Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Three therapeutic interventions were compared with no intervention for preventing progression to diabetes in Canadian individuals with impaired glucose tolerance (IGT). The interventions were acarbose, an intensive lifestyle modification programme, and metformin. In a secondary analysis, the authors also analysed the screening of general population for IGT.

Type of intervention
Secondary prevention and screening.

Economic study type
Cost-effectiveness analysis.

Study population
The target population for the model consisted of a hypothetical cohort of patients with IGT. For the base-case, just over half of the patients were male and the mean age was 54.5 years.

Setting
The setting was primary care. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness evidence dated from 1987 to 2002 and the resource use from 2001 to 2002. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a review of published studies and authors' assumptions.

Modelling
A Markov model was used to simulate the long-term outcomes under each treatment strategy. Each cohort was followed for 10 years in 6-month cycles, and treatment was assumed to be given for 5 years. The four main states considered were IGT, diabetes, normal glucose tolerance (NGT) and death. The authors stated that the development and progression of disease complications were also considered. These were calculated outside of the Markov model, based on risks estimated from several large epidemiological studies. In secondary analyses, the additional costs of screening the general population for IGT were also considered. A one-time prevalence screen is done at the start of the modelling period to identify those with IGT. Several assumptions were reported in the model:

- patients who transitioned to diabetes were assumed to stop the preventive intervention upon diagnosis;
- treatment of diabetes was assumed to be the same, both in terms of costs and health effects, for all patients regardless
of which preventive intervention they received while in the IGT state;
those patients who tested negative were assumed to incur no further costs relevant to the analysis; and
the development of IGT or diabetes at some later date was not considered.

**Outcomes assessed in the review**
The parameters incorporated in the model included the annual transition probabilities from IGT to diabetes, from IGT to NGT, and from NGT to IGT. Other parameters included:

- the reduction in risk for IGT to diabetes, relative to no treatment with the active treatments;
- the increase in risk for IGT to NGT for all active treatments, as well as the reduction in risk for NGT to IGT for all active treatments; and
- the increased mortality risk with IGT; and IGT prevalence.

The development and progression of disease complications were also stated.

**Study designs and other criteria for inclusion in the review**
No inclusion criteria were cited, but the study designs used to estimate intervention effects were randomised controlled trials. Large epidemiological studies were used to estimate the development and progression of disease complications. The study designs of other sources were not described.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Ten primary studies were included in the review.

**Methods of combining primary studies**
The primary studies were combined using a narrative method.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The annual transition probabilities were:

- from IGT to diabetes, 6.3%
from IGT to NGT, 16.2%; and
from NGT to IGT, 16.3%.

The reduction in risk for IGT to diabetes relative to no treatment was 24% with metformin and 36% with acarbose.

The increase in risk for IGT to NGT was 9% for all active treatments.

The reduction in risk for NGT to IGT was 7% for all active treatments.

The increased mortality risk was 45% with IGT.

IGT prevalence was 11%.

The development and progression of disease complications was taken from four large epidemiological studies, but the figures were not reported.

**Methods used to derive estimates of effectiveness**
The authors made assumptions, generally backed up by the literature, to derive some estimates of effectiveness.

**Estimates of effectiveness and key assumptions**
The reduction of transition to diabetes in the lifestyle group was conservatively assumed to be 58%.

Another assumption about the long-term horizon was that treatment would be equally effective over its entire course, but that the underlying risk of transitioning to diabetes would increase over time, reaching 20% after 10 years of follow-up.

Patients who reverted to NGT were assumed to have normal risk.

Compliance was assumed to be equal for all active treatments.

**Measure of benefits used in the economic analysis**
The measures of benefits were the life-years gained and diabetes-free time. Given the long-term horizon of the study, the benefits were appropriately discounted at an annual rate of 5%.

