Enhancing the Application of Real World Evidence with Episode of Care Analytics

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ABSTRACT

SAS® Real World Evidence (RWE) enables pharmaceutical companies and healthcare organizations to leverage the power of real-world data with episode-of-care analytics to investigate real-world healthcare questions. RWE can provide new insights that may be used to investigate safety and effectiveness of marketed pharmaceutical products in real-world clinical settings. In this paper, we used SAS® Real World Evidence to investigate use of unsupervised and supervised signal detection methods to identify potential associations of different medications indicated for diabetes condition with acute myocardial infarction (AMI). Our analyses focused on creating drug episode profiles for selected diabetes medications administered to a cohort of T2DM patients and then applying statistical signaling methods to identify occurrence of AMI event in this cohort. Further investigation was performed using the SAS causal estimation procedure to estimate the potential effect of exposure to each diabetes medication and AMI event. The three unsupervised signal detection methods showed greater than expected frequency count of metformin-AMI event pairs relative to other drug codes. Both unadjusted and adjusted results based on the supervised signal detection methods also showed larger estimated potential effect of metformin for AMI relative to other drugs. Using supervised signal detection methods to augment and validate commonly used disproportionality analysis techniques might allow for proper evaluation and estimation of adverse effects that might result from exposure to certain medications.

INTRODUCTION

Outside of clinical trials, real-world evidence studies provide new insights that may be used to investigate safety and effectiveness of marketed pharmaceutical products in real-world clinical settings. Leveraging the power of SAS Real World Evidence for clinical research and for predicting adverse health outcomes is a challenge with big data and often incomplete patient information obtained from electronic health records (EHR) and claims databases. Despite these obstacles, observational healthcare data are useful. Longitudinal patient information collected during routine clinical care are needed for epidemiological and comparative effectiveness research. In comparison with and to complement spontaneous adverse event reports, real-world data provide information about drug exposure and confounding variables that can be used to construct episode-of-care profiles for patients exposed to these drugs. Use of such drug exposure profiles enable proactive surveillance and monitoring of unexpected or adverse health outcomes that might be associated with such medications.

SAS recently released a visual real-world evidence and visual analytics platform that enables quick discovery and creation of patient cohorts for population health and epidemiological research. We used this platform to conduct exploratory analyses and to perform unsupervised signal detection of adverse events that might be associated with disproportionate reporting of diabetes medication drug codes. We further conducted a supervised comparative effectiveness analysis to investigate association between selected diabetes drug codes and incidence of AMI in T2DM patient cohort. Analyses presented in the paper also aimed to find out whether retrospective analysis of clinical care data could be used to signal and identify cardiovascular (CV) events that might be associated with certain diabetes medications that might warrant further investigation. Medications used in the treatment of diabetes have potential CV effects and could either be beneficial or harmful. That is why since 2008 the US Food and Drug Administration (FDA) has recommended that new drugs for type 2 diabetes must undergo clinical trials and demonstrate cardiovascular safety in addition to glycemic benefit. The European Medicines Agency (EMA) issued a similar rule in 2012 for such drugs.

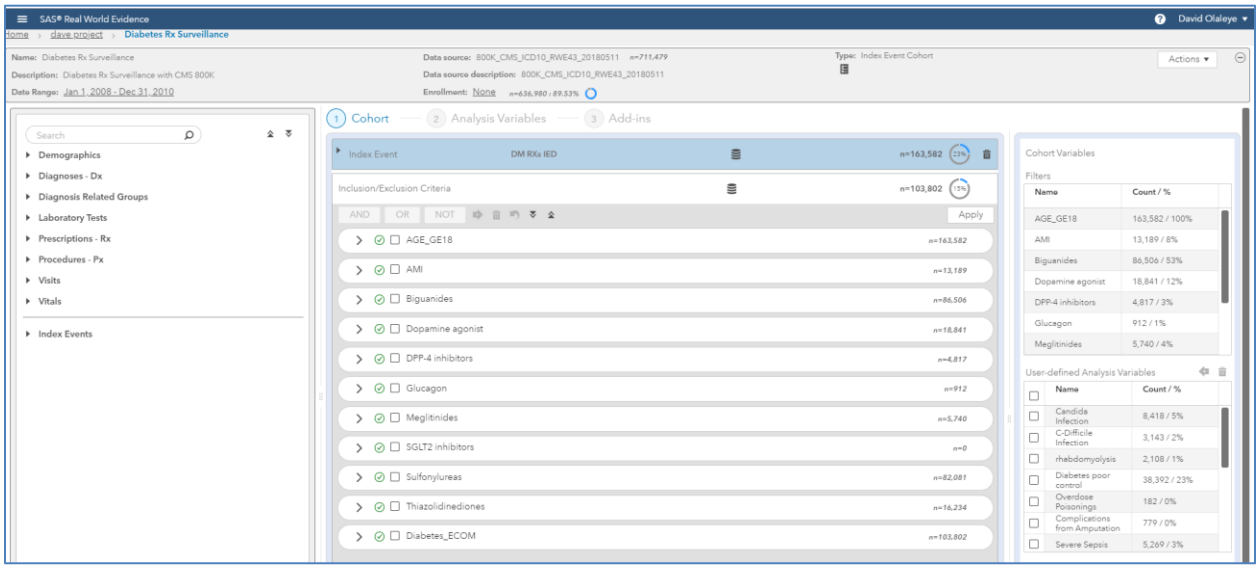
This paper is organized as follows: first, we present a brief overview of SAS® Real World Evidence. In subsequent sections, we present the data, the methodology and research design for the study cohort, the statistical signaling methods, and the study findings. In the appendix, we provide additional information about the most commonly used signal detection methods and strategies for preparing the

data to make them suitable for signal detection analyses. We note that these statistical tools enable computation of risks for drug safety signal evaluation, but due to known limitations of observational databases, additional research is required to properly make statistical inferences and clinical judgments in a meaningful manner.

