
# Evolution of Evidence-Based Medicine:

## Why we are replicating clinical trials using EHRs

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# Conflicts of Interest and Acknowledgement

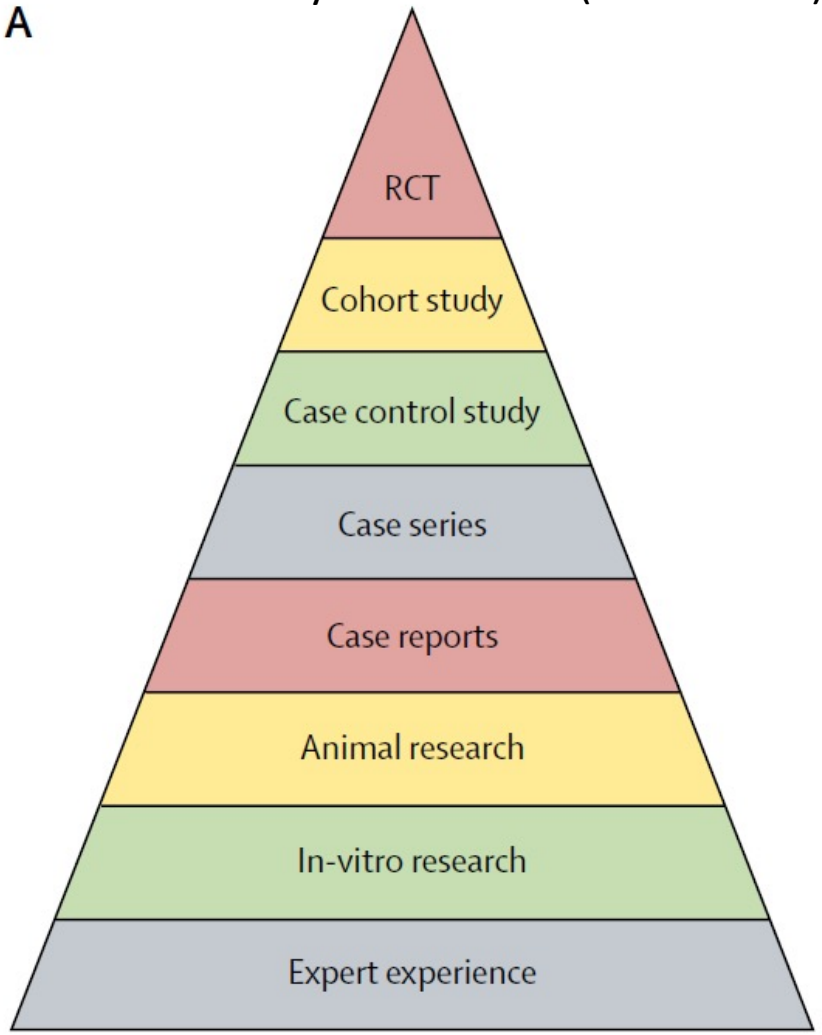
- Dr You reports being a CTO of PHI Digital healthcare.

- This research was supported by a grant (22213MFDS486) from Ministry of Food and Drug Safety in 2022

# Hierarchy of evidence

EBM hierarchy of evidence (1991–2004)

A




GRADE classification of the quality of evidence (2004~)

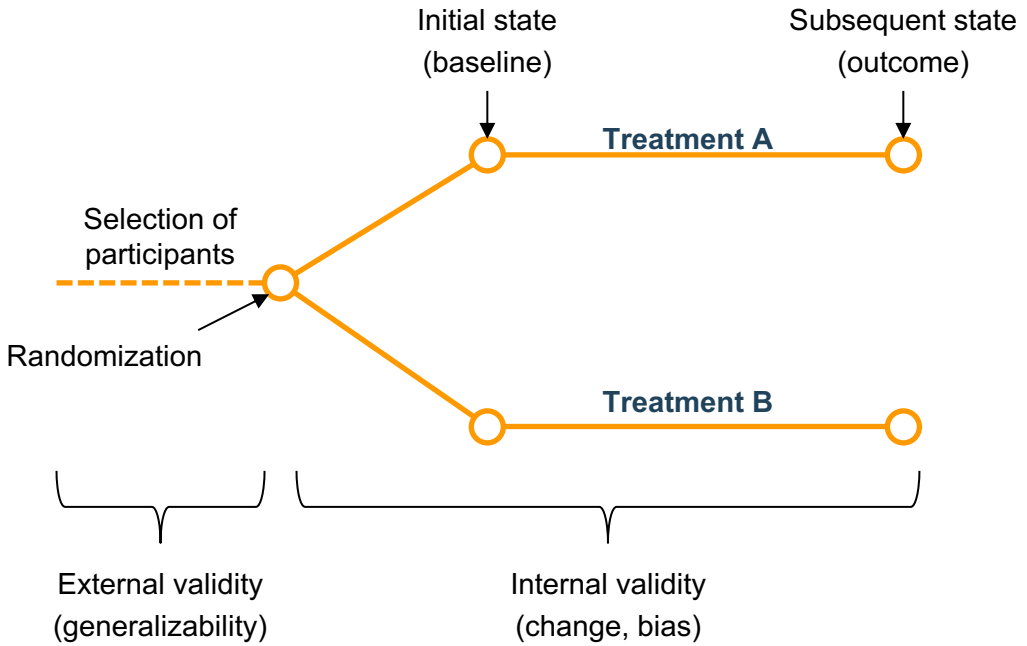
B

| Quality of evidence | Study design | Lower quality if* | Higher quality if† |
|---|---|---|---|
| High | Randomised trial | Study limitations<br>- 1 serious<br>- 2 very serious<br><br>Inconsistency<br>- 1 serious<br>- 2 very serious<br><br>Indirectness<br>- 1 serious<br>- 2 very serious<br><br>Imprecision<br>- 1 serious<br>- 2 very serious<br><br>Publication bias<br>- 1 likely<br>- 2 very likely | Large effect<br>+ 1 large<br>+ 2 very large<br><br>Dose response<br>+ 1 evidence of a gradient<br><br>All plausible confounders<br>+ Would reduce a demonstrated effect or<br>+ Would suggest a spurious effect when results show no effect |
| Moderate | | | |
| Low | Observational study | | |
| Very low | | | |

# Strengths and Weakness of Randomized Clinical Trial

| Type of study | Strengths |
|---|---|
| Randomized clinical trials | Best for studying an intervention<br>Randomized<br>High internal validity<br>Unbiased distribution of confounders<br>Evaluates efficacy |

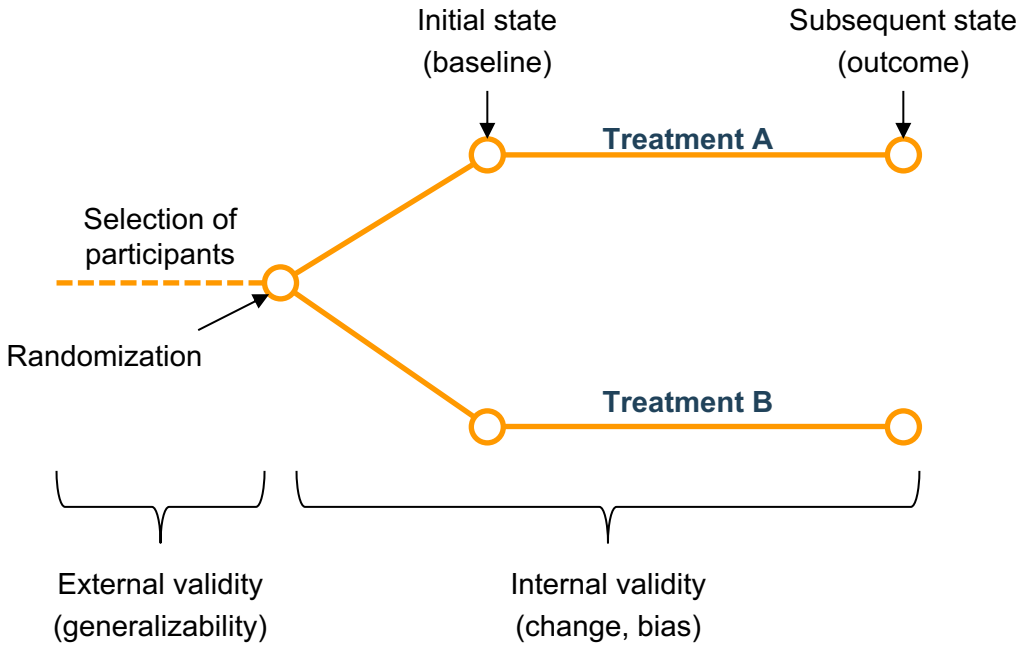
Monti et al., Randomized Controlled Trials and Real-World Data: Differences and Similarities to Untangle Literature Data, *Rheumatology*, 2018

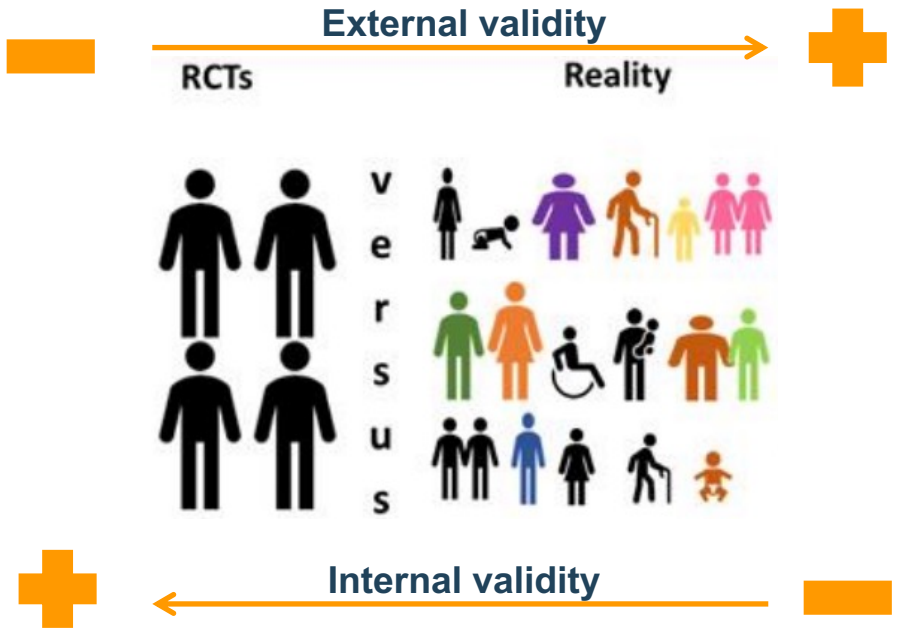


# Strengths and Weakness of Randomized Clinical Trial

| Type of study | Strengths | Weaknesses |
|---|---|---|
| Randomized clinical trials | Best for studying an intervention<br>Randomized<br>High internal validity<br>Unbiased distribution of confounders<br>Evaluates efficacy | Expensive: time and money<br>Short follow-up<br>Volunteer bias<br>Low generalizability to different or real-world population |

Monti et al., Randomized Controlled Trials and Real-World Data: Differences and Similarities to Untangle Literature Data, *Rheumatology*, 2018



# To whom do the results of this trial apply?

| Type of study | Weaknesses |
|---|---|
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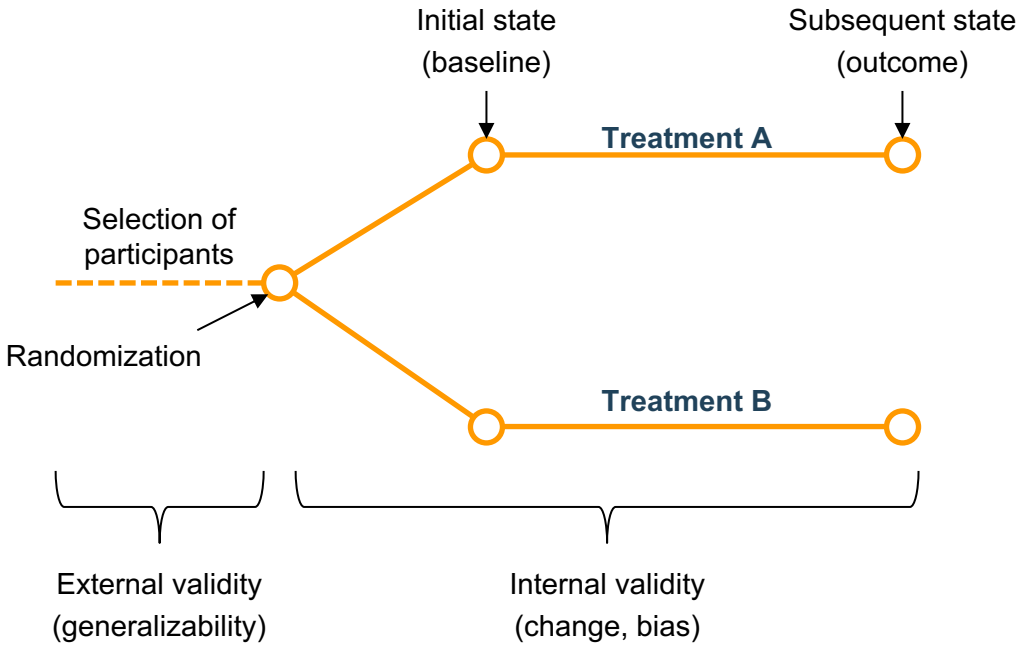