**Direct costs**
The authors adopted the perspective of a health care payer. The costs were broken down into the costs of screening and treatment of diabetes and diabetes-related costs. The cost items included oral glucose tolerance test, doctor visit for IGT testing, visit to dietician, exercise programme per month, and the daily costs of acarbose and metformin. The costs of treating diabetes and its complications (retinopathy, nephropathy, neuropathy, macrovascular disease, foot ulcer and hypoglycaemia) were calculated by developing treatment-related cost profiles specific to each complication, using published methodology. The items considered were acute hospitalisation, home health-care services, outpatient services, nursing home care, physician fees, laboratory tests, drugs, supplies, emergency room visits, and diagnostic and therapeutic procedures. The price year was 2000. The costs were appropriately discounted, given the long-term horizon of the study, at an annual rate of 5%. The primary Canadian sources were provincial physician fee schedules, provincial drug formularies, laboratory fee schedules, the Ontario Case Costing Project and published literature.

**Statistical analysis of costs**
The costs were treated deterministically. No statistical tests were undertaken.
Indirect Costs
No indirect costs were included.

Currency
Canadian dollars (Can$). The conversion rate was Can$1 = US dollars $0.64.

Sensitivity analysis
Extensive sensitivity analyses were reported to have been undertaken. These included, but were not limited to:

the baseline risks of transitioning to diabetes, returning to NGT, or reverting to IGT;
the risk reduction with each active intervention;
the cost of lifestyle intervention;
the prevalence of IGT;
the cost of screening;
the time horizon of the analysis;
the duration of treatment;
assumptions about the long-term risk of diabetes and impact of treatment; and
the discount rate.

In a secondary analysis, the additional costs of screening the general population for IGT were also considered. The criteria used to select the range of treatment effect included 95% confidence intervals; the criteria used to select the ranges of other parameters were not reported.

Estimated benefits used in the economic analysis
The following results were obtained for a hypothetical cohort of 1,000 individuals.

Survival was 12,756 years with no treatment, 12,897 years with metformin, 12,954 years with acarbose, and 13,067 years with lifestyle modification.

Diabetes-free time was 6,674 years with no treatment, 7,153 years with metformin, 7,369 years with acarbose, and 7,797 years with lifestyle modification.

Cost results
The following results were obtained for a hypothetical cohort of 1,000 individuals.

The total costs were Can$11,762,620 with no treatment, Can$10,763,120 with metformin, Can$10,865,204 with acarbose, and Can$11,995,898 with lifestyle modification.

Synthesis of costs and benefits
Lifestyle intervention had the strongest impact on health outcomes, but it was the only active intervention that increased costs relative to no intervention (by $233 per patient).

Acarbose and metformin reduced costs by up to almost $1,000 per patient compared with no intervention and conferred...
more benefits, being dominant relative to no treatment.

Acarbose was more costly and more beneficial than metformin, with an incremental cost per life-year gained (ICER) of Can$1,798.

Lifestyle intervention had an ICER of Can$749 versus no treatment, Can$7,252 versus metformin, and Can$9,988 versus acarbose.

In the secondary analysis, if patients were screened for IGT, acarbose and metformin remained dominant (i.e. cost less and were more effective) over no intervention, although the savings were somewhat smaller.

The results varied importantly in the sensitivity analyses. The sensitivity analyses showed the most influential parameter to be the impact of treatment on the risk of developing diabetes. For example, at the lower bound of the 95% confidence interval of acarbose effectiveness, acarbose would cease to dominate no intervention, although the ICER would be low at around Can$1,000. In contrast, at the upper bound estimate of acarbose effectiveness, acarbose would dominate metformin, and the ICER of lifestyle intervention relative to acarbose would increase to more than Can$50,000.

Using the same logic for the effectiveness of metformin and lifestyle intervention generally led to similar swings in the results. The exception was observed at the lower bound for the effectiveness of lifestyle modification where treatment remained highly cost-effective versus no treatment at an ICER of under Can$10,000. If the reduction in risk observed with metformin in all patients in the Diabetes Prevention Programme study were used instead of that for Caucasian patients, the ICER for acarbose relative to metformin would increase from Can$1,798 to Can$18,635.

