Cost-Effectiveness of Intensified Versus Conventional Multifactorial Intervention in Type 2 Diabetes

Results and projections from the Steno-2 study

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OBJECTIVE — To assess the cost-effectiveness of intensive versus conventional therapy for 8 years as applied in the Steno-2 study in patients with type 2 diabetes and microalbuminuria.

RESEARCH DESIGN AND METHODS — A Markov model was developed to incorporate event and risk data from Steno-2 and account Danish-specific costs to project life expectancy, quality-adjusted life expectancy (QALE), and lifetime direct medical costs expressed in year 2005 Euros. Clinical and cost outcomes were projected over patient lifetimes and discounted at 3% annually. Sensitivity analyses were performed.

RESULTS — Intensive treatment was associated with increased life expectancy, QALE, and lifetime costs compared with conventional treatment. Mean ± SD undiscounted life expectancy was 18.1 ± 7.9 years with intensive treatment and 16.2 ± 7.3 years with conventional treatment (difference 1.9 years). Discounted life expectancy was 13.4 ± 4.8 years with intensive treatment and 12.4 ± 4.5 years with conventional treatment. Lifetime costs (discounted) for intensive and conventional treatment were €45,521 ± 19,697 and €41,319 ± 27,500, respectively (difference €4,202). Increased costs with intensive treatment were due to increased pharmacy and consultation costs. Discounted QALE was 1.66 quality-adjusted life-years (QALYs) higher for intensive (10.2 ± 3.6 QALYs) versus conventional (8.6 ± 2.7 QALYs) treatment, resulting in an incremental cost-effectiveness ratio of €2,538 per QALY gained. This is considered a conservative estimate because accounting prescription of generic drugs and capturing indirect costs would further favor intensified therapy.

CONCLUSIONS — From a health care payer perspective in Denmark, intensive therapy was more cost-effective than conventional treatment. Assuming that patients in both arms were treated in a primary care setting, intensive therapy became dominant (cost- and lifesaving).

Diabetes Care 31:1510–1515, 2008

Cardiovascular disease mortality is the most common cause of death in patients with type 2 diabetes, with an incidence at least double that in the general population (1). Moreover, cardiovascular morbidity is a major illness burden in these patients and contributes substantially to the overall costs associated with type 2 diabetes. The total direct annual costs of diabetes in eight European countries were estimated at €29 billion, with an estimated yearly cost per patient of €2,834 (2). Similarly, in the U.S., diabetes is reported to be associated with annual direct medical expenditures of approximately $91.8 billion, with per capita costs totaling $13,243 for individuals with diabetes compared with $2,560 for those without (3). Cardiovascular disease in patients with type 2 diabetes presents serious health and economic concerns to health care systems, with health care policy makers having to decide how to make the most efficient use of limited health care budgets.

New interventions that improve patient outcomes are generally associated with increased costs. The American Diabetes Association recommends a multifactorial approach to the treatment of patients with diabetes, including strict attention to glycemic control and aggressive management of cardiovascular risk factors (4). Until the recent Steno-2 study, data on the long-term effect of such an approach was lacking. To determine whether the intensive approach aimed at treating patients with type 2 diabetes and microalbuminuria for 7.8 years to recommended targets in the Steno-2 study would represent good value for the money, this study aimed to assess the cost-effectiveness of intensive versus conventional therapy as applied in the Steno-2 study from the perspective of a national health care provider in Denmark.

RESEARCH DESIGN AND METHODS — The Steno-2 study was a randomized, open, parallel trial undertaken by the Steno Diabetes Center in Copenhagen, Denmark (5). At baseline, all patients had type 2 diabetes and microalbuminuria, a well-established independent risk factor for cardiovascular disease (6,7). Eighty patients were randomly assigned to receive conventional treatment for multiple risk factors from their general practitioner in accordance with national guidelines. The remaining 80 patients were assigned to intensive multifactorial treatment at the Steno Diabetes Center. The primary end point for the macrovascular analysis following 7.8 years of intervention was a composite of cardiovascular disease (nonfatal myocardial infarction, nonfatal stroke, percutaneous coronary intervention, and

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Received 27 December 2007 and accepted 18 April 2008.
Published ahead of print at http://care.diabetesjournals.org on 28 April 2008. DOI: 10.2337/dc07-2452.
Clinical trial reg. no. NCT00320008, clinicaltrials.gov.

coronary artery bypass grafting), revascularization of the leg, lower-extremity amputation, and cardiovascular disease–related death. Compared with patients in the conventional therapy arm, patients assigned to intensive therapy had a 53% (95% CI 27–76) lower relative risk of cardiovascular disease.

