Data Needs for Signal Refinement

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- Core data:
  - Hospitalizations
  - ED visits
  - Prescriptions
    - ≥ 65 years
    - Social assistance
  - MD billing claims
  - Vital stats

- Various registries
  - Stroke, MI, CHF, DM, dialysis, ICD
  - External linkages (e.g., Coroner's data)

Scenario 1
Diabetes drug and MI

- First, specify and refine the question
  - Are patients with DM treated with the drug at greater risk than *other highly similar patients* not treated with the drug?
- An example from Ontario
  - Retrospective cohort, 2002 to 2007
    - Patients > 66 years newly started on either rosiglitazone or pioglitazone
    - Observed until outcome
      - AMI / cessation / switch / end of study
  - AMI identified using ICD-10
    - Hospitalization for primary diagnosis of I20, I21, I22

Analysis
Time-to-event

- Cox regression, adjusting for
  - Demographics
    - Age, gender, income quintile, LTC, year of cohort entry
  - Cardiac history
    - AMI, CHF, angina, CABG, PCI admission in previous 5 years
  - Comorbidity
    - Charlson score, # distinct drugs in previous year\Renal disease in previous 5 years
  - Medication use
    - Other OHA classes (sulfonylureas, metformin, etc.)
    - ACEI, ARBs, B-blockers, CCBs, diuretics, statins, digoxin
    - NSAIDs

Table 1

Variable	Pioglitazone (n=16 951)	Rosiglitazone (n=22 785)	Standardised difference
Median (interquartile range) age (years)	72 (68-77)	72 (68-77)	0.01
Age group (years):			
66-75	11 637 (68.7)	15 744 (69.1)	0.01
76-85	4 785 (28.2)	6 349 (27.9)	0.01
≥86	529 (3.1)	692 (3.0)	0.00
Male sex	8 839 (52.1)	12 094 (53.1)	0.02
Duration of diabetes (years):			
<2	1 179 (7.0)	1 367 (6.0)	0.04
2-5	1 921 (11.3)	2 430 (10.7)	0.02
>5	13 851 (81.7)	18 988 (83.3)	0.04
Cardiovascular admissions and procedures in previous 5 years:			
Acute myocardial infarction	591 (3.5)	927 (4.1)	0.03
Congestive heart failure	260 (1.5)	401 (1.8)	0.02
Angina	962 (5.7)	1 426 (6.3)	0.02
Percutaneous coronary intervention	482 (2.8)	697 (3.1)	0.01
Coronary artery bypass grafting	447 (2.6)	684 (3.0)	0.02
Coronary angiography	1 478 (8.7)	2 168 (9.5)	0.03
Charlson score:			
0	4 704 (27.8)	6 322 (27.7)	0.00
1	2 909 (17.2)	4 041 (17.7)	0.02
≥2	3 472 (20.5)	4 978 (21.8)	0.03
Not available	5 866 (34.6)	7 444 (32.7)	0.04

Variable	Pioglitazone (n=16 951)	Rosiglitazone (n=22 785)	Standardised difference
History of drug use in previous year:			
Angiotensin converting enzyme inhibitors	10 252 (60.5)	14 414 (63.3)	0.06
Angiotensin receptor antagonists	5 248 (31.0)	6 260 (27.5)	0.08
Aspirin	2 993 (17.7)	3 846 (16.9)	0.02
Other antiplatelet drugs	793 (4.7)	1 108 (4.9)	0.01
β adrenergic antagonists	5 518 (32.6)	7 665 (33.6)	0.02
Calcium channel blockers	6 797 (40.1)	8 842 (38.8)	0.03
Nitrates	1 950 (11.5)	2 769 (12.2)	0.02
Thiazide diuretics	4 052 (23.9)	5 595 (24.6)	0.02
Other diuretics	3 156 (18.6)	4 461 (19.6)	0.02
Spironolactone	414 (2.4)	566 (2.5)	0.00
Statins	12 168 (71.8)	16 300 (71.5)	0.01
Digoxin	743 (4.4)	1 030 (4.5)	0.01
Non-steroidal anti-inflammatory drugs	6 996 (41.3)	9 178 (40.3)	0.02
Median (interquartile range) No of distinct drugs in previous year	10 (7-13)	10 (7-13)	0.03
Other oral hypoglycaemic agents in previous year:			
Metformin	13 677 (80.7)	18 496 (81.2)	0.01
Sulphonylureas	11 628 (68.6)	15 710 (68.9)	0.01
Acarbose	1 005 (5.9)	1 152 (5.1)	0.04
Meglitinides	159 (0.9)	176 (0.8)	0.02
History of renal disease in previous 5 years	575 (3.4)	867 (3.8)	0.02

