

ORIGINAL ARTICLE

Cost-utility analysis in a UK setting of self-monitoring of blood glucose in patients with type 2 diabetes

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ABSTRACT

Background: Self-monitoring of blood glucose (SMBG) in type 2 diabetes patients has been shown in meta-analyses of randomized trials to improve HbA_{1c} by ~0.4% when compared to no SMBG. However, the cost of testing supplies is high, improvements in health utility due to improved glycaemic control may be possible and cost-effectiveness has not been evaluated.

Methods: A peer-reviewed validated model projected improvements in lifetime quality-adjusted life years (QALYs), long-term costs and cost-effectiveness of SMBG versus no SMBG. Markov/Monte Carlo modelling simulated the progression of complications (cardiovascular, neuropathy, renal and eye disease). Transition probabilities and HbA_{1c}-dependent adjustments came from the United Kingdom Prospective Diabetes Study (UKPDS) and other major studies. Effects of SMBG on HbA_{1c} came from clinical studies, meta-analyses and population studies, but can only be considered 'moderate'

levels of evidence. Costs of complications were retrieved from published sources. Direct costs of diabetes complications and SMBG were projected over patient lifetimes from a UK National Health Service perspective. Outcomes were discounted at 3.5% annually. Extensive sensitivity analyses were performed.

Results: Depending on the type of diabetes treatment (diet and exercise/oral medications/insulin), improvements in glycaemic control with SMBG improved discounted QALYs anywhere from 0.165 to 0.255 years, with increased total costs of £1013–£2564/patient, giving incremental cost-effectiveness ratios of £4508:£15515/QALY gained, well within current UK willingness-to-pay limits. Results were robust under a wide range of plausible assumptions.

Conclusions: Based on the moderate level of clinical evidence available to date, improvements in glycaemic control with interventions, including SMBG, can improve patient outcomes, with acceptable cost-effectiveness ratios in the UK setting.

Introduction

As many as 200 million people worldwide are currently affected by diabetes^{1,2}. Without extensive intervention, this figure could rise to 350 million within the next 25 years^{1,2}. Diabetes is associated with a huge healthcare burden and accounts for approximately 10% of global healthcare expenditure, the majority of which is attributed to the treatment of diabetes-related complications². Over the last 15 years, clinical evidence has accumulated to indicate that the risk of complications can be reduced by improving control of blood glucose levels³⁻⁶. Despite this knowledge and the availability of numerous medications designed to control blood glucose, glycaemic control in patients with diabetes has not improved in the US and Europe since the early 1980s⁷⁻¹¹. Clearly, an improved approach and better implementation are required to improve glycaemic control in patients with diabetes worldwide and limit the development of diabetes-related complications.

HbA_{1c} measurements provide data on long-term glycaemic control by providing a value that is proportional to the average blood glucose concentration of the lifespan of a red blood cell (typically 2–3 months). Self-monitoring of blood glucose (SMBG), in contrast, provides information on the actual blood glucose levels at the time of testing, thus allowing immediate action to be taken. Interestingly, data from a recent meta-analysis indicated that SMBG, as part of a multi-component therapy in non-insulin-requiring patients with type 2 diabetes, was associated with improvements in HbA_{1c} levels¹². The analysis (eight randomized clinical trials and a total of 1307 adults treated over 3–10 months) showed that SMBG following education was associated with lower HbA_{1c} levels (0.4% lower on average after 3–10 months) compared to no blood glucose monitoring or education. A more recent meta-analysis pooled the results of six randomized, controlled clinical trials that compared the effects of SMBG and education versus no SMBG or education, and found that among non-insulin-using patients with type 2 diabetes, there was a statistically significant 0.39% decrease in HbA_{1c} (95% confidence intervals –0.56 to –0.21) in patients using SMBG versus controls^{13,14}.

In a recent publication of the proceedings of the International Diabetes Center (IDC), the World Health Organization (WHO) and the American Association of Diabetes Educators (AADE) global consensus conference on the self-monitoring of blood glucose (SMBG), a 16-point consensus statement was reported that included recommendations that measurements of glycosylated haemoglobin (HbA_{1c}) and SMBG are essential for assessing glycaemic control and that SMBG should be recommended to all

people with diabetes as an integral part of an overall diabetes management program¹⁵. However, there were differences in recommendations for patients receiving insulin and those who are not. SMBG was described as an essential component of management for insulin-treated patients with diabetes. However, the value of SMBG in patients with type 2 diabetes not receiving insulin is more controversial, due mainly to a lack of published data from well-designed longitudinal studies or randomized controlled trials. Current recommendations for SMBG use in patients with type 2 diabetes not using insulin vary widely in suggested methodology, technique, timing and frequency¹⁶⁻²¹. The global consensus conference indicated that SMBG practices should be determined by the needs of the individual patients, but suggested that SMBG at least twice daily would be appropriate for patients over glycaemic target, and at least once daily for those at glycaemic target on oral hypoglycaemic agents, including weekly profiles. These frequencies of SMBG are recommended to guide diet and physical activity as well as to detect hypoglycaemia or postprandial hyperglycaemia.

