-Lead
Darren Toh	Harvard Pilgrim Health Care Institute	Co-Lead
Xiao Ding	OTS/CDER/FDA	Member
Adrian Hernandez	Duke University School of Medicine	Member
Mark Levenson	OTS/CDER/FDA	Member
Lingling Li	Harvard Pilgrim Health Care Institute	Member
Carolyn McCloskey	OSE/CDER/FDA	Member
Azadeh Shoaibi	OMP/CDERFDA	Member
Mary Ross Southworth	OND/CDER/FDA	Member
Eileen Wu	OSE/CDER/FDA	Member
Gwen Zornberg	OSE/CDER/FDA	Member

Overview

- Background
- Methods
- Results
- Discussion

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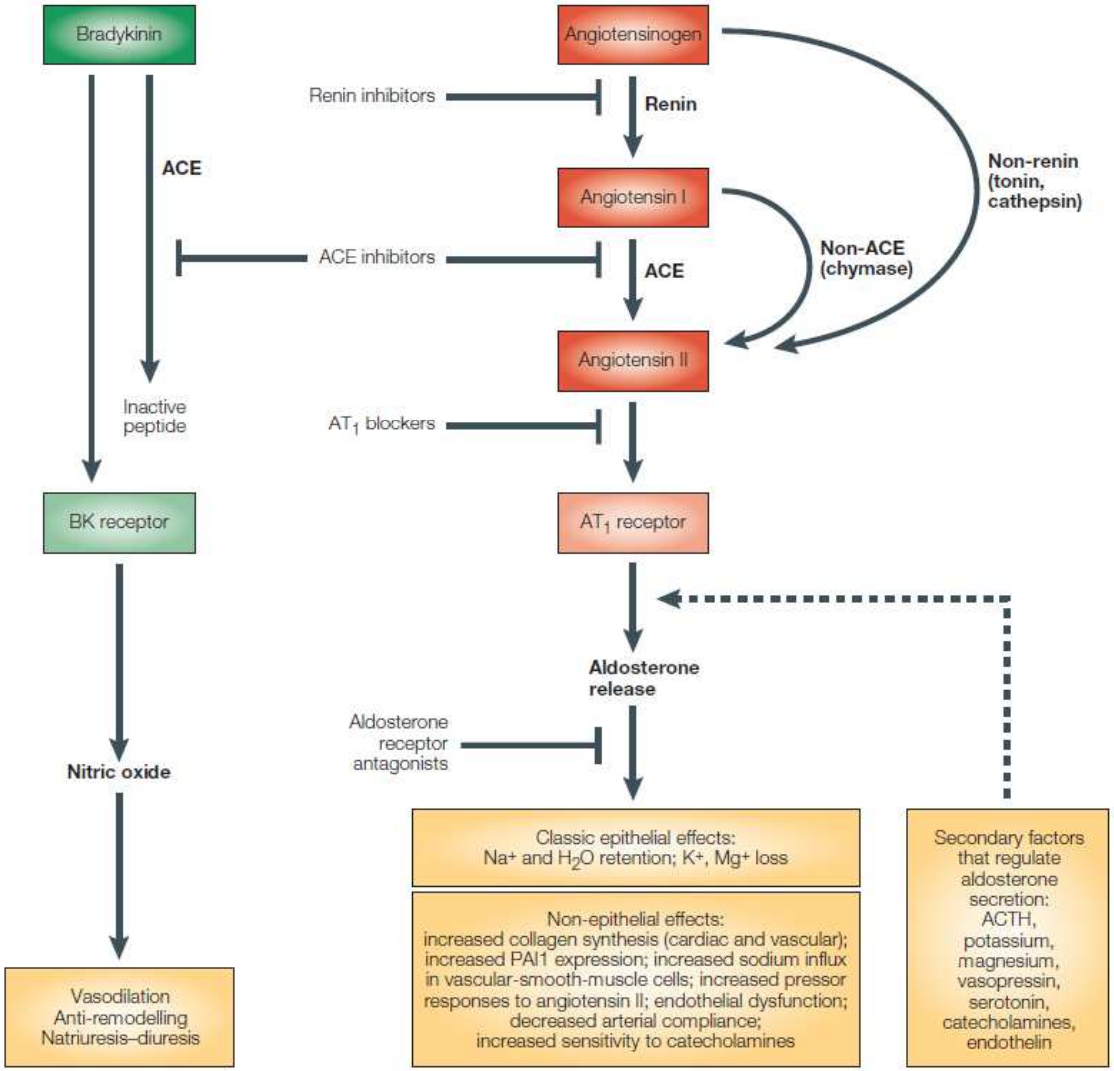
Mini-Sentinel partner organizations

