Cost Effectiveness and Resource Allocation

Research

Health and economic impact of combining metformin with nateglinide to achieve glycemic control: Comparison of the lifetime costs of complications in the U.K

Alexandra J Ward*[1], Maribel Salas[1], J Jaime Caro[1,2] and David Owens[3]

Address: [1]Caro Research Institute, Concord, MA USA, [2]Division of General Internal Medicine, McGill University, Montreal, Quebec, Canada and [3]Diabetes Research Unit, Llandough Hospital, Penarth, UK

Email: Alexandra J Ward* - alexward@caroresearch.com; Maribel Salas - msalas@caroresearch.com; J Jaime Caro - jcaro@caroresearch.com; David Owens - Owensdr@cardiff.ac.uk

* Corresponding author

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Abstract

Background: To reduce the likelihood of complications in persons with type 2 diabetes, it is critical to control hyperglycaemia. Monotherapy with metformin or insulin secretagogues may fail to sustain control after an initial reduction in glycemic levels. Thus, combining metformin with other agents is frequently necessary. These analyses model the potential long-term economic and health impact of using combination therapy to improve glycemic control.

Methods: An existing model that simulates the long-term course of type 2 diabetes in relation to glycosylated haemoglobin (HbA_{1c}) and post-prandial glucose (PPG) was used to compare the combination of nateglinide with metformin to monotherapy with metformin. Complication rates were estimated for major diabetes-related complications (macrovascular and microvascular) based on existing epidemiologic studies and clinical trial data. Utilities and costs were estimated using data collected in the United Kingdom Prospective Diabetes Study (UKPDS). Survival, life years gained (LYG), quality-adjusted life years (QALY), complication rates and associated costs were estimated. Costs were discounted at 6% and benefits at 1.5% per year.

Results: Combination therapy was predicted to reduce complication rates and associated costs compared with metformin. Survival increased by 0.39 (0.32 discounted) and QALY by 0.46 years (0.37 discounted) implying costs of £6,772 per discounted LYG and £5,609 per discounted QALY. Sensitivity analyses showed the results to be consistent over broad ranges.

Conclusion: Although drug treatment costs are increased by combination therapy, this cost is expected to be partially offset by a reduction in the costs of treating long-term diabetes complications.

Background

Type 2 diabetes is a prevalent disease with complications that cause substantial financial burden [1]. Improving glycemic control can influence the prognosis for patients with type 2 diabetes as it reduces the risk of developing microvascular complications (nephropathy, neuropathy and retinopathy) [2]. Recent guidelines from the National Institute of Clinical Excellence (NICE) recommend the initial use of diet and exercise and, when these fail to maintain glycemic control, metformin should be

prescribed [3]. Monotherapy with any treatment, however, is often unable to sustain target HbA_{1c} levels of 6.5–7.5% in the majority of patients. They are therefore expected to require additional therapy within six years [4].

Sulphonylureas have been frequently used in combination with metformin, but are not always appropriate choices as these may cause weight gain and increase the risk of hypoglycaemia [3]. The development of newer insulin secretagogues, such as nateglinide, provides physicians with an alternative to sulphonylureas when selecting the optimal combination of oral agents for an individual patient. Nateglinide (120 mg three times per day) is advantageous over other agents in that it helps to control postprandial glucose (PPG) levels, along with glycosylated hemoglobin, and also can be used in combination with metformin (500 mg three times per day) [5]. The use of combination therapy subsequent to the failure of monotherapy helps some patients to achieve the recommend levels of glycemic control. However, use of any combination is clearly also associated with an increased cost compared with metformin as monotherapy.

The purpose of this study was to estimate the potential long-term health and economic impact of adding nateglinide to metformin in order to improve glycemic control and thereby reduce complication rates. Together with the clinical data on the therapeutic efficacy of combination therapy, these economic analyses facilitate assessment of the long-term cost-effectiveness from the perspective of the health care system, of using this combination to achieve improved glycemic control.

