Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Lifetime health effects and costs of diabetes treatment

L.W. Niessen[1,2*], R. Dijkstra[3], R. Hutubessy[4], G.E.H.M. Rutten[5], A.F. Casparie[2]

Institutes of [1]Medical Technology Assessment and [2]Health Policy & Management, Erasmus Medical Centre, Erasmus University of Rotterdam, PO Box 1738, 3000 DR Rotterdam, the Netherlands, tel.: +31 (0)10-408 85 55, fax: +31 (0)10-408 90 92, e-mail: niessen@bmg.eur.nl, [3]Centre for Quality of Care Research, University Medical Centre, Nijmegen, the Netherlands, [4]Global Programme on Evidence for Health Policy, WHO, Geneva, Switzerland, [5]Julius Centre, University of Utrecht, the Netherlands, * corresponding author

ABSTRACT

Background: This article presents cost-effectiveness analyses of the major diabetes interventions as formulated in the revised Dutch guidelines for diabetes type 2 patients in primary and secondary care. The analyses consider two types of care: diabetes control and the treatment of complications, each at current care level and according to the guidelines.

Methods: A validated probabilistic diabetes model describes diabetes and its complications over a lifetime in the Dutch population, computing quality-adjusted life years and medical costs. Effectiveness data and costs of diabetes interventions are from observational current care studies and intensive care experiments. Lifetime consequences of in total sixteen intervention mixes are compared with a baseline glycaemic control of 10% HBA_{1c}.

Results: The interventions may reduce the cumulative incidence of blindness, lower-extremity amputation, and end-stage renal disease by >70% in primary care and >60% in secondary care. All primary care guidelines together add 0.8 quality-adjusted life years per lifetime.

Conclusion: In case of few resources, treating complications according to guidelines yields the most health benefits. Current care of diabetes complications is inefficient. If there are sufficient resources, countries may implement all guidelines, also on diabetes control, and improve efficiency in diabetes care.

INTRODUCTION

Ageing, lifestyle changes and improved case finding will increase the number of diabetes type 2 patients in most societies in the near future.[1] In the Dutch population, diabetes led to a loss of 87,000 disability-adjusted life years in the year 1996, ranking 10th of all diseases.[2] Diabetes contributes to the occurrence of cardiovascular disease, loss of vision and blindness, kidney failure, disorders of peripheral circulation and loss of sensitivity and pain in the legs, both leading to lower extremity ulcers and amputation. It is the largest cause of blindness in developed countries. About 15% of the dialysis patients in the Netherlands have diabetic nephropathy. In the United States, probably due to less diabetes control, this is 30%.[3] Lower extremity amputation (LEA) is about 15 times more frequent among diabetes patients than in the general population.[4,5] Healthcare costs related to diabetes and its complications are high in affluent societies and accounted for 2.5% of medical expenditures in the Netherlands in 1996.[6]

Cost-effectiveness analyses of diabetes guidelines are relevant for clinical and health policy reasons. Long-term clinical follow-up studies have demonstrated that intensive control of blood glucose is effective in reducing the risk of severe diabetes complications.[7] Health economic studies have shown that intensive treatment might lead to lower healthcare costs, especially through fewer institutional episodes.[8] Such studies typically report the costs and effects of an intervention given an existing level of control and treatment and hence are context-specific. It is in the interest of health policymakers to have more general

information on allocation options in diabetes care given the various prevention and treatment options for complications.[9,10] The premise of such analyses is that, for any given level of resources available, it is desirable to maximise the total aggregate health benefits.[11-13] A comparison of health effects and costs of optional intervention mixes against a baseline care level facilitates priority setting at varying resource levels. The efficiency of current interventions may be considered.[13] In this article a low diabetes control level of 10% glycosylated haemoglobin (HbA_{1c}) is taken as baseline.

In the Dutch setting, primary care physicians are the gatekeepers for secondary care facilities. About 80% of type 2 diabetes patients are treated in primary care and are referred only temporarily for secondary care consultation, for example for eye screening.[14] Specialists in ambulatory secondary settings only treat the more difficult cases. Here we present analyses for combinations of various intervention mixes as formulated in the Dutch guidelines for diabetes type 2 care[15-17] and report on the allocation options at different resource levels. We consider two sets of intervention mixes for diabetes patients: one for those in primary care and one for those in secondary care.

METHODS

We estimate health effects and medical costs of current care and care according to guidelines in the two groups compared with a baseline setting. We collected data on current care and used data on two experimental guideline settings.[18,19] We first summarise the application of the disease history model for diabetes. Then, we describe the computations to arrive at validated baseline estimates. Last, to obtain comparable cost-effectiveness results, we give the details on the input values for the effectiveness and costs for the two sets of, in total, eight possible intervention mixes for each set.

