Combination Therapy for Type 2 Diabetes: What Are the Potential Health and Cost Implications in Canada?

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ABSTRACT

OBJECTIVES

To estimate the lifetime costs associated with diabetes-related complications when monotherapy with metformin is used and to predict the health and economic effects of adding nateglinide (Starlix®).

METHODS

A cohort of 10 000 patients with type 2 diabetes was simulated using a validated model based on existing epidemiological studies. Rates of macrovascular disease, nephropathy, retinopathy, neuropathy and hypoglycemia were estimated, along with the resulting direct medical costs in 2000 Canadian dollars discounted at 3% per year.

RESULTS

With monotherapy, the average costs of managing complications that accumulate over the mean survival of 13.7 years are Can $24 450 per patient, and metformin treatment adds $9710. Combination therapy reduces the costs of complications by $3128 but increases treatment costs by $6550. The cost-effectiveness ratio of adding nateglinide to metformin is $10 504 (95% confidence interval [CI], $9143 to $11 690) per undiscounted life year gained and $16 657 (95% CI, $14 447 to $18 366) per discounted life year gained.

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RÉSUMÉ

OBJECTIFS

Estimer les coûts à vie liés aux complications du diabète lorsque la monothérapie par la metformine est administrée et prédire les effets sur la santé et sur les coûts de l'ajout du natéglinide (Starlix®).

MÉTHODES

Au moyen d'un modèle validé basé sur des études épidémiologiques existantes, on a simulé une cohorte de 10 000 patients atteints de diabète de type 2. On a estimé la fréquence des maladies macrovasculaires, néphropathies, rétinopathies, neuropathies et hypoglycémies, ainsi que les coûts médicaux directs qui en ont résulté en dollars canadiens de 2000 actualisés à 3 % par année.

RÉSULTATS

Avec la monothérapie, le coût moyen du traitement des complications qui s'accumulent au cours des 14 années de survie moyenne est de 24 450 $CAN par patient et le traitement par la metformine ajoute 9 710 $. Le traitement d'association réduit le coût des complications de 3 128 $ mais augmente le coût du traitement de 6 550 $. Le rapport coût:efficacité de l'ajout du natéglinide à la metformine est de 10 504 $ (intervalle de confiance [IC] de 95 %, de 9 143 $ à 11 690 $) par année de vie gagnée non actualisée et de 16 657 $ (IC de 95 %, de 14 447 $ à 18 366 $) par année de vie gagnée actualisée.

CONCLUSIONS

Le traitement d'association peut améliorer l'équilibre glycémique et réduire la fréquence des complications du diabète moyennant une hausse raisonnable des coûts. Les résultats doivent être interprétés avec prudence, car les effets à long terme de ce traitement d'association sont inconnus.

CONCLUSIONS

Combination therapy has the potential to improve glycemic control and reduce the rates of diabetes-related complications at a reasonable increase in costs. These results must be viewed with caution, as the long-term effects of this combination are unknown.

INTRODUCTION

Type 2 diabetes is a common disease (1,2) with serious consequences. To reduce the likelihood of complications, it is critical to control hyperglycemia (3,4), yet the currently available oral antihyperglycemic agents, when used as monotherapy, are unable to consistently achieve or maintain long-term euglycemia (5). With metformin monotherapy, for example, only about one-quarter of patients achieve glycemic control (6). In fact, even patients who initially respond to oral antihyperglycemic agents will generally require a second or third medication (6-9).

Most patients with type 2 diabetes suffer from deficiencies of insulin and resistance to its action (10). This provides a strong rationale for combining an agent that augments the effects of insulin with another drug that increases its release (11). Metformin is an excellent insulin enhancer (12-14) and sulfonylureas increase insulin release (15,16). This combination is limited, however, by adverse effects (17). Recently, several products that are also complimentary to metformin have been introduced. For example, nateglinide (Starlix®) decreases prandial plasma glucose (PG) excursions (18,19), and its efficacy as monotherapy (20,21) and in combination with metformin has been demonstrated in clinical trials (22).

