# MeRIT Project: Sulfonylureas and the risk of sudden death and ventricular arrhythmia – interim results

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## Background

- Persons with diabetes mellitus (DM) are at increased risk for sudden death, a significant public health problem
- Coronary heart disease, common in persons with DM, and DM itself are major risk factors for sudden death
- Sulfonylureas are a commonly-used therapy in type 2 DM
- Sulfonylureas differ in extrapancreatic effects on cardiac ion channels and in hypoglycemia risk, both of which may influence sudden death risk
- It is unknown whether extrapancreatic effects are proarrhythmogenic (e.g., via electrocardiographic QT interval prolongation, attenuated ischemic preconditioning) or antiarrhythmic (e.g., via prevented shortening of action potential duration)
- Data on sudden death will not be forthcoming from ongoing sulfonylurea trials

## Objective

- To examine the associations between glyburide and glimepiride, each vs. glipizide, and the risk of a composite outcome of outpatient-originating sudden death and ventricular arrhythmia (SD/VA)

## Methods

### Study Design

- High dimensional propensity score-adjusted retrospective cohort study

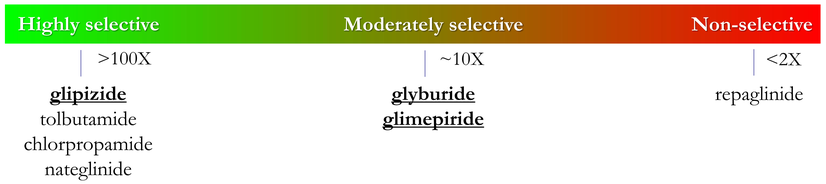
### Data Source / Population

- 1999–2010 Medicaid data from CA, FL, NY, OH, and PA—supplemented with Medicare claims for dual-eligible beneficiaries
- Persons 30–75 years of age that newly-initiate a sulfonylurea

### Exposure Ascertainment

- New use of glyburide, glimepiride, or glipizide, evidenced by prescription dispensings and duration assessed by days supply on claim
- Glipizide = active comparator reference exposure, given its very limited extrapancreatic effects

**Selectivity of insulin secretagogues for pancreatic (vs. cardiac) $K^+$ channels[1]**




### Outcome Ascertainment

- Primary: outpatient-originating SD/VA leading to hospital presentation
- Secondary: as above, but resulting in death on day of or day after presentation
- First-listed emergency department or principal inpatient ICD-9-CM discharge diagnosis indicative of SD/VA
  - PPV = 85% (95% confidence interval: 78%–91%)[2]

### Confounder Adjustment

- Pre-defined: demographics, dual-eligibility status, nursing home residence status, measures of healthcare utilization intensity, prior hypoglycemia
- Empiric: baseline covariates identified via high-dimensional approach → ranks and selects potential confounders (or proxies thereof) based on empirical associations with exposure and outcome

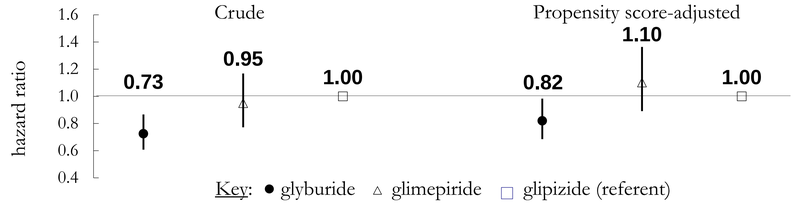
### Statistical Analysis

- Propensity score (PS) generation → multinomial logistic regression
- Outcome model adjusting for PS → Cox proportional-hazards regression

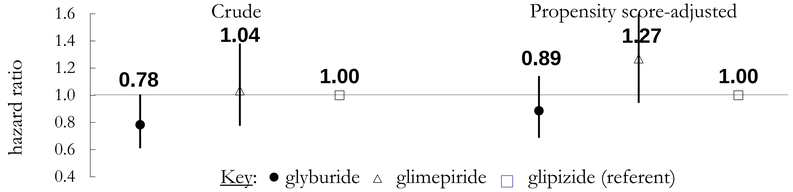
## Results

- 519,272 sulfonylurea users contributing 176,998 person-years (p-y) of exposure
- Mean age = 57.0 years, 60.3% female, 34.9% Caucasian
- N = 632 and N = 319 SD/VA and fatal SD/VA events, respectively
- Crude incidence rates: 3.6 and 1.8 per 1,000p-y, respectively

**Hazard ratios for association between sulfonylurea and SD/VA**




**Hazard ratios for association between sulfonylurea and fatal SD/VA**




## Conclusions

- These preliminary findings suggest that glyburide may be associated with a lower risk of SD/VA vs. glipizide, consistent with small clinical studies
- Forthcoming secondary analyses will examine sulfonylurea dose-response relationships and effect modification by pharmacokinetically- and pharmacodynamically-interacting drugs

1. *Pharmacol Ther* 2006;112(1):12-37
2. *Pharmacoepidemiol Drug Saf* 2010;19(6):555-562