

Sulfonylurea treatment in type 2 diabetes

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Clinical question

Does treating type 2 diabetes with sulfonylureas affect mortality or cardiovascular (CV) events?

Bottom line

There is a lack of evidence that sulfonylureas reduce CV events or mortality in patients with type 2 diabetes. If anything, sulfonylureas potentially increase CV harm.

Evidence

- Most RCTs of sulfonylureas versus placebo studied hemoglobin A_{1c} (HbA_{1c}) level, not patient outcomes.¹⁻³
- The largest RCT for outcomes (N=409) lasted about 5 years and compared tolbutamide with placebo^{4,5}:
 - Both all-cause mortality (14.7% vs 10.2%) and myocardial infarction (13.7% vs 10.7%) were non-significant.
 - There was a statistically significant increase in CV mortality (12.7% vs 4.9%; number needed to harm [NNH]=13).
 - Limitations were possible randomization imbalance, smoking not included in baseline characteristics, and use of a first-generation sulfonylurea.
- An RCT (N=304) over 5 years examined patients with coronary artery disease with a mean HbA_{1c} level of 7.6% and compared glipizide with metformin.⁶ Glipizide increased composite CV events (35% vs 25%, NNH=10).
- An RCT (N=2895) over 4 years (mean HbA_{1c} level of 7.4%) compared glyburide with metformin.⁷ Differences in all-cause mortality (2.2% vs 2.1%) and total CV events (2.9% vs 4.0%) were non-significant. However, about 40% withdrew after randomization.
- An RCT (N=3028) of about 5 years compared sulfonylureas with pioglitazone and found no difference in CV events when these were added to metformin.⁸
- A study of sulfonylureas versus dipeptidyl peptidase 4 inhibitors, both added to metformin, reported CV events as adverse events (3.4% vs 1.5%, NNH=53).⁹
- Studies comparing sulfonylureas with other agents were underpowered to find a difference in outcomes.¹⁰

Context

- A systematic review of observational studies reported increased CV risk with sulfonylureas; however, multiple confounders limited the conclusion.¹¹
- The UK Prospective Diabetes Study is often cited to support sulfonylureas, but it is confounded by insulin use.¹²
- Sulfonylureas increase the risk of hypoglycemia and

weight gain.¹³ Hypoglycemic risk increases with renal impairment and increasing doses.¹³

Implementation

The primary cause of death in patients with diabetes is CV disease.¹⁴ Sulfonylureas have been recommended as second-line treatment after metformin owing to evidence for improved glycemic control and low cost. Newer agents have shown evidence of CV benefit in patients with diabetes (most with CV disease), but are much more expensive and long-term effects are uncertain.^{15,16}

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Competing interests
None declared

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