Optimal methods approaches in Existing Data: Lessons from OMOP and OHDSI communities

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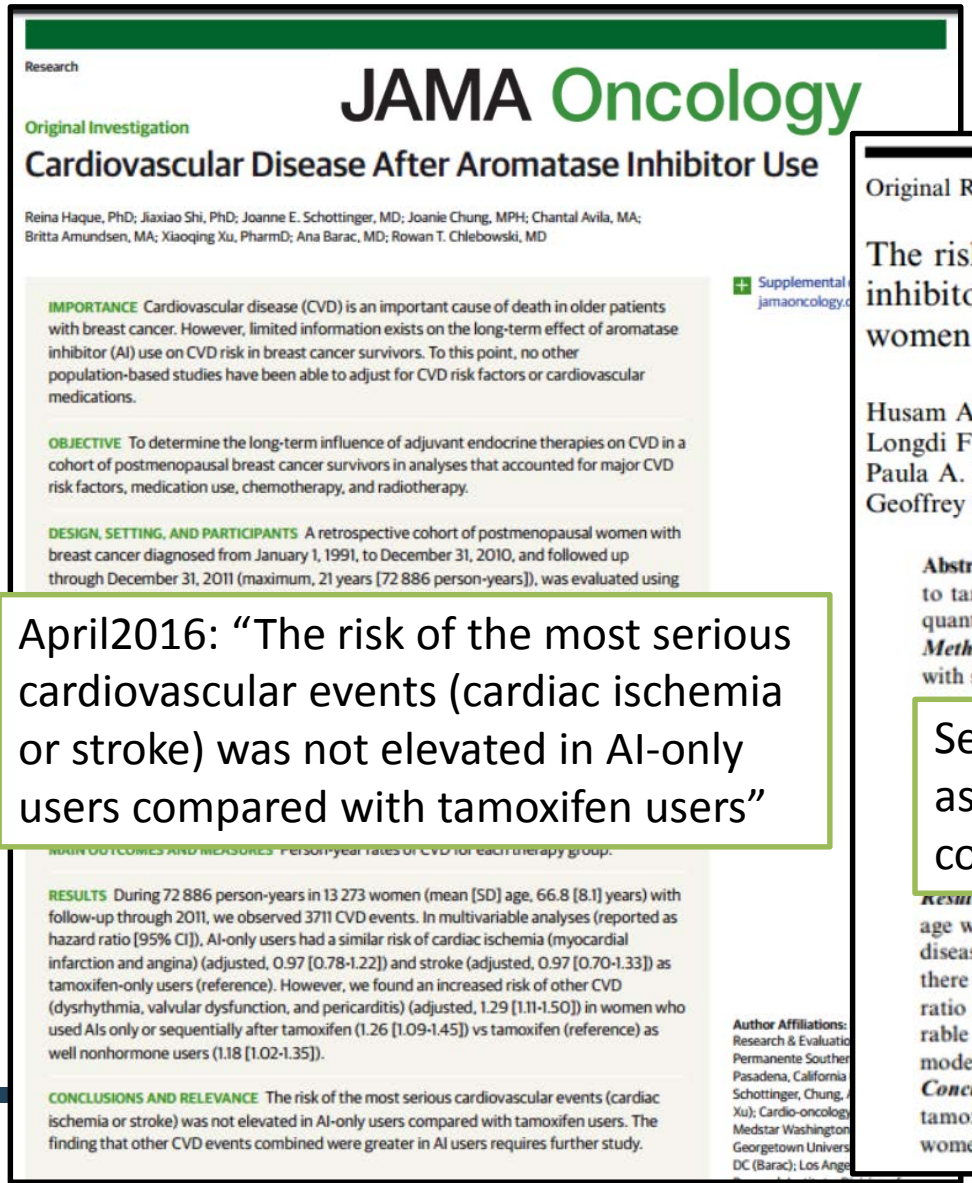
19 October 2016

What is the quality of the current evidence from observational analyses?



