Recent intervention trials have demonstrated the beneficial effects of intensive glycaemic control associated with a multifactorial approach to long-term diabetes complications. In type 2 diabetes (T2DM), the UKPDS first demonstrated the preventive effect of improving both glycaemic and blood pressure control in patients with recent onset diabetes. The same was true for patients at a more advanced stage of the condition in the intensive arm of ADVANCE. Finally, the Steno 2 study provided evidence of the beneficial effect of multifactorial approach in T2DM. These results led to changes in the management of T2DM patients, along with the publication of recommendations worldwide.

What are the effects of the implementation of lessons drawn from intervention trials? Some answers are provided by the recently published results of a collaborative study performed by the Centers for Disease Control and Prevention and the Emory University of Atlanta. The aim was to examine the progression of the incidence of diabetes-related complications in the USA over the last two decades (1990 to 2010). During this period, the US population size increased from 177.7 to 226.1 million people, while the number of patients with diagnosed diabetes increased from 6.5 to 20.7 million. No distinction was available for T1DM and T2DM, but most patients had T2DM. Incidence rates of lower-limb amputations, end-stage renal disease defined by dialysis or kidney transplantation (ESRD), acute myocardial infarction, stroke, and death from hyperglycaemic crisis were obtained from four US surveys and population registries and data between 1990 and 2010 were compared.

The rate of all complications declined during the two-decade period. The most important decline was observed for myocardial infarction, with a 67.8 % relative risk reduction, and an absolute reduction in number of cases of 95.6/10,000. Relative risk of death from hyperglycaemic crisis (ketoacidosis and hyperosmolar hyperglycaemia) decreased by 64.4 %, but absolute reduction in number of cases was low (2.7/10,000 fewer incident cases). Stroke and amputation rates were both reduced by half, with a 52.7 %, and a 51.4 % relative risk reduction, respectively. Compared with other complications, the 28.3 %relative risk reduction of end-stage renal disease (ESRD) was smaller. When ESRD incidence was examined in the population with diabetes according to age, reduction in relative risk was observed only in age-groups less than 64 years, while relative risk increased in older patients. This increase was 10.4 in patients in the 65 to 74 year age group, and 75.2 in patients older than 75 years, highlighting the need for a particular effort in preventing ESRD in patients with T2DM.

With the ADVANCE strategy of intensive glycaemic control (HbA1c 6.5 %) based on gliclazide MR compared with a conventional arm (HbA1c 7.3 %) as a control group, a significant reduction in the incidence or progression of renal complications was observed after a median 5-year follow-up. Moreover, the risk of ESRD was reduced by 65 % in the intensive glucose control group (P=0.02). This explains in part the 12 % decrease in the CV death rate obtained in this group.

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OBJECTIVE

While metformin is generally accepted as the first-line agent in treatment of type 2 diabetes, there is insufficient evidence and extensive debate about the best second-line agent.

We aimed to assess the benefits and harms of four commonly used antihyperglycaemic treatment regimens considering clinical effectiveness, quality of life, and cost.

RESEARCH DESIGN AND METHODS

We developed and validated a new population-based glycaemic control Markov model that simulates natural variation in HbA1c progression. The model was calibrated using a U.S. data set of privately insured individuals diagnosed with type 2 diabetes.

We compared treatment intensification of metformin monotherapy with sulfonylurea, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist, or insulin.

Outcome measures included life-years (LYs), quality-adjusted life-years (QALYs), mean time to insulin dependence, and expected medication cost per QALY from diagnosis to first diabetes complication (ischaemic heart disease, myocardial infarction, congestive heart failure, stroke, blindness, renal failure, amputation) or death.

RESULTS

According to our model, all regimens resulted in similar LYs and QALYs regardless of glycaemic control goal, but the regimen with sulfonylurea incurred significantly lower cost per QALY and resulted in the longest time to insulin dependence.

An HbA1c goal of 7% (53 mmol/mol) produced higher QALYs compared with a goal of 8% (64 mmol/mol) for all regimens.

CONCLUSIONS

Use of sulfonylurea as second-line therapy for type 2 diabetes generated glycaemic control and QALYs comparable with those associated with other agents but at lower cost.

A model that incorporates HbA1c and diabetes complications can serve as a useful clinical decision tool for selection of treatment options.

