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ARTICLE

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Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72)

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Abstract *Aims/hypothesis:* This study estimated the economic efficiency (1) of intensive blood glucose control and tight blood pressure control in patients with type 2 diabetes who also had hypertension, and (2) of metformin therapy in type 2 diabetic patients who were overweight. *Methods:* We conducted cost-utility analysis based on patient-level data from a randomised clinical controlled trial involving 4,209 patients with newly diagnosed type 2 diabetes conducted in 23 hospital-based clinics in England, Scotland and Northern Ireland as part of the UK Prospective Diabetes Study (UKPDS). Three different policies were evaluated: intensive blood glucose control with sulphonylurea/insulin; intensive blood glucose control with metformin for overweight patients; and tight blood pressure control of hypertensive patients. Incremental cost : effectiveness ratios were calculated based on the net cost of healthcare resources associated with these policies and on effectiveness in terms of quality-adjusted life years gained, estimated over a lifetime from within-trial effects using the UKPDS Outcomes Model. *Results:* The incremental cost per quality-adjusted life years gained (in year 2004 UK prices) for intensive blood glucose control was £6,028, and for blood pressure control was £369. Metformin therapy was cost-saving and increased quality-adjusted life expectancy. *Conclusions/interpretation:* Each of the three policies evaluated has a lower cost per quality-adjusted life year gained than that of many other accepted uses of healthcare resources. The results provide an economic rationale for ensuring that care of patients with type 2 diabetes corresponds at least to the levels of these interventions.

Keywords Cost-utility analysis · Hypertensive · Metformin · Overweight patients · Quality-adjusted life years · Type 2 diabetes · United Kingdom Prospective Diabetes Study

Abbreviations FPG: fasting plasma glucose · GP: general practitioner · MI: myocardial infarction · QALY: quality-adjusted life year · UKPDS: United Kingdom Prospective Diabetes Study · UKPDS OM: UKPDS Outcomes Model

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Introduction

The United Kingdom Prospective Diabetes Study (UKPDS) established that a more intensive blood glucose control policy (aiming for a fasting plasma glucose [FPG] concentration of <6.0 mmol/l) reduced the relative risk of any diabetes-related endpoint by 12% and of microvascular complications by 25% [1] in newly diagnosed patients with diabetes, and that the cost per year free of complications is less than £1,200 [2]. The UKPDS also showed that tighter blood pressure control (aiming at a blood pressure of less than 150/85 mmHg in hypertensive patients with type 2 diabetes) reduced diabetes-related endpoints by 24% and deaths related to diabetes by 32% [3], and that the cost per life year gained was approximately £720 [4]. Finally, the UKPDS showed that the use of metformin for more intensive blood glucose control in overweight patients conferred a 32% relative risk reduction for any diabetes-related endpoint and a 42% risk reduction for diabetes-related deaths [5], and that the increased life expectancy associated with this interven-

tion was accompanied by net expenditure savings over the trial due to lower complication costs [6].

In comparison with many other well-accepted health interventions, these diabetes interventions are highly cost-effective and implementing them would increase the total health benefits obtained from the current healthcare budget. However, such comparisons are restricted by the fact that the results reported to date from the UKPDS have only measured outcomes in terms of life years gained [4, 6] or endpoint-free time [2].

Maximum comparability will be obtained if the outcomes of all interventions can be expressed in the same units of measurement, and the measure that has gained most currency amongst health economists has been the quality-adjusted life year (QALY), a composite measure that aims to incorporate survival and quality of life in a single index [7]. Economic evaluations using QALYs as the principal measure of outcome—often termed cost-utility studies—have become increasingly popular in the literature and have also been adopted by a number of health technology assessment agencies as the methodology of choice [8]. We report here the cost-utility in type 2 diabetes of each of the three major UKPDS interventions: intensive blood glucose control with sulphonylureas/insulin, intensive blood glucose control with metformin therapy in overweight patients, and tight blood pressure control in hypertensive patients.

We make use of primary data on resource use and complications during the trial follow-up period, coupled with estimates modelled from UKPDS data on the immediate and long-term quality of life effects and cost implications of microvascular and macrovascular diabetes-related complications, to estimate the lifetime costs and effects of these interventions in terms of the cost per QALYs gained.

Materials and methods

Patients, setting and comparison The UKPDS has been described previously [9]. Briefly, between 1977 and 1991, a total of 5,102 patients with newly diagnosed type 2 diabetes aged 25–65 years, who were shown subsequently to have an FPG >6.0 mmol/l on two occasions, were recruited to the study. Following a dietary run-in period, 4,209 patients had FPG concentrations of 6.1–15 mmol/l without symptoms of hyperglycaemia. Of these, 3,867 were randomised either to a conventional glucose control policy (mainly through diet, 1,138 patients), or to an intensive glucose control policy with insulin (1,156) or sulphonylureas (1,573). A further 342 overweight patients (>120% ideal body weight), assigned to an intensive glucose control policy with metformin, were compared with 411 overweight patients assigned to the conventional glucose control policy [5]. The aim of the conventional policy was to maintain patients with an FPG <15 mmol/l without symptoms of hyperglycaemia while trying to obtain the lowest FPG attainable with diet alone. The intensive policy aimed for FPG <6.0 mmol/l and, in patients treated with short-acting in addition to long-acting insulin, pre-meal glucose concentrations of 4–7 mmol/l.

