Plans for Surveillance of Acute Myocardial Infarction in users of Oral Anti-Diabetes Drugs

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Aims

- Develop and assess a framework and infrastructure for monitoring drug safety in large populations using distributed databases.
- For this pilot effort :
  - monitor acute MI in users of anti-diabetes drugs, and more specifically:
    - examine the association of AMI risk with saxagliptin, a recently approved DPP-4 inhibitor used for treatment of diabetes.

Type 2 Diabetes Study Population

- Adults with a diabetes diagnosis and an oral anti-diabetes drug in 12 month baseline period.
- Members for 12+ continuous months in Humana, Health Core, Kaiser Permanente, other HMO_RN.
- Few exclusions: recent AMI (<30 days), age<18, patients who have been taking only insulin.
- Study period: July 2009 through June 2013 (with baseline data back to July 2007)
- 1.3 million with T2DM now, 5.2 million person years to be monitored, 47,000 AMIs expected.

New-users of Saxagliptin compared with new users of 4 comparator drugs

- The comparators:
  - sitagliptin
  - pioglitazone
  - sulfonylurea (glyburide, glipizide, glimipiride)
  - long-acting insulin
- Follow-up for AMI begins at 1st Rx of a study drug.
- Follow-up ends when user quits drug or health plan
- Inference only from users followed since 1st use.
  No inference about the drug-AMI association from
  - prevalent users of study drugs
  - within-person change in MI risk: on-drug versus off-drug

  due to possible bias from unmeasured confounders.

Outcomes

- Primary: AMI identified from
  - Hospitalization, principal dx: 410.x0 or 410.x1, (PPV≈95%)
  - Emergency department diagnosis code of 410 plus death in ER or within 24 hours.
- Secondary: Acute Coronary Syndrome, including
  - AMI, or
  - Hospitalization with principal diagnosis: 411.1 or 411.8, or
  - Hospitalization with principal diagnosis: 414 plus secondary diagnosis: 411.1 or 411.8
- Measures of drug-outcome association (over time):
  - Relative risk
  - Risk difference

Adjustment for possible confounders

- Prior Cardiovascular Disease
- Demographics
- Co-morbid conditions
- Concurrent Medication Use
- Use of health services
- Site, health plan
- Time

Several adjustment strategies/methods

- Restriction to new users, stratification by site and prior cardiovascular disease, covariate adjustment
- Propensity score (PS), matching 1:1
- Disease risk score (DRS), stratification by decile

PS matching and DRS stratification permit adjustment for covariates *without pooling patient-level data*

- Advantages of PS matching
  - Balances comparisons of new-users of comparator drugs with new-users of saxagliptin, intuitive as in RCT
  - 1:1 matching restricts to best matches, simplifies analysis
- Disadvantages of PS matching
  - Separate PS needed for each pair of study drugs, each site
  - Not much data available for deriving PS at outset of study
- Advantages of DRS stratification
  - A single DRS can be used to compare all study drugs
  - Even if saxagliptin uptake is slow at first (or throughout), there will be enough data to derive the DRS
  - Intuitive implications for confounding, interactions
- Disadvantages of DRS stratification
  - Less feasible with rare outcomes, multiple outcomes
  - Less familiar

Sequential surveillance

- 1st analysis planned for 3/2011, examining study population since the 2009 licensure of saxagliptin.
- Then 9 quarterly analyses monitoring accumulating data, with final analysis planned for 6/2013.
- Sequential statistics adjusted for multiple “looks”, each “look” includes all available data.
- Threshold p-value required for a signal is 0.0144, to ensure that the overall chance of a false signal (about a safe drug) is below 0.05 across all ten quarterly analyses.

Power and reassurance: the size of the relative risks that can be detected or ruled out

- Assuming that
  - we accumulate 23,000 person-years in saxagliptin users and 23,000 in PS-matched users of a comparator, and
  - we expect 9 MIs/1000 person-years in the comparator-users
- then we have
  - 61% power to detect a relative risk of 1.25
  - 81% power to detect a relative risk of 1.33
  - 91% power to detect a relative risk of 1.40
- If we accumulate only half as much person-time then we have 80% power to detect relative risk of 1.5
- If signals do not arise, confidence intervals will be informative about the size of the relative risk (and risk difference) that can be "ruled out", and the reassurance that is appropriate.

AMI surveillance is designed to be worthwhile even if saxagliptin is not used much

- Analyses stratified by the proposed MI risk score can be used for comparisons among all anti-diabetes drugs that are commonly used in the study population.
- Comparisons of MI risk in users of anti-diabetes drugs can yield
  - worthwhile reassurance (or safety signals),
  - lessons about statistical methods
  - evidence of the value of Sentinel's data and infrastructure

  regardless of saxagliptin uptake.
- This outcome-centered surveillance is especially promising for outcomes – such as MI – that are important to examine in relation to many drugs.

Summary: Mini-Sentinel has developed plans to

- Examine AMI risk in saxagliptin users versus users of four comparator drugs: sitagliptin, pioglitazone, sulfonylurea, and long-acting insulin.
- Assess the feasibility and value of AMI surveillance in users of anti-diabetes drugs, using the distributed databases of Sentinel's data partners.
- Evaluate statistical methods for monitoring drug safety in large dynamic populations.