JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Comparative Effectiveness and Real-World Evidence

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Just Two Examples of Designs for Studying the Effectiveness or Safety of a Product

Comparative effectiveness study
Cohort study conducted like a trial emulation

Example:

Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.)*, *34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Comparative safety study
Self-controlled design

Example:

Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377

Applied Example of a Comparative Effectiveness Study

Comparative effectiveness study:
Cohort study conducted like a trial emulation

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Comparative Effectiveness Study

- Question
- Stakeholders
- Design
- Results
- Limitations and strengths
- How this information might be used

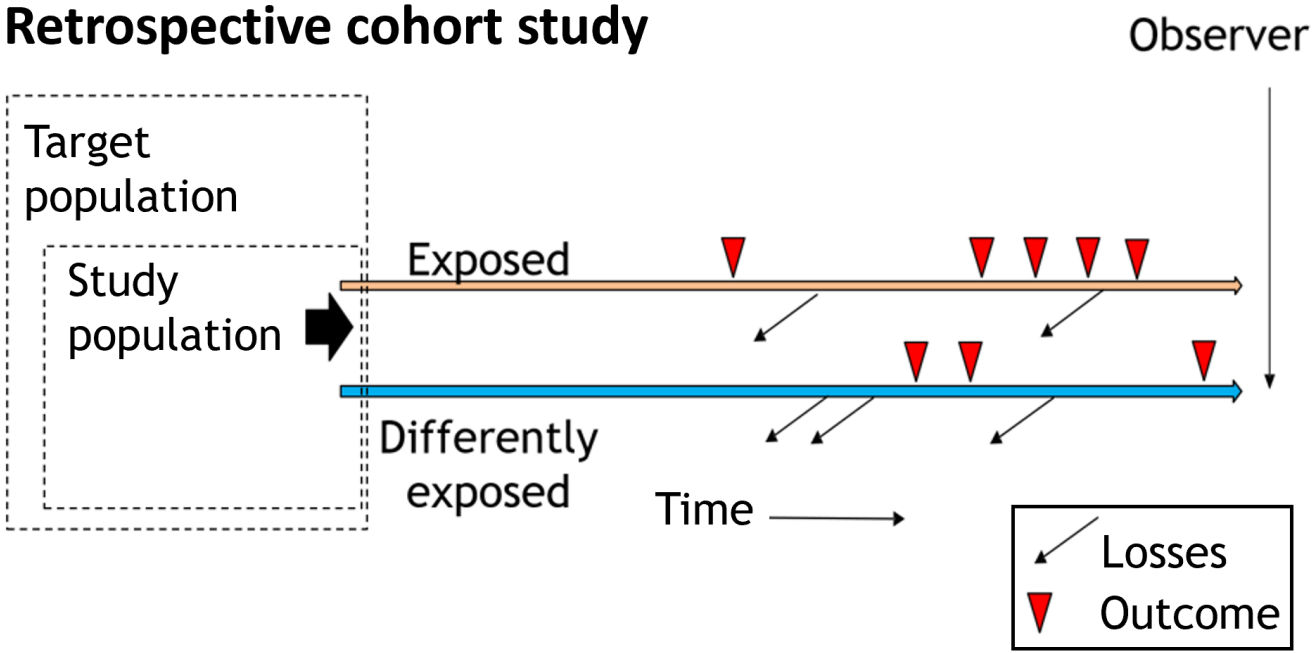

Image source: Jodi Segal, MD, MPH, with the Center for Teaching and Learning, Johns Hopkins Bloomberg School of Public Health.
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Evaluating Metformin Strategies for Cancer Prevention–1

- Question:
  - Prior observational studies have described lower cancer rates among users of metformin
  - It is infeasible to design such a large and long randomized controlled trial (RCT) to test this hypothesis
  - Does the use of metformin, when compared with no use of metformin, reduce the risk of cancer?

