# Management of Type 2 Diabetes Mellitus and Prediction of Cardiovascular Complications

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# Management of Type 2 Diabetes Mellitus and Prediction of Cardiovascular Complications

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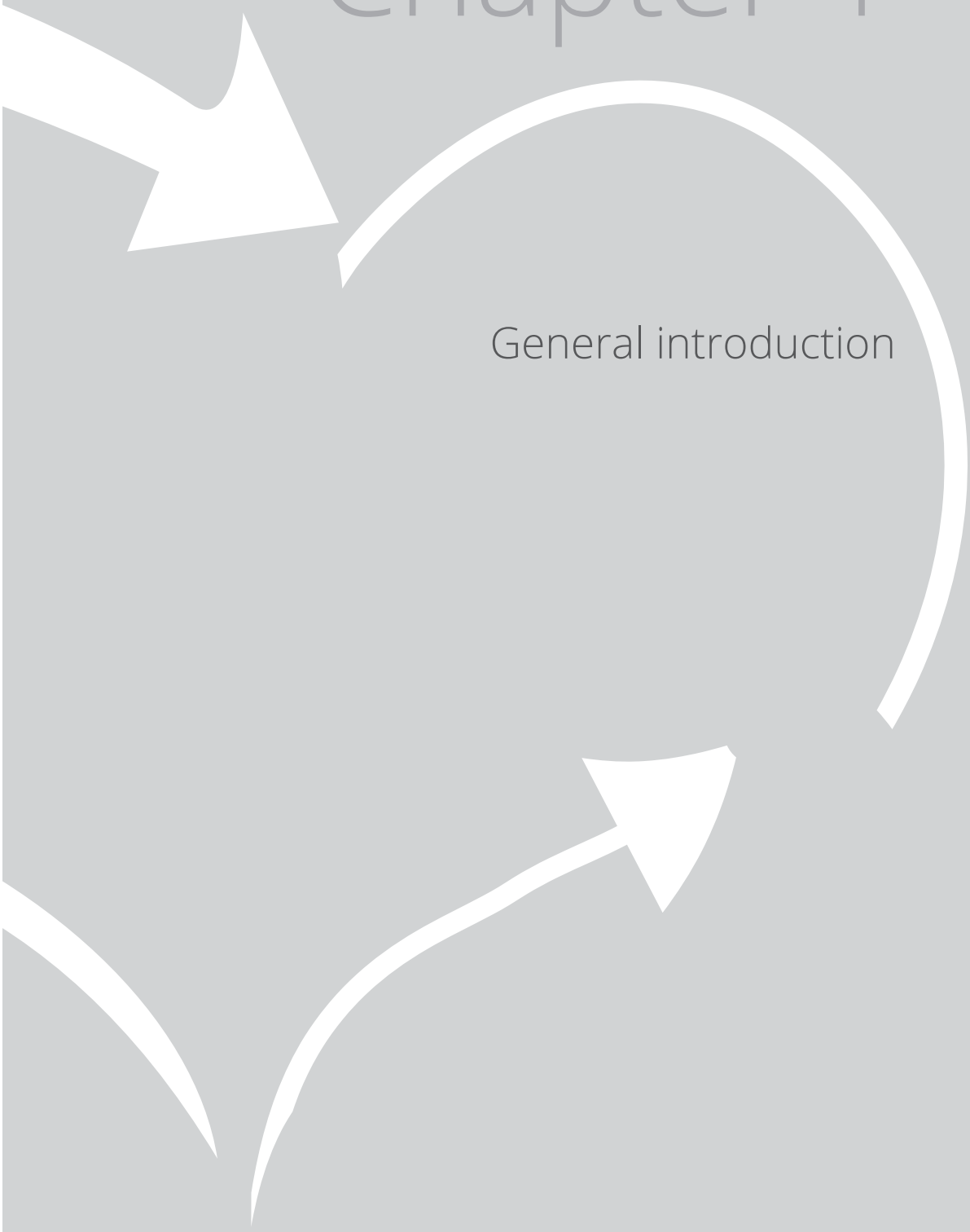
# Chapter 1



## General introduction

Obesity and lifestyle changes in combination with increased longevity have contributed to the rapidly increasing prevalence of diabetes worldwide. It is expected that diabetes prevalence will rise from 366 million in 2011 to 552 million people in 2030.[1;2] Type 2 diabetes mellitus is the most common form of diabetes, accounting for 90% of the cases globally[3], and is characterized by insulin resistance and/or abnormal insulin secretion.[4] Microvascular complications contribute considerably to the morbidity of the disease. Diabetic nephropathy is prevalent in 40% of the diabetes cases and is the most common cause of end stage renal disease.[5] Another complication is diabetic retinopathy, a progressive disorder and the most common cause of blindness in adults.[6;7] Furthermore 70% of the patients with diabetes have nervous system damage.[8] However, the main complication associated with diabetes is the increased risk of cardiovascular disease (CVD). Diabetes patients have a 2- to 4-fold increased risk for developing coronary heart disease, with a higher increased risk for women compared to men.[9] Cardiovascular disease occurs due to a number of factors. Hyperinsulinaemia has been shown to be associated with increased coronary heart disease in both people with and without diabetes. Even though diabetes is often associated with hypertension, overweight and dyslipidaemia, it has been shown that excess numbers of cardiovascular mortality associated with these factors is much higher in patients with diabetes compared to people with the same patient characteristics without diabetes.[10]

International guidelines advocate to treat diabetes patients multi-factorial; the general practitioner should focus both on blood glucose lowering, blood pressure lowering and treatment of dyslipidemia.[11;12] The Steno-2 study showed that long-term intensified treatment focusing on multiple risk factors reduces the risk of cardiovascular events by 50% among patients with type 2 diabetes and micro-albuminuria.[13] However, recent findings from the ADDITION trial failed to demonstrate a significant effect on cardiovascular events by multi factorial treatment in newly detected diabetes patients over 5 years. Nevertheless, a trend towards a long term cardiovascular risk reduction was observed, and longer follow-up of these patients might prove that multi-factorial treatment is beneficial.[14]

Lowering of the glucose levels of diabetes patients and people with impaired glucose tolerance may have a significant impact on cardiovascular risk. Each 1% lower HbA1c value above a concentration of 7.0% has been associated with a 38% lower cardiovascular risk

in observational studies.[15] Several trials have examined the effect of intensive glucose lowering therapy (targeting a low HbA1c level) on the occurrence of CVD compared to standard treatment. These studies showed a borderline significant effect on coronary morbidity and mortality combined, but no significant effects were obtained for all-cause mortality[16-19]. The ADVANCE trial showed only a significant effect when major macrovascular and microvascular events were combined, while the ACCORD trial even showed an increased risk of all cause mortality with intensive glucose lowering treatment[19]. Several reasons for this increased mortality risk have been proposed, such as severe weight gain, hypoglycaemia or the role of used drugs and drug interaction. Nevertheless the understanding of this phenomenon remains unclear.

Even though diabetes patients are often regarded as high risk for CVD there is still a gradient among diabetes patients. Some discussion still exists if diabetes patients should all be regarded as high risk for CVD and treated as such [20] or if treatment should focus particularly on diabetes patients with the highest cardiovascular risk. The latter approach requires the use of prediction models to identify those patients.[12] Over the past decades many risk scores for cardiovascular disease have been developed with several designed specifically for diabetes patients, like the UKPDS risk engine and the Fremantle risk score.[21] It remains uncertain which risk score provides the most accurate calibration (agreement between observed and predicted risk) and discrimination (ability to distinguish patients who will develop cardiovascular disease from those who will not).[21] Considering the fact that the performance of a risk score is often good in the development population, it might not be nearly as good in a different population. Therefore it is important to perform validation studies; i.e. examining the performance of a risk score in a new set of patients. However, validation studies are often lacking. This lack in validation studies is not only apparent for cardiovascular risk prediction but is also a representation of the prediction field in general, where many risk scores are being developed, but the number of published validation studies is much smaller.[22] Testing the performance of a risk score in a new set of patients often leads to a much lower performance than in the development set. When a validation study shows disappointing calibration and/or discrimination researchers frequently reject this original model and develop a new model, which has several disadvantages. Predictive information obtained from other models is

lost when a new model is being developed. Moreover redevelopment of models lead to a situation with many risk scores for the same outcome, making it difficult for clinicians to decide which model to use.[22] An alternative method for the redevelopment of a model with poor performance is to do a simple recalibration of the model, which can increase the calibration.[23] Furthermore addition of new predictors like biomarkers might increase the performance as well. Updating a model with a new biomarker should always be assessed by examining the incremental predictive value beyond the original risk score, especially when the measurement is costly or burdensome for the patient.[24] However detecting a significant improvement in the discrimination of a risk score by an added biomarker is difficult and new metrics for detecting an improvement in discrimination are being developed.[25]
Cardiovascular risk scores are used in clinical practice by general practitioners to examine the cardiovascular risk of diabetes patients.[12] Patients with type 2 diabetes have regular check-ups to monitor their disease progression. When a risk score is used to examine cardiovascular risk it often predicts 5 or 10 year risk at a specific point in time. General practitioners use only the current patient characteristics to predict the future cardiovascular risk. However inclusion of history of patient characteristics obtained through the regular visit of the patient, and thus inclusion of change, might improve the prediction of cardiovascular disease. It is unknown if incorporating this history and change in measurements might add to the prediction of diabetes or if simply recalculating the risk of the patient at the new time point is valid.