Multi-state disease model

We modified a probabilistic Markov model to describe the Dutch diabetes situation.[20] It describes the disease history of type 2 diabetes and calculates quality-adjusted life years (QALYs) lived with diabetes and its complications, as well as lifetime medical costs. We refer to the original publication for detailed description. *Figure 1* gives an overview of the model. It computes the occurrence of the mild and severe long-term diabetic complications and the excess mortality due to diabetes. The model distinguishes five health states for retinopathy, four for nephropathy and three for neuropathy. Patients may progress from states without specific complications, through less severe intermediate stages, towards three severe diabetes complications, leading to severe vision loss (<20/100), kidney failure or lower extremity amputation. The intermediate retinopathy states are background retinopathy, macula oedema and proliferative retinopathy. For nephropathy these are microalbuminuria and gross proteinuria, leading to end-stage renal disease (ESRD). The neuropathic complications are leg and foot ulcers and LEA, as results from 'diabetic foot'. The model describes cohorts of diagnosed diabetes patients. They enter the model one by one through stratified random sampling until a stabilisation of results occurs. It accounts

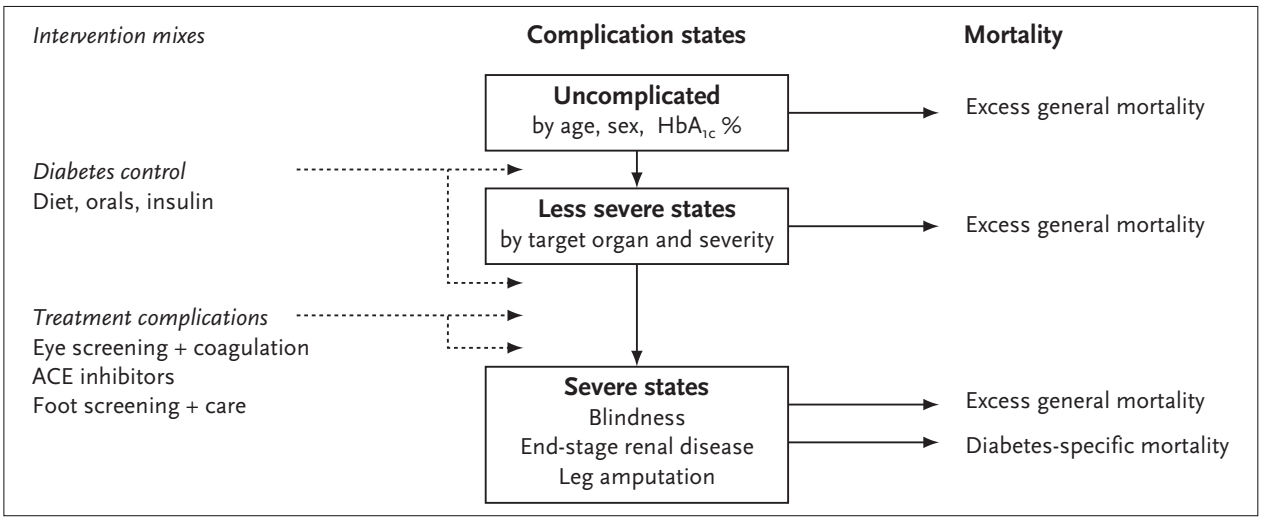

Figure 1

Overview of groups of disease states in diabetes model and action effects of intervention mixes

The actual number of possible disease states is higher; see text.[20]

for their age and sex distributions and the distribution of their HbA_{1c} levels (*table 1*). The complication probabilities are specific for age, gender and diabetes duration. There are two independent mortality risks. One accounts for diabetes-specific mortality and the other for the excess mortality. The latter includes the excess cardiovascular mortality risk. *Figure 1* indicates that progression towards severe states depends on both the level of diabetes control and the level of specific treatment during the less severe intermediate stages.

Table 1

Model input values for diabetes control and preventive treatment of complications by patient group characteristics, effectiveness and annualised medical costs (1996 €)[17-19,21,22]

	LEVEL OF CARE			
Input variables patients, intervention effects and medical costs	**Current primary care (P1.CC + P2.CC)**	**Primary guidelines care (P1.GC + P2.GC)**	**Current secondary care (S1.CC + S2.CC)**	**Secondary guidelines care (S1.GC + S2.GC)**
Patient characteristics				
No. of patients in survey	1371	459	929	1029
Mean age (SD)	65.2 (11.7)	66.1 (12.5)	69.2 (11.5)	69.2 (11.5)
Gender distribution (% men)	49	39	43	41
Diabetes control (P1 and S1)				
Effectiveness				
Average HbA_{1c} % (S.D.)	7.6 (1.5)	7.0 (1.3)	7.8 (1.5)	7.2 (1.3)
Proportion of patients <7.0%	0.44	0.54	0.25	0.35
Proportion of patients >8.5%	0.28	0.12	0.24	0.15
Proportion of insulin patients	0.04	0.16	0.74	0.85
Medical costs				
Visits to general practitioner	128	318	128	318
Visits to various diabetes specialists	144	120	212	298
Visits to diabetes nurses	63	218	109	218
Visits to paramedics	0	184	48	120
Oral drug, insulin; self-control	347	386	977	1937
Laboratory tests	40	187	40	271
Treatment less severe complications (P2 and S2)				
Effectiveness (probability reduction)				
Laser coagulation in ME, postponing blindness/low vision	0.05	0.03	0.05	0.03
Laser coagulation in PDR, postponing blindness/low vision	0.08	0.015	0.08	0.015
ACE inhibitors in gross albuminuria	0.08	0.05	0.27	0.05
Foot clinic treatment neuropathy	0.17	0.05	0.25	0.05
Medical costs				
Eye screening visit	27	55	27	55
Laser coagulation + follow-up		272		
ACE inhibitors	0	5	0	5
Visits diabetic foot clinic	20	58	20	29
Treatment severe complications				
Medical costs				
Blindness	1200	2550	660	3200
End-stage renal disease*		46,700		
Diabetic foot ulcer**		563		
LEA event/amputation status		12,000/450		

