Cost-Effectiveness of Prevention and Treatment of the Diabetic Foot

A Markov analysis

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OBJECTIVE — To estimate the lifetime health and economic effects of optimal prevention and treatment of the diabetic foot according to international standards and to determine the cost-effectiveness of these interventions in the Netherlands.

RESEARCH DESIGN AND METHODS — A risk-based Markov model was developed to simulate the onset and progression of diabetic foot disease in patients with newly diagnosed type 2 diabetes managed with care according to guidelines for their lifetime. Mean survival time, quality of life, foot complications, and costs were the outcome measures assessed. Current care was the reference comparison. Data from Dutch studies on the epidemiology of diabetic foot disease, health care use, and costs, complemented with information from international studies, were used to feed the model.

RESULTS — Compared with current care, guideline-based care resulted in improved life expectancy, gain of quality-adjusted life-years (QALYs), and reduced incidence of foot complications. The lifetime costs of management of the diabetic foot following guideline-based care resulted in a cost per QALY gained of <$25,000, even for levels of preventive foot care as low as 10%. The cost-effectiveness varied sharply, depending on the level of foot ulcer reduction attained.

CONCLUSIONS — Management of the diabetic foot according to guideline-based care improves survival, reduces diabetic foot complications, and is cost-effective and even cost saving compared with standard care.

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Diabetes is becoming one of the most common chronic diseases in the Netherlands. An age-related increase in the prevalence of diabetes of 32–36% is estimated for the period from 1995 to 2010, at the end of which 400,000–500,000 cases are expected (1). Diabetes is a leading cause of morbidity and mortality, imposing a burden on budget and human resources (2,3). Diabetic patients account for 12 and 18% of the total mortality of Dutch men and women, respectively (4), and 2.5% of total Dutch health care costs (5).

A costly complication affecting patients with diabetes is the diabetic foot. The high therapeutic costs and low quality of life caused by lower extremity amputation (LEA), the most severe consequence of the disease, account for a large part of these expenses. It is estimated that 80% of LEAs are preceded by foot ulcers. Accordingly, it has been demonstrated that preventing the development of foot ulcers in patients with diabetes reduces the frequency of LEAs by 49–85% (6).

Given the above, national clinical guidelines on the prevention and treatment of the diabetic foot have been recently issued as part of a project initiated by the Dutch Ministry of Health in 1998. The strategies contained in the guidelines follow the principles outlined in the International Consensus of the Diabetic Foot (7). Cornerstones of guidelines-based care are intensive glycemic control (IGC) and optimal foot care (OFC). Although health benefits and economic efficiency of intensive blood glucose control (8) and foot care programs (9–14) have been individually reported, the health and economic outcomes and the cost-effectiveness of both interventions have not been determined. Moreover, the long-term costs and outcome estimates of these interventions remain unknown; most of the few cost-effectiveness studies performed in diabetic foot management are based on short-term models, the results of which do not allow adequate estimates of the quality-adjusted life-years (QALYs) saved by these interventions.

To address these issues, we estimated the lifetime health and economic effects of the prevention and treatment of the diabetic foot according to international standards and determined its cost-effectiveness relative to current care in a group of diabetic patients in the Netherlands.

RESEARCH DESIGN AND METHODS

— A Markov model was built to simulate the health and economic outcomes of optimal care of the diabetic foot in a hypothetical population of diabetic patients. Markov models are well-recognized methods for analyzing clinical and economic consequences of medical decisions, particularly in long-term diseases characterized by repeating risks of events over time. Because of its chronic nature and the recurrent character of its major adverse outcomes, foot ulcers and

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Abbreviations: DFR, diabetic foot risk; ICER, incremental cost-effectiveness ratio; IGC, intensive glycemic control; IWGDF, International Working Group on the Diabetic Foot; LEA, lower extremity amputation; OFC, optimal foot care; QALY, quality-adjusted life-year.