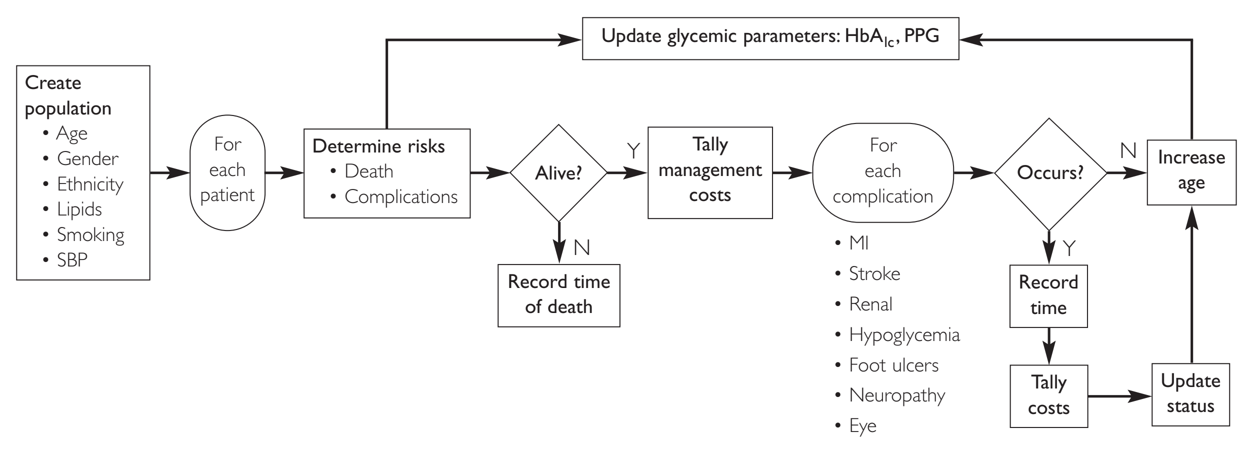
In this paper, we report the results of a study of the potential long-term economic impact of combining metformin with nateglinide in the treatment of type 2 diabetes in Canada.

METHODS

The model

An existing, validated model that simulates the long-term course of type 2 diabetes was updated to conform to recent data (Figure 1). The model has been described in detail elsewhere (23,24). Briefly, it considers the occurrence of both macrovascular (stroke and myocardial infarction [MI]) and microvascular (nephropathy, retinopathy and neuropathy) complications (Figure 1). Microvascular complications start at their mildest level but can advance irreversibly to more severe stages. For example, nephropathy has 3 levels: microalbuminuria, gross proteinuria and end stage renal disease (ESRD). Episodic complications, which can occur multiple times, such as hypoglycemia and foot ulcer, are also considered and are assumed to resolve within the modelling cycle of 1 year. Risk functions for each complication were determined from the best available data (25-31). Each patient is exposed to the risks of complications determined by his or her characteristics, including glycemia. Using a

Figure 1. Schematic representation of long-term model of type 2 diabetes and its complications



MI = myocardial infarction
N = no
PPG = postprandial plasma glucose
SBP = systolic blood pressure
Y = yes

Monte Carlo technique, each hypothetical patient is assigned gender, race and a starting age, which determine the cholesterol, smoking status, body mass index (BMI) and systolic blood pressure (SBP). The glycemic control attained, measured in terms of HbA_{1c}, is assigned the same way. Based on the observation that, despite treatment, HbA_{1c} levels tend to drift upward (8,32,33), glycemic control begins to deteriorate after a delay period.

At the start of each annual cycle, the model checks whether the simulated patient has survived to that point, updates the glycemic control and time-dependent characteristics, and recalculates all the risk functions appropriate to whatever complications may already be present. The risk of death is obtained by adjusting the general age- and gender-dependent mortality hazard by the relative risk associated with diabetes (25). An additional adjustment is made if nephropathy develops (34,35). Over the cycle, the patient is 'exposed' to the estimated risks by comparing each 1 to a corresponding random number—if the number is equal or lower, that event occurs. The direct costs of managing that patient, both of the diabetes itself and of any complications, are accumulated, as is the additional survival time, both absolute and weighted by the quality of life, which depends on the complications present. After processing thousands of simulated patients, the model yields the accumulated costs, the survival, and the number, type and timing of complications. These 'data' can then be analyzed in conventional ways.