Model

A Markov model was developed using TreeAge Pro (TreeAge Software, Williamstown, MA) to project the long-term clinical and cost outcomes associated with the conventional and intensive treatment arms applied in the Steno-2 study (8–10). The model incorporated event probabilities and risk data from the study (and accounted Danish-specific costs) to estimate life expectancy, quality-adjusted life expectancy, and lifetime direct medical costs associated with the two treatment arms.

A two-state Markov model (alive and dead) with a cycle length of 1 year was developed. The model was designed to capture the occurrence of the following events from the Steno-2 Study: myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, stroke (major and minor), hospitalization for congestive heart failure, revascularization of leg, revascularization of carotid artery, lower-extremity amputation (toe and major amputation) due to diabetes, end-stage renal disease, and dialysis.

For the modeling analysis, cohort characteristics and event rates were applied as observed in the Steno-2 study for years 1–8 of the analysis, after which mean event rates were carried forward for subsequent years of simulation (see tables in online appendices 1 and 2, available at http://dx.doi.org/10.2337/dc07-2452). Beyond year 8, mortality was adjusted for age by assuming the risk of mortality doubled every 10 years (11). Age-dependent risk adjustments were also applied for congestive heart failure, cardiovascular events (myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting), stroke, and revascularization of the leg (see online appendix 3).

Adjustment of the risk of hospitalization for congestive heart failure according to age was calculated from a risk appraisal function derived from 486 cases of heart failure over 38 years of follow-up (12). Risk adjustment for cardiovascular events according to patient age was performed using the risk regression function reported by the UK Prospective Diabetes Study (UKPDS) for first myocardial infarction (13) and was calculated for stroke using data from the UKPDS stroke risk engine (14). The age-related risk adjustment for leg revascularization was assumed to be the same as that for patients with intermittent claudication (15).

Costs

Direct medical costs were extracted from Danish cost databases by local experts and expressed in year 2005 Euros (€) (conversion rate: €1 = 7.45 Danish kroner). Costs accounted were those related to pharmacy; physician consultation; and interventions associated with complications, i.e., dialysis, revascularization procedures, and amputation (Table 1). Total costs for end-stage renal disease were adjusted according to the average duration of dialysis for patients in the Steno-2 study (1.64 years) (5).

Annual treatment costs were assumed to be the sum of annual pharmacy, remedy, and consultation costs. In the conventional treatment arm, patients were assigned pharmacy costs derived from the Steno-2 study and assumed to receive all their treatment in a primary care setting with cost of remedies and consultations (physician and dietitian) in accordance with previously published Danish estimates (16). Pharmacy costs for patients in the intensive treatment arm were also derived from the Steno-2 study, but in the analyses patients could receive treatment in either a primary care or specialist clinic setting. Pharmacy costs were based on actual prices of prescribed drugs, many of which were nongeneric. Costs for treatment and follow-up of microvascular complications such as retinopathy and neuropathy were not included in this analysis; indirect costs such as lost production were also not included. In the base case analysis, patients in the intensive treatment arm were assumed to attend the specialist clinic at the Steno Diabetes Center.

Quality of life

All patients were assigned a baseline health-state utility score of 0.814, the equivalent of the score for a patient with uncomplicated type 2 diabetes, which captures the reduction in quality of life from the perfect health score of 1 (17). Tracker variables were used in the model to keep a record of all the events experienced by simulated patients. At the beginning of each cycle (or year in the simulation), health-state utilities for each patient were calculated by adjusting their baseline utility scores depending on their history of complications (see online appendix 4). Quality of life for dialysis intervention was assumed to be captured in end-stage renal disease complication and set to zero to avoid double counting.

Discounting, time horizon, and perspective

Clinical and cost outcomes were discounted at a rate of 3% per annum in line with current recommendations for Denmark (18). We modeled a lifetime horizon as the base case analysis and assumed the perspective of a health care payer in Denmark.

Statistical approach

A nonparametric bootstrapping approach was taken in which 1,000 patients were run through the model 100 times using first-order Monte Carlo simulation to calculate the mean and SD of costs, life expectancy, and quality-adjusted life expectancy (QALE) (19). In the base case, mean results of each of the 100 iterations were used to create a scatter plot diagram showing the differences in clinical and cost outcomes for intensive versus conventional treatment. From the scatter plot, an acceptability curve was generated by calculating the proportion of points below a range of willingness-to-pay thresholds (20). This approach was designed to capture statistical uncertainty at the patient level with parameter level uncertainty (e.g., effect of treatment) captured using a qualitative approach (one-way sensitivity analysis).