*P = primary care, S = secondary care, 1 = diabetes control, 2 = care of complications, CC = current care, GC = guideline care, ME = macula oedema, PDR = proliferative diabetic retinopathy, LEA = lower extremity amputation. * Weighted average of haemodialysis, peritoneal dialysis, home dialysis and transplantation, ** weighted average of ambulatory and in-hospital treatment.*

Baseline estimates

We applied the disease model to compute a baseline situation (*table 1*). HbA_{1c} indicates the level of diabetes control and it is directly related to the occurrence of complicating events later in life.[7,20] We used this observed relation to simulate a situation of very low diabetes control. We assumed a HbA_{1c} level of 10% to estimate a baseline incidence of severe complications as this was used in the original model version. This level of control is similar to the Dutch level of control observed about 15 years ago in comparable groups of patients.[23] The present average control level is below 8% HbA_{1c}. We did not alter the baseline incidence figures for severe complications but did use Dutch mortality risk estimates. We multiplied the gender and age-specific national mortality figures for 1990 by the increased hazard ratios for Dutch diabetics. An incidence-prevalence-mortality model, used to compute consistent values for each of its three components, estimates at a hazard ratio of 1.55 for mortality for diabetic men and 2.27 for women as compared with the general population.[24,25] The ESRD case fatality rates are also based on national figures.[3]

Next, we validated model outputs, comparing model output data with empirical data from other sources. The model calculates a baseline life expectancy at age 65 for nondiabetic men of 14.0 and women of 18.6 years. The empirical figures are 14.1 and 18.6.[25] Computed baseline life expectancies for diabetic men and women are 11.3 and 14.9 years. These figures compare well with the (rough) historical estimates of 11.4 and 15.2.[26] We also compared model outcomes with the national registry figures for diabetes as well as neuropathy and nephropathy complications. This was not possible for retinopathy, due to lack of data. We found only minor differences, which we explain by the lack of an, increasing, incidence trend, underestimation in the registries and varying diagnostic criteria. We concluded that our model values are consistent with available empirical national data on diabetes occurrence.[6]

Last, we introduced utility weights to adjust the computed life years. We found a single weight of 0.75 for diabetes with or without mild complications based in our EuroQol survey.[27] The utility weight for blindness/low vision is 0.69, for ESRD 0.61 and for LEA 0.59.[3,20,28]

Input data for two sets of intervention mixes

We collected data for the two types of intervention sets (diabetes control and treatment of complications) for each of the two patient groups (*table 1*). The difference between the primary and secondary care group is that in the latter diabetes control is more difficult and severe complications are more frequent. Both conditions are indications for a referral according to the guidelines.[16] Both types of intervention are considered at two different levels of care i.e. current care and care according to the revised guidelines.[15,17] The guidelines for diabetes control aim at lower levels of HbA_{1c} and the guidelines for complications recommend frequent screening and preventive treatment though laser coagulation, ACE inhibitors and foot clinic visits.

So, the first group consists of primary care patients receiving current care interventions (P.CC) or receiving intervention mixes according to guidelines (P.GC). The second group consists of secondary care patients receiving current level of specialist interventions (S.CC) or receiving intervention mixes according to guidelines (S.GC). Each of four different intervention mixes distinguishes two components: diabetes control (P1 or S1) and treatment of complications (P2 or S2). *Table 1* lists the input values for diabetes control and treatment of complications by patient group and by level of care. This leads to two sets of four single (P1, P2 or S1, S2) and four combined (P1 + P2 or S1 + S2) mutually exclusive intervention options at current and guideline care level. For instance, the single option P1.CC means diabetes control as currently given and there is no treatment of complications in primary care. In total, we analyse sixteen of those options of diabetes interventions (*table 2* and *3*).

Effectiveness diabetes control

Empirical data regarding the level of diabetes control in current and guideline settings (P1.CC, P1.GC, S1.CC and S1.GC) have been collected in three studies.[18,19,21] The HbA_{1c} figures for primary care patients (P1.CC and P1.GC) are based on a two-year follow-up of 459 patients in 22 primary care practices.[19] Effectiveness figures for current secondary care patients are from a survey in ten general hospitals among 929 patients.[22] Accounting for control effectiveness (versus trial efficacy) we entered the observed distributions of all HbA_{1c} values into the probabilistic calculations instead of the observed means. *Table 1* shows the HbA_{1c} fractions for those values >8.5% and for those between 7.0 and 8.5%. It indicates, for example, that in all four groups more than 10% of the patients remain above the 8.5% HbA_{1c} level.