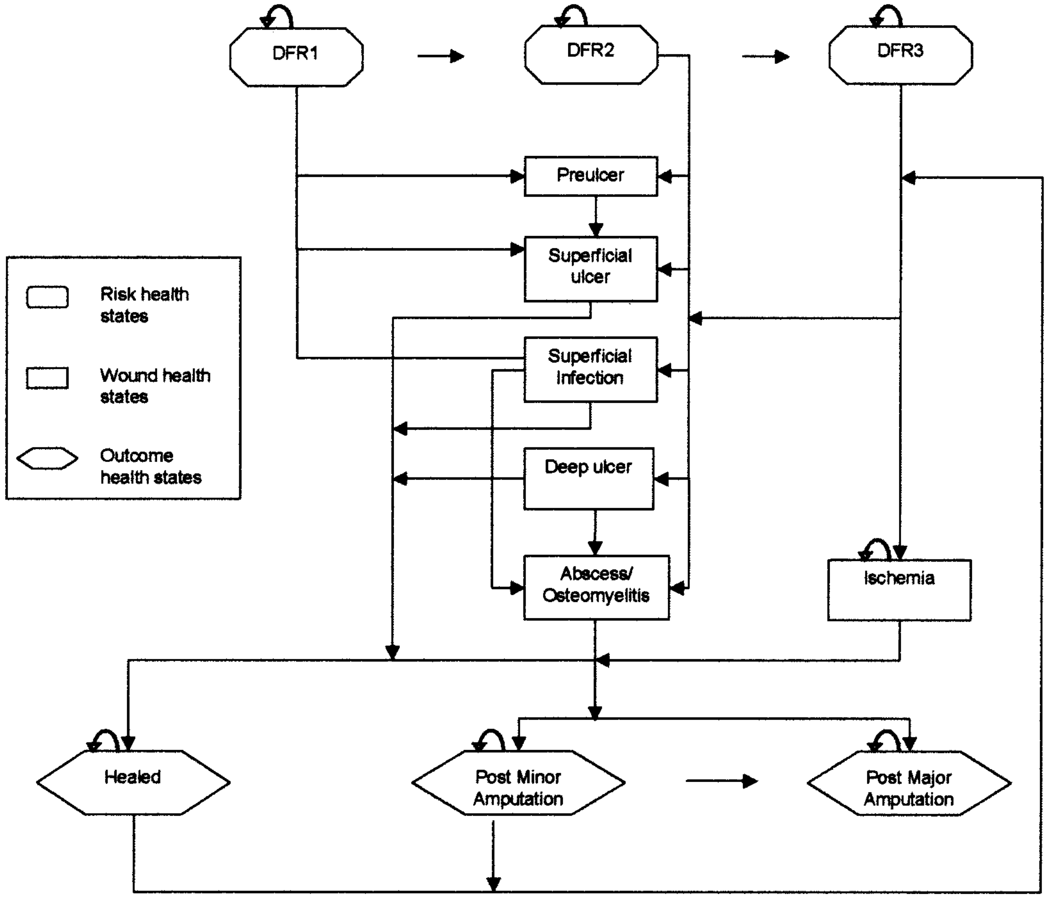

Figure 1—*Health states and transition paths. Not shown is the chance of death for all health states. The permanency in the ischemic state refers to treated ischemia. DFR1, no neuropathy; DFR2, sensory neuropathy; DFR3, sensory neuropathy and deformity or peripheral vascular disease.*

amputations, diabetic foot disease fulfills these criteria.

In this study, diabetic foot pathology was modeled by 13 health states describing the spectrum of the disease from causes to consequences: three risk health states, six wound type states, and four outcome states were included. Cohorts of 10,000 patients with newly diagnosed type 2 diabetes were followed through the model individually over their lifetime. In the simulations, optimal treatment and prevention were compared with present level of care. The clinical outcomes measured were life expectancy, QALYs, and incidence of foot ulcers and amputations. The economic outcomes studied were mean expected total lifetime cost and incremental cost-effectiveness ratio (ICER).

Model structure

Health states and transition probabilities. Health states were defined considering their clinical relevance within the history of the disease and their association with different health outcomes and resource costs (Fig. 1). The first three health states represented pathophysiologic precursors for development of ulcers. The presence or absence of these factors confer different risks for ulceration and, thus, have been included in the model as diabetic foot risk (DFR) states. Based on the classification system of the International Working Group on the Diabetic Foot (IWGDF) (7), these states were defined as: DFR1, no neuropathy; DFR2, sensory neuropathy; and DFR3, sensory neuropathy and deformity or peripheral vascular disease. Previous ulcer or amputation, the fourth risk factor identified by the IWGDF, was represented in the model by the healed and postminor amputation states since the entrance to these states implied the occurrence of a previous episode of an ulcer or amputation.