Research

JAMA Oncology

Original Investigation

Cardiovascular Disease After Aromatase Inhibitor Use

Reina Haque, PhD; Jiaxiao Shi, PhD; Joanne E. Schottinger, MD; Joanie Chung, MPH; Chantal Avila, MA; Britta Amundsen, MA; Xiaoqing Xu, PharmD; Ana Barac, MD; Rowan T. Chlebowski, MD

IMPORTANCE Cardiovascular disease (CVD) is an important cause of death in older patients with breast cancer. However, limited information exists on the long-term effect of aromatase inhibitor (AI) use on CVD risk in breast cancer survivors. To this point, no other population-based studies have been able to adjust for CVD risk factors or cardiovascular medications.

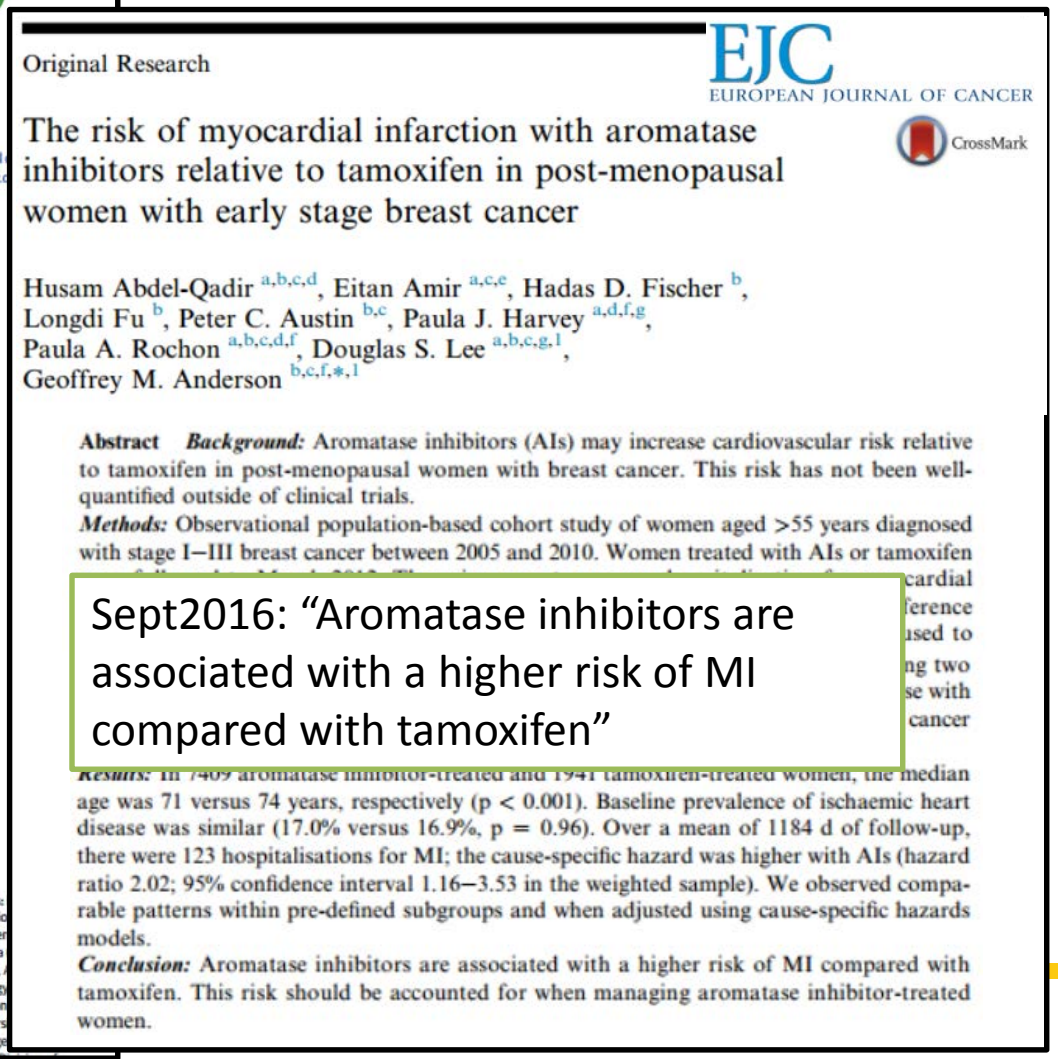
OBJECTIVE To determine the long-term influence of adjuvant endocrine therapies on CVD in a cohort of postmenopausal breast cancer survivors in analyses that accounted for major CVD risk factors, medication use, chemotherapy, and radiotherapy.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort of postmenopausal women with breast cancer diagnosed from January 1, 1991, to December 31, 2010, and followed up through December 31, 2011 (maximum, 21 years [72 886 person-years]), was evaluated using