Methods

Model framework

This model was developed to simulate the lifetime risk of developing diabetes-related complications rates (microvascular and macrovascular) in a cohort of patients diagnosed with type 2 diabetes [6,7] (Figure 1). In this updated version of the model, both the level of HbA_{1c} (glycosylated haemoglobin) and two-hour postprandial glucose (PPG) define the degree of glycemic control [8,9]. Each year of remaining life is simulated for all the patients in the cohort and during each cycle, the patient is exposed to the risks of developing each type of complication. These risks are determined from the degree of glycemic control, as well as other known risk factors, such as duration of diabetes.

The microvascular complications (nephropathy, retinopathy, and neuropathy) have several stages through which each patient can progress. The most severe stages for the microvascular complications are end stage renal disease, blindness or amputations. The stages of a complication are assumed irreversible – only progression to more severe stages is possible. Complications such as hypoglycaemia and foot ulcer were assumed to resolve in the course of each cycle of one year. For the purpose of this model, macrovascular complications (stroke and myocardial infarction) were considered as finite events, rather than progressive conditions.

Each simulated patient had clinical characteristics that were determined by the input distributions specified. Using a Monte Carlo technique, each patient in the cohort was assigned gender, race and age. The assignment of cholesterol level, smoking status, body mass index and systolic blood pressure was then determined using the distributions and associations observed amongst patients with type 2 diabetes [10-12].

For thirty annual cycles, the model checks each patient who has survived to that point, and updates the age, duration of disease and HbA_{1c} level. Over each cycle, the estimated risks of developing a new complication or progressing to the next stage of an established one are assigned to each simulated patient in the cohort. During a pre-model period of seven years, the patients were allowed to accumulate complications but costs from managing these complications are not considered in the comparisons.

The model was assessed for face validity by clinical experts and health authorities. Previous analyses using the model have been evaluated by peer review [6-9]. Source data and other independently obtained results were used as comparisons to determine predictive validity [2,13]. Model results for relative risk over 10 years for all-cause mortality and for microvascular disease and retinopathy at 12 years were consistent with UKPDS patients in intensive and conventional treatment groups.

Risk estimates

The risk of death in this updated model was linked to both PPG and HbA_{1c} levels. Weibull functions were derived from the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study [14,15] – and estimates were based on the patients' age, gender, systolic blood pressure, total cholesterol, body mass index, smoking status, and PPG level. As in the original model, the risk of death was also assessed from the age- and gender-dependent mortality for patients diagnosed with type 2 diabetes [16], with an adjustment if nephropathy develops [17,18]. The higher of these three death risk estimates in each model cycle was applied.

The estimates for microvascular complications (nephropathy, retinopathy, and neuropathy) were determined from the available epidemiological studies [19-21] and the risk gradients observed in the Diabetes Control and