For the present analysis, we hypothesized that the improvements in glycaemic control associated with SMBG in patients with type 2 diabetes observed in short-term clinical studies would translate into long-term clinical benefits, such as a reduced incidence of diabetes-related complications. The daily costs associated with SMBG are substantial but, over patient lifetimes, we hypothesized that this cost may be partially offset by a reduced cost of diabetes-related complications. We, therefore, performed a long-term cost-effectiveness analysis using an established and validated model of diabetes in different treatment cohorts to evaluate the impact of SMBG over patient lifetimes.

Methods

Three base case analyses were performed based on three cohorts of type 2 diabetes patients defined by treatment, previously reported by Karter *et al.*, to evaluate the impact of SMBG²². Long-term projections were made for each cohort with and without SMBG using the CORE Diabetes Model to evaluate the long-term clinical and cost outcomes associated with SMBG. Conservative assumptions on the effects of SMBG treatment were made based on published data, and the model was used to take into account costs associated with treatment and diabetes-related complications in UK settings. Following the base case analyses, sensitivity analyses were performed to investigate the impact of key assumptions made in the base case.

Model

Long-term projections were made using an Internet-based, interactive computer model designed to evaluate the long-term health outcomes and economic consequences of interventions in type 1 and type 2 diabetes. The model structure and validation procedures have been published previously^{23,24}, but a brief overview is provided here. The CORE Diabetes Model is based on 15 inter-dependent submodels that run in parallel to simulate the complications of diabetes (angina, myocardial infarction [MI], congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy, neuropathy, foot ulcer and amputation) as well as non-diabetes-specific mortality. Each one of the submodels is a Markov model created using time, state and diabetes type-dependent probabilities taken from published clinical and epidemiological studies. Tracker variables are utilized to overcome the memory-less properties of standard Markov models, and allow interconnectivity between submodels. The model performs real-time simulations and can take into account the complete range of diabetes interventions, including screening and treatment programs for complications. The model performs second-order Monte Carlo simulation to take into account uncertainty at the patient and parameter level. The CORE Diabetes Model has been validated by performing simulations designed to recreate published clinical and epidemiological studies in 66 separate analyses with a correlation coefficient (R^2) of 0.9224 ($y = 1.0187$) overall, indicating a close match to 'real-life' clinical progression. In the present analysis, the model was used to evaluate life expectancy, quality-adjusted life expectancy, lifetime cost of complications, and cost-effectiveness associated with SMBG in three different treatment cohorts.

Simulated cohorts

The simulated patient cohorts were defined using baseline demographics and complications data from the population with type 2 diabetes previously described by Karter *et al.*²². For the base case analysis, three cohorts defined by diabetes treatment were generated from the baseline population (Table 1). These treatments were a diet and exercise program, oral antidiabetic agents (OADs) and insulin therapy. Patient management practices, in terms of the proportion of patients taking concomitant medications (e.g. statins, aspirin, angiotensin converting enzyme inhibitors/angiotensin receptor blockers) and being screened for foot disease, retinopathy or renal disease, were taken from UK-specific published sources^{25–28}, and have been previously published²⁹.

Interventions

For the base case simulations, intervention effects were modelled for each of the three treatment cohorts according to published data, as summarized in Table 2. Estimates of treatment effects were based on the assumption that patients on diet and exercise were using one SMBG test per day, those on oral agents only were testing twice a day, and those on insulin were testing three times per day¹⁵. Treatment effects were applied in the simulation such that SMBG was associated with a reduction from baseline in HbA_{1c} of 0.3% in the diet and exercise cohort, 0.4% in the OAD cohort and 0.6% for patients taking insulin. Standard deviation (SD) of the change in HbA_{1c} was calculated from a weighted average of SDs reported in the SMBG arm of this study to be 1.84%, slightly larger than the SD of the effect of SMBG on HbA_{1c} reported by Coster *et al.*³⁰. This SD was applied to all treatment cohorts. For the purposes of the base case analysis, it was assumed that these differences in HbA_{1c} were maintained over the course of the simulation. Sensitivity analysis was performed on this assumption, by investigating the impact of the effects of SMBG on HbA_{1c} lasting for only 5 and 10 years. It was conservatively assumed that SMBG had no impact on hypoglycaemic event rates in the base case analysis, even though some evidence suggests that SMBG may help to avoid hypoglycaemic events^{31,32}.

A study by Murata *et al.*³³ reported 78% adherence to SMBG, and found that it was one of the main drivers of improvements in HbA_{1c} levels. We used an adherence rate of 78% in the base case analysis and 52%³⁴ in a sensitivity analysis. In 22% of simulated patients who were not adherent to SMBG, no improvements in HbA_{1c} were assumed, and the costs associated with SMBG were also no longer accounted for in the simulation.

