Large-scale analysis to transform the evidence generation process: lessons from the Observational Health Data Sciences and Informatics (OHDSI) collaborative

Patrick Ryan, PhD
Janssen Research and Development
Columbia University Medical Center
18 September 2017

Introducing OHDSI

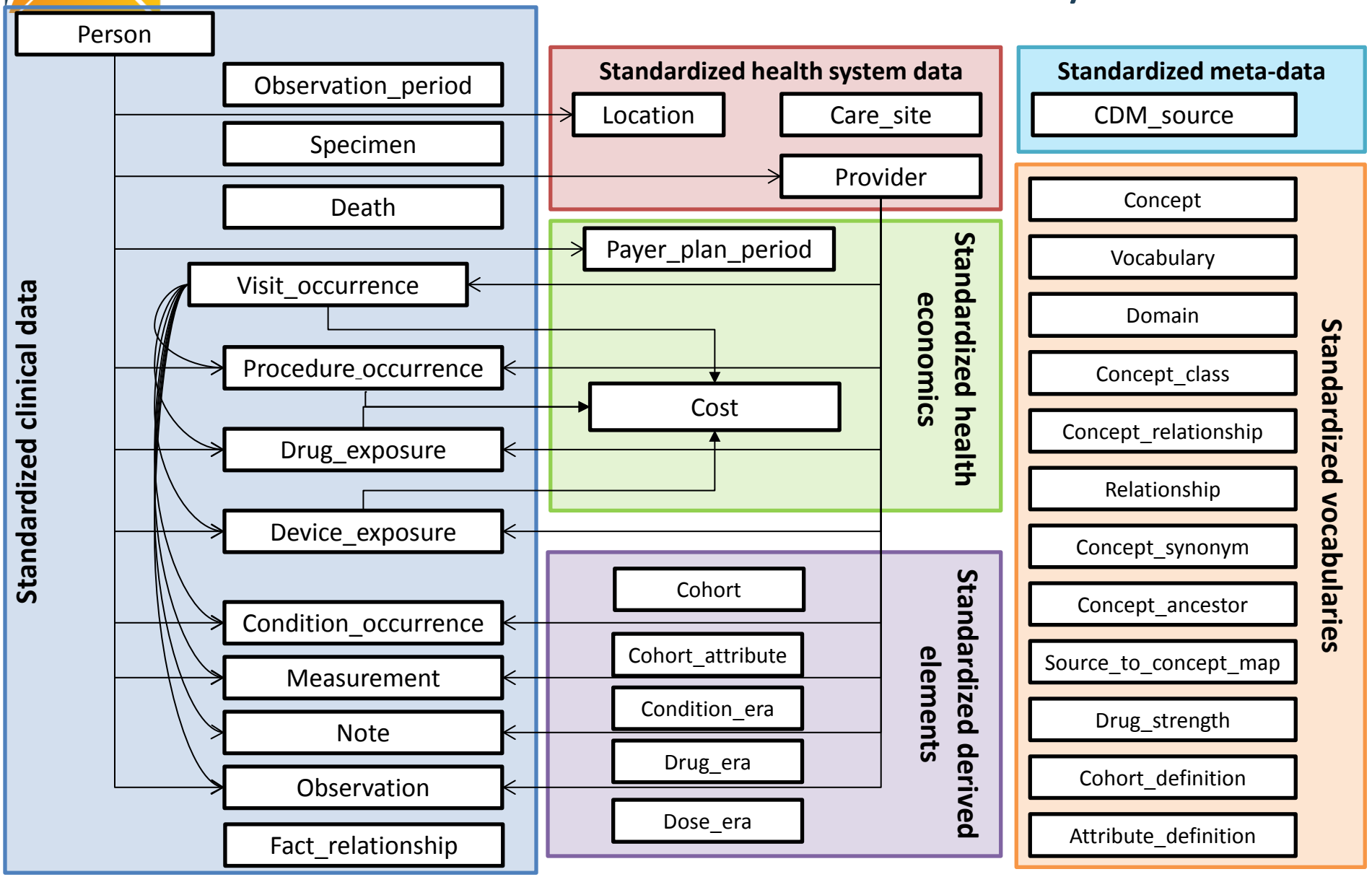
- The Observational Health Data Sciences and Informatics (OHDSI) program is a multi-stakeholder, interdisciplinary collaborative to create open-source solutions that bring out the value of observational health data through large-scale analytics
- OHDSI has established an international network of researchers and observational health databases with a central coordinating center housed at Columbia University

OHDSI's mission

To improve health, by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care.

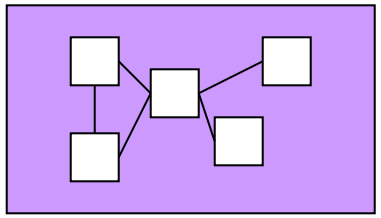
OHDSI: an open science community

Common data model to structure observational data and enable standardized analytics



Common data model to enable standardized analytics

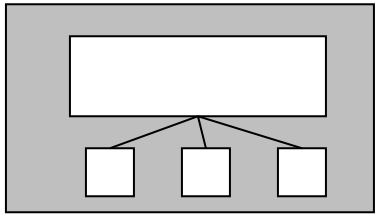
Source 1 raw data



Electronic health records

VA
PEDSNet
CPRD

Source 2 raw data



Administrative claims

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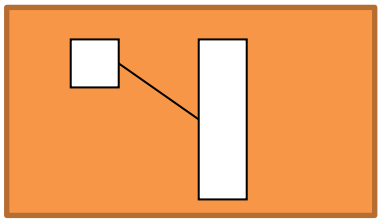
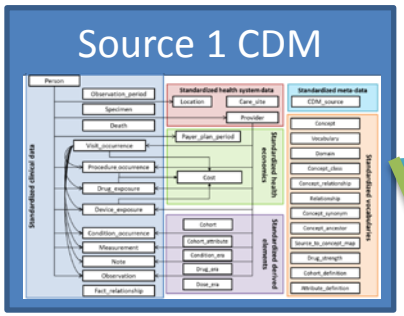
Source 3 raw data

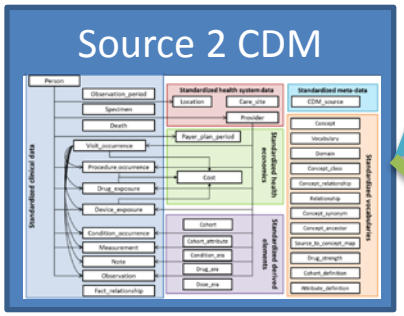


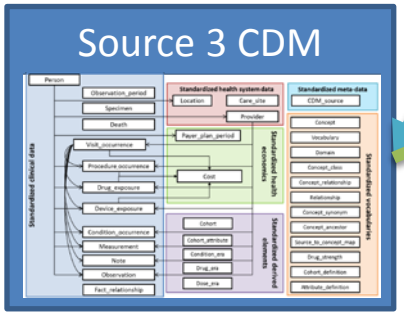
Clinical data

SEER
NHANES
BTRIS

Transformation to OMOP common data model







Open-source analysis code

Open evidence

What is OHDSI's strategy to deliver reliable evidence?