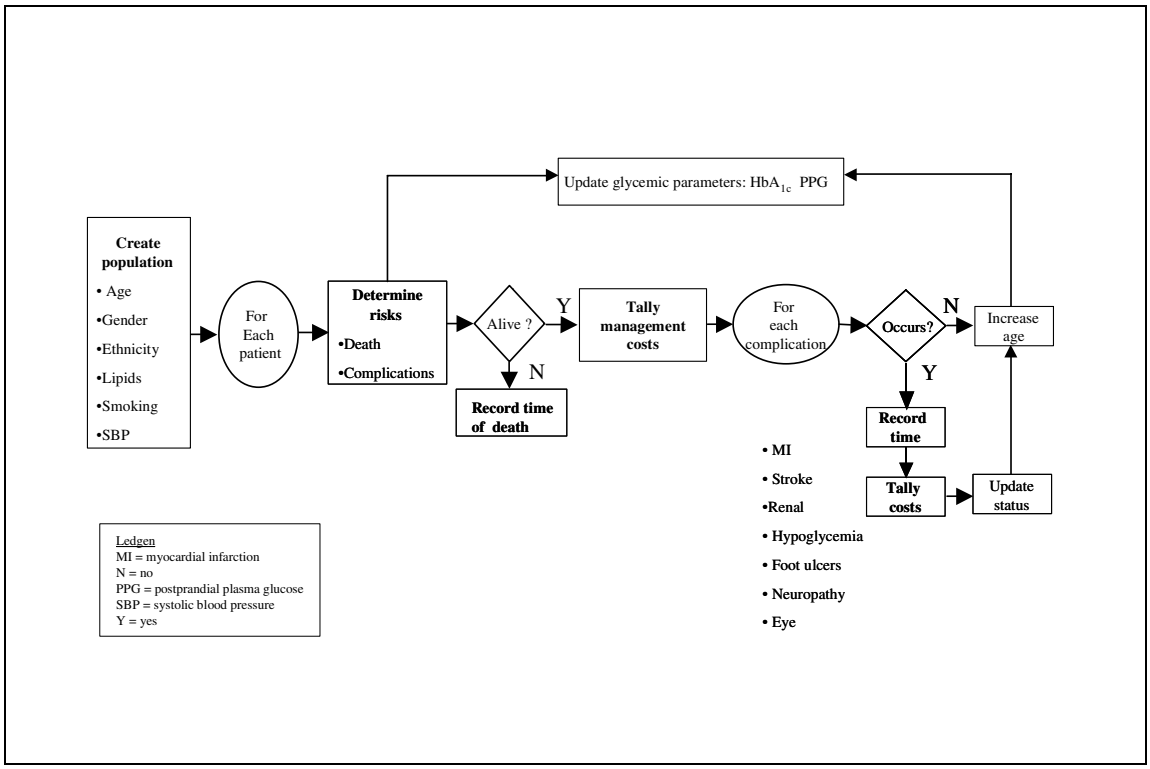

Figure 1
Schematic representation of model (Reprinted with permission from *Can J Diabetes*. 2003; 27(1): 33–41).

Complications Trial (DCCT) were assumed to apply to type 2 diabetes [22], an accepted assumption [23-25] confirmed by the UKPDS [2]. The risks of each microvascular complication are estimated by adjusting each according to the patient's HbA_{1c} level at a specific point in time (*risk* = $1 - e^{-\lambda \cdot t}$, where $\lambda = \lambda_b H_r^{\beta}$, and H_r is the HbA_{1c} value relative to a standard and β is a complication-specific coefficient) [16,26]. The base hazard for a complication depends on factors such as duration of diabetes, race and for the retinopathy module, for example, also the probability of detection and treatment.

Evidence has recently been published that indicates PPG is an independent predictor of the occurrence of macrovascular complications, as well as of mortality [14,27,28]. In this updated model, the risk of stroke or myocardial infarction was estimated using Weibull functions derived from the DECODE study [15]. The risk equations derived from the DECODE study include established risk factors for macrovascular disease such as age, gender, systolic blood pressure, total cholesterol, body mass index, smoking status, as well as PPG level.

Costs

For each complication, the direct medical costs were estimated for the immediate impact of the event (costs arising in the year the event occurs) and the subsequent impact of the complication (costs accrued in years subsequent to the year of the event). Clarke et al combined resource use data collected from the UKPDS with cost estimates for these services, and published regression equations for estimating the cost of major complications [29]. The annual hospital in-patient costs, and non-hospital costs (general practioners, nurses, podiatrists, opticians, dieticians, hospital outpatient clinics) were estimated using these regression equations for the event year and subsequent years. As the inpatient costs were estimated for myocardial infarction, stroke, blindness, or an amputation. The inpatient costs of less severe stages of these complications were not included in these estimates the cost estimates are quite conservative. All complication costs are expressed in 1999

Great Britain Pounds (£1 GBP = $1.7 USD = €1.4 Euros). It should be noted that the cost of end stage renal disease was estimated based on data from 1996 [30]. We elected not to inflate this cost, however, as the applicability of general inflation rates to something as specialized as the management of end stage renal disease is fraught with inaccuracy and this was the most expensive complication (£21,456 per year).

The drug treatment cost estimates conservatively assumed full compliance with the treatment. The daily cost for metformin (1500 mg per day) was £0.07 [31], and £0.87 for the combination of nateglinide (360 mg/day = £0.80) with metformin (1500 mg per day) [31].

