ENGELBERG CENTER for Health Care Reform at BROOKINGS

Sentinel Initiative Public Workshop

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Prospective Surveillance of Anti-Diabetes Drugs and Acute Myocardial Infarction

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Aims

- Develop and assess methods/infrastructure for monitoring drug safety in large populations using distributed databases
- Monitor acute myocardial infarction (AMI) in users of **saxagliptin,** a DPP-4 inhibitor approved in 2009 for treatment of diabetes
- Simulate what we would have learned from surveillance of **sitagliptin** had we started monitoring AMI in users of this DPP-4 inhibitor soon after it was approved in 2006

"Simulated" sitagliptin surveillance

New-user cohort design

- New users (age>=18) of sitagliptin or comparators
  - **Pioglitazone**
  - **2nd generation sulfonylureas**
  - **Long-acting insulin**

Surveillance period

- Q4 2006 to Q4 2013

Outcome

- **AMI** identified from
  - Hospitalization, principal (or non-secondary) diagnosis of 410.x0 or 410.x1
  - Emergency department diagnosis code of 410 plus death in ER or within 24 hours

Adjustment of possible confounders

- **Potential confounders**
  - Prior cardiovascular disease
  - Demographics
  - Co-morbid conditions
  - Concurrent medication use
  - Use of health services during baseline year
  - Site, health plan
  - Time (calendar time, time-on-study drug)

Adjustment of possible confounders

- Stratification by site and prior CVD
- Adjustment for AMI risk factors by
  - **Propensity score (PS) matching 1:1**
  - **Disease risk score (DRS) stratified by decile**
- PS-matching and DRS-stratification **allow adjustment for a large number of potential confounders without pooling patient-level information across sites**

Statistical analysis

Statistical analysis

- **Primary:** Stratified Cox regression using riskset-level data
- **Secondary:** Meta-analysis of site-specific effect estimates

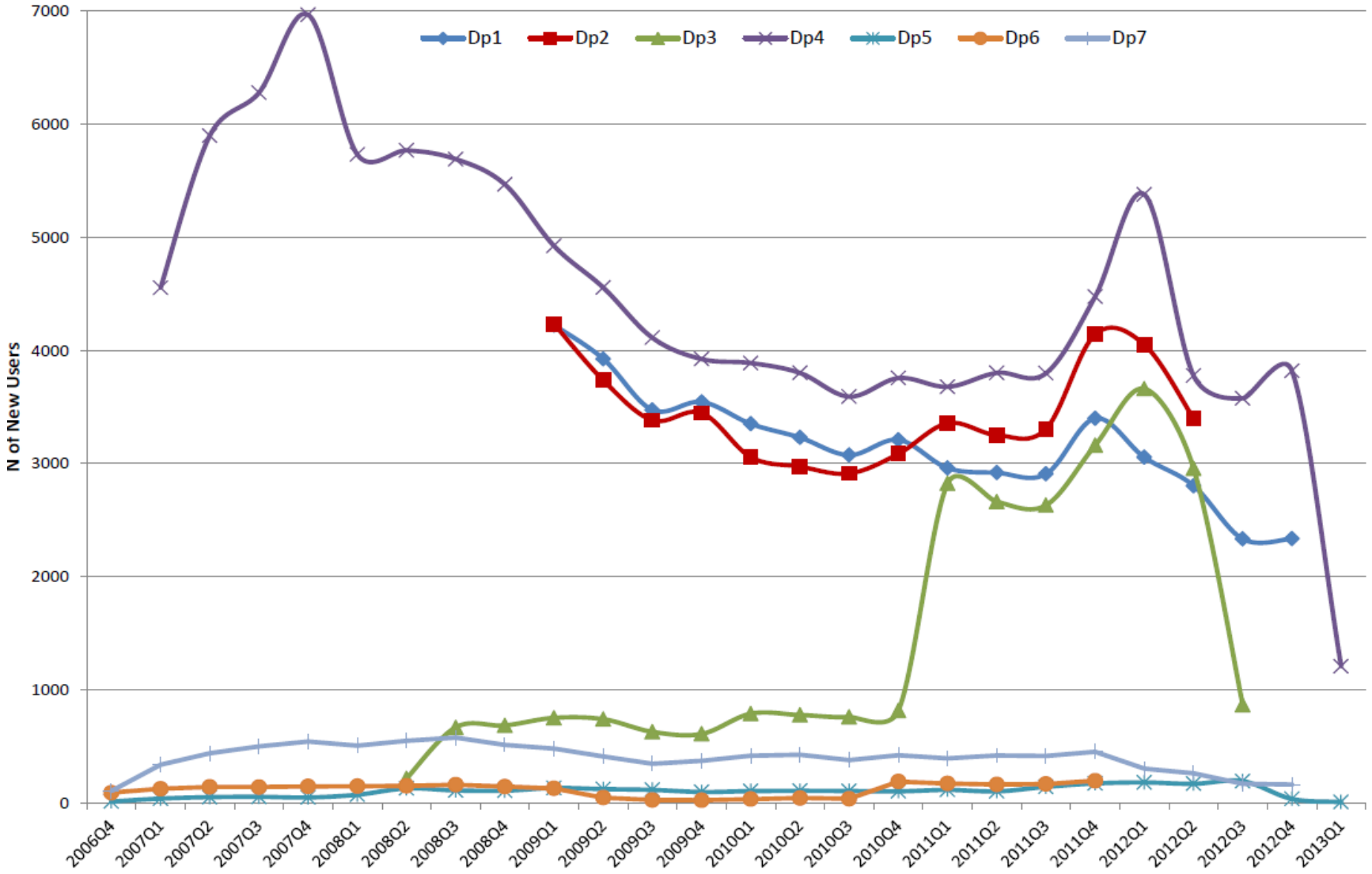
Subgroup analysis

- by site, prior CVD, DRS decile, and time

Sequential testing

- Sequential 1-sided statistical tests conducted at each “look”
- Each “look” includes all data since licensure of the target drug
- Overall chance of false positive signal kept below 0.05
- “Alpha-spending” plan specifies threshold level test statistic (nominal p-value) required for a signal
  - 25 simulated quarterly looks for sitagliptin; threshold nom. p = .0076
- A signal does not end surveillance