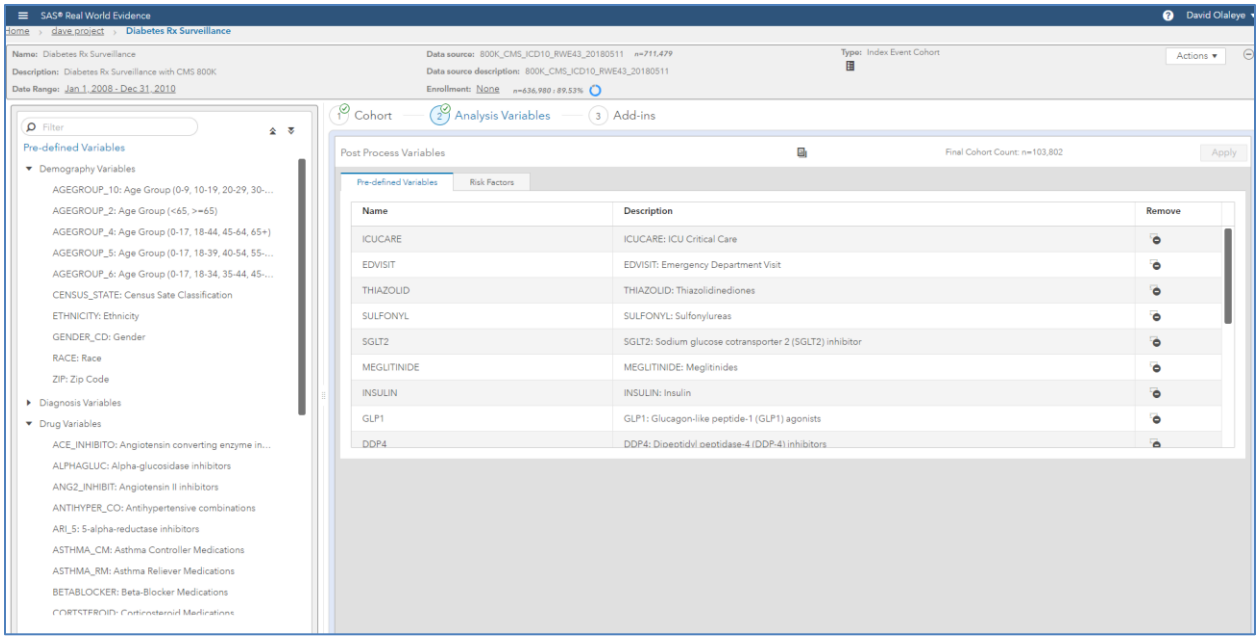
SAS REAL WORLD EVIDENCE

SAS Real World Evidence is a visual real-world evidence and analytics platform that enables quick discovery and creation of patient cohorts for population health and epidemiological studies. The platform workflows simplify the process of defining and building a cohort, which is a set of patients that meet some specific inclusion and exclusion eligibility criteria. The platform supports:

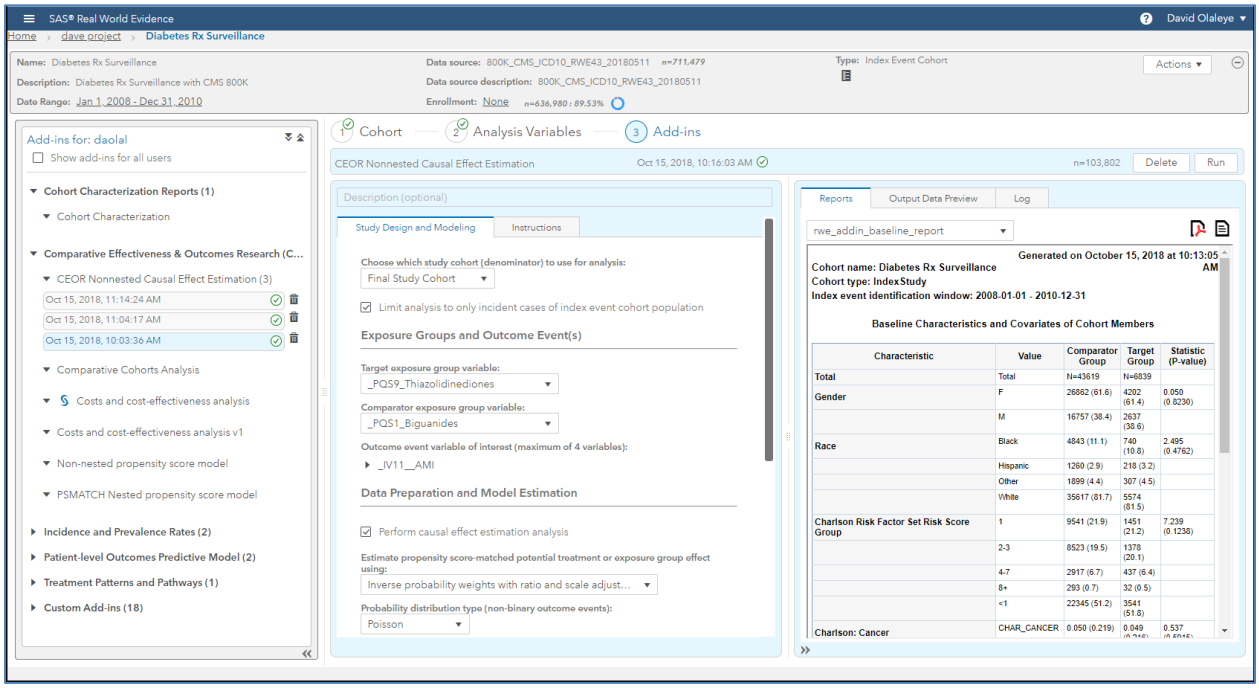
- a common data submission model for managing real-world data from multiple disparate data sources
- creation and processing of cohorts of patients based on simple and complex query logic and rules that are customized to address different clinical scenarios and temporal relationships across different event codes - diagnoses, procedures, prescriptions, vitals, and laboratory tests (see Display 1)
- easy-to-navigate point-and-click user interface to assist users with exploring and querying large data sources
- loading of predefined analysis variables and on-demand creation of user-defined analysis variables (see Display 2)
- add-in models and report templates that run against cohort outputs and leverage the power of SAS advanced analytics and machine learning algorithms for real-world data insights (see Display 3)
- add-in builder that enables users to develop and execute customized or user-written SAS programs and open-source code against cohort outputs



Display 1: SAS Real World Evidence for cohort discovery and processing workflow



Display 2: Predefined analysis variable and comorbidity risk factor workflow for cohort analysis



Display 3: SAS Real World Evidence add-in model job workflow

METHODOLOGY

The methodology for creating the study cohort consisted of three steps: (a) identification of index event cohort and construction of index medication exposure profiles; (b) AMI event identification during the exposure period; and (c) creation of analytic data sets for unsupervised and supervised signal detection analyses. We elaborate on the technical details involved in each of the three steps.