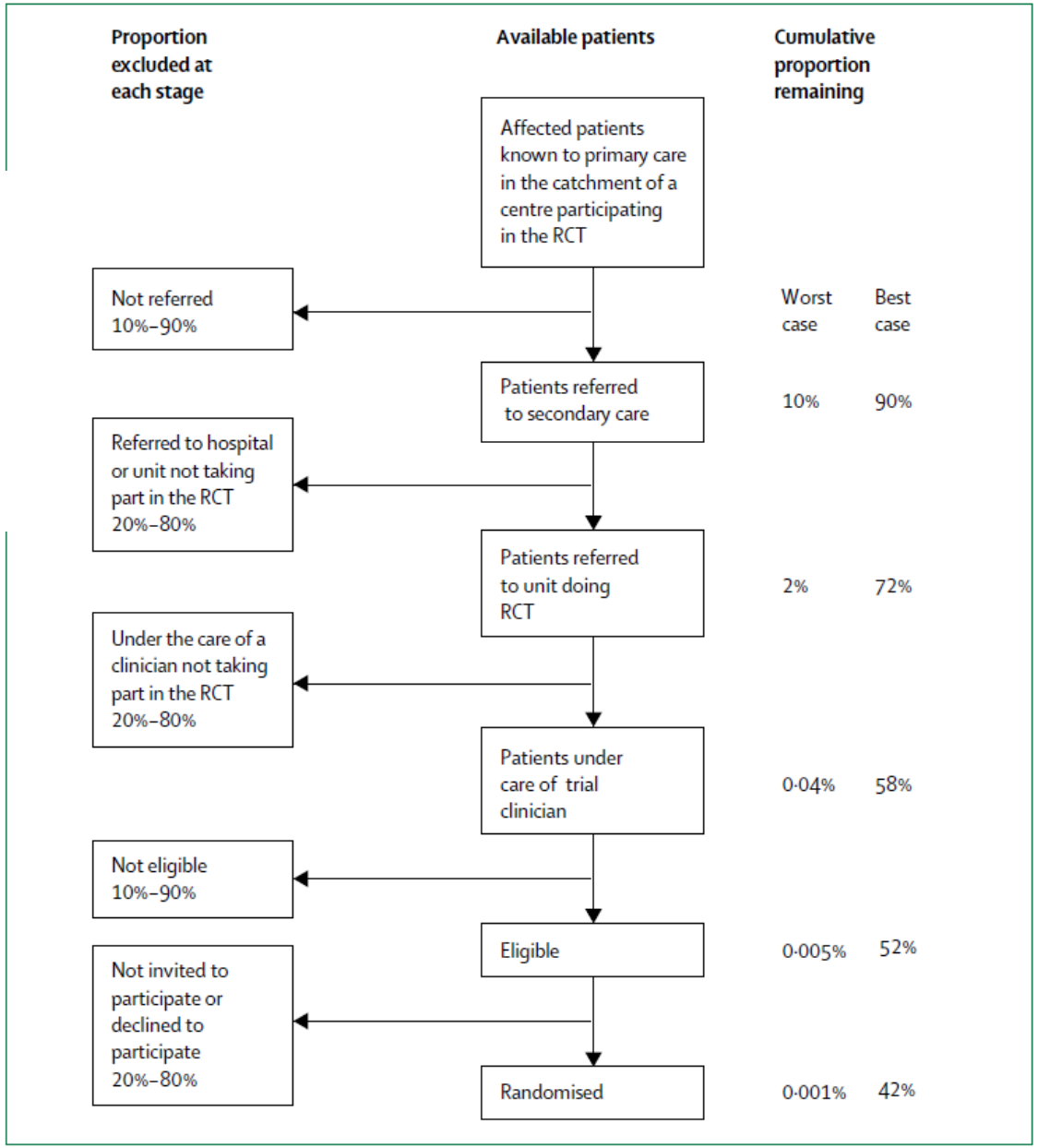

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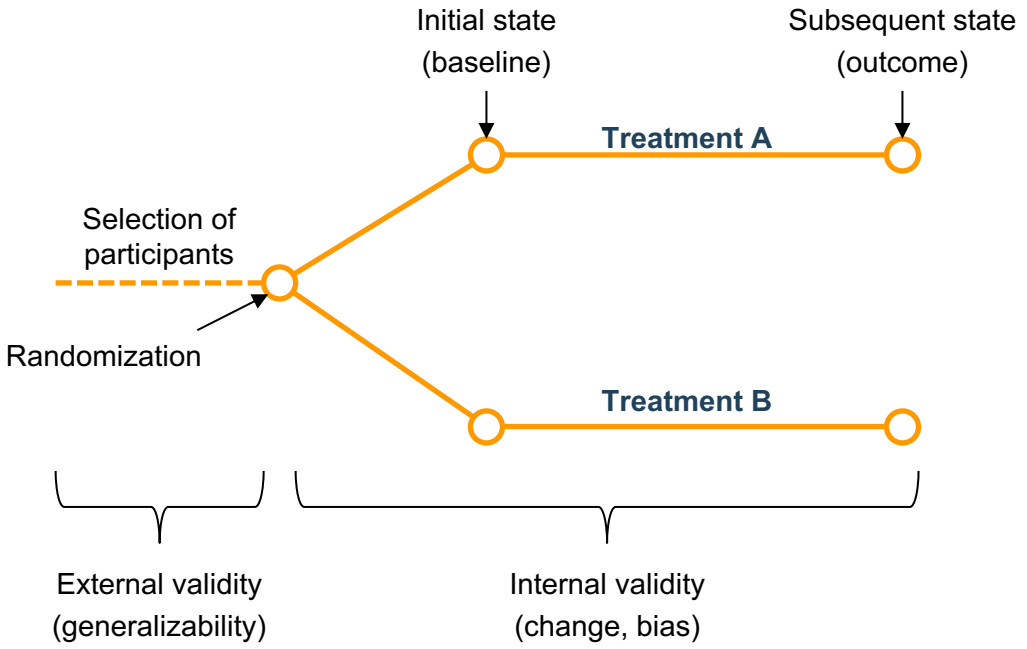
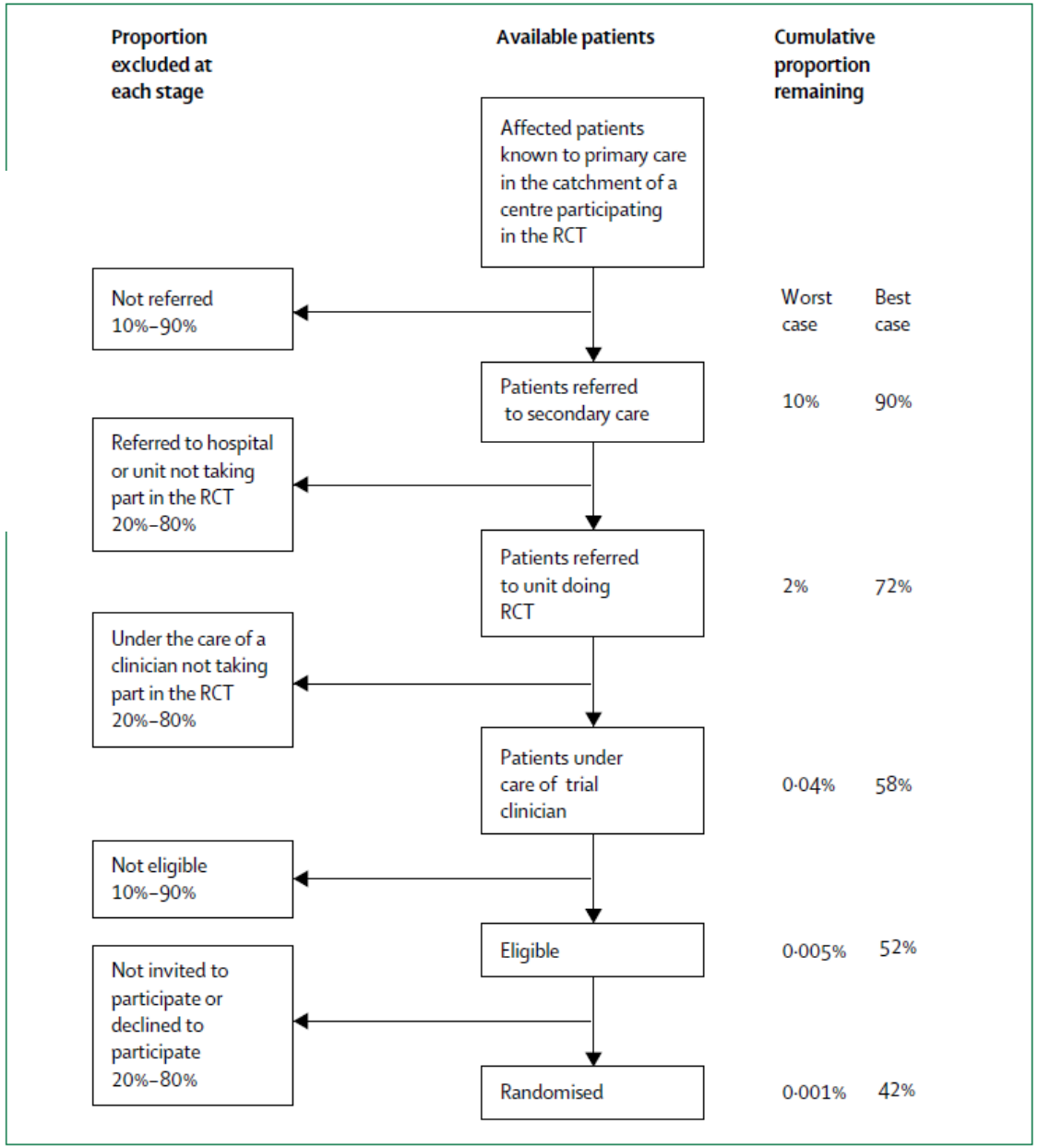


# Characteristics of RCTs and External Validity

- Eligibility criteria in RCTs
  - A comprehensive description of the eligibility criteria used to select the trial participants is needed to help readers interpret the study
  - A clear understanding of these criteria is one of several elements required to judge to whom the results of a trial apply (generalizability)
- External Validity
  - To whom do the results of this trial apply?
  - Can the results be reasonably applied to a definable group of patients in a particular clinical setting in routine practice?
  - Are the results generalizable beyond the trial setting?

# Evidence of the neglect of consideration of external validity of RCTs and systematic reviews

- Research into internal validity of RCTs and systematic reviews far outweighs research into how results should best be used in practice.
- Rules governing the performance of trials, such as good clinical practice, do not cover issues of external validity.
- Drug licensing bodies, such as the US Food and Drug Administration, do not require evidence that a drug has a clinically useful treatment effect, or a trial population that is representative of routine clinical practice
- None of the many scores for judging the quality of RCTs address external validity adequately.
- There are no accepted guidelines on how external validity of RCTs should be assessed.