- **Methodological research**
  - Develop new approaches to observational data analysis
  - Evaluate the performance of new and existing methods
  - Establish empirically-based scientific best practices
- **Open-source analytics development**
  - Design tools for data transformation and standardization
  - Implement statistical methods for large-scale analytics
  - Build interactive visualization for evidence exploration
- **Clinical evidence generation**
  - Identify clinically-relevant questions that require real-world evidence
  - Execute research studies by applying scientific best practices through open-source tools across the OHDSI international data network
  - Promote open-science strategies for transparent study design and evidence dissemination

Classifying questions across the patient journey

- **Clinical characterization:** What happened to them?
  - What treatment did they choose after diagnosis?
  - Which patients chose which treatments?
  - How many patients experienced the outcome after treatment?

- **Patient-level prediction:** What will happen to me?
  - What is the probability that I will develop the disease?
  - What is the probability that I will experience the outcome?

- **Population-level effect estimation:** What are the causal effects?
  - Does treatment cause outcome?
  - Does one treatment cause the outcome more than an alternative?

Channeling Donald Rumsfeld

“Now what is the message there? The message is that there are no "knowns." There are things we know that we know. There are known unknowns. That is to say there are things that we now know we don't know. But there are also unknown unknowns. There are things we do not know we don't know. So when we do the best we can and we pull all this information together, and we then say well that's basically what we see as the situation, that is really only the known knowns and the known unknowns. And each year, we discover a few more of those unknown unknowns.

It sounds like a riddle. It isn't a riddle. It is a very serious, important matter.

There's another way to phrase that and that is that the absence of evidence is not evidence of absence. It is basically saying the same thing in a different way. Simply because you do not have evidence that something exists does not mean that you have evidence that it doesn't exist. ”

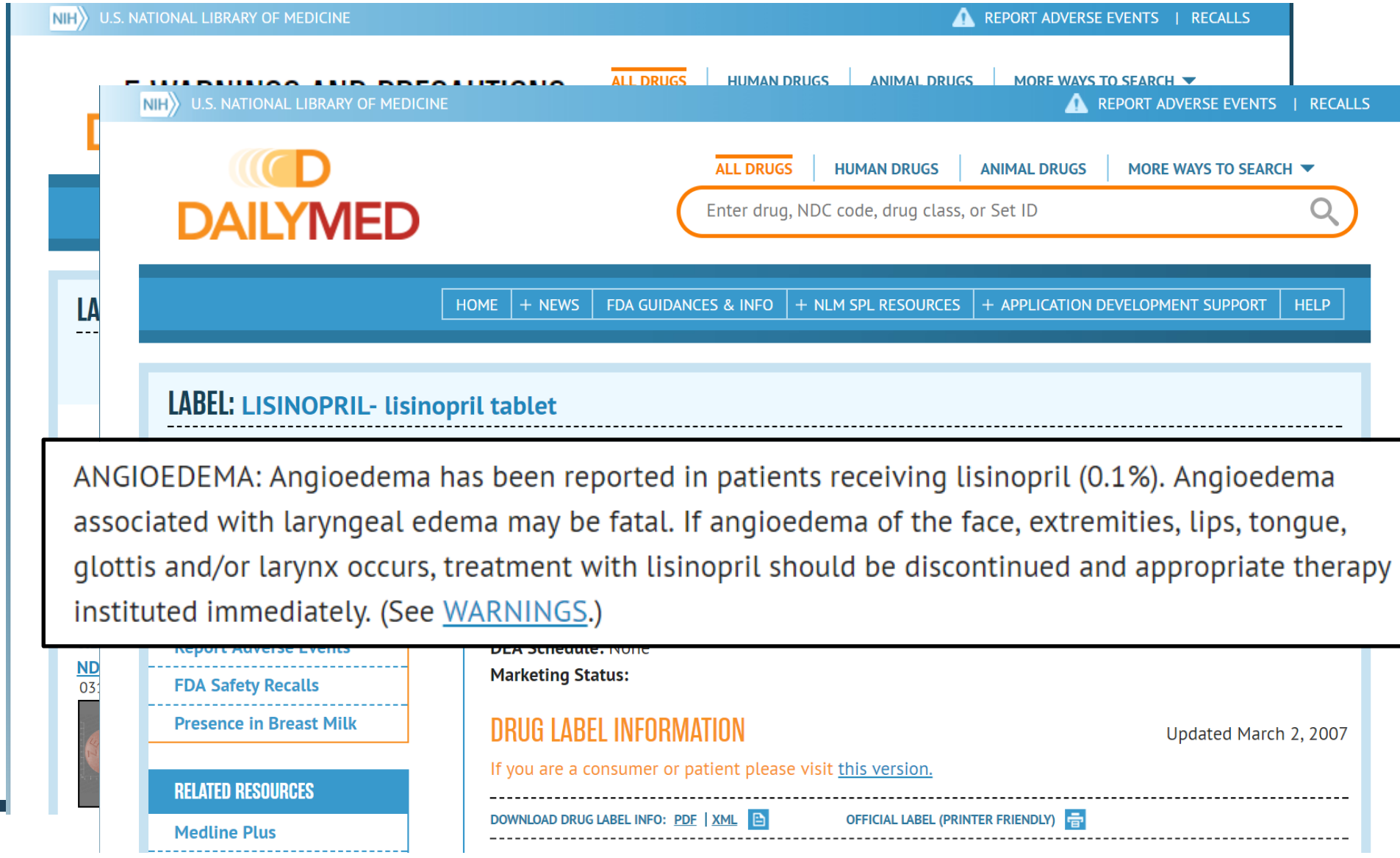
NATO 2002

“Things we know that we know”

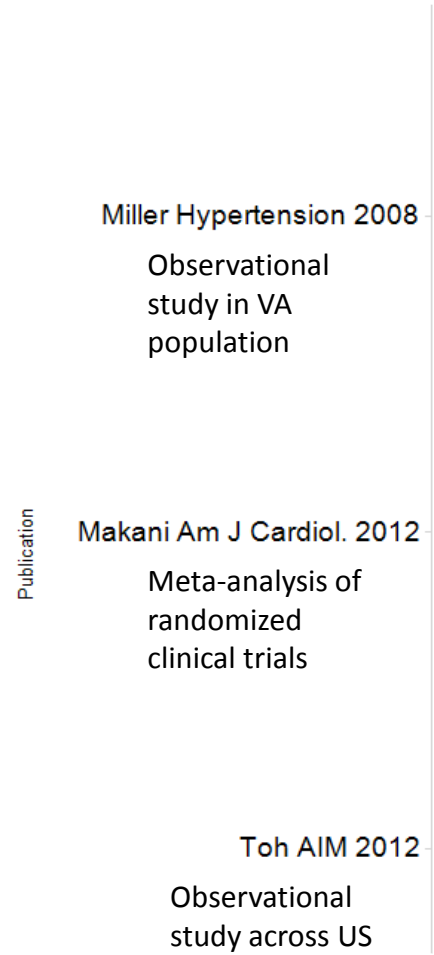
- What we think we know:
  - ACE inhibitors cause angioedema

- What we want to know:
  - Clinical characterization: Incidence of angioedema in patients exposed to ACE inhibitors
  - Population-level effect estimation:
    - Safety surveillance: Strength of association with ACE inhibitor vs. counterfactual
    - Comparative effectiveness: Strength of association with ACE inhibitor, relative to alternative treatments
  - Patient-level prediction: Probability that a patient will experience event, given baseline characteristics

What's on the product label?



What's the published evidence?



Incidence rate estimate predicated on 2 assumptions:

- Observed data represents a random sample of a target population
- Estimator in unbiased, so no systematic error

Publication	Person-years	Events	Incidence (per 1000 person-years)	95% CI (Incidence rate per 1000 person-years)
Miller Hypertension 2008	179,088	352	1.97	(1.76-2.17)
Makani Am J Cardiol. 2012	185,067	394	3.00	(2.80-3.20)
Toh AIM 2012	753,105	3,301	4.38	(4.23-4.53)

How does it get distilled to clinicians?