DATA SOURCE AND PATIENT POPULATION

Data used for this study came from the publicly available 2008-2010 Center for Medicare and Medicaid Services (CMS) DE-Synthetic Public Use File (DE-SynPUF) for Medicare recipients. As stated on the CMS website, DE-SynPUF was created with the goal of providing a realistic set of claims data in the public domain while providing the highest degree of protection to the Medicare beneficiaries' protected health information. A random sample of 800,000 members was obtained from the 2.3-million-member population represented in the database. The database provided de-identified patient information that included patient demographics, dates of service, diagnoses, procedures, and medications. For the analyses presented in the paper, we identified a cohort of patients with at least one record of prescription for diabetes medications in the following drug classes - alpha-glucosidase inhibitors, dopamine agonist, dipeptidyl peptidase-4, glucagon or meglitinides, sodium glucose transporter, sulfonylureas, thiazolidinediones, or biguanides (see Table 1)- either in the outpatient or inpatient setting, between January 1, 2008 and December 31, 2010 (see Figure 1). This is a retrospective cohort study of patients aged 18 years and older with diabetes mellitus diagnosis (ECQM value set = "2.16.840.1.113883.3.464.1003.103.12.1001"). The first identified prescription fill date in the database for each diabetes medication was tagged as the index event date and used to create the drug exposure profile for each drug. NDC codes were used to identify records of prescription and standardized to a common generic drug name, because a drug might be classified under one or multiple NDC codes. The final cohort sample used for analysis consisted of 103,802 patients.

CONSTRUCTING DRUG EXPOSURE PROFILES AND OUTCOME EVENTS

For signal detection analysis purposes, each drug exposure period (defined by the index prescription fill date and the study end date) was binned into one or more model periods. The model period is the time window used to accumulate and assign incurred prescription claims and refills to the associated window. The model period assignment logic breaks the drug exposure period into 90-day contiguous periods that are set between the exposure start and end dates, starting with the most recent 90 days from the index fill date. For example, for a given index drug, if the index fill date and last fill date were to match the study period start and end dates, then the possible maximum number of 90-day increment period is 12. For the study drugs analyzed in the paper, the minimum, median, and maximum number of contiguous model periods were 1, 7, and 9, respectively. Model periods were evaluated and constructed independently for each selected diabetes medication listed in Table 1. Binning the study period into contiguous model periods ensures that the study drugs are examined over a consistent time interval. This also allows for temporal analysis of diabetes medications - AMI event pairs over time. For cumulative trend analysis, all available data from the first to last model periods were analyzed, and prior model period data were iteratively added to subsequent model periods for each drug.

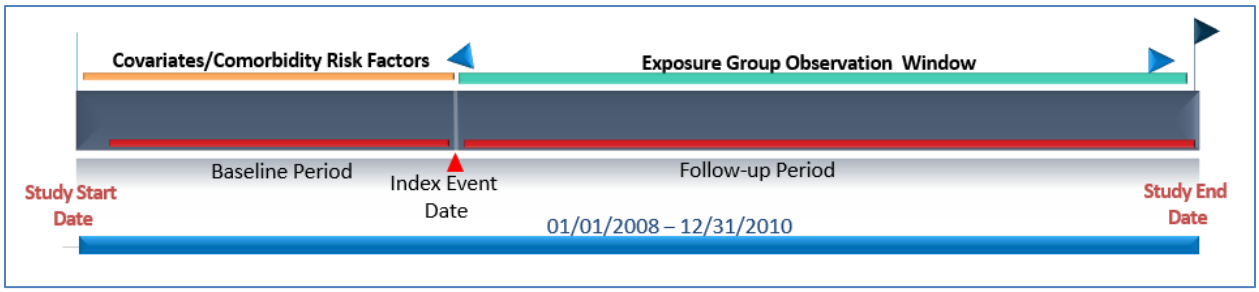


Figure 1 – Study cohort design and setup

For each patient, presence or absence of the health outcome of interest (in this case, AMI event) was checked for during each model period that spans the drug exposure window. The study endpoint for each evaluable patient for the AMI event (identified by ICD-10 code I12.x) was the date associated with the first occurrence of AMI event during the model period first detected during the drug exposure window, death (from any cause), the last known prescription claim interval, or the end of the study in 2010.

STATISTICAL ANALYSIS

For statistical analysis differentiation purposes, we use the term 'unsupervised signal detection analysis' to refer to the disproportionality analysis-type method used to compute signal scores that detect 'more-than-expected frequency count' of drug-event associations based on case reports of adverse events reported to spontaneous reporting systems such as the United States Food and Drug Administration Adverse Event Reporting System (FAERS). Because there is no target outcome variable to be predicted, the methods tend to discover and signal count anomalies or intrinsic association patterns involving different drugs and different adverse drug reactions that underlie the data. For supervised signal detection analysis, we assume there is a functional underlying distribution to model the association between the target outcome variable and the target independent variable represented by exposure to each diabetes medication.

For both types of analysis, we used the 'distinct' patient count method to obtain the frequency count of patients exposed to each diabetes medication and for those reporting AMI events. For each patient included in the study, the first encountered diabetes drug triggered in the data was assigned as the index drug for the patient. As illustrated in the frequency table displayed in Figure 2, **n..** equals the total number of patients in the database, $\mathbf{n_{11}}$ is the number of patients with exposure to the study drug during the model period and reporting AMI events, $\mathbf{n_{10}}$ is the number of patients that have used the study drug but did not experience AMI event during any of the model periods associated with the drug, $\mathbf{n_{01}}$ is the number of patients that did not use the study drug but experienced AMI event, and $\mathbf{n_{00}}$ is the number of patients that were not exposed to the study drug and did not report AMI condition. Crude reporting rates for the drug-AMI event pairs were computed for unsupervised signal detection analysis and crude rate ratios and average treatment effect (ATE) estimates were obtained using the supervised analysis method. For the latter method, we computed both the unadjusted and adjusted potential ATE estimates as signal measures to represent and characterize the diabetes medication-AMI event pairs. For each index study drug, the comparator drugs were all the other index diabetes medications identified in the drug classes mentioned earlier.