Overarching goals of the project

- To assess selected drug-event associations
- To build general strategies in Mini-Sentinel for signal refinement regarding medical products for which substantial post-market experience has accrued
- This project was NOT designed to
  - provide definitive evidence of a causal association

RAAS pathway



Zaman et al, *Nat Rev Drug Discov* 2002;1:621-636

Angioedema

- Rapid, localized swelling of the eyes, lips, tongue, mouth, upper respiratory tract, etc
- Potentially life-threatening

RAAS drugs and angioedema risk

- Incidence rate of angioedema (per 1,000 person-years)

ACEIs	**2.0**
ARBs	**1.0**
Aliskiren	**N/A***
ß-blockers	0.5
Calcium channel blockers	0.5
Loop diuretics	0.5
Thiazide diuretics	0.7

* **Aliskiren** is the only marketed direct renin inhibitor in US. Risk of angioedema/urticaria for aliskiren is similar to or lower than ACEIs and ARBs in pooled analysis of RCTs

Question of interest

- Are ACEIs, ARBs or aliskiren associated with similar risks of angioedema when compared with a common referent group, ß-blockers?

Overview

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Mini-Sentinel partner organizations

Exposure

ACEIs	ARBs	Direct renin inhibitors	ß-blockers
Benazepril (1991)	**Candesartan** (1998)	**Aliskiren** (2007)	**Acebutolo**l (1984)
Captopril (1981)	**Eprosartan** (1997)		**Atenolol** (1981)
Enalapril (1985)	**Irbesartan** (1997)		**Bisoprolol** (1992)
Fosinopril (1991)	**Losartan** (1995)		**Carvedilol** (1995)
Lisinopril (1987)	**Olmesartan** (2002)		**Labetalol** (1984)
Moexipril (1995)	**Telmisartan** (1998)		**Metoprolol** (1978)
Quinapril (1991)	**Valsartan** (1996)		**Nebivolol** (2007)
Perindopril (1993)			**Pindolol** (1982)
Ramipril (1991)			**Propranolol** (1967)
Trandolapril (1996)			**Timolol** (1981)

Cohort

- Individuals aged ≥18 years with a first Rx of an oral ACEIs, ARBs, aliskiren, or ß-blockers in 2001-2010

- **Index date**: Dispensing date of first Rx of a drug of interest

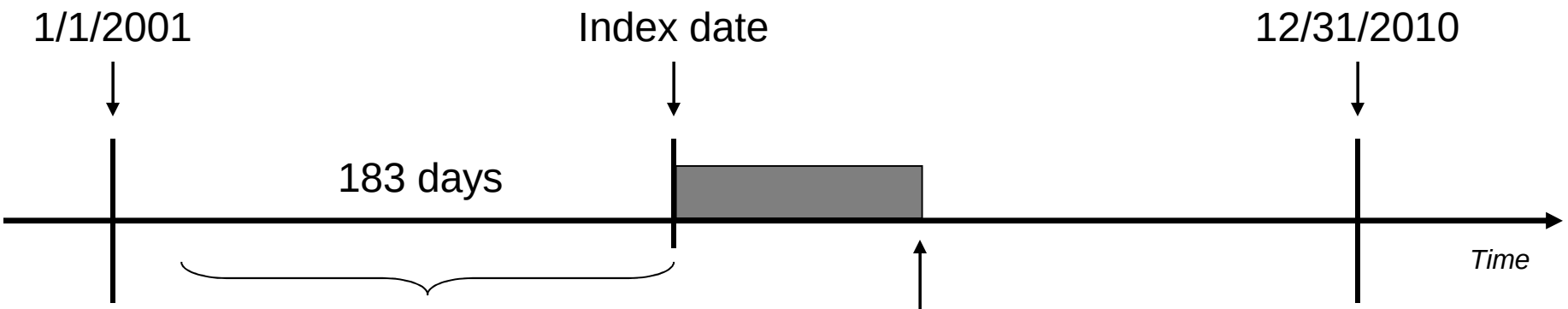
- Additional eligibility criteria
  - ≥183 days continuous enrollment with pharmacy & medical benefits prior to the index date
  - No Rx of any study drugs in 183 days prior to the index date
  - No diagnosis of angioedema in 183 days prior to the index date
  - No initiation of more than one drug of interest on the index date