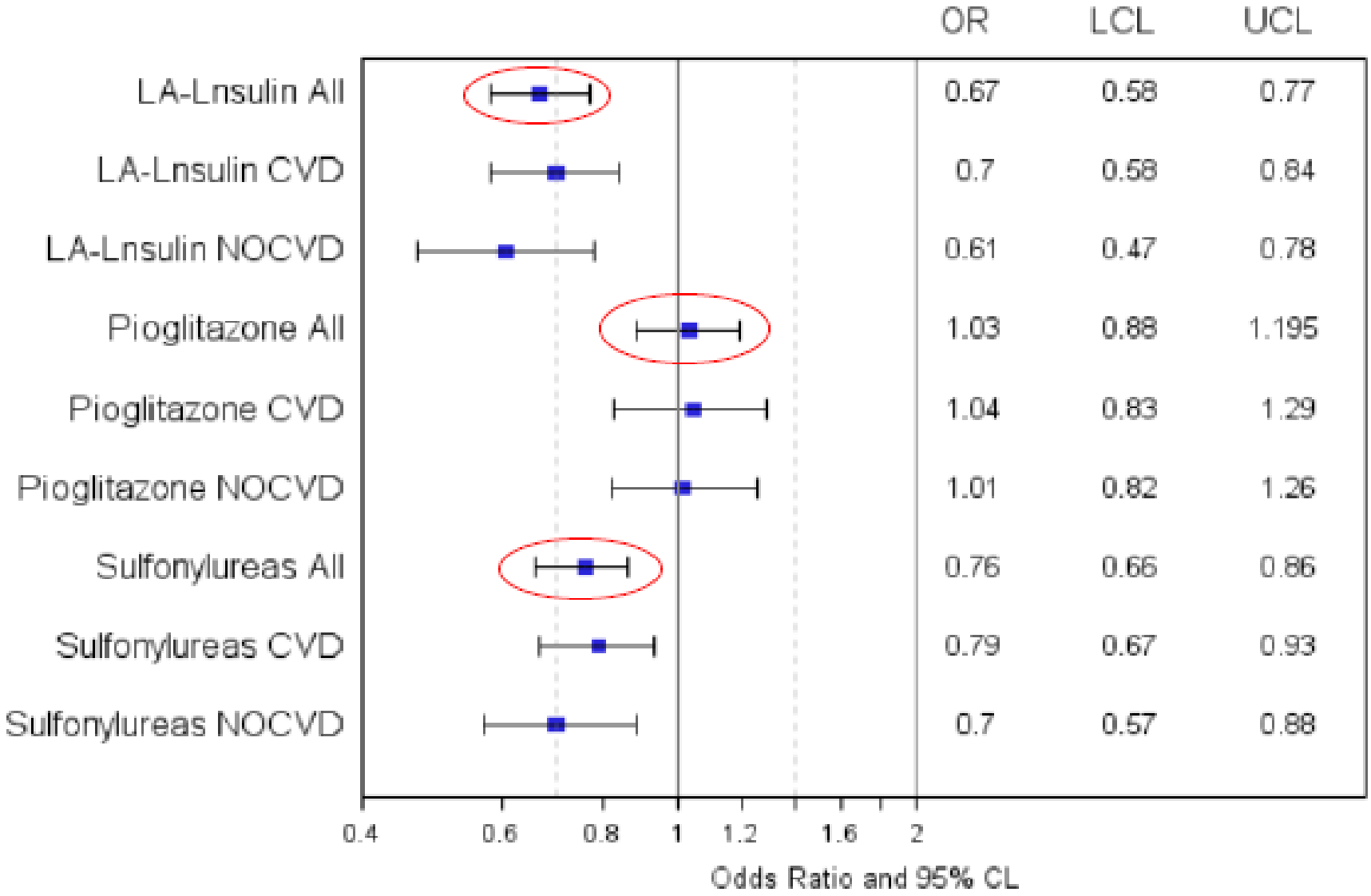
Number of New Users of Sitagliptin by Quarter and by Data Partner



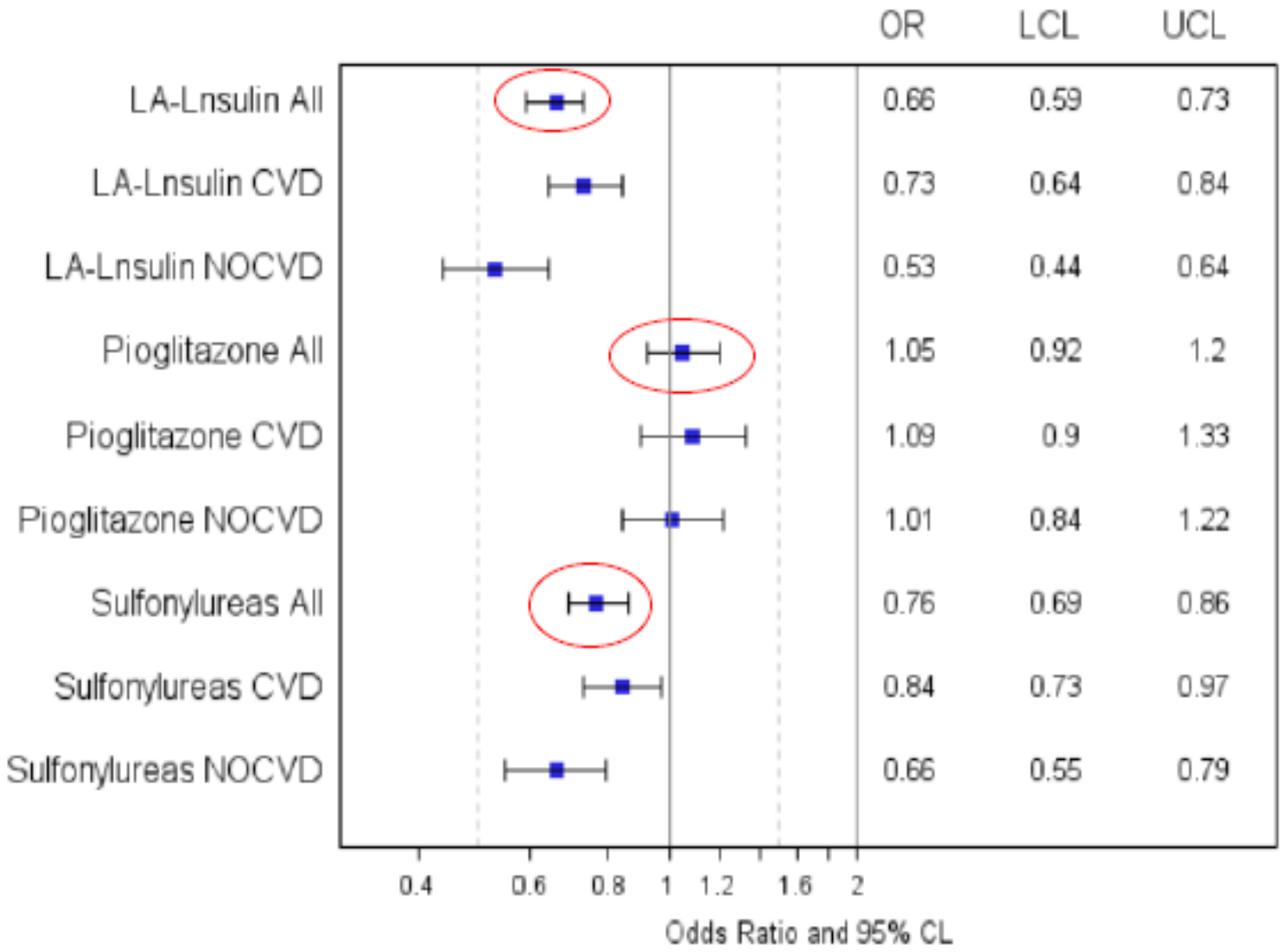
Incidence of AMI in the 3 comparisons, unadjusted