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Topic Outline

- INTRODUCTION
- EPIDEMIOLOGY
- CLINICAL FEATURES
  - Affected areas
    - Face, mouth, and upper airway
    - Intestine
  - Time course
  - Severity
  - Recurrence after stopping ACE inhibitor therapy
- PATHOPHYSIOLOGY
  - ACE inhibition
  - Role of bradykinin in angioedema
- RISK FACTORS
  - Possible risk factors
  - Predisposing genetic factors
- DIAGNOSIS
  - Evaluation of abdominal pain
- DIFFERENTIAL DIAGNOSIS
- TREATMENT
  - Airway management
  - Discontinue ACE inhibitor
  - Other interventions
  - Additional therapies for severe or persistent symptoms
    - Icatibant
    - Ecallantide
    - Fresh frozen plasma
    - Purified C1 inhibitor concentrate

ACE inhibit

Authors
Autumn Chandle
Aleena Banerji, M

INTRODUCTION

Angiotensin-conver
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pain due to intestina

This topic reviews t
induced angioedem
causes is found else
Pathogenesis and c

EPIDEMIOLOGY

Angiotensin-conver
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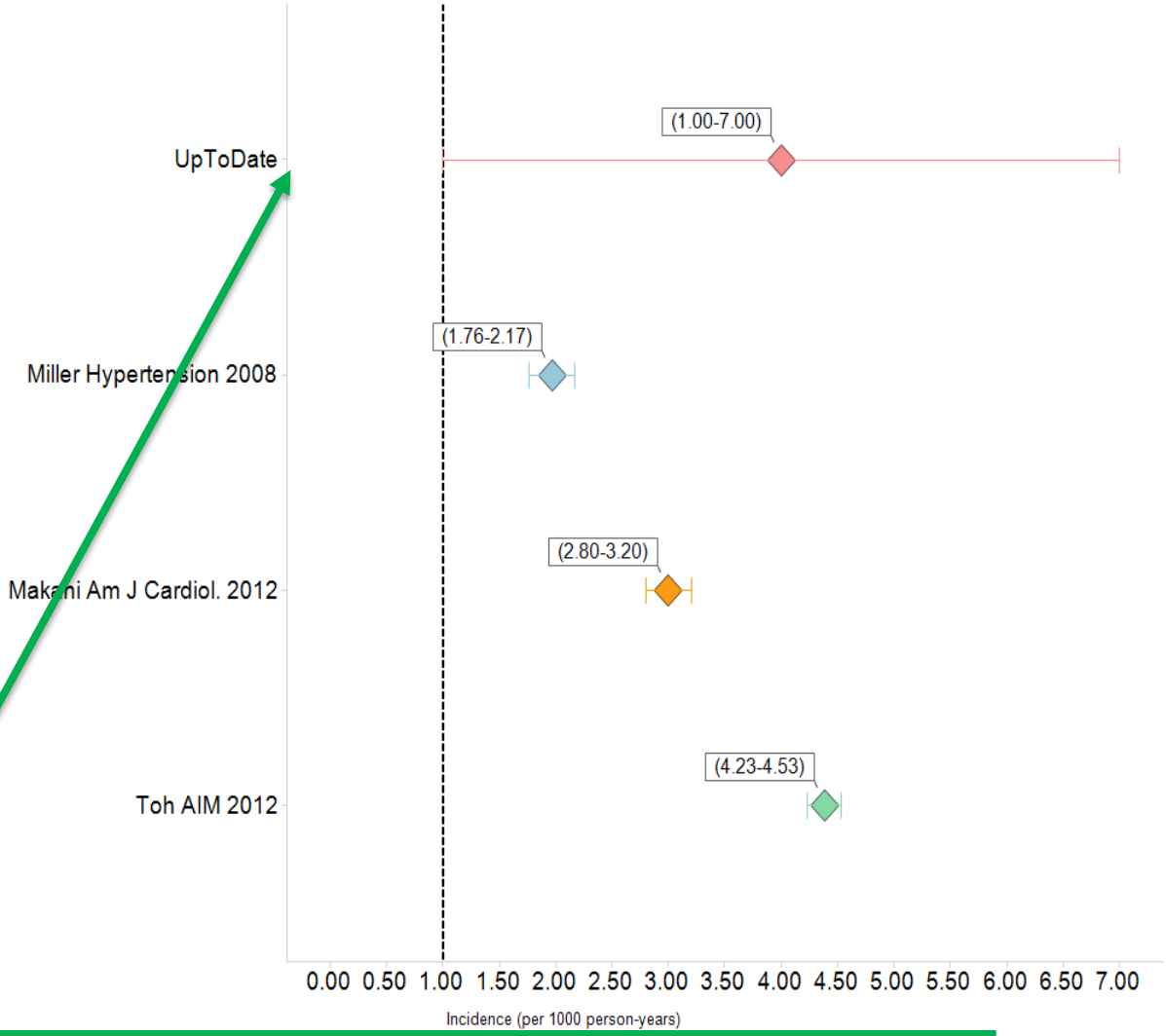
myocardial infarctio



The overall incidence of angioedema related to ACE inhibitors has been estimated between 0.1 percent and 0.7 percent [1-5,14-16]. However, the lower end of this range may overlap with the background rate of angioedema in the general population. In the TRANSCEND trial of ACE inhibitor-intolerant individuals given an angiotensin II receptor blocker (ARB) or placebo, rates of angioedema were 0.07 and 0.1 percent in the ARB and placebo groups, respectively [17].

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, Pha
Xiao Ding, PhD; Adrian F. Hernandez, MD; Mark Levenson, PhD; Lingling Li, PhD; Carolyn McCloskey
Azadeh Shoaibi, MS, MHS; Eileen Wu, PharmD; Gwen Zornberg, MD, MS, ScD; Sean Hennessy, Pharm

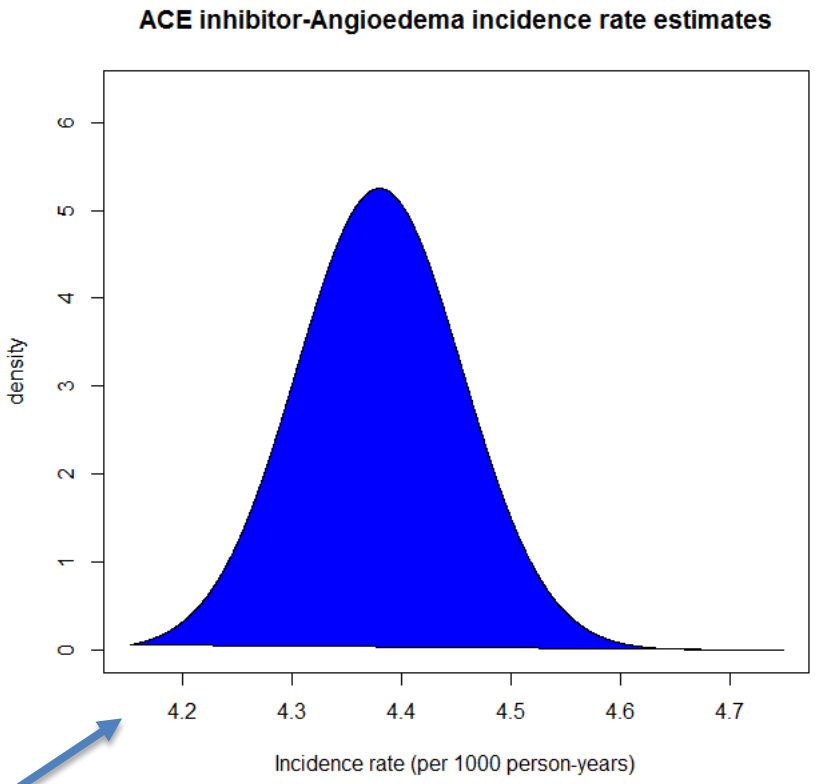
Background: Although certain drugs that target the renin-angiotensin-aldosterone system are linked to an increased risk for angioedema, data on their absolute and comparative risks are limited. We assessed the risk for angioedema associated with the use of angiotensin-converting enzyme inhibitors (ACEIs),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