The six wound health states reflect important characteristics of diabetic foot lesions, namely depth, presence of ischemia, and infection, and they attempt to reconcile two established wound classification systems: Wagner's (15) and the University of Texas (16) classification systems. The remaining four health states encompass all possible outcomes of the diabetic foot disease: healed, amputation (minor or major), and death.

Patients progressed to other health states, remained in the same state, or died, depending on the associated probabilities for each transition. Six-month transition probabilities were assigned for movement between the health states. Mean age at entry was 61 years, corresponding to the mean age of diagnosis of type 2 diabetes in the Netherlands (17). All patients began the model in DFR1 (88.5%) or DFR2 (11.5%) states, concurring with the prevalence of sensory neuropathy at time of diagnosis of diabetes (18).

Information on probabilities of morbid and mortal events was derived from studies on incidence and prevalence of diabetic foot pathology published from 1996 to 2002. Priority was given to national published articles and prospective cohort studies to obtain the best reflection of the history of the disease in a Dutch setting. To ensure consistency, all international studies used pertained to the same research group: the University of Texas study group. Data derived from the U.K. Prospective Diabetes Study group were only used in the transition to sensory neuropathy. These studies were selected based on comparability with Dutch diabetic population characteristics, sample size, follow-up period, reporting on variables of interest, and overall quality. Transition probabilities and study sources are summarized in Table 1.

Morbidity. Core information was obtained from the only Dutch prospective cohort study on diabetic foot disease (17). An annual ulcer incidence rate of 2.1% and an amputation incidence rate of 0.6% were among the reference country–specific parameters derived from this study and adopted in the model.

Transition probabilities to the different ulcer states were specific for each of the four risk categories. Incidence rates per risk subgroup were calculated using information from two of the few prospective cohort studies reporting ulcer incidence following the risk classification system of the IWGDF (19,20). Ulcer distribution per risk group was derived from local and international studies (21–23). A recategorization of the wound types was performed to meet the health states definition of the model. The progressions and associated probabilities of the wound types were derived from longitudinal studies on clinical outcomes of foot ulcers (22,23). In general, once in a wound state, four possible transitions were allowed: the wound healed primarily, the wound healed after amputation, the lesion remained unhealed, or the patient died. Wound healing probabilities were calculated as the residual of the probability of the other transition(s). The healed and postminor amputation states were considered to have the same wound progressions and associated transition probabilities. In the postmajor amputation state, the transition to a new ulcer was not allowed; in this state, patients either remained in the same state or died.

Mortality. Data were obtained from studies reporting on mortality of diabetic patients in the Netherlands (24,25). Mortality rates of the risk states were age specific. Age ranges per risk categories were

Table 1—*Six-month transition probabilities and input values for standard care*

From ↓ To →	Transition probabilities: DFR1	DFR2	DFR3	Preulcer	Superficial ulcer	Superficial infection	Deep ulcer	Abscess/ osteomyelitis	Ischemia	Healed	Post minor amputation	Post major amputation	Death	References	Utilities	Costs
DFR1	95.7	1.99	—	0.2	0.02	0.006	—	—	—	—	—	—	2	17–22,24	0.84	108
DFR2	—	90	5	0.6	0.06	0.01	0.01	0.04	—	—	—	—	4.5	17,19–22,24	0.74	108
DFR3		—	94.8	0.03	0.18	0.11	0.11	0.20	0.07	—	—	—	4.5	17,19,20,22–24	0.74	108
Preulcer	—	—	—	—	98* 95.5† 90‡	—	—	—	—	—	—	—	2* 4.5† 10‡	23,24	0.75	108
Superficial ulcer	—	—	—	—	—	—	—	—	—	98* 95.5† 90‡	—	—	2* 4.5† 10‡	23,24	0.75	874
Superficial infection	—	—	—	—	—	—	—	8	—	87.5*† 82‡	—	—	4.5*† 10‡	22–24	0.70	1,181
Deep ulcer	—	—	—	—	—	—	—	—	—	95.5† 90‡	—	—	4.5† 10‡	22–24	0.75	1,872
Abscess/osteomyelitis	—	—	—	—	—	—	—	16.5	—	21.5	20.5	31.5	10	22–24	0.59	4,834
Ischemia	—	—	—	—	—	—	—	—	22.3	22.7	17.4	27.2	10	22–24	0.59	2,621
Healed	—	—	—	0.21	1.3	0.77	0.78	1.43	0.54	84.9	—	—	10	17,19,20,23,24	0.68	108
Postminor amputation	—	—	—	0.21	1.3	0.77	0.78	1.43	0.54	—	76	17	1.69	17,19,20,23,25	0.68	923
Postmajor amputation	—	—	—	—	—	—	—	—	—	—	—	89	11	25	0.62	1,325