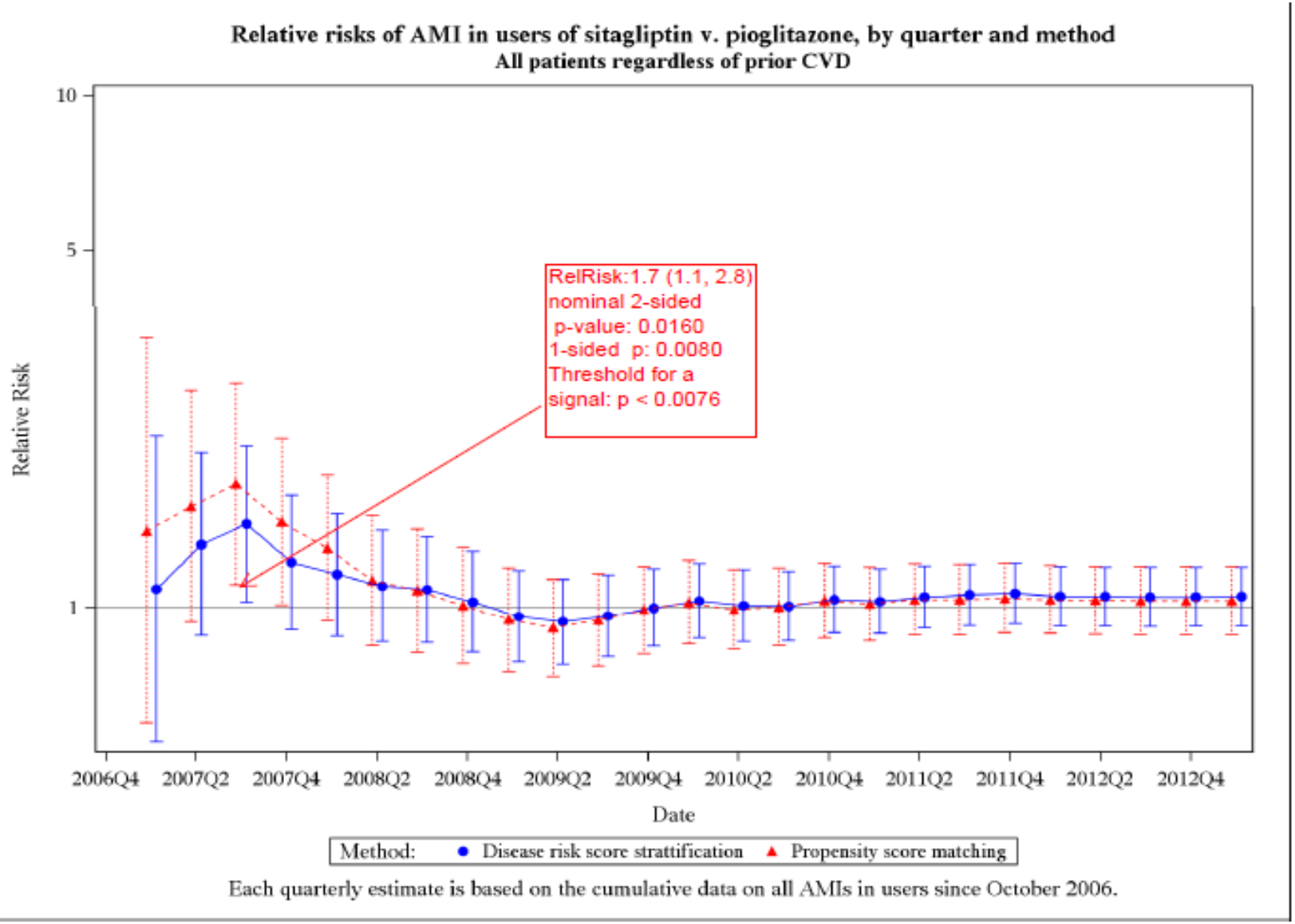
	Sitagliptin				Comparator				
Contrast	N of users	Mean follow-up (months)	N of AMIs	Incidence per 1,000 pys	N of users	Mean follow-up (months)	N of AMIs	Incidence per 1,000 Pys	Rate Ratio (not adjusted)
Sita v Insulin	226,223	6.3	784	6.6	310,731	3.4	1,141	13.1	0.51
Sita v piogli	184,421	6.1	558	6.0	230,236	5.9	661	5.8	1.03
Sita v sulfonyl	139,356	5.9	424	6.2	302,151	6.6	2,686	8.9	0.69