Condition Drug	Event	No Event	Total
Exposed	$\mathbf{n_{11}}$	$\mathbf{n_{10}}$	$\mathbf{n_{1.}}$
Not exposed	$\mathbf{n_{01}}$	$\mathbf{n_{00}}$	$\mathbf{n_{0.}}$
Total	$\mathbf{n_{.1}}$	$\mathbf{n_{.0}}$	**n..**

Score Metric =
O/E = Observed/Expected

Figure 2 – The 2x2 drug-event association tabular representation for signal detection analysis

For unsupervised signal detection analysis, we used the standard disproportionality methods that included the Bayesian Confidence Propagation Neural Network (BCPNN) Information Component (IC), the Relative Odds Ratio (ROR), and the Proportional Reporting Ratio (PRR). A risk ratio or score for each signaling method was represented by the lower bound of the 95% CI > 1.0 for ROR and PRR, or 95% CI >0 for BCPNN/IC. The score was computed as the ratio of the observed count of AMI to the expected count of AMI event, and if it exceeded the pre-specified method threshold, was considered as significant and flagged as a signal. Additional information about the analysis methods is provided in the appendix of the paper.

For supervised signal detection analysis, we used the causal estimation procedure (PROC CAUSALTRT) to compute both the unadjusted and adjusted effect of each diabetes medication on the AMI event (the target event), and the STDRATE procedure to obtain the unadjusted rate ratio estimates. The CAUSALTRT procedure uses various estimation methods to adjust for the effects of confounding variables by fitting models for the treatment assignment T (in this case, each single diabetes drug versus 'other' diabetes medications) or the outcome Y (in this case, AMI event), or both. For the analysis

presented in the paper, we used the augmented inverse probability weights (AIPW) estimation method to jointly fit both the treatment assignment and outcome event models, and to compute the ATE for each target diabetes medication relative to other diabetes medications. The AIPW estimation method fits the propensity score model for treatment assignment and incorporates a model for the outcome variable into the estimation of the potential outcome means and ATE. The AIPW estimation method is doubly robust and provides unbiased estimates for the ATE even if one of the outcome or treatment models is mis-specified. For more detailed information about this procedure, see *SAS/STAT® 14.3 User's Guide: The CAUSALTRT Procedure.*

The supervised unadjusted model is simply an average treatment effect (ATE) model with the effects of covariates or confounding variables unaccounted for. This is to provide a somewhat close approximation to the previously mentioned unsupervised disproportionality analysis. To obtain the adjusted ATE for each drug-AMI event pair, we included and adjusted for demographic factors, number of concomitant medications (excluding the study drugs or medications in their drug class), and comorbidity risk factors in the outcome event multivariate model. Because we used the ECQM value set to identify the diabetes cohort, this might also have included patients who are likely on insulin therapy. We adjusted for use of insulin therapy in the multivariate model. Also, the sample size for patients on insulin therapy was not large enough to allow for stratification and sensitivity analyses. Charlson comorbidity diagnosis codes were used to capture the patient's comorbidity status prior to the start of the index medication event and transformed into binary variables, coded as a 1 or 0 flag, based on information known prior to the index event date.

For supervised adjusted and unadjusted models estimated using the CAUSALTRT procedure, the lower bound of the 95% CI for estimated ATE > 0 was flagged as a safety signal. For unadjusted rate ratio derived using the STDRATE procedure, the lower bound of the 95% CI for rate ratio > 1 was flagged as a safety signal. All analyses were performed using SAS statistical software and SAS Real World Evidence 4.3 (SAS Institute, Cary, NC).

RESULTS

STUDY POPULATION

For the study period between January 1, 2008 and December 31, 2010, we identified 103,802 diabetic patients treated with at least one prescription fill for diabetes medications in the following drug classes: alpha-glucosidase inhibitors, dopamine agonist, dipeptidyl peptidase-4, glucagon or meglitinides, sodium glucose transporter, sulfonylureas, thiazolidinediones, or biguanides. In all, there were 20 diabetes medications that met the study inclusion and exclusion eligibility criteria and characterized the 103,802 patients that made up the final analysis study cohort. In the paper, we focused and reported only diabetes medications with at least 100 patients and with 5 or more AMI events. Of the total 149,973 evaluable drug exposure window model periods, the numbers range from 76,112 periods of metformin therapy (42,742 patients with 1,060 AMI events), 23,704 periods of glyburide therapy (17,864 patients with 273 AMI events), 21,875 periods of glipizide therapy (16,826 patients with 266 AMI events), 6,045 periods of pioglitazone therapy (5,431 patients with 52 AMI events), 5,290 periods of ropinirole therapy (4,842 patients with 46 AMI events), to 1,491 periods of rosiglitazone therapy (1408 patients with 18 AMI events) and 248 periods of tolbutamide therapy (248 patients with 5 AMI events). The respective number of patients for each diabetes medication and associated AMI events is reported in Table 1.