Costs, perspective, time horizon and discounting

The analysis accounted costs from a third-party healthcare payer perspective (National Health Service [NHS] perspective), taking into account only direct medical costs (treatment and complication costs). Diabetes-specific costs of complications in the UK in 2004 were derived from published sources and have been previously summarized^{125–29,35}. Published evidence indicates that the cost of treating complications in patients with diabetes may be higher than in the general population³⁶. For example, it has been reported that the annual hospital costs associated with a fatal MI event (£1567) and a nonfatal MI event (£5104) in a patient with diabetes were higher than the reference

Table 1. Baseline characteristics of the simulated patient cohorts

| Characteristic | Number (%) or mean \pm SD | | |
|------------------------------------|-----------------------------|------------------|-----------------|
| | Diet and exercise | Oral agents only | Insulin-treated |
| HbA _{1c} (%) | 7.9 \pm 2.1 | 8.6 \pm 2.2 | 8.5 \pm 2.0 |
| Age (years) | 60.1 \pm 12.3 | 61.1 \pm 11.5 | 61.8 \pm 10.7 |
| Female | 2293 (48) | 5881 (46) | 2902 (52) |
| Ethnicity | | | |
| Non-Hispanic white | 2869 (60) | 7533 (59) | 3386 (61) |
| African-American | 507 (11) | 1352 (11) | 822 (15) |
| Hispanic | 406 (8) | 1094 (9) | 413 (7) |
| Asian-Pacific Islander | 584 (12) | 1749 (14) | 481 (9) |
| Native American | 29 (0.6) | 94 (0.7) | 34 (0.6) |
| Other | 20 (0.4) | 37 (0.3) | 12 (0.2) |
| Multi-ethnic | 400 (8.3) | 927 (7) | 404 (7) |
| Duration of diabetes (years) | 6.6 (8.7) | 7.2 (8.7) | 12.8 (9.3) |
| Annual eye exam | 1818 (38) | 5621 (44) | 3419 (62) |
| Current smokers | 544 (11) | 1359 (11) | 535 (10) |
| Baseline total cholesterol (mg/dL) | 217 \pm 48 | 215 \pm 48 | 220 \pm 149 |
| Baseline HDL-C (mg/dL) | 38 \pm 11 | 37 \pm 11 | 38 \pm 12 |
| Baseline LDL-C (mg/dL) | 139 \pm 37 | 136 \pm 36 | 139 \pm 38 |
| Baseline triglycerides (mg/dL) | 210 \pm 246 | 219 \pm 209 | 212 \pm 210 |
| Body mass index (BMI) | 30 \pm 7 | 30 \pm 7 | 31 \pm 6 |
| Prevalent myocardial infarction | 240 (5) | 630 (5) | 431 (8) |
| Prevalent PVD | 97 (2) | 229 (2) | 249 (4) |
| Prevalent stroke | 88 (2) | 277 (2) | 185 (3) |
| Prevalent CHF | 183 (4) | 399 (3) | 377 (7) |
| Prevalent overt nephropathy | 77 (2) | 147 (1) | 239 (4) |
| Prevalent BDR | 245 (5) | 1167 (9) | 1231 (22) |
| Prevalent PDR | 1 (0.02) | 7 (0.1) | 13 (0.2) |
| Prevalent foot ulcer | 69 (1) | 136 (1) | 220 (4) |
| Prevalent neuropathy | 351 (7) | 1091 (9) | 1046 (19) |
| Prevalent amputation | 20 (0.4) | 51 (0.4) | 96 (2) |
| Taking ACE inhibitor or ARB | 1178 (25) | 4637 (36) | 2549 (46) |
| Taking statins | 436 (9) | 1632 (13) | 942 (17) |

ACE inhibitor = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BDR = background diabetic retinopathy CHF = congestive heart failure; PDR = proliferative diabetic retinopathy; PVD = peripheral vascular disease

costs for a completed consultation episode for MI with complications in the general population (£1479)^{36,37}. Therefore, in the present analysis, we used costs data specific to patients with diabetes as opposed to NHS reference costs. All costs data that were not available in 2004 values were inflated using the composite NHS price inflation index³⁸.

Acquisition costs of the treatment interventions used in the analysis were all based on published NHS costs in the UK. SMBG costs were based on the following: the monitor was supplied for free in the UK, in the first year of treatment patients were trained for 1 h by a diabetes nurse (£10.74)³⁹, each testing strip cost (£0.306) (data on file, Lifescan UK) and each lancet cost (£0.0324) (mean NHS reimbursement price). The annual costs associated with each treatment regimen are summarized in Table 3. The costs of alcohol swabs were not included.