AMI Risk in Users of Sitagliptin vs.Comparators by the PS Method

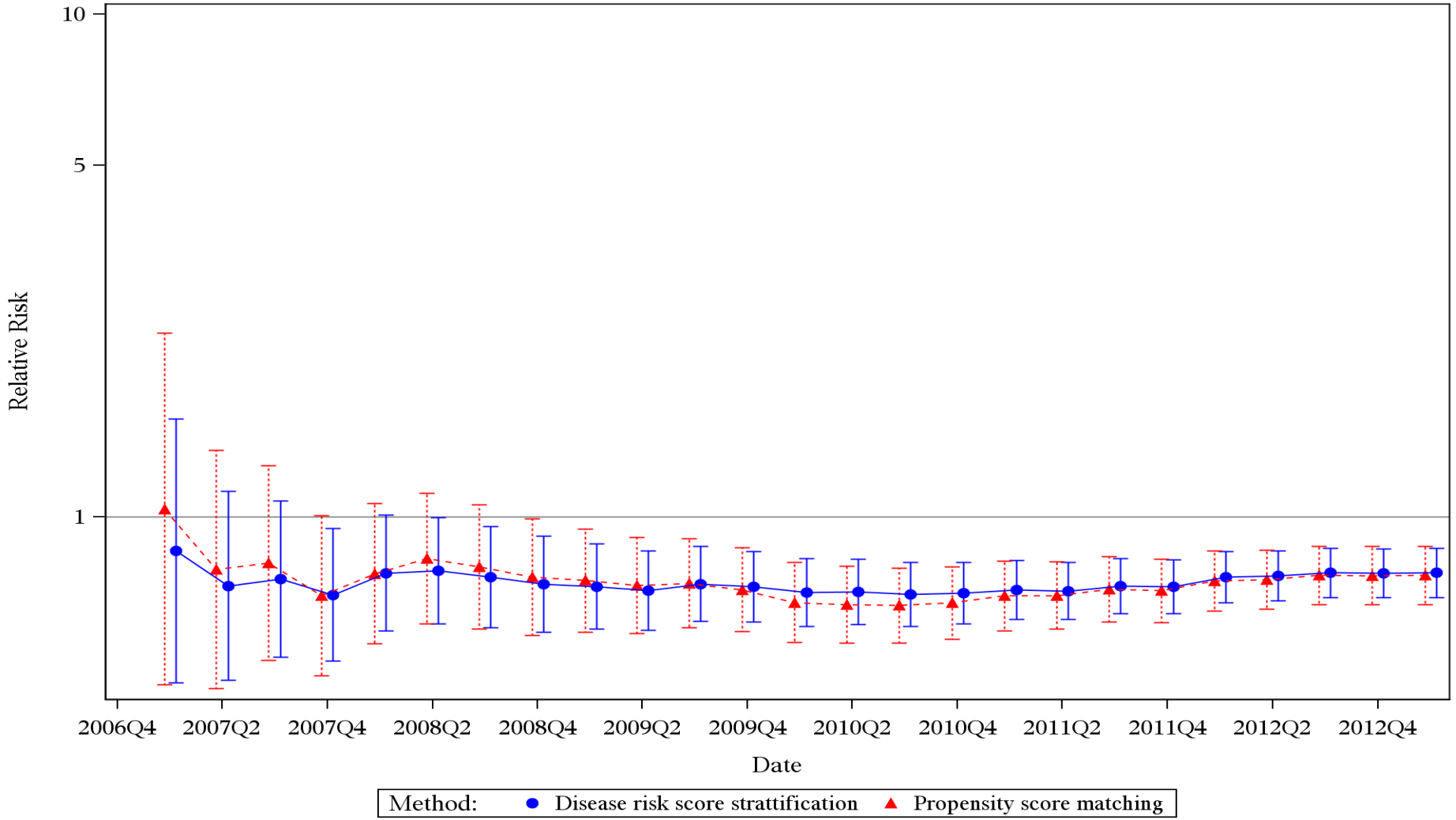


AMI Risk in Users of Sitagliptin vs.Comparators by the DRS Method




Relative risks of AMI in users of sitagliptin v. pioglitazone, by quarter and method
All patients regardless of prior CVD
10
5
1
Relative Risk
RelRisk:1.7 (1.1, 2.8)
nominal 2-sided
p-value: 0.0160
1-sided p: 0.0080
Threshold for a
signal: p < 0.0076
2006Q4
2007Q2
2007Q4
2008Q2
2008Q4
2009Q2
2009Q4
2010Q2
2010Q4
2011Q2
2011Q4
2012Q2
2012Q4
Date
Method:
Disease risk score strattification
Propensity score matching
Each quarterly estimate is based on the cumulative data on all AMIs in users since October 2006.

Relative risks of AMI in users of sitagliptin v. sulfonylureas, by quarter and method
All patients regardless of prior CVD



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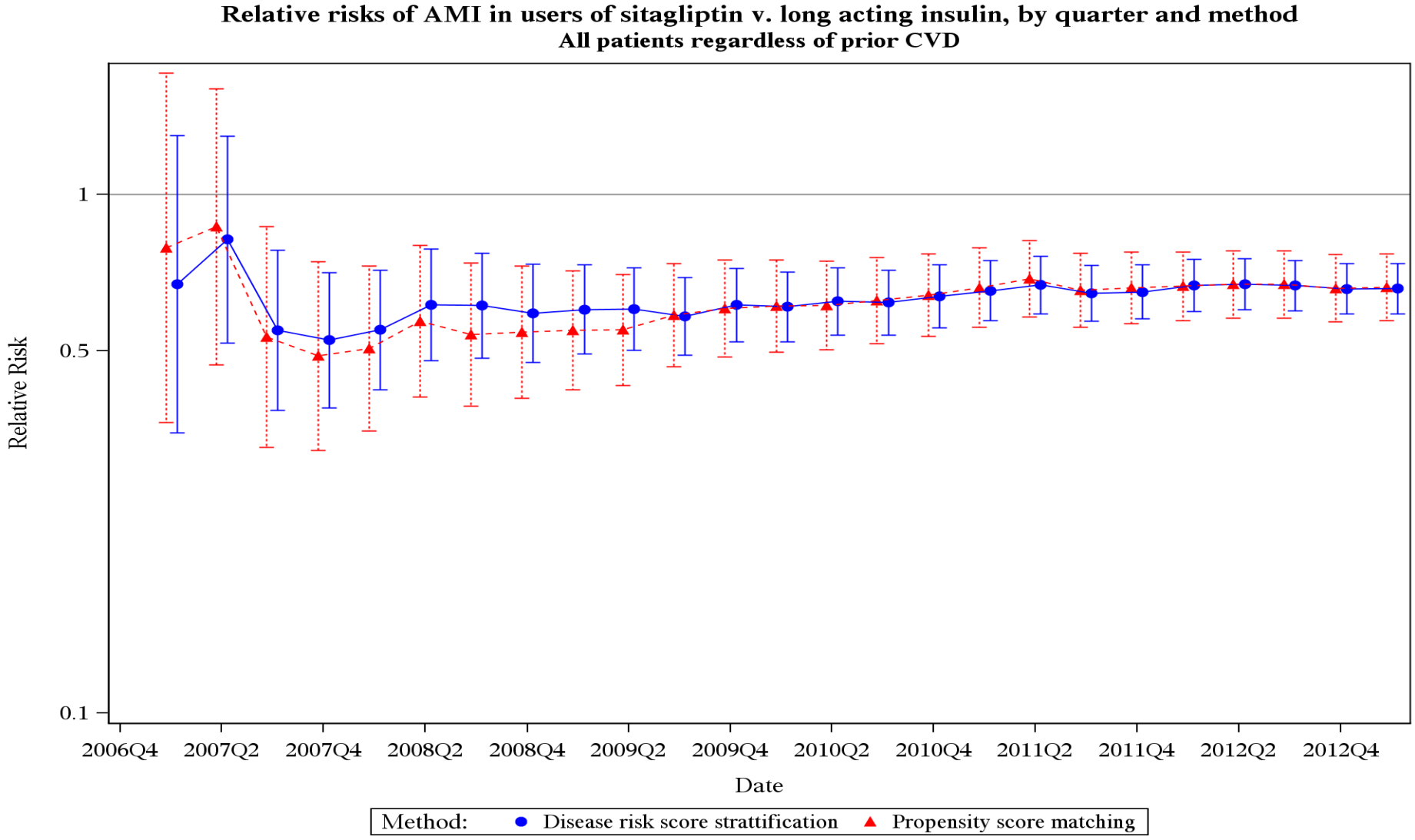

