# PROMISE & PITFALLS OF OUTCOMES RESEARCH USING EMR DATABASES

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# GOALS OF STUDY

**Determine Whether Studies Using EMR Database Yield Valid Outcome Assessment**

- Major PITFALLS
  - **Unrecognized CONFOUNDING** in observational studies
    - Randomized trials balance comorbidities and treatments.
    - Clinical care is provided to patients who the doctor believes will benefit from it.
  - **Validity of data** in the EMR Database

# UK GENERAL PRACTICE RESEARCH DATABASE (GPRD)

- Established in 1987
- Medical records from approximately:
  - 700 General Practices (representative sample of approximately 5.5% of UK population)
  - > 3.5 M active patients
  - 25 M patient years of information

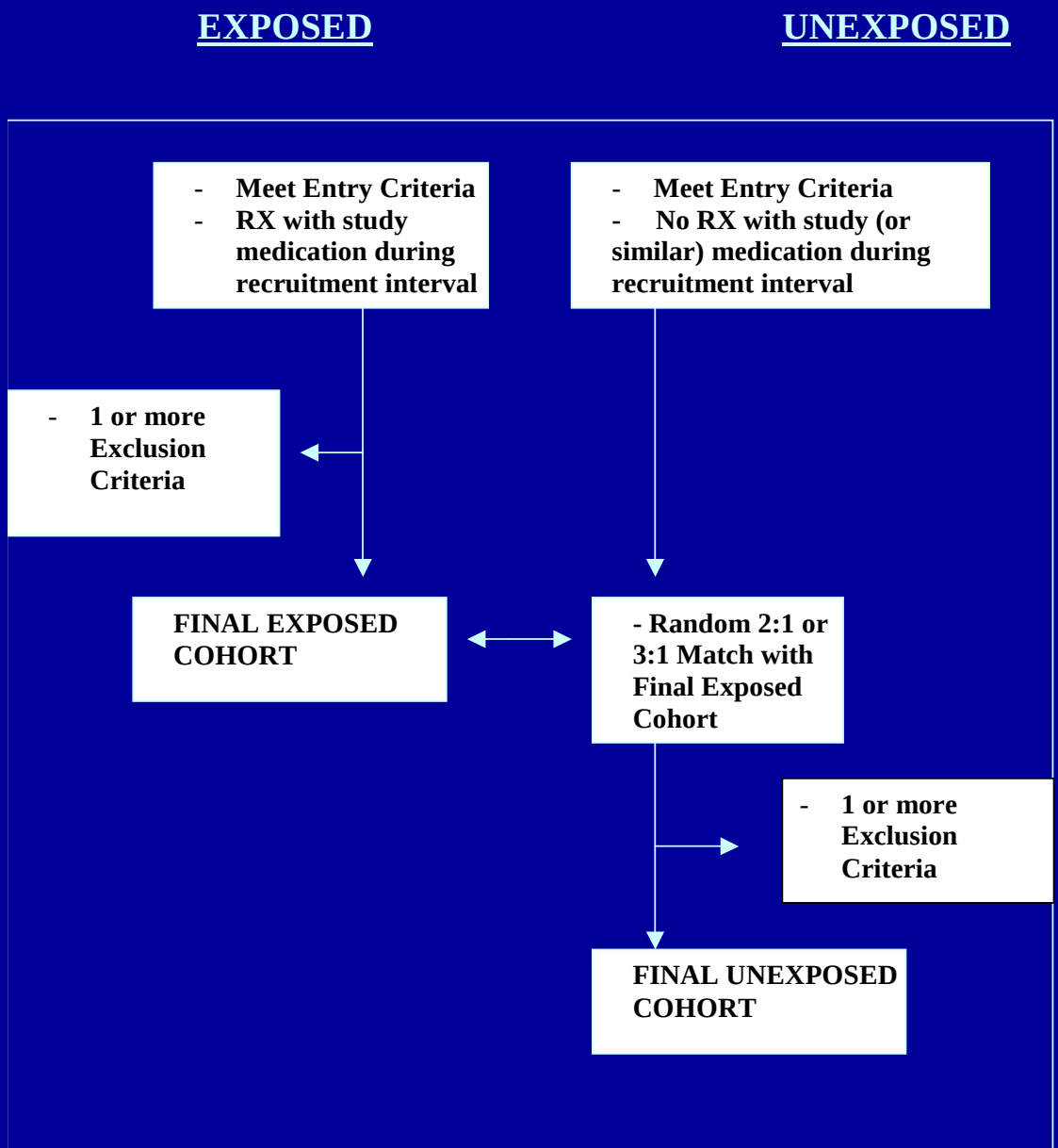
# GPRD Database Attributes

| ADVANTAGES | LIMITATIONS |
| --- | --- |
| • Comprehensive National Health Care System<br>• Representative sample entire population<br>• All care centralized in GP record<br>• All medications prescribed by GP – generated by computer<br>• Size - 8.0 M patients | • Lacks direct link to laboratory data (laboratory data inadequate)<br>• Missing data on smoking, SBP, BMI, FH (approx 30%)<br>• Limited data onset menopause<br>• Limited data on hospitalization<br>• Lacks direct link to death certificates (cause death not reliable) |

