



# CHAPTER 8

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General discussion

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In the Netherlands, as well as internationally, the organization of care for diabetes patients is receiving a lot of attention. This thesis focussed on the effectiveness and cost-effectiveness of managed and protocolized diabetes care compared to usual diabetes care. Furthermore, a model to estimate long-term (cost-)effectiveness of diabetes related interventions was developed. Finally, methods to facilitate personalized diabetes care, based on patients' risk profile, were explored.

In this chapter the main findings will be described and some methodological considerations will be addressed. Finally, we will discuss recommendations for clinical practice and further research.

## MAIN FINDINGS FROM THIS THESIS

Managed diabetes care with a central organization and central management of care, was statistically significantly associated with a better process of the diabetes care and lower direct costs compared to usual diabetes care. This persisted after adjustment for differences in patient characteristics at baseline. To a lesser extent, protocolized diabetes care was also associated with lower direct costs compared to usual diabetes care. This difference disappeared after adjustment for differences in patient characteristics between groups (chapter 2). No statistically significant differences were seen in change in coronary heart disease (CHD) risk according to the UKPDS risk function in managed and protocolized care during follow-up compared to usual diabetes care. Thus, lower health care costs were observed in managed and protocolized care compared to usual diabetes care, without affecting clinical outcomes. Similar trends were seen when considering costs from the societal perspective, however not statistically significant (chapter 3). Cross-sectionally, patients treated by managed diabetes care reported a better experience with the continuity of the diabetes care compared to patients receiving protocolized or usual care. This difference between groups decreased during follow-up, most likely because of improvements in protocolized and usual care. Patients in the managed care group had a lower risk of a negative experience with the dietician compared to the other two groups (chapter 4).

For long-term evaluation of cost-effectiveness of diabetes-related interventions, the MICADO model can be used. MICADO is a population-based markov-type multistate transition model. We tested its external validity and showed that it accurately estimated the incidence of microvascular complications in the Dutch diabetes population (chapter 5).

To facilitate personalized care, methods to distinguish between patients at low and high risk for complications were explored. The predictive ability of the UKPDS, SCORE and Framingham risk functions in the estimation of incidence of coronary heart disease

during ten years of follow-up was low to moderate. In absence of a more valid tool, the SCORE and UKPDS functions are the best options in a Caucasian population (chapter 6).

In persons with a history of cardiovascular disease, persons at increased risk of a recurrent cardiovascular event can be identified based on patients' risk profile before the first event. Male sex, age, systolic blood pressure, HbA1c and family history of a myocardial infarction predicted a recurrent cardiovascular event in the general population (chapter 7).

## EXPLANATION OF OUR FINDINGS AND COMPARISON TO OTHER LITERATURE

### Quality and cost-effectiveness of managed and protocolized diabetes care

In recent years, targeted programs have become important means for improving the quality of diabetes care and overcoming existing deficiencies.<sup>1,3</sup> A wide array of approaches exist such as the Chronic Care Model,<sup>4,5</sup> and managed care.<sup>6</sup> A common aspect of chronic care programs is their underlying assumption that the quality of care will be increased, resulting in improved health outcomes, decreased health care use and costs and improved patient satisfaction.

Outcomes of studies investigating effects of diabetes care based on different principles of managed diabetes care models, are heterogeneous.<sup>2</sup> Some studies showed no difference or no improvement in guideline adherence<sup>7</sup> or clinical outcomes,<sup>7,8</sup> while other studies showed improved guideline adherence.<sup>8,9</sup> Our study showed that managed diabetes care and, to a lesser extent, protocolized diabetes care were associated with lower secondary health care use, higher primary health care use and lower medical costs. No statistically significant differences in change in CHD risk compared to usual diabetes care was observed. This substitution of secondary care by primary care was not associated with a lower quality of care compared to usual care. Instead, managed care performed better regarding the process of care. More patients in the managed care group received the assessments and screenings according to diabetes guidelines. This might have resulted in the detection of complications in an early stage, and early initiation of appropriate treatment, which could consequently reduce the number of complications in the long run. Substitution of secondary care by primary care was also seen previously.<sup>9</sup> Some studies showed no difference or no improvement in costs,<sup>7,8,10</sup> while other studies showed short-term costs savings<sup>9,11</sup>. Studies evaluating both effects and costs showed positive long-term cost-effectiveness with QALY<sup>10,12</sup> or self-management<sup>12</sup> as the outcome measure. In these studies information on costs from a societal perspective was unavailable. In our study, lack of effect on the clinical outcome measure might be explained by already low baseline values of HbA1c, cholesterol and blood pressure levels in all three groups. Improvements