Relative risks of AMI in users of sitagliptin v. long acting insulin, by quarter and method
All patients regardless of prior CVD
Relative Risk
1
0.5
0.1
2006Q4
2007Q2
2007Q4
2008Q2
2008Q4
2009Q2
2009Q4
2010Q2
2010Q4
2011Q2
2011Q4
2012Q2
2012Q4
Date
Method:
Disease risk score strattification
Propensity score matching
Each quarterly estimate is based on the cumulative data on all AMIs in users since October 2006.

Summary of findings

- There was not a safety “signal” – we did not find evidence that sitagliptin increases AMI risk – during simulated quarterly surveillance of AMI in new-users of sitagliptin since 2006 licensure

Limitations

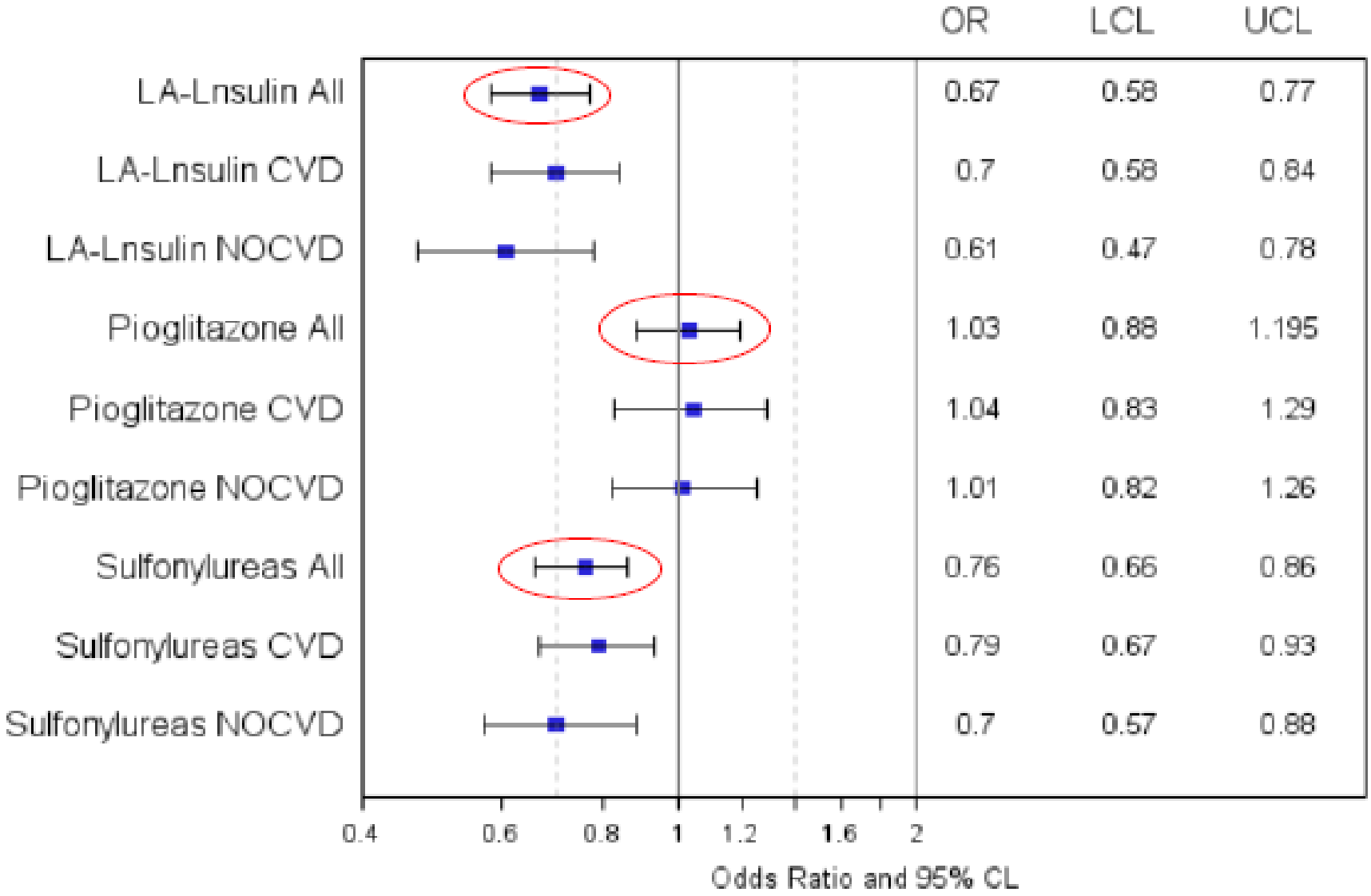
- Limited information in database, or no information, on obesity, smoking, race/ethnicity, test/procedure results

Next steps

- Prospective saxagliptin surveillance to be completed in March 2014

- Methodological refinements to be considered, including
  - Finer DRS stratification (to reduce bias)
  - 1:N PS matching (to increase precision)
  - Indirect treatment comparisons, network-meta-analysis, and differences-in-differences, to help interpret primary pairwise comparisons
  - Integrate sequential design with plans for follow-up analyses that would be done after a signal