With the increase in costs associated with SMBG on OAD-treated patients, we assumed that patients

starting on diet and exercise therapy would all be on OAD treatment after 5 years, but we conservatively assumed that there would be no further improvement in glycaemic control associated with SMBG when switching from diet and exercise to OAD treatment. Similarly, we assumed that those patients on OAD treatment would all be using insulin after 5 years of OAD treatment, with the associated increase in costs but no further improvement in glycaemic control.

In addition to considering the costs of SMBG and the costs of diabetes complications, other costs, including those of outpatient consultations, education, medications and other investigations, were accounted for. By making a conservative assumption potentially biasing against SMBG, we assigned the annual mean costs per patient for routine treatment in the intensive arm of the United Kingdom Prospective Diabetes Study (UKPDS)⁴⁰ (£4350 over the mean 10-year study period expressed in 1997 values), inflated to 2004

Table 2. Summary of published data used to estimate effects of SMBG in patients with type 2 diabetes

| Source | Study type | Follow-up | Intervention | Comparison | Change in HbA _{1c} in type 2 diabetes patients | |
|--|---|-------------|---|---|---|--|
| | | | | | Diet and exercise | Oral agents only Insulin-treated |
| Sarol <i>et al.</i> ¹² | Systematic review/ meta-analysis | 3–10 months | SMBG + education | No SMBG | -0.39% (-0.21 to -0.54) | |
| Welschen <i>et al.</i> ^{13,14} | Systematic review/ meta-analysis | 3–12 months | SMBG ± education | No SMBG | -0.39% (-0.21 to -0.56) | |
| Guerci <i>et al.</i> ⁴⁸ | Randomized, controlled trial | 5 months | SMBG (testing ≥ 6 times a week) | No SMBG | -0.28% (-0.05 to -0.51) | |
| Schwedes <i>et al.</i> ⁴¹ | Randomized, controlled trial | 12 months | SMBG (testing ≥ 6 times a week) + structured counselling | No SMBG + unstructured counselling | -0.46% (-0.13 to -0.79) | |
| Karter <i>et al.</i> ²² | Outcome study, retrospective cohort | 24 months | SMBG at or above ADA-recommended rates: 1/day on diet and exercise 2/day on oral medication 2/day on insulin | SMBG below ADA- recommended rates | -0.4% (-0.3 to -0.6) | -0.6% (-0.5 to -0.7) |
| Franciosi <i>et al.</i> ⁴⁹ | Outcome study, retrospective | - | More SMBG testing | Less SMBG testing | | HbA _{1c} is independently associated with insulin-self management and SMBG testing frequency once a day or more |
| Murata <i>et al.</i> ³³ | Outcome study, retrospective cohort | 8–52 weeks | Compliant with recommended test frequency for SMBG | Not compliant with recommended test frequency for SMBG | | HbA _{1c} is independently associated with SMBG testing at ADA- recommended frequencies |
| Schiel <i>et al.</i> ⁵⁰ | Outcome study, retrospective cohort | 1 year | More SMBG testing | Less SMBG testing | | HbA _{1c} is independently associated with more frequent SMBG testing |

Table 3. Summary of annual costs of SMBG for three cohorts of patients with type 2 diabetes

| | Annual cost of SMBG in each cohort | |
|--------------------------|------------------------------------|----------|
| | Year 1 | Years 2+ |
| Diet and exercise cohort | £134.34 | £123.60 |
| Oral agents only cohort | £257.94 | £247.20 |
| Insulin cohort | £381.54 | £370.80 |

These costs include the costs of 1 h of education/training by a nurse in the first year (£10.74), as well as 1, 2 or 3 strips and lancets per day in the diet and exercise, OAD, or insulin-treated cohorts respectively (1 strip = £0.31; 1 lancet = £0.03). SMBG monitors are supplied free of charge by the manufacturers in the UK. In addition to the costs outlined here, £469 per patient per year for patients using SMBG was added to account for other routine treatments and medications, as was £394 per patient per year for patients not using SMBG.

values for patients using recommended UK inflation rates³⁸. This amounted to an additional £469 per patient per year (2004 values) when using SMBG. These additional costs were accounted for when patients were not using SMBG (either in the 'no SMBG' treatment arm, or in the 22% deemed to be noncompliant with SMBG) by assigning the routine treatment costs of conventional control from the UKPDS, amounting to £394 per year (2004 values) per patient not using SMBG.

In line with the National Institute for Health and Clinical Excellence (NICE) Guidelines, costs and clinical benefits were discounted 3.5% annually in the base case analysis. A patient-lifetime horizon was used in the base case. The impact of both of these settings on cost and clinical outcomes was investigated in sensitivity analyses.