## Outline of thesis

In this thesis we aim to investigate several aspects of management and treatment of type 2 diabetes and prediction of cardiovascular complications. Part 1 of this thesis focuses on management of type 2 diabetes mellitus and effects of therapies. Part 2 is focussed on the prediction of cardiovascular complications among type 2 diabetes patients.

**Part 1**
In order to clarify differences in findings from the ADVANCE trial and other similarly large diabetes trials, several aspects of the ADVANCE trial were examined, i.e. characteristics associated with weight change, determinants of effective glycaemic control and the effect of blood

pressure lowering across cardiovascular risk groups.
**Chapter 2** provides an overview of the global burden of diabetes and impaired glucose tolerance at present and the expected rise of the diabetes burden in the future. Moreover it describes the burden and economic costs of the complications associated with type 2 diabetes.
**Chapter 3** reports on the patient characteristics and glucose lowering therapies associated with weight change among patients with type 2 diabetes from the ADVANCE trial. In **Chapter 4** the effects of treatment intensification by addition of an oral glucose lowering therapy or commencement of insulin on glycaemic control in the ADVANCE trial has been described. **Chapter 5** focuses on the relative and absolute effects of blood pressure lowering therapy on cardiovascular risk in moderate, high and very high cardiovascular risk groups among patients with type 2 diabetes.
Lipid levels are affected by fasting status. **Chapter 6** describes the effects of postprandial time on the associations between lipid levels and cardiovascular disease and examines the predictive value of non fasting lipid levels on cardiovascular risk among patients with type 2 diabetes.

**Part 2**
In this part the performance of cardiovascular risk scores among type 2 diabetes patients is examined and we attempt to optimize the performance of cardiovascular risk prediction among diabetes patients.
**Chapter 7** provides an overview of all cardiovascular risk scores applicable to type 2 diabetes patients. The most used cardiovascular risk score for patients with type 2 diabetes (UKPDS risk engine) has been externally validated and described in **Chapter 8**. After the external validation of the UKPDS risk engine, a full validation and recalibration of all cardiovascular risk scores applicable to type 2 diabetes patients has been performed and reported in **Chapter 9**. **Chapter 10** focuses on the added prognostic value of heart type fatty acid binding protein to the prediction of cardiovascular disease among type 2 diabetes patients. In **Chapter 11** the methodological issue of using repeated measurements of patients characteristic to predict a specific outcome has been examined using an example of prediction of CVD among type 2 diabetes patients. The main findings of this thesis are discussed in **Chapter 12**. Finally a summary of the results reported in this thesis is provided in **Chapter 13**.

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# Part 1

## Management and treatment of type 2 diabetes mellitus

# Chapter 2

# The global burden of diabetes and its complications: an emerging pandemic

van Dieren S, Beulens JWJ, van der Schouw YT, Grobbee DE, Neal B

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## Abstract

The number of patients with type 2 diabetes is increasing rapidly in both developed and developing countries around the world. The emerging pandemic is driven by the combined effects of population ageing, rising levels of obesity and inactivity, and greater longevity among patients with diabetes that is attributable to improved management. The vascular complications of type 2 diabetes account for the majority of the social and economic burden among patients and society more broadly. This review summarizes the burden of type 2 diabetes, impaired glucose tolerance, and their vascular complications. It is projected that by 2025 there will be 380 million people with type 2 diabetes and 418 million people with impaired glucose tolerance. Diabetes is a major global cause of premature mortality that is widely underestimated, because only a minority of persons with diabetes dies from a cause uniquely related to the condition. Approximately one half of patients with type 2 diabetes die prematurely of a cardiovascular cause and approximately 10% die of renal failure. Global excess mortality attributable to diabetes in adults was estimated to be 3.8 million deaths.

## Introduction

The prevalence and incidence rates of type 2 diabetes and impaired fasting glucose (IFG) are rising rapidly throughout most regions of the developed and developing world.[1;2] In large part the emergence of the diabetes pandemic is attributable to established causes, primarily the increasing number of older people and growing levels of obesity and physical inactivity. In addition, enhanced management of patients with type 2 diabetes is improving longevity among this patient group further adding to their numbers. Diabetes greatly increases the risks of vascular disease and much of the burden of type 2 diabetes is caused by macrovascular and microvascular complications.[3;4] Quantifying the number of patients with type 2 diabetes and its complications is of great importance to governments and healthcare providers, not least because of the huge drain that it puts on already scarce healthcare resources. This is particularly true for developing regions of the world in which the greatest expansion in the numbers with diabetes is projected to occur.[1] We summarize here key data describing the global burden of type 2 diabetes, impaired glucose tolerance (IGT), and their complications.

### Type 2 diabetes

The prevalence of type 2 diabetes is increasing rapidly worldwide (Figure 1). In 1995, the prevalence of type 2 diabetes was estimated to be 135 million people, which increased to 171 million people in 2000 and to 220 million in 2004.[5] Although type 2 diabetes is predominantly a disease of adulthood, there is substantial variation in the age groups of patients with type 2 diabetes between developed and developing countries. In developed countries the risk of type 2 diabetes increases progressively throughout life, and it is the 65 years and above age group that accounts for the majority of cases of diabetes. In contrast, in most developing countries for which data are available, the greatest number of individuals with type 2 diabetes are aged between 45 and 64 years with both the prevalence and absolute number of individuals with diabetes declining above 65 years.[2]

Worldwide, there are more women living with type 2 diabetes than men. Although the prevalence of diabetes is slightly greater in men under the age of 60 years, it is higher in women above this age, reflecting the greater likelihood of premature mortality among men with diabetes against a rising incidence of type 2 diabetes with age in both sexes.[2] The global imbalance in diabetes between the sexes is

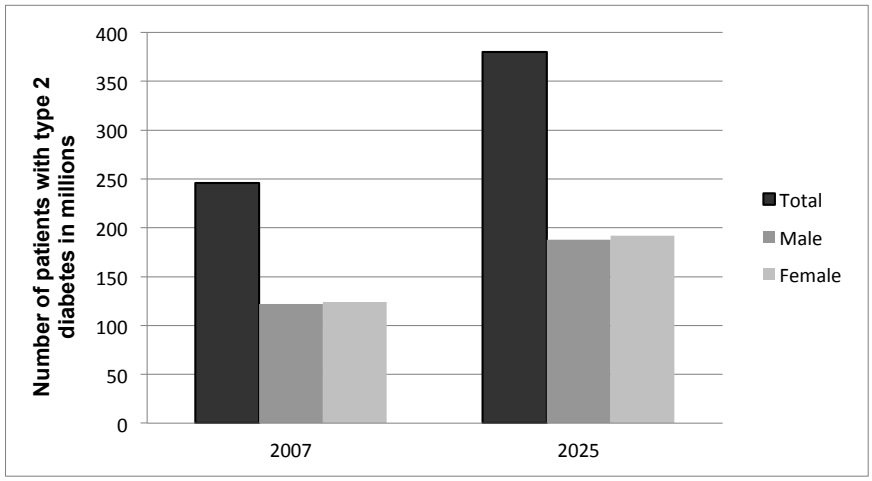


**Figure 1.** Total number of patients with type 2 diabetes in 2007 and estimated for 2025; total and by sex

driven entirely by developed countries, with equal numbers of men and women affected by type 2 diabetes in developing countries.[6]

The number of patients with type 2 diabetes is likely to be even higher than current estimates[1] because a substantial proportion of patients with type 2 diabetes go undetected. The onset of type 2 diabetes may occur up to 7 years before clinical diagnosis[7] even in high-income settings such as the United States and The Netherlands, whereas the prevalence of undiagnosed diabetes is probably approximately 3% of adults.[8;9] Failure to detect diabetes typically rises with age[8] although there is some evidence that enhanced screening systems are decreasing the prevalence of undiagnosed diabetes in some developed countries.[10] The percentage of undiagnosed diabetes is higher in developing countries in which it is not unusual for half[11] or three quarters[1] of all cases of diabetes to remain undiagnosed.