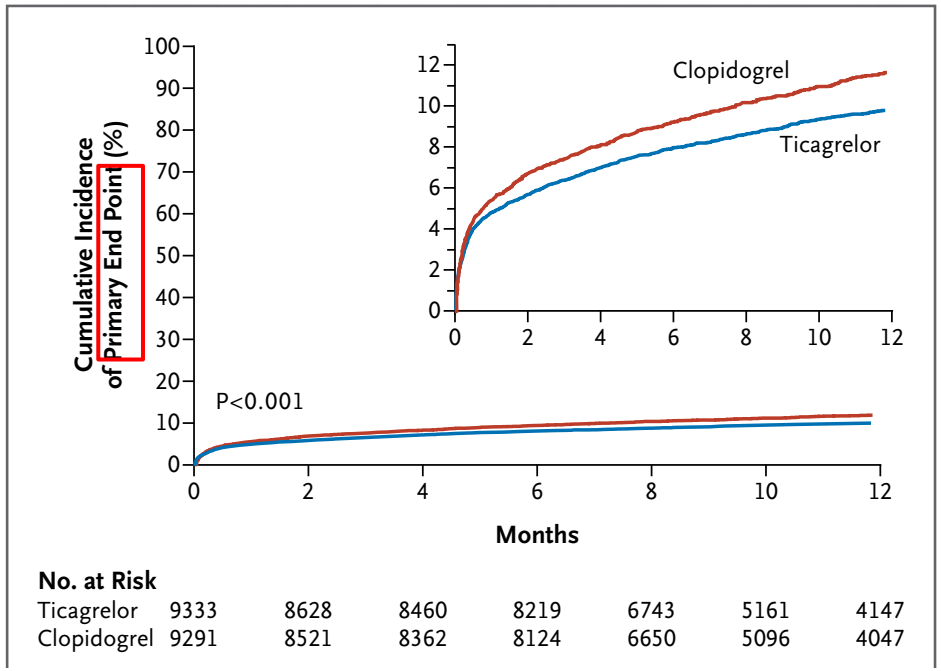
Rothwell, External Validity of Randomised Controlled Trials: 'To Whom Do the Results of This Trial Apply?', *Lancet*, 2005

# RCT and OHDSI: Ticagrelor vs clopidogrel

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

## Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ticagrelor | 9333 | 8628 | 8460 | 8219 | 6743 | 5161 | 4147 |
| Clopidogrel | 9291 | 8521 | 8362 | 8124 | 6650 | 5096 | 4047 |

**Primary End Point: Vascular death, myocardial infarction and stroke**

Wallentin et al., *NEJM*, 2009

Research

JAMA | Original Investigation

## Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Seng Chan You, MD, MS; Yeunsook Rho, PhD; Behnood Bikdeli, MD, MS; Jiwoo Kim, MS; Anastasios Siapos, MSc; James Weaver, MSc; Ajit Londhe, MPH; Jaehyeong Cho, BS; Jimyung Park, BS; Martijn Schuemie, PhD; Marc A. Suchard, MD, PhD; David Madigan, PhD; George Hripcsak, MD, MS; Aakriti Gupta, MD, MS; Christian G. Reich, MD; Patrick B. Ryan, PhD; Rae Woong Park, MD, PhD; Harlan M. Krumholz, MD, SM

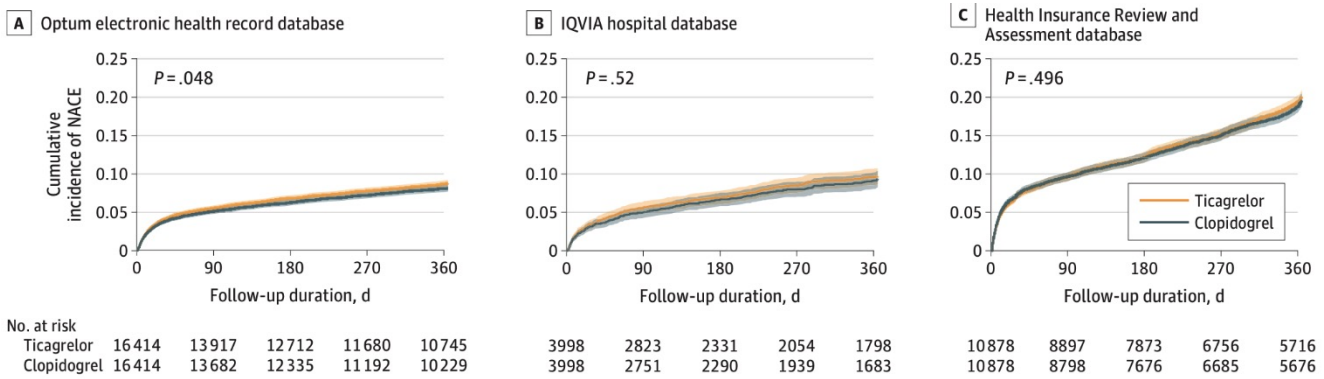
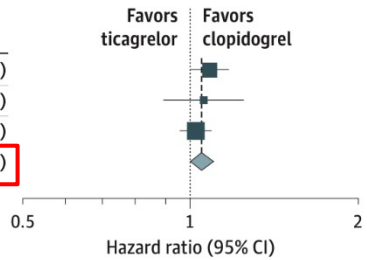



**Figure 3. Risk of the Primary Outcome (NACE) at 1 Year**

| Source | No. of events/total No. Ticagrelor | Clopidogrel | Hazard ratio (95% CI) |
|---|---|---|---|
| Optum electronic health record | 1307/16414 | 1192/16414 | 1.08 (1.00-1.17) |
| IQVIA hospital | 294/3998 | 272/3998 | 1.06 (0.90-1.24) |
| Health Insurance Review and Assessment | 1883/10878 | 1826/10878 | 1.02 (0.96-1.09) |
| Overall: $I^2$ = 0.0%; P = .06 | 3484/31290 | 3290/31290 | 1.05 (1.00-1.10) |




**Primary End Point: Recurrent MI, revascularization, stroke, and GI bleeding**

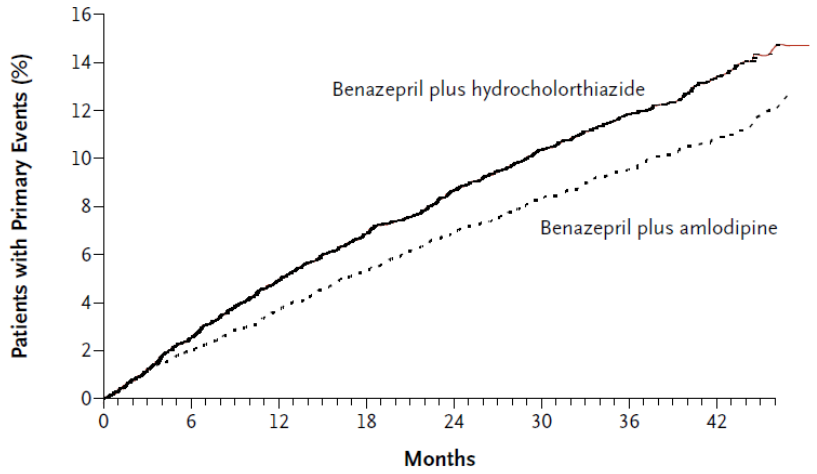
You et al., *JAMA*, 2020

# RCT and OHDSI: ACEi+CCB vs ACEi+Diuretics

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 4, 2008 VOL. 359 NO. 23

## Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients




**No. at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Benazepril plus amlodipine | 5512 | 5317 | 5141 | 4959 | 4739 | 2826 | 1447 |
| Benazepril plus hydrochlorothiazide | 5483 | 5274 | 5082 | 4892 | 4655 | 2749 | 1390 |

Korean Circ J. 2020 Jan;50(1):e2
https://doi.org/10.4070/kcj.2019.0173
pISSN 1738-5520·eISSN 1738-5555

kcj Korean Circulation Journal

Original Article

Check for updates

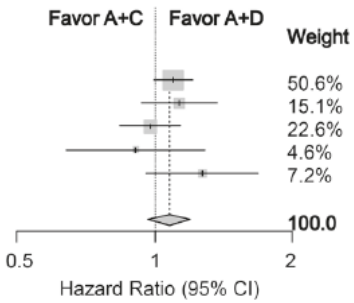
## Comparison of First-Line Dual Combination Treatments in Hypertension: Real-World Evidence from Multinational Heterogeneous Cohorts

**A**

| Data Source | A+C Total No. | A+C Event No. | A+C Person-Years | A+C Event rate* | A+D Total No. | A+D Event No. | A+D Person-Years | A+D Event rate* | HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| CEDM | 66,894 | 1,893 | 200,097 | 9.5 | 66,894 | 1,731 | 200,514 | 8.6 | 1.10 (1.00-1.21) |
| CCAE | 112,710 | 502 | 326,432 | 1.5 | 112,710 | 452 | 326,919 | 1.4 | 1.13 (0.94-1.37) |
| Medicare | 34,329 | 806 | 121,680 | 6.6 | 34,329 | 739 | 119,344 | 6.2 | 0.98 (0.84-1.14) |
| Medicaid | 4,006 | 127 | 13,105 | 9.7 | 4,006 | 125 | 13,304 | 9.4 | 0.91 (0.64-1.29) |
| NHIS-NSC | 4,747 | 198 | 16,407 | 12.1 | 4,747 | 170 | 17,072 | 10.0 | 1.27 (0.96-1.69) |
| **Overall** | **222,686** | **3,526** | **677,721** | **5.2** | **222,686** | **3,217** | **677,153** | **4.8** | **1.08 (0.97-1.20)** |

Heterogeneity: $I^2$ = 4.6%

p=0.127




Jamerson et al., *NEJM*, 2008

You et al., *KCJ*, 2019

# Difference in baseline characteristics

npj | Digital Medicine

www.nature.com/npjdigitalmed

ARTICLE OPEN

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## Translating evidence into practice: eligibility criteria fail to eliminate clinically significant differences between real-world and study populations

Amelia J. Averitt[1], Chunhua Weng[1], Patrick Ryan[1,2] and Adler Perotte[1]✉

# Difference in baseline characteristics: Enrolled in the RCT *vs* Indication only *vs* eligibility criteria

**Table 4.** Results for benazepril-amlodipine vs. benazepril and hydrochlorothiazide (HCTZ) trial (ACCOMPLISH).

| Baseline characteristics | The ACCOMPLISH Trial NEJM[40] | | | | Columbia University Irving Medical Center (CUIMC) | | | |
|---|---|---|---|---|---|---|---|---|
| | Benazepril-amlodipine | Benazepril– HCTZ Group | Pooled | | Indication only | | With eligibility criteria | |
| | $n = 5744$ | $n = 5762$ | $n = 11{,}506$ | $\sigma$ | $n = 36{,}854$ | $\Delta_{RCT}$ | $n = 4198$ | $\Delta_{RCT}$ |
| Age | | | | | | | | |
| ≥65 years | 3813 | 3827 | 66.40% | | 17.98% | −0.451 | 60.05% | −0.063 |
| ≥70 years | 2363 | 2340 | 40.87% | | 9.59% | −0.295 | 43.22% | 0.023 |
| Gender | | | | | | | | |
| Female | 2296 | 2246 | 39.48% | | 67.81% | 0.283 | 70.41% | 0.309 |
| Male | 3448 | 3515 | 60.52% | | 32.18% | −0.283 | 29.56% | −0.310 |
| Unknown | 0 | 0 | 0.00% | | 0.01% | 0.000 | 0.02% | 0.000 |
| Race | | | | | | | | |
| White | 4817 | 4795 | 83.54% | | 25.31% | −0.595 | 10.65% | −0.729 |
| Black | 697 | 719 | 12.31% | | 14.38% | 0.010 | 12.51% | 0.002 |
| Hispanic | 300 | 323 | 5.41% | | 30.25% | 0.230 | 36.45% | 0.310 |
| Other | 230 | 247 | 4.15% | | 19.41% | 0.167 | 30.12% | 0.260 |
| Unknown | 0 | 0 | 0.00% | | 7.25% | 0.134 | 10.26 | 0.103 |
| Weight | 88.7 | 88.5 | 88.60 | 18.95 | 78.01 | −0.346 | 74.65 | −0.514 |
| Waist circumference | 103.9 | 103.8 | 103.85 | 15.30 | NED | – | NED | – |
| Body mass index | 31 | 31 | 31.00 | 6.20 | 30.13 | −0.061 | 29.95 | −0.096 |
| Blood pressure | | | | | | | | |
| Systolic | 145.3 | 145.4 | 145.35 | 18.25 | 129.75 | −0.704 | 133.41 | −0.537 |
| Diastolic | 80.1 | 80.1 | 80.10 | 10.75 | 76.78 | −0.251 | 73.85 | −0.479 |
| Pulse | 70.5 | 70.3 | 70.40 | 11.00 | 79.33 | 0.552 | 77.95 | 0.496 |
| eGFR | 78.9 | 79 | 78.95 | 21.35 | NED* | – | NED* | – |