- Stakeholders:
  - Authors don't address this explicitly
  - I think that patients want to know the answer; clinicians want to know
  - The answer is not so important to manufacturers because metformin is a generic product
  - Insurance companies would benefit if they can avoid expensive cancer in their beneficiaries

Source: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.)*, *34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–2

- Design:
  - Retrospective cohort study designed to emulate a target trial

- Data:
  - Large database of linked electronic health records from primary care, hospitalizations, and mortality registrations (Clinical Practice Research Database [CPRD], Hospital Episode Statistics, and Office of National Statistics)

Source: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.)*, *34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–3

	Target trial	Emulation with observational data
Eligibility criteria	• Aged ≥30 years between April 1, 2009, and February 29, 2016 • Type 2 diabetes mellitus • No history of cancer • No metformin contraindication • No prescription for metformin or other glucose-lowering medication within the past year • Information on lab values (HbA1c) measured during the past year and lifestyle factors (body-mass index, smoking status) during the past year	Same as in target trial

Source: Adapted from Table 1, in: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.)*, *34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–4

	Target trial	Emulation with observational data
Treatment strategies	Treatment strategies (1) Initiation of metformin at baseline and continuation over follow-up until the development of a contraindication (hepatic or renal impairment or lactic acidosis) or diagnosis of cancer (2) No initiation of metformin over follow-up until the development of an indication (HbA1c ≥64 mmol/mol [≥8.0%]) When clinically warranted, patients and their physicians will decide whether to start, stop, or switch therapy.	Same as for the target trial. We defined the date of medication initiation to be the **first date of a prescription.**

Source: Adapted from Table 1, in: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.)*, *34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–5

	Target trial	Emulation with observational data
Treatment assignment	Individuals are randomly assigned to a strategy at baseline.	Classified individuals into 1 of 2 groups according to the strategy that their data were compatible **with at baseline** and assumed randomization conditional on baseline covariates.
Outcomes	Total cancer and the 4 most common site-specific invasive cancers in this population: female breast, colorectal, lung (non-small cell), prostate.	Same as for the target trial.

Source: Adapted from Table 1, in: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.)*, *34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–6

	Target trial	Emulation with observational data
Follow-up	Follow-up starts at treatment assignment and ends on the month of the cancer outcome of interest, death, loss to follow-up, or administrative end of follow-up.	Same as for the target trial
Causal contrast	Intention-to-treat effect and per-protocol effect.	Observational analogues of the intention-to-treat and per-protocol effects.

Source: Adapted from Table 1, in: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.)*, *34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–7

	Target trial	Emulation with observational data
Statistical analysis	Logistic regression to estimate hazard ratios and standardized risk curves.	• Same as for the target trial with sequential emulation and adjustment for baseline covariates. • Intention-to-treat analysis: apply inverse-probability weights to adjust for pre- and post-baseline prognostic factors associated with loss to follow-up. [NOT USUALLY NEEDED IN AN RCT] • Per-protocol analysis: **Censor** individuals when they deviate from their assigned treatment strategy, and apply inverse-probability weights to adjust for pre- and post-baseline prognostic factors associated with adherence and loss to follow-up. • They emulated the target trial as a sequence of trials starting at each of the 71 months between April 2009 and February 2015 (and pooled the results).

Source: Adapted from Table 1, in: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.)*, *34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–8

- Baseline characteristics of eligible individuals with type 2 diabetes mellitus
- Applied inverse-probability of treatment weights to the population in every simulated trial (71 trials) to balance these treatment groups

Characteristic[b]	Among Individuals With Diabetes	
	Metformin Initiators (N = 9,835)	Non-initiators (N = 1,021,112)
Age (years), mean (SD)	63.4 (12.1)	68.6 (12.2)
Sex, no. (%)		
Female	4,501 (46)	475,710 (47)
Male	5,334 (54)	545,402 (53)
Body-mass index (kg/m^2), mean (SD)	32.3 (6.7)	30.2 (6.0)
Hemoglobin A1c (mmol/L), mean (SD)	53.7 (6.2)	47.1 (6.5)
Time since type 2 diabetes diagnosis (months), mean (SD)	31.5 (35.4)	50.3 (37.9)
Smoking status, no. (%)		
Never	4,692 (48)	494,622 (48)
Former	3,552 (36)	387,066 (38)
Current	1,591 (16)	139,424 (14)
Comorbidities, no. (%)		
Coronary heart disease	709 (7)	73,391 (7)
Hypertension	3,085 (31)	338,909 (33)
Cerebrovascular disease	163 (2)	19,911 (2)
Other cardiovascular disease[c]	2,377 (24)	285,398 (28)
Medications, no. (%)		
Antihypertensive use[d]	6,541 (67)	717,506 (70)
Aspirin use	2,453 (25)	276,140 (27)
Nonsteroidal anti-inflammatory drug use	906 (9)	78,921 (8)
Hormonal replacement therapy, no. (% of women)	80 (2)	5,195 (1)
Oral contraceptive use, no. (% of women)	83 (2)	5,469 (1)
Any specialist referral in the past 3 months, no. (%)	2,205 (22)	106,862 (10)