Unsupervised signal detection analysis

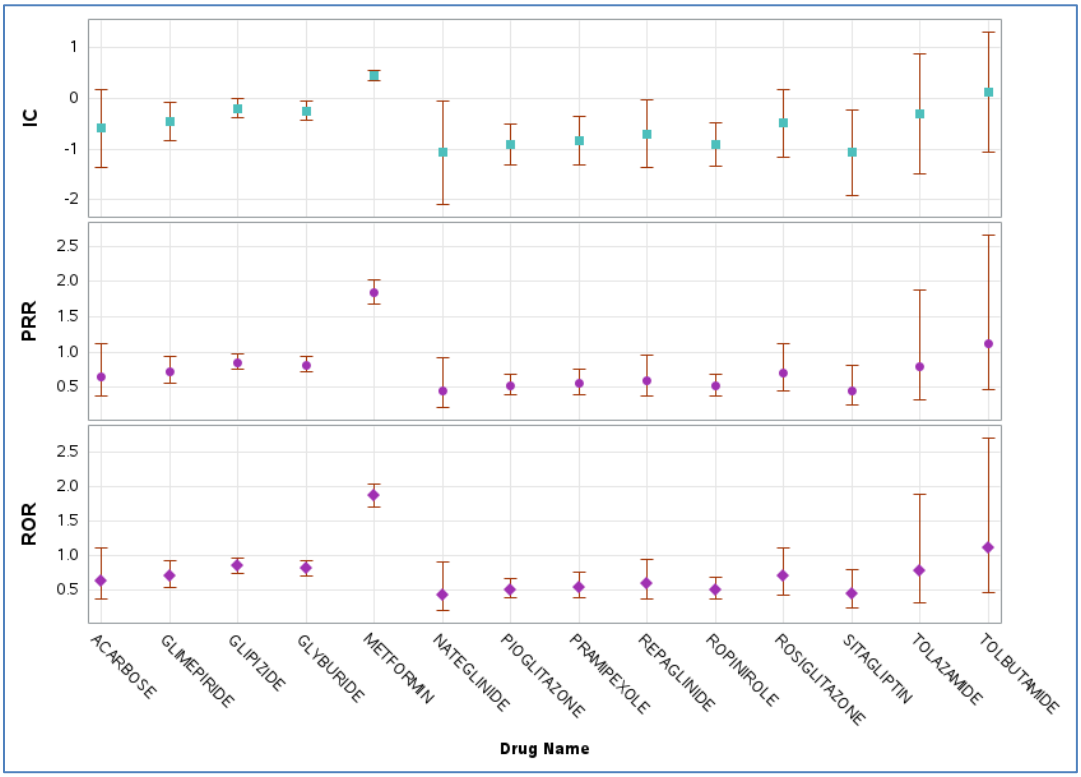
Table 1 also shows the results of the unsupervised signal detection analysis for the three disproportionality analysis methods. Of the fourteen diabetes medications reported, the expected count of AMI events, based on PRR disproportionality signaling method, range from 573 AMI events for metformin therapy, about 334 AMI events for glyburide therapy, to 5 AMI events for each of tolazamide and tolbutamide therapy. The associated lower 95% CI PRR values were 1.85, 0.82, 0.78 and 1.11, respectively. Given the PRR threshold [(PRR – 1.96SE) > 1] used to signal disproportionate reporting of

AMI condition, only metformin therapy showed an evidence of increased risk of AMI with unadjusted reporting ratio of 1.85 (95% CI 1.69-2.02) compared with all other diabetes medications. The AMI signal results for metformin therapy were consistent with those obtained for unsupervised ROR and BCPNN/IC disproportionality methods. Unadjusted signal results based on these three methods also showed decreased AMI risk for certain diabetes medications such as glimepiride and glipizide relative to the other drugs in the database, but the association might need to be investigated further. Display 4 shows the disproportionality analysis plot for the signal scores and 95% CI values for the three signaling methods.

			Unsupervised disproportionality signaling method								
			PRR			ROR			BCPNN		
Generic Drugname	No. of Patients	Observed Events	Expected Events	PRR	95% CI	Expected Events	ROR	95% CI	Expected Events	IC	IC-2SD
ACARBOSE	1107	13	20.11	0.646	(0.375, 1.113)	20.25	0.642	(0.371, 1.112)	20.04	-0.590	-1.368
GLIMEPIRIDE	4402	58	80.64	0.719	(0.554, 0.933)	81.07	0.715	(0.550, 0.931)	79.68	-0.453	-0.836
GLIPIZIDE	16826	266	312.04	0.852	(0.749, 0.970)	312.91	0.850	(0.746, 0.969)	304.58	-0.196	-0.385
GLYBURIDE	17864	273	333.84	0.818	(0.720, 0.929)	335.00	0.815	(0.716, 0.927)	323.37	-0.244	-0.431
METFORMIN HCL	42742	1060	573.30	1.849	(1.689, 2.024)	566.68	1.871	(1.706, 2.051)	773.71	0.453	0.342
NATEGLINIDE	873	7	15.88	0.441	(0.210, 0.925)	16.04	0.436	(0.207, 0.919)	15.80	-1.073	-2.100
PIOGLITAZONE HCL	5431	52	100.87	0.516	(0.392, 0.679)	101.79	0.511	(0.387, 0.674)	98.31	-0.907	-1.310
PRAMIPEXOLE DIHYDROCHLORIDE	3570	36	65.64	0.548	(0.395, 0.762)	66.20	0.544	(0.390, 0.758)	64.62	-0.828	-1.309
REPAGLINIDE	1654	18	30.13	0.597	(0.376, 0.949)	30.36	0.593	(0.372, 0.946)	29.94	-0.705	-1.374
ROPINIROLE	4842	46	89.69	0.513	(0.383, 0.687)	90.51	0.508	(0.379, 0.682)	87.65	-0.916	-1.344
ROSIGLITAZONE	1408	18	25.59	0.703	(0.443, 1.117)	25.73	0.700	(0.438, 1.116)	25.49	-0.481	-1.151
SITAGLIPTIN	1337	11	24.37	0.451	(0.250, 0.815)	24.62	0.447	(0.246, 0.810)	24.20	-1.072	-1.911
TOLAZAMIDE	352	5	6.38	0.784	(0.327, 1.878)	6.40	0.781	(0.323, 1.891)	6.37	-0.301	-1.491
TOLBUTAMIDE	248	5	4.49	1.114	(0.466, 2.661)	4.48	1.116	(0.460, 2.710)	4.49	0.123	-1.071

Note: For unsupervised disproportionality analysis, only drugs with N>=100 patients and drug/event combination with N>=5 cases are shown.