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BACKGROUND
In short-term randomized trials (duration, 1 to 2 years), bariatric surgery has been associated with improvement in type 2 diabetes mellitus.

METHODS
We assessed outcomes 3 years after the randomization of 150 obese patients with uncontrolled type 2 diabetes to receive either intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The primary end point was a glycated haemoglobin level of 6.0 % or less.

RESULTS
The mean (±SD) age of the patients at baseline was 48±8 years, 68 % were women, the mean baseline glycated haemoglobin level was 9.3±1.5 %, and the mean baseline body-mass index (the weight in kilograms divided by the square of the height in meters) was 36.0±3.5 kg/m².

A total of 91 % of the patients completed 36 months of follow-up. At 3 years, the criterion for the primary end point was met by 5 % of the patients in the medical-therapy group, as compared with 38 % of those in the gastric-bypass group (P<0.001) and 24 % of those in the sleeve-gastrectomy group (P=0.01). The use of glucose-lowering medications, including insulin, was lower in the surgical groups than in the medical-therapy group.

Patients in the surgical groups had greater mean percentage reductions in weight from baseline, with reductions of 24.5±9.1 % in the gastric-bypass group and 21.1±8.9 % in the sleeve-gastrectomy group, as compared with a reduction of 4.2±8.3 % in the medical-therapy group (P<0.001 for both comparisons). Quality-of-life measures were significantly better in the two surgical groups than in the medical-therapy group.

There were no major late surgical complications.

CONCLUSIONS
Among obese patients with uncontrolled type 2 diabetes, 3 years of intensive medical therapy plus bariatric surgery resulted in glycaemic control in significantly more patients than did intensive medical therapy alone. Analyses of secondary end points, including body weight, use of glucose-lowering medications, and quality of life, also showed favourable results at 3 years in the surgical groups, as compared with the group receiving medical therapy alone.

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Schauer, PR, Bhatt, DL, Kirwan, JP, et al. for the STAMPEDE Investigators
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Measurement of glycated haemoglobin (HbA1c) plays a central role in the clinical management and treatment of type 2 diabetes (T2DM), as it represents a surrogate marker of risk of complications. While the association of HbA1c levels with microvascular complications in T2DM is not disputed, the effects of glucose lowering on coronary heart disease (CHD) and risk of other macrovascular complications among these patients is more controversial.

Different reasons may explain this. First, factors other than hyperglycaemia are involved in the pathogenesis of macrovascular complications of T2DM, including high blood pressure, dyslipidaemia, and platelet disorders. Second, the effects of glucose lowering need a longer delay to be effective on macrovascular than on microvascular complications. Third, differences in practical management between some recent intervention trials may have blurred the effects of intensive glucose control on macrovascular events and mortality, with negative results for ACCORD and VADT, and a favourable trend for ADVANCE.

However, it should not be forgotten that numerous data support the relationship between long-term glycaemic control and macroangiopathy in T2DM. These data include results of the epidemiological analysis of UKPDS and ADVANCE, results of the DECODE study, and different meta-analyses. New results still support this evidence. Recently, this question was investigated in a 6-year follow-up study, performed in 30 000 low income American patients with T2DM, either of African (n=17 510), or European ascent (n=12 592). The association between HbA1c and risk of coronary heart disease (CHD) (7258 incident coronary events during follow-up) was analyzed using Cox proportional hazards models, after multiple adjustments for all factors known to be associated with CHD in T2DM. Hazard ratios (HR) of CHD increased through increasing categories of HbA1c values at baseline, reaching statistical significance in the 7-7.9 % HbA1c category (HR 1.16; 95 % CI 1.04–1.31, and 1.15; 1.03–1.28, respectively). The same graded association of HbA1c with CHD risk was observed for the mean HbA1c during follow-up in both groups, HRs in the 7-7.9 % HbA1c category being 1.25 (CI 1.13-1.31), and 1.17 (CI 1.05-1.31) (P trend =0.002, and 0.001, respectively). Furthermore, when HbA1c was considered as a continuous variable, a linear relationship of HbA1c with CHD risk was observed. Such a linear relation had been previously observed, in UKPDS and in ADVANCE.

Finally, if a longer delay is needed for observing the protective effects of lowering glucose on macrovascular complications, as suggested by UKPDS or Steno 2 long-term results, the results of ADVANCE-On, the 10-year post-trial follow-up of ADVANCE patients are awaited in 2015.