# Difference in baseline characteristics: Enrolled in the RCT *vs* Indication only *vs* eligibility criteria

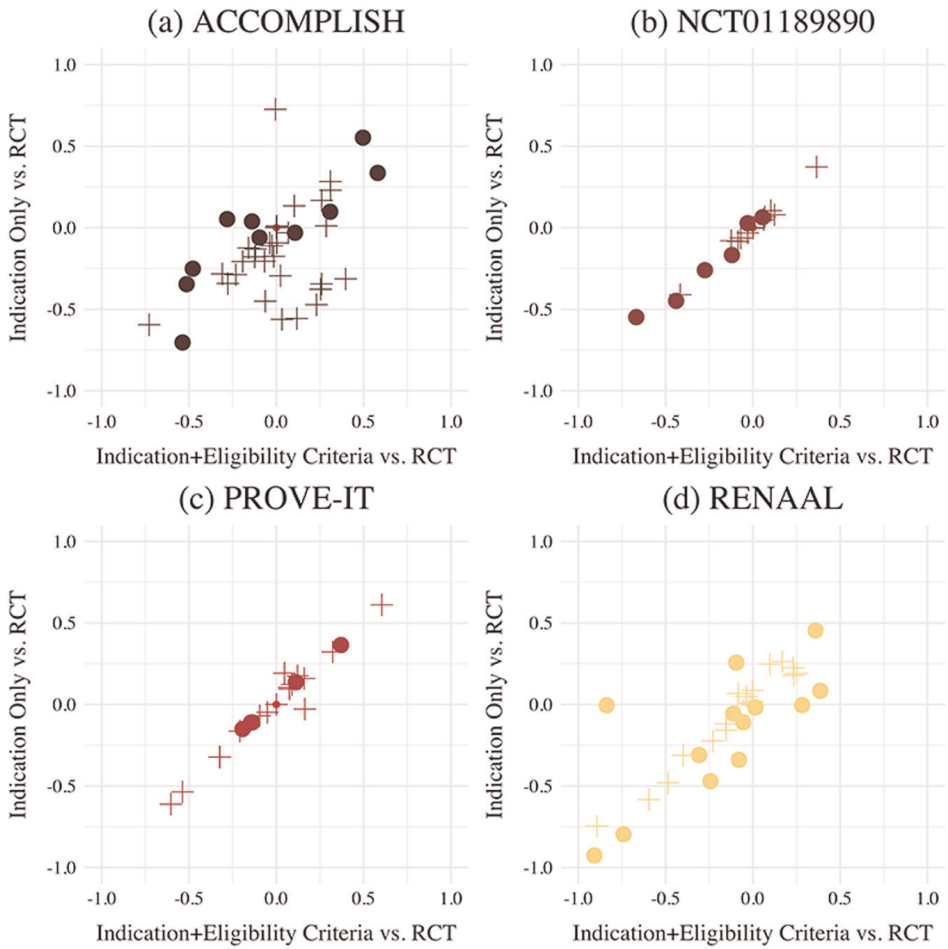



**Fig. 1 Summary of $\Delta_{RCT}$ for baseline characteristics of Indication Only vs RCT and $\Delta_{RCT}$ Indication + Eligibilty Criteria vs. RCT.** **a** ACCOMPLISH trial **b** NCT01189890 trial (sitagliptin vs. glimepiride), **c** PROVE-IT trial **d** RENAAL trial. The shape of the marker corresponds to the data type. Circles (●) denote the standardized difference in the mean of continuous data. Pluses (+) denote the difference in percentage points of discrete data.

# Difference in baseline characteristics: How this affects? DAPT and EXTEND-DAPT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 4, 2014 VOL. 371 NO. 23

## Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., and Joseph M. Massaro, Ph.D., for the DAPT Study Investigators*

ABSTRACT

**BACKGROUND**

Dual antiplatelet therapy is recommended after coronary stenting to prevent thrombotic complications, yet the benefits and risks of treatment beyond 1 year are uncertain.

**METHODS**

Patients were enrolled after they had undergone a coronary stent procedure in which a drug-eluting stent was placed. After 12 months of treatment with a thienopyridine drug (clopidogrel or prasugrel) and aspirin, patients were randomly assigned to continue receiving thienopyridine treatment or to receive placebo for another 18 months; all patients continued receiving aspirin. The coprimary efficacy end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) during the period from 12 to 30 months. The primary safety end point was moderate or severe bleeding.

**RESULTS**

A total of 9961 patients were randomly assigned to continue thienopyridine treatment or to receive placebo. Continued treatment with thienopyridine, as compared with placebo, reduced the rates of stent thrombosis (0.4% vs. 1.4%; hazard ratio, 0.29 [95% confidence interval {CI}, 0.17 to 0.48]; P<0.001) and major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%; hazard ratio, 0.71 [95% CI, 0.59 to 0.85]; P<0.001). The rate of myocardial infarction was lower with thienopyridine treatment than with placebo (2.1% vs. 4.1%; hazard ratio, 0.47; P<0.001). The rate of death from any cause was 2.0% in the group that continued thienopyridine therapy and 1.5% in the placebo group (hazard ratio, 1.36 [95% CI, 1.00 to 1.85]; P=0.05). The rate of moderate or severe bleeding was increased with continued thienopyridine treatment (2.5% vs. 1.6%, P=0.001). An elevated risk of stent thrombosis and myocardial infarction was observed in both groups during the 3 months after discontinuation of thienopyridine treatment.

**CONCLUSIONS**

Dual antiplatelet therapy beyond 1 year after placement of a drug-eluting stent, as compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding. (Funded by a consortium of eight device and drug manufacturers and others; DAPT ClinicalTrials.gov number, NCT00977938.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Mauri at the Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at lmauri1@partners.org.

*A complete list of investigators and committee members in the Dual Antiplatelet Therapy (DAPT) study is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 16, 2014, at NEJM.org.

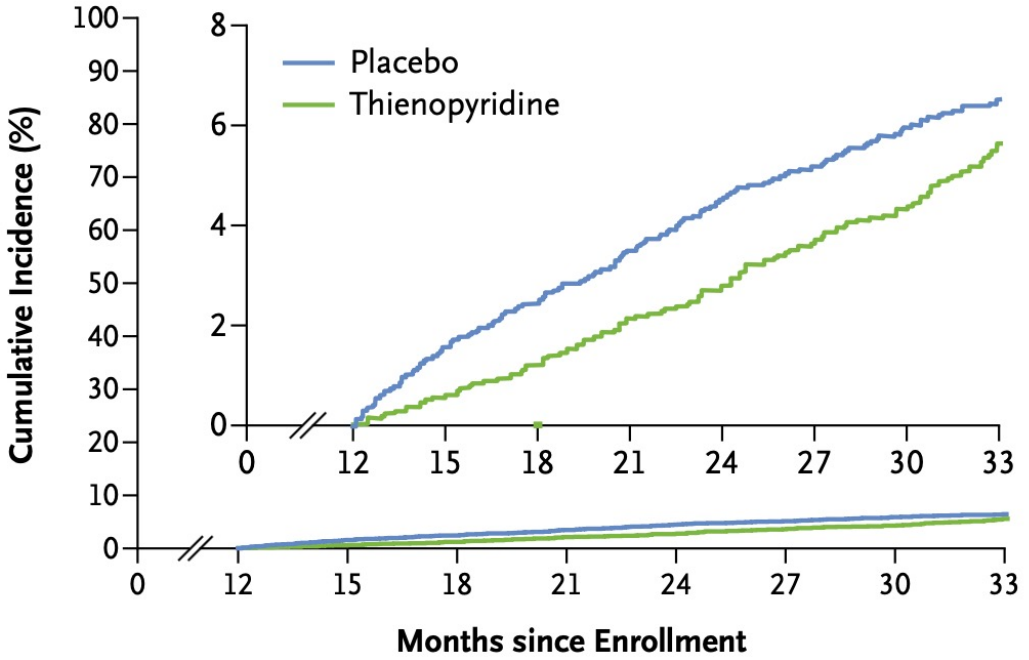
N Engl J Med 2014;371:2155-66.
DOI: 10.1056/NEJMoa1409312



**Major Adverse Cardiovascular and Cerebrovascular Events**

12–30 mo Thienopyridine vs. placebo, 4.3% vs. 5.9%; hazard ratio, 0.71; P<0.001

12–33 mo Thienopyridine vs. placebo, 5.6% vs. 6.5%; hazard ratio, 0.82; P=0.02




**No. at Risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Thienopyridine | 5020 | 4917 | 4840 | 4778 | 4702 | 4611 | 4554 | 3029 |
| Placebo | 4941 | 4799 | 4715 | 4635 | 4542 | 4476 | 4412 | 2997 |

# Difference in baseline characteristics: How this affects? DAPT and EXTEND-DAPT

Circulation

ORIGINAL RESEARCH ARTICLE

## Estimation of DAPT Study Treatment Effects in Contemporary Clinical Practice: Findings From the EXTEND-DAPT Study

Neel M. Butala, MD, MBA; Kamil F. Faridi, MD, MSc; Hector Tamez, MD, MPH; Jordan B. Strom, MD, MSc; Yang Song, MSc; Changyu Shen, PhD; Eric A. Secemsky, MD, MSc; Laura Mauri, MD, MSc; Dean J. Kereiakes, MD; Jeptha P. Curtis, MD; C. Michael Gibson, MD, MS; Robert W. Yeh, MD, MSc

**BACKGROUND:** Differences in patient characteristics, changes in treatment algorithms, and advances in medical technology could each influence the applicability of older randomized trial results to contemporary clinical practice. The DAPT Study (Dual Antiplatelet Therapy) found that longer-duration DAPT decreased ischemic events at the expense of greater bleeding, but subsequent evolution in stent technology and clinical practice may attenuate the benefit of prolonged DAPT in a contemporary population. We evaluated whether the DAPT Study population is different from a contemporary population of US patients receiving percutaneous coronary intervention and estimated the treatment effect of extended-duration antiplatelet therapy after percutaneous coronary intervention in this more contemporary cohort.

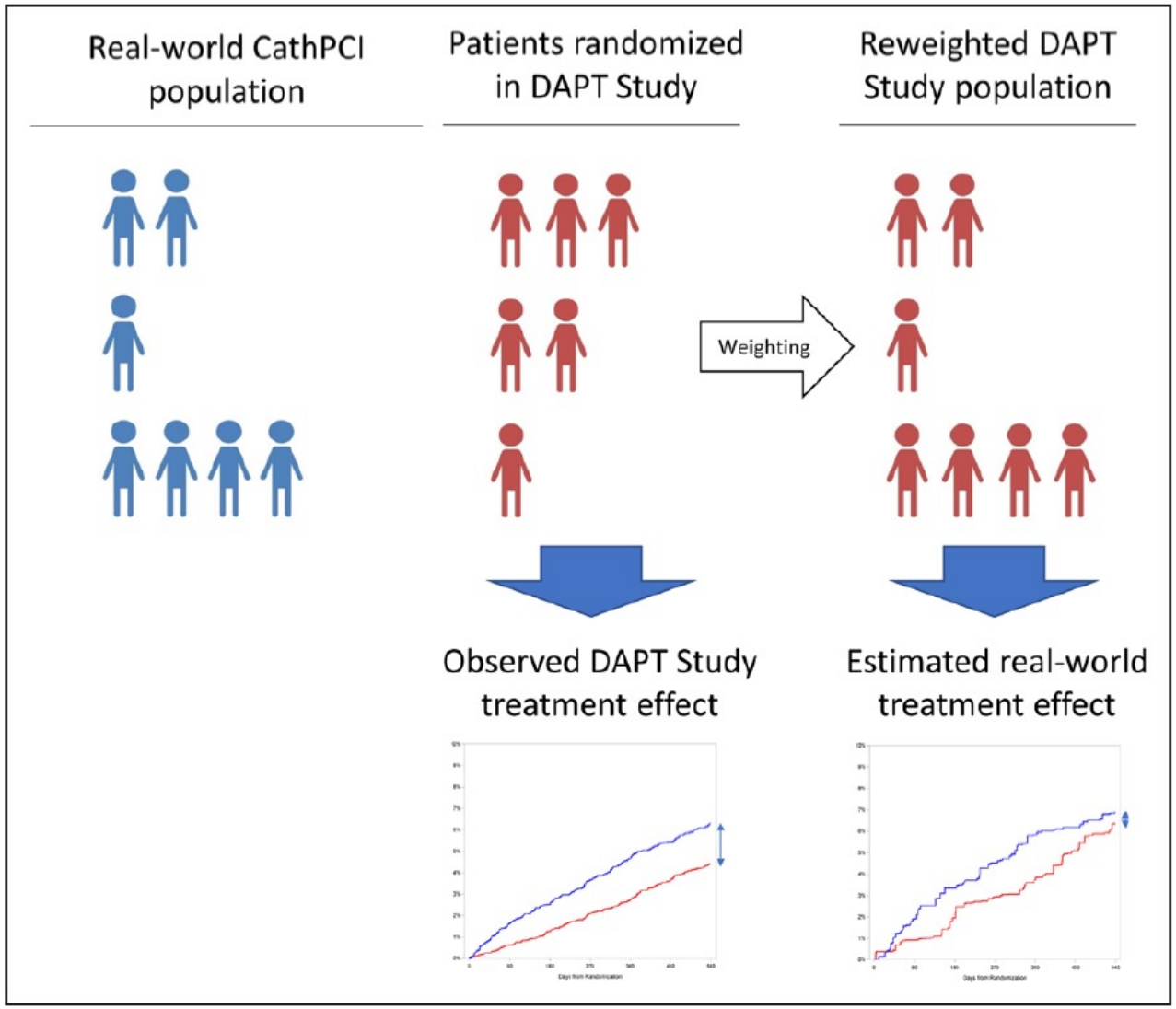
**METHODS:** We compared the characteristics of drug-eluting stent–treated patients randomly assigned in the DAPT Study to a sample of more contemporary drug-eluting stent–treated patients in the National Cardiovascular Data Registry CathPCI Registry from July 2016 to June 2017. After linking trial and registry data, we used inverse-odds of trial participation weighting to account for patient and procedural characteristics and estimated a contemporary real-world treatment effect of 30 versus 12 months of DAPT after coronary stent procedures.