The prevalence of type 2 diabetes is projected to rise from the current estimated 240 million affected (6% of adults) to some 380 million (7%) by 2025.[1] Most of this growth will be in developing countries and will be substantially attributable to major changes in the number and average ages of the population of countries such as India and China.[6] By 2025 there will be some 192 million women and some 188 million men with type 2 diabetes with a substantially greater number of individuals with diabetes living in urban (179 million) compared with rural areas (81 million).[1]

**Impaired glucose tolerance and impaired fasting glucose**

The progression from normal-to-abnormal glucose homeostasis is a continuous one and the terms IGT and IFG describe the intermediate stage before the diagnosis of diabetes. IGT[12] is essentially an asymptomatic condition in which glucose regulation is found to be impaired in the 2-hour period after a 75 g oral glucose challenge. IFG[12] in contrast describes the state in which fasting plasma glucose concentration is elevated above usual levels (6.10 and 6.99 mmol/l) but not sufficiently to meet the thresholds defined for diabetes.[12] There is some overlap between the two, and these states are often referred to as 'prediabetes'.[7]

Patients with IGT or IFG are at a high risk of progressing to type 2 diabetes with annual progression rates of 17% for IGT and 12% for IGF observed in European populations.[13] Similarly, Mexicans and other developing country populations with impaired glucose homeostasis have been observed to be at markedly greater risk of developing diabetes.[14;15] Progression to type 2 diabetes is not, however, inevitable among this population and 30% of people with IGT or IFG will have normal glucose levels on subsequent follow-up.[1] Both IGT and IFG increase the risks of vascular complications and contribute importantly to the total disease burden attributable to deranged glucose metabolism.[16;17]

In 2007, there were an estimated 308 million people (7.5% of adults) with IGT,[1] of which 80% were believed to be living in developing countries. Most people with IGT are between 40 and 59 years of age.[1] In Europe, China, and Japan, prevalence of IGT rises linearly with age but in India the prevalence of IGT seems to be constant across age groups. Women in Europe and India were more likely to have IGT than men, but in China and Japan the prevalence of IGT was higher in men than in women. The pattern observed for IGT was somewhat different, appearing to be stable across ages in Europe, China, and Japan, and higher in men than in women. For Indian people the prevalence of IFG was higher in women than in men and increased with age until the age of 69 for men and 79 for women.

Overall the prevalence of IGT is higher than IFG with global estimates of 8.4 and 6.3%, respectively, for people aged 40–59 years and a similar pattern for other age groups.[13;16] It is estimated that the global prevalence of IGT will rise to 418 million (8% of adults) by 2025 with an absolute increase in number of approximately 30–70% depending on the region. The greatest absolute increase will be for African, Eastern Mediterranean, and Middle East countries and by 2025 the highest prevalence of IGT will be in people between 40 and 59 years of age.[1]

**Macrovascular complications**

Cardiovascular disease (CVD) is the leading complication of type 2 diabetes and approximately one half of patients with type 2 diabetes will die of a cardiovascular cause. Angina, myocardial infarction, stroke, peripheral artery disease, and congestive heart failure are all common among patients with type 2 diabetes. IFG or IGT and the risks are further compounded by smoking, abnormal blood lipids, high blood pressure, and the other determinants of vascular risk established in non diabetic populations.[1;18]

Among some subgroups of patients the incidence of coronary heart disease (CHD) is comparable with that of patients without diabetes and with a history of CHD,[19] and the rates of prevalent CHD reported among patients with type 2 diabetes are ranged between 5 and 36% depending on the setting.[1] Diabetes seems to confer an approximate doubling of the risk of CHD in men and a quadrupling of risk among women.[20;21] Therefore, although women in general have a lower absolute risk of CVD than men, the greater proportional increase in risk they experience leads to rates of CHD that are directly comparable (29 per 1000 person years for men and 23 per 1000 person years for women).[22]

The prevalence estimates of stroke among patients with type 2 diabetes range from 4 to 12% in clinic-based populations and between 4 and 5% in population-based studies.[1] The incidence of stroke in patients with type 2 diabetes can be more than three times the risk for the general population and seems to be more marked for men than for women. The prevalence of stroke increases linearly with age, the relative risk of stroke among diabetic patients older than 60 years is approximately five times the risk for patients under 50 years of age.[23] In Italy the incidence of stroke was 5.5 per 1000 person years in men and 6.3 per 1000 person years in women.[24]

**Microvascular complications**

The microvascular complications of type 2 diabetes are principally nephropathy, retinopathy, neuropathy, and small vessel vasculopathy causing lower extremity amputation. The complications account for much of the social and financial burden of diabetes,[3] and type 2 diabetes is a leading cause of blindness, renal failure, and lower limb amputations.[25;26] However, although the burden is undoubtedly large, the few high quality population based studies and the use of different diagnostic tools make it difficult to accurately describe the burden of these complications or make comparisons across different settings.[1]

**Diabetic nephropathy**

Diabetes has recently become the leading cause of end stage renal disease in many developed countries accounting for up to 50% of patients receiving renal replacement therapy.[26;27] Worldwide, the number of patients with diabetes receiving renal replacement therapy has doubled from 12.7 million in 1990–1991 to 23.6 million in 1998–1999.[28] This increase reflects both a change in referral and acceptance rates and a real increase in incidence. Incidence rates of renal failure among patients with type 2 diabetes are approximately six per 1000 person years, with approximately one-third dying and two-thirds becoming dialysis dependent.[29] Incidence of renal failure was highest among Native Americans (10.7), lowest among Europeans (2.9), and intermediate for East Asians (7.5). Incidence increased with age and duration of diabetes.[29] The incidence of diabetic nephropathy has increased over time in European countries though remaining stable in non-European countries[30] with the difference most likely explained by the rise of type 2 diabetes in developed countries.

Proteinuria is an important marker of diabetic nephropathy that is strongly associated with increases in vascular risk. Estimates vary widely depending on the populations studied and the methods used. In studies included in the Diabetes Atlas,[1] prevalence of micro albuminuria ranged from 3 to 57% in clinic-based populations and from 19 to 42% in population-based studies. The prevalence of overt nephropathy was between 5 and 20% in clinic-based studies and 9 to 33% in population-based studies. Comparisons are difficult between countries because of the sporadic nature of the data available, but prevalence of diabetic nephropathy is typically higher among men and rises with age.[31;32]

**Diabetic retinopathy**

Diabetic retinopathy is a progressive disorder of the retinal microcirculation and is the most common cause of blindness among people aged 30–69 years.[33;34] It is estimated to account for 5% of all cases of blindness globally.[25;35] Among patients with type 2 diabetes the prevalence of retinopathy ranges from 11 to 65% in clinic-based populations and from 10 to 55% in population-based studies.[1] Projections of prevalence of diabetic retinopathy and vision-threatening diabetic retinopathy in the United States for the years 2005–2050 suggest a tripling from 5.5 to 16.0 million and from 1.2 to 3.4 million, respectively.[36] Increased prevalence of diabetes, greater longevity among those with the disease, and changes in the age and racial background of the US population are the key drivers of change.[36]

With many other parts of the world experiencing qualitatively similar changes, the global prevalence of diabetic retinopathy is likely to mirror that projected for the United States. The annual incidence of proliferative retinopathy is approximately 1% and approximately five times that for any retinopathy with slightly greater rates in women and increased risks with longer duration of diabetes.[37] In developed countries, incidence of serious retinopathy seems to have decreased over time, probably because improved patient management[38-40] and rates of retinopathy in recent trials are much lower.[41] Risks of diabetes-related blindness also increase with age and duration of diabetes but seem to be higher among males[42;43] with prevalence ranging from 3 to 7%. A further 10 to 24% of patients with type 2 diabetes are reported to be visually impaired.[38;44-47]

**Diabetic neuropathy and lower extremity amputations**

Patients with type 2 diabetes have a more than 25 times greater risk of amputation than those without diabetes.[48] The prevalence of diabetic neuropathy ranges from 8 to 68% for clinic-based studies and from 13 to 45% for population-based studies. The prevalence of lower limb amputation is much lower (0.2–4.8%) with annual incidence rates for amputation ranging from 46 to 936 per 100 000. Reported rates are heavily dependent on the diagnostic tools and definitions used and the population studied, but rates seem to increase with duration of diabetes and age.[49-51]

**Mortality and total disease burden**

Diabetes is a major global cause of premature mortality that is widely underestimated, because only a minority of patients with diabetes dies from a cause uniquely related to the condition such as diabetic ketoacidosis or hypoglycaemia. Approximately 50% of persons with diabetes die of CVD, and 10% die of renal failure[52;53] both of which are directly attributable to diabetes. In the WHO report of 2004 it is described that 508 000 men have died from direct diabetes-related causes, which is 1.6% of all deaths and 633 000 women have died from type 2 diabetes, which is 2.3%. However, it is possible that this is heavily underestimated as the International Diabetes Federation estimates the deaths caused by diabetes in 2007 to be 3.8 million (6%) of total world mortality in persons between 20 and 79 years of age.[1]

The risk of suffering a diabetes-related death is strongly related to age. In individuals with type 2 diabetes under 35 years of age, 75% of all deaths were attributable to diabetes, decreasing to 59% among

those aged 35–64 years and 29% among those aged 64 years or older.[54] Women have a higher risk of diabetes-related mortality than men with a relative risk for women of 3.4 and a relative risk for men of 1.9.[19] There are huge differences in mortality numbers across regions (Figure 2). For countries with a high income diabetes is the eighth leading cause of death, whereas in middle-income countries it is the 10th leading cause of death. Again, this ranking is likely to be underestimated.