AMI Risk in Users of Sitagliptin vs.Comparators by the PS Method



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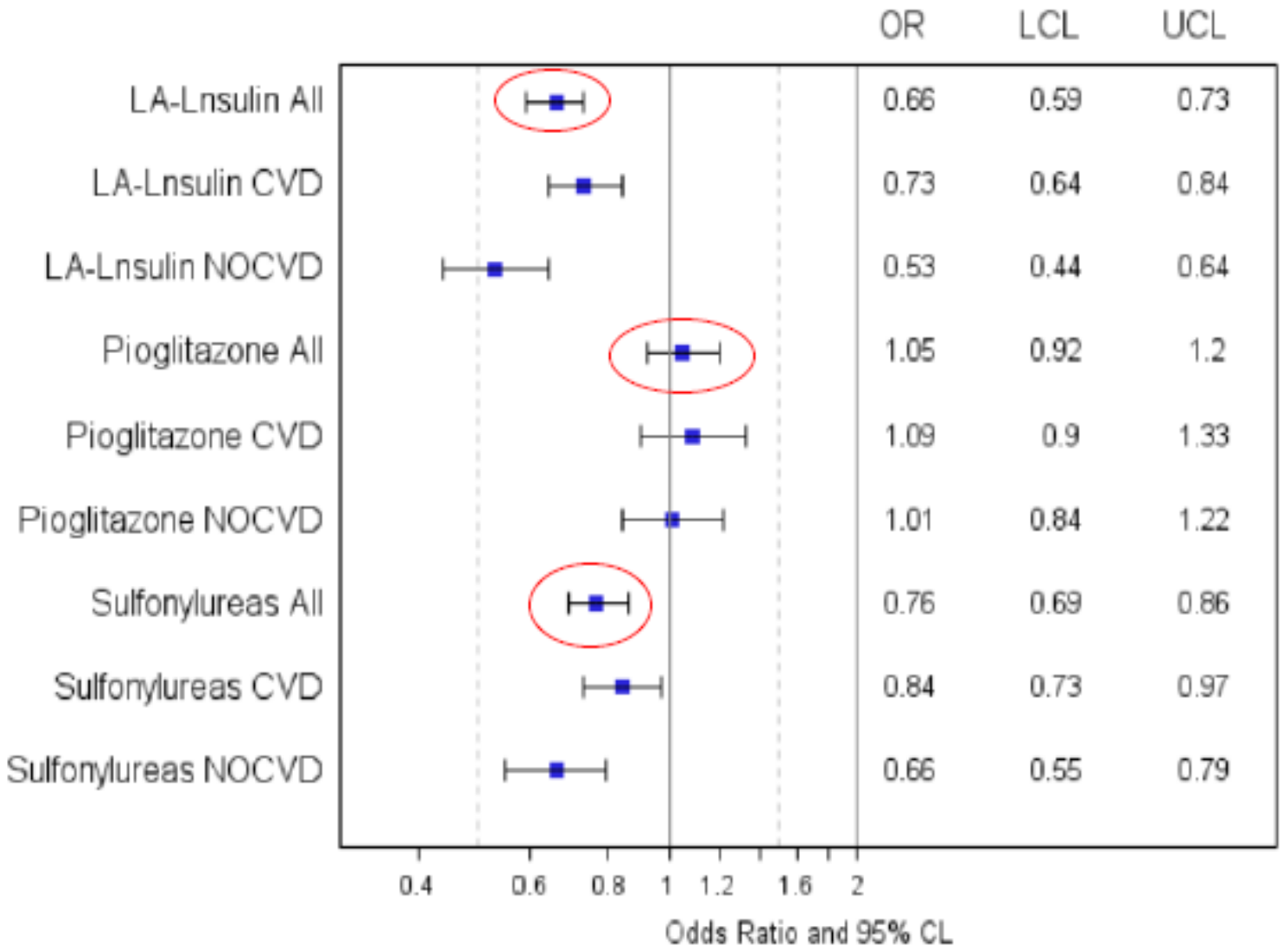