Outcome

- **Primary outcome** – Angioedema
  - ICD-9-CM code 995.1 in any position during an outpatient, inpatient, or emergency department visit (PPV 90% to 95%) (Brown et al 1996 & Miller et al 2008)

- **Secondary outcome** – Serious angioedema
  - Angioedema w/ airway obstruction requiring inpatient care
  - Inpatient ICD-9-CM code 995.1 *plus* a code indicating ICU admission, intubation, tracheostomy, or laryngoscopy occurring within two days of the date of hospital admission

Follow-up



- Continuous enrollment w/ benefits
- No Rx of drugs of interest
- No Dx of angioedema

- Angioedema
- 12/31/2010
- Death
- Health plan disenrollment
- Cessation of treatment
- Initiation of another study drug
- 365 days of follow-up

Contributing person-times

Potential confounders

Confounder*	Categorization
Age as of the index date	18-45, 45-54, 55-64, ≥65 yrs
Sex	Male/Female
Diagnosis of	
Allergic reactions	Yes/No
Diabetes	Yes/No
Heart failure	Yes/No
Ischemic heart disease	Yes/No
Prescription NSAID use	Yes/No

*Identified during the 183-day baseline period prior to the index date

Statistical analysis

- Descriptive analysis
  - Baseline characteristics
  - Unadjusted incidence and incidence rate

- Statistical analysis
  - Pair-wise comparison with ß-blockers as referent group
  - Site-adjusted and PS-adjusted HRs and 95% CIs
  - PSs calculated at each site; common PS model
  - MS-wide estimates
    - Case-centered logistic regression (primary)
    - Inverse variance-weighted meta-analysis

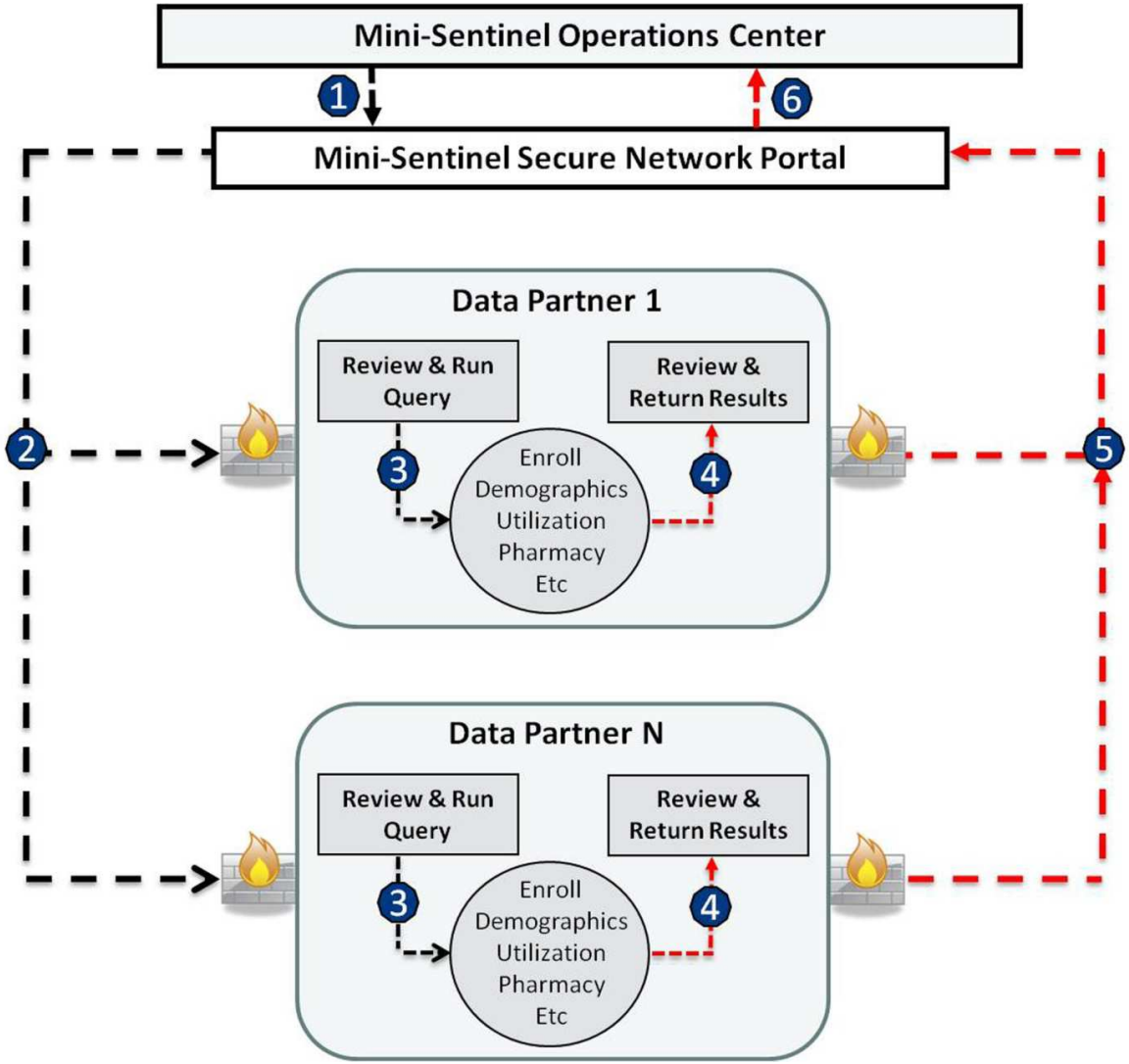
Fireman et al, *Am J Epidemiol* 2009;170:650-656