Data for transition probabilities are percentages. *Risk 1; †Risk 2–3; ‡Risk 4. Transition from DFR1 to DFR2 corresponds to baseline incidence rates. Discrepancies due to rounding. Costs expressed as 1999 U.S. dollars.

Table 2—*Clinical and economic outcomes of standard care and guidelines care simulations*

		Guideline care				
			10% foot lesion reduction		90% foot lesion reduction	
Life expectancy	Standard care	IGC	OFC	IGC + OFC	OFC	IGC + OFC
Life expectancy (years)	8.14	8.21	8.15	8.23	8.33	8.41
SD of life expectancy (years)	0.43	0.43	0.43	0.43	0.44	0.44
Difference in life expectancy	NA	0.07	0.01	0.09	0.19	0.27
QALY	6.49	6.56	6.50	6.58	6.65	6.74
SD of QALY	0.34	0.35	0.34	0.35	0.35	0.35
Difference in QALY	NA	0.07	0.01	0.09	0.16	0.25
Total lifetime costs	2,142	4,386	4,343	4,352	4,088	4,107
SD of total lifetime costs	259	337	329	323	232	232
Difference in total lifetime costs	NA	2,244	2,201	2,210	1,946	1,965
ICER	NA	32,057	220,100	24,556	12,163	7,860
Cumulative incidence of ulcers (%)	17.8	17.7	15.8	15.84	1.31	1.28
Cumulative incidence of amputations (%)	3.62	3.46	3.28	3.24	0.25	0.24
Ulcer reduction (%)	NA	0.56	11.2	11.2	92.7	92.8
Amputation reduction (%)	NA	4.4	9.4	10.5	93.1	93.4

Costs expressed as 1999 U.S. dollars. SD of mean was derived using 10,000 Monte Carlo simulations, each consisting of 100 individuals.

calculated based on mean duration of diabetes reported in a previous study (19). Risk group 1 patients were assigned the mortality rate of the diabetic population in the Netherlands aged 55–64 years (newly diagnosed diabetic patients). Risk groups 2 and 3 were assigned the mortality of diabetic patients aged 65–74 years, and risk group 4 patients were assigned the mortality of diabetic patients aged ≥75 years (24). Similarly, these mortality rates were assigned to the wound states according to severity and risk category.

Interventions

The treatment effects of conventional glycemic control and IGC simulated in the model were based on U.K. Prospective Diabetes Study results (18). The neuropathy rates reported for both groups were incorporated into our model in the transition from DFR1 (no neuropathy) to DFR2 (sensory neuropathy).

OFC according to guidelines includes professional protective foot care, education of patients and staff, regular inspection of the feet, identification of the high-risk patient, treatment of nonulcerative lesions, and a multidisciplinary approach to established foot ulcers. These strategies have been reported to decrease the incidence of LEA by 49–85% (6). Because the major goal of these interventions is to decrease the occurrence of foot pathology, the effect of OFC in the model was incorporated by reducing the probabilities of development of foot lesions. To overcome the uncertainty around the decrease in frequency of foot lesions required to attain a decrease in LEA, the probabilities describing the transitions to the different wound states were varied across a range of 10–90% and the effects on LEA rates were recorded.

The clinical and economic outcomes of the two intervention strategies contained in the guidelines (IGC and OFC) were analyzed separately and in combination to determine their individual weight and additive impact on the results.