Analyses

The distributions of HbA_{1c} and PPG at the beginning of the model period, as well as the effects of each treatment regimen were obtained from a clinical trial assessing the efficacy of combining nateglinide (360 mg/day) with metformin (1500 mg per day) compared with metformin alone [5] (Table 1). The mean HbA_{1c} at baseline was 8.4%, at the trial end point the HbA_{1c} was reduced with both metformin and for the combination (-0.8%, and -1.5% respectively), as was the PPG level (-0.9, and -2.3 respectively).

After processing each cohort of 10,000 patients over thirty years, the model provides estimates of the mean survival time, the frequency of each type of complication, and the mean accumulated complication and treatment costs per patient. Survival time is also weighted by the quality of life; the utility assigned depending on the complications present. The utilities assigned were as follows; amputation 0.50, stroke 0.62, blindness 0.71 and myocardial infarction 0.73 [32], end stage renal disease 0.59 [33]. The cost per life year gained (LYG) and cost per quality adjusted life year (QALY) was determined. Consistent with NICE recommendations, costs were discounted at 6% and benefits at 1.5% [34]. Sensitivity analyses were conducted on model parameters and uncertainty in the base case estimates was examined using the bootstrap technique with 250 model replications, and 1000 re-samples from the results of these simulations.

Results

Our analyses simulated a cohort of patients treated with metformin and estimated the mean survival time to be 13.5 years. Over their lifetime, microvascular complications were frequent – retinopathy was the most common affecting over a quarter of the patients, as well as foot ulcers and microalbuminuria (Table 2). The model predicted mean lifetime discounted costs per patient of about five thousand pounds (Table 3). Macrovascular disease was common (Table 2) and accounted for about 40% of the lifetime costs due to complications, with myocardial infarction being the slightly larger component of the macrovascular costs (63%). Amputation comprised one third of the cost estimate for management of microvascular complications.

Table 1: Clinical characteristics of simulated cohort

Parameter	Value
Age (years)	
Mean	58
Range	29–88
Gender (% Female)	38%
Race	
Caucasian	92%
Afro-Caribbean	4%
Asian	4%
Initial resulting HbA_{1c} level (mean)	
Metformin monotherapy	7.6%
Combination therapy	6.9%
HbA_{1c} annual upward drift	0.15%

Base case

The improvement in glycemic control, in terms of both the HbA_{1c} and the PPG, expected with the combination nateglinide with metformin is estimated to increase survival on average 0.39 years per patient (0.32 discounted years) or 0.46 (0.37 discounted) QALY (Table 3). Moreover, complications were expected to occur less frequently, or at least progress more slowly (Table 2).

Combination therapy is expected to reduce the frequency of complications and prolong survival, but also increase the average costs by an average of £2,066 per patient. To determine the impact of the nateglinide-metformin combination on the cost of managing complications, the difference in mean cost between metformin alone and the combination group was determined (Table 3). Thus, savings of £464 were estimated regarding the lifetime cost of managing complications. These arise mainly from a reduction in the costs of treating end stage renal disease (72%) and neuropathy (19%). The increase in the treatment costs due to combination therapy are therefore predicted to be partially offset by this reduction in the cost of managing complications, leaving an increment of £2,066 in the lifetime costs per patient (Table 3). This translates into a cost-effectiveness ratio of £6,772 (95%CI: £6,134 to 7,464) per additional discounted year of life, and £5,609 per discounted QALY.

Sensitivity analyses

Table 2: Frequency of microvascular and macrovascular complications by treatment

Complication	**Metformin** (/100 pt)	**Combination** (/100 pt)	**Improvement**	
			Absolute	Relative (%)
Nephropathy				
Microalbuminuria	21.1	18.1	3.0	14.2
Gross proteinuria	18.8	13.4	5.4	28.7
End stage renal disease	5.9	4.4	1.5	25.4
Retinopathy				
Background retinopathy	30.7	23.7	7.0	22.7
Macular edema:				
Detected	25.4	20.6	4.7	18.7
Photocoagulated	24.3	19.9	4.5	18.4
Proliferative retinopathy:				
detected	12.3	7.9	4.5	36.3
photocoagulated	12.1	7.7	4.4	36.3
Blindness	9.4	8.0	1.4	14.9
Neuropathy				
Foot ulcer	21.1	16.3	4.8	22.7
Neuropathy	12.7	9.6	3.2	24.8
1st Lower-extremity amputation	9.0	7.5	1.5	16.5
2nd Lower-extremity amputation	5.1	4.3	0.7	14.6
Macrovascular Disease				
Myocardial infarction	15.0	14.6	0.4	2.4
Stroke	13.7	13.4	0.3	1.9