Secondary & sensitivity analysis

- Stratified analysis
  - Age group
  - Sex
  - Follow-up period

- Sensitivity analysis
  - 365-day look-back period
  - Restricted to inpatient and ED diagnosis of angioedema
  - Restricted to data after aliskiren approval (Mar 2007)

Mini-Sentinel distributed analysis



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

Curtis et al, *Pharmacoepidemiol Drug Saf* 2012;21(S1):23-31

Overview

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Cohort

Health plan members aged ≥18 years between 1/1/2001 and 12/31/2010

n=65,006,161

↓

Restricting to individuals with a Dx of any of oral ACEIs, ARBs, aliskiren, or ß-blockers

n=11,952,726

↓

Restricting to individuals with ≥183 days continuous enrollment w/ medical and Rx benefits

n=5,322,438

↓

Restricting to individuals with no Rx of any study drugs during the baseline period

n=4,098,337

↓

Restricting to individuals with no Dx of angioedema during the baseline period

n=4,094,909

↓

Excluding individuals dispensed with more than one study drug on the index date

n=3,909,596

Baseline patient characteristics

Characteristics	ACEIs (n=1,845,138)		ARBs (n=467,313)		Aliskiren (n=4,867)		ß-blockers (n=1,592,278)
	%	*Std. diff.*	*%*	*Std. diff.*	*%*	*Std. diff.*	*%*
Age (years)							
18-44	24.5	0.15	22.8	0.19	22.5	0.19	31.2
45-54	28.7	0.11	29.4	0.13	29.8	0.14	23.7
55-64	25.2	0.10	27.0	0.14	27.1	0.15	21.2
≥65	21.6	0.06	20.8	0.07	20.6	0.08	23.9
Female sex	46.8	0.20	50.7	0.12	46.7	0.20	56.6
Diagnosis of							
Allergic reactions	8.0	0.04	9.7	0.02	11.7	0.09	9.1
Diabetes	18.8	0.33	16.0	0.30	17.7	0.39	7.4
Heart failure	2.2	0.07	2.2	0.07	2.5	0.05	3.4
IHD	4.7	0.24	5.8	0.18	8.3	0.09	11.2
NSAID use	15.2	0.01	14.6	0.03	14.0	0.04	15.6