Table 1. Baseline inputs for the main analyses

Parameter		Main analyses
Age (%)	29–40 years	5
	41–52 years	25
	53–64 years	41
	65–76 years	25
	77–88 years	4
Female (%)		38
Ethnicity (%)	White	81
	Black	12
	Hispanic	3
	Native-American	3
	Asian	2
HbA_{1c}	Mean baseline level (%)	8.4
	Upward drift (%/year)	0.15
Mean decrease in HbA_{1c} (%)		
	Monotherapy	0.81
	Combination therapy	1.48
Mean decrease in PPG (g/dL)		
	Monotherapy	0.90
	Combination therapy	2.30
Premodel period (years)		5
Model time horizon (years)		30
Discount rate (%)		3

PPG = postprandial plasma glucose

Updating

Several changes were made to the model for these analyses. The most important one was incorporation of 2-hour postprandial plasma glucose (PPG) as an additional measure of glycemic control. This was done because of emerging evidence that PPG is an independent predictor of the occurrence of complications (36,37), particularly macrovascular complications. The PPG for each patient is determined by first sampling the joint distribution of HbA_{1c} and PPG and then applying any treatment effects. Second, based on evidence from the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study (37), the risk of macrovascular complications was redefined in terms of the PPG level. New risk equations were derived from the DECODE study (38,39), including those for age, gender, SBP, total cholesterol, BMI, smoking status and PPG level. The third major change was incorporation of the mortality estimates based on the DECODE risk equations. These are Weibull functions that link mortality to the PPG and to the same characteristics as for risk of macrovascular complications. Rather than replace the mortality function already in the model, both are calculated at each cycle and the higher of the death risk estimates is applied. This was done because the DECODE functions predict higher risks earlier on but are then superceded by the Gompertz functions in the original model.

Data sources

For these analyses, the distributions of age, race and gender (Table 1), were taken from a clinical trial that assessed the efficacy of combining nateglinide with metformin (22). Those of cholesterol, smoking, BMI and SBP, which are conditional on the demographic features, correspond to incident adult cases of clinically diagnosed type 2 diabetes (40-42). The distributions of HbA_{1c} and PPG at the beginning of the model period, as well as the effects of each antihyperglycemic regimen, were also obtained from the clinical trial. From the United Kingdom Prospective Diabetes Study (UKPDS) (7), it was estimated that the HbA_{1c} drifts upward 0.15% per year, on average.

Details of the sources and methods used to estimate the direct medical costs (in 2000 Canadian dollars) are provided elsewhere (43). For each complication, costs were estimated separately for the year in which the event occurs ('event' cost) and for subsequent years ('state' cost). In both cases, these exclude the routine costs of managing diabetes (such as home PG monitoring or supplies) and preventive screening, which are estimated separately. All costs include initial management (inpatient or outpatient setting) and subsequent care (subacute inpatient facilities such as rehabilitation or nursing home, home healthcare and outpatient therapy). Physician visits and diagnostic and therapeutic procedures are also included.

Acute care inpatient resource-use profiles were derived primarily from the most up-to-date data available (1994 to 1996) from the Ontario Case Costing Initiative (OCCI), selecting patients with diabetes and the relevant complications (44,45). For the few instances where specific Canadian data were lacking (e.g. the site for care after discharge for acute MI), information was used from our analyses for the United States (US). Data on resources consumed beyond the inpatient stay were obtained from government reports, practice guidelines, provider survey data and the literature. The annual costs of routine care for managing diabetes included physician visits, laboratory tests, home PG monitoring, supplies and drugs. Each patient was assumed to have 4 physician visits per year, not including those for management of complications. The costs of an annual visit to an ophthalmologist and a dietitian were also included. Unit cost information for

Table 2. Frequency of diabetes-related complications by treatment

	Monotherapy	***Combination***	***Improvement***	
	(per 100 patients)	(per 100 patients)	***Absolute***	***Relative (%)***
Events				
Nephropathy				
Microalbuminuria	25.7	22.5	3.2	12.4
Gross proteinuria	21.6	15.3	6.3	29.1
ESRD	6.2	4.5	1.7	27.2
Retinopathy				
Background retinopathy	34.2	25.8	8.4	24.6
Proliferative retinopathy	14.6	9.4	5.3	36.0
Macular edema	29.2	23.4	5.9	20.1
Photocoagulation	30.2	23.9	6.2	20.7
Blindness	9.9	8.2	1.7	16.7
Neuropathy				
Symptomatic neuropathy	14.3	11.1	3.2	22.4
1st LEA	9.3	8.0	1.3	13.9
2nd LEA	4.9	4.2	0.7	13.9
Macrovascular disease				
MI	14.8	14.0	0.8	5.3
Stroke	13.1	12.7	0.4	2.9
Recurrent events				
Retinal exams	91.6	92.0	-0.4	-0.4
Diabetic foot ulcers	21.3	16.2	5.1	24.0