# GPRD MODELLED COMPARISON WITH RCT

- Retrospective cohort study
- Same inclusion/exclusion criteria as RCT
- Intervention & control matched to RCT to extent possible (except for placebo)
- Same outcomes
- Same confounders examined
- LACKS RANDOMIZATION

# SELECTION OF PARTICIPANTS IN GPRD STUDY



# ANALYSIS & STATISTICS

- Analysis
  - Simulated “Intention to Treat”
  - “As Treated”
- Statistics
  - Cox adjusted Hazard Ratio’s
  - Propensity Score Analysis
- Missing Data
- Non-Study Medication Utilization

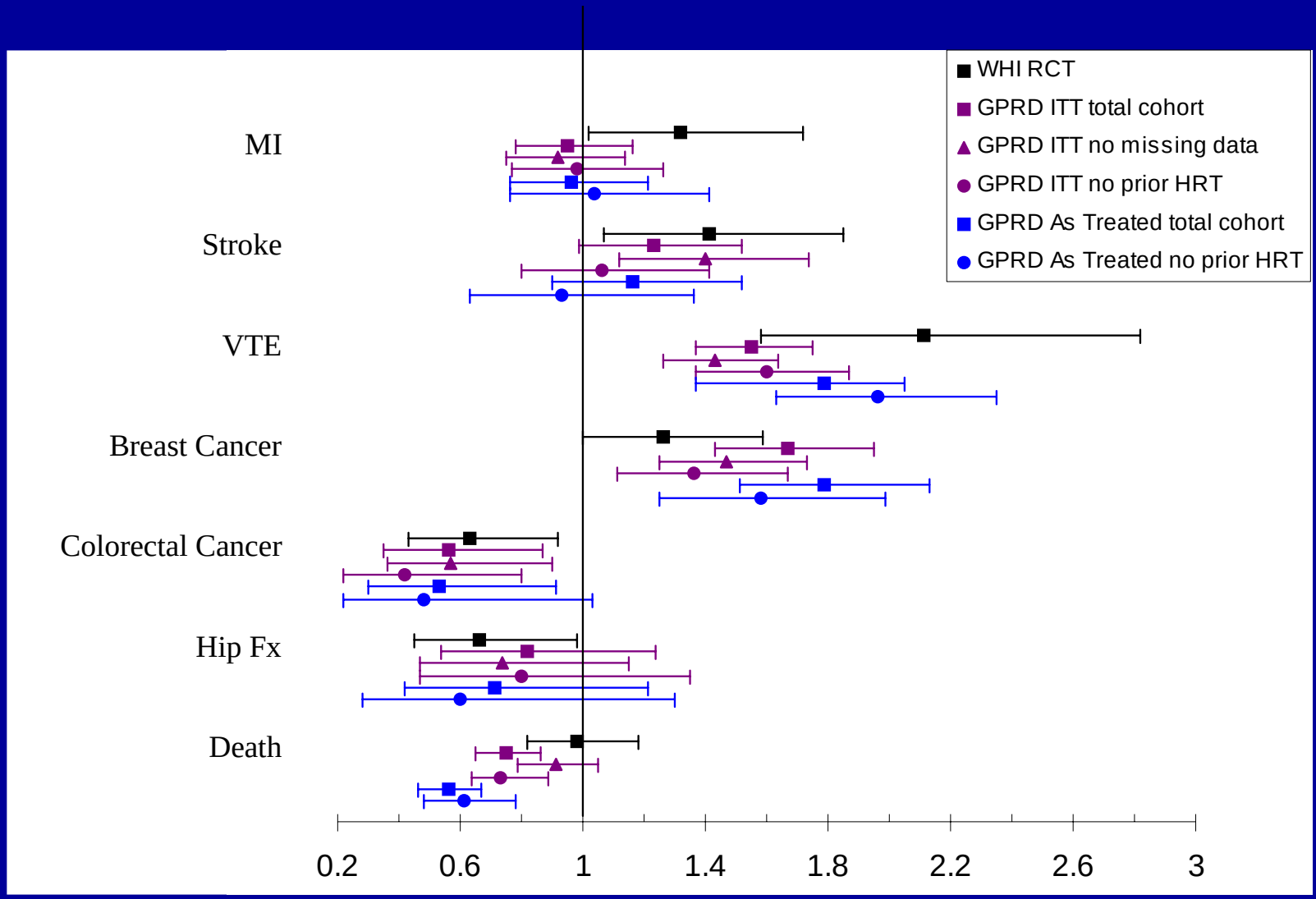
# OVERVIEW OF STUDIES

- PROBLEMS
  - Limited to CV studies because of limited lab data
  - Baseline characteristics Exposed & Unexposed usually differ
  - Missing data on SBP, BMI & Smoking
  - Unable to exactly replicate treatment in terms of product and duration

# RCT REPLICATIONS PERFORMED

- Syst Eur – isolated systolic hypertension
- WHI Trial (intact uterus) – Combined HRT
- WHI Trial (prior hysterectomy) - Estrogen
- Scandinavian Simvastatin Survival Study (4S) – Statin treatment
- HOPE – ACEI treatment
- EUROPA – ACEI treatment

