



# **Evaluation of Diabetes Treatment Patterns and Adverse Events in a Usual Care Setting**

# Evaluation of diabetes treatment patterns and adverse events in a usual care setting

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## BACKGROUND

- Approximately 20.8 million people in the U.S. have diabetes mellitus (DM) (Type 1 and 2) with type 2 DM accounting for 90%-95% of all DM cases in the U.S.<sup>1</sup>
- The annual cost of DM in the U. S healthcare system is estimated to be \$132 billion, of which 70% is directly related to medical care; \$23 billion is related to DM specific care, \$25 billion related to DM related complications, and \$44 billion to excess prevalence of general medical conditions.<sup>2</sup>
- Among those with type 2 DM: 65% of the deaths are attributed to coronary artery disease and stroke, and DM is the leading cause of blindness, renal failure and non-traumatic lower-limb amputations in the U.S.<sup>1</sup>
- Complications of DM can be reduced with aggressive disease control that maintains glycosylated hemoglobin (A1C) levels below 7.0%.<sup>3</sup>
- Pharmacotherapy is recommended if diet and exercise fail to achieve and maintain glycemic control.
- 70% of type 2 DM patients are treated with oral antidiabetics (OADs) including sulfonylureas, biguanides, thiazolidinediones, and combinations (fixed or free).<sup>4</sup>
- More than one third of new type 2 DM patients change OAD medication within the first year due to therapy failure and side effects.<sup>4</sup>
- Thus, it is important to understand the efficacy, safety and cost effectiveness of OADs in the initial treatment of type 2 DM.

## OBJECTIVE

The primary objective of this study is to evaluate the relationship between effectiveness and occurrence of adverse events (AEs) in leading OAD therapeutic classes.

## METHODS

- Study Design**
  - A retrospective cohort analysis based on an electronic medical record (EMR) database.
- Data Source**
  - GE Centricity database contains de-identified, Health Insurance Portability and Accountability Act compliant data on 3.5 million lives from 1995 until 2005.
  - Contains ambulatory electronic longitudinal patient data: demographic information, vital signs, laboratory orders and results, medication list entries/prescriptions, and diagnoses or problems.
  - Includes EMRs maintained by over 20,000 clinicians: solo practitioners, community clinics, academic medical centers, and large integrated delivery networks.
- Study Population**

Inclusion criteria:

  - Age 18 years of age or older.
  - Type 2 diabetes as defined by diagnosis, laboratory value or drug treatment:
    - A diagnosis code for type 2 diabetes (250.XX, last digit ending in 0 or 2).
    - A prescription order for an OAD, as listed in Table 2.
    - At least one value for fasting blood glucose (FBG) that is  $\geq 125$  mg/dl.
  - Prescription order for a sulfonylurea (SU), metformin (MET), thiazolidinedione (TZD), or fixed-dose combination of drugs from these classes. (Indicated by \* in Table 2).
    - The first observation date of the study medication defines the index date.
  - Continuously followed within the study time frame (395 days before and after the index date). The use of 395 day windows allows for an annual medication re-order lag of one month.
  - No anti-diabetic prescription in the 395 days prior to the index date.
  - Having at least 2 A1C tests  $\geq 90$  days apart and within the study time frame.
    - The first A1C must be no more than 90 days prior and no more than 7 days post index date.
    - The second A1C must be between 90 and 395 days post index date.

## METHODS

Table 2. Oral pharmacotherapy, by drug and class, for the treatment of type 2 diabetes.