ESRD = end stage renal disease
LEA = lower extremity amputation
MI = myocardial infarction

Table 3. Cost, survival and cost-effectiveness results of the addition of nateglinide to metformin treatment

	Metformin monotherapy	***Combination therapy (metformin and nateglinide)***	***Difference***
Management cost (Can $)	9710	16 260	-6550
Complication cost (Can $)	24 450	21 322	3128
Total cost (Can $)	34 160	37 582	-3422
Mean survival (years)	13.70	14.02	-0.33
Discounted mean survival (years)	10.60	10.80	0.21
Cost/LYG			10 504
Cost/discounted LYG			16 657

LYG = life year gained

physician visits, laboratory tests and medications were obtained primarily from the *Ontario Schedule of Benefits* and formulary (46-48) to maintain consistency with the OCCI data. The treatment cost estimates conservatively assumed full compliance with the treatment. Cost data from years prior to 2000 were adjusted using annual medical inflation.

Analyses

The initial analyses involved modelling a cohort of 10 000 patients with inadequate glycemic control who remain on monotherapy (metformin 500 mg TID, Can $0.36 per day). This dose was selected because it was studied in combination with nateglinide in the combination therapy clinical trial (22), although in practice the average dose, and therefore its cost, may be higher. The mean cost of each type of complication, and of its management, over 30 years was calculated by summing each patient's costs and dividing by the total number of patients simulated, thus reflecting all patients, not just survivors. To address the implications of combination therapy, these same 10 000 patients (i.e. with the same baseline characteristics) were simulated again but with the addition of nateglinide (120 mg TID, an additional $1.62 per day). The subgroup analyses were carried out in patients not previously treated with oral antihyperglycemic agents, comparing the cost-effectiveness of nateglinide monotherapy vs. metformin monotherapy.

Sensitivity analyses were conducted on all model inputs, and uncertainty was examined using the bootstrap technique with 250 simulations.

RESULTS

In a population like that studied in the trial (22), i.e. with moderate lack of glycemic control after an average of 5 years of diabetes, treatment with metformin is expected to cost just under $10 000 ($9710), on average per patient. This cost accrues over an average survival of 13.7 years. During this time, 26% of patients will expect to have renal disease, one-quarter of whom will progress to ESRD within 20 years. Retinopathy is expected to develop in 34% of patients, and the majority of them will require photocoagulation at some point in time. Diabetic foot ulcers will be expected to occur at least once in 21% of patients, while symptoms of neuropathy are expected to affect 14%. Almost 10% of patients will be expected to require some form of lower extremity amputation. These and other microvascular complications contribute 33% of the $24 450 average cost per patient of managing complications. Almost all remaining cost is due to macrovascular disease: 14% of patients will be expected to suffer an MI and 13% a stroke. While the microvascular complications, especially the more costly severe stages, tend to appear after a decade or more, 50% of the macrovascular events occur within 8 years. Thus, early on, the vast majority of the cost is due to stroke and MI.

Combination therapy with the addition of nateglinide to metformin improves glycemic control both in terms of HbA_{1c} and PPG. This initial improvement is expected to increase survival by an average 0.33 years per patient. Moreover, based on projections of the short-term results of the trials, complications are expected to occur less frequently, or at least progress more slowly (Table 2). ESRD would be reduced by nearly 30%, retinopathy of any kind by about one-quarter, and neuropathy by more than 20%. These beneficial effects, in turn, reduce the costs by almost one-quarter for microvascular complications and by 13% when all complications are considered.