An embedded study randomised 1,148 hypertensive patients to a less tight blood pressure control policy (n=390, aiming to maintain blood pressure <200/<105 mmHg, modified in 1992 to <180/<105 mmHg) or to a tight blood pressure control policy (n=758, aiming for <150/85 mmHg) using an ACE inhibitor (captopril) or a beta blocker (atenolol). If blood pressure control criteria were not met, additional antihypertensive agents were added in a predefined stepwise fashion.

The study design and protocol amendments, which conform to the guidelines of the Declarations of Helsinki as revised in 2000, were approved by the Central Oxford Research Ethics Committee and by the equivalent committees at each centre. Each patient gave informed witnessed consent.

Economic evaluation Incremental cost-effectiveness analyses were undertaken for each intervention in which the incremental net cost and net effectiveness were calculated in relation to the comparator, and expressed as a ratio. As the economic evaluation perspective was that of the healthcare purchaser, only direct health service costs were included. These included treatment costs, visits to a nurse or a general practitioner (GP) based on 'standard practice' assumptions (see below) and the costs of treating diabetic complications. Not included in this analysis were non-medical costs such as out-of-pocket expenses incurred when visiting clinics, cost of informal care provided by family members and production losses resulting from work absences, long-term disability or premature death, information on which was not readily available. We adopted the QALY [7] as this measure captures both increases in life expectancy and improved quality of life which result from prevention of complications, providing a composite outcome measure of fatal and non-fatal events that permits comparison between many health interventions.

We compared the following treatment policies: (1) conventional vs intensive blood glucose control (with insulin or sulphonylureas); (2) conventional vs intensive blood glucose control (with metformin) in overweight patients; and (3) less tight blood vs tight blood pressure control (with ACE inhibitors or beta blockers) in hypertensive patients. In our main analyses we treated each of these interventions as an independent policy.

Resource data and costs For each patient, doses of allocated medications for blood glucose and blood pressure lowering were collected routinely. Patients were asked also on a regular basis if they were taking aspirin, hormone replacement therapy, antidepressants, steroids, or other drugs. To measure hospital inpatient episode costs, the date and duration of any admissions were collected at each clinic visit and the costs estimated using previously reported methods [2]. The use of non-inpatient healthcare resources was estimated using data from a cross-sectional survey conducted between January 1996 and September 1997, which collected information on domiciliary, clinic and telephone contacts with GPs, nurses, podiatrists, opticians, dieticians and with eye and other hospital clinics over the previous 4 months.

Table 1 summarises the main sources of information on therapy unit costs, taken from UK national statistics [10, 11]. To obtain a cost per patient within the trial period, the resource volumes used by each patient were multiplied by these unit costs. We used previously reported equations [12] to estimate the immediate (year of occurrence) and long-term (all subsequent years) cost of major diabetes-related complications, some of which are reproduced in Table 1. The estimated immediate inpatient cost for a typical individual ranged from £1,366 for a fatal myocardial infarction (MI) event to £10,029 for an amputation. In all subsequent years—that is, for patients with a history of these conditions—hospital costs were elevated by £550 and £358, respectively. Similarly, estimates for the increase in average annual non-inpatient costs associated with any macrovascular complications were £373 in the year of occurrence and £306 in subsequent years, while for microvascular complications the increased cost was £324 and £242, respectively.

Undiscounted costs are reported as well as net present values using the UK Treasury recommended 3.5% discount rate [13]. The effect of either a higher or lower discount rate was examined in the sensitivity analysis. All costs are reported in year 2004 values of pounds sterling (£1=~€1.5).

All patients participating in the UKPDS, regardless of their randomised allocation, attended clinics four or three times a year. As the pattern of visits is likely to be different in routine practice—especially for the conventional group—we have reported incremental costs removing UKPDS protocol-driven elements and using a pattern of clinic visits reflecting a previously reported survey of GP and specialist clinical opinion on the implementation of intensive policy and blood pressure policy [11]. The cost of implementation by policy and type of therapy is listed in Table 1. The effects of higher implementation costs are considered in the sensitivity analyses. The incremental annual cost of intensive blood glucose control over conventional therapy was £111 when the patient was on tablets and £266 on insulin. Using a similar method it was estimated that patients on tight blood pressure control cost an additional £49 per annum regardless of their glucose policy.

Outcomes We estimated the difference in QALY expectancy for the different treatment policies. The QALY adjusts length of life for quality of life by assigning a value or health utility (where zero represents death and one represents full health) for each year of life. Complications have been