**RESULTS:** The US drug-eluting stent–treated trial cohort included 8864 DAPT Study patients, and the registry cohort included 568 540 patients. Compared with the trial population, registry patients had more comorbidities and were more likely to present with myocardial infarction and receive 2nd-generation drug-eluting stents. After reweighting trial results to represent the registry population, there was no longer a significant effect of prolonged DAPT on reducing stent thrombosis (reweighted treatment effect: −0.40 [95% CI, −0.99% to 0.15%]), major adverse cardiac and cerebrovascular events (reweighted treatment effect, −0.52 [95% CI, −2.62% to 1.03%]), or myocardial infarction (reweighted treatment effect, −0.97% [95% CI, −2.75% to 0.18%]), but the increase in bleeding with prolonged DAPT persisted (reweighted treatment effect, 2.42% [95% CI, 0.79% to 3.91%]).

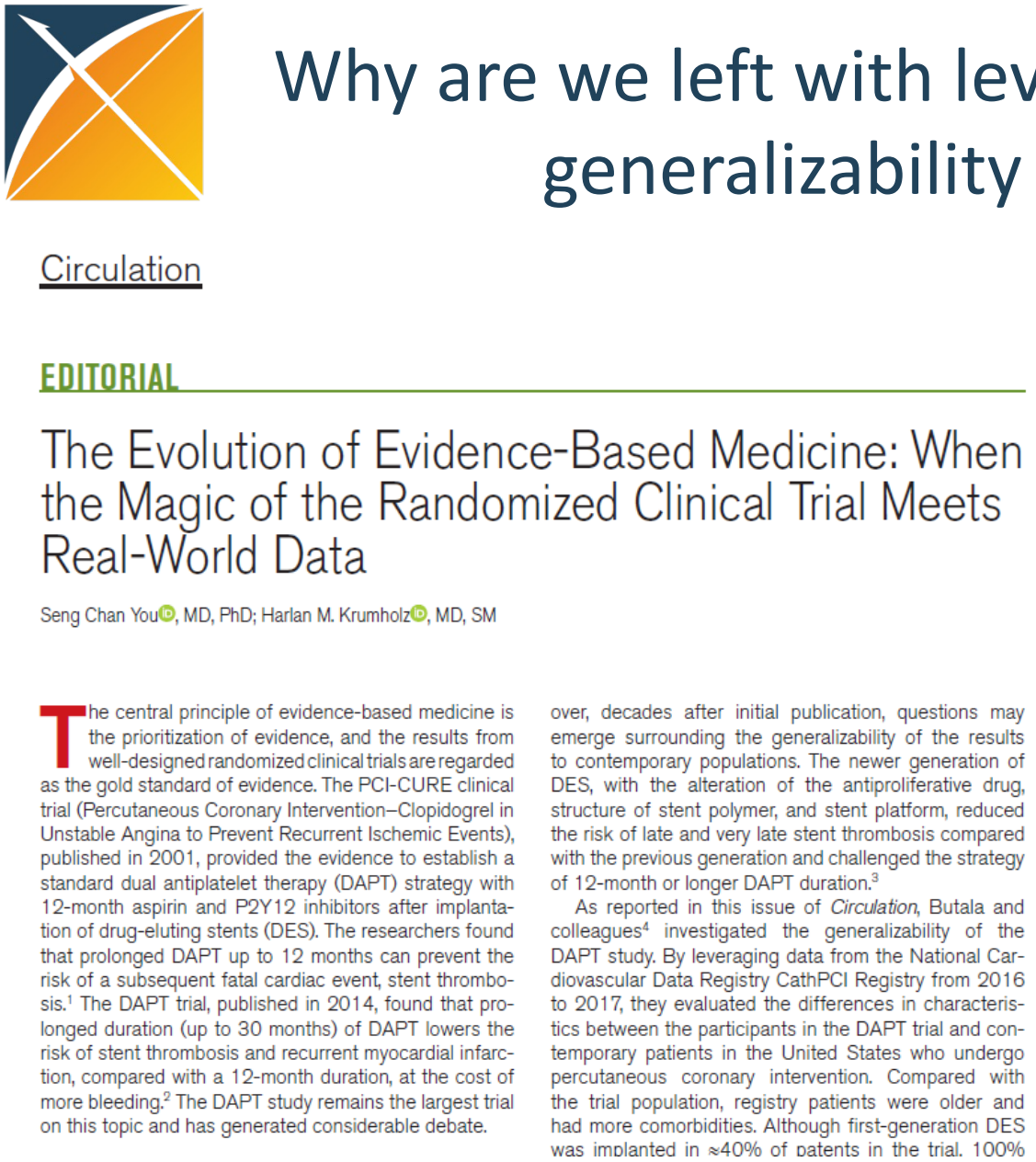
**CONCLUSIONS:** The differences between the patients and devices used in contemporary clinical practice compared with the DAPT Study were associated with the attenuation of benefits and greater harms attributable to prolonged DAPT duration. These findings limit the applicability of the average treatment effects from the DAPT Study in modern clinical practice.

**Key Words:** percutaneous coronary intervention ■ platelet aggregation inhibitors ■ pragmatic clinical trials as topic





# Why are we left with leveraging real-world data to address the generalizability of the results of clinical trials?



Circulation

EDITORIAL

The Evolution of Evidence-Based Medicine: When the Magic of the Randomized Clinical Trial Meets Real-World Data

Seng Chan You, MD, PhD; Harlan M. Krumholz, MD, SM

The central principle of evidence-based medicine is the prioritization of evidence, and the results from well-designed randomized clinical trials are regarded as the gold standard of evidence. The PCI-CURE clinical trial (Percutaneous Coronary Intervention–Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), published in 2001, provided the evidence to establish a standard dual antiplatelet therapy (DAPT) strategy with 12-month aspirin and P2Y12 inhibitors after implantation of drug-eluting stents (DES). The researchers found that prolonged DAPT up to 12 months can prevent the risk of a subsequent fatal cardiac event, stent thrombosis.[1] The DAPT trial, published in 2014, found that prolonged duration (up to 30 months) of DAPT lowers the risk of stent thrombosis and recurrent myocardial infarction, compared with a 12-month duration, at the cost of more bleeding.[2] The DAPT study remains the largest trial on this topic and has generated considerable debate.

over, decades after initial publication, questions may emerge surrounding the generalizability of the results to contemporary populations. The newer generation of DES, with the alteration of the antiproliferative drug, structure of stent polymer, and stent platform, reduced the risk of late and very late stent thrombosis compared with the previous generation and challenged the strategy of 12-month or longer DAPT duration.[3]

As reported in this issue of *Circulation*, Butala and colleagues[4] investigated the generalizability of the DAPT study. By leveraging data from the National Cardiovascular Data Registry CathPCI Registry from 2016 to 2017, they evaluated the differences in characteristics between the participants in the DAPT trial and contemporary patients in the United States who undergo percutaneous coronary intervention. Compared with the trial population, registry patients were older and had more comorbidities. Although first-generation DES was implanted in ≈40% of patents in the trial, 100%

- The characteristics of enrolled patients passing eligibility criteria in the trial may differ from the patients under routine clinical practice.
- Over time, the characteristics of people of indication have changed. The evidence from trials may not be durable over time

You and Krumholz., *Circulation*, 2022


TROY:
Trials Replication through
Observational study by Yonsei

# Trials Replication through Observational study by Yonsei (TROY)

- The TROY project seeks to generate real-world evidence of drugs for each emulated pivotal RCTs using the OHDSI network
  - Difference in baseline characteristics (what we are doing now)
  - Estimating heterogeneous treatment effect (what we hope to accomplish)
- Replication study design for 15 target trials:
  - Target-Comparator cohort design: In a placebo-controlled trial without an active comparator, a similar drug is replaced (2 cohorts)
  - Eligibility Criteria-Indication Only cohort design: In the clinical practice patients who met the eligibility criteria for target RCT and those who had any indications (2 cohorts)

# Trials Replication through Observational study by Yonsei (TROY)

- The 15 randomized clinical trials to be replicated in the TROY

| Study | Target drug (class) | Comparator drug (class) | Note |
|---|---|---|---|
| LEADER | Liraglutide (GLP-1) | DPP-4 | Placebo-controlled RCT |
| DECLARE-TIMI 58 | Dapagliflozin (SGLT-2) | DPP-4 | Placebo-controlled RCT |
| EMPA-REG OUTCOME | Empagliflozin (SGLT-2) | DPP-4 | Placebo-controlled RCT |
| CANVAS | Canagliflozin (SGLT-2) | DPP-4 | Placebo-controlled RCT |
| CARMELINA | Linagliptin (DPP-4) | Sulfonylureas | Placebo-controlled RCT |
| TECOS | Sitagliptin (DPP-4) | Sulfonylureas | Placebo-controlled RCT |
| SAVOR-TIMI 53 | Saxagliptin (DPP-4) | Sulfonylureas | Placebo-controlled RCT |
| CAROLINA | Linagliptin (DPP-4) | Glimepiride (Sulfonylureas) | |
| TRITON-TIMI 38 | Prasugrel + Aspirin | Clopidogrel + Aspirin | |
| PLATO | Ticagrelor + Aspirin | Clopidogrel + Aspirin | |
| ROCKET AF | Rivaroxaban | Warfarin | |
| ARISTOTLE | Apixaban | Warfarin | |
| ENGAGE AF-TIMI 48 | Edoxaban | Warfarin | |
| ORAL | Tofacitinib | TNF inhibitor | |
| STAR-RA | Tofacitinib | TNF inhibitor | |