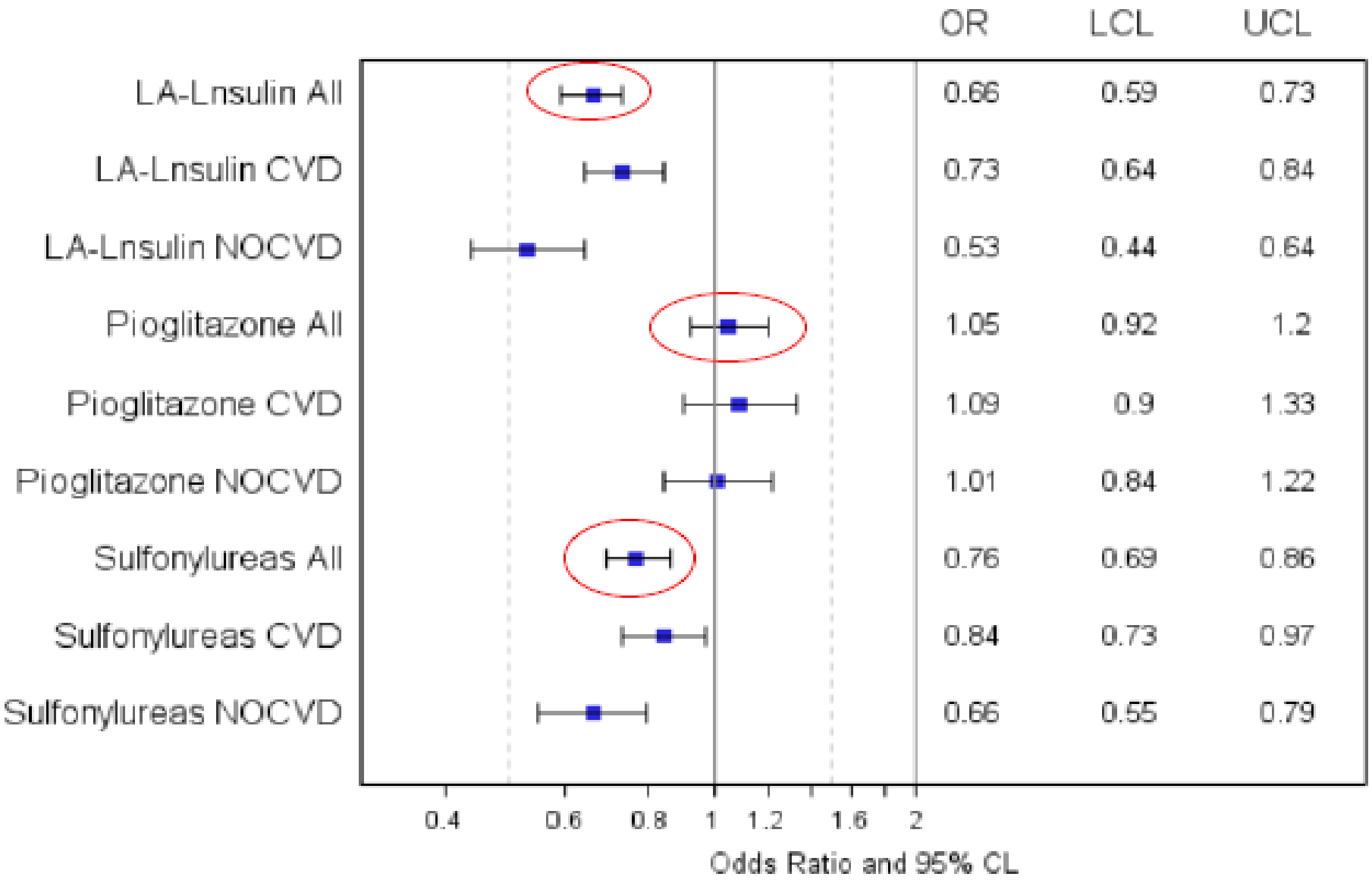
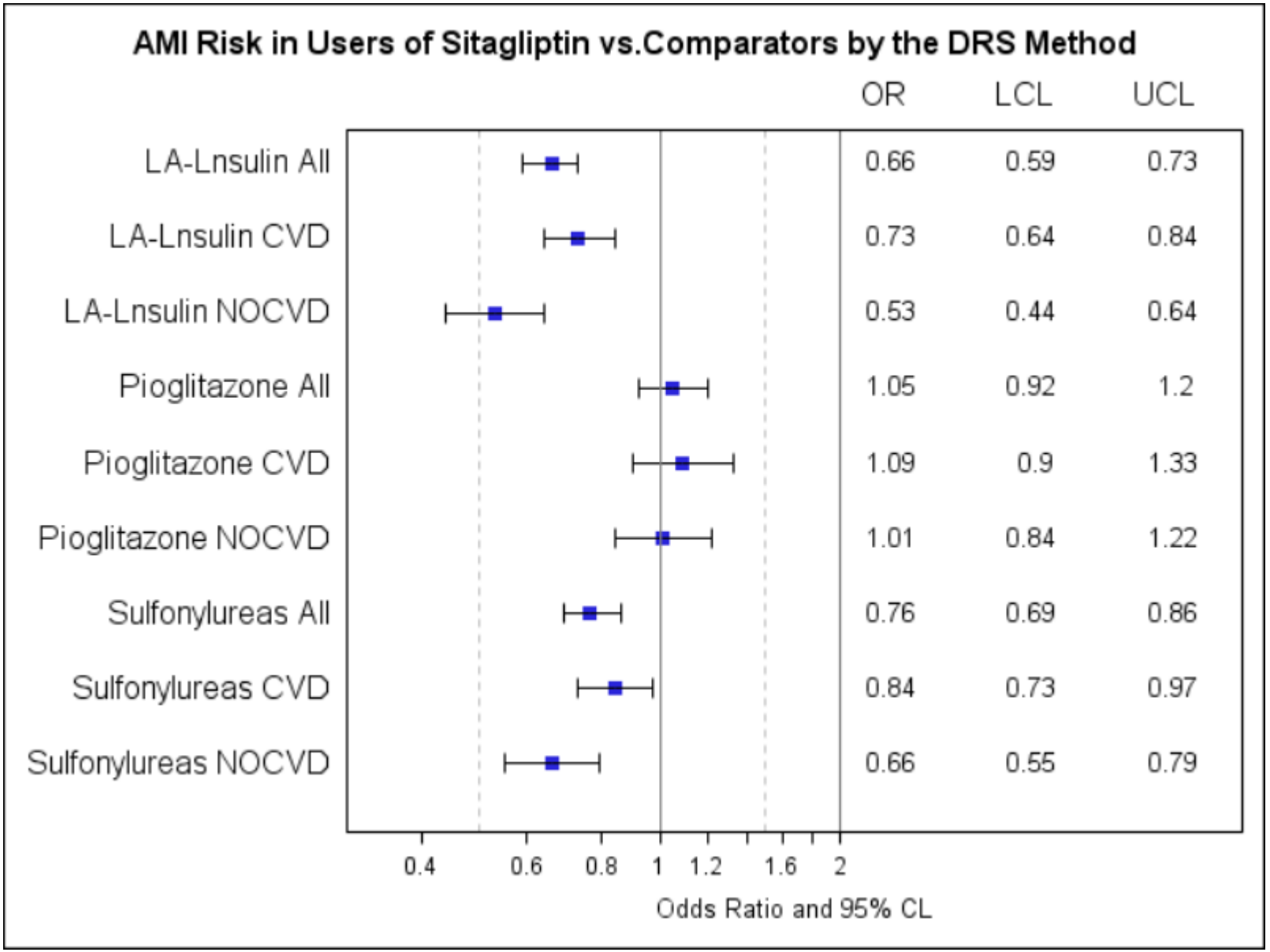
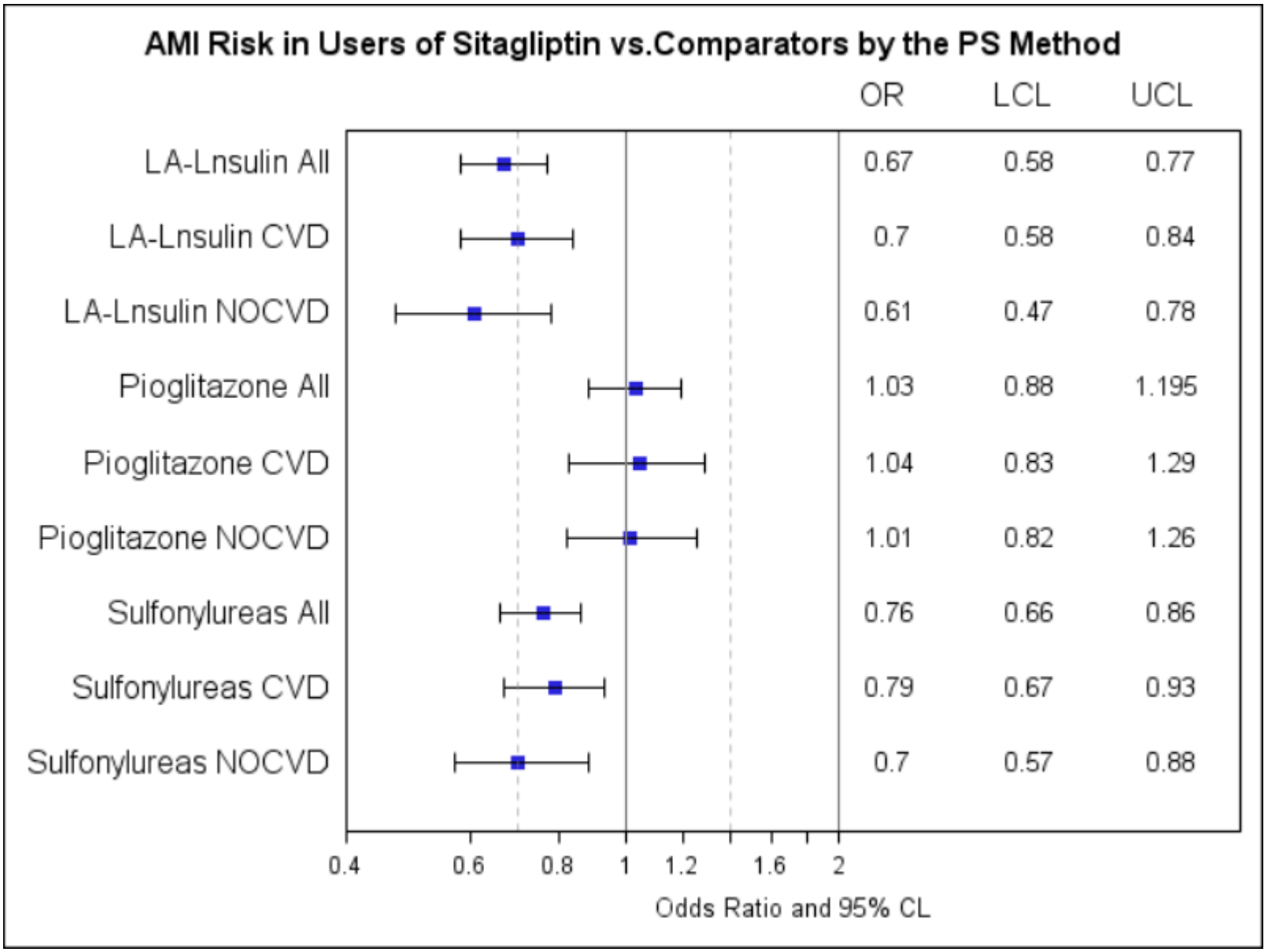
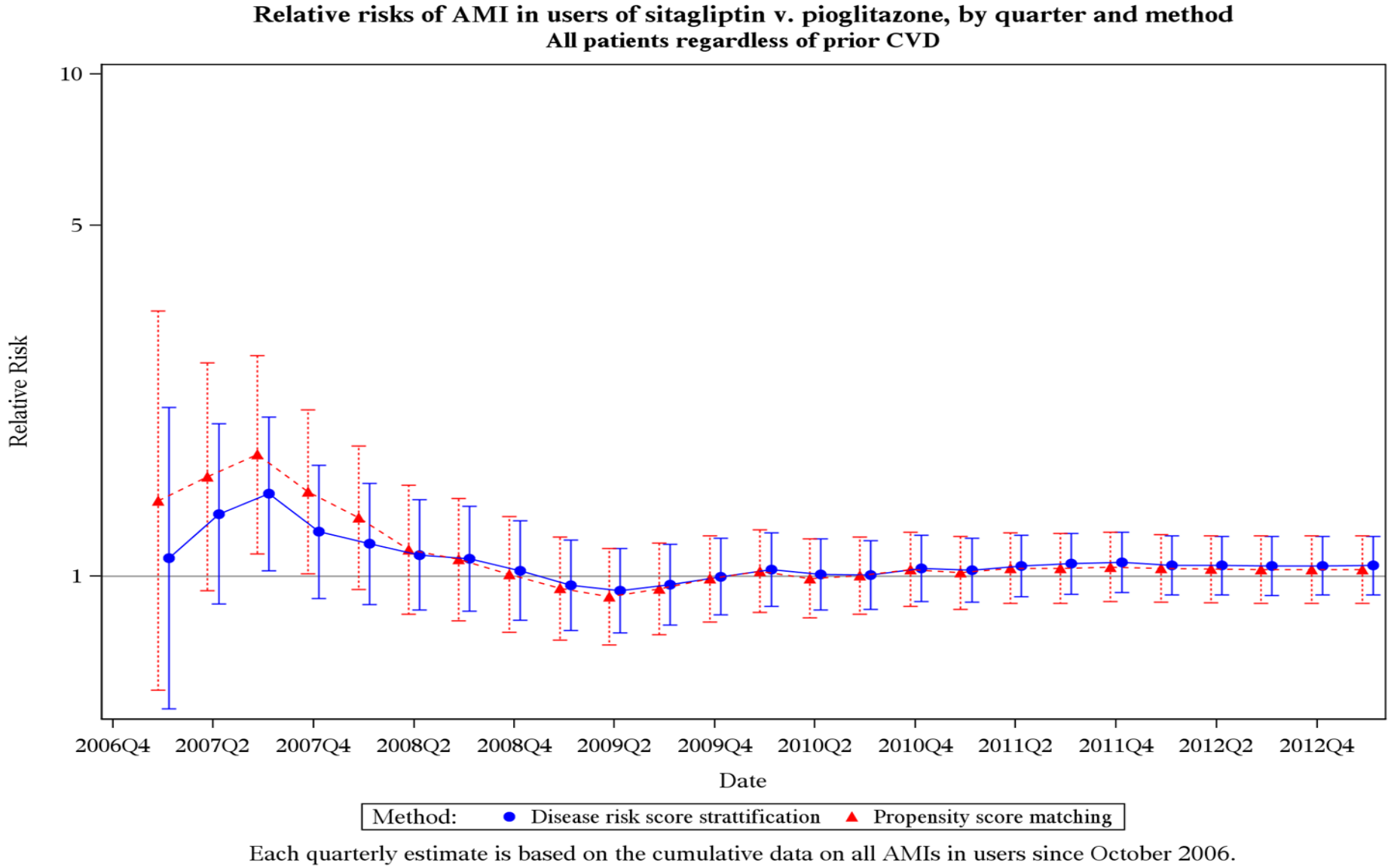