Costs

Resource use associated with the various health states and transitions was obtained from a published study comparing standard and intensive treatment protocols in general practices in the Netherlands (26,27) and from an economic study on the treatment of diabetic foot ulcers (28). Only direct medical costs were considered. The costs of each health state were determined by the health care utilization associated with that state and included expenses such as labor, medication, laboratory, materials (shoes, insoles, contact casts), and procedure (diagnostic tests, debridement, bone resection) (Table 1 and Fig. 3). Costs used in the model were expressed as 1999 U.S. dollars and discounted by 3%.

Utilities

The utility weights needed to calculate QALY were derived from a Dutch study on foot ulcers and amputation state valuations (29). Utility weights ranged from 0 to 1, where 0 represented a quality of life equal to death and 1 represented perfect health (Table 1).

Utilities were discounted by 3%.

Sensitivity analysis

Sensitivity analyses were performed on effectiveness of preventive foot care strategies (level of foot lesion reduction), utility weights, and costs. The utility weights were varied according to the results from a previous study on quality of life and foot ulcers (30). These values were adapted to meet our ulcer categorization. Costs were changed by varying the length of stay of inpatient care. The length of stay reported for inpatient care of foot ulcers in the U.S. was used as a reference in the sensitivity analysis (31). This model was constructed using TreeAge (DATA 3.5) software.

RESULTS — The lifetime health and economic outcomes for patients under standard care and guidelines care are summarized in Table 2. Results are shown for the three types of guidelines care scenarios considered: IGC, OFC, and IGC + OFC. For the cohorts under OFC intervention, results are shown for the lowest (10%) and highest (90%) level of ulcer reduction simulated.

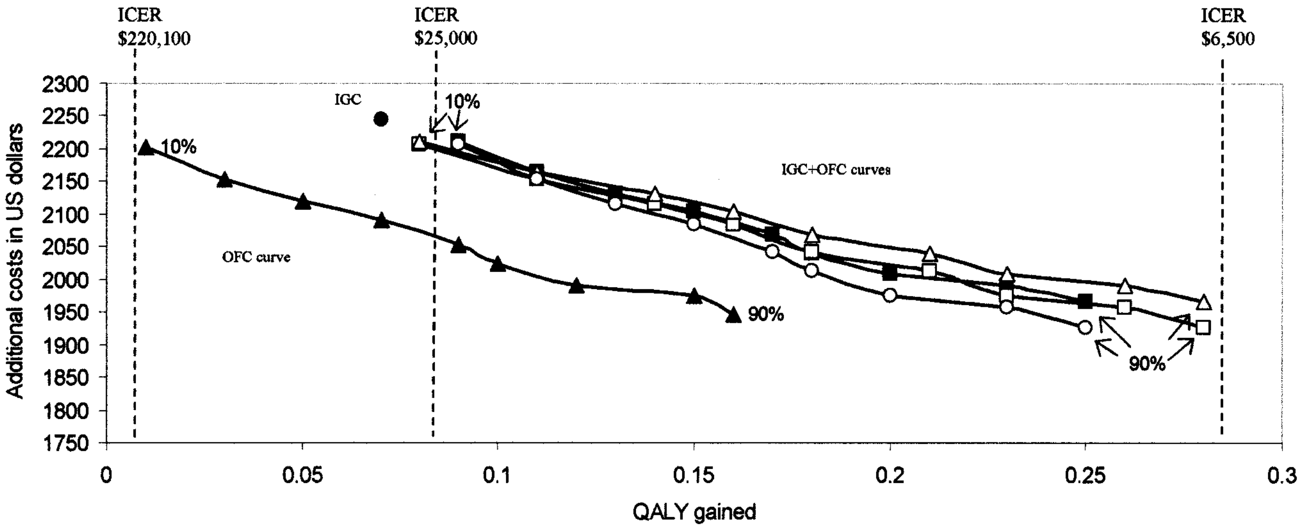

Figure 2—*Costs, effects, and sensitivity analysis results for guidelines care scenarios compared with standard care. Curves correspond to foot ulcer reduction levels of 10–90% (10% intervals). Black symbols represent simulation results obtained using reference input parameters; white symbols represent simulation results obtained using alternative input parameters results.* ●*, IGC point estimate;* ▲*, OFC curve;* ■*, IGC + OFC curve;* △*, IGC + OFC curve using alternative utility weights;* ○*, IGC + OFC curve using alternative costs;* □*, IGC + OFC curve using alternative utility weights and costs simultaneously.*