Source: Table 2. In: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.), 34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–9

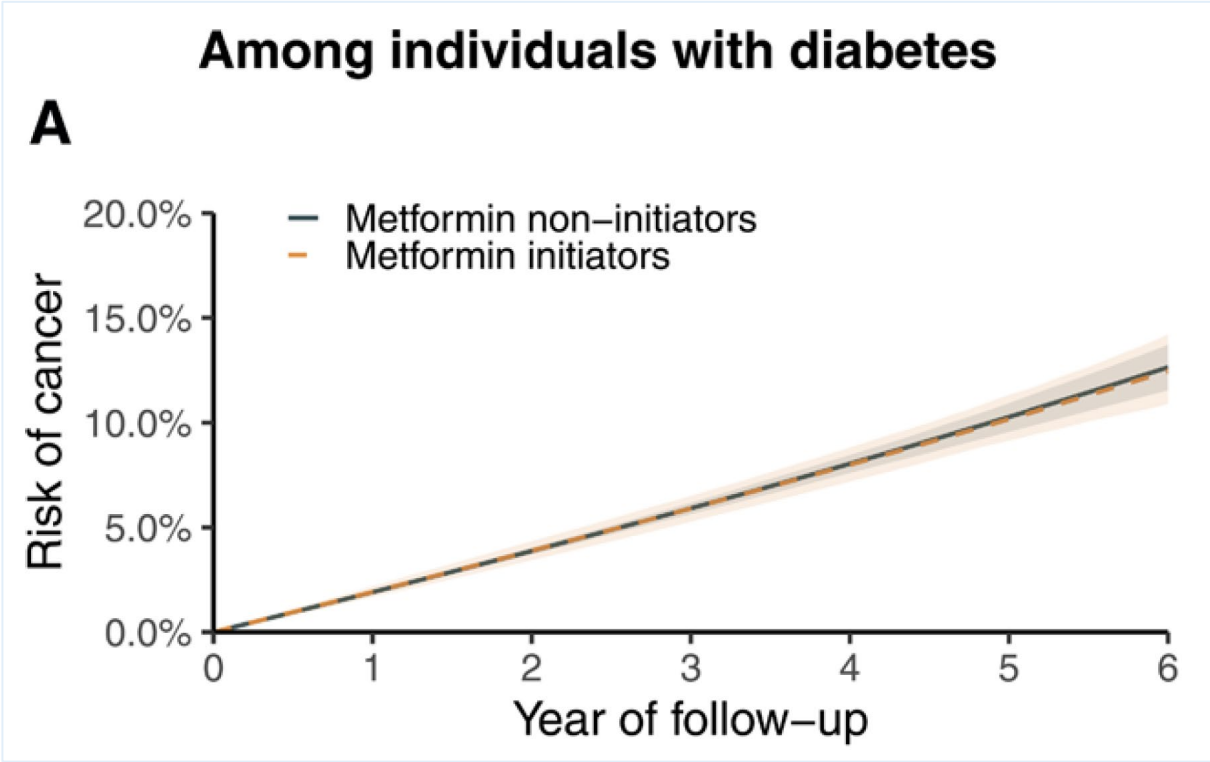
Hazard ratios for cancer comparing metformin therapy with no metformin therapy