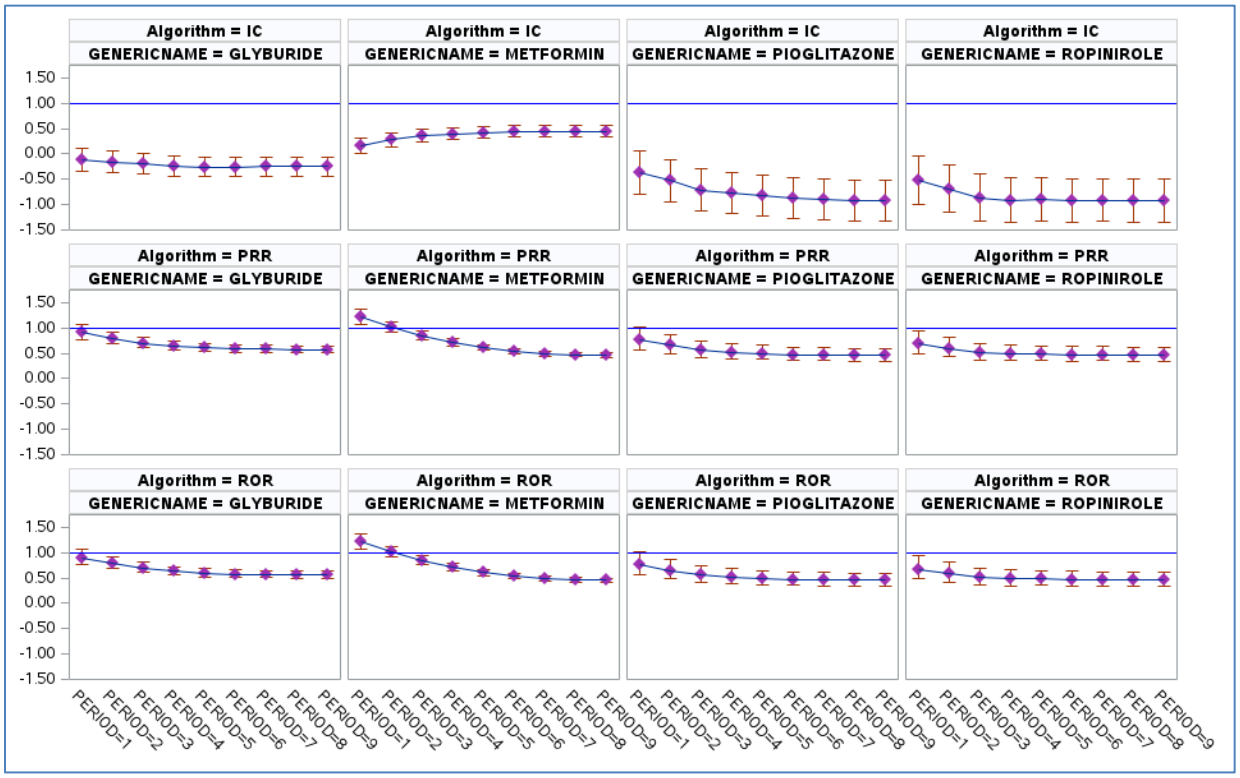
Table 1: Unsupervised signal detection analysis results for selected diabetes medications and AMI event



Display 4: Plot of unsupervised signal detection scores for selected diabetes medications and AMI event by disproportionality method

Unsupervised signal detection trend analysis

The cumulative trend analysis plot (shown in Display 5) was used to examine which of the model periods associated with each diabetes medication is likely to contain the safety signal for AMI event. As previously reported for unadjusted analysis, only metformin therapy initially showed an elevated risk of AMI event, and the risk gradually disappeared by the end of the cumulative therapy window. Based on the pre-specified signal threshold and consistency across the three signaling methods, we did not find any evidence of elevated risk or signaled AMI event with other diabetes medications. Again, given the known limitation of the database that we analyzed, additional studies will need to be performed to further investigate the association.



Display 5: Trend analysis plot of unsupervised signal detection scores for selected diabetes medications and AMI event by disproportionality method

Supervised signal detection analysis

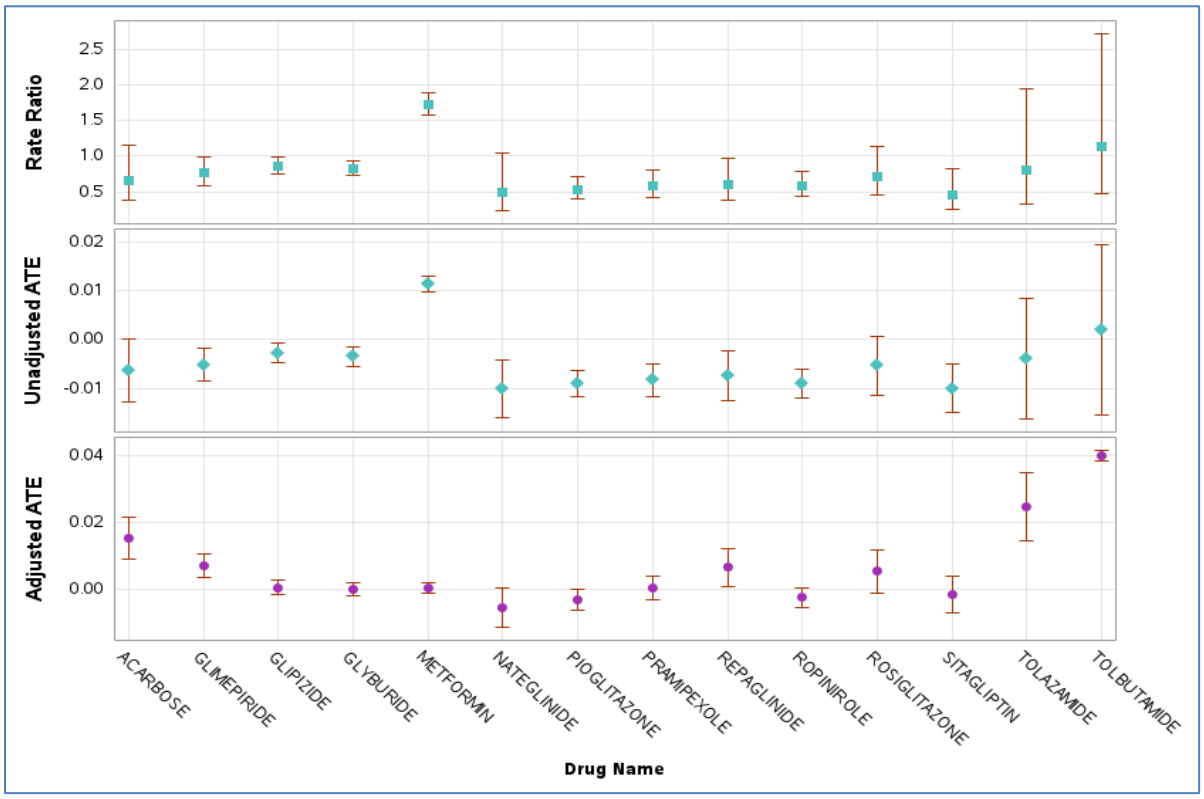
We report the unadjusted rate ratio and adjusted ATE estimates for the diabetes medications based on the supervised signal detection methods in Table 2. In comparison with the unadjusted results from unsupervised disproportionality analysis, the signaling results for most of the diabetes medication are somewhat similar with relatively few changes. The association of metformin therapy with AMI event still showed unadjusted increased rate ratio of 1.72 (95% CI 1.57-1.89) and ATE of 0.071 (95% CI 0.010-0.013). However, when we adjusted for the effects of covariates in the adjusted model, the elevated signal risk of AMI attenuated with ATE of 0.0004 (95% CI -0.001-0.003). This might suggest a varying degree of AMI event risk for different risk groups with exposure to metformin therapy. Similar results and conclusions can be assumed for acarbose drug based on its ATE and 95% CI ATE values. The results shown in Table 2 are somewhat consistent with previously published studies that showed protective effect for metformin, neutral effect for pioglitazone, and mixed effect result for rosiglitazone. We also observed