Table 1 Main unit costs for therapies and cost of complications

Item	Unit cost £s 2004	Source
Therapy costs		
Metformin (500 mg/850 mg tablet)	0.03/0.04	Drug tariff 2004
Chlorpropamide (100 mg/250 mg)	0.09/0.10	Drug tariff 2004
Glibenclamide (2.5 mg/5 mg)	0.03/0.05	Drug tariff 2004
Glipizide (2.5 mg/5 mg)	0.05/0.08	Drug tariff 2004
Ultralente insulin 1,000-unit vial/750-unit cartridge	9.80	Drug tariff 2004
Soluble insulin 1,000-unit vial/750-unit cartridge	9.80/10.20	Drug tariff 2004
Atenolol (25/50/100 mg)	0.06/0.07/0.09	Drug tariff 2004
Captopril (12.5/25/50 mg)	0.04/0.06/0.07	Drug tariff 2004
Other drugs	Cost per item	Drug tariff 2004
Implementation unit costs		
General practitioner (clinic visit)	23	Netten and Curtis 2003 [10]
Practice nurse (home visit/surgery visit)	10/8	
Dietician	9	
Hospital eye clinic	42	
Estimated standard practice costs by treatment		
Conventional primarily on diet/or tablets	57	Unit costs multiplied by average resource use reported in Table 3 of UKPDS 63 [11]
Conventional on Insulin	140	
Intensive on tablets	168	
Intensive on insulin	405	
Immediate (subsequent years) costs of selected complications[a]		
Hospital costs		
Fatal myocardial infarction	1,366	UKPDS 65 [12] adjusted for inflation using the Hospital & Community Services Pay And Price Index
Non-fatal myocardial infarction	4,825 (550)	
Non-fatal stroke	2,806 (295)	
Amputation	10,029 (358)	
Non-hospital costs		
Macrovascular events	373 (306)	
Microvascular events	324 (242)	

[a]All costs for complications are for a representative individual (set to the UKPDS mean population values, i.e. a 58.63-year-old male)

shown to affect the quality of life of patients with type 2 diabetes [14]. Unlike previous evaluations of treatment for diabetes that have used reference values for a limited number of complications [15], we estimated the effect of complications using health utilities measured using the EQ-5D health status questionnaire in a survey of 3,192 patients still participating in the UKPDS in 1997 [16]. Using these data the mean utility for a patient with diabetes who was free of microvascular and macrovascular complications was found to be 0.79, which is similar to people of the same age who do not have diabetes. Patients with a history of complications were found to have lower utility, and the following decrements were estimated: −0.06 for an MI; −0.09 for other ischaemic heart disease or angina; −0.16 for stroke; −0.11 for heart failure; −0.28 for amputation; and −0.07 for blindness in one eye [16]. It was assumed that the occurrence of multiple complications has an additive effect on utility and the same decrements were applied to patients with comparable health states regardless of their treatment policy.

For each patient available at the end of follow-up, the UKPDS Outcomes Model (UKPDS OM), a newly developed simulation model which has been fully documented elsewhere [17], was used to estimate the time from end of follow-up to the first occurrence of each of the seven diabetes-related endpoints (MI, angina, stroke, heart failure, amputation, renal failure and blindness in one eye) and to death in order to estimate expected QALYs. In brief, the UKPDS OM is based on an integrated system of parametric equations which predict the annual probability of any of the above endpoints occurring and Monte Carlo methods to predict the occurrence of events. A key aspect of this model is its ability to capture the clustering or interaction of different types of complications at the individual patient level. This may arise not only because many events share common risk factors, but also due to event-related dependence, i.e. when the occurrence of an event substantially increases the likelihood of another event occurring [18]. The model is a probabilistic discrete-time illness-death model [19], rather than a Markov model, which simulates a patient's life experience using annual cycles to calculate the probability of death or of experiencing any of the specified complications. Patients start with a given health status (e.g. no complications) and can have one or more non-fatal complications and/or die in any model cycle by comparing estimated probabilities with random numbers drawn from a uniform distribution ranging from zero to one to determine whether an event occurs. When a patient experiences a complication, their utility is permanently decremented such that they accumulate QALYs at a slower rate. Trial cohorts were run through the model until all patients had died. For further details of the model see http://www.dtu.ox.ac.uk/Outcomesmodel.

In these simulations we assume that every patient from the end of the trial has the overall mean HbA_1c and blood pressure levels, regardless of randomised policy. The only difference in hazard between the groups is due to complications experienced during the trial. The estimated QALY gain using our model will therefore be conservative as it assumes that there is no continuing benefit of therapy. We report undiscounted benefits along with outcomes discounted at 3.5% and 6% per year.

Analysis Results are reported as mean values and SDs or mean differences with CIs, and as cost to effectiveness ratios. To provide a visual representation of the results, the costs and health outcomes are mapped onto the cost-effectiveness plane and reported as acceptability curves [20]. The effect on our main results of uncertainty surrounding some aspects of cost and the utility values used in the study were examined using sensitivity analyses.

Results

Costs Tables 2, 3, 4 show the mean cost per patient over the duration of the study for each of the three interventions considered, by category of cost and by randomised allo-

Table 2 Mean and SD costs per patient during the trial follow-up period and mean (95% CI) cost differences for conventional vs intensive blood glucose control with insulin or sulphonylureas, by cost category (£s 2004)

	Conventional		Intensive		Mean cost difference (95% CI) per patient[a]
	Mean	SD	Mean	SD	
Antidiabetic treatment	620	957	1,299	1,196	678 (607, 750)
Anti-hypertensive treatment	430	668	427	666	−3 (−49, 43)
Cost of implementation	699	315	2,160	865	1,461 (1,424, 1,498)
Total cost of treatment	1,749	1,399	3,885	1,992	2,136 (2,009, 2,263)
Within-trial hospital inpatient costs	5,212	15,492	4,159	8,557	−1,053 (288, 1,818)
Within-trial non-hospital and outpatient costs	2,528	1,084	2,538	1,092	10 (−66, 85)
Projected hospital inpatient costs	13,322	38,052	13,476	37,428	154 (−3,265, 3,573)
Projected non-hospital and outpatient costs	3,708	3,821	3,807	3,881	98 (−259, 455)
Total cost of complications	24,771	43,276	23,980	41,106	−791 (−4,586, 3,003)
Total costs, undiscounted	26,516	43,438	27,865	41,310	1,349 (−2,455, 5,153)
Total costs, 3.5% discount rate	14,984	17,888	15,868	14,465	884 (−483, 2,250)
Total costs, 6% discount rate	11,169	13,340	11,852	9,261	683 (−230, 1,597)