Model validity

The health outcomes results of the cohort following standard care were comparable to figures reported for diabetic patients in the Netherlands. The undiscounted mean life expectancy was 14 years (discounted mean life expectancy, 8.1 years). In the 10,000 patients followed until death, a total of 1,780 ulcer episodes occurred, corresponding to a cumulative ulcer incidence of 17.8% and an annual ulcer incidence of 2.2% (mean annual ulcer incidence for the Netherlands is 2.1%) (17). The number of amputations observed was 362 (250 major and 112 minor), corresponding to a cumulative incidence of 3.6% and an annual incidence of 0.4% (mean annual amputation incidence reported for the Netherlands is 0.6%) (17). Mean lifetime costs totaled $2,142.

Health and economic outcomes

All cohorts of patients simulated for the different scenarios of guidelines care resulted in improved life expectancy, QALYs gained, and reduced incidence of foot ulcers and LEA compared with standard care. The largest effects on these outcomes were obtained when patients received IGC + OFC. When comparing the independent health effects of the two guidelines strategies, OFC resulted in a greater reduction in ulcer and amputation rates than IGC. Moreover, patients who received IGC + OFC showed approximately the same LEA incidence as patients who received OFC alone. The LEA decrease obtained was proportional to the level of foot ulcer reduction attained.

The mean total lifetime costs of a patient under either of the three guidelines care scenarios ranged from $4,088 to $4,386. For patients receiving IGC + OFC, these costs resulted in <$25,000 per QALY gained (relative to standard care). For patients receiving IGC alone, the ICER obtained was $32,057 per QALY gained, and for those receiving OFC alone, this ICER ranged from $12,169 to $220,100 per QALY gained, depending on the level of ulcer reduction attained.

Figure 2 is a graphical representation of the additional costs, QALYs gained, and ICER of the three guidelines care scenarios compared with standard care. All levels of foot ulcer reduction (10–90%) considered in the sensitivity analysis are represented. Also shown are the results of the sensitivity analyses performed on the QALY weights and length-of-stay input parameters. The results of the simulations for the combined scenario (IGC + OFC) were used to illustrate the effects of these variations (curves to the right). Results are shown for both input parameters varied simultaneously and separately (Fig. 3).

ICERs of <$25,000 were obtained for levels of preventive foot care of ≥10% for patients under IGC + OFC and for levels of preventive foot care of >40% for patients receiving OFC alone (Table 2).

Sensitivity analyses

Increasing the effectiveness of preventive foot care in patients under OFC and IGC + OFC resulted in more QALYs gained, lower costs, and a more favorable ICER. The results of the simulations for the combined scenario (IGC + OFC) were rather insensitive to changes in utility weights and costing parameters. Similar results were obtained for parameter variations in the other two scenarios (IGC and OFC separately).

CONCLUSIONS— The results of this study suggest that IGC + OFC reduces foot ulcers and amputations and leads to an improvement in life expectancy. Greater health benefits are obtained with higher levels of foot ulcer prevention. Although care according to guidelines increases health costs, the cost per QALY gained is <$25,000, even for levels of preventive foot care as low as 10%. ICERs of this order are cost-effective according to the stratification of interventions for diabetes recently proposed (32).

OFC strategy alone is only cost-effective at levels of preventive foot care >40%. In a previous economic study performed in Sweden (13), intensified foot care intervention was cost-effective when