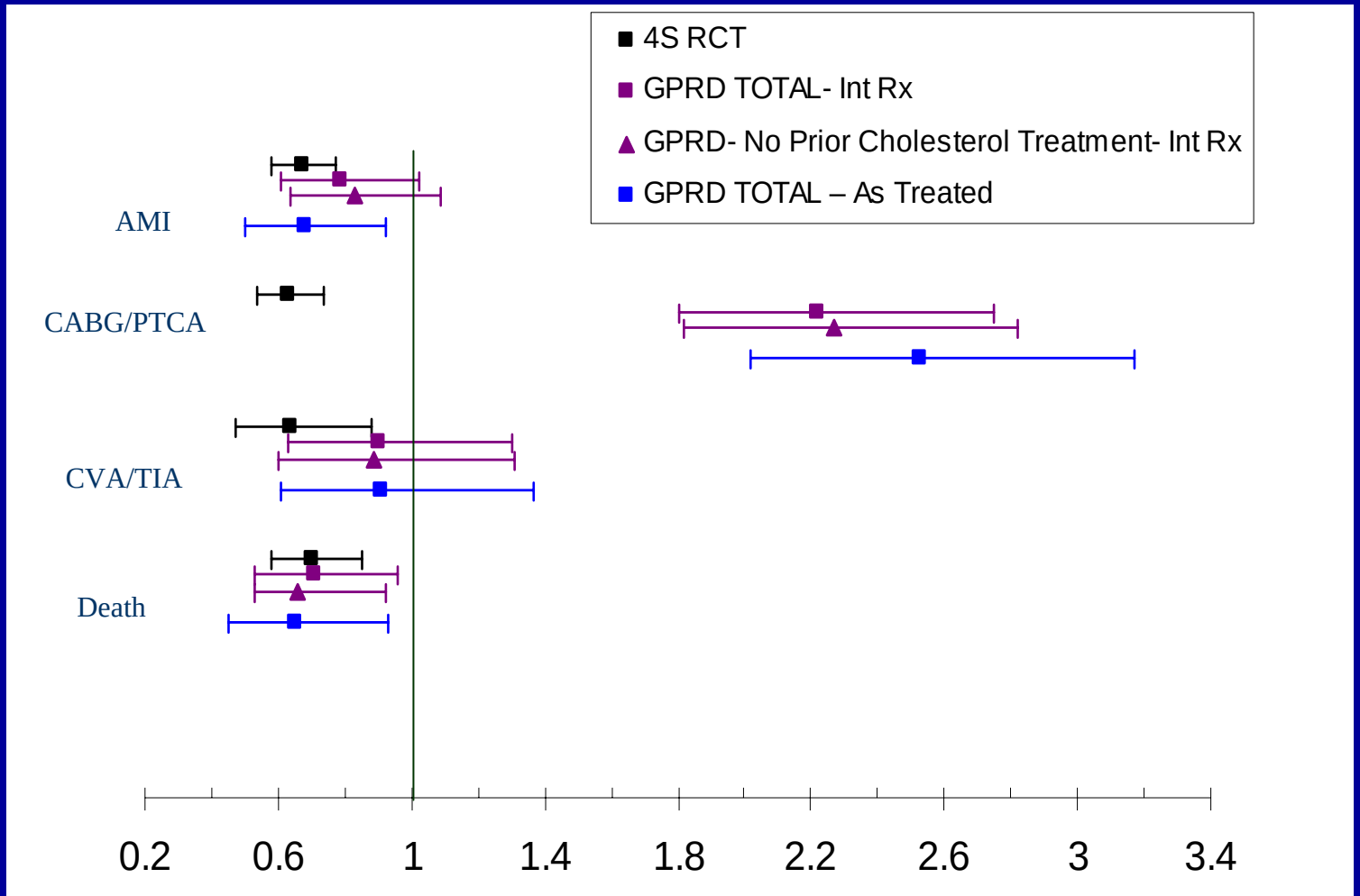
# WHI RCT versus GPRD REPLICATION



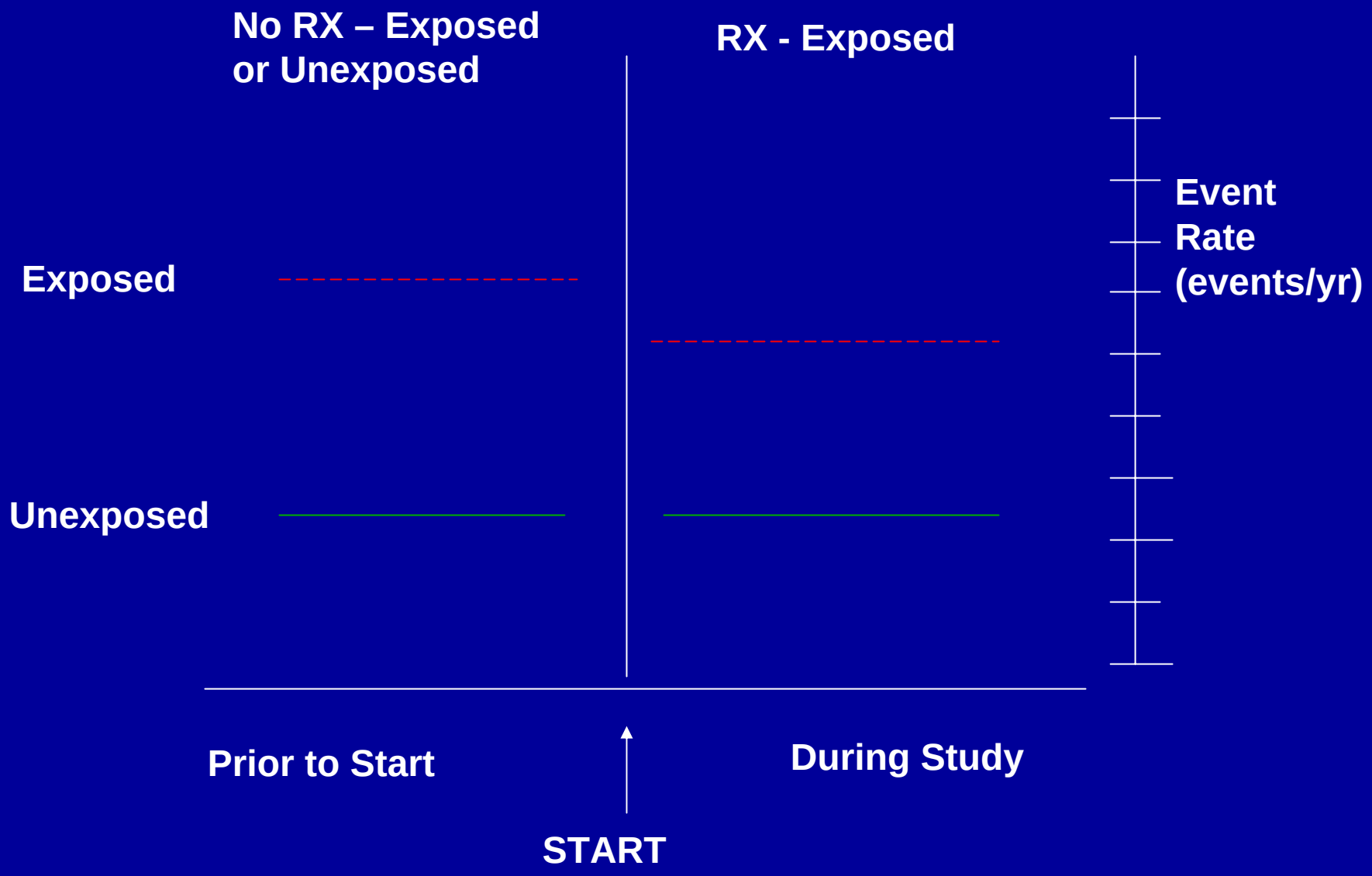
# 4S

- STATIN THERAPY OF HYPERCHOLESTEROLEMIA
- Total Cholesterol  >215 mg/dl
- H/O –
  - Myocardial Infarction and/or
  - Angina