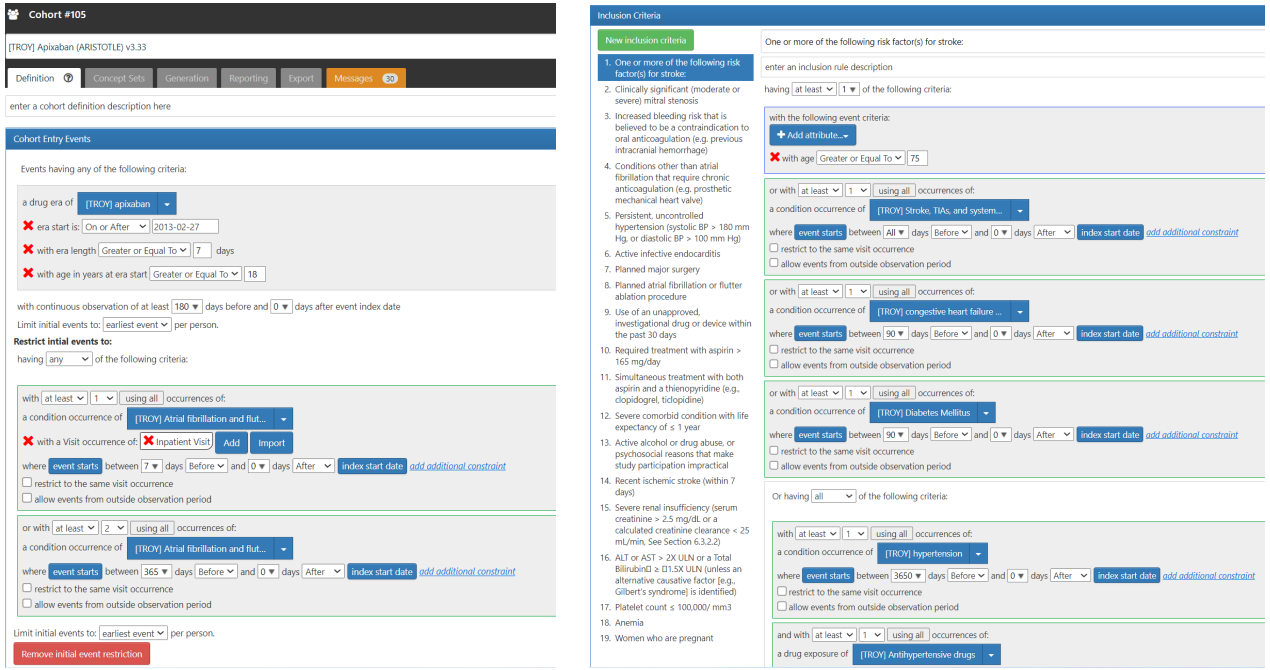
# TROY process: Eligibility criteria cohort

- Eligibility criteria cohort: In the given data, replicate the inclusion/exclusion criteria as closely as possible to the targeting RCT

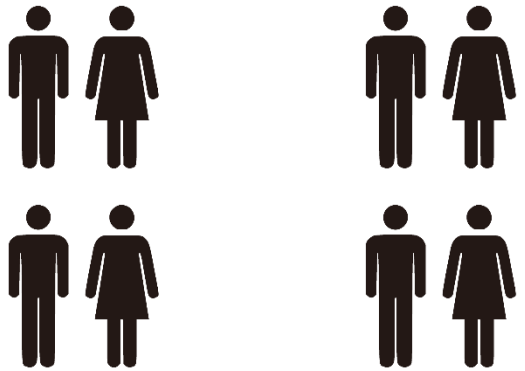
| PLATO trial |
| --- |
| **Inclusion** |
| • Hospitalized for potential ST-segment elevation (STE) or non-STE ACS with symptom onset in prior 24 hours lasting ≥10 minutes while at rest; either<br>  • 1) persistent STE ≥1 mm in ≥2 contiguous leads or new LBBB plus planned primary PCI<br>  • 2) ≥2 of the following: STE changes on ECG indicating ischemia, positive biomarker indicating myocardial necrosis, or one of seven clinical risk factors<br>  • Risk factors: age ≥60 years, prior MI or CABG, stenosis ≥50% in ≥2 vessels, prior stroke, TIA, carotid stenosis, or cerebral revascularization, diabetes, peripheral artery disease, or chronic renal dysfunction |
| **Exclusion** |
| • Contraindication to clopidogrel<br>• Fibrinolytic therapy within 24 hours prior to randomization<br>• Need for oral anticoagulation therapy<br>• Increased risk of bradycardia<br>• Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer |

# TROY process: Eligibility criteria cohort

- Eligibility criteria cohort: In the given data, replicate the inclusion/exclusion criteria as closely as possible to the targeting RCT




Replicate



Target



Comparator

# TROY process: Indication only cohort

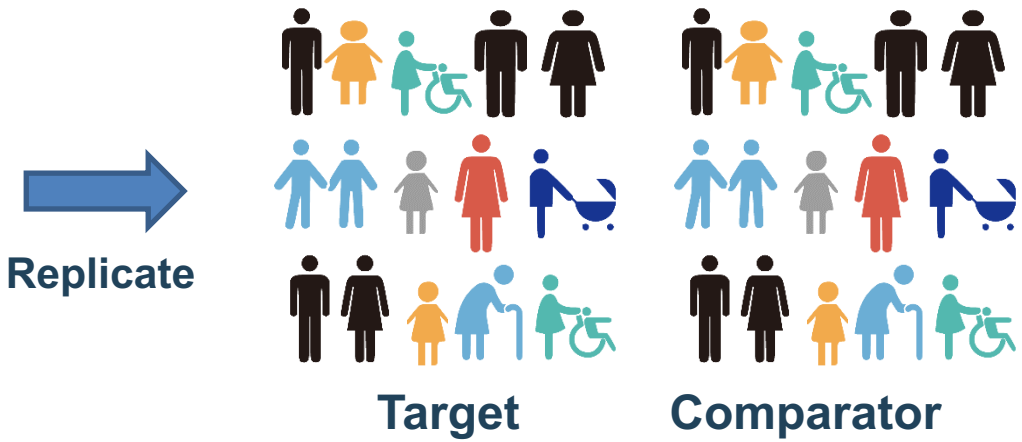
- Indication only cohort: A cohort of all patients who use and have an indication for each drug found on the FDA's drug label, including those who meet the eligibility criteria

**---------- INDICATIONS AND USAGE ----------**

BRILINTA is a P2Y$_{12}$ platelet inhibitor indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). For at least the first 12 months following ACS, it is superior to clopidogrel. BRILINTA also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS. (1)

**----------INDICATIONS AND USAGE----------**

ELIQUIS is a factor Xa inhibitor anticoagulant indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. (1)



# TROY process: Difference in baseline characteristics

- The index date is the drug start date and only patients who were observable within the database during the previous 180 days were included
  - Also, the index date is after the date the target drug was approved by the Korean FDA
- ΔRCT: Indicators of baseline characteristics differences from replicated cohort and reported pooled RCT data
  - Standardized mean difference for the mean variable
  - Difference in percentage points for categorical variable
- All source codes for this work are available at https://github.com/ohdsi-studies/Troy

# Data sources

- Korean EMR databases:
  - **Yonsei University Health System (YUHS) CDM (5.7M)**
  - Ajou University School of Medicine (AUSOM) CDM (2.8M)
  - Other FEEDER-NET data partners as Research Free Zone

# Replication results: With eligibility criteria / indication only cohort

- Replicated drugs: antidiabetics

| Pivotal trial | With eligibility criteria | | | | Indication only | | | | Eligibility criteria / Indication only | |
|---|---|---|---|---|---|---|---|---|---|---|
| | YUHS | | AUSOM | | YUHS | | AUSOM | | YUHS | AUSOM |
| | Target | Comparator | Target | Comparator | Target | Comparator | Target | Comparator | | |
| LEADER | NA (liraglutide) | 1,273 (DPP-4) | NA (liraglutide) | 700 (DPP-4) | NA (liraglutide) | 11,897 (DPP-4) | NA (liraglutide) | 6,717 (DPP-4) | NA / 0.107 | NA / 0.104 |
| DECLARE-TIMI 58 | 248 (dapagliflozin) | 1,584 (DPP-4) | 133 (dapagliflozin) | 1,008 (DPP-4) | 2,412 (dapagliflozin) | 11,897 (DPP-4) | 1,190 (dapagliflozin) | 6,717 (DPP-4) | 0.103 / 0.203 | 0.112 / 0.150 |
| EMPA-REG OUTCOME | 362 (empagliflozin) | 3,714 (DPP-4) | 445 (empagliflozin) | 2,167 (DPP-4) | 887 (empagliflozin) | 11,897 (DPP-4) | 1,016 (empagliflozin) | 6,717 (DPP-4) | 0.408 / 0.313 | 0.438 / 0.323 |
| CANVAS | NA (canagliflozin) | 1,781 (DPP-4) | NA (canagliflozin) | 1,008 (DPP-4) | NA (canagliflozin) | 11,897 (DPP-4) | NA (canagliflozin) | 6,717 (DPP-4) | NA / 0.150 | NA / 0.150 |
| CARMELINA | 446 (linagliptin) | 199 (sulfonylureas) | 30 (linagliptin) | 48 (sulfonylureas) | 6,143 (linagliptin) | 5,610 (sulfonylureas) | 2,931 (linagliptin) | 5,818 (sulfonylureas) | 0.073 / 0.035 | 0.010 / 0.008 |
| TECOS | 129 (sitagliptin) | 93 (sulfonylureas) | 143 (sitagliptin) | 298 (sulfonylureas) | 6,375 (sitagliptin) | 5,610 (sulfonylureas) | 3,919 (sitagliptin) | 5,818 (sulfonylureas) | 0.02 / 0.017 | 0.036 / 0.051 |
| SAVOR-TIMI 53 | NA (saxagliptin) | 1,689 (sulfonylureas) | 353 (saxagliptin) | 1691 (sulfonylureas) | NA (saxagliptin) | 5,610 (sulfonylureas) | 1,063 (saxagliptin) | 5,818 (sulfonylureas) | NA / 0.301 | 0.331 / 0.291 |
| CAROLINA | 352 (linagliptin) | 343 (glimepiride) | 135 (linagliptin) | 265 (glimepiride) | 6,143 (linagliptin) | 5,610 (glimepiride) | 2,931 (linagliptin) | 5,766 (glimepiride) | 0.057 / 0.061 | 0.046 / 0.046 |

**NA means that the use of the drug could not be observed in the database or was not sufficient**

**With placebo-controlled RCT, the comparator is replaced with a similar therapeutic drug**

**>0.3** **>0.1** **<=0.1**

# Replication results: With eligibility criteria / indication only cohort

- Replicated drugs: antiplatelets, NOACs, tofacitinib

| Pivotal trial | With eligibility criteria | | | | Indication only | | | | Eligibility criteria / Indication only | |
|---|---|---|---|---|---|---|---|---|---|---|
| | YUHS | | AUSOM | | YUHS | | AUSOM | | YUHS | AUSOM |
| | Target | Comparator | Target | Comparator | Target | Comparator | Target | Comparator | | |
| TRITON-TIMI 38 | NA (prasugrel) | 485 (clopidogrel) | 28 (prasugrel) | 654 (clopidogrel) | NA (prasugrel) | 5,972 (clopidogrel) | 245 (prasugrel) | 4,495 (clopidogrel) | - / 0.081 | 0.114 / 0.145 |
| PLATO | 1,252 (ticagrelor) | 4,345 (clopidogrel) | 693 (ticagrelor) | 3,295 (clopidogrel) | 1,587 (ticagrelor) | 5,972 (clopidogrel) | 871 (ticagrelor) | 4,495 (clopidogrel) | 0.789 / 0.728 | 0.796 / 0.733 |
| ROCKET AF | 820 (rivaroxaban) | 891 (warfarin) | 265 (rivaroxaban) | 210 (warfarin) | 4,569 (rivaroxaban) | 3,461 (warfarin) | 812 (rivaroxaban) | 1,032 (warfarin) | 0.179 / 0.257 | 0.326 / 0.203 |
| ARISTOTLE | 2,452 (apixaban) | 1,721 (warfarin) | 159 (apixaban) | 441 (warfarin) | 3,272 (apixaban) | 3,461 (warfarin) | 419 (apixaban) | 1,032 (warfarin) | 0.749 / 0.497 | 0.379 / 0.427 |
| ENGAGE AF-TIMI 48 | 316 (edoxaban) | 145 (warfarin) | 116 (edoxaban) | 47 (warfarin) | 2,693 (edoxaban) | 3,461 (warfarin) | 985 (edoxaban) | 1,032 (warfarin) | 0.117 / 0.042 | 0.118 / 0.046 |
| ORAL | NA (tofacitinib) | NA (TNFi) | NA (tofacitinib) | NA (TNFi) | NA (tofacitinib) | NA (TNFi) | NA (tofacitinib) | NA (TNFi) | NA | NA |
| STAR-RA | NA (tofacitinib) | NA (TNFi) | NA (tofacitinib) | NA (TNFi) | NA (tofacitinib) | NA (TNFi) | NA (tofacitinib) | NA (TNFi) | NA | NA |

NA means that the use of the drug could not be observed in the database or was not sufficient