some interesting signal results for other diabetes medications, especially for those in the sulfonylureas and alpha-glucosidase inhibitors drug classes. Adjusted ATE estimates for tolazamide, tolbutamide, and glimepiride drugs were 0.025 (95% CI 0.014-0.035), 0.040 (95% CI 0.039-0.042), and 0.007 (95% CI 0.003-0.010), respectively. The ATE estimates suggest elevated risk of AMI event for these three drugs relative to the other diabetes medications when we account for other covariates' effects. The ATEs are significantly different from 0 based on the 95% CI values. Display 6 shows the plot for the unadjusted and adjusted signal scores and 95% CI values for the three supervised signal detection methods.

		Supervised method								
		Unadjusted			Unadjusted			Adjusted		
Generic Drugname	N(Patients)	Rate Ratio	Z Score	95% CI	ATE	Z Score	95% CI	ATE	Z Score	95% CI
ACARBOSE	1107	0.6668	-1.45636	(0.386, 1.150)	-0.0064	-1.96866	(-0.013, -0.000)	0.0152	4.85830	(0.009, 0.021)
GLIMEPIRIDE	4402	0.7601	-2.05667	(0.585, 0.987)	-0.0051	-2.90546	(-0.009, -0.002)	0.0068	3.74226	(0.003, 0.010)
GLIPIZIDE	16826	0.8629	-2.22744	(0.758, 0.982)	-0.0027	-2.56976	(-0.005, -0.001)	0.0003	0.31049	(-0.002, 0.002)
GLYBURIDE	17864	0.8283	-2.87741	(0.729, 0.942)	-0.0034	-3.31455	(-0.005, -0.001)	-0.0001	-0.07938	(-0.002, 0.002)
METFORMIN HCL	42742	1.7223	11.68550	(1.572, 1.887)	0.0114	12.87206	(0.010, 0.013)	0.0004	0.53812	(-0.001, 0.002)
NATEGLINIDE	873	0.4929	-1.86815	(0.235, 1.035)	-0.0102	-3.33729	(-0.016, -0.004)	-0.0057	-1.91351	(-0.012, 0.000)
PIOGLITAZONE HCL	5431	0.5351	-4.44679	(0.406, 0.705)	-0.0090	-6.47450	(-0.012, -0.006)	-0.0033	-2.08268	(-0.006, -0.000)
PRAMIPEXOLE DIHYDROCHLORIDE	3570	0.5850	-3.18590	(0.421, 0.814)	-0.0083	-4.81301	(-0.012, -0.005)	0.0002	0.10577	(-0.003, 0.004)
REPAGLINIDE	1654	0.6057	-2.11722	(0.381, 0.963)	-0.0073	-2.83770	(-0.012, -0.002)	0.0064	2.17497	(0.001, 0.012)
ROPINIROLE	4842	0.5846	-3.59644	(0.436, 0.783)	-0.0090	-6.18627	(-0.012, -0.006)	-0.0027	-1.83875	(-0.006, 0.000)
ROSIGLITAZONE	1408	0.7149	-1.41685	(0.449, 1.137)	-0.0054	-1.78333	(-0.011, 0.001)	0.0052	1.58168	(-0.001, 0.012)
SITAGLIPTIN	1337	0.4540	-2.61133	(0.251, 0.821)	-0.0100	-3.99247	(-0.015, -0.005)	-0.0019	-0.65863	(-0.007, 0.004)
TOLAZAMIDE	352	0.8089	-0.47348	(0.336, 1.946)	-0.0039	-0.61867	(-0.016, 0.008)	0.0246	4.67275	(0.014, 0.035)
TOLBUTAMIDE	248	1.1281	0.26925	(0.469, 2.714)	0.0021	0.23106	(-0.015, 0.020)	0.0401	52.05805	(0.039, 0.042)

Note: For supervised signaling method, only drugs with N>=100 patients and drug/event combination with N>=20 cases are shown.

Table 2: Supervised signal detection analysis results for selected diabetes medications and AMI event.



Display 6: Plot of supervised signal detection scores for selected diabetes medications and AMI event

CONCLUSION

Given the known limitations of spontaneous adverse drug events data often used to generate and monitor safety signals, especially for newly marketed drugs, real-world data provide an additional source of information that can be used to investigate and validate the validity and reliability of such signals. Advantages of using real-world data include evidence of utilization of health care services collected at points of care. This enables proactive surveillance of diagnoses and medications for detecting adverse health outcomes that might be associated with exposure to certain types of medication. Further, real-world data provide longitudinal patient information collected during routine clinical care that is useful and necessary for conduct of epidemiological studies, such as comparative treatment effectiveness research, that are otherwise not possible with SRS data. It is noteworthy that real-world data has its own limitations and biases and that would need to be addressed when conducting studies of this nature.