# 4S RCT versus GPRD Replication



# “PRIOR EVENT RATE RATIO” Analysis



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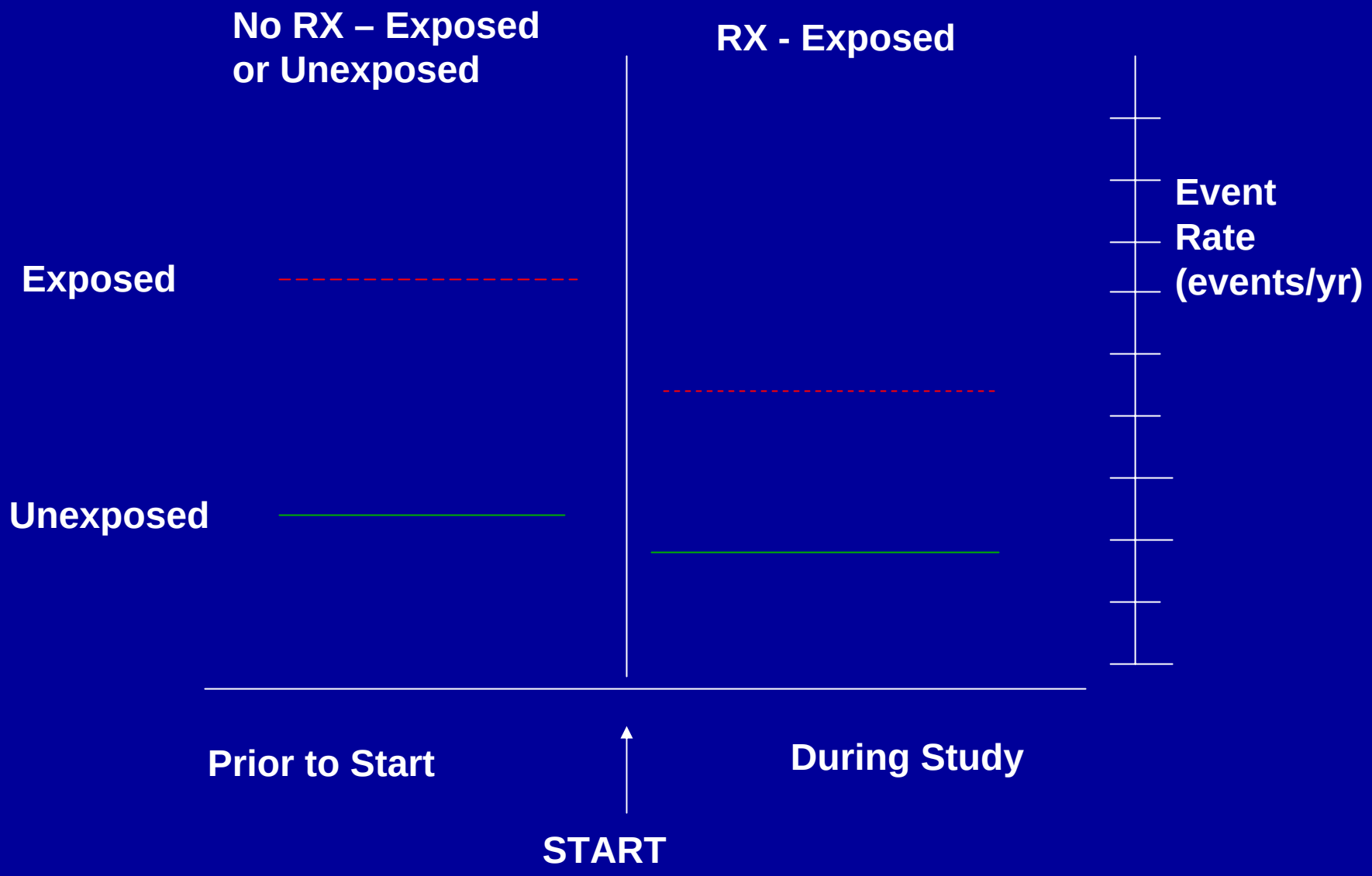


