Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34).

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BACKGROUND: In patients with type 2 diabetes, intensive blood-glucose control with insulin or sulphonylurea therapy decreases progression of microvascular disease and may also reduce the risk of heart attacks. This study investigated whether intensive glucose control with metformin has any specific advantage or disadvantage. METHODS: Of 4075 patients recruited to UKPDS in 15 centres, 1704 overweight (>120% ideal bodyweight) patients with newly diagnosed type 2 diabetes, mean age 53 years, had raised fasting plasma glucose (FPG; 6.1-15.0 mmol/L) without hyperglycaemic symptoms after 3 months' initial diet. 753 were included in a randomised controlled trial, median duration 10.7 years, of conventional policy, primarily with diet alone (n=411) versus intensive blood-glucose control policy with metformin, aiming for FPG below 6 mmol/L (n=342). A secondary analysis compared the 342 patients allocated metformin with 951 overweight patients allocated intensive blood-glucose control with chlorpropamide (n=265), glibenclamide (n=277), or insulin (n=409). The primary outcome measures were aggregates of any diabetes-related clinical endpoint, diabetes-related death, and all-cause mortality. In a supplementary randomised controlled trial, 537 non-overweight and overweight patients, mean age 59 years, who were already on maximum sulphonylurea therapy but had raised FPG (6.1-15.0 mmol/L) were allocated continuing sulphonylurea therapy alone (n=269) or addition of metformin (n=268). FINDINGS: Median glycated haemoglobin (HbA1c) was 7.4% in the metformin group compared with 8.0% in the conventional group. Patients allocated metformin, compared with the conventional group, had risk reductions of 32% (95% CI 13-47, p=0.002) for any diabetes-related endpoint, 42% for diabetes-related death (9-63, p=0.017), and 36% for all-cause mortality (9-55, p=0.011). Among patients allocated intensive blood-glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021), and stroke (p=0.032). Early addition of metformin in

sulphonylurea-treated patients was associated with an increased risk of diabetes-related death (96% increased risk [95% CI 2-275], p=0.039) compared with continued sulphonylurea alone. A combined analysis of the main and supplementary studies showed fewer metformin-allocated patients having diabetes-related endpoints (risk reduction 19% [2-33], p=0.033). Epidemiological assessment of the possible association of death from diabetes-related causes with the concurrent therapy of diabetes in 4416 patients did not show an increased risk in diabetes-related death in patients treated with a combination of sulphonylurea and metformin (risk reduction 5% [-33 to 32], p=0.78).

INTERPRETATION: Since intensive glucose control with metformin appears to decrease the risk of diabetes-related endpoints in overweight diabetic patients, and is associated with less weight gain and fewer hypoglycaemic attacks than are insulin and sulphonylureas, it may be the first-line pharmacological therapy of choice in these patients.