Sensitivity analyses

The base case analysis was run over a 30-year (patient lifetime) time horizon and captured patient outcomes until year of death. In a sensitivity analysis, the time horizon was set to 8 years, in line with the duration of the Steno-2 study. A further sensitivity analysis was performed on the annual discount rates for cost and clinical outcomes, with discount rates varying from 0 to 6% (base case 3%). In the base case it was assumed that patients in the intensive treatment arm would be treated at the Steno Diabetes Center (it was assumed that patients in the conventional arm received their treatment in a primary care setting). In a sensitivity analysis, it was assumed that patients in the intensive

Table 1—*Summary of cost inputs*

	Annual cost of pharmaceuticals (€)
Conventional arm pharmacy (Steno-2)	967
Hypoglycemic agents (insulin and oral agents)	646
Oral agents	144
Insulin	502
Antihypertensive agents	242
Aspirin	12
Lipid-lowering agents	67
Conventional arm remedies*	139
Intensive arm pharmacy (Steno-2)	1,577
Hypoglycemic agents (insulin and OADs)	756
Oral agents	242
Insulin	514
Antihypertensive agents	390
Aspirin	30
Lipid-lowering agents	401
Intensive arm remedies†	310
Annual costs of consultations	
Conventional arm primary care consultation‡	187
Intensive arm specialist clinic consultation	840
Base case analysis§	
Intensive arm primary care consultation	187
Annual costs of complications	
End-stage renal disease	65,604
CHF (hospitalization)	3,391
Myocardial infarction	3,117
Stroke (major with rehabilitation)	10,138
Stroke (minor without rehabilitation)	5,372
Annual costs of interventions	
Dialysis (acute)	6,137
Revascularization of leg	9,978
Revascularization of carotid artery	6,181
PCI	9,566
CABG	16,178
Amputation (major)	12,058
Amputation (toe)	8,128

Data are 2005 Euros. *Conventional arm remedies include 50 strips for home measurement of blood glucose, 2.7 measurements of blood glucose at the general practitioner (GP), 3.3 measurements of A1C, 0.2 measurements of lipid values, and 0.5 measurements of urinary albumin-to-creatinine ratio (16). †Intensive arm remedies include 200 strips for home measurement of blood glucose, 4.0 measurements of blood glucose at the GP, 4.0 measurements of glycated hemoglobin A1C, 4.0 measurements of lipid values, and 4.0 measurements of urinary albumin-to-creatinine ratio. ‡Conventional arm consultations include an average of 4.5 yearly consultations at the general practitioner and 0.6 consultations at a diabetes clinic including dietary consultations by a dietitian (16). §Intensive arm consultations include 4 yearly consultations at Steno Diabetes Center with dietary consultations by a dietitian as needed. According to Danish reimbursement rules the price for a visit at a specialist clinic is 15 times higher than a GP consultation (16). All pharmacy and consultation costs were calculated based on resource use data from the Steno Diabetes Center and published prices. All annual costs of complications and annual costs of interventions were based on Danish National Health Board 2005 data (26). CABG, coronary artery bypass grafting; CHF, congestive heart failure; ESRD, end-stage renal disease; PCI, percutaneous coronary intervention.

treatment arm also received their treatment in a primary care setting. This sensitivity analysis was run over both an 8- and 30-year time horizon. A sensitivity analysis was also performed on the clinical benefit observed in the Steno-2 study, whereby patients in the intensive treatment arm were assumed to receive up to 20% less clinical benefit than in the base case (i.e., risk reduction versus that in conventional treatment was decreased by 20%).

RESULTS

Base case analysis

In the base case, intensive treatment was associated with increased life expectancy, QALE, and lifetime costs compared with conventional treatment. Mean ± SD undiscounted life expectancy was 18.1 ± 7.9 life-years with intensive treatment and 16.2 ± 7.3 life-years with conventional treatment (difference 1.9 years). Discounted life expectancy was improved by ~1.1 year in the intensive arm compared with the conventional treatment group (13.4 ± 4.8 vs. 12.4 ± 4.5 years). Taking patients' quality of life into account, simulated patients were projected to live for 10.2 ± 3.6 and 8.6 ± 2.7 quality-adjusted life years (QALYs) for intensive and conventional treatments, respectively (difference 1.66 QALYs).