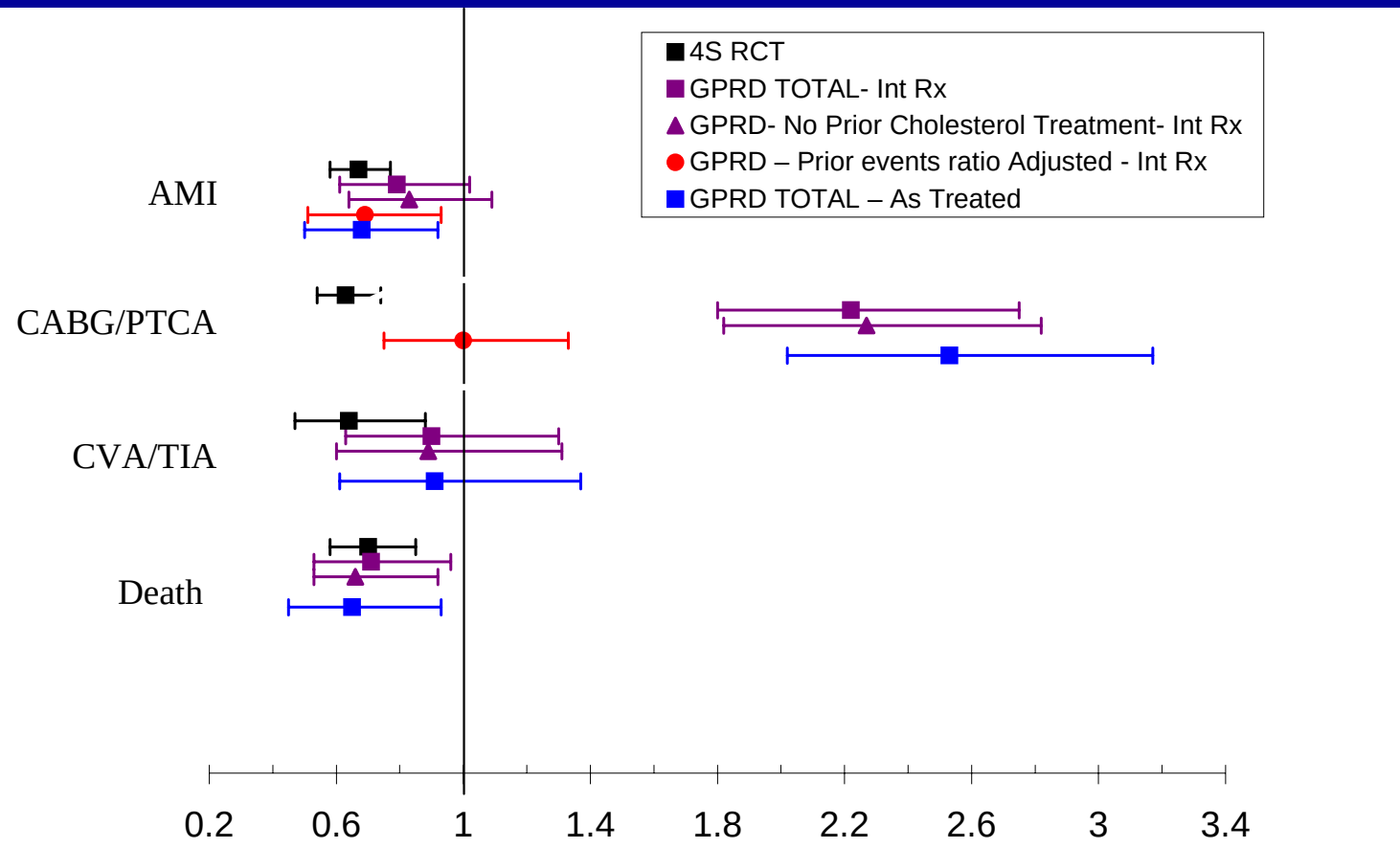
# “PRIOR EVENT RATE RATIO (PERR)” ADJUSTMENT