Incidence & incidence rate of angioedema

Drug	Number of events	Persons	Person-years	Cumulative incidence per 1,000 persons	Incidence rate per 1,000 person-years
ACEIs	3,301	1,845,138	753,105	1.79 (1.73, 1.85)	4.38 (4.24, 4.54)
ARBs	288	467,313	173,438	0.62 (0.55, 0.69)	1.66 (1.47, 1.86)
Aliskiren	7	4,867	1,498	1.44 (0.58, 2.96)	4.67 (1.88, 9.63)
β-blockers	915	1,592,278	548,684	0.58 (0.54, 0.61)	1.67 (1.56, 1.78)

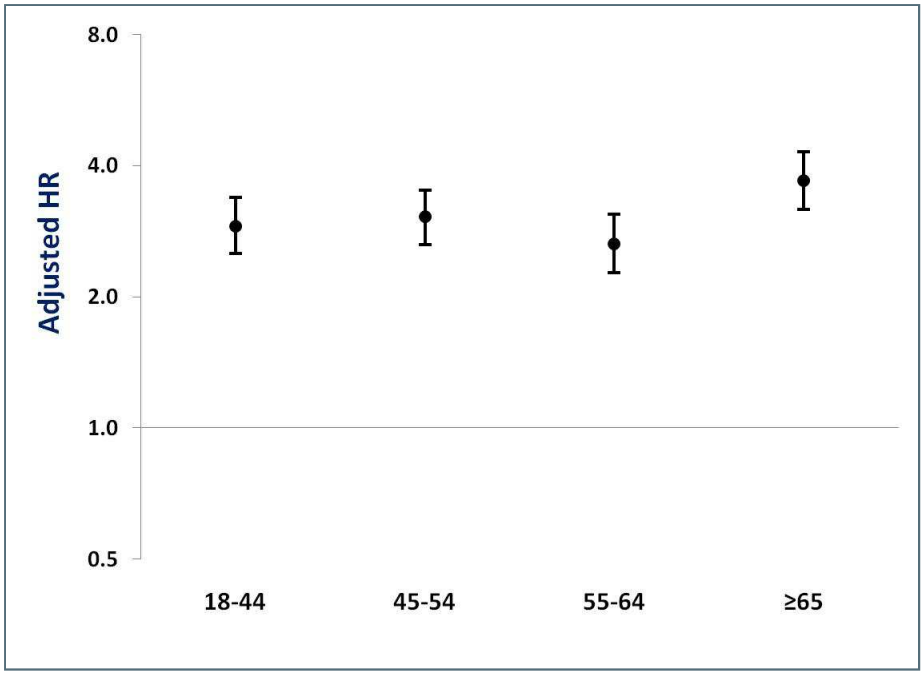
Adjusted HRs of angioedema

Drug	Site-adjusted	PS-adjusted
ACEIs	2.77 (2.57, 2.98)	3.04 (2.81, 3.27)
ARBs	1.11 (0.97, 1.28)	1.16 (1.00, 1.34)
Aliskiren	2.75 (1.30, 5.81)	2.85 (1.34, 6.04)