Lifetime direct medical costs for intensive and conventional treatment were projected to be €45,520 ± 19,697 and €41,319 ± 27,500, respectively (difference €4,201). A breakdown of costs revealed that the increased costs associated with intensive versus conventional treatment were attributable to increased pharmacy and consultation costs (€25,400 versus €11,289, respectively). However, the incremental costs for intensive treatment were less than those for conventional treatment for all complications and interventions modeled in the analysis, despite patients living longer in the intensive treatment arm.

The incremental cost-effectiveness ratio for intensive versus conventional treatment was €2,538 per QALY gained (Table 2). A scatter plot of mean incremental costs and effectiveness for all 100 iterations was created. From this, an acceptability curve was generated showing that, using a willingness-to-pay threshold of €40,000 per QALY gained (21), there was a 74% probability that the intensive treatment would be considered cost-effective versus conventional treatment in a Danish cost setting (Fig. 1).

Sensitivity analyses

The results of the base case were most sensitive to assumptions regarding the costs associated with physician consultation and variation in the time horizon. In the base case, it was assumed that patients in the conventional treatment arm received all of their medical care in a primary care setting, whereas patients in the intensive treatment arm attended consultations at the Steno Diabetes Center. As-

Table 2—*Summary of cost and clinical outcomes in the base case analysis*

	Intensive	Conventional	Difference
Undiscounted life expectancy (years)	18.1 ± 7.9	16.2 ± 7.3	1.9
Life expectancy (years)*	13.4 ± 4.8	12.4 ± 4.5	1.1
QALE (QALYs)*	10.2 ± 3.6	8.6 ± 2.7	1.7
Direct medical costs (€)*	45,521 ± 19,697	41,319 ± 27,500	4,202
Incremental cost-effectiveness ratio		€3,927 per life year gained* €2,538 per QALY gained*	

Data are means ± SD unless otherwise indicated. *Values were discounted at 3% annually. All Euros are in 2005 values.

suming that patients in both treatment arms received their care in the same primary care setting, intensive treatment was found to be dominant (cost- and lifesaving) versus conventional treatment (Table 3).

Shortening the time horizon to 8 years (from a lifetime horizon in the base case) led to the incremental cost-effectiveness ratio for intensive versus conventional treatment increasing to €41,934 per QALY gained. When it was assumed that consultation costs were equal for both treatment arms over this shorter time horizon, intensive treatment was highly cost-effective versus conventional treatment (€320 per QALY gained). Sensitivity analyses on the discount rates applied for cost and clinical outcomes and reducing the clinical effectiveness of intensive treatment by up to 20% had little impact on the overall findings. The application of different methodologies to estimate QALE (multiplication only or addition only versus multiplication and addition in the base case) also had little impact on the overall findings.

CONCLUSIONS — The current health economic modeling analysis based on the 8-year Steno-2 study outcome indicates that in a Danish setting, intensive treatment is likely to be associated with increased life expectancy and QALE compared with conventional treatment, thus representing good value for the money in patients with type 2 diabetes and microalbuminuria. For simplicity and transparency, the model was designed only to simulate events (not states). Therefore, state costs in the years following clinical events were not captured. Furthermore, the costs of medications used in the intensive arm were those of the original patented drugs and not the cheaper generic versions. This very conservative approach was likely to underestimate the economic benefits of intensive versus conventional therapy. Despite this, and given that the overall results were most sensitive to variation in assumptions regarding the costs associated with physician consultation, intensive treatment became dominant (cost- and lifesaving) compared with conventional therapy when it was assumed that patients in both treatment arms received care in a primary care setting. Even in the case where patients in the intensive group were assumed to continue the most expensive treatment in a specialist setting and the treatment effect between the intensive and conventional groups was assumed to decline after the end of the 7.8-year intervention period, this case would still represent good value for the money compared with other well-established interventions.

In the base case analysis, costs and clinical outcomes were projected over patient lifetimes, beyond the duration of intervention in the Steno-2 study. This is common practice in health economic–cost-effectiveness analyses because many important events occur after the study has finished. However, assumptions need to be made on modeled data, and these could introduce uncertainty in long-term projections and are a limitation of such an approach. In the present analysis, beyond year 8 of simulation, mean Steno-2 study event rates were applied in the model with risk of congestive heart failure, myocardial infarction, and revascularization procedures adjusted according to patient age. These age-related risk adjustments were based on calculations from the UKPDS and studies by Kannel et al. and Murabito et al. (12–15).