[a]Negative cost differences indicate cost-savings associated with more intensive therapies. Sub-totals may not sum exactly due to rounding

Table 3 Mean and SD costs per patient during the trial follow-up period and mean (95% CI) cost differences for conventional vs intensive blood glucose control with metformin in overweight patients, by cost category (£s 2004)

	Conventional		Intensive		Mean cost difference (95% CI) per patient[a]
	Mean	SD	Mean	SD	
Antidiabetic treatment	640	997	776	639	136 (18, 254)
Anti-hypertensive treatment	626	796	612	814	−15 (−131, 101)
Cost of implementation	674	193	2,295	748	1,621 (1,539, 1,702)
Total cost of treatment	1,941	1,486	3,682	1,598	1,742 (1,521, 1,963)
Within-trial hospital inpatient costs	7,283	23,498	4,233	8,151	−3,050 (−5,666, −433)
Within-trial non-hospital and outpatient costs	2,834	1,077	2,834	1,044	0 (−153, 152)
Projected hospital inpatient costs	13,515	38,531	13,591	35,580	76 (−8,118, 8,270)
Projected non-hospital and outpatient costs	3,717	3,941	3,927	3,829	209 (−373, 792)
Total cost of complications	27,350	46,842	24,585	39,609	−2,765 (−11,695, 6,166)
Total costs, undiscounted	29,290	47,056	28,267	39,764	−1,023 (−9,972, 7,926)
Total costs, 3.5% discount rate	16,941	23,193	15,920	13,678	−1,021 (−4,291, 2,249)
Total costs, 6% discount rate	12,798	18,836	11,792	8,557	−1,006 (−3,251, 1,239)

[a]Negative cost differences indicate cost-savings associated with more intensive therapies. Sub-totals may not sum exactly due to rounding

cation. The intensive blood glucose control policy increased the antidiabetic treatment costs by £678 (95% CI 607, 7,50) and the incremental costs of visits and self-testing in a standard practice setting by £1,461 (1,424, 1,498), when compared with conventional glucose control (Table 2). However, the effect of this policy was also to reduce mean hospitalisation cost per patient over the median 10.4 years of follow-up, from £5,212 in the conventional policy group to £4,159 in the intensive policy group. Simulated post-trial hospitalisation costs were similar in the conventional and intensive groups (£13,322 vs £13,476). When non-hospital costs also were taken into account, the overall intensive policy reduction in cost of complications was £791 (−4,586, 3,003). Combining both therapy costs and savings achieved, the incremental cost of intensive blood glucose control with insulin or sulphonylureas was £1,349 (−2,455, 5,153), or £884 (−483, 2,250) when discounted.

Intensive blood glucose control with metformin in overweight patients increased therapy costs by £1,742 (1,521, 1,963) compared with those on conventional therapy, mainly due to the costs associated with implementing this policy in a standard practice setting (Table 3). The cost of complications was £−2,765 (−11,695, 6,166) less per patient in the metformin group, compared with conventional policy. As the increased cost of metformin therapy (including standard practice costs) is less than the reduction in the cost of complications, there is on average a net cost-saving from the intervention of £−1,023 (−9,972, 7,926) per patient.

The costs for the embedded hypertension study, which had a shorter median duration of follow-up of 8.4 years, are

Table 4 Mean and SD costs per patient during the trial follow-up period and mean (95% CI) cost differences for tight vs less tight blood pressure control, by cost category (£s 2004)

	Less tight		Tight		Mean cost difference (95% CI) per patient[a]
	Mean	SD	Mean	SD	
Antidiabetic treatment	1,027	1,028	1,119	1,163	92 (−40, 224)
Anti-hypertensive treatment	554	628	1,102	720	549 (468, 630)
Cost of implementation	1,332	777	1,782	858	450 (351, 548)
Total cost of treatment	2,913	1,605	4,003	1,931	1,090 (867, 1,314)
Within-trial hospital inpatient costs	4,414	9,549	3,555	9,229	−860 (−2,002, 282)
Within-trial non-hospital and outpatient costs	2,116	788	2,144	799	−28 (−125, 70)
Projected hospital inpatient costs	13,702	36,117	13,657	38,715	−46 (−6,115, 6,024)
Projected non-hospital and outpatient costs	3,505	3,755	3,634	3,808	129 (−425, 684)
Total cost of complications	23,738	40,415	22,989	42,561	−749 (−7,371, 5,873)
Total costs, undiscounted	26,651	40,577	26,993	42,713	342 (−6,295, 6,978)
Total costs, 3.5% discount rate	15,786	16,378	15,895	16,025	108 (−2,347, 2,563)
Total costs, 6% discount rate	11,984	11,082	12,042	10,671	58 (−1,490, 1,606)

[a]Negative cost differences indicate cost-savings associated with more intensive therapies. Sub-totals may not sum exactly due to rounding

reported in Table 4. Overall the difference in the cost of the antihypertensive therapies between policies of tight and less tight control was £549 (468, 630). More intensive blood pressure control reduced the cost of complications by £749 (7,371, 5,873), and so the overall cost-effect of more intensive blood pressure control was a net increase in cost of £342 (−6,295, 6,978), or £108 (−2,347, 2,563) when discounted to present value.