SU	MET or SU+MET or TZD+MET	TZD	AGI	MEGL	INCR	
Acetohexamide*	Glyburide*	Metformin HCL* (MET)	Rosiglitazone maleate*	Acarbose	Nateglimide	Exenatide**†
Chlorpropamide*	Glyburide micronized*	Glipizide-metformin* (SU+MET)	Pioglitazone HCL*	Miglitol	Repaglimide	
Glimepiride*	Tolazamide	Glyburide-metformin* (SU+MET)				
Glipizide*	Tolbutamide	Rosiglitazone metformin* (TZD+MET)				

\*Pharmacotherapy for study inclusion; †No Exenatide patients met inclusion criteria  
SU-Sulfonylureas; MET-Metformin; TZD-thiazolidinediones; AGI-Alpha glucosidase inhibitors; MEGL- Meglitinides; INCR-Incretins

### Stratification

- Study subjects were stratified at the index date according to therapy\*:
- Monotherapy** (initial  $\geq 90$  days): SU, MET or TZD
  - Dual therapy** (initial  $\geq 90$  days): SU+MET, SU+TZD or MET+TZD
  - Triple therapy** (initial  $\geq 90$  days): SU+MET+TZD \*(with or without insulin)

### Adverse Events (AEs)

- Identified AEs over one year post index date using combinations of: ICD-9 codes, specific terms in medical complaints, and specific laboratory values.
- AE categories: hypoglycemia, weight gain, dizziness, headache, nervousness, diarrhea, nausea/vomiting, dyspepsia, abdominal pain, lactic acidosis, heart failure, edema, and elevated liver functioning tests.
- Measured change in A1C from index date to 90+days post index date as a measure of treatment efficacy.

### Pre-Therapy Event

- Events that were similar to drug related AEs occurring 395 days prior to the index date were measured to control for pre-existing conditions that resemble AEs.

### Analysis

- Pearson's Chi-square test was used to identify differences in AEs by drug class.
- Differences in A1C levels by drug class and occurrence of AEs were evaluated using student's t-test.
- All study analyses were performed using Stata 9.0 at significance level  $p < 0.05$ .

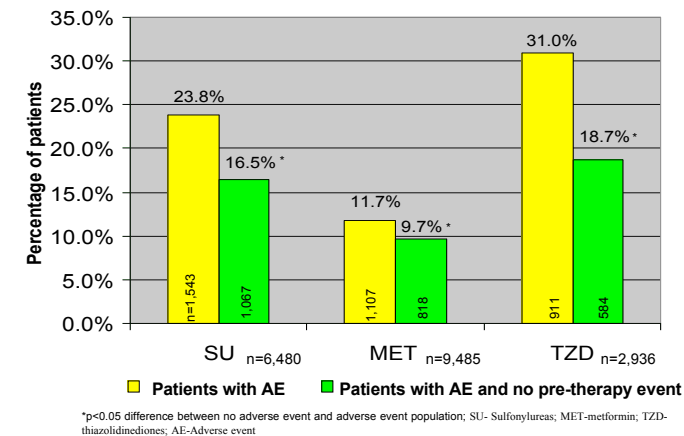
## RESULTS

### Study population

- A total of 16,635 OAD naive DM patients with SU, MET and TZD therapy were identified from the GE centricity database, of these:
  - The average age was 65.2 years (SD=17.5)
  - 87.2% (14,512) subjects were on monotherapy.
  - 46.6% (7,911) are male.
  - 9.3% (1,551) were prescribed insulin in addition to study OAD.
  - 86.6% (14,238) had a BMI reading and of those 54.5%(7072) were obese (Body mass index  $\geq 30$ kg/m<sup>2</sup>).
- Of those having an AE, weight gain was the most frequently identified in the SU (79.9%) and TZD (79.9%) groups whereas abdominal pain/dyspepsia was the most dominant AE for MET(81.4%).

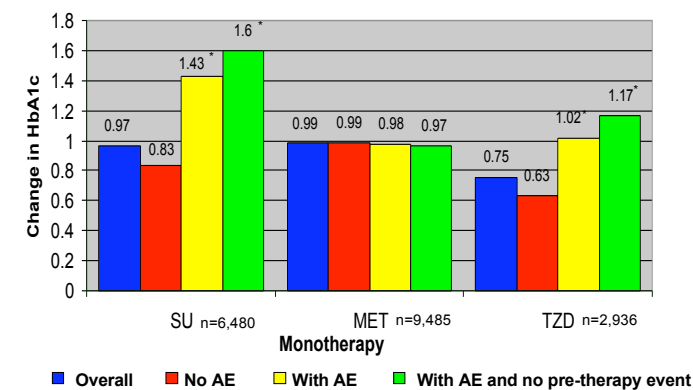
## RESULTS

Figure 1. Adverse event variations within therapeutic class (% of class).