In addition to being a substantial cause of death, diabetes also contributes a large total disease burden. In 2004, diabetes was estimated to be the eighth leading cause of years of life lost to premature mortality with approximately 2.3 million years of life lost equating to 3.4% of all life years lost that year. The total disease burden attributable to diabetes rises to 19.7 million disability adjusted life years (DALYs) once the nonfatal disease burden attributable to diabetes is incorporated into the equation. This was 1.3% of all DALYs in 2004 and it is projected that diabetes will rise from 19th place in 2004 to be the 10th leading cause of DALYs in 2030, causing 2.3% of all DALYs that year.[5]

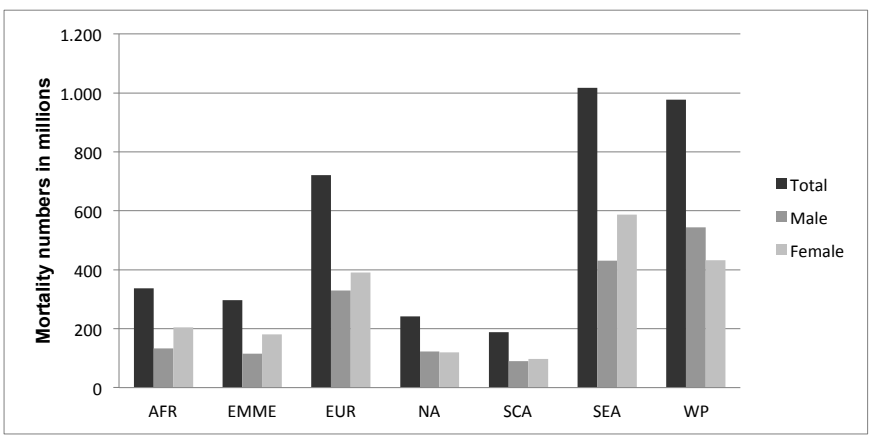


**Figure 2. Mortality numbers by regions total and split by sex.**
AFR, African Region; EMME, Eastern Mediterranean and Middle East; EUR, Europe; NA, North America; SCA, South and Central Asia; SEA, South Eastern Asia; WP, West Pacific.

## Economic costs

Diabetes is one of the world's most important causes of expenditure, mortality, disability, and economic loss. Global health expenditure to treat and prevent diabetes and its complications was approximately 232 billion US dollars in 2007, a figure that will exceed 302 billion by 2025. Approximately 80% of this money is spent in the few wealthy

countries and very little in low and middle incomes where some 80% of the people with diabetes live.[1] The costs for patients with macrovascular complications are approximately three times higher than for patients with type 2 diabetes without macrovascular complications and approximately seven times higher than for people with neither type 2 diabetes nor with macrovascular diseases. Outpatient, inpatient, and pharmacy costs are all higher in patients with type 2 diabetes but inpatient costs are the main drive among those with macrovascular diseases, and pharmacy costs are the greatest component overall.[55;56] Costs for patients with microvascular complications are approximately two times higher compared with patients with type 2 diabetes and with no microvascular complications. Patients with microvascular complications used more oral antidiabetic drugs and insulin, and have had more and longer hospital stays and more outpatient visits.[57]
The costs of chronic conditions associated with type 2 diabetes are unevenly distributed with approximately two-thirds of the costs accounted for by cardiovascular complications and much smaller sums for neurological, renal, ophthalmic, and peripheral vascular diseases.[24]

## Conclusion

The number of patients with type 2 diabetes is increasing, especially in developing countries. Patients with type 2 diabetes have greater increased risks of CVDs, renal failure, neurological conditions, and retinopathy. The economic costs for diabetes are high and will continue to rise. The identification of effective new strategies for the control of diabetes and its complications is a public health priority.

## Acknowledgements

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# Chapter 3

# Intensification of medication and glycaemic control among patients with type 2 diabetes – the ADVANCE study

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*Submitted*

## Abstract

**Aims:** To assess the associations between patient factors and intensification of treatment (by addition of oral glucose lowering therapy or commencement of insulin) and effective glycaemic control.
**Methods:** 11,140 patients from the ADVANCE trial who were randomized to intensive glucose control or standard glucose control and followed for a median of 5 years were categorized into 2 groups: effective glycaemic control (HbA1c≤7.0% or a reduction in HbA1c>10%) or ineffective glycaemic control (HbA1c>7.0 and a reduction in HbA1c≤10%) during follow-up. Intensification was defined as addition of an oral glucose-lowering agent or commencement of insulin. Pooled logistic regression models examined the associations between patient factors, intensification and effective glycaemic control.
**Results:** Overall 11140 patients were included and 7768 patients (3198 in the standard treatment group) achieved effective glycaemic control. Compared to patients with ineffective glycaemic control, patients with effective glycaemic control had lower body mass index, shorter duration of diabetes and lower HbA1c at baseline and at the time of treatment intensification. Treatment intensification with addition of an oral agent or commencement of insulin was associated with an 18% (95%CI: 17-20%) and 27% (24-29%) greater chance of achieving effective glycaemic control, respectively. These associations were robust to adjustment for several baseline characteristics and not modified by the number of oral medications taken at the time of treatment intensification.
**Conclusions:** Effectiveness of glycaemic control at all stages of the disease course and in both arms of the ADVANCE trial is associated with treatment intensification at lower HbA1c levels.

## Introduction

Achieving and maintaining near normal glucose levels remains a main target in the treatment of patients with type 2 diabetes.[1-3] However, achieving and maintaining good glycaemic control is often difficult.[4] Thus in the UKPDS a gradual rise in HbA1c over time was demonstrated in both treatment arms, within 3 years of diagnosis of diabetes, 50% of patients required more than one pharmacological agent and by 9 years, 75% of patients needed multiple therapies to control blood glucose levels.[4] This progressive deterioration in glycaemic control has been ascribed to a decline in beta cell function. However, it is also likely that the UKPDS treatment algorithm (which required patients to get to a fasting plasma glucose level >15 mmol/L before additional therapy was added) made a rising HbA1c inevitable despite increasing therapy and independent of any proposed effect of progressive beta cell failure.

Whether an inexorable deterioration in glycaemic control is observed over time in contemporary populations with type 2 diabetes is unknown. Preliminary data from the ADVANCE trial suggest otherwise.[2] In ADVANCE, the mean HbA1c values at the end of the follow-up period were 6.5% in the intensive group and 7.3% in the standard group. Once achieved these levels were maintained until the end of 5 years follow-up. In other trials such as ACCORD[5] and VADT[6] a stable HbA1c was achieved as well. The reasons for this maintained therapeutic efficacy remain unknown. And may involve contribution of patient factors, drug factors and clinical practice factors has yet to be determined.

The ADVANCE trial provides a unique opportunity to ascertain whether contemporary practice of glucose lowering may restrict or prevent the progressive and apparently inexorable deterioration in glucose control that was observed in the UKPDS trial. The aim of this study was to investigate which factors were associated with effective glycaemic control during follow-up. In particular, we examine the influence of (1) baseline patient characteristics on effective glycaemic control and (2) intensification of glucose lowering therapy by the addition of oral glucose agents, with or without insulin, on effective glycaemic control.

## Methods

### Study design and participants

ADVANCE was a 2x2 factorial randomized controlled trial evaluating the effects of blood pressure lowering and intensive blood glucose control on vascular outcomes in participants with type 2 diabetes.

Detailed descriptions of the design have been published previously.[2;7] In brief, 11,140 participants with type 2 diabetes, aged 55 years or older, with a history of major macrovascular or microvascular disease, or at least one other risk factor for vascular disease, were recruited from 215 centres in 20 countries. Approval for the trial was obtained from the institutional ethics committee of each centre and all participants signed an informed consent form.

All potentially eligible participants entered a 6-week active run-in period during which they continued their usual methods of glucose control and received a fixed combination of perindopril-indapamide (2mg/0.625mg). Participants who tolerated and were compliant with the run-in treatment were subsequently randomized to continued treatment with perindopril-indapamide or matching placebo and randomly assigned to intensive glucose control strategy aiming for an $HbA_{1c} \leq 6.5\%$ or standard glucose lowering therapy. The intensive glucose control regimen was based on gliclazide modified release (gliclazide MR; 30-120mg daily), with the ability to use all other glucose lowering therapies at the discretion of the general practitioner, which were introduced incrementally and progressively as clinically indicated. The standard glucose control regimen was based on the relevant national or regional guidelines. Participants were seen at 2 pre-randomization visits, at 3, 4 and 6 months after randomization and subsequently every 6 months. The median follow-up time for the glucose control arm of the study was 5 years.[2]

HbA1c was measured at baseline and every 6 months for the intensive group and at baseline, 6 months and every twelve months in the standard group. Clinical and laboratory examinations were performed at each study centre. Weight, height and systolic blood pressure were recorded at baseline.