Outcomes The main measure of effectiveness in this analysis is expected QALYs gained per patient. Table 5 shows mean quality-adjusted life expectancy from date of randomisation, by allocation, for the within-trial period and projected over their remaining lifetime. Patients allocated to an intensive blood glucose control policy with insulin and sulphonylureas were estimated to live 16.62 QALYs compared with 16.35 QALYs for patients on conventional therapy. This was a non-significant trend of 0.27 (−0.48, 1.03), or 0.15 (−0.20, 0.49) when discounted.

The estimated number of QALYs in overweight patients allocated to an intensive blood glucose control policy with metformin showed a non-significant increase of 0.88 (−0.54, 2.29), compared with overweight patients on the conventional glucose control policy (Table 5). Patients allocated to a tight blood pressure control policy were estimated to obtain 14.16 QALYs, compared with 13.71 amongst those allocated to a less tight blood pressure control policy. The overall lower number of QALYs in this randomisation compared with the glucose control analyses reflects the older age at which these hypertensive patients were randomised into this embedded study (56.4 vs 53.3 years).

Cost-effectiveness One way of representing the combinations of cost and effect differences reported above for each intervention is to plot the changes on a cost-effectiveness plane, which simultaneously represents the difference in the mean costs (on the *y*-axis) and life expectancy (on the *x*-axis) [20]. Figure 1a–c shows cost-effectiveness planes for the intensive blood glucose, metformin and tight blood pressure control analyses, respectively. The vertical I-bars show the 95% CI for the cost-difference (from Table 2) and the horizontal I-bars show the 95% CI for the difference in QALYs (from Table 5). The two I-bars cross at the point estimates of cost and effect and the slope of the line joining that point to the origin of the plane represents the point estimate of cost per QALY. The discounted cost of an intensive blood glucose control policy with insulin or sulphonylureas was on average £884 more per patient and the discounted benefits gained were 0.15 QALYs, giving a cost to utility ratio of £6,028 per QALY gained. The discounted cost of intensive blood glucose control policy with metformin in overweight patients was on average £1,021 (−4,291, 2,249) less than the conventional policy and had a longer discounted life expectancy of 0.55 QALYs, making this treatment strategy both cost-saving and more effective. In these circumstances, calculation of a cost to effectiveness ratio is not appropriate, as such a ratio would fail to differentiate between an intervention that was cost-saving and outcome-enhancing, and an intervention that increased costs with poorer outcomes [21]. Finally, the discounted cost of tight blood pressure control policy was on average £108 more per patient, and discounted life expectancy was 0.29 QALYs longer, giving a cost to utility ratio of £369 per QALY gained.

The joint uncertainty in costs and QALYs is shown by the elliptical contours in Fig. 1a–c, which cover 95% of the integrated joint density (assuming joint normality). In all three cases the 95% confidence surface extends beyond a single quadrant of the cost-effectiveness pane and in these situations the calculation of 95% CIs for cost-effectiveness can be problematic due to the inherent instability of ratio statistics. An alternative presentation is given in Fig. 2, which shows, for different values of the maximum willingness to pay for a QALY, the probability that the intervention under evaluation is cost-effective. These curves are known as cost-effectiveness acceptability curves and have become an accepted way of presenting uncertainty in cost-effectiveness information that can simultaneously summarise

Table 5 Within-trial and lifetime modelled quality-adjusted life expectancy of conventional vs intensive blood glucose control with insulin or sulphonylureas; conventional vs intensive blood glucose control with metformin in overweight patients; and tight vs less tight blood pressure control, at varying discount rates

Item	Mean (SD) undiscounted QALYs per patient		Mean difference (95% CI) in QALYs per patient		
	Conventional	Intensive	Discount rate per year		
			0%	3.5%	6%
Within-trial					
Intensive blood glucose control	7.62 (2.71)	7.72 (2.69)	0.10 (−0.09, 0.29)	0.08 (−0.07, 0.22)	0.06 (−0.05, 0.17)
Metformin therapy	8.09 (2.50)	8.37 (2.33)	0.28 (−0.09, 0.63)	0.22 (−0.04, 0.48)	0.18 (−0.02, 0.39)
Tight blood pressure control	7.63 (2.36)	7.77 (2.18)	0.12 (−0.10, 0.34)	0.10 (−0.08, 0.28)	0.08 (−0.06, 0.24)
Total					
Intensive blood glucose control	16.35 (8.36)	16.62 (8.35)	0.27 (−0.48, 1.03)	0.15 (−0.20, 0.49)	0.10 (−0.12, 0.31)
Metformin therapy	16.44 (8.49)	17.32 (7.94)	0.88 (−0.54, 2.29)	0.55 (−0.10, 1.20)	0.40 (−0.01, 0.80)
Tight blood pressure control	13.71 (8.00)	14.16 (7.81)	0.45 (−0.70, 1.60)	0.29 (−0.26, 0.85)	0.22 (−0.14, 0.59)