in the organizational structure and increasing the expertise in the primary care settings of managed and protocolized care might be the reason for the substitution of secondary care by primary care, leading to lower health care costs. We found higher indirect costs in patients receiving managed care compared to patients receiving protocolized or usual diabetes care. The higher costs due to productivity loss in the managed care group might be explained by differences in patient characteristics. In managed care, more patients were treated with glucose lowering medication (90.1%) compared to protocolized care (75.9%) or usual care (81.7%). This might indicate that there were more complex patients in the managed care group, leading to a higher frequency of sick leaves.

Studies that investigated quality of diabetes care showed that the implementation of managed diabetes care improved the process of care as well as patient satisfaction with care<sup>13-15</sup> and that patient experience with the continuity of diabetes care was positively associated with patient satisfaction with diabetes care.<sup>16</sup> Our study on patient experience with managed or protocolized diabetes care compared to usual diabetes care added information on patient experience with different health care providers involved in the diabetes care. Patients receiving usual care were at lower risk for a negative experience with the diabetes care by the GP. The shared responsibility for patient care in managed care might have resulted in a decreased involvement of the GP in the diabetes care, leading to less positive experiences with the GP in this group compared to usual diabetes care. Lowest risk of a negative experience with the quality of care was seen in the care delivered by the dietician and was in favour of managed care. Dieticians connected to the Diabetes Care Centre, in the managed care group are highly educated and experienced in the treatment of patients with type 2 diabetes and it may be anticipated that these dieticians have a higher level of expertise in the field of diabetes compared to the dieticians in the usual care group. Managed care was associated with fewer negative experiences with the continuity of care at baseline. During follow-up the results of none of the groups improved statistically significantly regarding the quality of care. The continuity of care improved significantly in protocolized and usual care, closing the gap with managed care, which had the best continuity of care.

### **Long-term evaluation of diabetes care**

In clinical trials aiming at improving patients' risk profile, effects on the incidence of complications might occur after several years. Monitoring long-term (cost-)effectiveness of diabetes-related interventions can be very time-consuming and expensive. Simulation models can assist in diabetes policy by giving projections of future health care use and costs, evaluating policy scenarios for prevention and treatment and extrapolating trial results over time. Several models for the estimation of cost-effectiveness of diabetes-related interventions already exist. Most of these models use data derived from trials.<sup>17</sup>

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R1 An advantage of the existing Chronic Diseases Model (CDM)<sup>18</sup> is that macrovascular  
R2 complications are extensively modelled based on large nationwide GP registries,  
R3 representative for the Dutch diabetes population and diabetes care. Furthermore,  
R4 existing diabetes models are developed to simulate disease progression of known  
R5 diabetes patients. The inclusion of persons with and without diabetes in the CDM gives  
R6 us the opportunity to estimate long-term effects of preventive interventions in persons  
R7 with and without diabetes.

