

Does metformin prevent cardiovascular events?

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Metformin, when allocated to overweight UKPDS patients with newly-diagnosed type 2 diabetes randomised to an intensive glucose control policy, compared with a conventional diet-based glucose control policy, reduced risk of diabetes-related death by 42% (0.58, 0.37–0.91, $p=0.017$), myocardial infarction by 39% (0.61, 0.41–0.89, $p=0.010$) and all-cause mortality by 36% (0.64, 0.45–0.91, $p=0.001$). These reductions were greater than non-significant reductions of 10%, 16% and 6% respectively seen with a sulphonylurea or insulin-based intensive policy, despite metformin achieving a smaller HbA1c difference of 0.6% compared with 0.9%. Patients allocated to metformin showed a greater effect than those allocated sulphonylurea or insulin for all-cause mortality ($p=0.021$) and stroke ($p=0.032$). These results, obtained with no weight gain and minimally increased risk of hypoglycaemia, suggest metformin's beneficial effects may not relate directly to improved glycaemia.

At least two retrospective cohort analyses of sulphonylurea and metformin therapies support the UKPDS findings. In the 8-year DARTS study of 5,730 patients there was a 30% lower risk for all-cause mortality in the metformin group, after adjustment for baseline confounders, and 41% lower risk for cardiovascular mortality. In the 5-year Saskatchewan Health databases study of 12,272 new users of oral antidiabetic agents, the adjusted odds ratio (OR) for all-cause mortality for metformin monotherapy was 0.60 (95% CI 0.49–0.74) compared with sulphonylurea monotherapy and 0.64 (0.49–0.84) for cardiovascular deaths. Sulphonylurea plus metformin combination therapy was associated also with reduced all-cause mortality (OR 0.66, 0.58–0.75) and cardiovascular deaths (OR 0.64, 0.54–0.77).