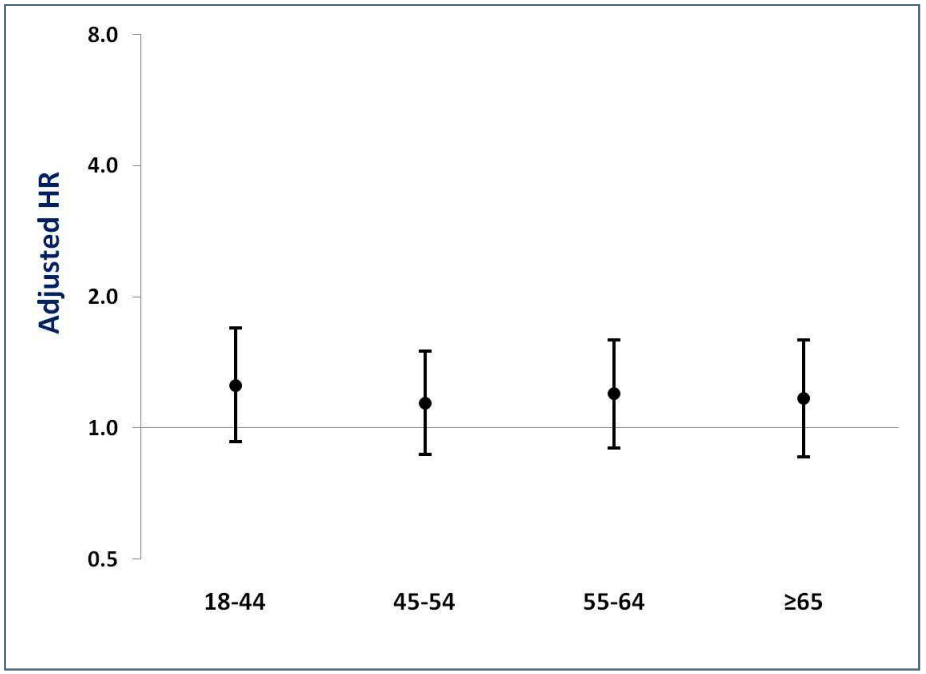
Adjusted HRs of angioedema

Drug	Site-adjusted		PS-adjusted	
	Case-centered	Meta-analysis	Case-centered	Meta-analysis
ACEIs	2.77 (2.57, 2.98)	2.70 (2.50, 2.90)	3.04 (2.81, 3.27)	2.98 (2.76, 3.21)
ARBs	1.11 (0.97, 1.28)	1.15 (1.00, 1.32)	1.16 (1.00, 1.34)	1.15 (1.00, 1.33)
Aliskiren	2.75 (1.30, 5.81)	2.83 (1.34, 5.98)	2.85 (1.34, 6.04)	2.86 (1.35, 6.04)