Table 3: Health benefits and costs for metformin and the combination of metformin with nateglinide

	Metformin	**Combination**	**Difference**
Cumulative cost (mean per patient)			
Complications	£3,548	£3,084	£-464
Total	£5,093	£7,159	£2,066
Survival (mean, years)			
Life years (discounted)	13.5 (11.7)	13.9 (12.1)	0.39 (0.32)
Quality Adjusted (discounted)	12.2 (10.7)	12.6 (11.0)	0.46 (0.37)
Cost-effectiveness			
Cost per LYG (discounted LYG)			£5,403 (6,772)
Cost per QALY (discounted QALY)			£4,500 (5,609)

LYG = Life Year Gained QALY = Quality Adjusted Life Year

The model inputs were varied to reflect different scenarios and Table 4 shows the impact on the estimates. The degree of upward drift of HbA_{1c} and initial HbA_{1c} were influential parameters. If a population with higher glycemic levels at baseline is modeled, a larger proportion of the cohort develops severe complications on metformin alone. Varying the discount rate had a major effect on the cost-effectiveness results.

Varying the efficacy of the combination of nateglinide and metformin on PPG values had a minor effect, a 50% reduction in efficacy led to a 3% increase in macrovascular disease related costs. Varying the impact of the combina-

Table 4: Sensitivity analysis

Parameter	Net Cost	Change in Outcome		CER	
		LYG	QALY	Cost/LYG	Cost/QALY
Base values	£2,066	0.32	0.37	£6,772	£5,609
Age (mean)					
46.5 years	£2,531	0.34	0.45	£7,476	£5,589
82.5 years	£718	0.14	0.12	£5,303	£5,804
Cost of complications					
+20%	£1,973	0.32	0.37	£6,213	£5,357
-20%	£2,159	0.32	0.37	£6,799	£5,861
Duration of disease before oral agent prescribed					
5 years	£2,101	0.27	0.33	£7,680	£6,320
10 years	£1,971	0.31	0.35	£6,260	£5,553
Utilities					
+20%	£2,066	0.32	0.36	£6,506	£5,807
-20%	£2,066	0.32	0.38	£6,506	£5,426
Race					
100% Caucasian	£2,105	0.31	0.36	£6,686	£5,771
HbA1c level					
HbA1c before prescription = 9.4% Metformin = 8.6% Combination = 7.9%	£1,782	0.37	0.42	£4,784	£4,287
HbA1c before prescription = 7.9% Metformin = 7.1% Combination = 6.4%	£2,184	0.28	0.34	£7,904	£6,516
HbA1c upward drift					
Metformin = 1.5%; Combination = 0%	£1,478	0.54	0.65	£2,761	£2,272
Metformin = 0%; Combination = 0%	£2,307	0.28	0.31	£8,336	£7,338
HbA1c drift delay					
Metformin = 0 years; Combination = 1 year	£1,987	0.35	0.41	£5,715	£4,870
Discount					
Cost = 3%; Benefit = 3%	£2,420	0.26	0.30	£9,319	£8,058
Cost = 6%; Benefit = 6%	£2,066	0.18	0.21	£11,369	£9,888
Cost = 6%; Benefit = 0%	£2,066	0.39	0.46	£5,237	£4,500

tion of nateglinide and metformin treatment on HbA_{1c} values had a larger impact on the total cost predicted. Decreasing the efficacy by 10%, or 25% led to total cost increases of 3%, and 9%, respectively. Also a 10% increase in efficacy led to a 4% decrease in costs.

