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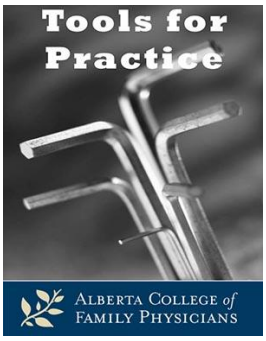


# Sulfonylureas in Diabetes: Sweet on the Heart or Surrogate Charlatan?

## Clinical Question: Does treating type 2 diabetes with sulfonylureas affect mortality or cardiovascular events?

## Bottom Line: There is a lack of convincing evidence that sulfonylureas reduce cardiovascular events or mortality in type 2 diabetic patients. If anything, sulfonylureas potentially increase cardiovascular harm.

**Evidence:**

Sulfonylurea versus placebo:

- Most Randomized Controlled Trials (RCTs) investigate HbA1c, not patient-oriented outcomes.[1-5]
- Largest RCT for patient outcomes (n=409), ~5 years, tolbutamide versus placebo:[6,7]
  - Non-significant: All-cause mortality (14.7% versus 10.2%), myocardial infarction (13.7% versus 10.7%).
  - Significant increase: Cardiovascular (CV) mortality (12.7% versus 4.9%), Number Needed to Harm (NNH)=13.
  - Limitations: Possible randomization imbalance, smoking not included in baseline demographics, first generation sulfonylurea.

Sulfonylurea versus metformin:

- RCT (n=304) five years, patients with coronary artery disease, mean HbA1c 7.6%, glipizide versus metformin:[8]
  - Sulfonylureas increased composite CV events: 35% versus 25%, NNH=10.
- RCT (n=2,895), four years, mean HbA1c 7.4%, glyburide versus metformin:[9]
  - Non-significant: All-cause mortality (2.2% versus 2.1%), total CV events (2.9% versus 4.0%).
  - Limitations**:** ~40% withdrew after randomization.
- Systematic review: No other RCTs with more than one death.[10]

Sulfonylurea added to metformin:

- RCT (n=3028), ~5 years, sulfonylurea versus pioglitazone:
  - No difference in CV events.[11]
- Other studies reported CV events or mortality as adverse events:
  - Sulfonylurea versus DPP-4 inhibitors:
    - No difference in death:[12] 0.5% versus 0.4%.

        - Major CV events:[13] 3.4% versus 1.5%, NNH=53.
    - Versus other drugs:
        - Studies underpowered to find a difference in patient outcomes compared to GLP-1 agonists, SGLT2 inhibitors, or insulin.[14,15,16]

**Context:**

- Two systematic reviews of observational studies report increased CV risk with sulfonylureas, however multiple confounders limit conclusions.[17,18]
- UKPDS is frequently cited to support sulfonylureas, but confounded by use of insulin.[19]
- CV disease causes ~50% of diabetes type 2 deaths.[20]
- Sulfonylureas increase risk of severe hypoglycemia (<1% overall) and weight gain (~2.1kg).[21]
- We need to think critically about the use of sulfonylureas beyond HbA1C reduction (~0.8%) and low cost.[21]

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