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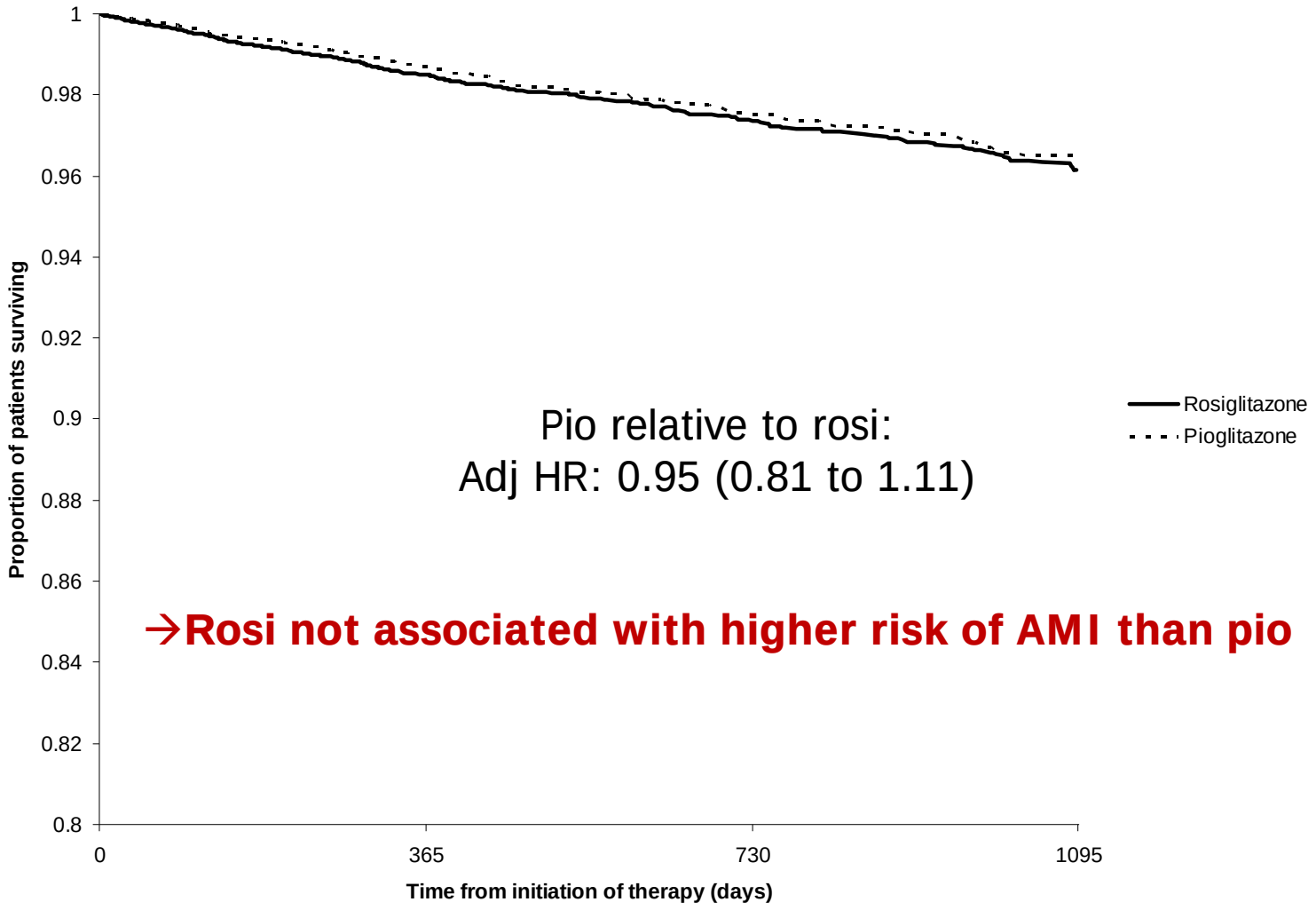