Stratified analysis by: Age group

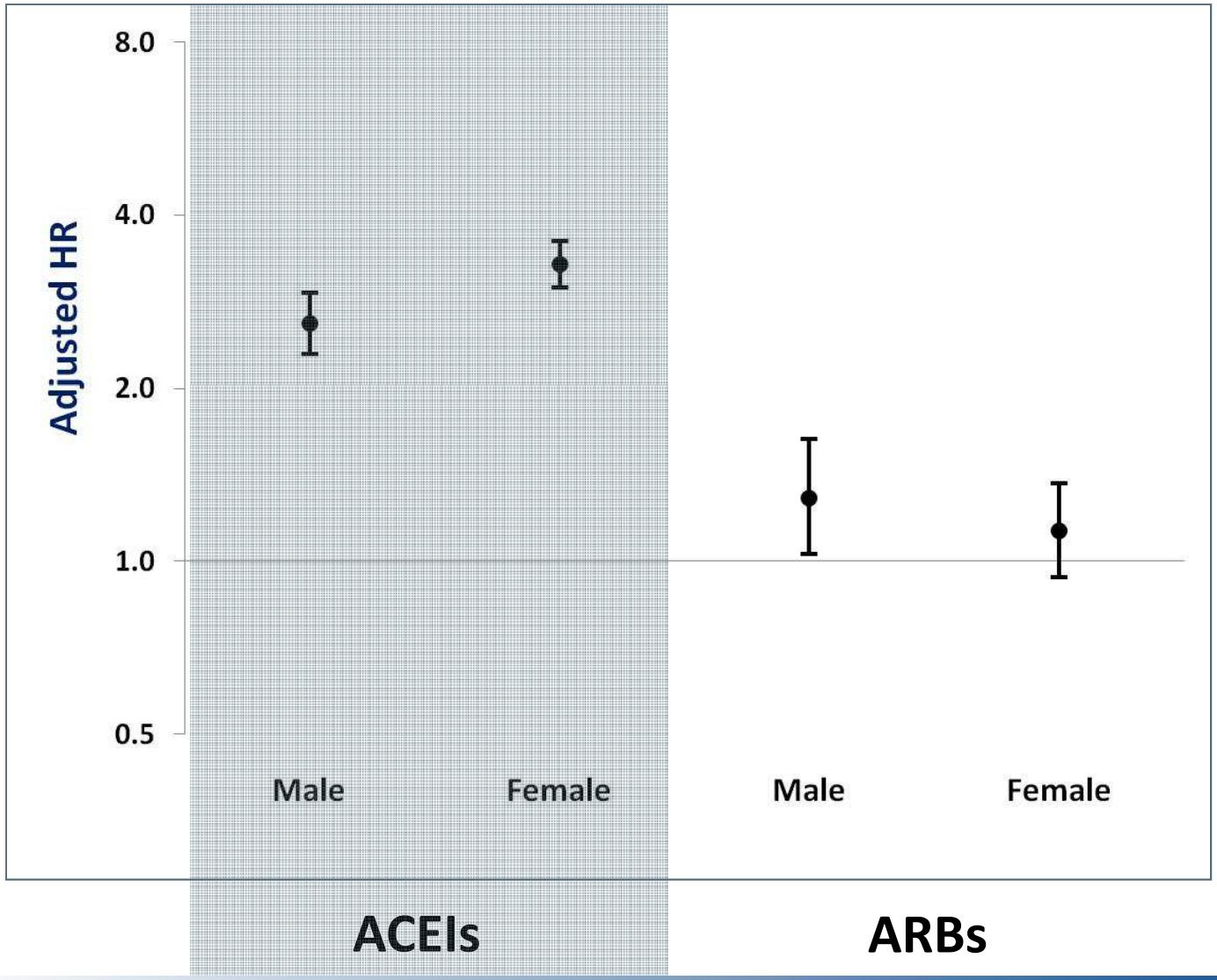


ACEIs

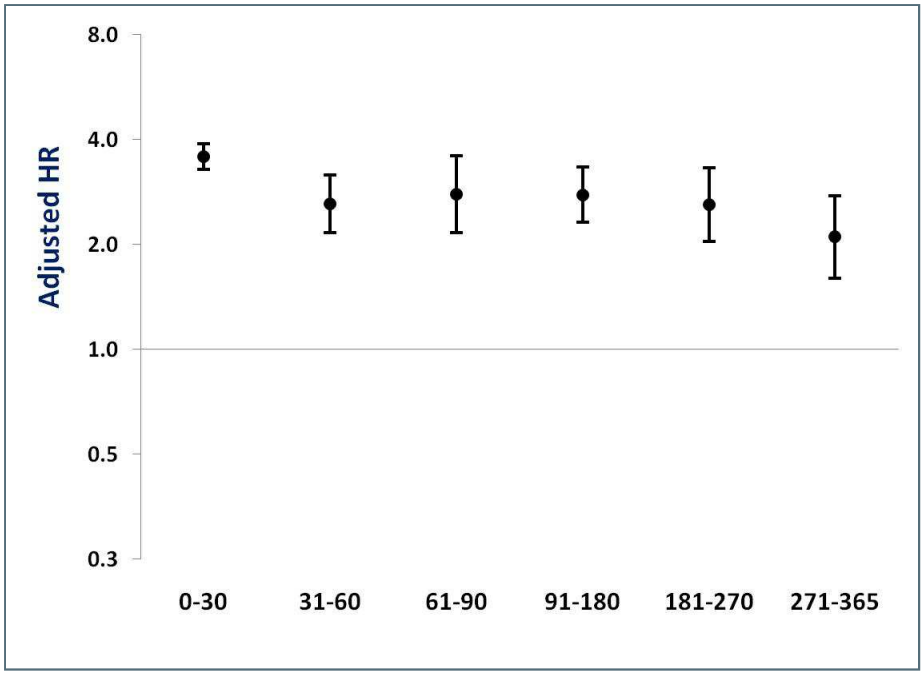


ARBs

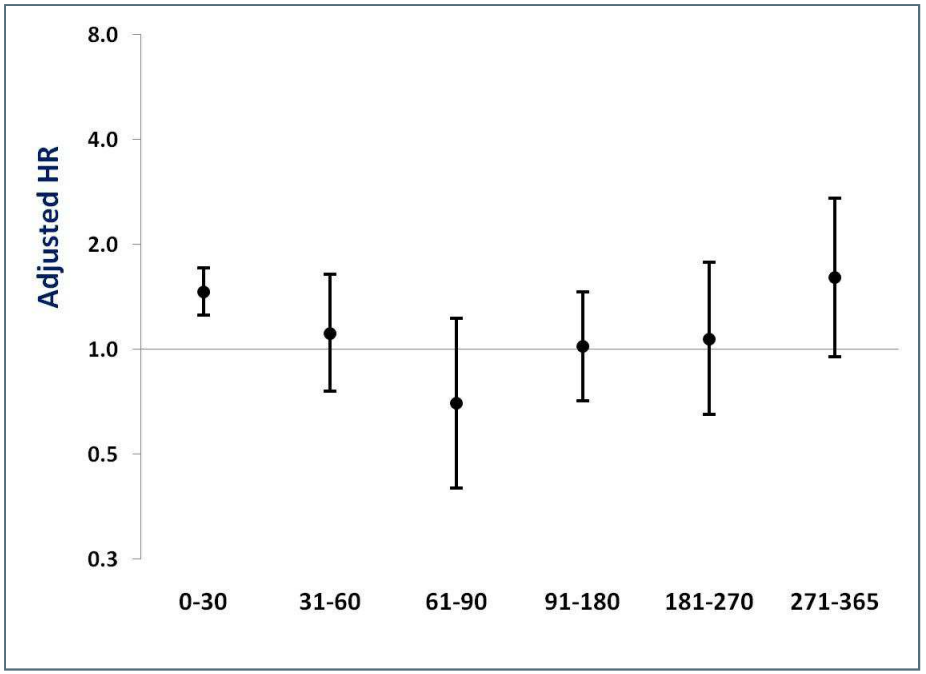
Stratified analysis by: Sex



Stratified analysis by: Follow-up period



ACEIs



ARBs

Sensitivity analysis: 365-day look-back

Drug	Incidence rate per 1,000 person-years		PS-adjusted HR	
	Primary	365-day	Primary	365-day
ACEIs	4.38 (4.24, 4.54)	4.49 (4.32, 4.66)	3.04 (2.81, 3.27)	3.36 (3.07, 3.67)
ARBs	1.66 (1.47, 1.86)	1.52 (1.31, 1.76)	1.16 (1.00, 1.34)	1.21 (1.01, 1.45)
Aliskiren	4.67 (1.88, 9.63)	2.90 (0.60, 8.48)	2.85 (1.34, 6.04)	4.01 (1.28, 12.57)

Sensitivity analysis: INP & ED diagnosis

Drug	Incidence rate per 1,000 person-years		PS-adjusted HR	
	Primary	INP & ED only	Primary	INP & ED only
ACEIs	4.38 (4.24, 4.54)	2.37 (2.26, 2.48)	3.04 (2.81, 3.27)	5.34 (4.69, 6.07)
ARBs	1.66 (1.47, 1.86)	0.48 (0.38, 0.59)	1.16 (1.00, 1.34)	1.09 (0.83, 1.42)
Aliskiren	4.67 (1.88, 9.63)	1.33 (0.16, 4.82)	2.85 (1.34, 6.04)	2.72 (0.67, 11.07)

Sensitivity analysis: Post aliskiren approval

Drug	Incidence rate per 1,000 person-years		PS-adjusted HR	
	Primary	Post aliskiren	Primary	Post aliskiren