>0.3 >0.1 <=0.1

# Difference in baseline characteristics: Enrolled in the PLATO *vs* Indication only *vs* eligibility criteria

| Characteristic | RCT | | | RWE | | | |
|---|---|---|---|---|---|---|---|
| | | | | With eligibility criteria | | Indication only | |
| | Ticagrelor (n=9,333) | Clopidogrel (n=9,291) | Pooled (n=18,264) | n=4,971 | ΔRCT | n=6,747 | ΔRCT |
| Median age — yr | 62.0 | 62.0 | 62.0 | 68.0 | - | 67.0 | - |
| Age ≥75 yr — no./total no. (%) | 1,396/9,333 (15.0) | 1,482/9,291 (16.0) | 2878 (15.5) | 1407 (28.3) | 0.129 | 1,841 (27.3) | 0.118 |
| Female sex — no./total no. (%) | 2,655/9,333 (28.4) | 2,633/9,291 (28.3) | 5288 (28.4) | 1982 (39.9) | 0.115 | 2,672 (39.6) | 0.112 |
| Median body weight — kg (range) | 80.0 (28–174) | 80.0 (29–180) | 80 | 65.7 | - | 65.4 | - |
| Body weight <60 kg — no./total no. (%) | 652/9,333 (7.0) | 660/9,291 (7.1) | 1312 (7.0) | 1158 (23.3) | 0.163 | 1,610 (23.9) | 0.168 |
| BMI — median (range) | 27 (13–68) | 27 (13–70) | 27 | 24.36 | - | 24.31 | - |
| Race — no./total no. (%) | | | | | | | |
| White | 8,566/9,332 (91.8) | 8,511/9,291 (91.6) | 17,077 (91.7) | 0 (0) | -0.917 | 0 (0) | -0.917 |
| Black | 115/9332 (1.2) | 114/9291 (1.2) | 229 (1.2) | 0 (0) | -0.012 | 0 (0) | -0.012 |
| Asian | 542/9332 (5.8) | 554/9291 (6.0) | 1,094 (5.9) | 4,892 (98.4) | 0.925 | 6,644 (98.5) | 0.926 |
| Other | 109/9332 (1.2) | 112/9291 (1.2) | 221 (1.2) | 79 (1.6) | 0.004 | 103 (1.6) | 0.004 |
| Cardiovascular risk factor — no./total no. (%) | | | | | | | |
| Habitual smoker | 3,360/9,333 (36.0) | 3,318/9,291 (35.7) | 6678 (35.9) | NA | NA | NA | NA |
| Hypertension | 6,139/9,333 (65.8) | 6,044/9,291 (65.1) | 12183 (65.4) | 2459 (49.5) | -0.159 | 3,342 (49.5) | -0.159 |
| Dyslipidemia | 4,347/9,333 (46.6) | 4,342/9,291 (46.7) | 8689 (46.7) | 2234 (44.9) | -0.017 | 2,925 (43.4) | -0.033 |
| Diabetes mellitus | 2,326/9,333 (24.9) | 2,336/9,291 (25.1) | 4662 (25.0) | 575 (11.6) | -0.135 | 809 (12.0) | -0.130 |

**Characteristics that are difficult to observe in the observational health care database were excluded**

Wallentin et al., *NEJM*, 2009

# Difference in baseline characteristics: Enrolled in the PLATO *vs* Indication only *vs* eligibility criteria

| Characteristic | RCT | | | RWE | | | |
|---|---|---|---|---|---|---|---|
| | | | | With eligibility criteria | | Indication only | |
| | Ticagrelor (n=9,333) | Clopidogrel (n=9,291) | Pooled (n=18,264) | n=4,971 | ΔRCT | n=6,747 | ΔRCT |
| Other medical history — no./total no. (%) | | | | | | | |
| MI | 1,900/9,333 (20.4) | 1,924/9,291 (20.7) | 3,824 (20.5) | 1,463 (29.4) | 0.089 | 1,790 (26.5) | 0.060 |
| Percutaneous coronary intervention | 1,272/9,333 (13.6) | 1,220/9,291 (13.1) | 2,492 (13.4) | 407 (8.2) | -0.052 | 512 (7.6) | -0.058 |
| Coronary-artery bypass grafting | 532/9,333 (5.7) | 574/9,291 (6.2) | 1,106 (5.9) | 35 (0.7) | -0.052 | 70 (1.0) | -0.049 |
| Congestive heart failure | 513/9,333 (5.5) | 537/9,291 (5.8) | 1,050 (5.6) | 20 (0.4) | -0.052 | 46 (0.7) | -0.050 |
| Nonhemorrhagic stroke | 353/9,333 (3.8) | 369/9,291 (4.0) | 722 (3.9) | 68 (1.4) | -0.025 | 106 (1.6) | -0.023 |
| Peripheral arterial disease | 566/9,333 (6.1) | 578/9,291 (6.2) | 1,144 (6.1) | 194 (3.9) | -0.022 | 297 (4.4) | -0.017 |
| Chronic renal disease | 379/9,333 (4.1) | 406/9,291 (4.4) | 785 (4.2) | 309 (6.2) | 0.020 | 539 (8.0) | 0.038 |
| History of dyspnea | 1,412/9,333 (15.1) | 1,358/9,291 (14.6) | 2,770 (14.9) | 40 (0.8) | -0.141 | 74 (1.1) | -0.138 |
| Chronic obstructive pulmonary disease | 555/9,333 (5.9) | 530/9,291 (5.7) | 1,085 (5.8) | 95 (1.9) | -0.039 | 142 (2.1) | -0.037 |
| Asthma | 267/9,333 (2.9) | 265/9,291 (2.9) | 532 (2.9) | 136 (2.7) | -0.001 | 199 (2.9) | 0.001 |
| Gout | 272/9,333 (2.9) | 262/9,291 (2.8) | 534 (2.9) | 64 (1.3) | -0.016 | 124 (1.8) | -0.010 |
| Final diagnosis of ACS — no./total no. (%) | | | | | | | |
| ST-elevation MI | 3,496 | 3,530 | 7,026 (37.3) | 1,129 (22.7) | -0.150 | 1,390 (20.6) | -0.171 |
| Non-ST-elevation MI | 4,005 | 3,950 | 7,955 (42.7) | 1,404 (28.2) | -0.145 | 1,850 (27.4) | -0.153 |
| Unstable angina | 1,549 | 1,563 | 3,112 (16.7) | 2,676 (53.8) | 0.371 | 3,797 (56.3) | 0.396 |

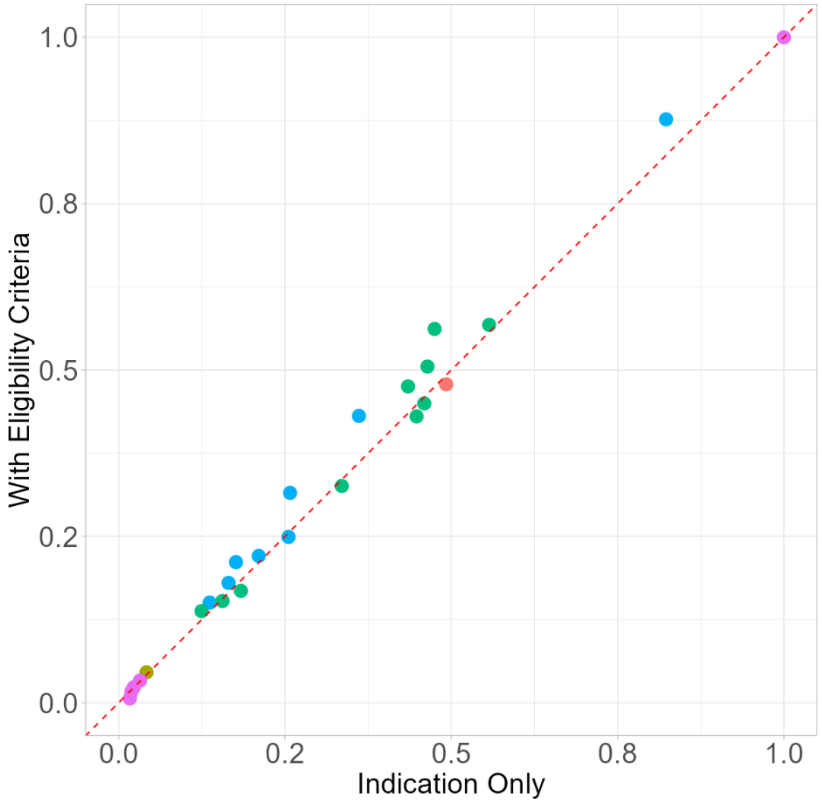
**Characteristics that are difficult to observe in the observational health care database were excluded**

Wallentin et al., *NEJM*, 2009

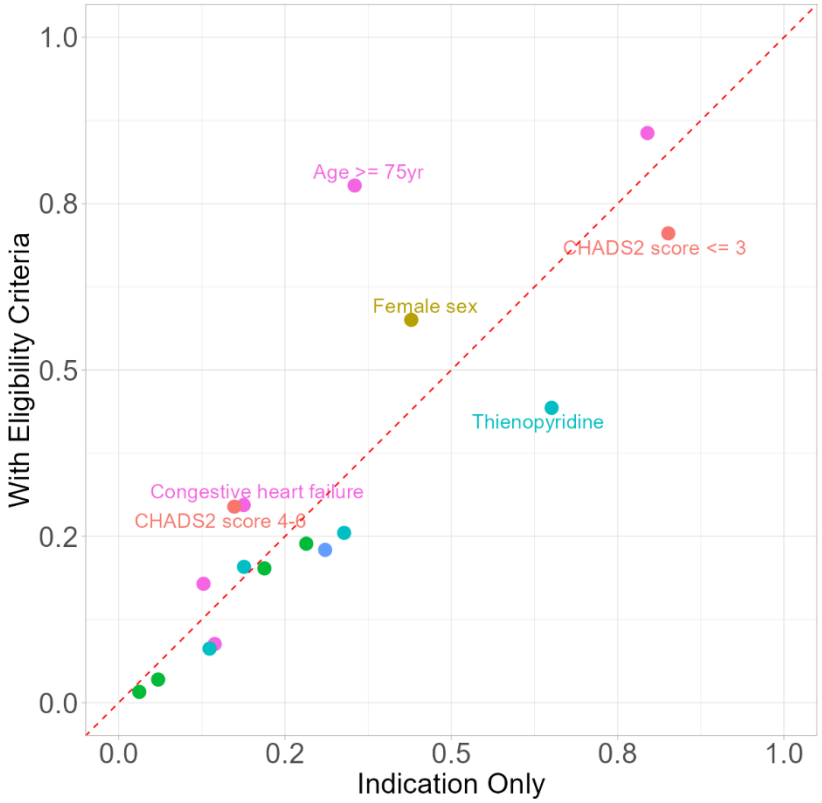
# Difference in baseline characteristics: Enrolled in Indication only *vs* eligibility criteria cohorts

- NOACs (target) *vs* Warfarin (comparator)