The relationship between HbA_{1c} level and progression to diabetic complications is estimated by a function reported earlier.[20] It has been validated for the Netherlands[3] and is based on the formula $((HbA_{1c}/10)^{\beta})$. The calculated fraction is the reduction of the transition probabilities towards each of the three complication categories. The β-coefficients are specific for each type of less severe complication.[20] The function shows diminishing returns when lowering HbA_{1c} level through more intensive diabetes control. The UKPDS study has confirmed the degree of diminishing returns.[30]

Effectiveness preventive treatment of complications

The effectiveness figures for the treatment of retinopathy and nephropathy are from experimental trials and have been reported before.[3,20] In macula oedema, laser coagulation

Table 2

Lifetime cumulative incidence (%) of diabetes complications by intervention mix component

TYPE OF COMPLICATION	INTERVENTION MIX COMPONENT								
	BASELINE	PRIMARY CARE PATIENTS				SECONDARY CARE PATIENTS			
		P1.CC	P2.CC	P1.GC	P2.GC	S1.CC	S2.CC	S1.GC	S2.GC
Background retinopathy	73.6	17.9	69.7	8.4	68.9	32.2	70.3	24.8	71.7
Macular oedema	38.5	7.2	36.0	3.3	35.9	12.9	34.3	9.1	35.3
Proliferative retinopathy	8.7	1.2	8.6	0.5	9.4	1.0	7.1	0.3	5.2
Low vision/blindness	13.5	2.5	9.1	1.0	8.1	4.1	7.4	2.9	4.0
Microalbuminuria	36.4	15.2	30.5	12.0	30.1	22.9	33.6	19.5	30.6
Macroalbuminuria	25.2	4.4	20.0	1.7	19.8	5.6	22.2	2.3	21.4
ESRD	5.6	0.9	4.1	0.3	2.5	1.1	2.8	0.4	1.7
Neuropathy	19.7	6.3	17.6	3.3	17.3	8.8	18.1	6.5	19.7
Lower extremity amputation	7.7	2.1	5.7	1.2	4.0	3.0	5.3	2.2	2.9

P = primary care, S = secondary care, 1 = diabetes control, 2 = care of complications, CC = current care, GC = guideline care, ESRD = end-stage renal disease.

Table 3

QALYs lived and medical costs (1996 €) per average remaining diabetic lifetime for the two independent sets P and S of intervention mixes, ordered by QALYs lived

INTERVENTION MIXES				MODEL OUTPUTS		COST-EFFECTIVENESS RESULTS		
NO.	SINGLE SET MIXES	NO.	COMBINED P AND S MIXES	QALYs LIVED	LIFETIME COSTS	POINT ESTIMATE CER	EXPANSION PATH + STEPWISE CER	
0	**Baseline care**			**9.294**	**2626**	**Reference**	**0**	**No option**
1	**S2.CC**			**9.384**	**349**	**Most dominant**	**1**	**Reference**
2	S1.CC			9.410	1403	Dominant		40,852
3	**S2.GC**			**9.424**	**411**	**Dominant**	**2**	**1561**
4	S1.GC + S2.CC			9.425	2642	123		
5	S1.CC + S2.CC			9.427	1384	Dominant		
6	S1.CC + S2.GC			9.433	1427	Dominant		104,691
7	S1.GC			9.442	2637	76		
8	S1.GC + S2.GC			9.446	2699	485		103,549
9	P2.CC			9.689	3247	1575		
10	P2.GC			9.695	1355	Dominant		
		17	**P2.GC + S2.GC**	**9.784**	**1704**	**Dominant**	**3**	**3587**
		18	Ibid + S1.CC	9.833	2782	291		21,897
11	P1.CC			9.945	3189	866		
12	P1.CC + P2.CC			9.963	3141	771		
13	P1.CC + P2.GC			9.986	3811	1714		
14	P1.GC + P2.CC			10.020	8099	7543		
		19	Ibid + P1.GC	10.225	8648	6469		15,738
		20	Ibid + P1.GC + S1.CC	10.235	9665	7483		17,654
		21	Ibid + P1.GC + S1.GC	10.248	10,937	8720		19,927
		22	**Ibid + P1.CC**	**10.115**	**4222**	**1945**	**4**	**7607**
15	P1.GC			10.128	8078	6543		
16	P1.GC + P2.GC			10.130	8238	6716		
		23	**Ibid + P1.GC**	**10.225**	**8648**	**6469**	**5**	**40,153**
		24	**Ibid + P1.GC + S1.CC**	**10.236**	**9665**	**7483**	**6**	**94,916**
		25	**Ibid + P1.GC + S1.GC**	**10.249**	**10,937**	**8720**	**7**	**99,444**

Each set includes eight mutual exclusive mixes. Mixes in bold indicate one optimal expansion path. In the last column the CERs are relevant to this expansion path. Here, in each step, the preceding optimum mix is the reference intervention. QALYs = quality-adjusted life years, baseline care = exclusively treatment of severe complications (see costs in table 1), SD = standard deviation, CER = cost-effectiveness ratio (Euros/QALY), P = primary care, S = secondary care, 1 = diabetes control, 2 = care of complications, CC = current care, GC = guideline care.

slows progression to a vision <20% at a hazard ratio of 1.17. In proliferative retinopathy, the hazard ratio is 1.71. Data on the effectiveness of the prevention and treatment of diabetic foot are scarce, especially on lowering amputation rates. The Saint Vincent declaration states a 50% reduction as the attainable goal. A Dutch study and others report some supportive evidence for this, relatively pessimistic, estimate. We applied hazard ratio to the amputation transition probability of 3.72 for primary care patients and for 2.41 in secondary care patients. *Table 1* lists the resulting changes in probabilities. Unless stated otherwise, we present these three types of specific preventive treatments combined as one intervention mix. We distinguish one for current care (P2.CC and S2.CC) and for guideline care (P2.GC and S2.GC).