ACEIs	4.38 (4.24, 4.54)	4.80 (4.59, 5.02)	3.04 (2.81, 3.27)	2.94 (2.65, 3.27)
ARBs	1.66 (1.47, 1.86)	1.91 (1.64, 2.23)	1.16 (1.00, 1.34)	1.17 (0.97, 1.41)
Aliskiren	4.67 (1.88, 9.63)	4.67 (1.88, 9.63)	2.85 (1.34, 6.04)	2.83 (1.33, 6.00)

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Summary of findings

- **ACEIs:** Replicated known ACEI–angioedema relation
  - Risk ~3-fold higher with ACEIs vs. ß-blockers
- **Aliskiren:** Increased risk of angioedema
  - Based on 7 exposed cases
- **ARBs:** Slightly elevated risk of angioedema
  - Magnitude much lower than that in ACEIs and aliskiren

Limitations

- Did not adjust for race
  - Race a probable confounder for ACEI-angioedema relation
  - Likely led to underestimation of relative risk

Strengths

- Large and demographically diverse study population
- Robust results

Timeline

- Kickoff meeting — Mar 28, 2011
- First workplan sent — Sep 1, 2011
- Completion of data analysis — Jan 27, 2012
- Draft final report — Feb 10, 2012

Thank you!

ENGELBERG CENTER for Health Care Reform at BROOKINGS

Roundtable Discussion and Questions

View this and past Active Medical Product Surveillance webinars at:

http://www.brookings.edu/health/Projects/surveillance/roundtables.aspx