To achieve these gains by adding nateglinide to metformin, the costs of treatment would increase by an average $6550 per patient, with a total cost increment of $3422 (Table 3). The most impressive results were related to

Figure 2. Predicted savings per patient in lifetime complication costs for combination therapy with nateglinide and metformin compared to metformin monotherapy

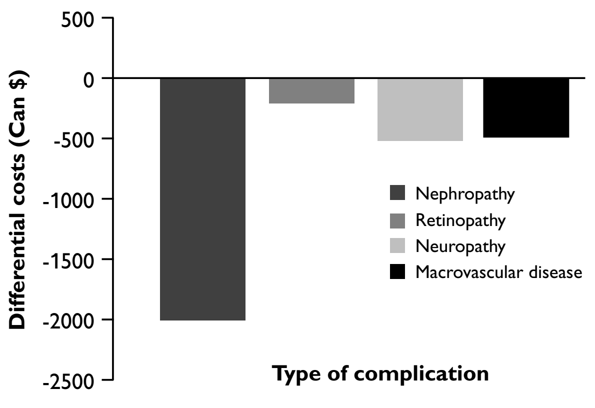
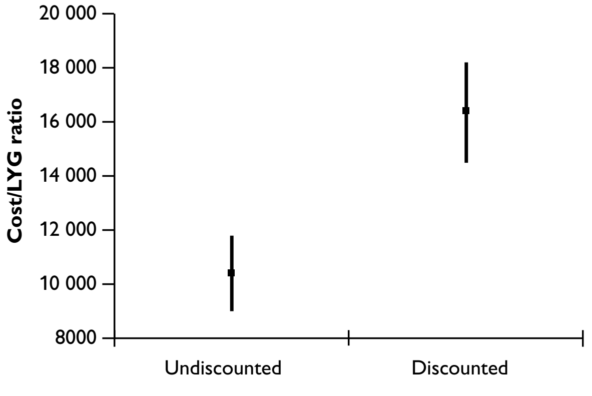


Figure 3. Cost per undiscounted and discounted LYG comparing combination therapy with metformin monotherapy



LYG = life year gained

nephropathy, neuropathy, macrovascular disease and retinopathy (Figure 2). This puts combination therapy in a 'cost-effectiveness' position: it provides substantial health benefits but it increases net costs. Table 3 shows the results of this analysis if life years are taken as the measure of effectiveness. The cost-effectiveness ratio of adding nateglinide to metformin is estimated at \$10 504 (95% confidence interval [CI], \$9143 to \$11 690) per undiscounted life year gained or \$16 657 (95% CI, \$14 447 to \$18 366) per additional discounted year of life (Figure 3).

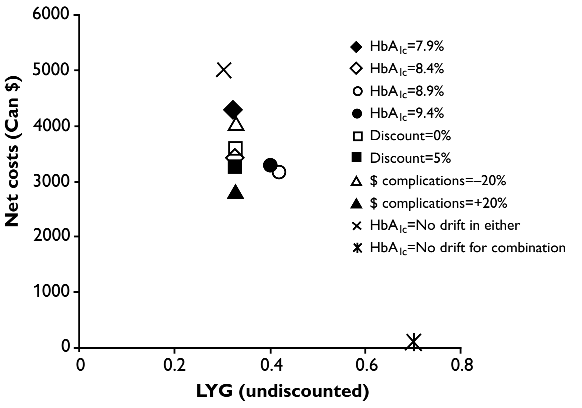
The subgroup analyses with patients not previously treated with oral antihyperglycemic agents compare nateglinide monotherapy with metformin monotherapy. The cost of nateglinide would increase drug cost by an average \$4933 per patient. The total cost is expected to be \$68 651 (95% CI, \$59 233 to \$88 571) per additional discounted year of life.

Sensitivity analyses

A disease-simulation model permits changing inputs to reflect other populations or settings. These analyses are not conducted because of a matter of uncertainty but rather as an exploration of the change in outcomes resulting from consideration of alternative values. The parameters considered for sensitivity analyses were the HbA_{1c} levels at baseline, age, race and gender. The most salient result is that patients who have poorer control initially (HbA_{1c} >9.4%) would have greater improvement in survival with combination therapy than with metformin monotherapy.

Apart from interest in other values of some of the inputs, there is often uncertainty surrounding many of the parameters. To gain a better understanding of the sensitivity of the results to these inputs, analyses were conducted using a range of values expected to cover the uncertainty of these estimates. The key inputs to the model for which statistical uncertainty is an issue are the effect of combination therapy, upward drift in HbA_{1c}, costs of complications and discount rate (Figure 4). Varying the costs of complications and discount rate did not have an important impact on the findings.