Healthcare costs by intervention mix

We collected data regarding healthcare utilisation from the same three studies and did a large cross-sectional study of primary care patients. This study reports the actual health utilisation and costs from 29 general practices of 1371 primary care patients. Health utilisation estimates for current secondary care are from a hospital survey.[21] The cost estimates for the implementation of guideline care are from two experimental studies applying intensive treatment protocols in primary and secondary care patients.[18,19] *Table 1* lists the cost input values for diabetes control and treatment for four categories of patients (P.CC, P.GC, S.CC, and S.GC). Medical costs of amputation, follow-up after amputation, end-stage renal disease and blindness are assumed the same in all four patient groups. The calculated lifetime cost estimates do not include the medical costs of nondiabetes-specific conditions. We provide more cost details in the report.[17]

RESULTS

We computed lifetime health effects and medical costs for the sixteen diabetes intervention mixes in the two sets. One set includes all possible mutual exclusive intervention mixes for primary care (P) and the other (S) includes all possible mutual exclusive mixes for secondary care. We first present the specific health effects for the eight single components of the intervention mixes (P1, P2, S1, S2) for current care and guideline care (CC and GC). Next, we present effects and costs of the eight single components and eight combined mixes for control and preventive treatment (P1 + P2 en S1 + S2). This leads to results for in total sixteen intervention mixes as listed in *table 2*.

Health effects

Table 2 shows the incidence of complications for patients under the four intervention mixes (P.CC, P.GC, S.CC, and S.GC). It compares the effects of each single component, i.e. diabetes control (P1 or S1) and preventive treatment of complications (P2 or S2) with the baseline estimates. The first column gives the results of the baseline scenario. Diabetes control reduces the incidence of all complications. Once less severe complications occur, preventive treatment reduces progression to severe complications. Some 74% of type 2 diabetes patients developed background retinopathy under the baseline scenario, whereas blindness occurs in 13.5%. Under current level of control, this is reduced by more than 75%. Implementation of control guidelines among primary care patients reduces the cumulative incidence of blindness by more than 90%, whereas ESRD falls by 67% from 5.6% to less than 0.5%. The cumulative incidence of diabetes-related amputations decreases from 7.7% in the baseline to 2.1% in the current primary care setting. Similar, less substantial declines take place among the more complex patients in ambulatory secondary care. Implementation of secondary care guidelines leads to a reduction of blindness by 29%, of ESRD by 62%, and of LEAs by about 27%.
Table 2 also shows that the incidence of these severe complications results in more patients with less severe complications in the case of blindness (P2.GC and S2.GC) and amputations (S2.GC). This leads to a relative increase in costs. Reductions due to specific single treatments of complications (not listed) are substantial, but lower. Patients in current care with higher initial HbA_{1c} levels benefit more from guideline control than those with lower initial values of HbA_{1c}.

Costs-effectiveness of diabetes interventions

Figure 2 and *table 3* present the means of the computed QALYs lived and the discounted additional lifetime costs per average diabetes patient for the sixteen possible combinations of the four intervention mixes (P.CC, P.GC, S.CC, and S.GC). The standard deviations for the QALYs lived vary between 5.04 and 6.01 years and for the lifetime costs between € 3103 and € 8265. The calculated baseline life expectancy is 9.29 QALYs (SD=5.3). The SD value compares well with observed figures for the unadjusted life expectancy (CBS, 1992). The large SDs for lifetime costs are due to the large variation in remaining life years lived and the less frequent occurrence of the most costly complications. This reflects clinical reality in the treatment of older individual patients: given the high individual risks of dying from other causes, future health benefits and medical costs are uncertain at the individual level.

The higher costs of guideline control (*table 1*) and the treatment costs of complications are partially offset by reductions in the costs of severe complications, especially by savings on the care of severe renal and lower extremity

complications. All primary care guideline interventions together (P1.GC + P2.GC) show the highest health yield for a single intervention set: about 0.8 QALY per average lifetime. As a single intervention, eye screening and laser coagulation (not listed) fall within the same range of cost-effectiveness. The cost-effectiveness ratios for current treatment for renal and lower extremity complications (not listed), as single interventions, are much higher. Diabetes control in secondary care patients is still more costly per unit HbA_{1c} reduction. This explains why primary control is more cost-effective than specialist control. As the current control level is already high in both primary and secondary care, even tightened control shows increasing costs and diminishing returns.

The two guideline intervention mixes for complications (P2.GC and S2.GC) are dominant compared with the current care of complications (P2.CC and S2.CC). Guideline treatment of complications (P2.GC and S2.GC) is cost-effective for three reasons: the intervention costs are low, the effects are immediate in a large majority of patients, and the indicated patient subgroup is relatively small. In diabetes control, annual costs are higher, health gains occur later in life, and many patients need to be treated to prevent relatively few, severe and costly complications. Therefore, current control is less cost-effective than preventive treatment of complications. Intensive control is even less cost-effective.