	No. of Incident Cancers[b]		6-year Risk (%) (95% CI)		Risk Difference (%) (95% CI)	Hazard Ratio (95% CI)
	Initiators	Non-initiators	Initiators	Non-initiators		
Among individuals with diabetes						
Intention-to-treat[c]						
Total cancer	467	2,694	12.5 (10.9, 14.2)	12.6 (11.5, 13.7)	−0.2 (−1.6, 1.3)	1.00 (0.90, 1.10)
Breast, female	48	265	3.3 (2.0, 5.0)	2.7 (1.9, 3.6)	0.7 (−0.5, 2.0)	1.00 (0.74, 1.36)
Colorectal	60	355	1.4 (1.0, 2.1)	1.4 (1.1, 1.7)	0.1 (−0.4, 0.7)	1.02 (0.77, 1.33)
Lung	58	360	2.3 (1.5, 3.3)	1.8 (1.4, 2.3)	0.5 (−0.3, 1.4)	1.00 (0.76, 1.33)
Prostate	79	399	3.2 (2.3, 4.3)	3.5 (2.8, 4.5)	−0.4 (−1.4, 0.7)	1.07 (0.85, 1.35)

Source: Table 3, "Estimated 6-Year Standardized Risks and Hazard Ratios for Cancer Comparing Metformin Therapy with no Metformin Therapy, Using Linked Electronic Health Records from Clinical Practice Research Datalink, Hospital Episode Statistics, and Office of National Statistics, 2009–2016." In: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.), 34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–10

Risk of cancer over time among people with diabetes who did and did not initiate metformin



Source: Figure 2A, "Estimated risk of cancer by metformin therapy among individuals with diabetes (observational analog to an intention-to-treat analysis)." In: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.), 34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–11

- Strengths:
  - These basic principles of study design can avoid time-related biases in observational studies
  - Electronic health records capture rich longitudinal data on demographic and clinical features that allowed us to characterize individuals with high resolution and adjust for many potential confounders
  - Emulating a sequence of target trials is more statistically efficient than emulating a single target trial

Source: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.), 34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–12

- Limitations:
  - There could be unmeasured confounders
  - We relied on prescription records and diagnosis codes
  - Follow-up time might have been too short for some cancers

Source: Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2023). Evaluating metformin strategies for cancer prevention: A target trial emulation using electronic health records. *Epidemiology (Cambridge, Mass.), 34*(5), 690–699. https://doi.org/10.1097/EDE.0000000000001626

Evaluating Metformin Strategies for Cancer Prevention–13

- How can this information be used?
  - Don’t use metformin to prevent cancer

Applied Example of a Comparative Safety Study

Comparative safety study:
Self-controlled design

Example:

Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377

Comparative Safety Study

- Question
- Stakeholders
- Design
- Results
- Limitations and strengths
- How this information might be used