Another input with a relatively strong effect was the untreated risk of transitioning to diabetes, although it did not change substantially the incremental comparisons. With a 50% reduction in lifestyle intervention costs, attainable if an informal programme were applied, this strategy would lower costs compared with all other treatment options, and hence be dominant over the other three. Although a lifestyle modification with 50% higher costs would increase the economic impact substantially, its cost-effectiveness would remain within acceptable bounds, ranging from $6,312 per life-year gained versus no treatment to $25,287 per life-year gained versus acarbose.

Changes in other input parameters, such as time horizon and discount rate, can also lead to significant changes in the results (further details provided). Other aspects, such as changes in assumptions about the long-term risk of diabetes and persistence of treatment effect, transitions rates for untreated patients between IGT and NGT, and relative risks for reverting to NGT or converting back to IGT, did not alter the direction of the results. Similarly, under most scenarios, both metformin and lifestyle modification either led to savings or were highly cost-effective in comparison with no treatment.

Authors' conclusions
This model suggested that the treatment of impaired glucose tolerance (IGT) in Canada may be a cost-effective way to prevent diabetes and may generate savings. Intensive lifestyle modification, if maintained, led to the greatest health benefits at reasonable incremental costs. Pharmacological treatments were less costly than both lifestyle modification and no treatment, and had intermediate benefits. Screening asymptomatic patients for IGT in order to initiate active treatment also seems to be an economically feasible option.

CRD COMMENTARY - Selection of comparators
The authors justified the inclusion of the comparators, citing that there was evidence for their benefits. It was not stated that these were the only comparators to have shown benefits. You should decide if they represent valid comparators in your own setting.

Validity of estimate of measure of effectiveness
Although it was not stated that a systematic review had been undertaken, the evidence of effectiveness was based on randomised controlled studies, which represent an adequate study design. Uncertainty around the literature search and
possible omission of relevant studies remains, as details of the search strategy were not reported. The lack of a head-to-head comparison among strategies is problematic because of the differences in trial design and patient characteristics. Moreover, all studies were relatively short term for chronic conditions such as IGT and diabetes.

Validity of estimate of measure of benefit
The benefits were adequately derived using modelling. The comments in the 'Validity of estimate of measure of effectiveness' field (above) apply here.

Validity of estimate of costs
Most important cost categories for the perspective stated were included. Discounting was appropriately performed as the time horizon exceeded two years. Although the unit costs and their sources were reported, resource use was derived using modelling and was not reported in detail. This may limit extrapolation exercises to other settings. The authors reported the price year, which will enhance any future inflation exercises. The extensive sensitivity analyses improve the generalisability of the findings.

Other issues
With the exception of the Diabetes Prevention Program, which used different methods for the cost analysis, the authors did not compare their findings with those from other studies. The authors addressed generalisability issues stating that, while even less expensive lifestyle interventions may be possible, it is unlikely that these would achieve the consistent effectiveness of the programmes studied in the trials and modelled in their study. In addition, the characteristics of the patients in the trials included in the review may differ from those in the general population, and this may potentially reduce the generalisability of the results. The authors highlighted other limitations. First, patient compliance and the issue of treatment duration were not fully addressed. Second, other benefits such as blood pressure reduction and its implications were not considered. Finally, the rate of patient drop-out observed in clinical trials may differ from that which would happen in actual practice.

Implications of the study
The study suggested that metformin, acarbose and lifestyle modification are efficient strategies for reducing the risk of diabetes in patients with IGT. If the costs of lifestyle modification can be contained and compliance maintained, this strategy can be recommended as the first course of action. If this is not the case, or for patients who cannot or will not comply with a lifestyle programme, pharmacological prevention strategies are economically viable alternatives.

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