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

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

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

Arch Intern Med. 2012;172(20):1582-1589.
Published online October 15, 2012.
doi:10.1001/2013.jamainternmed.34



Successful Comparison of US Food and Drug Administration Sentinel Analysis Tools to Traditional Approaches in Quantifying a Known Drug-Adverse Event Association

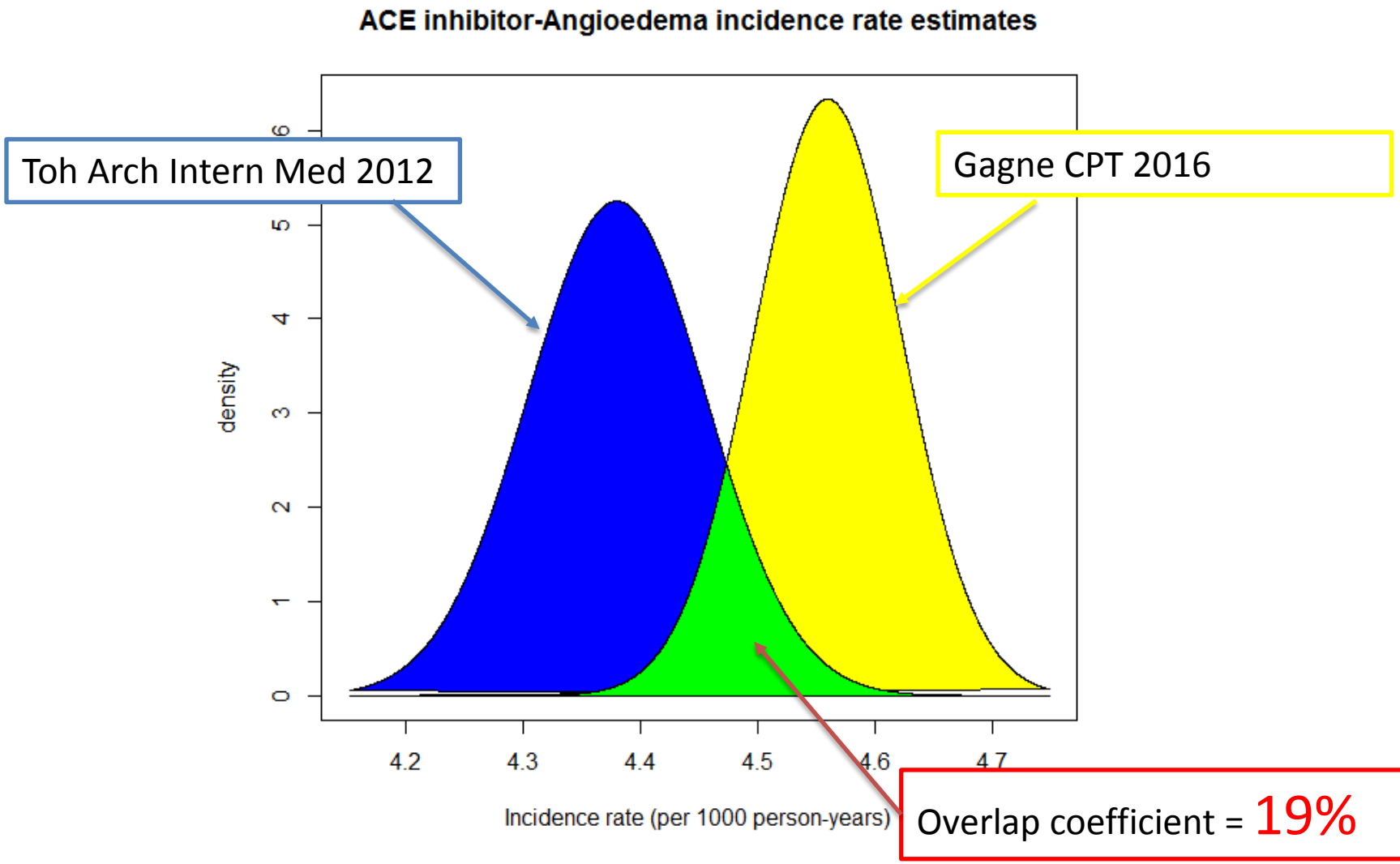
JJ Gagne[1], X Han[2], S Hennessy[2], CE Leonard[2], EA Chrischilles[3], RM Carnahan[3], SV Wang[1], C Fuller[4], A Iyer[4], H Katcoff[4], TS Woodworth[4], P Archdeacon[5], TE Meyer[6], S Schneeweiss[1] and S Toh[4]

The US Food and Drug Administration's Sentinel system has developed the capability to conduct active safety surveillance of marketed medical products in a large network of electronic healthcare databases. We assessed the extent to which the newly developed, semiautomated Sentinel Propensity Score Matching (PSM) tool could produce the same results as a customized protocol-driven assessment, which found an adjusted hazard ratio (HR) of 3.04 (95% confidence interval [CI], 2.81–3.27) comparing angioedema in patients initiating angiotensin-converting enzyme (ACE) inhibitors vs. beta-blockers. Using data from 13 Data Partners between 1 January 2008, and 30 September 2013, the PSM tool identified 2,211,215 eligible ACE inhibitor and 1,673,682 eligible beta-blocker initiators. The tool produced an HR of 3.14 (95% CI, 2.86–3.44). This comparison provides initial evidence that Sentinel analytic tools can produce findings similar to those produced by a highly customized protocol-driven assessment.

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
Unmatched Analysis (Data Partner-adjusted only)					
ACE inhibitors	2,211,215	1,131,526	0.51	5,158	4.56

Comparing incidence rate estimates between Sentinel analyses



“Known unknowns”

“Known unknowns” #1: Do PPIs increase risk of death?

Open Access Research

BMJ Open

Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans

Yan Xie,[1] Benjamin Bowe,[1] Tingting Li,[1,2] Hong Xian,[1,3] Yan Yan,[1,4] Ziyad Al-Aly[1,2,5,6]

To cite: Xie Y, Bowe B, Li T, *et al*. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. *BMJ Open* 2017;**7**:e015735. doi:10.1136/bmjopen-2016-015735

► Prepublication history and additional material are available. To view these files, please visit the journal online (http://dx.doi.org/ 10.1136/bmjopen-2016-015735).

Received 23 December 2016
Revised 20 March 2017
Accepted 22 March 2017

ABSTRACT

Objective Proton pump inhibitors (PPIs) are widely used, and their use is associated with increased risk of adverse events. However, whether PPI use is associated with excess risk of death is unknown. We aimed to examine the association between PPI use and risk of all-cause mortality.

Design Longitudinal obser

Setting US Department of

Participants Primary coho
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(n=349 312); additional coh
(n=3 288 092) and PPI vers
(n=2 887 030).