AMI Risk in Users of Sitagliptin vs.Comparators by the DRS Method




AMI Risk in Users of Sitagliptin vs.Comparators by the DRS Method
OR
LCL
UCL
LA-Lnsulin All
0.66
0.59
0.73
LA-Lnsulin CVD
0.73
0.64
0.84
LA-Lnsulin NOCVD
0.53
0.44
0.64
Pioglitazone All
1.05
0.92
1.2
Pioglitazone CVD
1.09
0.9
1.33
Pioglitazone NOCVD
1.01
0.84
1.22
Sulfonylureas All
0.76
0.69
0.86
Sulfonylureas CVD
0.84
0.73
0.97
Sulfonylureas NOCVD
0.66
0.55
0.79
0.4
0.6
0.8
1
1.2
1.6
2
Odds Ratio and 95% CL


AMI Risk in Users of Sitagliptin vs.Comparators by the PS Method
OR
LCL
UCL
LA-Lnsulin All
0.67
0.58
0.77
LA-Lnsulin CVD
0.7
0.58
0.84
LA-Lnsulin NOCVD
0.61
0.47
0.78
Pioglitazone All
1.03
0.88
1.195
Pioglitazone CVD
1.04
0.83
1.29
Pioglitazone NOCVD
1.01
0.82
1.26
Sulfonylureas All
0.76
0.66
0.86
Sulfonylureas CVD
0.79
0.67
0.93
Sulfonylureas NOCVD
0.7
0.57
0.88
0.4
0.6
0.8
1
1.2
1.6
2
Odds Ratio and 95% CL



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