The Steno-2 study was not designed to identify those factors in the intensive treatment arm that were most effective in reducing the incidence of diabetes-related complications. Had this been the case, costs of treatment could be optimized by specifically targeting those factors that contribute most to improved patient outcomes, thereby improving the cost-effectiveness of intensive versus conventional treatment. However, in this respect, previous publications from single–risk factor intervention in patients with newly diagnosed type 2 diabetes in the UKPDS study have demonstrated the cost-effectiveness of interventions against hyperglycemia (22) and hypertension (23), whereas the cost-effectiveness of cholesterol-lowering therapy is well documented from other studies (24,25).

The cost-effectiveness of intensive versus conventional multifactorial treatment could also vary among patient subgroups and in different patient settings. In the Steno-2 study, all patients had type 2

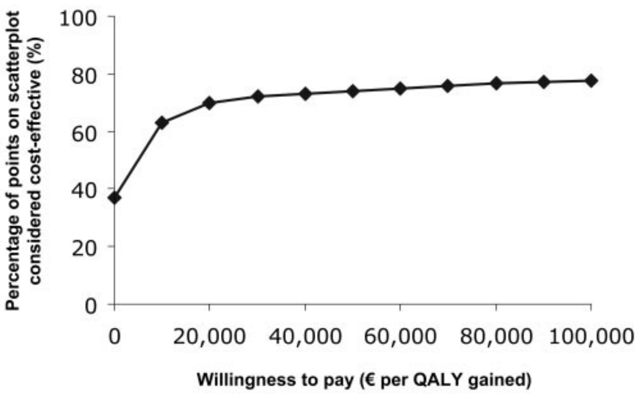

Figure 1—*Acceptability curve from base case analysis.*

Table 3—Summary of cost and clinical outcomes: sensitivity analyses

	QALE (QALYs)			Direct medical costs (€)			ICER
	Intensive	Conventional	Difference	Intensive	Conventional	Difference	(€ per QALY gained)
8-year time horizon	5.4 ± 0.8	5.3 ± 0.7	0.1	21,577 ± 5,953	17,081 ± 12,324	4,495	41,934
0% discount rate	13.5 ± 5.7	10.8 ± 4.2	2.8	62,122 ± 32,261	57,154 ± 43,242	4,969	1,828
6% discount rate	8.1 ± 2.4	7.0 ± 1.9	1.1	35,114 ± 12,994	31,438 ± 19,025	3,676	3,517
Same consultation costs	10.2 ± 3.6	8.5 ± 2.7	1.7	36,681 ± 16,860	41,428 ± 27,721	−4,747	Dominant
30-year time horizon							
Same consultation costs	5.4 ± 0.8	5.3 ± 0.7	0.1	17,105 ± 5,644	17,071 ± 12,317	34	320
8-year time horizon							
Clinical benefit reduced by 20%*	9.6 ± 3.5	8.5 ± 2.7	1.1	44,308 ± 20,243	41,378 ± 27,543	2,930	2,865

Data are means ± SD. ICER = incremental cost-effectiveness ratio. *Applies to the intensive treatment arm. All Euros are in 2005 values.

diabetes and microalbuminuria (an independent risk factor for cardiovascular disease), representing approximately one-third of patients with type 2 diabetes (7). Patients with newly diagnosed type 2 diabetes who have no cardiovascular risk factors would not be expected to receive the same clinical benefit from intensified mutifactorial treatment as patients in the Steno-2 study, but treatment costs would be the same. Another factor that could affect the cost-effectiveness of the intensive treatment arm is common to all intensified treatments in real-life settings. Patients recruited for the Steno-2 study may have been more motivated, compliant, and persistent with treatment than patients in a more realistic treatment environment. Implementing the intensive treatment arm in a real-life setting would require training on the part of physicians and patients and a firm commitment from patients to adhere to strict treatment guidelines.

In conclusion, intensive multifactorial intervention as applied in the Steno-2 study is likely to be highly cost-effective from a third-party health care payer perspective in patients with type 2 diabetes and microalbuminuria versus conventional multifactorial intervention. If the intensified intervention is implemented in a primary care setting, cost savings would be anticipated.

Acknowledgments— This study was supported by unrestricted grants from the Steno Diabetes Center and from Novo Nordisk A/S.

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