RESULTS During 72 886 person-years in 13 273 women (mean [SD] age, 66.8 [8.1] years) with follow-up through 2011, we observed 3711 CVD events. In multivariable analyses (reported as hazard ratio [95% CI]), AI-only users had a similar risk of cardiac ischemia (myocardial infarction and angina) (adjusted, 0.97 [0.78-1.22]) and stroke (adjusted, 0.97 [0.70-1.33]) as tamoxifen-only users (reference). However, we found an increased risk of other CVD (dysrhythmia, valvular dysfunction, and pericarditis) (adjusted, 1.29 [1.11-1.50]) in women who used AIs only or sequentially after tamoxifen (1.26 [1.09-1.45]) vs tamoxifen (reference) as well nonhormone users (1.18 [1.02-1.35]).

CONCLUSIONS AND RELEVANCE The risk of the most serious cardiovascular events (cardiac ischemia or stroke) was not elevated in AI-only users compared with tamoxifen users. The finding that other CVD events combined were greater in AI users requires further study.

April2016: "The risk of the most serious cardiovascular events (cardiac ischemia or stroke) was not elevated in AI-only users compared with tamoxifen users"



Original Research

EJC EUROPEAN JOURNAL OF CANCER

The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer

Husam Abdel-Qadir [a,b,c,d], Eitan Amir [a,c,e], Hadas D. Fischer [b], Longdi Fu [b], Peter C. Austin [b,c], Paula J. Harvey [a,d,f,g], Paula A. Rochon [a,b,c,d,f], Douglas S. Lee [a,b,c,g,1], Geoffrey M. Anderson [b,c,f,*,1]

Abstract ***Background:*** Aromatase inhibitors (AIs) may increase cardiovascular risk relative to tamoxifen in post-menopausal women with breast cancer. This risk has not been well-quantified outside of clinical trials.

Methods: Observational population-based cohort study of women aged >55 years diagnosed with stage I–III breast cancer between 2005 and 2010. Women treated with AIs or tamoxifen

Results: In 7409 aromatase inhibitor-treated and 1941 tamoxifen-treated women, the median age was 71 versus 74 years, respectively ($p < 0.001$). Baseline prevalence of ischaemic heart disease was similar (17.0% versus 16.9%, $p = 0.96$). Over a mean of 1184 d of follow-up, there were 123 hospitalisations for MI; the cause-specific hazard was higher with AIs (hazard ratio 2.02; 95% confidence interval 1.16–3.53 in the weighted sample). We observed comparable patterns within pre-defined subgroups and when adjusted using cause-specific hazards models.

Conclusion: Aromatase inhibitors are associated with a higher risk of MI compared with tamoxifen. This risk should be accounted for when managing aromatase inhibitor-treated women.