\*p<0.05 difference between no adverse event and adverse event population; SU- Sulfonylureas; MET-metformin; TZD-thiazolidinediones; AE-Adverse event

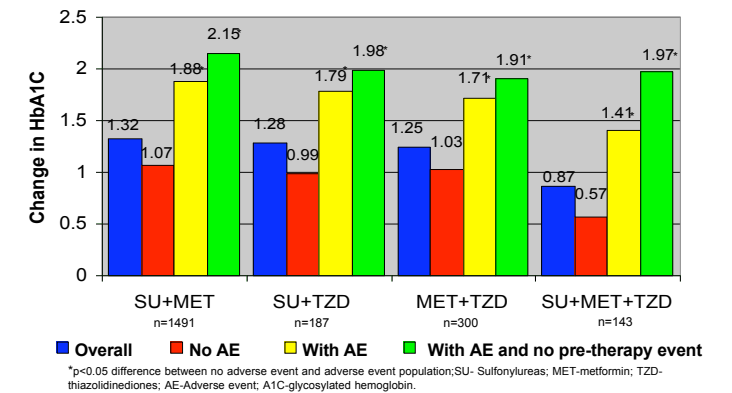
Figure 2. Reduction in A1C from baseline for subjects on monotherapy.



\*p<0.05 difference between no adverse event and adverse event population;SU- Sulfonylureas; MET-metformin; TZD-thiazolidinediones; AE-Adverse event; A1C-glycosylated hemoglobin

## RESULTS

Figure 3. Reduction in A1C from baseline for subjects on combination therapy.



\*p<0.05 difference between no adverse event and adverse event population;SU- Sulfonylureas; MET-metformin; TZD-thiazolidinediones; AE-Adverse event; A1C-glycosylated hemoglobin.

## LIMITATIONS

- EMR data indicates that a patient has been prescribed a medication but it is not possible from the data to determine whether the prescription was filled or medications consumed.
- Many of the AEs are relatively common medical occurrences, and it was generally not possible to tell from the EMR whether the AE was directly attributable to the drug therapy. However, stratifying AE by the existence of similar events prior to index date should help control for pre-existent conditions that present in a manner similar to an AE of the prescribed OAD.
- Future analysis will incorporate additional clinical data and regression analysis to more robustly control for AE confounders.

## CONCLUSIONS

- AEs associated with SU, MET, and TZD were relatively common, and similar to rates observed in clinical trials, though rates varied significantly by therapeutic class.
- Improvement in A1C by class overall also varied, with treatments associated with lower AEs trending towards greater improvements in A1C.
- A trend within treatment class was observed, patients with adverse events tended to have greater reduction in A1C. Future research will assess if there is an association between AE and change in A1C or if other factors such as dosing may be driving this trend
- Additional research will assess if changes in treatment patterns associated with AEs help explain these observed therapeutic outcomes for OAD naive patients.

## References

- Centers for Disease Control. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005. <http://www.cdc.gov/diabetes/pubs/pdf/nf05.pdf>. Accessed 14 Feb. 2006.
- American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2002. Diabetes Care. March 1, 2003 26(3):917-932.
- American Diabetes Association. Standards of care for patients with diabetes mellitus (Position Statement). Diabetes Care 24 (Suppl 1): S33-S43, 2001. You may want to look at the latest one that was published in January 2005; also there is a new one that will be out on January 1, 2006.
- Bocuzzi S, Wogen J, Fox J, Sung J, Shah A, Kim J. Utilization of oral hypoglycemic agents in a drug-insured US population. Diabetes Care. 2001;24(8):1411-1415.

## Disclosure

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:  
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