**If:** R =rate, E = Exposed, U = Unexposed,

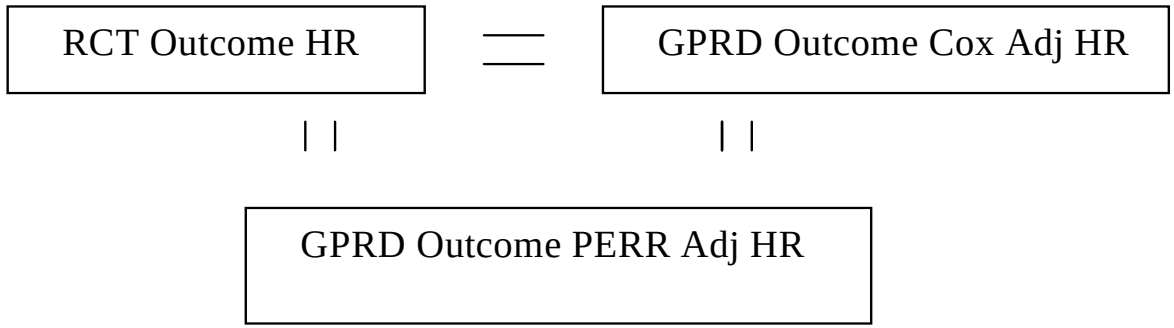
p = prior event, s = study event

- PERR Adj IRR = $\frac{(REs/RUs)}{(REp/RUp)}$
- PERR Adj HR = HRs / HRp

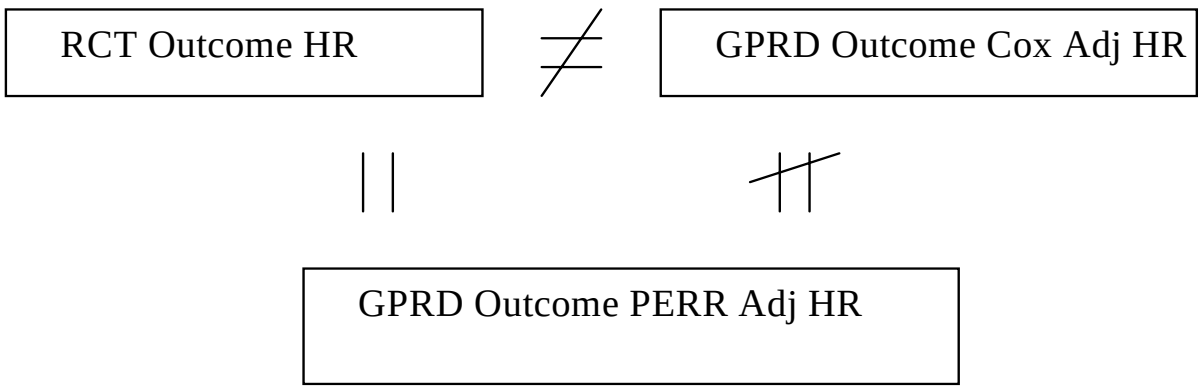
# 4S RCT- PERR adjustment



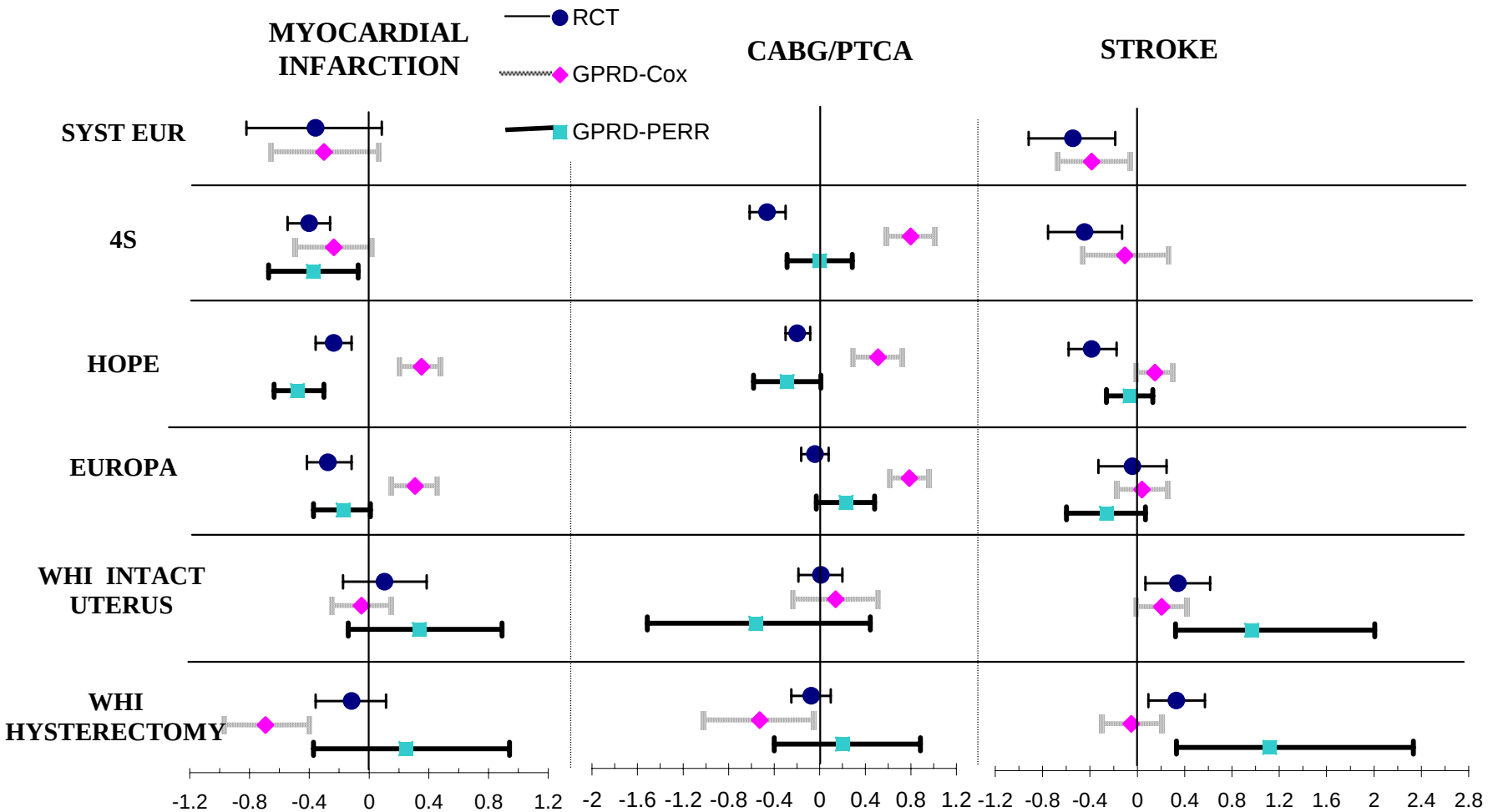
**“UNMEASURED CONFOUNDING” NOT PRESENT**