Sept2016: "Aromatase inhibitors are associated with a higher risk of MI compared with tamoxifen"

EXTENDED REPORT

Non-steroidal anti-inflammatory drugs and myocardial infarctions: comparative systematic review of evidence from observational studies and randomised controlled trials

P A Scott, G H Kingsley, C M Smith, E H Choy, D L Scott

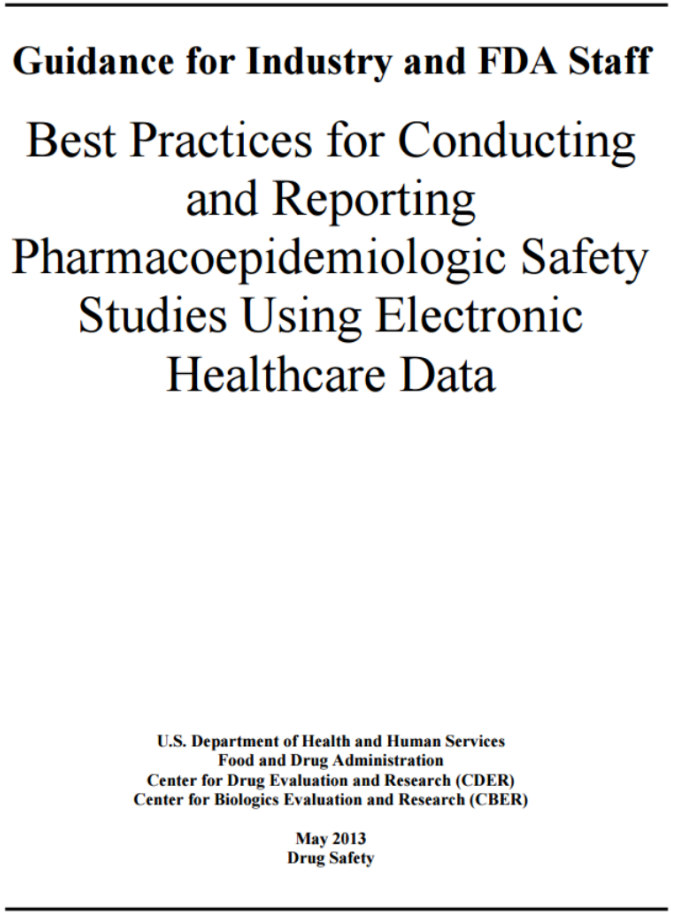
Ann Rheum Dis 2007;**66**:1296–1304. doi: 10.1136/ard.2006.068650

Study or subcategory	Treatment n/N	Control n/N	OR (random) 95% CI	Year
García Rodríguez[18]	167/669	581/3014		2000
Rahme[19]	1062/12 024	708/12 376		2002
Schlienger[20]	231/1733	745/6981		2002
Solomon[21]	390/3702	1506/14 865		2002
Garcia Rodriguez[22]	580/2458	1989/10 198		2004
Kimmel[23]	200/1055	1357/4153		2004
Fischer[24]	650/3853	2339/15 890		2005
Graham[25]	1765/6423	6518/25 238		2005
Hippisley-Cox[26]	1624/8886	10 532/81 605		2005
Johnsen[27]	805/4983	4808/51 930		2005
Kimmel[28]	364/1718	2309/6800		2005
Levesque[29]	607/1400	10 736/27 416		2005
Andersohn[30]	1350/2145	4637/7902		2006
Helin-Salmivaara[31]	2979/23 624	8076/100 600		2006
Total (95% CI)	74 673	368 968		
Total events: 12 774 (treatment), 56 841 (control)				
Test for heterogeneity: $\chi^2 = 622.31$, df = 13 (p<0.001), $I^2 = 97.9\%$				
Test for overall effect: Z = 1.85 (p = 0.06)				

Study or subcategory	Treatment n/N	Control n/N	RR (fixed) 95% CI	Year
Mamdami[34]	282/24 454	419/51 194		2003
Ray[32]	841/65 502	3049/257 069		2002
Ray[33]	577/47 721	3085/237 975		2002
Patel[35]	138/4345	684/13 035		2004
Chan[36]	574/220 613	1467/544 472		2006
Solomon[37]	3003/25 348	1847/17 067		2006
Total (95% CI)	387 983	1 120 812		
Total events: 5415 (treatment), 10 551 (control)				
Test for heterogeneity: $\chi^2 = 63.28$, df = 5 (p<0.001), $I^2 = 92.1\%$				
Test for overall effect: Z = 1.76 (p = 0.08)				

Figure 1 Analysis of 14 case-control and six cohort studies of myocardial infarction in users and non-users of non-steroidal anti-inflammatory drugs. n, events; N, subjects.

