Replication Of Protocol-based Analyses Of Saxagliptin And Sitagliptin Using Sentinel Modular Programs

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Disclosures

The authors have no conflict of interest to disclose

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Background

2016:

Annals of Internal Medicine

ORIGINAL RESEARCH

Risk for Hospitalized Heart Failure Among New Users of Saxagliptin, Sitagliptin, and Other Antihyperglycemic Drugs

A Retrospective Cohort Study

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2018:

Prospective Postmarketing Surveillance of Acute Myocardial Infarction in New Users of Saxagliptin: A Population-Based Study

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Background

Since the publication of these protocol-based analyses (PBAs), the capability of semi-automated modular programs in FDA's Sentinel system has expanded greatly.

Objective:

We aimed to evaluate the performance of Sentinel modular programs in replicating the previous PBAs for saxagliptin and sitagliptin, using similar study design, parameters, and data.

Methods

- Cohort study with health plan members from up to 17 Sentinel Data Partners enrolled between 2006 and 2015.
- New users, 1:1 propensity score matched, 7 pairwise comparisons:

Saxagliptin	Sitagliptin		
Saxagliptin	Pioglitazone	Sitagliptin	Pioglitazone
Saxagliptin	2nd gen sulfonylureas	Sitagliptin	2nd gen sulfonylureas
Saxagliptin	Long-acting insulin	Sitagliptin	Long-acting insulin

- Cox proportional hazards models assessed the hazard ratios (HRs) of AMI and hHF.
- We compared 14 assessments from the PBAs with results from two modular program analyses:
  - primary "replication" analysis mirrored, as closely as possible, every study parameter and data from the PBAs,
  - a secondary "updated" analysis included data not available at the time of the PBAs.

Comparison of Study Methods

	PBA	Replication	Updated
Data Partners	13 (AMI), 10 (hHF)		16, including Medicare
Study period	Saxa: 8/2009-7/2014 (AMI), 8/2009-3/2014 (hHF)*		8/2009-9/2015*
Inclusion/Exclusion criteria	365 days' eligibility prior to first exposure to study drug, ≥ 18 years of age, diabetes diagnosis or antidiabetic drug use (other than short acting insulin), no gestational diabetes, no AMI or hHF within 60 days before index		
Covariates	Assessed during 365 days' baseline period: demographics, comorbidities (CVD, others), drug exposure, healthcare utilization		Add'l covariates., (e.g., concomitant medication exposure)
Follow-up	First dispensing until end of exposure (considering 33% gap**, 12-day extension), disenrollment, death, end of query period, use of comparison drug, study outcome		
Endpoint	Primary inpatient diagnosis of AMI or hHF		

*sitagliptin, study period start: 10/2006 **PBA: 1/3 day's supply of latest dispensing, minimum 10 days

Results

Saxagliptin – sitagliptin matched comparison

		PBA		MP (Replication)		MP (Updated)	
AMI		Saxagliptin	Sitagliptin	Saxagliptin	Sitagliptin	Saxagliptin	Sitagliptin
	Cohort size	<82,264*	<82,264*	63,821	63,821	182,777	182,777
	IR [/1,000 p-yrs]	3.2-4.0*	4.3*	4.41	4.66	7.29	7.97
	Hazard ratio	**0.96 (0.77–1.18)**		**0.96 (0.77, 1.22)**		**0.93 (0.85-1.03)**	
hHF	Cohort size	<78,553*	<78,553*	59,966	59,966	182,098	182,098
	IR [/1,000 p-yrs]	~2-4*	~7*	5.04	5.58	12.40	14.14
	Hazard ratio	**0.93 (0.75–1.15)**		**0.91 (0.73, 1.15)**		**0.90 (0.83-0.96)**	

Covariate distributions were comparable to those in the PBA and well-balanced after matching.