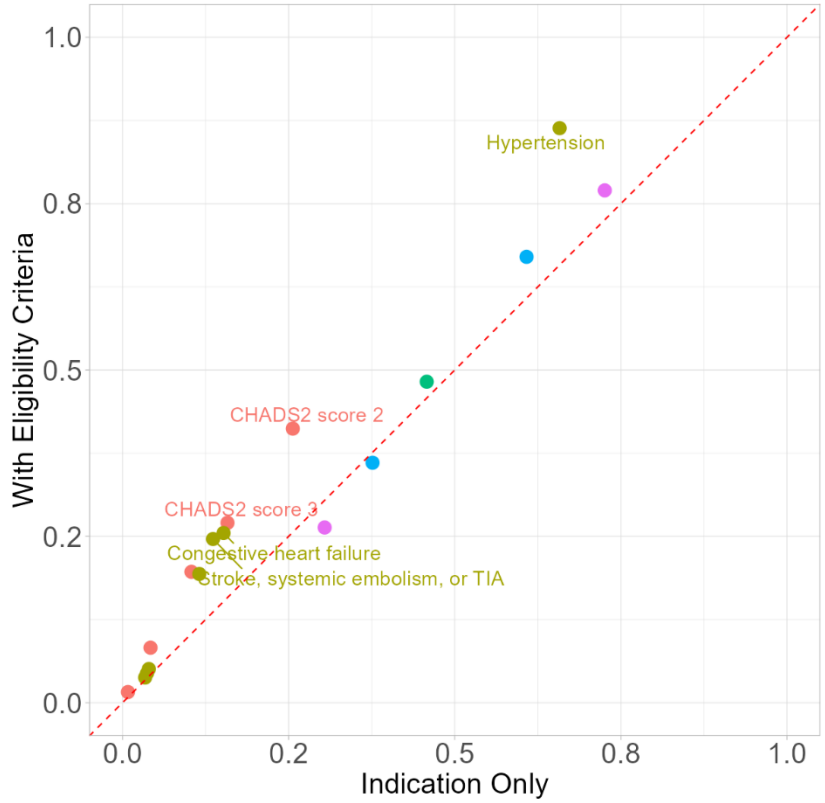
**ARISTOTLE (apixaban)**




**ENGAGE AF-TIMI48 (edoxaban)**



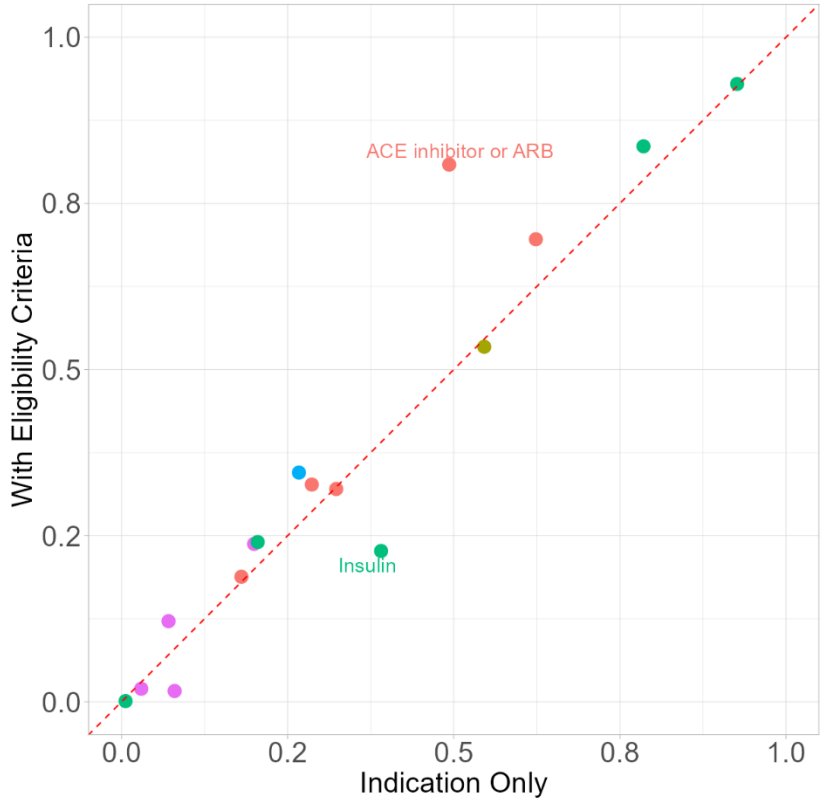

**ROCKET-AF (rivaroxaban)**



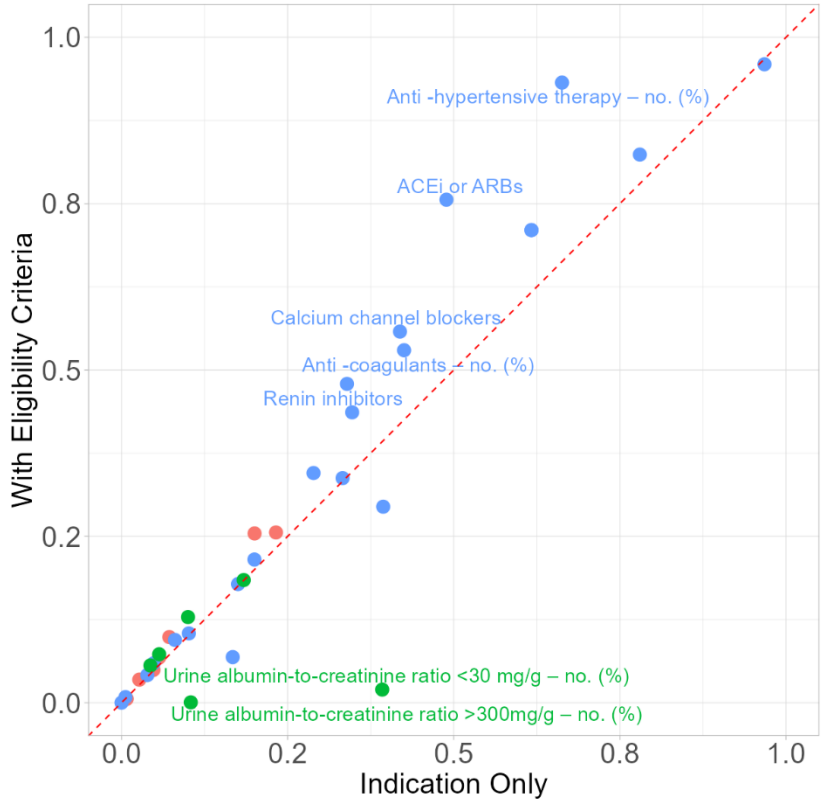
# Difference in baseline characteristics: Enrolled in Indication only *vs* eligibility criteria cohorts

- SGLT2is (target) *vs* DPP-4 inhibitors (comparator)

**DECLARE-TIMI 58 (dapagliflozin)**



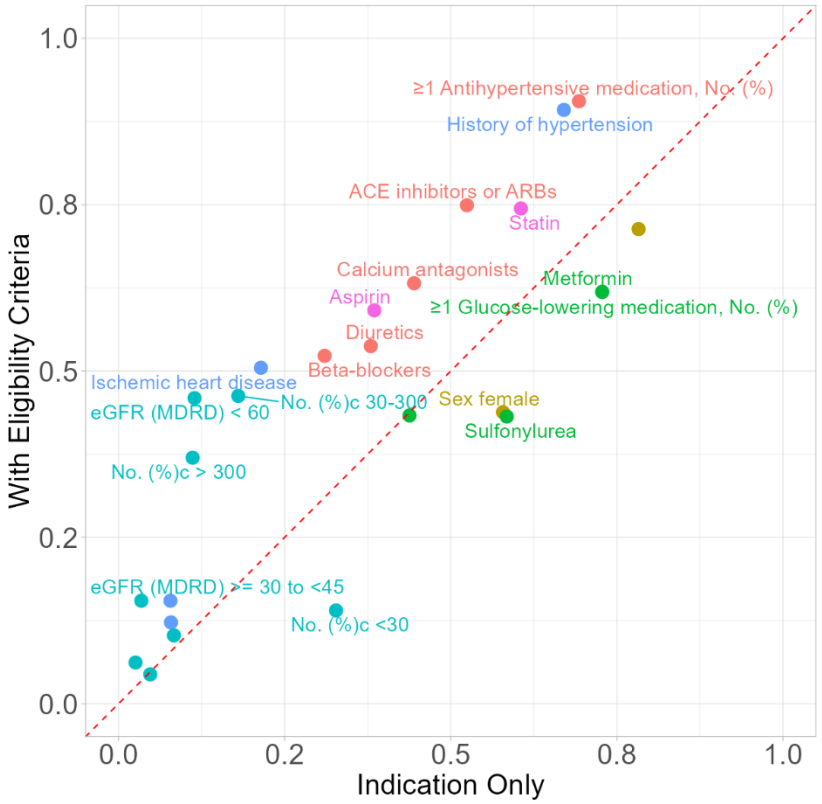

**EMPA-REG OUTCOME (empagliflozin)**



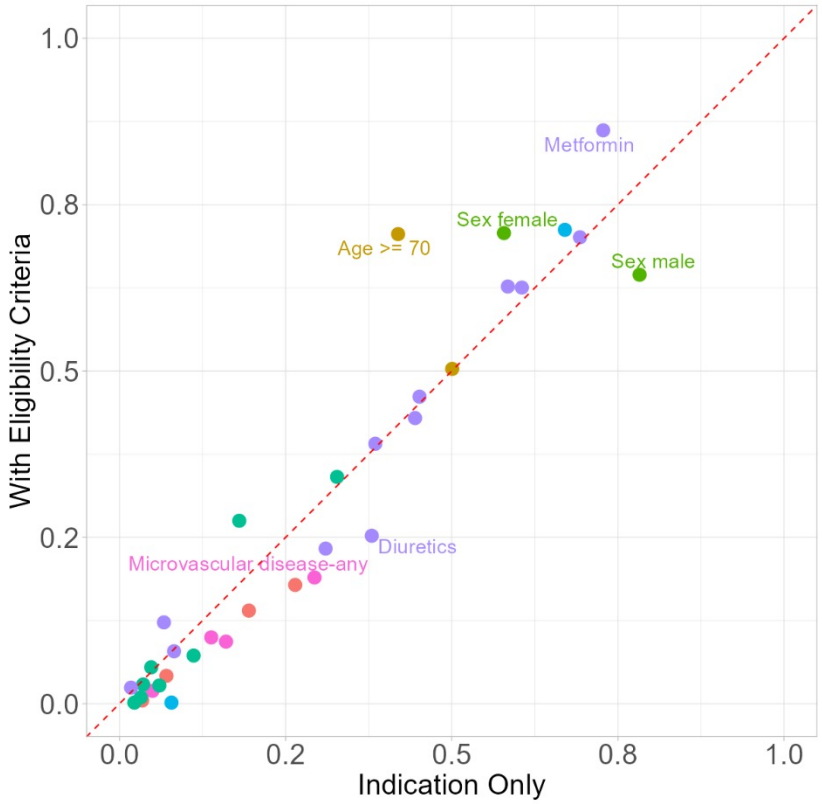
# Difference in baseline characteristics: Enrolled in Indication only *vs* eligibility criteria cohorts

- DPP-4 inhibitors (target) *vs* Sulfonylureas or Glimepiride (comparator)

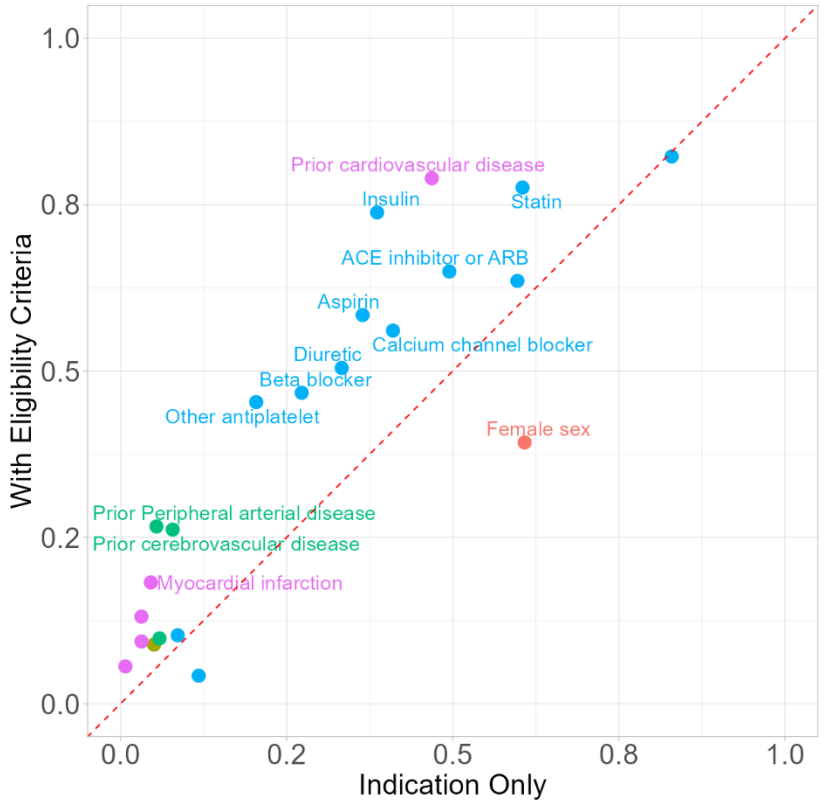
**CARMELINA (linagliptin)**




**CAROLINA (linagliptin)**




**TECOS (sitagliptin)**



# Conclusion

- The results from clinical trials do not guarantee external validity in contemporary routine clinical practice
- Our results reveal clinical differences between the population enrolled in RCT and the population replicated from an observational database
- These findings emphasize once again the need for examining evidence using real-world data to generalize the evidence from RCT

*Between measurements based on RCTs and benefit… in the community there is a gulf which has been much under-estimated*

A L Cocharne, 1971

*At its best a trial shows what can be accomplished with a medicine under careful observation and certain restricted conditions. The same results will not invariably or necessarily be observed when the medicine passes into general use*

Austin Bradford Hill, 1984