Table 3 and *figure 2* indicate one possible optimal resource expansion option, namely how to prioritise implementation of efficient diabetes care starting from a baseline level. Here, one would start by choosing the most cost-effective option at the lowest budget needed, followed by the next cost-effective and so forth, until resources are exhausted.[11] In *table 3*, only the relevant combinations of P and S are listed (colum three, numbers 17-25). Other combinations are possible but not relevant for the path. For the sets of mutual inclusive interventions (P and S) the order would be to start with the guidelines treatment for complications, next to add primary control, and lastly to implement intensive secondary control. The optimum expansion path for all combinations of all possible P and S mixes starts with S2.CC. This is the most efficient and least expensive option: in other words, it gives most savings, compared with baseline level (*table 3*). The specific implementation steps would be to improve this to S2.GC, add P2.GC, add P1.CC, improve this to P2.GC, and lastly to include the remaining S2.GC option. At mid-range budgets also other, single and combined, mixes are on other expansion frontiers, for example adding S1.CC after the implementation of P2.GC and S2.GC. S1.CC (*figure 1*) can be implemented

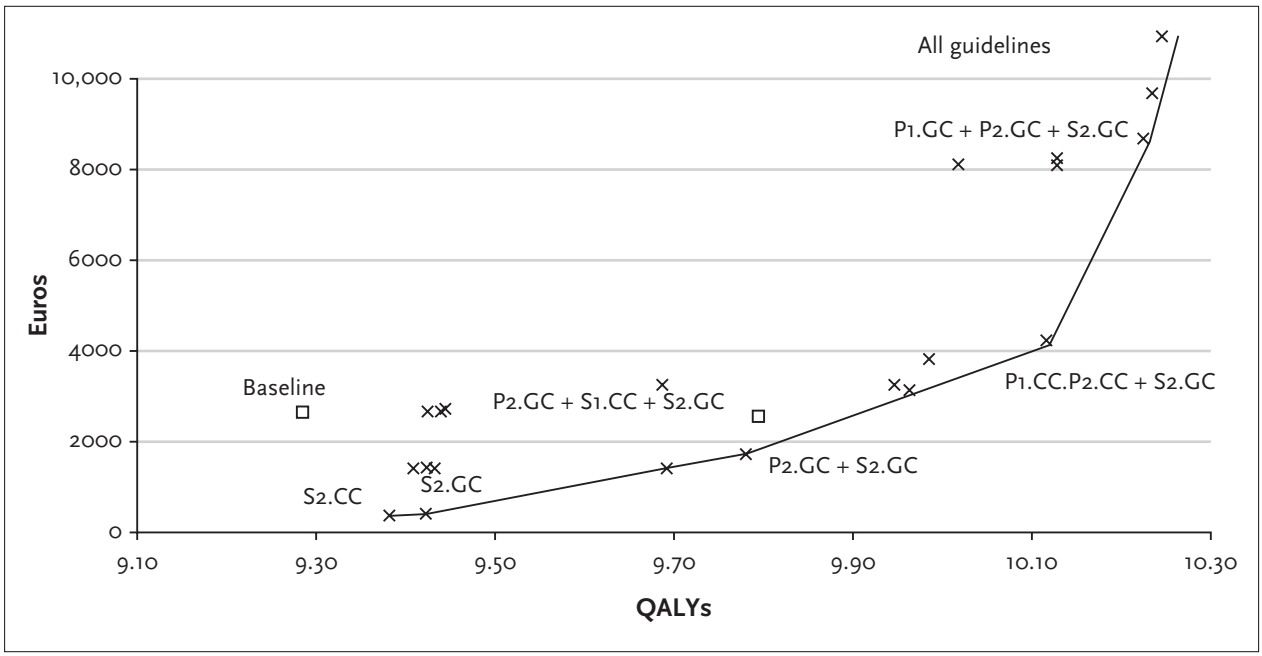

Figure 2
The cost-effectiveness plane: QALYs lived and lifetime medical cost (3% discounted) for each intervention mix, the baseline value and combinations of P and S mixes

P = primary care, S = secondary care, 1 = diabetes control, 2 = care of complications, CC = current care, GC = guideline care, QALYs = quality-adjusted life years.

at much lower costs, but is three times less cost-efficient, at € 21,897 per QALY. At higher budgets, health effects and the absolute costs for secondary care patients are less influential due to the relatively small size of this group. Health gains in this group, although very inefficient (*figure 2*), need few additional euros per average lifetime. Many more expansion paths are possible if uncertainties such as standard deviations of health effects and lifetime costs are taken into account. In the uncertainty analysis all these paths are considered together; however this did not change the conclusions.[29]

DISCUSSION

Our analyses show that the diabetes care guidelines are cost-effective in reducing severe and expensive complications. This reconfirms the results of other studies.[3,8] They also show that implementation of the guidelines for complications both in primary and secondary care reduces the current inefficiencies in diabetes care. In case of low available resources, a combination with moderate diabetes control (P1.CC) is a good option. Also while including uncertainties, the mixes that include guideline treatment of complications continue to be a likely optimum choice. At high resource levels, all primary and secondary care guidelines are relevant. The interventions in secondary care are cost saving compared with baseline; those for primary control cost about € 6000 to € 7000 per QALY gained.

Cost-effectiveness methodology

The inclusion of a baseline scenario as a reference level is one way to operationalise the generalised cost-effectiveness analysis (CEA) approach of the WHO.[11,13] Our baseline scenario represents the average low controlled diabetic still receiving care for severe complications. Estimates for this situation can be relatively well documented as the relationship between HbA_{1c} blood values and the occurrence of complications is well established. However, the exact natural history of diabetes, when no treatment at all is given, remains unknown.