Discussion

Improving glycemic control using combination therapy will inevitably increase drug treatment costs when compared with monotherapy. However, the reduction in HbA1c and PPG levels when treating patients with type 2 diabetes with a combination of nateglinide and metformin has the potential to translate into reduced complication rates. Long term therefore, combination treatment is likely to result in substantial offsets in overall costs. Thus, the additional glycemic control is achieved at a rate of £6,772 per year of additional life, an estimate generally considered cost-effective [35].

These results are consistent with the evidence emerging from the UK. Diabetes-related complications have been shown in several UK studies to require expensive medical interventions, frequently provided in a hospital inpatient setting [36-39]. The UKPDS demonstrated that keeping

glucose levels near normal decreased the incidence of microvascular complications over ten years [40]. In addition, cost-effectiveness analyses based on the UKPDS results indicate the costs of managing complications would be expected to be reduced, [41,42] and, specifically, intensive blood glucose control with metformin is predicted to result in lower complications costs amongst overweight patients [42]. The DCCT results showed improved glycemic control can lower microvascular complication rates in patients with type 1 diabetes, and one key assumption of this model is that these rates also apply to type 2 diabetes. This assumption was demonstrated to be tenable by similar findings in the UKPDS [2,3]. This model predicts comparable results to those of the UKPDS patients in the intensive and conventional treatment groups in terms of relative risk over ten years for microvascular disease or retinopathy at 12 years.

The economic implications of combination therapy depend to some extent on the characteristics of the cohort analyzed. For example, the sensitivity analyses illustrate that greater savings are predicted for patients diagnosed when they are young, with longer duration of disease and poorer glycemic control initially. These characteristics tend to identify patients at higher risk of developing complications later on.

Macrovascular disease is predicted to be the major component of the costs accounting for over one third of the costs accrued over a lifetime from managing diabetes related complications. This is of particular importance as these complications tend to arise earlier in the course of the disease than those that are microvascular in nature, and are the leading cause of death [43,44]. Thus, from both the clinical and economic perspectives, it is important that in addition to glycemic control, any risk factors for cardiovascular disease that are known to be modifiable are managed such as smoking cessation, reducing obesity, high blood pressure and hypercholesterolaemia [3,45].

The equations developed for predicting the risk of stroke and of myocardial infarction included the PPG level. These predictions are based on the results of the DECODE study that investigated the prevalence of macrovascular disease and mortality in Europe [14,28,46]. Thus, the assumption in the model that reducing PPG levels will reduce the risk of macrovascular disease remains to be proven conclusively[3,47].

The long-term predictions were based on the efficacy of combining nateglinide with metformin demonstrated in clinical trials [5]. Even though these analyses were based on the efficacy observed in a randomized, controlled trial, it was necessary to make some assumptions about long-term glycemic control. Given the lack of specific data on the combination over longer timeframes, it was assumed that after the initial improvement in glycemic control, the HbA_{1c} would begin to drift upward as it did with metformin and other hypo glycemic agents employed in the UKPDS [4,48]. This is a conservative assumption as it is quite possible that with the combination there will be a slower, or at least delayed, upward drift.

The cost inputs for these economic analyses were limited to only the most severe stages of the complications. This was done in order to accord with the estimates' source, the UKPDS. The costs also did not include the less severe stages of the complications (such as gross proteinuria, foot ulcers or photocoagulation). Similarly, the macrovascular costs do not include the management of milder conditions such as angina or transient ischaemic attacks. Thus, the cost estimates are quite conservative implying that the savings are underestimated.

Conclusion

In conclusion, prescribing the combination of nateglinide and metformin for patients who are not maintaining good glycemic control on monotherapy alone should be cost-effective, as the combination is expected to reduce the rates of diabetes-related complications at an acceptable additional cost. Long-term data are needed to confirm these predictions.

Competing interests

Caro Research of which Jaime Caro is a shareholder, received a grant from Novartis Pharma AG, (United Kingdom), which provided funding for portions of the study.

Authors' contributions

All authors participated in the design of the study and interpreted the results. All authors have read and approved the final draft of this manuscript. AW and MS conducted the analyses and drafted the manuscript.

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