QALY quality-adjusted life year

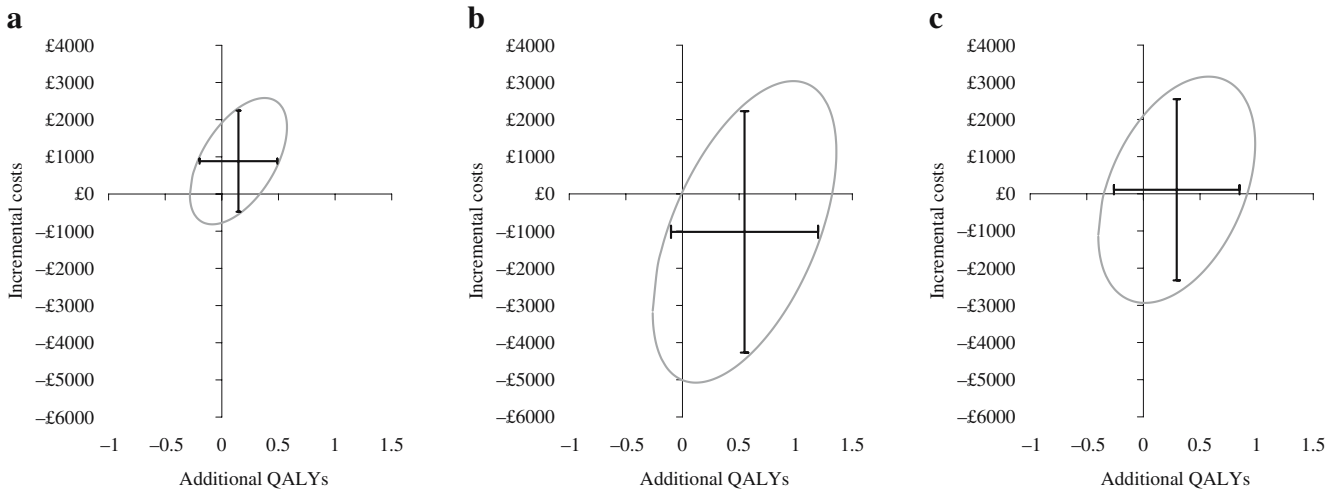

Fig. 1 Cost-effectiveness planes showing mean difference in cost and effect and 95% CI and 95% confidence ellipses for cost-effectiveness for **a** intensive vs conventional blood glucose control with insulin or sulphonylureas, **b** intensive vs conventional blood glucose control with metformin in overweight patients and **c** tight vs less tight blood pressure control in type 2 diabetes. *QALY* Quality-adjusted life year

uncertainty due to sampling variation, but also uncertainty concerning the appropriate threshold for cost-effective decision-making [20]. The point at which the curves cross the vertical axis shows the probability that treatment is cost-saving.

With costs and effects discounted at a 3.5% rate, intensive blood glucose control has a 10% chance of being cost-saving. At a ceiling ratio of £20,000 per QALY there is a 74% chance that it is cost-effective. There is a 77% probability that metformin would prove to be cost-saving compared with a conventional policy, and due to the position of the point estimate of cost-effectiveness in the dominant quadrant of the cost-effectiveness plane, the chance that metformin is cost-effective at a ratio of £20,000 per QALY is 98%. Tight blood pressure control has a 47% chance of being cost-saving and an 86% chance of being cost-effective compared with less tight control.

Sensitivity analysis Sensitivity analyses performed to examine whether the results in the main analysis are robust to different assumptions are displayed in Fig. 3. The effect of a 50% higher standard practice cost than in the baseline estimates, after discounting, was an increase in the average cost per QALY for intensive blood glucose control with insulin or sulphonylurea from £6,028 to £10,051, while a 50% reduction in standard practice costs reduced the cost per QALY to £2,251. Lowering the costs of complications had the effect of increasing the cost per QALY, as the value of averted events was lessened and so net cost rose, and the same effect was found with the tight blood pressure control policy. The sensitivity analyses of intensive blood glucose control with metformin are not shown in Fig. 3 as this was an intervention dominated by the comparator (lower costs and better outcomes); neither a 50% increase in antidiabetic therapy costs or standard practice costs, nor a 50%