Figure 4. Costs and effectiveness by variations in HbA_{1c} at baseline, costs of complications, discount rate and upward drift in HbA_{1c}



LYG = life year gained

If combination treatment were to reduce the upward drift in HbA_{1c}, complication rates would be further reduced and there would be an even greater gain in survival. For example, if the upward drift was eliminated with combination therapy, an additional reduction of \$3340 would be expected. Conversely, if glycemic control were to deteriorate faster than estimated in the base case, the results would not be as positive. For example, if the upward drift doubled, an increase of \$3158 would be expected.

DISCUSSION

The potential economic impact of more widespread use of combination therapy for such a prevalent disease as diabetes is important to understand because diabetes is costly for both patients and society (2) and complications of diabetes represent a substantial burden to Canada's healthcare system (49). We used a validated model of diabetes to assess the potential effect of the addition of nateglinide to treatment with metformin in patients with type 2 diabetes. This combination therapy is predicted to improve glycemic control, and thus, to reduce the risk of developing diabetes-related complications. These predictions are consistent with current data but remain to be confirmed in longer-term studies.

Other studies have shown that intensive glycemic control reduces the risk of progression of diabetes-related complications such as retinopathy (67%), photocoagulation (77%), nephropathy (66%), albuminuria (100%) and clinical neuropathy (64%) (50). The reduction in these diabetes-related complications has a direct impact on costs associated with diabetes. In fact, economic analyses based on the Kumamoto study (50) and on the UKPDS with a 10-year follow-up have shown that the additional costs of intensive management are largely offset by significant reductions in the costs of treating complications of diabetes (51).

According to our results, the costs of managing complications are expected to be reduced and survival to be increased at what is generally considered a reasonably efficient rate (52) of \$10 504 (\$16 657 discounted) per year of additional life.

The results of our analysis are somewhat conservative for several reasons, particularly since we did not consider quality of life or indirect costs.

Our long-term predictions were based on the efficacy of combining nateglinide with metformin demonstrated in a clinical trial (22). In principle, this model could be used to test any combination therapy provided that efficacy data for that specific combination were available. If the efficacy of combining nateglinide with metformin were assumed to apply equally to other combination therapies, differences among combinations would be based purely on costs (and possibly on side effects), but such analyses would be speculative at best.

Even in a study based on actual trial data, however, numerous assumptions must be made. In this study, several assumptions, although based on empirical evidence as much as possible, may have a considerable effect on the results. Given the lack of data over long periods of time, it was assumed that after the initial improvement in glycemic control, the HbA_{1c} would begin to drift upward again, but that it would not deteriorate faster so would not 'catch-up' with the levels in the metformin group. Although this assumption remains to be confirmed, it is important to consider the clinical consequences of improving glycemic control beyond the duration of the trials because of the slow, chronic nature of the disease. For example, according to the UKPDS, intensive PG control over a decade or more would reduce microvascular complications by 25% and MI or sudden death by 16% (53).

Another key feature of this model is that the level of postprandial hyperglycemia was incorporated as a predictor of the risk of macrovascular disease. This assumption is based on the results of the DECODE study that investigated the prevalence and mortality of subjects with diabetes involved in prospective studies in Europe (54). The DECODE study found that one-third of the older subjects with diabetes who were undiagnosed at baseline had isolated postchallenge hyperglycemia and an elevated risk of mortality (37,38). Other recent studies have shown a relationship between PPG levels and the risk of developing macrovascular disease (55-57). The equations used to predict risk factors for stroke and MI included PPG levels in addition to well-established risk factors such as blood pressure (BP), cholesterol, smoking status, BMI and other demographic factors.

The long-term model of type 2 diabetes is based on the best epidemiological data currently available: gender and race distributions are based on incident cases of clinically diagnosed type 2 diabetes in the US population (58,59), and cholesterol, smoking and SBP data were obtained from US patients with diabetes (40,41).

This economic analysis is based on Canadian data, but its relevance should not be limited to this population. There is no reason to believe that the clinical benefits observed with the addition of nateglinide would not be applicable elsewhere. Thus, the efficacy should remain fairly consistent for the given patient characteristics. The economic implications, however, may vary according to each healthcare system. In particular, the price of the drug and the management of diabetes complications may substantially alter the cost-effectiveness ratios. It is for this reason that efforts were made to ensure appropriate Canadian estimates were used in this analysis.

In conclusion, evidence suggests that the combination of nateglinide with metformin has the potential to reduce the rates of diabetes-related complications with reasonable additional costs (60,61). Long-term data are required to confirm these findings.

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