**Definition of effective and ineffective glycaemic control**

Glycaemic control was assessed by comparing HbA1c concentrations between 2 sequential annual post-randomization visits, for each set of visits at which patients in both the intensive and the standard glucose control groups had these measured (i.e. baseline, 12 months, 24 months, 36 months, 48 months and 60 months). Effective glycaemic control was then defined as a reduction in HbA1c of ≥10% points or down to levels of ≤7.0% (which was the target for the standard treatment arm). Ineffective glycaemic control was defined as a reduction in HbA1c of <10% points in a participant with an HbA1c> 7.0%.

To examine the effects of intensification by commencement of insulin or additional oral glucose lowering therapy during follow-up, HbA1c reductions were calculated between consecutive annual visits until the end of follow-up.

**Statistical analyses**

All patients with at least one follow-up measurement were included in this study(n=10780). Baseline characteristics were compared between participants with effective and those with ineffective glycaemic control at baseline and the end of follow-up, separately by randomized glucose control strategy. Interactions between randomized treatment, glycaemic control and baseline variables were examined by including the interaction term in generalized linear regression models.

Pooled regression models were used to assess the associations between effective glycaemic control and treatment intensification by adding an oral glucose lowering medication or commencement of insulin during follow-up. Intensification by oral glucose lowering therapy was defined by the commencement of a new oral glucose lowering medication between two visits. Intensification by insulin was defined as commencement of insulin between two visits. Analyses were adjusted for age and sex and further adjusted for age at diabetes diagnosis, diabetes duration, ethnicity, weight, systolic blood pressure, history of macrovascular disease, history of microvascular disease, randomized treatment arms, the number of oral medications at intensification and HbA1c concentration. Assuming a Poisson distribution, relative risks and 95% confidence intervals were calculated. The effects of commencement of an added oral glucose treatment or insulin on glycaemic control was stratified by number of oral medication at time of intensification to examine the effects of intensification when patients are already on mono, dual or triple oral therapy.

Furthermore in sensitivity analyses the same associations were assessed using a cut-off of 6.5% and using different cut-offs for the two treatment arms (6.5% for the intensive arm and 7.0% for the standard arm). SAS version 9.2 for Windows (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

## Results

In the standard glucose control arm 3198 participants (59.5%) were classified as achieving effective glycaemic control between baseline and end of follow-up, while in the intensive arm 4570 participants

(84.5%) were classified in this manner. In the standard arm HbA1c decreased by a mean of 0.88% from baseline to 60 months of follow-up in the effective group and increased by a mean of 0.78% in the ineffective group (Figure 1a). In the intensive arm HbA1c decreased by a mean of 1.20% in the effective group from baseline to 60 months of follow-up and increased by a mean of 0.52% in the ineffective group (all p-value<0.003 for difference in HbA1c from baseline) (Figure 1b).

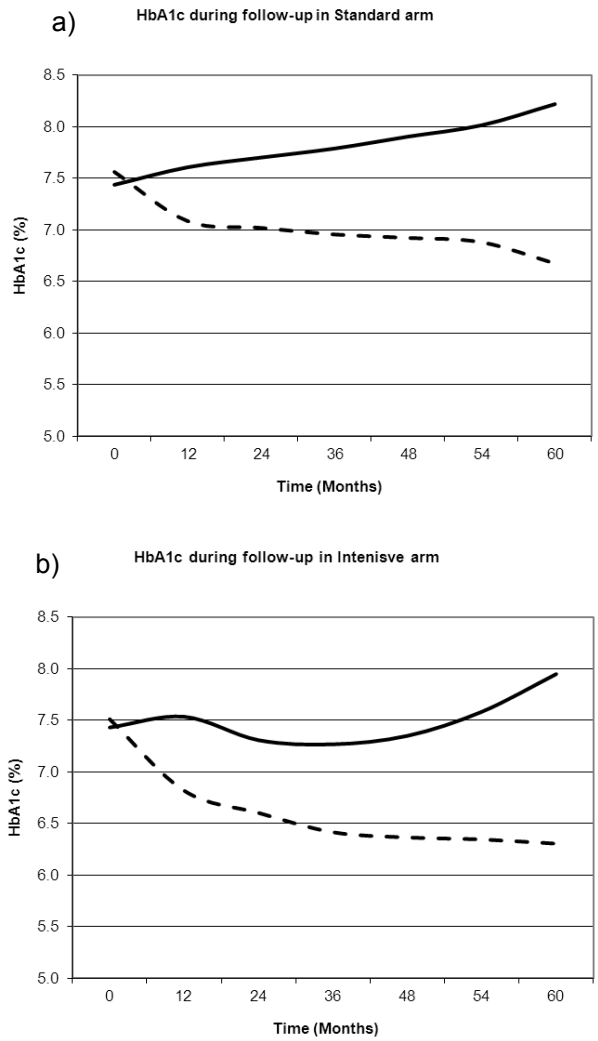


**Figure 1.** HbA1c during follow-up stratified by ineffective (solid) and effective (dashed) glycaemic control for a) standard arm and b) intensive arm

**Patient characteristics associated with effective glycaemic control**
In both the standard and intensive arm of the study, duration of diabetes was shorter and baseline HbA1c levels slightly higher in the effective glycaemic control group compared to the ineffective glycaemic control group (Table 1). In addition, in the intensive arm of the study only, weight and BMI were lower and non-Caucasian ethnicity more frequent in the effective glycaemic control group compared to the ineffective glycaemic control group. A significant interaction by treatment arm was only observed for ethnicity ($p<0.001$).
In multivariable analyses, duration of diabetes and HbA1c at the time of intensification were both independently associated with effective glycaemic control. For every additional 5 years of diagnosed diabetes and every 1% higher HbA1c level at time of intensification, the relative likelihood of achieving effective glycaemic control was reduced by 1% (95% CI: 0 to 2%) and 43% (95%CI: 42-44%) respectively (Supplementary material Table 1).

**Time to treatment intensification and HbA1c at intensification**
A difference in the time to intensification between the effective and ineffective glycaemic control groups was observed for intensification by additional oral glucose lowering therapy in the intensive arm. Time to intensification was 14.4 months for the effective glycaemic control group and 17.6 months for the ineffective glycaemic control group, p-value<0.001 (Table 2). HbA1c at time of intensification was significantly lower in the effective glycaemic control group compared to the ineffective glycaemic control group ($p<0.001$) in both the standard and intensive arms (Table 2).

**Treatment intensification and effectiveness of glucose control during follow-up**
Effective glycaemic control was clearly associated with intensification by addition of oral agents. After adjustment for age at diagnosis of diabetes, sex, ethnicity, diabetes duration, number of oral medications, treatment arm, weight, systolic blood pressure, history of macrovascular disease and history of microvascular disease, the likelihood for effective glycaemic control was increased by 24% (22 to 26%) by addition of an oral agent (Table 3). A similar association between intensification by commencement of insulin and effective glycaemic control was observed (16% [13 to 19%]). Further adjustment for the HbA1c at time of intensification slightly attenuated the chance for effective glycaemic control by addition of an oral agent (18% [17 to 20%]) and enhanced the likelihood of effective glycaemic control by commencement of insulin (27% [24 to 29%]).

**Table 1.** Baseline characteristics by effective and ineffective glycaemic control treatment. Effective glycaemic control is defined as having an HBA1c below 7.0% at end of follow-up or an HbA1c reduction of more than 10%.

| | Standard arm | | | Intensive arm | | | |
|---|---|---|---|---|---|---|---|
| | Effective (n=3198) | Ineffective (n=2174) | P-value | Effective (n=4570) | Ineffective (n=838) | P-value | P-value interaction |
| Age (years) | 65.9 (6.34) | 65.6 (6.40) | 0.205 | 65.7 (6.36) | 65.7 (6.45) | 0.878 | 0.381 |
| Sex (female), n (%) | 1380 (43.2) | 892 (41.0) | 0.122 | 1943 (42.5) | 360 (43.0) | 0.812 | 0.267 |
| Weight (Kg) | 77.5 (16.4) | 78.3 (16.5) | 0.073 | 77.8 (16.7) | 79.7 (16.8) | 0.003 | 0.171 |
| BMI (Kg/m$^2$) | 28.2 (5.25) | 28.4 (5.08) | 0.081 | 28.3 (5.18) | 28.9 (5.07) | 0.002 | 0.143 |
| Diabetes duration (years) | 7.65 (6.26) | 8.37 (6.49) | <0.001 | 7.75 (6.23) | 8.53 (6.80) | 0.002 | 0.826 |
| Systolic blood pressure (mmHg) | 145 (21.4) | 145 (21.2) | 0.659 | 145 (21.7) | 145 (21.2) | 0.479 | 0.754 |
| Glucose (mmol/L) | 8.48 (2.95) | 8.45 (2.46) | 0.670 | 8.49 (2.83) | 8.50 (2.53) | 0.887 | 0.726 |
| Baseline HbA1c (%) | 7.56 (1.77) | 7.44 (1.14) | 0.002 | 7.51 (1.63) | 7.43 (1.15) | 0.080 | 0.550 |
| Ethnicity (Caucasian), n (%) | 1889 (59.1) | 1301 (59.8) | 0.570 | 2667 (58.4) | 566 (67.5) | <0.001 | <0.001 |
| History macrovascular disease, n (%) | 1014 (31.7) | 705 (32.4) | 0.578 | 1484 (32.5) | 244 (39.1) | 0.056 | 0.061 |
| History microvascular disease, n (%) | 318 (9.9) | 236 (10.9) | 0.281 | 459 (10.0) | 88 (10.5) | 0.686 | 0.752 |