How do you *judge* what is a 'good' observational analysis?



Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2013
Drug Safety

- Validity of pre-specified protocol?
- Choice of study design?
- Selection of database?
- Quality of research team?
- Precision of confidence interval?

How could we **objectively measure** the reliability of observational evidence?

- **Consistency**: to what extent are the results robust to study design choices?
  - Reproducibility and external validity in multiple databases
  - Stability of exposure/outcome/covariate phenotype definitions
  - Statistical analysis parameter sensitivity
- **Discrimination**: to what extent can the analysis distinguish between null effects and positive effects?
  - Area under ROC curve (AUC) for estimates of negative and positive controls
  - Sensitivity/specificity/positive predictive value at decision thresholds
- **Calibration**: to what extent are the estimated statistics consistent with ground truth?
  - Systematic error distribution to evaluate magnitude of bias for effect estimates
  - Empirical null distribution using negative controls to determine if p-value truly represents probability of estimate when true RR = 1
  - Using positive controls to measure coverage probability to assess if 95% confidence interval actually contains the true effect size 95% of the time

Drug Saf (2013) 36 (Suppl 1):S143–S158
DOI 10.1007/s40264-013-0108-9

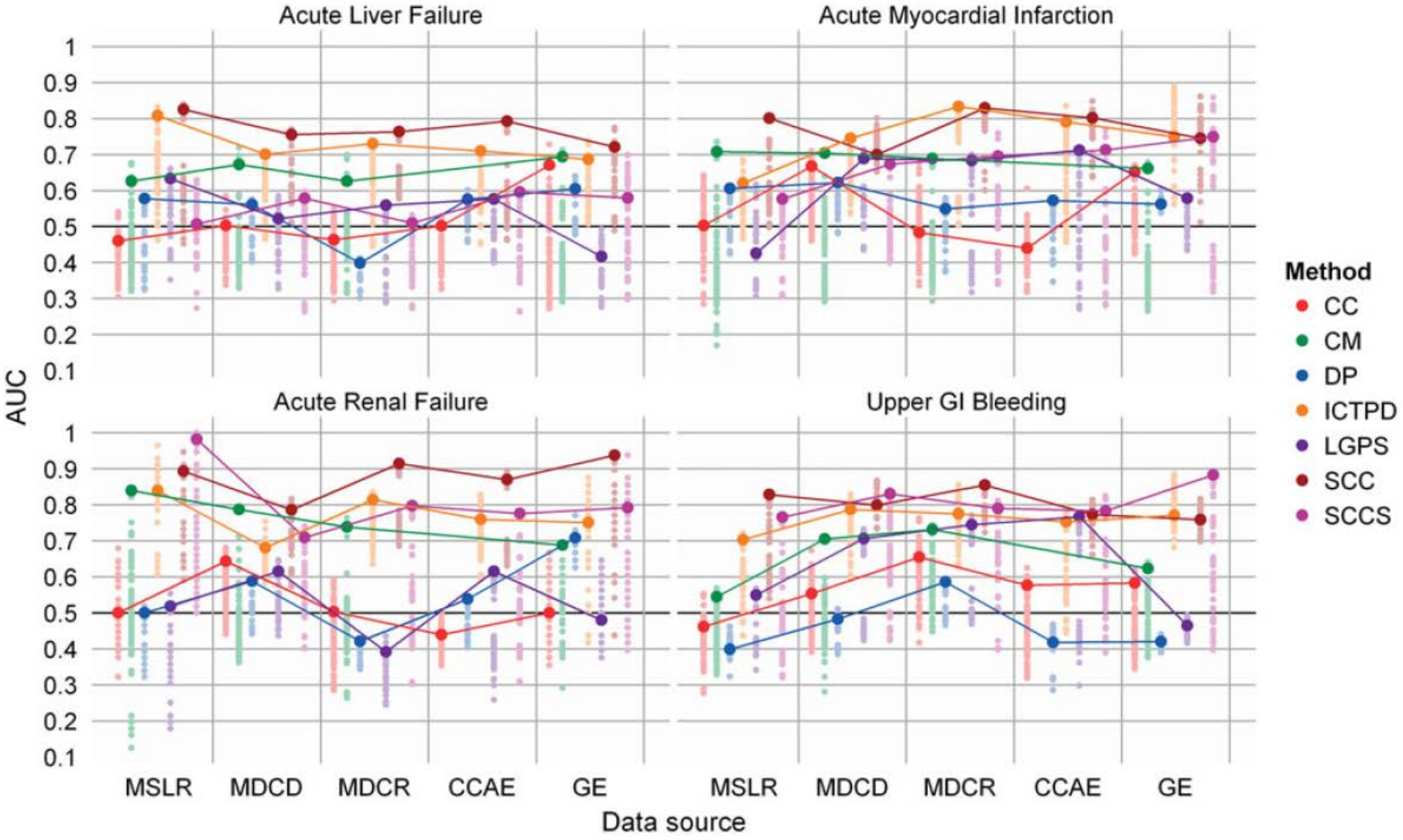
ORIGINAL RESEARCH ARTICLE

A Comparison of the Empirical Performance of Methods for a Risk Identification System

Patrick B. Ryan · Paul E. Stang · J. Marc Overhage · Marc A. Suchard · Abraham G. Hartzema · William DuMouchel · Christian G. Reich · Martijn J. Schuemie · David Madigan