**“UNMEASURED CONFOUNDING” PRESENT**



# Summary of RCT versus GPRD Replications with PERR correction



# DISCOVERY of PRIOR EVENTS RATIO

- Direct comparison observational study with RCT
  - Identify invalid results
  - Address reasons disparity
  - Consider alternative analytic approaches
- Random matching technique Unexposed
  - ? Eliminate start time bias
- Use similar Inclusion & Exclusion Criteria for Exposed & Unexposed subjects

# CONCLUSIONS

- Observational studies using data from primary care EMR database can yield valid results
- Especially, when the results are analyzed with “Prior Event Rate Ratio” adjustment, which overcomes “unmeasured confounding”
- “Prior Event Rate Ratio” requires additional study to
  - Definitively prove its validity
  - Understand the breadth of its applicability
  - Understand its shortcoming

| STUDY | NUMBER SUBJECTS | | | | TREATMENT PROTOCOL | |
|---|---|---|---|---|---|---|
| | RCT | | GPRD | | RCT | GPRD |
| | Rx | Placebo | EXP | UNEXP | | |
| SYST EUR | 2,398 | 2,297 | 2,815 | 13,956 | Nitrendipine, enalapril or HCTZ;<br>Target – 20 mmHg decrease SBP | DHP calcium channel blocker, ACEI, or thiazide;<br><br>No target |
| WHI | 8,506 | 8,902 | 13,658 | 37,730 | Conjugated estrogen .625 mg/d<br>Medroxyprogesterone 5.0 mg/d | Conjugated estrogen .625 mg/d<br><br>Norgestrel – 150 µg on days 17-28 |
| WHI - Hyst | 5,310 | 5,429 | 6,890 | 11,572 | Conjugated estrogen .625 mg/d | Conjugated estrogen .625 mg/d |
| 4S | 2,221 | 2,223 | 1,280 | 2,871 | Simvatstatin 20 mg/d<br>Target – total chol 115-200 mg/dl | Any statin drug ( 80% received simvastatin)<br>No target |
| HOPE | 4,645 | 4,652 | 9,235 | 26,286 | Ramipril 10 mg/d | Any dose ACEI<br>Avg Ramipril equivalent dose = 3.8 mg/d |
| | | | 2,812 | | | >4 mg/d ramipril equivalent<br>Avg Ramipril equivalent dose = 6.8 mg/d |
| EUROPA | 6,110 | 6,108 | 7,253 | 12,705 | Perindopril 8 mg/d<br>(Ramipril Equivalent =10 mg/d) | Any dose ACEI<br>Avg ramipril equivalent dose =3.9 mg/d |
| | | | 2,668 | | | >4 mg/d ramipril equivalent<br>Avg Ramipril equivalent dose = 6.5 mg/d |

# WHI RCT REPLICATIONS

Figure 1