Metformin reduced diabetes-related end points and all-cause mortality in overweight patients with type 2 diabetes

UK Prospective Diabetes Study Group. **Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34).** Lancet. 1998 Sep 12;352:854-65.

Question

In overweight patients with type 2 diabetes mellitus, what is the effect of intensive plasma glucose control with metformin on the risk for macrovascular and microvascular complications?

Design

Randomized controlled trial with median follow-up of 10.7 years.

Setting

15 U.K. hospital-based diabetes clinics.

Patients

1704 patients (mean age 53 y, 54% women) who had body weight ≥ 120% of ideal, newly diagnosed type 2 diabetes, and fasting plasma glucose (FPG) levels between 6.1 mmol/L and 15.0 mmol/L after 3 months of dietary therapy. Follow-up was 97%.

Intervention

Patients were allocated to dietary advice and intensive blood glucose control with metformin (n = 342), 1700 to 2550 mg/d; chlorpropamide (n = 265); glibenclamide (n = 277); or insulin (n = 409) aiming for FPG levels of < 6 mmol/L or to conventional dietary treatment (n = 411) aiming for normal body weight and FPG levels < 15 mmol/L.

Main outcome measures

A first diabetes-related predefined end point, deaths from diabetes, all-cause mortality, myocardial infarction (MI), stroke, peripheral vascular disease, and microvascular disease.

Main results

Analysis was by intention to treat. Median hemoglobin A_{1c} values for 10 years of follow-up were 7.4% for patients receiving metformin and 8.0% for patients receiving conventional treatment. Compared with conventional treatment, metformin reduced diabetes-related end points (P = 0.002), diabetes-related deaths (P = 0.017), all-cause mortality (P = 0.011), and MI (P = 0.01) (Table). Patients receiving metformin had fewer diabetes-related end points (P = 0.003), less all-cause mortality (P = 0.021) (Table) or stroke (3.5% vs 6.3%, Kaplan-Meier P = 0.032), and fewer hypoglycemic episodes than those receiving other intensive treatments.

Conclusion

In overweight patients with type 2 diabetes mellitus, early use of metformin reduced the risk for diabetes-related end points and all-cause mortality.

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Metformin vs conventional or other intensive treatments in overweight patients with type 2 diabetes mellitus over 10 years of follow-up*

Outcomes	Metformin	Conventional	RRR (95% CI)	NNT (CI)
Diabetes end points	29%	39%	26% (10 to 40)	10 (6 to 29)
Deaths from diabetes	8%	13%	39% (6 to 60)	19 (10 to 138)
All-cause mortality	15%	22%	32% (8 to 51)	14 (8 to 67)
Myocardial infarction	11%	18%	36% (8 to 55)	16 (9 to 78)
		Intensive		
Diabetes end points	29%	37%	22% (7 to 36)	12 (7 to 43)
All-cause mortality	15%	20%	27% (3 to 45)	19 (10 to 172)

*Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

Commentary (continued from page 10)

In light of these results, what can we conclude? First, clear and consistent evidence now exists that hyperglycemia in diabetes is a continuous, modifiable risk factor for clinically important outcomes and that reduction in glucose is the key to improving outcomes. Interventions that maintain optimal glucose levels for long periods are likely to result in even larger clinical benefits. Second, intensive therapy with sulfonylureas and insulin, but not metformin, modestly increases the risk for severe hypoglycemia and weight gain, but these adverse effects are offset by the clinical benefits. The higher rate of these adverse effects with insulin suggests that oral agents should be the initial therapeutic choice. Third, these data support the choice of metformin as a first-line agent for obese patients, unless contraindicated. Fourth, type 2 diabetes is clearly a progressive disease. Increased effort and several types of therapies need to be applied over time for adequate glycemic control. Finally, the UKPDS provides no support for the belief that exogenous insulin causes cardiovascular disease; indeed, there was a strong trend in the opposite direction.

We now have convincing evidence that glucose control is an important goal for type 2 diabetes. Unless patients are seriously ill or have a short life expectancy, the long-term benefits of intensive therapy clearly outweigh the few risks. Merely eliminating symptoms of hyperglycemia is unsatisfactory. Our task is to convince patients of the value of this approach and to work with the health care team to teach patients how to improve glycemia and reduce their risk for the many complications of diabetes.

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Reference

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