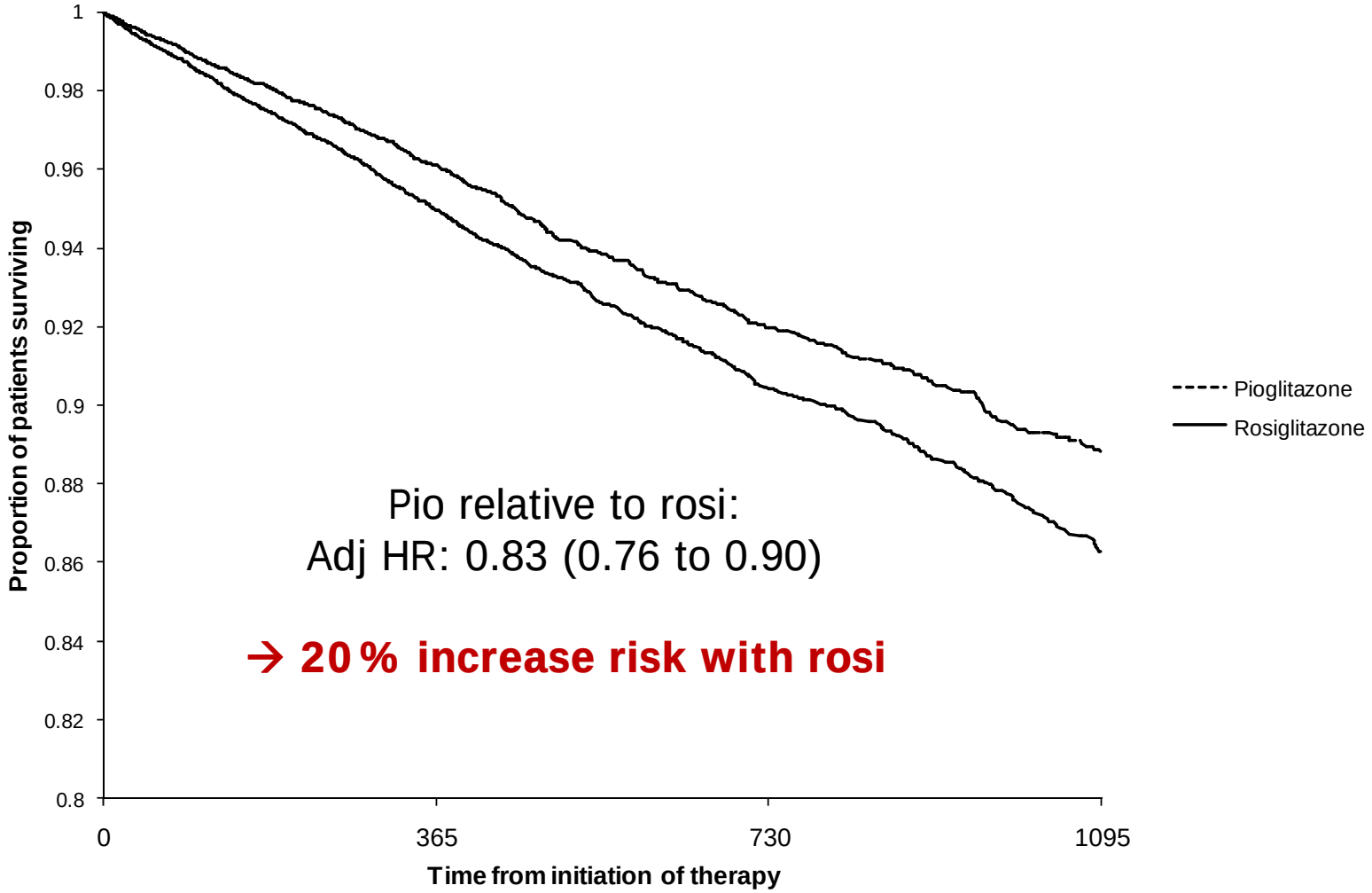
AMI (secondary outcome)
n=653 events in total