**Table 2.** Time to intensifications in months and HbA1c at intensification by added oral glucose lowering medication and by commencement of insulin. Stratified by effective and ineffective glycaemic control and treatment arm.

| | Intensive arm | | | Standard arm | | |
|---|---|---|---|---|---|---|
| | effective | Ineffective | P-value | effective | Ineffective | P-value |
| **Oral intensification** | | | | | | |
| Time to intensification (months), mean (SD) | 14.4 (14.1) | 17.6 (16.5) | <0.001 | 14.8 (14.8) | 15.7 (14.9) | 0.120 |
| HbA1c at intensification (%), mean (SD) | 7.08 (1.40) | 7.33 (1.11) | <0.001 | 7.27 (1.61) | 7.43 (1.22) | 0.003 |
| **Insulin intensification** | | | | | | |
| Time to intensification (months), mean (SD) | 28.4 (16.3) | 28.0 (15.9) | 0.669 | 28.8 (16.3) | 28.6 (16.8) | 0.747 |
| HbA1c at intensification (%), mean (SD) | 6.79 (1.19) | 7.43 (1.17) | <0.001 | 7.27 (1.61) | 7.72 (1.43) | <0.001 |

**Table 3.** Relative risk and 95% confidence intervals for associations between intensification through oral glucose lowering drugs and insulin and effective glycaemic control (defined by an HbA1c below 7.0 or an HbA1c reduction of greater than 10%)

| | Oral intensification | Insulin intensification |
|---|---|---|
| Sex & age adjusted | 1.31 (1.29-1.33) | 1.18 (1.15-1.21) |
| Multivariable adjusted[1] | 1.24 (1.22-1.26) | 1.16 (1.13-1.19) |
| Multivariable adjusted[1] & HbA1c at intensification | 1.18 (1.17-1.20) | 1.27 (1.24-1.29) |

[1]Adjusted for age at diagnosis of diabetes, sex, duration of diagnosed diabetes, ethnicity, history of microvascular disease, treatment arm, number of oral medications at intensification

Furthermore this association between effective glycaemic control and intensification by either oral agents or insulin commencement was consistent and independent of the number of oral medications at time of intensification (Figure 2). The multivariable adjusted likelihood of achieving effective glycaemic control was increased by 5% (0% to 9%) by the addition of oral glucose lowering therapy for patients on no oral medication, by 10% (8 to 12%) for patients taking one oral medication and the chance was increased by 6% (3 to 8%) for those taking two oral agents at the time of intensification (Figure 2). Equivalent increased likelihoods of achieving effective glycaemic control were observed for commencement of insulin therapy. An 8% (-9 to 29%) increased likelihood for effective glycaemic control was observed for those on no oral medication, 13% (8 to 18%) for those taking one oral medication, 12% (9 to 15%) for those taking two oral agents and 10% (5 to 15%) among those on three or more oral agents at the time of insulin commencement.

When analyses were repeated using a cut-off for effective glycaemic control of 6.5% or using different cut-offs for the two treatment arms (intensive 6.5% and standard 7.0%), similar results were observed (data not shown).

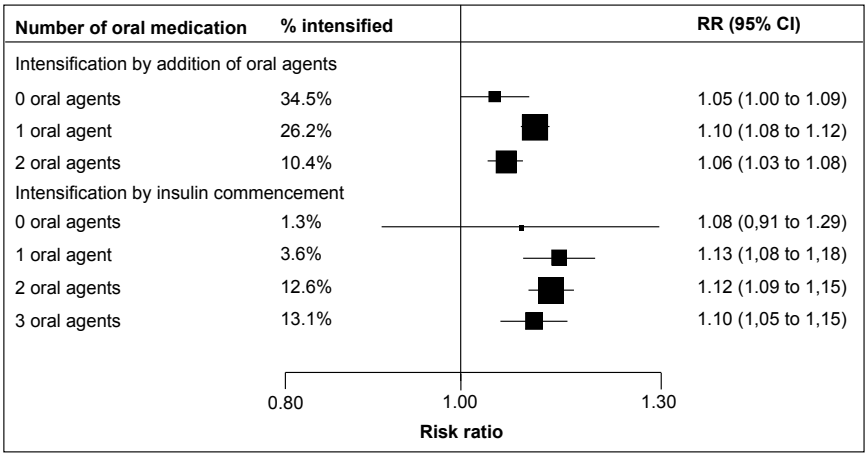


**Figure 2.** Relative risk and 95% confidence interval of achievement of glycaemic control by intensification by oral agents or insulin split out by number of oral agents patient is already prescribed.

## Discussion

In this large cohort of patients with type 2 diabetes who took part in the ADVANCE trial, we have classified participants as having effective (declining or stable HbA1c at a satisfactory level) or ineffective glycaemic control (rising HbA1c). During follow-up HbA1c levels decreased by about 1% in the effective glycaemic control group and increased by the same degree in the ineffective control group. Earlier introduction of insulin and addition of oral agents was associated with more effective glycaemic control in both the standard and intensive glucose control arms. The beneficial effect of intensification by addition of oral glucose lowering therapy or commencement of insulin was observed regardless of disease progression. A recent study of newly diagnosed patients with type 2 diabetes has indicated that intensive treatment with insulin or three oral agents not only keeps the HbA1c at target but preserves beta-cell function for at least 3.5 years.[8] Our data suggest that achieving and maintaining glycaemic control at target by earlier intensification of treatment is also observed in patients with long standing diabetes. Furthermore, the effect appears independent of the number of medications the patient is taking, in that the likelihood of effective glycaemic control was similar in patients who were on 1, 2 or more oral agents, and after adjusting for diabetes duration and age. Previous clinical trials have reported a progressive rise in HbA1c

(UKPDS, ADOPT, FIELD).[3;9;10] In the conventional arm of the UKPDS trial, the HbA1c at the start of the study was 6.9% and after an initial decline of 0.1% rose to 8.0%.[11] A similar rise was observed in those allocated to sulfonylurea, (from 6.0% to 7.1%) and in those allocated to insulin therapy (from 6.3% to 7.1%).[3;4;11;12] A more contemporary trial of patients with long standing diabetes (FIELD) has also reported a rise in HbA1c over 5 years although the rise was much smaller than that observed in the UKPDS trial (average of 0.22%).[10] In contrast in the present study we demonstrate that effective glycaemic control and stable HbA1c levels can be maintained over time by early intensification using oral agents or insulin. We also show that the likelihood of achieving effective glycaemic control for both approaches is comparable and independent of HbA1c level at the time.

Over the last decades management of type 2 diabetes has improved, diabetes is detected at an earlier stage and medications are prescribed at lower HbA1c levels.[13] However, the number of patients with poorly controlled diabetes who do not receive appropriate treatment is still up to 40%.[14;15] In our study the group of patients who experienced a rise in HbA1c during the trial and who were classified as having ineffective glycaemic control, had higher HbA1c levels at the time of treatment intensification. In fact the HbA1c rise observed in this group was of similar magnitude to that reported by the UKPDS trial. Therefore, it is likely that the HbA1c rise observed in the UKPDS trial was partially due to the higher glucose levels at which treatment was intensified and possibly a direct glucotoxic effect on the pancreas.[11;16;17]

International treatment guidelines have recently recommended different approaches to achieving and maintaining HbA1c targets. The ADA/EASD algorithm recommends initiation of monotherapy and when this fails the addition of a second oral agent or insulin.[18] The AACE/ACE algorithm stratifies treatment choices by starting HbA1c level and advocates for dual therapy and insulin at lower HbA1c levels.[19] The AACE/ACE algorithm thus places greater emphasis on the early employment of combination therapy.[20] Our data provide further support for this second approach of earlier intensification of therapy at any stage of the disease.

The strengths of this study are the large sample size, the use of patients from 20 different countries and the multiple measurements during follow-up that made possible the application of robust methods such as pooled regression analyses. The limitations of this study include the post hoc observational nature of the study and the fact that the

intensive group had a set HbA1c target of 6.5% whereas the standard group had a target that will have varied according to local guidelines. However, sensitivity analyses defining effectiveness at HbA1c target levels of 6.5% or 7.0%, yielded similar results. In conclusion, in patients with type 2 diabetes early treatment intensification with use of more oral glucose lowering therapy and of insulin at lower HbA1c levels is associated with a favorable glycaemic control trajectory at any stage of the disease.