Main outcome measures

Results Over a median fol
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score (HR 1.16, CI 1.13 to 1
inclusion estimation (HR 1.2
time-dependent propensity
1.34, CI 1.29 to 1.39). The
when considering PPI use v
to 1.15), and PPI use versus
(HR 1.23, CI 1.22 to 1.24).
with PPI use was increased
gastrointestinal conditions:
1.24, CI 1.21 to 1.27), PPI u
CI 1.18 to 1.20) and PPI us
blockers (HR 1.22, CI 1.21
there was a graded associa
exposure and the risk of de

Conclusions The results suggest excess risk of death

Strengths and limitations of this study

- ► National large-scale data from a network of integrated health systems.
- ► Employed a new user design and developed a number of analytical approaches where we consistently found a significant association between

of osteoporotic fractures, including hip and

ABSTRACT

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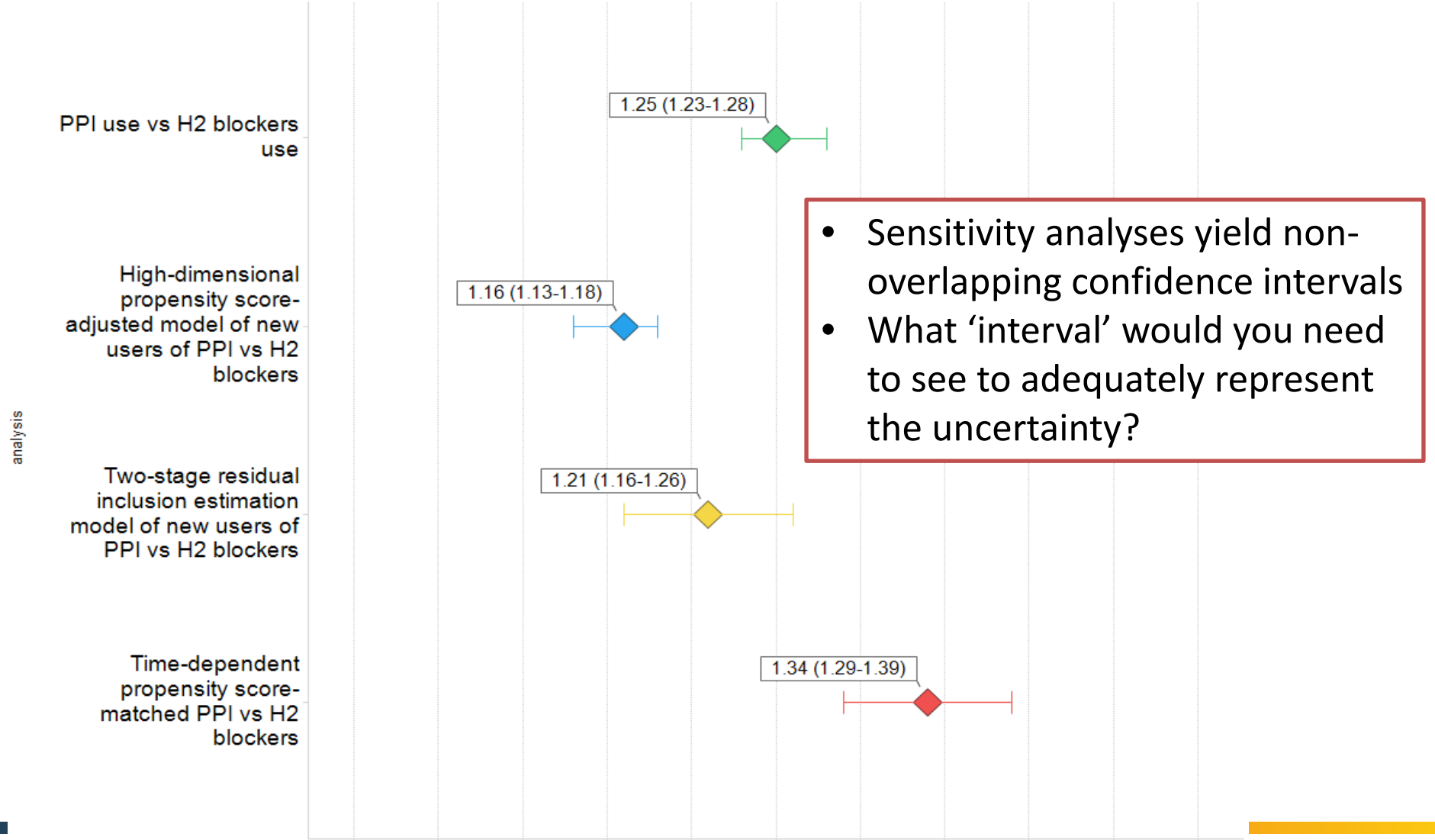
Results Over a median follow-up of 5.71 years (IQR 5.11–6.37), PPI use was associated with increased risk of death compared with H2 blockers use (HR 1.25, CI 1.23 to 1.28). Risk of death associated with PPI use was higher in analyses adjusted for high-dimensional propensity score (HR 1.16, CI 1.13 to 1.18), in two-stage residual inclusion estimation (HR 1.21, CI 1.16 to 1.26) and in 1:1 time-dependent propensity score-matched cohort (HR 1.34, CI 1.29 to 1.39). The risk of death was increased when considering PPI use versus no PPI (HR 1.15, CI 1.14 to 1.15), and PPI use versus no PPI and no H2 blockers (HR 1.23, CI 1.22 to 1.24). Risk of death associated with PPI use was increased among participants without gastrointestinal conditions: PPI versus H2 blockers (HR 1.24, CI 1.21 to 1.27), PPI use versus no PPI (HR 1.19, CI 1.18 to 1.20) and PPI use versus no PPI and no H2 blockers (HR 1.22, CI 1.21 to 1.23). Among new PPI users, there was a graded association between the duration of exposure and the risk of death.

Conclusions The results suggest excess risk of death

outcomes.[1] A number of studies have shown that PPI use is associated with significant risk of acute interstitial nephritis.[3–5] Recent studies established an association between exposure to PPI and risk of chronic kidney disease (CKD), kidney disease progression and end-stage renal disease.[2 6 7] Results from a large prospective observational German cohort suggest that patients receiving PPI had a higher risk of incident dementia.[8] Several reports highlighted a rare but potentially fatal risk of hypomagnesemia among users of PPI.[9–11] PPI use has been associated with increased risk of both incident and recurrent *Clostridium difficile* infections.[12] Several observational analyses have shown that PPI use was also associated with increased risk of osteoporotic fractures, including hip and

The risk of death was increased when considering PPI use versus no PPI (HR 1.15, CI 1.14 to 1.15), and PPI use versus no PPI and no H2 blockers (HR 1.23, CI 1.22 to 1.24).