Sensitivity analyses

Sensitivity analyses were performed to investigate the influence of discount rates, time horizon, and the duration of SMBG effect on HbA_{1c} levels reported in the base case analysis. In addition to the currently recommended discounts of 3.5% per annum for clinical and cost outcomes in the UK, discounting was also performed varying using rates of 6.0% for costs and 1.5% for quality-adjusted life years (QALYs) gained. Sensitivity analysis was performed using time horizons of 10 years and 20 years. To test the impact of duration of HbA_{1c} effect on the base case outcomes, sensitivity analyses were performed assuming that the effects on HbA_{1c} associated with SMBG only lasted for 5 years (glycaemic control was subsequently identical to the no SMBG treatment arm).

We used an adherence rate of 78% in the base case analysis, with 52%³⁴ used in a sensitivity analysis.

In the base case analysis, it was assumed that there is no negative impact of SMBG on health utility, as described by Schwedes *et al.*⁴¹ and Muchmore *et al.*⁴², who found that there were no differences in quality of life, well-being and treatment satisfaction in patients using SMBG versus those not using SMBG. Sensitivity analysis was performed by assuming an equivalent decrement in utility in patients treated either with diet and exercise or an oral hypoglycaemic agent as would be attributed to that seen by patients on insulin therapy⁴³.

Statistical approach

For each simulation performed in the present study (base case and sensitivity analyses), 1000 patients were run through the model 1000 times and mean results and SDs were generated using a nonparametric bootstrapping approach⁴⁴.

Results

Base case analysis

The improvements in glycaemic control seen with SMBG were projected to lead to improvements in life expectancy, quality-adjusted life expectancy, but moderately increased total direct costs per patient, with incremental cost per QALY gained falling within an attractive range.

Clinical outcomes

SMBG was associated with improvements in life expectancy and quality-adjusted life expectancy in all three treatment cohorts (Table 4). In patients on a treatment regimen of diet and exercise, improvements in glycaemic control with once-daily SMBG was projected to lead to an improvement in undiscounted life expectancy of 0.371 years compared to no SMBG. In patients receiving OADs, twice-daily SMBG was projected to improve life expectancy by 0.489 years, and in the cohort of type 2 diabetes patients receiving insulin, SMBG led to an improvement in life expectancy of 0.521 years compared to no monitoring. A similar pattern was observed with quality-adjusted life expectancy, where improvements of 0.165, 0.225 and 0.255 discounted QALYs were associated with SMBG in patients receiving diet and exercise, OADs, and insulin therapy, respectively.

Analysis of mean time to onset of diabetes-related complications indicated that SMBG was associated with delays in the onset of all major diabetes-related complications (Table 5).

Table 4. Summary of base case results for three cohorts of patients with type 2 diabetes

| Outcomes | SMBG | No SMBG | Difference |
|--|----------------|----------------|------------|
| Diet and exercise cohort | | | |
| Undiscounted life expectancy, mean (SD) (years) | 12.302 (2.481) | 11.931 (2.397) | 0.371 |
| Quality-adjusted life expectancy (QALYs), mean (SD) (years)* | 6.342 (1.864) | 6.177 (1.753) | 0.165 |
| Total lifetime costs (£)* | 20 668 (7469) | 18 105 (6724) | 2564 |
| Incremental costs/QALY gained | | 15 515 | |
| OADs cohort | | | |
| Undiscounted life expectancy, mean (SD) (years) | 11.807 (2.453) | 11.318 (2.330) | 0.489 |
| Quality-adjusted life expectancy (QALYs), mean (SD) (years)* | 6.158 (1.839) | 5.933 (1.708) | 0.225 |
| Total lifetime costs (£)* | 21 650 (7019) | 20 636 (6807) | 1013 |
| Incremental costs/QALY gained | | 4508 | |
| Insulin cohort | | | |
| Undiscounted life expectancy, mean (SD) (years) | 10.339 (2.281) | 9.818 (2.190) | 0.521 |
| Quality-adjusted life expectancy (QALYs), mean (SD) (years)* | 5.269 (1.665) | 5.014 (1.577) | 0.255 |
| Total lifetime costs (£)* | 23 712 (7276) | 22 541 (6617) | 1171 |
| Incremental costs/QALY gained | | 4593 | |

QALY = quality-adjusted life years. Values shown are means with standard deviation in parentheses

*Discounted at 3.5% per annum

Table 5. Mean time alive and free of new complications (years) for three cohorts of patients with type 2 diabetes