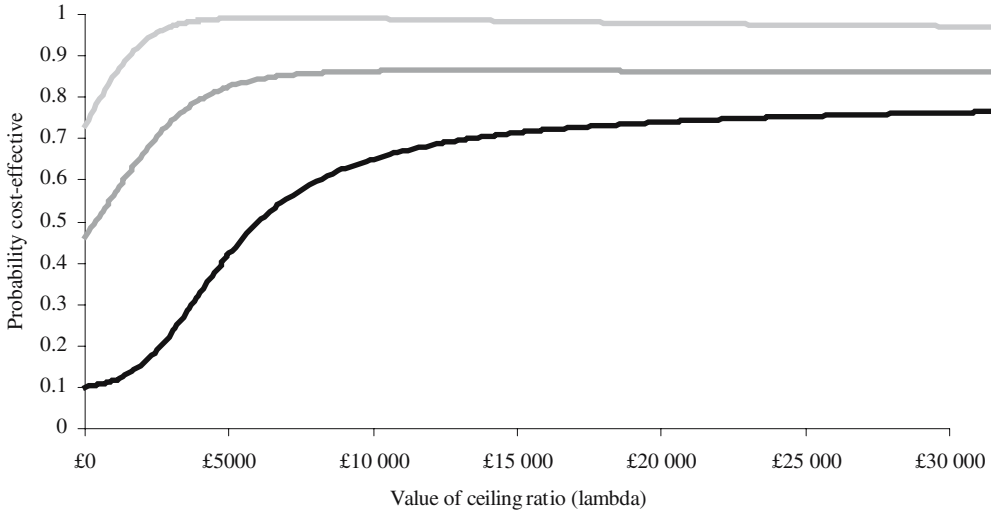

Fig. 2 Cost-effectiveness acceptability curves: probability that the cost per quality-adjusted life year gained is cost-effective as a function of the decision-maker's ceiling cost to effectiveness ratio. *Top curve* metformin, *middle curve* tight blood pressure control, *lower curve* intensive blood glucose control

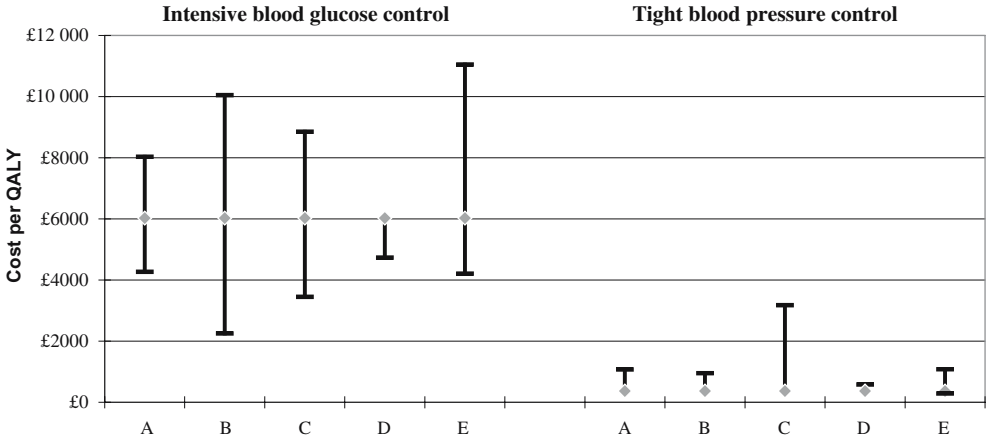

Fig. 3 Sensitivity of cost-effectiveness of intensive blood glucose control with insulin or sulphonylureas and tight blood pressure control to changes in assumptions concerning antidiabetic treatment costs, standard practice costs, costs of complications, quality of life and treatment benefit beyond trial

A = Anti-diabetic therapy costs 50% higher/lower; B = Standard practice costs 50% higher/lower; C = Cost of complications 50% lower/higher; D = Utility of 1 when free of complications; E = Treatment benefit beyond trial: none/continuing

reduction in complication costs, altered the status of intensive blood glucose control with metformin as a cost-reducing intervention.

We also show the impact of different assumptions regarding continuing health effects beyond the trial and utility weights used to estimate QALYs. In regard to health effects, we have estimated the cost : effectiveness ratios: (1) using only the benefits attained within the trial; and (2) assuming that the average difference in HbA_1c (or blood pressure) between policies continues beyond the trial as a way of capturing continuing treatment effects. In regard to intensive blood glucose control, disregarding benefits beyond the trial increased the average cost per QALY to £11,050, while assuming a continuing treatment effect reduced the average cost to effectiveness ratio to £4,209. To examine the impact of adopting a higher utility weight for people without complications when calculating QALYs, we re-ran the simulation adopting the assumption that the mean utility for people without complications is 1.0 (i.e. they are in full health), rather than 0.79 as used in the main analysis. After a discounting, the differences in conventional vs intensive blood glucose control with insulin or sulphonylureas, conventional vs intensive blood glucose control with metformin and tight vs less tight blood pressure control were 0.19 (−0.17, 0.55), 0.69 (−0.02, 1.41) and 0.36 (−0.29, 1.00), respectively. As the figure shows for intensive blood glucose control with insulin or sulphonylureas and for tight blood pressure control, these changes did not have a major impact on the estimated cost-effectiveness.

Discussion

Summary of main findings This paper presents the results of a set of cost-effectiveness studies based on the primary results from the UKPDS with model-derived extrapolation to 100% mortality of the trial cohort. These indicate that intensive blood glucose control with insulin or sulphonylureas, intensive blood glucose control with metformin and tight blood pressure control in hypertensive patients with type 2 diabetes each has a cost per QALY gained that is lower than other accepted uses of healthcare resources. In the UK, interventions appear to have a high chance of acceptance by the National Institute for Clinical Excellence if their cost-effectiveness is more favourable than approximately £30,000 per QALY [22]. As the results are based primarily on clinical trial information, the effectiveness and resource use data used are less likely to be affected by the sources of bias, confounding and uncertainty that often impair non-randomised study designs.

These results mark an important advance on our previous estimates of the cost-effectiveness of diabetes treatment policies, in that the outcome measures used here capture the improved quality of life associated with lower rates of complications in patients randomised to policies of more intensive blood glucose or tighter blood pressure control as well as the survival benefit from a reduced number of fatal events. The estimated gains in quality-adjusted life expectancy range from 0.17 QALYs for intensified blood glucose control with insulin or sulphonylureas to 0.88 QALYs for metformin therapy in overweight patients. The cost estimates also include many changes in the unit cost of drugs in the UK, for example the total cost of antihypertensive drugs in the tight blood pressure control group of patients are estimated to be £1,102 per patient, which is approximately 15% lower than those reported in a previous study due to reductions in the cost of captopril following the expiration of its patent in the UK [4].