Self-controlled design

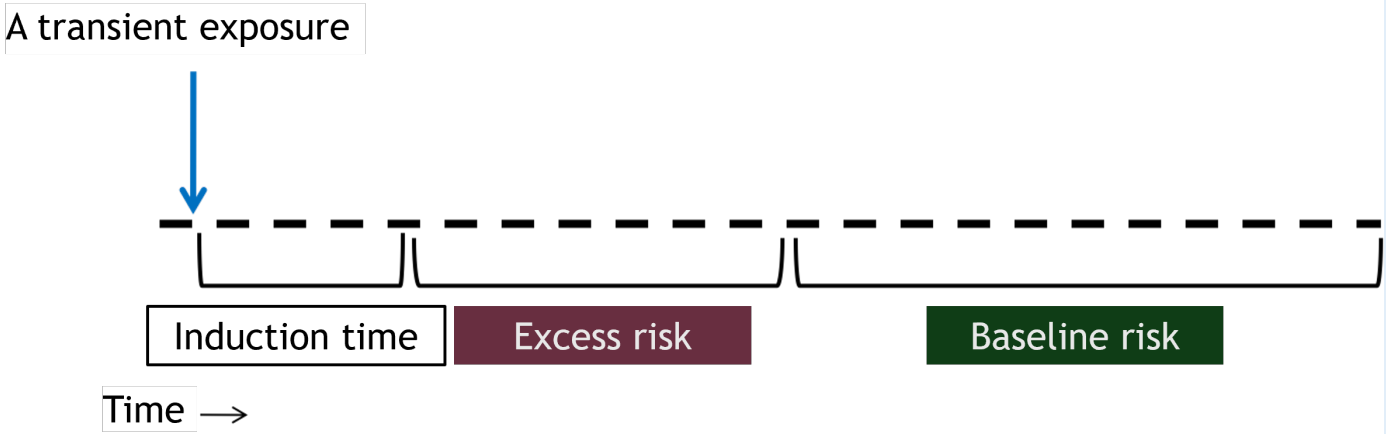


Image source: Jodi Segal, MD, MPH, with the Center for Teaching and Learning, Johns Hopkins Bloomberg School of Public Health.

Safety of Angiotensin-Converting Enzyme Inhibitors–1

- Question:
  - Is concomitant use of insulin secretagogues (sulfonylureas or meglitinides) with angiotensin-converting enzyme inhibitors (ACEIs) associated with an increased rate of serious hypoglycemia compared with use of insulin secretagogues without ACEIs?
- Stakeholders:
  - Authors don't explicitly address
  - Patients and clinicians need this information to lessen risk of dangerous hypoglycemia
  - Guideline developers need this information, as most guidelines recommend use of ACEIs in individuals with diabetes
  - Regulators care, as they might include warnings on medicines if there is an important drug–drug interaction
  - Online prescribing system developers care, as they include warnings to prescribers about drug–drug interactions

Source: Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377

Safety of Angiotensin-Converting Enzyme Inhibitors–2

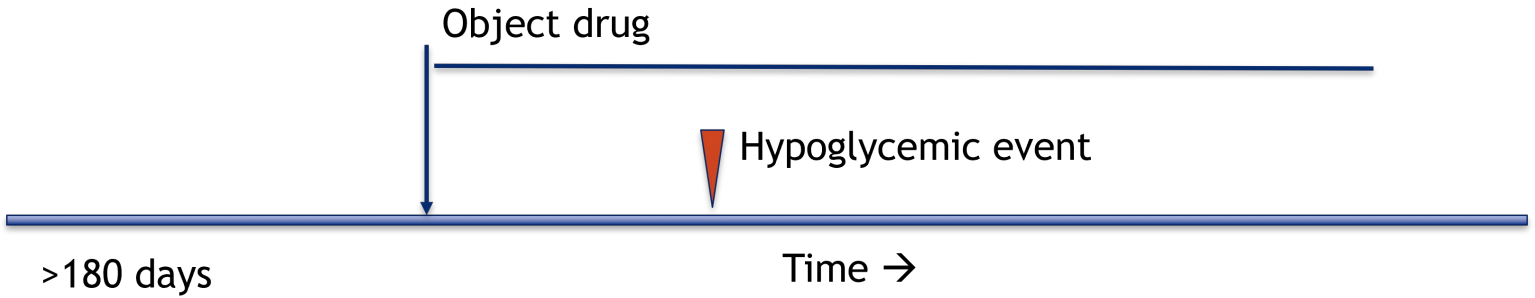
- Design:
  - Self-controlled case series
  - When studying drug–drug interactions, one drug is considered the “object” (affected by the other drugs); one drug (or more) is considered the “precipitant” drug (affecting the other drug)
  - Insulin secretagogues are the OBJECTS, and ACEIs are the PRECIPITANTS
  - Authors used metformin as a “negative-control object”; it should not cause hypoglycemia, so the ACEI interaction should not affect metformin users

- Data:
  - Insurance claims from publicly insured individuals in the US and the Social Security Death Master file for dates of death

Source: Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377

Safety of Angiotensin-Converting Enzyme Inhibitors–3

- Population:
  - Adults who had a hypoglycemic event (known from claims for hospital services) during the time when they were prescribed the object drug (insulin secretagogues)