| Complication | Diet and exercise | | Oral agents only | | Insulin therapy | |
|---------------------------------------|-------------------|---------|------------------|---------|-----------------|---------|
| | SMBG | No SMBG | SMBG | No SMBG | SMBG | No SMBG |
| Retinopathy BDR | 9.33 | 9.00 | 8.61 | 8.12 | 6.45 | 5.99 |
| Retinopathy PDR | 12.08 | 11.72 | 11.58 | 11.08 | 10.06 | 9.54 |
| Macular edema | 10.43 | 10.09 | 9.18 | 8.69 | 8.02 | 7.49 |
| Cataract | 11.55 | 11.20 | 10.83 | 10.36 | 9.54 | 9.04 |
| Severe vision loss | 11.67 | 11.31 | 10.84 | 10.37 | 9.47 | 8.97 |
| Microalbuminuria | 7.33 | 7.05 | 6.98 | 6.49 | 6.10 | 5.59 |
| Gross proteinuria | 10.93 | 10.60 | 10.56 | 10.05 | 9.06 | 8.52 |
| End-stage renal disease | 12.05 | 11.70 | 11.59 | 11.10 | 10.11 | 9.59 |
| Ulcer, first | 10.95 | 10.60 | 10.53 | 10.06 | 8.75 | 8.27 |
| Amputation, first | 11.98 | 11.62 | 11.51 | 11.03 | 9.87 | 9.37 |
| Neuropathy, onset | 7.37 | 7.07 | 7.11 | 6.60 | 5.38 | 4.86 |
| Peripheral vascular disease, onset | 10.81 | 10.46 | 10.42 | 9.60 | 8.87 | 8.31 |
| Congestive heart failure, first event | 10.45 | 10.07 | 10.16 | 9.64 | 8.55 | 8.02 |
| Angina | 10.45 | 9.99 | 10.41 | 9.97 | 8.96 | 8.46 |
| Myocardial infarction, first event | 10.57 | 10.16 | 10.16 | 9.62 | 8.42 | 7.91 |
| Stroke, event | 11.40 | 11.08 | 11.06 | 10.62 | 9.52 | 9.05 |

Mean life expectancy was 12.302 and 11.931 years in the SMBG or no SMBG treatment arms, respectively, for patients receiving diet and exercise initially; 11.807 and 11.318 years in the SMBG or no SMBG treatment arms, respectively, for patients receiving OADs initially; 10.339 and 9.818 years in the SMBG or no SMBG treatment arms, respectively, for patients receiving insulin. If time alive and free of complications is close to the projected life expectancy, this indicates that these complications occurred towards the end of patients lives

BDR = background (non-proliferative) diabetic retinopathy; PDR = proliferative diabetic retinopathy

Lifetime costs and cost-effectiveness

Mean direct medical costs over patient lifetimes were higher with SMBG than without in the UK setting (Table 4). Incremental lifetime costs were £2564 per patient in the diet and exercise group, £1013 in the OAD group and £1171 in the insulin therapy group. A breakdown of costs showed that the additional treatment costs associated with SMBG were, for a large part, offset by the reduced cost of diabetes-related complications in all three cohorts. Calculation

of incremental cost-effectiveness ratios (ICERs) for SMBG versus no SMBG produced values of £15 515 per QALY gained in patients treated with diet and exercise, £4508 per QALY gained in those receiving OADs and £4593 per QALY gained in patients taking insulin (Table 4).

The statistical approach used in the analysis (generating 1000 means for incremental costs and incremental effectiveness in terms of quality-adjusted life expectancy) allowed us to generate estimates of the probability that incremental costs per QALY for

SMBG versus no SMBG would fall below a given willingness-to-pay threshold. This analysis showed that at a willingness-to-pay threshold of £30 000 for each QALY gained, SMBG would have a 51% likelihood of being cost-effective in patients treated with diet and exercise, a 51% likelihood of being cost-effective in those taking OADs and a 55% likelihood of being cost-effective in patients receiving insulin therapy.

Sensitivity analyses

Results of the various sensitivity analyses that were performed are summarized in Table 6. Using discount rates of 6.0% for costs and 1.5% for QALYs improved the cost-effectiveness ratios in all cohorts.

Shorter time horizons resulted in less attractive incremental cost-effectiveness ratios. This was to be expected, as improvements in glycaemic control require time to allow the reductions in the incidence and progression of complications to become obvious. Using a 10-year time horizon, SMBG remained attractive in the insulin-treated cohorts, was borderline

in the OAD-treated cohort, and was less attractive in the diet and exercise-treated cohort. Using a 20-year time horizon or longer, SMBG was cost-effective in all cohorts.

When the effects of SMBG on improved glycaemic control compared to no SMBG were assumed only to last for 5 years (instead of lifetime HbA_{1c} differences if patients were adherent to SMBG as was assumed in the base case analysis), the cost-effectiveness ratios became less attractive, although the incremental costs per QALY gained still fell below £30 000–£57 000 in all cohorts.

If a 52% adherence rate was assumed (instead of the 78% adherence rate used in the base case analysis), improvements in QALYs decreased, but total costs also decreased, leading to overall improvements in the ICERs in all treatment cohorts.