R8 Microvascular complications were not included in the CDM. Because of the  
R9 aforementioned advantages of the CDM compared to other models, we extended  
R10 the existing CDM with modules on the development of microvascular complications  
R11 (diabetic foot, nephropathy and retinopathy) enabling a complete assessment of diabetes  
R12 interventions, resulting in the MICADO (Modelling Integrated Care for Diabetes  
R13 based on Observational data) model. We validated the MICADO model by checking  
R14 whether the inter-quantile limits of our model-based estimates included the empirical  
R15 estimates of the incidence of end-stage microvascular complications in the Netherlands.  
R16 MICADO performed well for nephropathy and the diabetic foot. For blindness, lack of  
R17 data prohibited a proper validation. The model can be used to evaluate and compare  
R18 diabetes-related interventions aiming to reduce the risk of vascular diseases. Given the  
R19 lack of statistical significance of the short term follow-up clinical outcomes of our study  
R20 on the cost-effectiveness of diabetes management programs, a long term evaluation was  
R21 not performed since it would not provide any additional insight.

### R23 **Methods to facilitate personalized diabetes care**

R24 To enable a more efficient routine diabetes care, the possibility to distinguish complex  
R25 diabetes patients from well-controlled diabetes patients was explored. Our study on the  
R26 performance of the UKPDS<sup>19</sup>, SCORE<sup>20</sup> and Framingham<sup>21</sup> risk functions in participants of  
R27 the Hoorn Study was low to moderate. The risk functions overestimated the risk of a first  
R28 coronary heart disease during ten years of follow-up. The UKPDS risk function, which  
R29 was specifically designed for the diabetes population, also showed overestimation of  
R30 CHD risk<sup>22-24</sup> while it showed underestimation<sup>25, 26</sup> in other populations. Overestimation  
R31 of CHD risk was also seen in other studies validating the SCORE risk function<sup>27</sup> and  
R32 Framingham risk function.<sup>28, 29</sup> In contrast to our findings, underestimation of CHD risk  
R33 by the Framingham risk function was also seen.<sup>30, 31</sup> This might be explained by differences  
R34 between the validation cohorts (type 1 and type 2 diabetes patients<sup>31</sup> or different risk  
R35 profiles).<sup>30, 31</sup>

R36 The low to moderate predictive ability of the three risk functions in diverse populations  
R37 can be explained. Firstly, the aforementioned models are based on older data. Baseline  
R38 measurements of the studies were performed between 1977 and 1991 (UKPDS), 1970  
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and 1988 (SCORE) and between 1971 and 1974 (Framingham). Because of improved treatment strategies for diabetes patients, risk of a cardiovascular event has decreased during recent decades, having an impact on the predictive value of risk factors. Secondly, the UKPDS, SCORE and Framingham models are all static models, meaning that the model is applied using an individuals' cross-sectional risk profile. Changes in previously measured risk factor levels that are related to cardiovascular events are not taken into account and could lead to a more precise risk estimation that is more closely linked to clinical practice usage. Thirdly, the UKPDS, SCORE and Framingham models do not take medication use into account while patients' responses to medication use most likely are of predictive value for further progress of the disease. Distinguishing between risk factor levels that are or are not affected by medication use could improve the accuracy of the prediction models.

Because of the increase in obesity and diabetes prevalence worldwide, and improved care after a first cardiovascular event, the number of people at risk for a recurrent cardiovascular event is rising. Therefore, it is important to enable identification of persons at high risk of a recurrent cardiovascular event. Methods to identify patients who develop a cardiovascular event and who are at high risk of a recurrent event are less frequently investigated. Male sex, age, systolic blood pressure, HbA1c and family history of a myocardial infarction predicted a recurrent event. Cholesterol levels were not predictive of a recurrent event which was also found in a recent study investigating predictors for a recurrent cardiovascular disease in type 2 diabetes patients.<sup>32</sup> The Framingham model for estimation of risk of a recurrent coronary heart disease within 2 years included, among others, total and HDL cholesterol level.<sup>33</sup> The longer follow-up after the first cardiovascular event in our study, might have resulted in other predicting factors.

## METHODOLOGICAL CONSIDERATIONS

### Evaluation of diabetes care: pragmatic controlled trial

#### *Design*

A randomized controlled trial is considered the gold standard to test the effectiveness of an intervention. Using this design, individuals are randomly allocated to a specific intervention or to the control group and all participants of the study have the same likelihood of allocation to one of the groups. The aim of randomisation is to increase the similarity between groups regarding measured and unmeasured characteristics, except for the intervention under study, and to reduce the effects of confounding or bias.