## Acknowledgements

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## Supplementary materials



**Table 1.** Patient characteristics associated with effective glycaemic control

| Patient characteristic | RR (95% CI) |
|---|---|
| Age at diagnosis of diabetes (years) | 0.99 (0.99-1.00) |
| Sex (women) | 1.01 (0.99-1.02) |
| Ethnicity (non Caucasian) | 1.01 (0.99-1.02) |
| Diabetes duration (5 years) | 0.99 (0.98-1.00) |
| Treatment arm (intensive) | 1.03 (1.02-1.04) |
| History of microvascular disease | 0.99 (0.97-1.01) |
| HbA1c at intensification | 0.57 (0.56-0.57) |

# Chapter 4

## Weight changes and their predictors amongst 11 140 patients with type 2 diabetes in the ADVANCE trial

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## Abstract

**Aims:** To determine the baseline characteristics and glucose-lowering therapies associated with weight change among patients with type 2 diabetes.

**Methods:** Eleven thousand one hundred and forty participants in the ADVANCE trial were randomly assigned to an intensive [aiming for a haemoglobin A1c (HbA1c) ≤6.5%] or a standard blood glucose-control strategy. Weight was measured at baseline and every 6 months over a median follow-up of 5 years. Multivariable linear regression and linear mixed effect models were used to examine predictors of weight change.

**Results:** The mean difference in weight between the intensive and standard glucose-control arm during follow-up was 0.75 kg (95% CI:0.56–0.94), p-value <0.001. The mean weight decreased by 0.70 kg (95% CI: 0.53–0.87), p < 0.001 by the end of follow-up in the standard arm but remained stable in the intensive arm, with a non-significant gain of 0.16 kg (95% CI: −0.02 to 0.34), p = 0.075. Baseline factors associated with weight gain were younger age, higher HbA1c, Caucasian ethnicity and number of glucose-lowering medications. Treatment combinations including insulin [3.22 kg (95% CI: 2.92–3.52)] and thiazolidinediones [3.06 kg (95% CI: 2.69–3.43)] were associated with the greatest weight gain while treatment combinations including sulphonylureas were associated with less weight gain [0.71 kg (95%CI:0.39–1.03)].

**Conclusions:** Intensive glucose-control regimens are not necessarily associated with substantial weight gain. Patient characteristic associated with weight change were age, ethnicity, smoking and HbA1c. The main treatment strategies predicting weight gain were the use of insulin and thiazolidinediones.

## Introduction

Excess weight is a prevalent condition in patients with type 2 diabetes and drives the ongoing and projected epidemic of type 2 diabetes.[1;2] Excess weight and weight gain also interfere with the achievement of optimal glycaemic control and have been shown to be associated with increased mortality risk.[3;4]

Patients with type 2 diabetes often require several types of glucose-lowering therapy in order to achieve optimal blood glucose control. However, the administration of glucose-lowering therapies is often accompanied by weight gain, which may increase the risk of adverse events and complications.[5;6] Fear of weight gain among both physicians and people with diabetes has been cited as a major barrier to the uptake of intensive glucose-lowering strategies.[7;8] As a result, many patients are unable to achieve lower glucose levels over prolonged periods of time and do not benefit from intensified glucose-lowering strategies that reduce the risk of the major complications of diabetes.

Different patterns of weight change have been described with intensified glucose-lowering therapy in three recent large-scale clinical trials.[9-11] Although all studies reported a net greater weight in the intensive arm compared to the standard arm at the end of follow-up [the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Groups (3.1 kg),[9] Veterans Affairs Diabetes Trial (VADT) (4.1 kg)[10] and the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) (0.9 kg) trials,[11] the reasons for the weight differences between the treatment groups in each trial varied. In the ACCORD and VADT trial, the difference was attributable to net weight gain in the intensive arm, while the observed difference in the ADVANCE trial was due to significant weight loss in the standard arm.[9-11]

Understanding which glucose-lowering strategies are associated with weight gain or with weight loss is of great importance for the treatment of patients with type 2 diabetes. Accordingly, in this study, we have examined the possible influence of patient characteristics at baseline and of glucose-lowering therapies used both at baseline and during follow-up on the weight changes observed during the ADVANCE trial.

## Materials and methods

### Study design and participants

ADVANCE was a 2 × 2 factorial randomized controlled trial evaluating the effects of blood pressure lowering and intensive blood glucose control on vascular outcomes in participants with type 2 diabetes. Detailed descriptions of the design have been published previously.[11;12] In brief, 11 140 participants with type 2 diabetes, aged 55 years or older, with a history of major macrovascular or microvascular disease, or at least one other risk factor for vascular disease, were recruited from 215 centres in 20 countries. Approval for the trial was obtained from the institutional ethics committee of each centre and all participants signed an informed consent form.

All potentially eligible participants entered a 6-week active run-in period during which they continued their usual methods of glucose control and received a fixed combination of perindopril–indapamide (2 mg/0.625 mg). Participants who tolerated and were compliant with the run-in treatment were subsequently randomized to continued treatment with perindopril–indapamide or matching placebo and randomly assigned to intensive glucose-control strategy aiming for a haemoglobin A1c (HbA1c) ≤6.5% or standard glucose therapy. The intensive glucose-control regimen was based on gliclazide modified release (30–120 mg daily), with free access to all other glucose-lowering therapies, which were introduced incrementally and progressively as clinically indicated. The standard glucose-control regimen was based on the relevant national or regional guidelines. The median follow-up time for the glucose-control arm of the study was 5 years.

### Measurements

Weight was assessed at baseline and every 6 months during follow-up. Weight change was calculated as the difference between weight at last visit and baseline weight. Clinical examination and laboratory examinations were performed at each study centre. Self-reported data on cigarette, cigar and pipe smoking was used for categorization into current or non-smokers. Duration of diabetes was calculated as the time between clinical diagnosis and entering the trial. Concomitant treatments were recorded at all follow-up visits.

### Statistical analyses

Patients were divided into five groups according to degrees of weight change. Substantial weight gain and weight loss were defined as >5

kg, while moderate weight gain or weight loss were defined as <5 kg but >1 kg. Neutral weight change was defined as a change between −1 kg and +1 kg. The effects of baseline characteristics, of treatment at randomization and of treatment at end of follow-up were examined across these groups. Differences in weight change between the standard and intensive treatment arms were further examined by sex, ethnicity and history of macrovascular disease. The association between potential predictors and either baseline weight or weight change was assessed with univariable and multivariable linear regression analyses. Potential predictors of weight change were entered into the multivariable model if they were found to be significant at a p-value <0.10 in a univariable model. Backward elimination was then applied to retain the final predictors in the model, based on a p-value <0.05. Potential predictors of baseline weight and weight change were age, sex, ethnicity, smoking, systolic and diastolic blood pressure, hypertension, duration since diagnosis of diabetes, HbA1c level, history of macrovascular disease, history of microvascular disease, occurrence of hypoglycaemia, total number of hypoglycaemic events (minor and severe) and different glucose-lowering treatments.

Treatment at the end of follow-up was considered as the most appropriate surrogate of on-trial treatment. Furthermore, two sensitivity analyses were conducted. In the first analysis, a linear-mixed effect model for repeated weight measurements was used. For this analysis, repeated data on treatment and HbA1c values at every 12 months and until the end of follow-up were used together with baseline characteristics to predict weight change. A second sensitivity analysis examined body mass index (BMI) change from baseline. Both baseline predictors and the effects of glucose-lowering treatment on BMI change were assessed. All analyses were performed using SAS® version 9.2 for Windows (SAS Institute Inc., Cary, NC, USA).

## Results

Table 1 displays the baseline characteristics and treatments at the start and end of the study by categories of weight change, as described earlier. Similar proportions of participants fell into each of these five groups. Patients who gained more weight during follow-up had a higher baseline HbA1c level, were more likely to be in the intensive treatment arm and were on more than two oral glucose-lowering agents at the start of the study. While at the end of the study, these patients were on more than two oral glucose-lowering agents, more likely to be receiving