When an equivalent decrement in utility, as would be attributed to that seen by patients on insulin therapy, was assumed for patients using SMBG, improvements in QALYs were decreased, with subsequently higher costs/QALY gained of £34 259, £6985 and £6586 per

Table 6. Cost-utility results from sensitivity analyses

| | Quality-adjusted life expectancy (QALYs) | Δ Costs (£) | Incremental costs/QALY gained (£) |
|--|--|-------------|-----------------------------------|
| Base case analyses | | | |
| Diet and exercise | 0.165 | 2564 | 15 515 |
| OADs | 0.225 | 1013 | 4508 |
| Insulin | 0.255 | 1171 | 4593 |
| Discount rates 6% for costs, 1.5% for QALYs | | | |
| Diet and exercise | 0.224 | 2192 | 9772 |
| OADs | 0.302 | 879 | 2346 |
| Insulin | 0.329 | 1016 | 3087 |
| Time horizon 10 years | | | |
| Diet and exercise | 0.030 | 2266 | 74 528 |
| OADs | 0.025 | 829 | 33 724 |
| Insulin | 0.060 | 668 | 11 082 |
| Time horizon 20 years | | | |
| Diet and exercise | 0.108 | 2352 | 21 824 |
| OADs | 0.126 | 1522 | 12 102 |
| Insulin | 0.065 | 717 | 11 057 |
| Effect on HbA _{1c} lasting for 5 years | | | |
| Diet and exercise | 0.118 | 3052 | 25 802 |
| OADs | 0.163 | 1491 | 9141 |
| Insulin | 0.183 | 1810 | 9909 |
| 52% annual adherence rate | | | |
| Diet and exercise | 0.135 | 1221 | 9020 |
| OADs | 0.187 | 467 | 2501 |
| Insulin | 0.196 | 682 | 3479 |
| Assuming disutility of SMBG equivalent to taking insulin | | | |
| Diet and exercise | 0.077 | 2623 | 34 259 |
| OADs | 0.140 | 976 | 6985 |
| Insulin | 0.172 | 1132 | 6586 |

Δ = difference between SMBG and control value

ICER values are given as cost per QALY gained with SMBG versus control

QALY gained for patients on diet and exercise, OADs or insulin, respectively – the OAD and insulin values generally considered to be good value for money, even with this assumption biasing against SMBG. A disutility result of -0.04 or lower associated with SMBG versus no SMBG would completely negate the QALYs gained due to lower complication rates associated with improvements in glycaemic control.

Discussion

This manuscript reports the first study to evaluate the long-term cost-effectiveness of SMBG in patients with type 2 diabetes. Our projections, using an established and validated model of diabetes, indicate that over patient lifetimes the improvements in HbA_{1c} associated with SMBG, delay or prevent the onset and progression of diabetes complications and subsequently improve life expectancy and quality-adjusted life expectancy. The additional costs of SMBG were in large part offset by a reduction in the cost of diabetes-related complications. ICERs for SMBG versus no monitoring all fell well below the threshold range of around £30 000–£57 000 per QALY gained that represents good value for money in the UK setting^{45,46}. Plotting an acceptability curve demonstrated that in the base analysis there was a 51–55% likelihood that SMBG would be below a threshold of £35 000 per QALY gained in the UK. This is to be expected due to the diverse nature of the simulated baseline cohort, and the relatively broad dispersion of the treatment effects of SMBG.

The data used to design the model are primarily from clinical and large-scale observational studies. The advantages are that many real-life factors such as patient demographics and effectiveness of SMBG were demonstrated in a number of clinical trials and subsequent meta-analyses, as well as large-scale cross-sectional database analyses of real-life populations. Adherence to and effectiveness of SMBG in a real-life population, rather than efficacy as demonstrated in a clinical trial setting, have been confirmed and these parameters applied within the modelling setting.

Extensive sensitivity analysis showed that these findings were robust under a wide range of assumptions regarding discount rates, time horizons (although using shorter time horizons led to less attractive cost-effectiveness ratios, as would be expected due to the length of time required for improvements in glycaemic control to translate to reductions in long-term complications and associated improvements in costs and quality-adjusted life expectancy), duration of effect of SMBG on improved glycaemic control, adherence rates to SMBG, and disutilities associated with SMBG.

Our base case analysis assumed no decrement in utility associated with SMBG itself, as has been suggested in other studies^{41,42}, although intuitively, one may suspect that patients would prefer not to have to prick themselves in order to draw a blood sample for SMBG. We examined the potential impact of this on quality-adjusted life expectancy. When we assumed an annual disutility of -0.034 associated with SMBG (equivalent to that seen in type 2 patients using insulin seen in a survey of type 2 diabetes patients in Michigan), incremental costs per QALY increased, and were in the vicinity of a £30 000–£35 000 threshold, indicating that despite a potential decrement in utility associated with finger pricking, SMBG is likely to remain cost effective versus no SMBG. If the disutility associated with SMBG was -0.04 or lower, any improvements in QALYs due to improved glycaemic control in the diet and exercise-treated cohort in the SMBG treatment arm would be negated. More rigorous studies are required to identify the potential 'true' disutility associated with SMBG in patients treated with diet and exercise, OADs or insulin.