In clinical studies comparing effects of different organizations, randomization is not always feasible. In our study, diabetes care delivered by the Diabetes Care System

R1 which started in 1996, was compared with diabetes care delivered according to a new  
R2 organizational structure which was prepared and introduced a few years ago. We  
R3 performed a pragmatic controlled study comparing the effects of these two different  
R4 types of diabetes care, on several patient outcomes, to a control group receiving usual  
R5 diabetes care.

R6 Strength of a pragmatic trial such as the current study is that it is closely linked to  
R7 clinical practice. In combination with the wide inclusion criteria that we used, the external  
R8 validity of the intervention is high.<sup>34</sup> The results might be of direct interest of policy  
R9 decision makers because the intervention was tested after implementation in clinical  
R10 practice. Further implementation of a pragmatic trial might be more feasible because the  
R11 gap between evidence and practice is usually smaller in pragmatic trials compared to  
R12 randomized controlled trials.

R13 A limitation might be the non-random allocation of patients and especially care  
R14 givers to different types of care. However, the data analysis can account for this in part,  
R15 by careful consideration of patient group similarity and controlling for covariates.  
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#### R17 *Usual diabetes care*

R18 Because of the rapidly increasing prevalence of persons with type 2 diabetes during the  
R19 last decades, interventions to improve diabetes care have had much attention. Diabetes  
R20 care models focussing on improved coordination of care, collaboration between involved  
R21 health care professionals, guideline adherence and increasing self-management skills of  
R22 patients have been implemented in general practices in the Netherlands. These elements,  
R23 based on the Chronic Care Model are included, to different extents, in managed and  
R24 protocolized diabetes care evaluated in our study. The increasing focus on and  
R25 implementation of innovations in diabetes care throughout the Netherlands has reduced  
R26 the contrast between our intervention groups and usual care. This reduced contrast  
R27 between intervention and usual care was reflected in outcomes on patients' experience  
R28 with diabetes care by decreasing differences in patient experience with the continuity of  
R29 care during one year of follow-up of the study.  
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#### R31 *Measurement of costs:*

R32 In general, the three main study perspectives in health economic evaluations are the  
R33 perspective of 1) the healthcare provider, 2) the patient and 3) society. The societal  
R34 perspective is the broadest perspective and includes all costs incurred by society,  
R35 including those of the patient and health care provider and loss of productivity. An  
R36 economic evaluation from a societal perspective is recommended to enable optimal  
R37 societal decision making.<sup>35,36</sup>  
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Precise estimation of resource use and costs is important in health economic evaluations. Data to estimate costs can be obtained from administrative databases of health care insurance providers, medical records of health care providers or patients. Not all data necessary for an economic evaluation from a societal perspective, can be obtained from administrative databases. Especially, information on informal care, and absence from work is missing from medical records or insurance data in the Netherlands. To obtain data on costs from the societal perspective, we used three-month prospective cost diaries. Patients were asked to specify visits to medical specialists, therapists and complementary health care professionals. Furthermore, performed laboratory tests, hospitalization, use of home care and loss of productivity (absenteeism of paid and unpaid work) was reported. Prospective cost diaries have the advantage that recall bias and underreporting of data is unlikely. Previous research comparing data obtained by cost diaries with data retrieved from insurance companies showed that cost diaries are a feasible and valid tool to measure costs.<sup>37</sup>

A disadvantage of the use of cost diaries is that it requires a lot of effort from the participants resulting in a relatively high loss to follow-up. In our study, loss to follow-up was associated with younger age, living alone, former smoking status and higher BMI, resulting in an underestimation of the costs. Multiple imputation was used to impute missing cost data.<sup>38</sup> Variables that were found to be related to missing cost data and cost outcomes, were included in the multiple imputation model.