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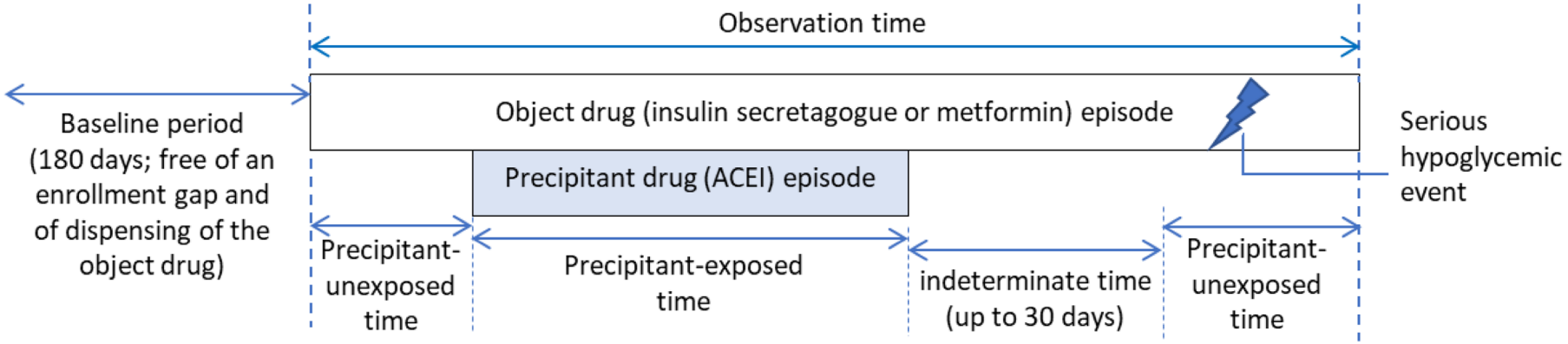
Safety of Angiotensin-Converting Enzyme Inhibitors–4

- Outcome:
  - Hospital presentation with serious hypoglycemia
  - Used a validated outcome ascertainment algorithm (with a positive predictive value of 89% in emergency department claims and 78% in inpatient claims) that used International Classification of Disease-9 (ICD-9) codes

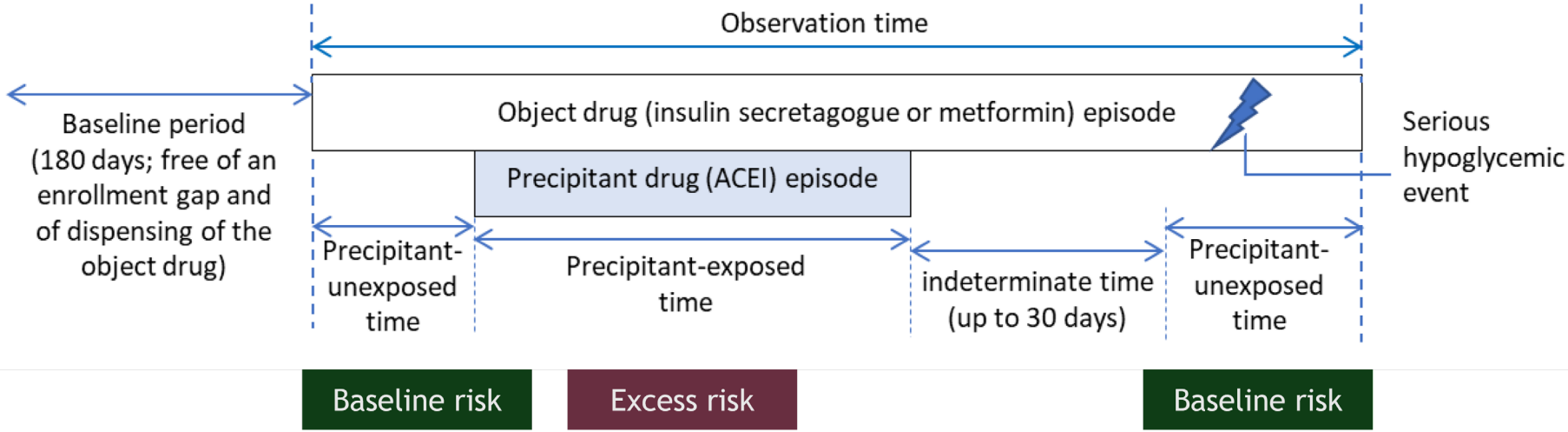
Source: Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377