A previous modelling study which reported the cost-utility of an intensive blood glucose policy with insulin or sulphonylureas and tighter blood pressure control [23] produced similar outcome estimates, but the cost of implementing these policies appeared to be much higher in a US healthcare setting, resulting in somewhat less favourable cost to effectiveness ratios. For example, the incremental cost of treatment with a policy of intensive blood glucose control was estimated to be $12,213 (equivalent to £6,600 at 2004 exchange rates), over three times the estimated UK

incremental cost. These differences suggest the need to undertake country-specific cost-effectiveness analyses when costs differ markedly between healthcare systems. This may be due to differences in the cost of diabetes therapies, or the cost of treating complications that may influence the scope for savings. While our sensitivity analyses also highlight the impact of changes in the cost of therapy/implementation and the cost of complications, our results suggest that all three policies are likely to remain cost-effective under a wide range of assumptions.

Implications of results The objective of undertaking economic evaluation is to improve the allocation of health resources by stimulating the adoption of cost-effective interventions and curtailing those that offer poor value for money. Our results would indicate that there is potential for the cost of therapies to be partly offset by reductions in the costs of treating complications of diabetes. However, these costs and benefits may well be incurred by different parties or funding streams, depending on the configuration of the healthcare system. Mechanisms may therefore have to be devised to ensure that the correct incentives are in place to improve diabetes care. It should also be noted that any saving from reduced complications may not be realised as financial savings, but a reduction in hospitalisations may free up resources that may be reallocated elsewhere.

Decision-makers will be interested not only in cost-effectiveness but also in the total cost of implementing these interventions. We have estimated previously that improved glycaemic and blood pressure control would cost approximately £101 m per annum for the entire population of people with type 2 diabetes in England [11]. This represents a small proportion (<1%) of the incremental growth in UK healthcare spending between 2001 and 2005 and should be similarly affordable in other healthcare systems.

Limitations Although the sensitivity analyses we undertook suggest that our conclusions should be robust over a wide range of assumptions made, a number of limitations should be noted. First, we included only the costs of diabetic therapy during the within-trial period and, secondly, our extrapolation beyond the trial period does not assume continuing treatment effects in the main analysis (e.g. patients in the blood glucose study were assumed to have the same mean HbA_1c from the end of the trial). Analysts are likely to be interested in the lifetime costs and benefits of therapies based on various assumptions about treatment costs and benefits continuing, but this would require further simulation modelling. Thirdly, we have reported the cost-utility of three interventions which have been considered separately. However, in clinical practice it is likely that many patients will be treated simultaneously for hyperglycaemia and hypertension as well as other risk factors such as dyslipidaemia. Joint delivery of these interventions will lower implementation costs and therefore should further improve the cost to effectiveness ratios reported here.

Since the UKPDS was first designed, the standards of normal care for people with diabetes have risen and further intensification of treatment has occurred following publication of the UKPDS results. One consequence is that the incremental benefits obtained from the randomised comparisons reported here may now be more difficult to achieve, although the incremental costs would also be reduced. However, epidemiological analyses of the UKPDS have indicated linear relationships between HbA_1c and risk of complications and between blood pressure and risk of complications, but further evidence is required in order to assess both the effectiveness and cost-effectiveness of further intensifying treatment. Meanwhile, it should be noted that considerable scope still exists to attain recommended standards of diabetes care, in the UK and elsewhere [24].

Care was taken as part of the modelling exercise to propagate parameter uncertainties through the model. The results of the analysis show that, while the point estimates of cost-effectiveness fall within the acceptable range, we cannot be confident, at conventional error probabilities, that the modelled interventions are cost-effective. This is due to the non-significant differences associated with the QALY outcomes reported in Table 5. Nevertheless, the balance of probabilities favours greater intervention in diabetes being cost-effective, and the non-negligible chance that these interventions turn out not to be cost-effective if implemented must be weighed against the even greater probability that, if these interventions are not implemented, patients will have been denied cost-effective care. Information on the 5-year follow-up of the UKPDS will offer the opportunity of testing the model predictions and further refining the cost-effectiveness estimates and the precision with which they are estimated.

Conclusion In conclusion, the analyses reported here provide further evidence that the cost-effectiveness of interventions to reduce the burden of diabetes-related complications compares favourably with that of other accepted uses of healthcare resources. The results should be of interest and use to other economists and health service researchers, and in particular should be considered by decision-makers when considering the allocation of resources to diabetes care. We believe the results illustrate a convincing economic rationale for improving standards of care for patients with type 2 diabetes.

Conflict of interest declaration. The authors are employed by the University of Oxford. This paper makes use of a simulation model that we have called the UKPDS Outcomes Model. All of the information necessary to reproduce the UKPDS Outcomes Model is in the public domain, but it is conceivable that a future user with a commercial interest in the UKPDS Outcomes Model might prefer to use the software already created by University programmers. Depending on the nature of the proposed use of the UKPDS Outcomes Model, the University of Oxford might charge a fee in this case.

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