 *prior to matching

Results: Replication vs. PBA

Outcome	Treatment	Comparator	PBA	MP (Replication)	Replication vs PBA
AMI	Saxagliptin	Sitagliptin	0.96 (0.77–1.18)	0.96 (0.77, 1.22)	0%
	Saxagliptin	Pioglitazone	1.17 (0.86–1.57)	1.08 (0.81, 1.46)	-8%
	Saxagliptin	Second-generation sulfonylureas	0.70 (0.53–0.91)	0.76 (0.57, 1.02)	9%
	Saxagliptin	Long-acting insulin	0.54 (0.41–0.71)	0.56 (0.43, 0.73)	4%
	Sitagliptin	Pioglitazone	1.11 (0.95–1.31)	1.11 (0.94, 1.30)	0%
	Sitagliptin	Second-generation sulfonylureas	0.66 (0.58–0.76)	0.72 (0.62, 0.83)	9%
	Sitagliptin	Long-acting insulin	0.63 (0.54–0.74)	0.67 (0.58, 0.78)	6%
hHf	Saxagliptin	Sitagliptin	0.93 (0.75–1.15)	0.91 (0.73, 1.15)	-2%
	Saxagliptin	Pioglitazone	0.58 (0.41–0.83)	0.72 (0.49, 1.05)	24%
	Saxagliptin	Second-generation sulfonylureas	0.81 (0.59–1.10)	0.68 (0.50, 0.93)	-16%
	Saxagliptin	Long-acting insulin	0.66 (0.51–0.85)	0.64 (0.49, 0.83)	-3%
	Sitagliptin	Pioglitazone	0.68 (0.58–0.81)	0.79 (0.66, 0.94)	16%
	Sitagliptin	Second-generation sulfonylureas	0.83 (0.73–0.93)	0.81 (0.72, 0.93)	-2%
	Sitagliptin	Long-acting insulin	0.71 (0.63–0.81)	0.75 (0.67, 0.85)	6%

Different conclusion related to stat significance

Relative difference in point estimates	≤5%	≤10%	≤20%
Proportion of pairwise analyses	43%	79%	93%

Results: Updated Analysis vs. PBA

Outcome	Treatment	Comparator	PBA	MP (Updated)	Updated vs PBA
AMI	Saxagliptin	Sitagliptin	0.96 (0.77–1.18)	0.93 (0.85; 1.03)	-3%
	Saxagliptin	Pioglitazone	1.17 (0.86–1.57)	1.04 (0.92; 1.18)	-11%
	Saxagliptin	Second-generation sulfonylureas	0.70 (0.53–0.91)	0.81 (0.72; 0.92)	16%
	Saxagliptin	Long-acting insulin	0.54 (0.41–0.71)	0.68 (0.61; 0.76)	26%
	Sitagliptin	Pioglitazone	1.11 (0.95–1.31)	1.04 (0.94; 1.14)	-6%
	Sitagliptin	Second-generation sulfonylureas	0.66 (0.58–0.76)	0.82 (0.77; 0.87)	24%
	Sitagliptin	Long-acting insulin	0.63 (0.54–0.74)	0.73 (0.68; 0.78)	16%
hHf	Saxagliptin	Sitagliptin	0.93 (0.75–1.15)	0.90 (0.83; 0.96)	-3%
	Saxagliptin	Pioglitazone	0.58 (0.41–0.83)	0.67 (0.60; 0.76)	16%
	Saxagliptin	Second-generation sulfonylureas	0.81 (0.59–1.10)	0.72 (0.66; 0.80)	-11%
	Saxagliptin	Long-acting insulin	0.66 (0.51–0.85)	0.67 (0.61; 0.73)	2%
	Sitagliptin	Pioglitazone	0.68 (0.58–0.81)	0.69 (0.63; 0.76)	1%
	Sitagliptin	Second-generation sulfonylureas	0.83 (0.73–0.93)	0.87 (0.84; 0.91)	5%
	Sitagliptin	Long-acting insulin	0.71 (0.63–0.81)	0.88 (0.85; 0.92)	24%

Different conclusion related to stat significance

Relative difference in point estimates	≤5%	≤10%	≤20%
Proportion of pairwise analyses	36%	43%	79%

Stratified Analyses

Analyses were stratified by:

- Prior CVD: yes/no
- Sex: males/female
- Age: <65, ≥65
- Medicare: all other DPs/Medicare only

Slightly more variation was found in stratified analyses, likely due to fewer events per stratum, increased random error

Limitations

- Close, but not complete replication in methods
- Underlying data could have changed since the PBA due to claims adjustments and or other reasons
- Limitations inherent in current and replicated analyses:
  - Residual confounding (e.g., diabetes duration, severity, lifestyle factors)
  - Short average follow-up (~7 months)

Conclusions

Sentinel modular programs were able to replicate findings of prior PBAs, which did not indicate an increased risk of AMI or hHF associated with saxagliptin or sitagliptin exposure.

An updated analysis with additional data yielded similar findings.

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Coauthors

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- Rongmei Zhang
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- Sheryl Kluberg
- Darren Toh
- Justin Bohn

Data Partners

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