- Systematically applied multiple methods (cohort, case-control, self-controlled designs) to multiple databases (claims, EHR) for a large set of positive and negative control drug-outcome pairs
- Measured performance of each method in each database for each health outcome of interest (including AMI)
  - Consistency: database heterogeneity, parameter sensitivity
  - Discrimination: AUC
  - Calibration: systematic error, coverage probability

Performance of analysis varies by database and outcome, but self-controlled designs showed highest discrimination for AMI



Ryan et al, Drug Safety 2013

Lessons from the OMOP experiments

1. Database heterogeneity:
   Holding analysis constant, different data may yield different estimates

Madigan D, Ryan PB, Schuemie MJ et al, American Journal of Epidemiology, 2013
"Evaluating the Impact of Database Heterogeneity on Observational Study Results"

2. Parameter sensitivity:
   Holding data constant, different analytic design choices may yield different estimates

Madigan D, Ryan PB, Scheumie MJ, Therapeutic Advances in Drug Safety, 2013: "Does design matter? Systematic evaluation of the impact of analytical choices on effect estimates in observational studies"

3. Empirical performance:
   Most observational methods do not have nominal statistical operating characteristics

Ryan PB, Stang PE, Overhage JM et al, Drug Safety, 2013:
"A Comparison of the Empirical Performance of Methods for a Risk Identification System"

4. Empirical calibration can help restore interpretation of study findings

Schuemie MJ, Ryan PB, DuMouchel W, et al, Statistics in Medicine, 2013:
"Interpreting observational studies: why empirical calibration is needed to correct p-values"