Key Points

- Observational healthcare databases with longitudinal data on patient medical conditions and treatment information can be used in the surveillance and signal detection of unexpected and serious adverse events.

- Use of multiple signaling algorithms to signal disproportionately reported counts of drug-adverse event pairs might provide more accurate information and minimize the number of false positives for signaling unexpected and serious adverse events than can be predicted using a single signaling method.

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APPENDIX

DISPROPORTIONALITY ASSOCIATION SIGNALING METHODS

A brief discussion of some of the common disproportionality association and statistical safety data mining methods is presented. In the reference section, we also list some useful articles and textbooks where readers can get more information about each method.

One way to characterize and summarize an association between a drug and an event (for example, adverse event or health outcome of interest) is to use a 2x2 frequency table as shown in figure A. The table usually displays the counts of the cross-classification of the two variables and uses an association metric or measure such as risk ratio or rate ratio to quantify the relative importance and significance of the association between the two variables. Data used to derive these measures can originate from spontaneous adverse event reports such as those collected by the United States Food and Drug Administration (FDA), or from longitudinal heath records or administrative claims databases. Statistical techniques or algorithms used to derive such association metrics (often called disproportionality analysis methods when applied to spontaneous reports data) can be as simple as proportional reporting ratio (PRR), or reporting odds ratio (ROR), and some embedded in Bayesian logic such as the Bayesian Confidence Propagation Neural Network (BCPNN) or the Multi-Gamma Poisson Shrinker. In its simplest form, the analysis metric that connects all the three disproportionality methods is the ratio of the observed count of reports to the expected count of reports for the drug-event pair given the assumption of statistical independence in the reporting of the drug and reporting of the event in question. The score serves as a statistical measure of deviation and the extent that the number of reports associated with a drug-event combination is reported to the SRS database more often than expected relative to the rest of the reports in the database. Each of the three statistical algorithms attempts to quantify the disproportionality between the observed and expected values for the drug-event combination to a chosen threshold. The representation of the association between the drug and event and the definition for each method metric are provided in the following table. (See Table)

Table A: The 2x2 drug-event association tabular representation for signal detection analysis

Measure	Definition/Formula
Drug-Event Pair Association Representation	**Score = Observed(O)/Expected(E)**
Proportional Reporting Ratio (PRR)	Score metric/threshold = (PRR – 1.96SE) > 1, where **PRR = $(n_{11}/n_{1.}) / (n_{01} / n_{0.})$** **SE(ln PRR) = $\sqrt{(1/n_{11} - 1/n_{1.} + 1/n_{01} - 1/n_{0.})}$**
Reporting Odds Ratio (ROR)	Score metric/threshold = (ROR – 1.96SE) > 1, where **ROR = $(n_{11}*n_{00}) / (n_{10}*n_{01})$** **SE(ln ROR) = $\sqrt{(1/n_{11} + 1/n_{10} + 1/n_{01} + 1/n_{00})}$**
Bayesian Confidence Propagation Neural Network (BCPNN/IC)	Measures strength of dependency between a product and a specific AE term. Score metric/threshold (IC): E(IC) -2√V(IC) > 0 **$E(IC_{ij}) = \log_2\{ [(c_{ij}+\gamma_{ij})(C+\alpha)(C+\beta)] / [(C+\gamma)(c_i+\alpha_i)(c_j+\beta_j)] \}$ and** **$V(IC_{ij}) = 1/(\log_2)^2 \{ [(C - c_{ij} + \gamma - \gamma_{ij})/((c_{ij} + \gamma_{ij})(1+C+\gamma))] +$** **$[(C- c_i + \alpha - \alpha_i)/((c_i + \alpha_i)(1+C+\alpha))] + [(C - c_j + \beta - \beta_j)/((c_j +\beta_j)(1+C+\beta))]$** **}, where** **$\gamma = \gamma_{ij}\{ [(C+\alpha)(C+\beta)] / [(c_i+\alpha_i)(c_j+\beta_j)] \}$ and** **$\gamma_{ij}=1$, $\alpha_i=1$, $\alpha=2$, $\beta_j=1$, $\beta=2$; $C= n_{..}$, $c_{ij}= n_{11}$, $c_i= n_{1.}$, $c_j= n_{.1}$**

Multi Gamma Poisson Shrinkage /Empirical Bayes (MGPS/EB05)	Derived from the expectation value of the logarithm of relative ratios (RR=N/E) under the posterior probability distributions of each true RR. Score metric (EBGM): $EB_{05} > 2$ $\mathbf{EBGM_{ij} = 2^{EBlog2ij}}$ $\mathbf{EB_{05} \approx EBGM_{ij} * \exp\{-1.645/\sqrt{(c_{ij} + 1)}\}}$ **and** $\mathbf{EB_{95} \approx EBGM_{ij} * \exp\{1.645/\sqrt{(c_{ij} + 1)}\}}$ **where** $\mathbf{c_{ij} = n_{11}}$

For the supervised signal detection analysis, the unadjusted method used the Mantel-Haenszel rate ratio statistic from the STDRATE procedure, and the unadjusted average treatment effect (ATE) estimate from the intercept-only treatment and outcome model using the CAUSALTRT procedure. The latter method is the same as computing the Mantel-Haenszel risk difference statistic for two-sample populations. The supervised adjusted method approach used the doubly robust estimation method to obtain ATE which in this case measures the estimated potential outcome means difference of the event occurrence between the drug of interest relative to the other drugs in the database. The method fits models for both the outcome event and the treatment drug groups being compared. They combine inverse probability weighting and regression adjustment to estimate the potential outcome means. The methods are said to be doubly robust because they provide unbiased estimates for μ even if one of the models is mis-specified (Bang and Robins 2005). The CAUSALTRT procedure implements two doubly robust estimation methods: the augmented inverse probability weighting (AIPW) method described in Lunceford and Davidian (2004) and the inverse probability weighted regression adjustment (IPWREG) method described in Wooldridge (2010). For more detailed information about this procedure, see *SAS/STAT® 14.3 User's Guide: The CAUSALTRT Procedure* and *The STDRATE Procedure*