The first advantage of our approach is the possibility to assess the relative efficiency of the current mix of care. For the Netherlands, data on the level of current diabetes care have recently become available.[22] The present study shows that, due to undertreatment, current primary care of complications is inefficient as more costs due to severe complications can be prevented (*table 3*). In a direct, context-defined, comparison of current care and guidelines care this would show as cost savings such as those we demonstrated elsewhere for diabetes nephropathy.[3] The comparison with a baseline level makes the information for health policymakers more complete and indicates the level of expenditures still needed.

The second advantage is the possibility to consistently compare intervention mixes for two (or more) different subpopulations at different available budgets after choosing the right denominator. The unit of analysis is the average cost per diabetic lifetime. Given the small numbers of patients, the provision of secondary care leads to low average lifetime costs for all diabetics, in spite of high individual costs and higher cost-effectiveness ratios. In case of a low budget, preventive treatment of these patients according to this analysis deserves priority. This is only one way to define the optimum benefit given a fixed health budget to spend for the diabetes population. QALYs and costs for both groups of patients in our analysis have the same weights and have the same denominator (the average diabetic lifetime). Different health policy criteria, such as equity considerations, might lead to different weights, for example priority to the more disabled.[31] In this case, the policymaker might choose one of the less likely, nevertheless optimum, options.

There is an indirect interdependence between the health gain and costs due to diabetes control and due to the specific treatment of mild complications. Both reduce severe complications. In a sense, the diabetes health states act as communicating vessels. Better control leads to fewer patients needing preventive treatment of complications. Absence of diabetes control leads to more patients with complications. Treatment of complications in the absence of control leads, on average, to more health gain and higher costs. The disease history model accounts for this interdependence. *Table 2* illustrates these results in both the single and combined scenarios.

The baseline estimates are difficult to validate. It might be possible to use a specific calendar as a reference situation, computing 'backwards'.[3,22] We did this and presented some historical evidence. Our baseline quality-adjusted life expectancy of 9.3 QALYs due to low diabetes control is probably an overestimation. At a mean 10% HbA_{1c} level, there will be loss of health due to direct metabolic complications, leading to less QALYs and higher costs in the baseline scenario. This would lead to more favourable cost-effectiveness ratios for the intervention sets.

Certainly within limits, it does not make an essential difference which baseline is chosen as long as its health effect values are substantially lower than the computed gains for the actual interventions.

Our main conclusions on the optimum mixes, however, are based on the *relative* values for health benefits and costs of the studied intervention mixes, starting with the optimum choice at the lowest budget level. This does not change for different baseline values, nor would the relative values for the interventions change. A comparison with interventions for other diseases to compute the net population benefit, however, would mean that the baseline values need redefining to include the characteristics of the other patient (or

population or high-risk) groups involved. Uncertainties in other model input values, such as those for discounting, utility weights or transition probabilities, do not change the set of relative values substantially either.

CONCLUSION

In case of low resource availability (<€ 300 per diabetes lifetime), none of the diabetes mixes is a relevant policy option. Highly likely optimal strategies in resource-poor countries are the implementation of guideline treatment of complications and primary diabetes control (P2.GC, S2.GC, and P2.CC). Our study shows the most likely cost-effective options. However, other allocation criteria will influence the decision-making.

In countries with high resources, priority should also be given to the guideline treatment of complications as current diabetes care shows inefficiencies. At a budget of over € 12,000 per diabetes lifetime, one can afford the implementation of all interventions, although at the individual level uncertainties are high.

The implementation results depend very much on the strategies followed.[32] Simply distributing guidelines seldom leads to (cost)effective implementation.[33,34] Other constraints in a cost-effective implementation are an already high existing level of control and the lack of sufficient improvement in many diabetics. There are diminishing returns in intensive diabetes control. Further selection of high-risk subgroups, by age, sex, risk factor status and HbA_{1c} level, may lead to the identification of more specific, targeted and cost-effective implementation strategies. For this, it will be necessary to conduct wider-scale and more targeted evaluations of impact and costs of different implementation practices of diabetes guidelines.

ACKNOWLEDGEMENTS

We thank the members of the consensus committees as well as our colleagues at Erasmus, Dr H. Crijns, N. van Os, R. Jansen, Dr K. Redekop, Dr M. Koopmanschap and, at WHO, Dr D. Evans, for their contributions or comments on the manuscript. We thank Dr Eastman for making available the model software and Ms H. Smit Westerink (SSCH, Hardenberg, Coevorden) for data on secondary care.

NOTE

The Dutch Ministry of Health funded the study as part of a general institutional grant for economic evaluations in support of medical guidelines development.