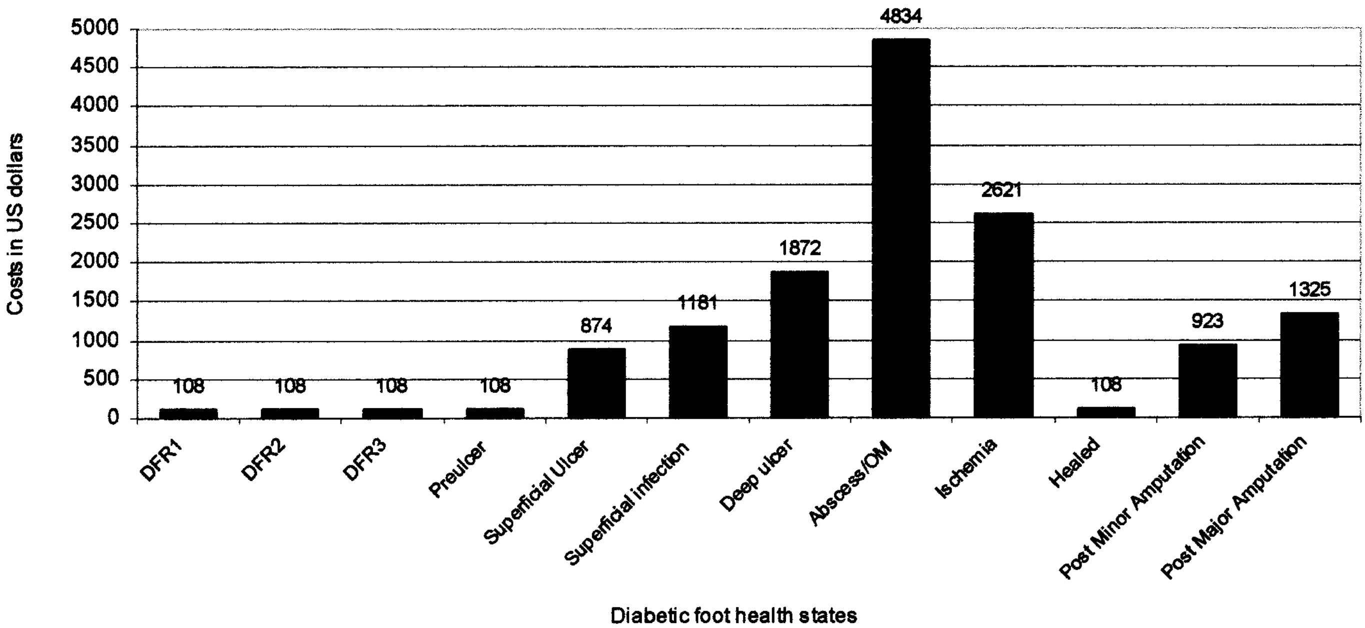

Figure 3—*Six-month costs per health state for standard care. Not shown for the amputation states are the one-time costs for surgery and hospitalization. OM, osteomyelitis.*

a 25% reduction in incidence of foot ulcers and amputations was assumed. This difference in the level of preventive foot care between their study and our study, albeit not large, may be attributed to differences in model architecture, follow-up period, and information used in the models, including country-specific parameters such as incidence of foot complications, prevalence of foot wounds, and costs.

The cost-effectiveness of IGC alone was estimated to be $32,057 per QALY and the reduction in incidence of LEA was estimated to be 4.4%. Our results are comparable to those reported by the Centers for Disease Control and Prevention (CDC) group (8), in which an ICER of $41,384 and an LEA reduction of ~3% were reported. IGC falls into the category of a possibly cost-effective intervention in the management of the diabetic foot. Although it does not produce significant reduction in foot ulcers and LEA, its effectiveness resides in the slowing of neuropathy progression rates.

Extrapolating our results to a practical situation, if IGC + OFC was to be given to all diabetic patients in the Netherlands, with the aim of reducing LEA by 50% (St. Vincent's declaration), the cost per QALY gained would be $12,165 and the cost for managing diabetic ulcers and amputations would decrease by 53 and 58%, respectively. From a policy perspective, this is clearly cost-effective and cost saving compared with current care. From a clinical perspective, this goal is achievable considering that LEA reductions of 49–85% have been reported in the literature for strategies containing only foot care preventive measures (6). For OFC alone, these results would be achieved at an ICER of $22,812, which is twice the ratio seen for the combined scenario.

The results of our study are supported by the robustness of the model. The agreement of the epidemiologic outputs with known data on incidence and prevalence of the diabetic foot provides evidence of the model's ability to adequately reflect disease progression. In building the model, great effort was put into collecting updated, representative, and consistent information; therefore, the conclusions that can be drawn from it are valid and the probability for bias is small. Although the input parameters used were based on a Dutch setting, the model's structure has worldwide applicability.

In conclusion, guidelines care comprising metabolic and foot care interventions combined is cost-effective and may even be cost saving in the management of the diabetic foot in the Netherlands. A valid and comprehensive Markov model that can be used for future cost-effectiveness analysis of diabetic foot disease prevention has been developed.

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