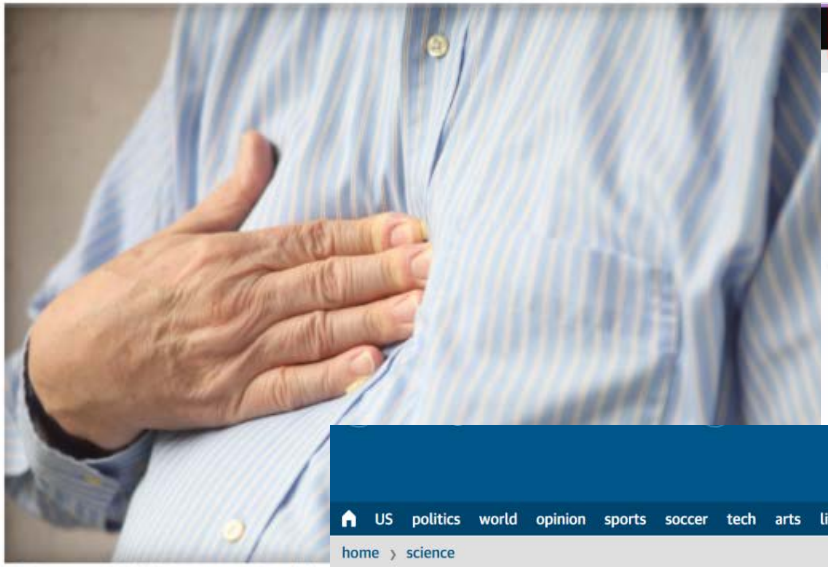
"Known unknowns" #1: Do PPIs increase risk of death?



- Sensitivity analyses yield non-overlapping confidence intervals
- What 'interval' would you need to see to adequately represent the uncertainty?

By MARY BROPHY MARCUS / CBS NEWS / July 3, 2017, 6:30 PM

Some heartburn drugs linked with higher risk of death



Proton pump inhibitors, used by million observational study suggests. / GET

CNN Health » Diet + Fitness | Living Well | Parenting + Family Live TV U.S. Edition +

Heartburn drugs tied to increased risk of early death, study says

By Susan Scutti, CNN

Updated 2:59 PM ET, Tue July 4, 2017

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Drugs

People taking heartburn drugs could have higher risk of death, study claims

Research suggests people on proton pump inhibitors are more likely to die than those taking different antacid or none at all

Illustration of heartburn. The researchers urged people to check if they really need PPIs. Photograph: Getty Images/Fanatic Studio

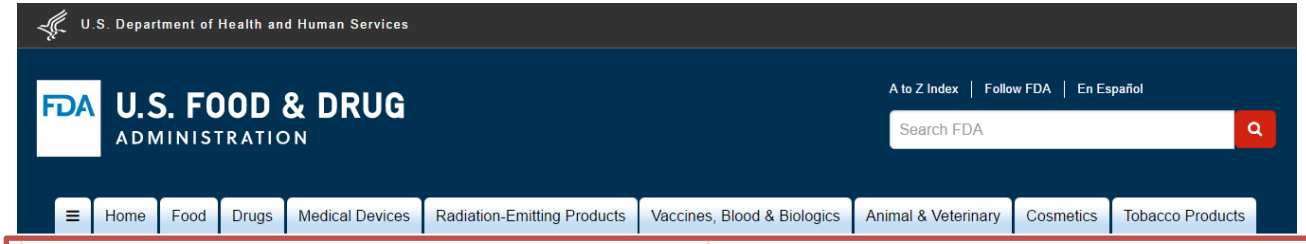
3,397

James Rudd

@jhfrudd

Tuesday 4 July 2017 01.00 EDT

“Known unknowns” #2: Levetiracetam and Angioedema



Keppra (levetiracetam) tablet, oral solution, injection	Angioedema	FDA is evaluating the need for regulatory action.

FDA Adverse Events Reporting System (FAERS)

- FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files
- FDA Adverse Events Reporting System (FAERS) Public Dashboard
- Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)
- FDA Adverse Events Reporting System (FAERS) Electronic Submissions

Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS) between October - December 2015

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

Product Name: Trade (Active Ingredient) *or* Product Class	Potential Signal of a Serious Risk / New Safety Information	Additional Information (as of March 31, 2016)
Calcium gluconate injection	Potential for wrong drug error	The container labels for calcium gluconate were revised to better differentiate the product from sterile water for injection. Calcium gluconate labeling
Epinephrine auto-injectors	Clostridium perfringens infection	FDA is evaluating the need for regulatory action.
Epipen (epinephrine) injection Epipen Jr (epinephrine) injection	Lacerations and embedded needles	FDA is evaluating the need for regulatory action.
Harvoni (ledipasvir/sofosbuvir) tablet Olysio (simeprevir) capsule Sovaldi (sofosbuvir) tablet	Rhabdomyolysis	FDA is evaluating the need for regulatory action.
Iodinated contrast agents (numerous products)	Myasthenia gravis exacerbation	FDA is evaluating the need for regulatory action.
Keppra (levetiracetam) tablet, oral solution, injection	Angioedema	FDA is evaluating the need for regulatory action.

https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm491645.htm

Levetiracetam and Risk of Angioedema in patients with Seizure Disorder

Objective: To assess the risk between exposure to Keppra (levetiracetam) and angioedema.

Rationale: The Food and Drug Administration (FDA) has recently announced that they are evaluating the need for regulatory action regarding a potential association between exposure to the anti-seizure drug Keppra and angioedema. OHDSI seeks to support evidence generation for questions of importance to FDA and other stakeholders seeking to protect and promote the public's health.

Project Lead(s): Jon Duke, Patrick Ryan, Marc Suchard, George Hripcsak, [?Adler], Christian Reich, Yuriy Khoma, Marie-Sophie Schwalm, Yonghui Hu, [Stanford- Juan?], Martijn Schuemie.

Coordinating Institution(s): Regenstrief Institute / Georgia Tech

Participating Institution(s): Regenstrief Institute, Georgia Tech, Janssen Research and Development, Columbia University, University of California Los Angeles, University of Texas Houston, Stanford University, QuintilesIMS.

Full Protocol: Keppra and Angioedema Risk Protocol

Initial Proposal Date: 5/3/2016

Launch Date: 5/18/2016

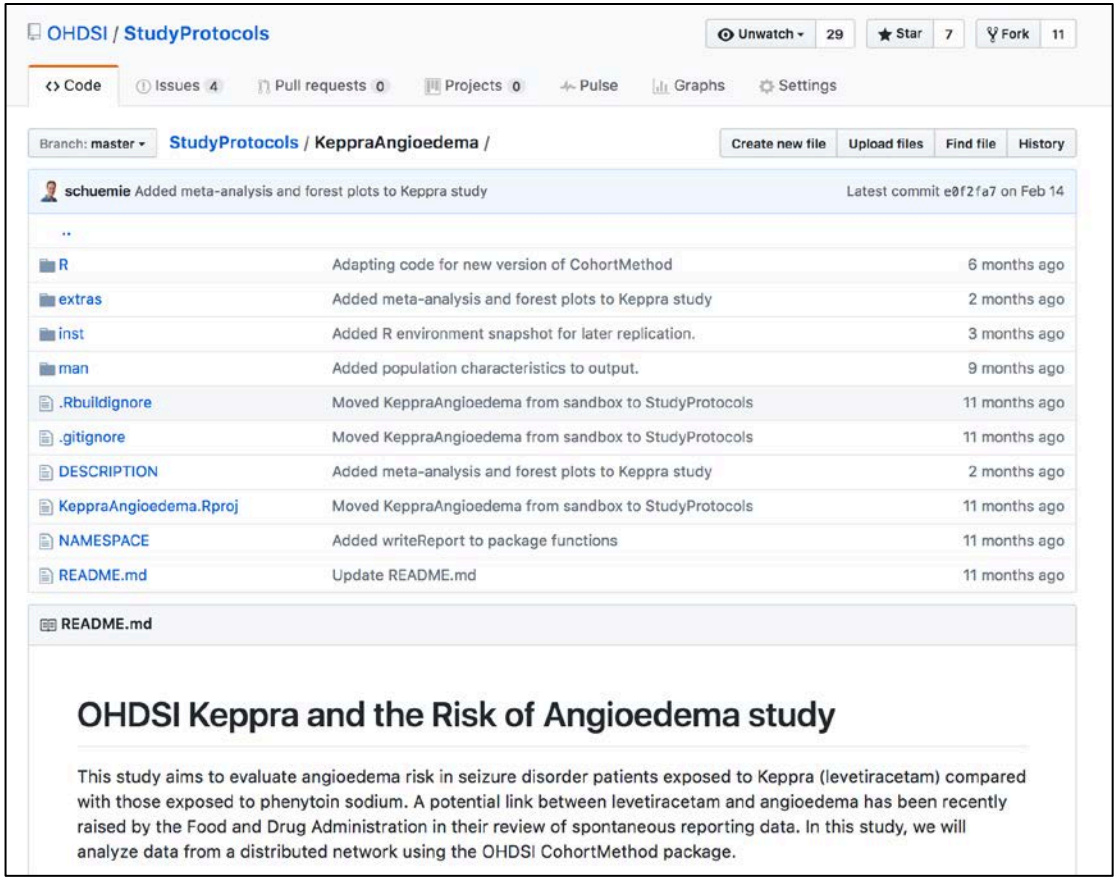
Receive Results for Analysis Date: 7/15/2016