REFERENCES

1. King H. Global Burden of Diabetes, 1995-2025. Diabetes Care 1998;21(9):1414-34.
2. Melse JM, Essink-Bot ML, Kramers PG, Hoeymans N. A national burden of disease calculation: Dutch disability-adjusted life-years. Dutch Burden of Disease. Am J Public Health 2000;90(8):1241-7.
3. Os N van, Niessen LW, Bilo HJ, Casparie AF, Hout BA van. Diabetes nephropathy in the Netherlands: a cost effectiveness analysis of national clinical guidelines. Health Policy 2000;51(3):135-47.
4. Houtum WH. Diabetes mellitus related lower extremity amputations [Thesis]. Amsterdam: Free University, 1998.
5. Holstein P, Ellitsgaard, N, Bornefeldt Olsen, B, Ellitsgaard, V. Decreasing incidence of major amputations in people with diabetes. Diabetologia 2000;43:844-7.
6. Os N van, Niessen LW, Koopmanschap MA, Lei J van der. Gedetailleerde raming van de maatschappelijke kosten van diabetes mellitus. Ned Tijdschr Geneeskd 2000;144(18):842-6.
7. UKPDS group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998;352:837-53.
8. Klonoff DC, Schwartz DM. An economic analysis of interventions for diabetes. Diabetes Care 2000;23(3):390-404.
9. Gulliford M. Design of cost-effective packages of care for non-insulin-dependent diabetes mellitus. Defining the information needs. Int J Technol Assess Health Care 1997;13(3):395-400.
10. Niessen LW, Grijseels EWM, Rutten FFH. The evidence-based approach in health policy and health care delivery. Soc Sci Med 2000;51(6):859-69.
11. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 1977;296(13):716-21.
12. Granata AV, Hillman A. Competing practice guidelines: using cost-effectiveness analysis to make optimal decisions. Ann Intern Med 1998;128:56-63.
13. Murray CJ, Evans DB, Acharya A, Baltussen RM. Development of WHO guidelines on generalised cost-effectiveness analysis. Health Econ 2000;9(3):235-51.
14. Rutten GEHM, Maaijen J, Valkenburg ACH, Blankestijn JG, Valk HW de. Telemedicine Support improves GP Care in Diabetes Type 2. Diabetic Med 2001;18(6):459-63.
15. Ballegooie E van, Everdingen JJ van. CBO-richtlijnen over diagnostiek, behandeling en preventie van complicaties bij diabetes mellitus: retinopathie, voetulcera, nefropathie en hart- en vaatziekten. Ned Tijd Geneeskd 2000;144(9):413-8.
16. NHG-Standaard 'Diabets Mellitus type 2', 1e revisie. Huisarts en Wetenschap 1999;42(2):67-83.
17. Niessen LW, Casparie AF. Effecten en kosten van de herziene richtlijnen voor diabetes. CBO/NDS/iMTA. Alphen a/d Rijn: Van Zuiden Communications B.V., 2001. ISDN 90-76906-19-x.
18. Smith H, Have P ten. Benchmarking in de diabeteszorg. Medisch Contact 1999;9:308-10.
19. Sonnaville JJJ de, Bouma M, Colly LP, Deville W, Wijkel D, Heine RJ. Sustained good glycemic control in NIDDM patients by implementation of structured care in general practice. Diabetologia 1997;40:1334-40.

20. Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Zbrozek AS, Dong F. Model of complications of NIDDM. I. Model construction and assumptions. Diabetes Care 1998;20(5):725-32.
21. Dijkstra RF, Braspenning JC, Uiters E, Ballegooie E van, Grol RT. Perceived barriers to the implementation of diabetes guidelines in hospitals in the Netherlands. Neth J Med 2000;56(3):80-5.
22. Redekop K, Koopmanschap MA, Rutten G, Wolffenbuttel B, Stolk RP, Niessen LW. Resource consumption and costs in Dutch patients with Type 2 diabetes mellitus. Diabet Med 2002;19:246-53.
23. Verhoeven S, Ballegooie E van, Casparie AF. Impact of late complications in Type 2 diabetes in a Dutch population. Diabet Med 1991;8:435-8.
24. CBS. Sterfte naar belangrijke doodsoorzaken 1970-1990. Voorburg: Central Bureau of Statistics, 1992.
25. Hoogenveen RT, Gijsen R, Genugten MLL van, Kommer GJ, Hollander AM de. Dutch DisMod. Constructing a consistent data set for chronic disease modelling. RIVM Report No, 260751 001. Bilthoven: RIVM, 2000.
26. Ruwaard D. Diabetes mellitus; from epidemiology to health policy [Thesis]. Rotterdam: Erasmus University, 1996.
27. Redekop K, Koopmanschap MA, Rutten GEHM, Wolffenbuttel B, Stolk RP, Niessen LW. Quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. Diabetes Care 2002;25:458-63.
28. Tangelder MJ, McDonnel J, Busschbach JJ van, Buskens E, Algra A, Lawson JA. Quality of life after infra-inguinal bypass grafting surgery. J Vasc Surg 1999;29(5):913-9.
29. Niessen LW. Roads to Health; multi-state modelling of population health and resource use. Dutch University Press, 2002. ISBN 90 5170 663 4.
30. Stratton IM, Adler AI, Neil HA, et al. Association of glycemia with macro-vascular and micro-vascular complications of type 2 diabetes. BMJ 2000;321:405-12.
31. Ubel PA, Richardson J, Prades JL. Life-saving treatments and disabilities. Are all QALYs created equal? Int J Technol Assess Health Care 1999;15(4):738-48.
32. Renders CM, Valk GD, Griffin S, Wagner EH, Eijk JThM van, Assendelft WJJ. Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings. Oxford: Cochrane Library, 2001:no. 2.
33. Grimshaw J, Freemantle N, Wallace S, et al. Developing and implementing clinical practice guidelines. Qual Health Care 1995;4:55-64.
34. Grol R. National standard setting for quality of care in general practice: attitudes of general practitioners and response to a set of standards. Br J Gen Pract 1990;40(338):361-4.

2 bijsluiters B