Safety of Angiotensin-Converting Enzyme Inhibitors–5



Source: Figure S1, "Observation time," in online Supplementary Material for: Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377

Safety of Angiotensin-Converting Enzyme Inhibitors–6



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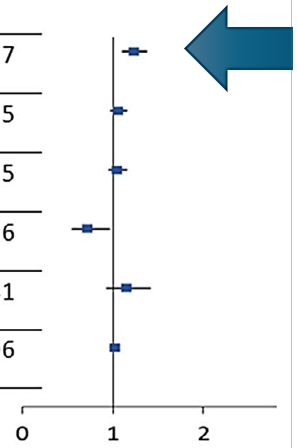
Safety of Angiotensin-Converting Enzyme Inhibitors–7

- Analyses:
  - Conditional Poisson regression to generate rate ratios
  - The self-controlled case series (SCCS) design inherently eliminates confounding by measured and unmeasured factors that are time-invariant within a person during the observation time
  - Authors controlled time-varying potential confounders that were ascertained on the person-day level (such as other drugs associated with hypo- or hyperglycemia and conditions associated with hypoglycemia, like serious infections)

Source: Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377

Safety of Angiotensin-Converting Enzyme Inhibitors–8

Object drug	Precipitant-exposed time[a] during observation time		Precipitant-unexposed time during observation time		Rate ratio[b] of serious hypoglycemia	95% CI
	Person-days	Number of serious hypoglycemia occurrences	Person-days	Number of serious hypoglycemia occurrences		
glimepiride	616,833	3,478	865,209	4,461	1.23	1.11, 1.37
glipizide	1,104,652	6,254	1,430,354	7,692	1.06	0.98, 1.15
glyburide	739,981	4,755	1,012,011	6,054	1.05	0.96, 1.15
nateglinide	71,654	662	125,968	894	0.73	0.56, 0.96
repaglinide	143,972	1,221	205,786	1,593	1.15	0.94, 1.41
metformin	3,996,889	14,880	4,511,824	16,983	1.02	0.97, 1.06



CI = confidence interval.

Source: Adapted from: Figure 2, "Rate ratios of serious hypoglycemia occurrence from the use of insulin secretagogues or metformin with versus without concomitant angiotensin-converting enzyme inhibitors," in: Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377 (modified with arrow)

Safety of Angiotensin-Converting Enzyme Inhibitors–9

- Strengths:
  - Use of a large health care database
  - Self-controlled design that eliminates confounding by time-invariant factors
  - Adjustment for time-varying potential confounders
  - Use of validated outcome ascertainment algorithm with high positive predictive values
  - Performance of sensitivity analyses, and study of a vulnerable population who might be most likely to show an adverse effect if one is present

Source: Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377

Safety of Angiotensin-Converting Enzyme Inhibitors–10

- Limitations:
  - Lack of information on actual intake of drugs
  - Lack of information about diet, exercise, and other health behaviors that could affect hypoglycemia risk
    - However, such factors could have introduced bias only if they varied within a person and were temporally associated with both ACEI use and serious hypoglycemia

Source: Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377

Safety of Angiotensin-Converting Enzyme Inhibitors–11

- Conclusion:
  - Authors conclude that these findings, together with lack of compelling mechanistic data indicative of ACEI-associated increased risk of hypoglycemia in sulfonylurea users, suggest that widely used drug compendia that warn of potential drug–drug interaction between sulfonylureas and ACEIs and electronic medical record systems generating interruptive alerts on this potential drug–drug interaction (DDI) should consider updating their current advice …
  - **Not an important drug–drug interaction**

Source: Hee Nam, Y., Brensinger, C. M., Bilker, W. B., Flory, J. H., Leonard, C. E., & Hennessy, S. (2022). Angiotensin-converting enzyme inhibitors used concomitantly with insulin secretagogues and the risk of serious hypoglycemia. *Clinical Pharmacology and Therapeutics*, *111*(1), 218–226. https://doi.org/10.1002/cpt.2377

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Comparative safety study
Self-controlled design

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