Study Closure Date: 12/1/2016 (**Study closed**)

Results Submission: Via the OHDSI Sharing module embedded in study or via Email.

Open-source code development

- Leveraged OHDSI CohortMethod R package
- Code tested at 2 sites prior to study start
- All code posted on GitHub



Study Overview

- New user comparative cohort design
  - T: levetiracetam
  - C: phenytoin
  - O: incident angioedema
- Time at risk defined in two ways: 1) per protocol and 2) intent to treat
- Model: Propensity score-matched Cox proportional hazards
- To identify residual bias, calculated HRs for 100 negative controls in order to compute calibrated p-values for angioedema in each dataset
- Performed meta-analysis and evaluated heterogeneity between databases

Epilepsia
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BRIEF COMMUNICATION

Risk of angioedema associated with levetiracetam compared with phenytoin: Findings of the observational health data sciences and informatics research network

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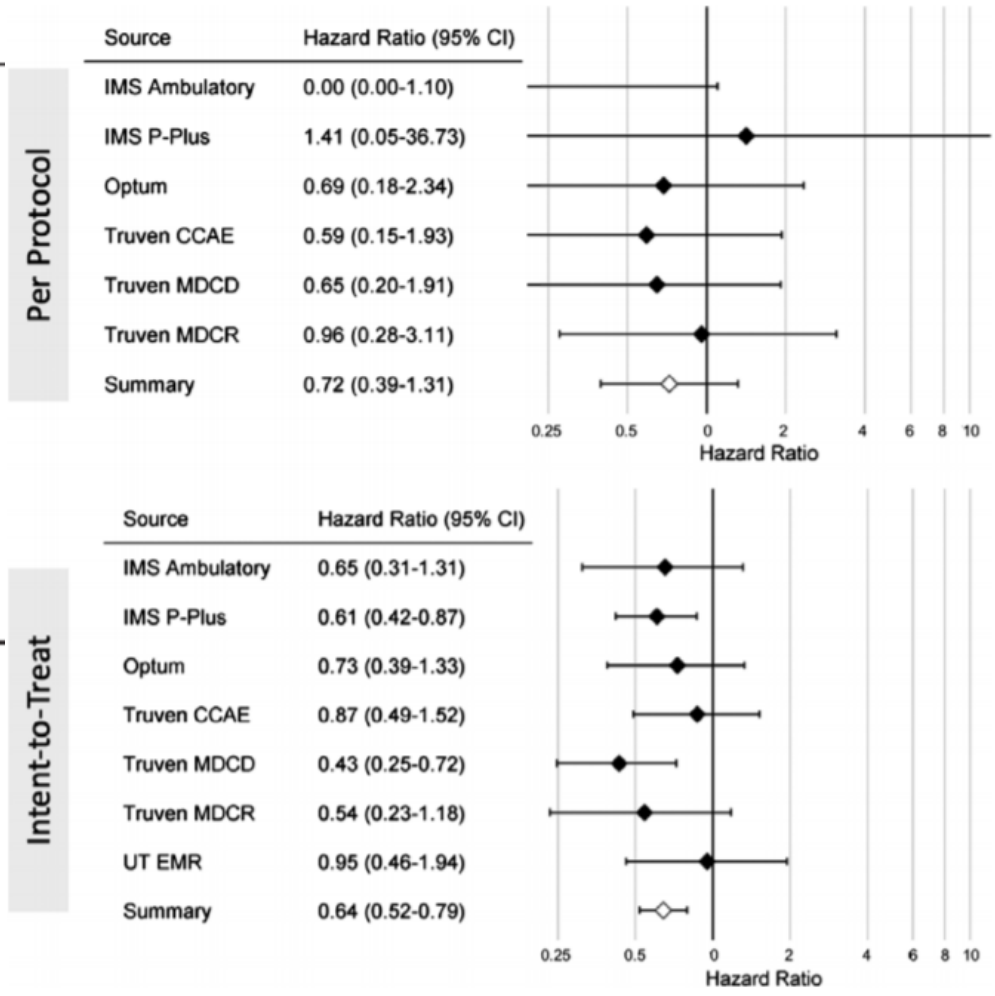
Summary

Recent adverse event reports have raised the question of increased angioedema risk associated with exposure to levetiracetam. To help address this question, the Observational Health Data Sciences and Informatics research network conducted a retrospective observational new-user cohort study of seizure patients exposed to levetiracetam (n = 276,665) across 10 databases. With phenytoin users (n = 74,682) as a comparator group, propensity score-matching was conducted and hazard ratios computed for angioedema events by per-protocol and intent-to-treat analyses. Angioedema events were rare in both the levetiracetam and phenytoin groups (54 vs. 71 in per-protocol and 248 vs. 435 in intent-to-treat). No significant increase in angioedema risk with levetiracetam was seen in any individual database (hazard ratios ranging from 0.43 to 1.31). Meta-analysis showed a summary hazard ratio of 0.72 (95% confidence interval [CI] 0.39–1.31) and 0.64 (95% CI 0.52–0.79) for the per-protocol and intent-to-treat analyses, respectively. The results suggest that levetiracetam has the same or lower risk for angioedema than phenytoin, which does not currently carry a labeled warning for angioedema. Further studies are warranted to evaluate angioedema risk across all antiepileptic drugs.