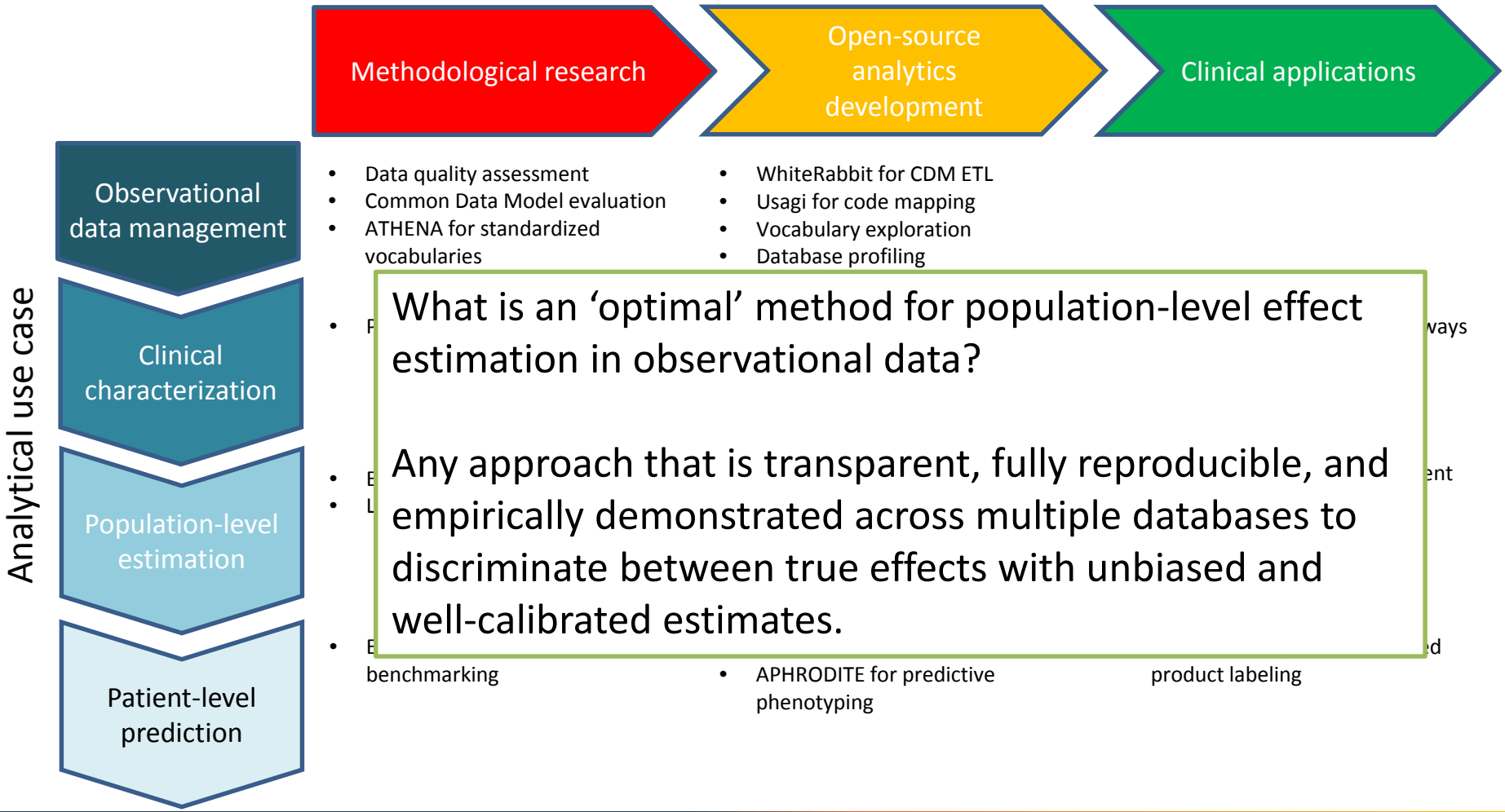
OHDSI best practices for population-level effect estimation

- Write and share protocol
- Open source study code
- Use validated software
- Replicate across databases

- Produce standard diagnostics
- Include negative controls
- Create positive controls
- Calibrate confidence interval and p-value

- Don’t provide only the effect estimate
- Also share protocol, study code, diagnostics and evaluation
- Produce evidence at scale

OHDSI's collaborative journey to reliable evidence generation



Join the journey

http://ohdsi.org