Sensitivity analysis of adherence rates demonstrated that consideration of adherence is a double-edged sword. While the QALY improvements were lower assuming lower adherence rates, the overall costs per patient also decreased in the SMBG arm, resulting in more attractive incremental cost-effectiveness ratios. Murata *et al.*³³ reported that compliance with SMBG testing was an independent predictor of improvements in glycaemic control, with benefits seen only in patients with compliance exceeding 75%. When assumed that only 52% of patients would be adherent (assuming no effect of SMBG on glycaemic control in patients not adherent), SMBG was still shown to be cost-effective.

There are a number of potential shortcomings of this health economics analysis. One limitation may be the clinical data used to drive the analysis. Welschen *et al.* reported only a moderate level of available evidence for the effect of SMBG on glycaemic control in patients with type 2 diabetes not using insulin in their meta-analysis/systematic review, but suggest that the results of their meta-analysis should be interpreted with caution due to the relatively poor methodological quality of the trials included^{13,14}. They further stated that while the body of evidence in favour of SMBG to date is only moderate, it is clinically relevant in a positive direction, and highlights the need for large-scale randomized, controlled clinical trials to further elucidate the potential beneficial effects of SMBG⁴⁷. A UK Health Technology Assessment report published in 2000 found insufficient clinical evidence to support recommendations for SMBG in patients with type 2 diabetes, but acknowledged small independent effects of SMBG on improvements in glycaemic control³⁰. In

studies assessing an intervention like SMBG, it may be difficult to disentangle causes and effects. SMBG has been postulated as a powerful stimulus for changing subjects' behaviours, but exactly which behavioural changes lead to improvements in HbA_{1c} have not been readily identifiable. Positive changes in patient behaviour, including improved medication usage/compliance/self-titration, improved rates of consultation with medical personnel, or improvements in diet and exercise levels may all contribute. Selection bias may occur in studies comparing SMBG with no SMBG.

Computer simulation models allow the projection of short-term data from observational studies or clinical trials to evaluate clinical outcomes and long-term costs, providing information that is often unavailable or impossible to collect. In the present study, data from nine published studies were used to estimate the effects of SMBG on glycaemic control to form the basis of a long-term modelling simulation. A key assumption in the base case analysis was that the improvements in HbA_{1c} associated with SMBG were maintained throughout the lifetime horizon of the simulation. Murata *et al.*³³ reported persistent decreases in HbA_{1c} of $-0.31 \pm .17\%$ in insulin-treated subjects with type 2 diabetes followed for 1 year. These subjects were not provided with any self-care recommendations, referrals, or treatment modifications. Sensitivity analysis confirmed that even under conservative assumptions regarding the duration of improvement of HbA_{1c} (5 years, after which there would be no difference in HbA_{1c} between SMBG and no SMBG), or shorter time horizons, SMBG was cost-effective in a UK setting. However, additional research will be needed to evaluate other settings such as the United States, where planning horizons may be shorter, and SMBG and health care costs differ from that used in this simulation study.

It was conservatively assumed that SMBG does not lead to a reduction in hypoglycaemic event rates, although at least one clinical study has demonstrated a reduction in asymptomatic hypoglycaemia associated with SMBG⁴⁸. No studies to date have reported reductions in major (serious) hypoglycaemic event rates.

We did not compare SMBG to urine monitoring of blood glucose. Bergenstal *et al.*¹⁵, state that urine glucose testing is not recommended as a replacement for SMBG; its use should be restricted to those rare situations where there is no access to SMBG. The main limitation of urine glucose measurements is that it provides only a rough estimate of prevailing glucose levels, and no information on blood glucose levels below the renal threshold, which may be within the target range for blood glucose.

Another potential shortcoming of this analysis is that it only takes into account direct medical costs from the NHS perspective. The study does not include indirect or direct non-medical costs such as lost productivity or transportation costs, and is therefore likely to underestimate costs from a social perspective. Given that SMBG is associated with improved glycaemic control and fewer complications, it seems likely that inclusion of indirect costs would improve its cost-effectiveness compared to no monitoring.

Conclusions

The importance of SMBG in monitoring and improving glycaemic control and its endorsement as an integral part of an overall diabetes management program were made clear at the recent IDC, WHO and AADE global consensus conference¹⁵. Within the limitations of modelling and the available clinical data, the results of the present cost-effectiveness analysis provide initial evidence that financial implementation of SMBG can be an efficient and cost-effective intervention in patients with type 2 diabetes, but should be regarded as hypothesis-generating rather than providing a definitive result. Based on the clinical evidence available to date, improvements in glycaemic control with interventions, including SMBG, were projected to improve patient outcomes with an acceptable cost-effectiveness ratio in the UK setting. High quality, large-scale, prospective, randomized controlled studies of SMBG in this patient group are required to enable a more accurate estimation of the cost-effectiveness of SMBG in patients with type 2 diabetes.

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