→Rosi not associated with higher risk of AMI than pio

Primary Outcome -
Death, AMI or CHF



Scenario 2
Parenteral antibotic and liver failure

- Inpatient medication data not available
  - This study question could not be addressed using administrative data in Ontario
- Our approach to a similar question -
  - Moxifloxacin and the risk of acute liver injury
  - Study question:
    - Is moxifloxacin more strongly associated with ALI than other comparable antibiotics?

Nested Case-Control Design

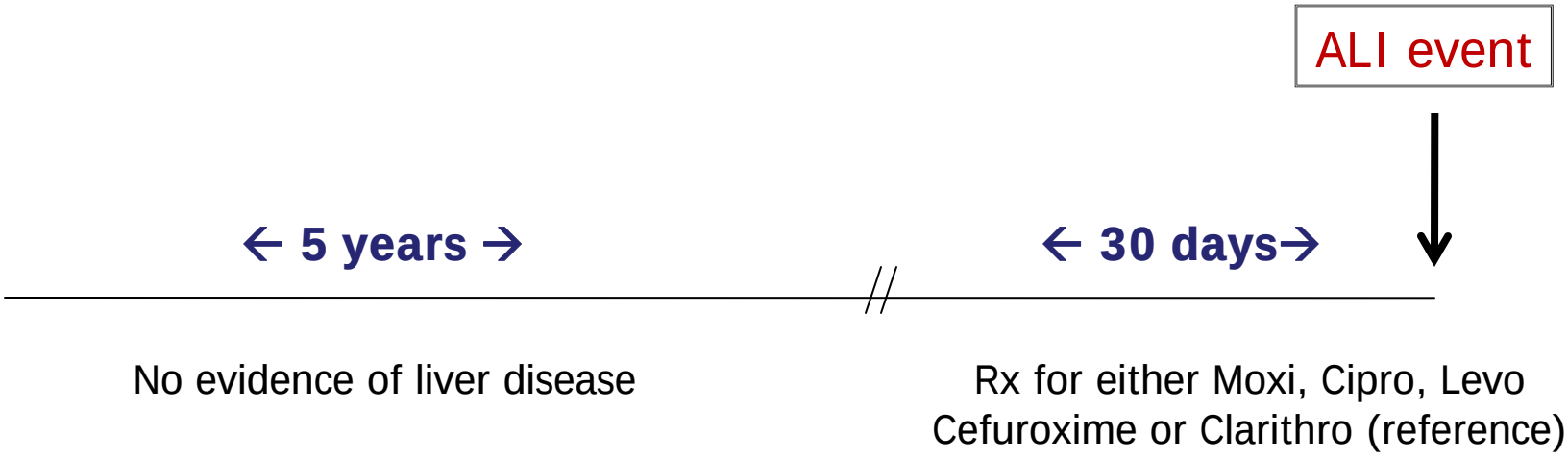
- Patients and Setting
  - Ontarians > 66 years
  - April 1, 2002 to March 31, 2009
- Start with the outcome
  - ED visit or hospitalization for any of
    - K711: Toxic liver disease with hepatic necrosis
    - K712: Toxic liver disease with acute hepatitis
    - K716: Toxic liver disease with hepatitis, not elsewhere classified
    - K719: Toxic liver disease, unspecified
    - K720: Acute and subacute hepatic failure
    - K729: Hepatic failure, unspecified

Nested Case-Control Design

- Restrict the analysis to patients who had one of the following in the 30 days before ALI:
  - Moxifloxacin
  - Ciprofloxacin
  - Levofloxacin
  - Cefuroxime
  - Clarithromycin

Exclusions

- > 1 antibiotic in previous 30 days
- Any other hospitalization in previous 90 days
- Rx for a “classic” hepatitis drug in previous 90 days
  - Phenytoin, allopurinol, isoniazid, amox-clav, valproic acid, SMX/TMP
- Any pre-existing liver disease or alcohol use
  - Admissions, MD claims, procedures, etc. in five years preceding antibiotic therapy



Results

- to be presented at meeting

Challenges with both scenarios

- Exposures
  - Unquantifiable drugs (OTC, samples, uninsured benefits)
  - Dose, adherence
- Outcomes
  - Coding validity
    - The sensitivity vs. specificity tradeoff
  - Complex outcomes
  - Lab data
- Potential confounders / modifiers
  - Countless
  - Sometimes surmountable by design