#### *Risk prediction: observational study*

For the validation of three existing risk algorithms and to study predictors of a recurrent cardiovascular event we used longitudinal data of the Hoorn Study. In contrast to clinical trials, observational studies, such as the Hoorn Study, are designed to investigate the development and natural course of diseases. The Hoorn Study is a prospective cohort study of glucose metabolism, cardiovascular risk factors and cardiovascular diseases in the general Dutch population. It provides information on diseases as they occur in the real world. Also, because the Hoorn Study cohort consists of persons who were randomly selected from municipal registries with a high participation rate (70%) the population is representative for the general population and external validity of study outcomes is high.

Information on morbidity and mortality was obtained using data from general practitioners, hospitals and the municipal registry. Of the Hoorn Study population, 561 participants did not give permission for registry of morbidity and mortality. We compared cardiovascular risk factor levels of participants who gave permission with participants who did not give permission for registry. We did not observe major differences in risk factor levels at baseline between these two groups, reducing the chance that the internal validity was affected by these missing values on the outcome measure.

*Long-term evaluation: simulation model (MICADO)*

An important aspect in modelling is the external validation of the model. MICADO was validated to external data as reported in chapter 5. A further validation of the model was performed by participating in the sixth Mount Hood challenge. These meetings were set up to stimulate diabetes model cross validation (comparing outcomes to those of other models).

The aim of the challenge was to test the ability of the eight participating models to replicate major macro- and microvascular diseases and mortality rates across a number of different country settings using information on baseline characteristics of patients with type 2 diabetes during five years of follow-up. For this challenge data of the Kaiser Permanente insured diabetes patients (USA), patients with type 2 diabetes in the Swedish National Diabetes Registry, and all patients in the ADVANCE study (Asia, Eastern Europe, and the Established Market Economies) were used.<sup>39</sup>

Compared to the other participating models, the MICADO model performed well in the validation of population-based cohorts (Swedish and US population). The extrapolation of trial results (ADVANCE) was less accurate. Reasons for a less precise estimation might lay in the fact that it is not possible to extrapolate a selected high-risk diabetes population with a population-based model such as the MICADO model, designed for projections for public health scenarios.

Accuracy of the models' estimation of long-term complications is highly dependent of the input parameters. The MICADO model differs from most other diabetes models by its' structure that is best described as a dynamic population model following overlapping cohorts of patients as they age over time. Most other diabetes models are patient level simulation models. Furthermore, MICADO's incidence and prevalence of complications as well as mortality risks are estimated from representative large national registries and systematic literature reviews, resulting in a model that reflects the Dutch population and effects of care as usual treatment in daily practice. Most other diabetes models based their risk algorithms for the prediction of micro- and macrovascular complications on data of the UKPDS.<sup>17</sup> The UKPDS is a trial of glycaemic therapies with newly diagnosed type 2 diabetes patients of which the baseline measurement was performed between 1977 and 1991. Our study validating the predictive ability of the UKPDS risk function for the incidence of a first coronary heart disease showed that the discriminatory ability and calibration was low to moderate. These results were confirmed by a recent review.<sup>40</sup> This may explain why our model was relatively good at predicting cardiovascular events in the Swedish and KP populations.

Despite this performance of the MICADO model during the Mount Hood Challenge, the model can still be improved. Progression through most stages of the microvascular complications is dependent of HbA1c. In the progression through stages of nephropathy

and retinopathy, blood pressure is an important risk factor besides HbA<sub>1c</sub>. The inclusion of blood pressure could possibly improve the accuracy of the model.