Illustrating the value of a global network study

Table 1. Angioedema events in propensity score-matched levetiracetam and phenytoin exposed patients using per-protocol analysis and intent-to-treat analysis

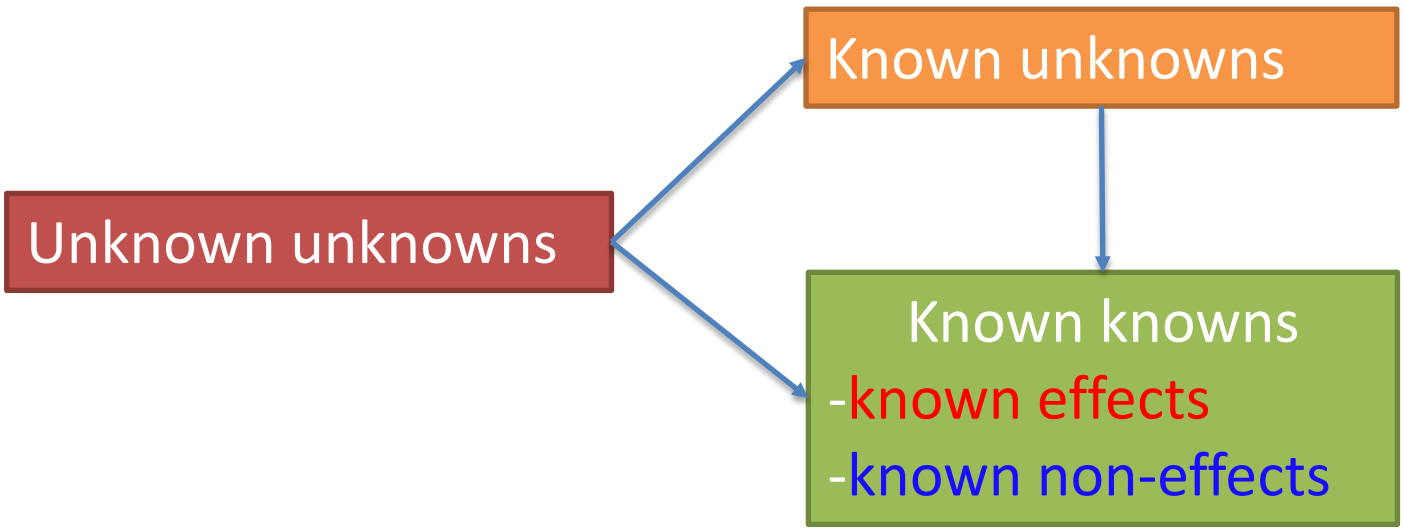
		Levetiracetam		
	Source	Patients	Days treated	Events
Per protocol	IMS P-Plus	6,893	351,090	2
	Optum Clinformatics	10,819	3,150,504	14
	Truven CCAE	13,088	3,549,812	13
	Truven MDCD	8,227	1,883,518	15
	Truven MDCR	4,592	1,400,797	8
	IMS Ambulatory	8,762	618,757	1
	Cerner Health Facts (UT)	5,584	54,852	1
	Columbia	501	111,307	0
	IMS French EMR	7	552	0
	Stanford EMR	404	12,313	0
Intent-to-treat	IMS P-Plus	18,213	16,233,093	78
	Optum Clinformatics	10,890	9,101,161	31
	Truven CCAE	13,434	11,347,801	41
	Truven MDCD	8,536	7,328,658	41
	Truven MDCR	4,656	4,317,982	15
	IMS Ambulatory	8,762	9,978,497	19
	Cerner Health Facts (UT)	9,094	5,842,344	22
	Columbia	553	523,215	1
	IMS French EMR	7	5,542	0
	Stanford EMR	404	342,136	0



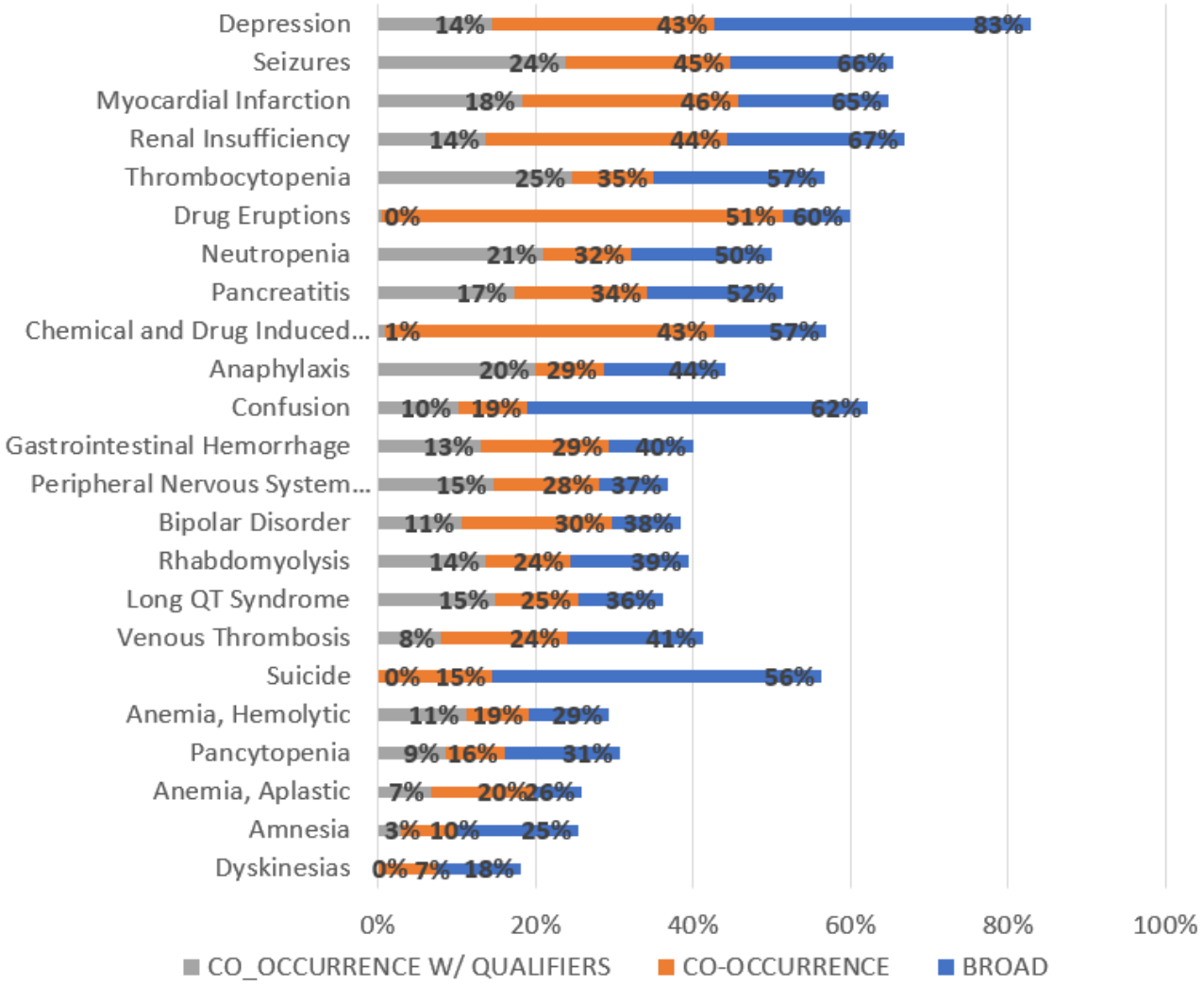
- >55,000 patients exposed across 10 sites
- Quantify observed incidence of event for public health impact
- Population-level effect estimation provides strength and consistency toward causality assessment (which couldn't have been done by any one site alone)

“those unknown unknowns”

A framing of a goal for a ‘risk identification’ system:



Existing evidence in published literature



HOMER implementation of Hill's viewpoints

Potential uses of a public 'big data' evidence generation system

- Clinical characterization: descriptive summary to put real-world context around treatment utilization
  - Demographics
  - Prior conditions
  - Prior health service utilization (drugs, procedures, measurements)
- Outcome incidence: descriptive summary of frequency that outcomes occur during or after exposure
- Population-level effect estimation
  - Monitor known risks
  - Search for event known to be on label to estimate incidence and magnitude of effect
  - Compare risk of known effect between alternative treatments
  - Search for effects for potential risk
  - Explore outcomes that show increased effects across databases
  - Explore outcomes that are 'high incidence' and 'high seriousness'

Questions?

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