### The future of type 2 diabetes

Obesity is a prominent risk factor for type 2 diabetes, and with global obesity rates rising, the ensuing burden of type 2 diabetes looks set to worsen. There are already an estimated 1.46 billion overweight and 495 million obese adults worldwide.<sup>41</sup> Even more disturbing is that childhood obesity rates are also increasing. In the USA, approximately 17% of children and adolescents are obese. In the Netherlands, between 2002 and 2004 about 15% of the children were overweight or obese.<sup>42, 43</sup> The prevalence of diabetes is also rising rapidly. The worldwide prevalence of type 2 diabetes is estimated to increase from 366 million in 2011 to 552 million by the year 2030.<sup>44</sup> In the Netherlands, in 2007, the estimated number of persons diagnosed with type 2 diabetes was about 740,000.<sup>45</sup> This growing number of type 2 diabetes has major implications for diabetes care and as a result also for our society. Persons with type 2 diabetes are at increased risk for several diabetes related complications<sup>46-51</sup>, resulting in a high health care consumption and high health care costs and a decreased health-related quality of life. The increasing prevalence of diabetes and diabetes-related complications lead to an increased use of health care and health care costs.<sup>52</sup>

We showed that managed and protocolized care were less costly than usual care. Recently the cost-effectiveness was debated by health insurance companies (ref:Edgar, MC). It was clear from all kind of resources that diabetes care organised by so-called diabetes care groups leads to substitution from secondary care to primary care. The extent of substitution depends on the way the care was organised, with centrally organised care leading to more substitution. The question arises what the reason may be that in the calculation models of the health insurance companies substitution did not lead to less costs. The main reason was that local hospitals did negotiate much higher prices for the diabetes care in the so-called DBC (Diagnose Behandel Combinatie). Moreover, within the hospital, internal referral make the main contribution of the total referral to newly opened diabetes DBC. In West-Friesland GP's referred only 1,6% of the diabetes patients in 2011 to secondary care. Still another 8% was referred by other specialists to an internist by internal referral. In our region, almost all diabetes patients are treated by the GP with the help of a diabetes expert within the diabetes care group. In most other parts of the Netherlands almost 85% of all patients were treated in primary care. We have seen from the results of this thesis that centrally organised care was able to diminish referral to secondary care.

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*Personalized care*

Good clinicians have always tailored treatments to alleviate symptoms and reduce side effects, but generally this relied upon trial and error. Personalized medicine may improve upon 'reactive' medical diagnosis by predicting treatment response or preventing complications before symptoms appear. Explaining the environmental, genetic and other biological sources of human variation will alter the way diseases are diagnosed, drugs are developed, and the way care is provided. This is also true for the way diabetes care is presented. The 'one size fits all approach' meaning that all patients with type 2 diabetes need a three monthly control, an annual extensive control, a one yearly retina photography and examination of the feet, is not the most efficient way to deliver the diabetes care.

Recently it was shown that identification of a set of risk factors for retinopathy optimised diabetes retinopathy screening.<sup>53,54</sup> Some persons may need a yearly screening, other persons only once in every six years. Simulation models for the long-term cost-effectiveness of diabetes-related interventions, such as the MICADO model can help determine which treatment strategy is most cost-effective.

We showed that persons who already developed a cardiovascular event are at high risk to develop a second event, mostly in the first year after the first event. Furthermore we showed that the existing risk models for predicting cardiovascular disease are over- or underestimating the risk in type 2 diabetes patients. With the International Diabetes Federation, we are currently constructing a dynamic model for the development of cardiovascular disease in type 2 diabetes patients. We believe that the construction of a risk model together with the development of new therapeutic possibilities will lead to a more personalized care. However, personalized medicine holds also cause for concern. Selective treatment may limit access to some who may benefit, whereas following a 'one size fits all' approach to medical research and development may have benefited the widest number of potential patients.

**CONCLUSION**

In this thesis, we investigated the effectiveness and cost-effectiveness of managed and protocolized diabetes care compared to usual diabetes care. A model to estimate long-term (cost-)effectiveness of diabetes related interventions was developed. Finally, methods to facilitate personalized diabetes care were explored.

The results of this thesis indicate that managed or protocolized care result in equal clinical outcomes at lower health care costs compared to usual care. Managed care is associated with a better process of diabetes care and better continuity of care according to patients' opinion.

Models to identify high-risk patients based on patients' risk profile might be a useful tool to facilitate personalized care but should be further explored.

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