**Table 1.** Baseline characteristics of ADVANCE and treatment at start and end of trial by categories of weight change.

| | Weight loss >5 kg [b] | Weight loss ≤5 kg [b] | Weight change Weight change neutral [a,b] | Weight gain ≤5 kg [b] | Weight gain >5 kg [b] | P-value Linear trend |
|---|---|---|---|---|---|---|
| Sex (female), n (%) | | 920 (43.0) | 1204 (43.0) | 763 (40.4) | 864 (42.8) | 0.433 |
| Age (years), mean (SD) | | 65.8 (6.37) | 66.0 (6.46) | 65.3 (6.22) | 64.9 (6.19) | <0.001 |
| Weight (kg), mean (SD) | | 76.8 (15.5) | 75.6 (15.5) | 75.3 (15.7) | 79.3 (18.0) | <0.001 |
| Difference weight (kg), mean (SD) | | -2.92 (0.82) | 0 (0.76) | 2.88 (0.81) | 9.11 (4.70) | <0.001 |
| BMI ($kg/m^2$) , mean (SD) | | 28.0 (4.77) | 27.6 (4.69) | 27.4 (4.86) | 28.6 (5.56) | <0.001 |
| Diabetes duration (years) | | 7.78 (6.23) | 8.09 (6.45) | 8.05 (6.39) | 8.15 (6.46) | 0.002 |
| $HbA_{1c}$ (%), mean (SD) | | 7.44 (1.48) | 7.46 (1.51) | 7.57 (1.63) | 7.75 (1.78) | <0.001 |
| Systolic blood pressure (mmHg) | | 145 (21.2) | 145 (21.3) | 145 (21.5) | 144 (21.4) | <0.001 |
| Caucasian, n (%) | | 1157 (54.1) | 1590 (56.8) | 1082 (57.3) | 1389 (68.7) | <0.001 |
| History macrovascular, n (%) | | 662 (31.0) | 891 (31.8) | 592 (31.4) | 651 (32.2) | 0.139 |
| History microvascular, n (%) | | 196 (9.2) | 285 (10.2) | 198 (10.5) | 246 (12.2) | 0.009 |
| Treatment arm (intensive), n (%) | | 997 (46.6) | 1340 (47.8) | 1010 (53.5) | 1158 (57.3) | <0.001 |
| Glucose lowering treatment before entering trial | | | | | | |
| No drug, n (%) | 212 (9.25) | 194 (9.07) | 242 (8.64) | 178 (9.43) | 162 (8.02) | 0.269 |
| Any oral, n (%) | 2073 (90.5) | 1939 (90.7) | 2557 (91.3) | 1706 (90.4) | 1854 (91.7) | 0.241 |
| More than 2 oral, n (%) | 100 (4.36 ) | 97 (4.54) | 162 (5.78) | 130 (6.89) | 201 (9.95) | <0.001 |
| Any insulin, n (%) | 33 (1.44) | 19 (0.89) | 33 (1.18) | 35 (1.85) | 39 (1.93) | 0.023 |
| Sulphonylurea only , n (%) | 659 (28.8) | 606 (28.3) | 716 (25.6) | 458 (24.3) | 365 (18.1) | <0.001 |
| Metformin only, n (%) | 350 (15.3) | 298 (13.9) | 448 (16.0) | 311 (16.5) | 381 (18.9) | <0.001 |
| Thiazolidinedione only, n (%) | 5 (0.22) | 5 (0.23) | 3 (0.11) | 4 (0.21) | 2 (0.10) | 0.347 |
| Alpha glucosidase only, n (%) | 26 (1.13) | 25 (1.17) | 32 (1.14) | 21 (1.11) | 11 (0.54) | 0.080 |
| Sulphonylurea+metformin,n(%) | 825 (36.0) | 766 (35.8) | 1019 (36.4) | 668 (35.4) | 765 (37.9) | 0.321 |
| Sulphonylurea+thiazol, n (%) | 13 (0.57) | 11 (0.51) | 18 (0.64) | 7 (0.37) | 25 (1.24) | 0.033 |
| Metformin+thiazol, n (%) | 12 (0.52) | 9 (0.42) | 20 (0.71) | 11 (0.58) | 15 (0.74) | 0.257 |

**Table 1.** Continued

| | Weight loss >5 kg [b] | Weight loss ≤5 kg [b] | Weight change Weight change neutral [a,b] | Weight gain ≤5 kg [b] | Weight gain >5 kg [b] | P-value Linear trend |
|---|---|---|---|---|---|---|
| Glucose lowering treatment at end of trial | | | | | | |
| No drug, n (%) | 105 (4.58) | 61 (2.85) | 89 (3.18) | 51 (2.70) | 33 (1.63) | <0.001 |
| Any oral, n (%) | 2013 (91.2) | 1933 (93.8) | 2294 (91.7) | 1660 (90.8) | 1759 (90.0) | 0.009 |
| More than 2 oral, n (%) | 317 (13.8) | 353 (16.5) | 439 (16.5) | 342 (18.1) | 389 (19.3) | <0.001 |
| Any insulin, n (%) | 444 (20.1) | 514 (24.9) | 739 (29.5) | 714 (39.0) | 1013 (51.8) | <0.001 |
| Sulphonylurea only , n (%) | 300 (13.6) | 304 (14.8) | 411 (16.4) | 300 (16.4) | 324 (16.6) | 0.002 |
| Metformin only, n (%) | 297 (13.5) | 217 (10.5) | 254 (10.2) | 168 (9.2) | 239 (12.2) | 0.067 |
| Thiazolidinedione only, n (%) | 7 (0.32) | 2 (0.10) | 6 (0.24) | 6 (0.33) | 10 (0.51) | 0.116 |
| Alpha glucosidase only, n (%) | 31 (1.40) | 28 (1.36) | 26 (1.04) | 24 (1.31) | 20 (1.02) | 0.282 |
| Sulphonylurea+metformin,n(%) | 919 (41.6) | 863 (41.9) | 943 (37.7) | 654 (35.8) | 594 (30.4) | <0.001 |
| Sulphonylurea+thiazol, n (%) | 12 (0.54) | 21 (1.02) | 33 (1.32) | 48 (2.63) | 72 (3.69) | <0.001 |
| Metformin+thiazol, n (%) | 27 (1.22) | 19 (0.92) | 31 (1.24) | 23 (1.26) | 37 (1.89) | 0.038 |

[a] The weight change neutral group is defined as -1 kg to 1 kg of weight gain.

[b] Weight loss >5.0 Kg: intensive arm, n=1066 and standard arm n=1226; n the weight loss ≤5Kg: intensive arm, n=997 and standard arm, n=1141; in the weight neutral group: intensive arm, n=1340 and standard arm, n=1461; ≤5 Kg weight gain group: intensive arm, n=1010 and standard arm; n=878; in the >5Kg weight gain group intensive arm, n=1158 and standard arm, n=863.

any insulin and less likely to be receiving sulphonylurea combined with metformin. More participants in the standard arm lost weight and more participants in the intensive arm gained weight (figure 1). Overall, weight remained stable for patients in the intensive treatment arm, who had a mean weight gain of 0.16 kg (95% CI:−0.02 to 0.34), p=0.075, while patients from the standard treatment arm had a mean weight loss of 0.70 kg (95% CI: 0.53–0.87, p<0.001) (p=0.001 for difference between treatment arms). Furthermore, participants in the standard treatment arm were more likely to lose weight or gain less weight compared to the intensive arm regardless of sex, ethnicity, history of macrovascular disease or treatment with insulin, thiazolidinedione or more oral drugs. In the intensive treatment arm, Caucasians, patients without a history of macrovascular disease, current smokers, those ≤65 years and those with an HbA1c >7.2% were more likely to gain weight, while non-Caucasians (largely Asians in this trial), patients with a history of macrovascular disease, those >65 and those with an HbA1c ≤7.2% were more likely to lose weight. Despite the absolute differences

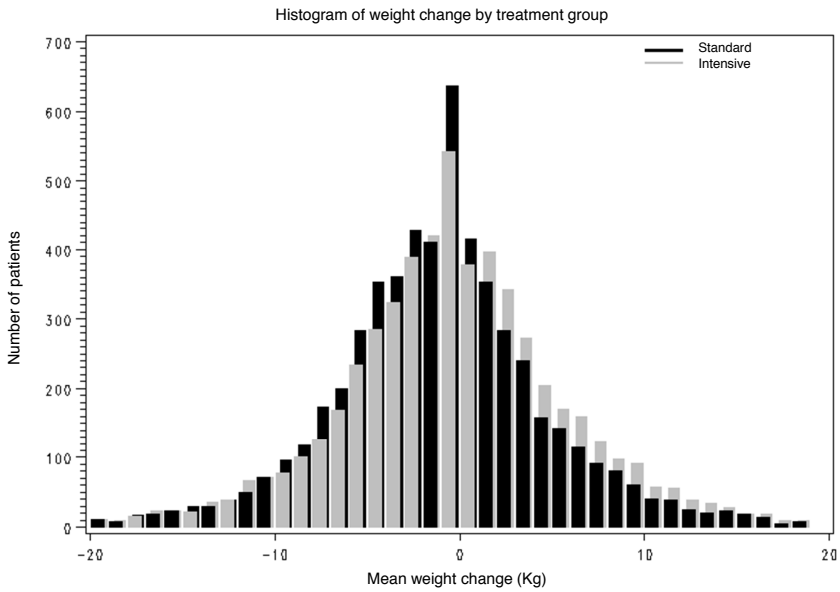


**Figure 1. Weight change by randomized treatment arm.** Weight change is separated by randomized treatment arm, standard arm represented by the black bars and the intensive arm by the grey bars. The lengths of the bars are proportional to the number of participants within mean weight change strata.

in weight change between the standard and intensive arm, a significant interaction in the relative effects by treatment arm was only observed for those with and without a history of macrovascular disease (figure 2). Age, sex, ethnicity, smoking, duration since diagnosis of diabetes and HbA1c level were all significant independent predictors of baseline weight. History of macrovascular and microvascular events and hypertension were not significantly associated with baseline weight. As expected, these characteristics were also associated with baseline BMI with similar effects.



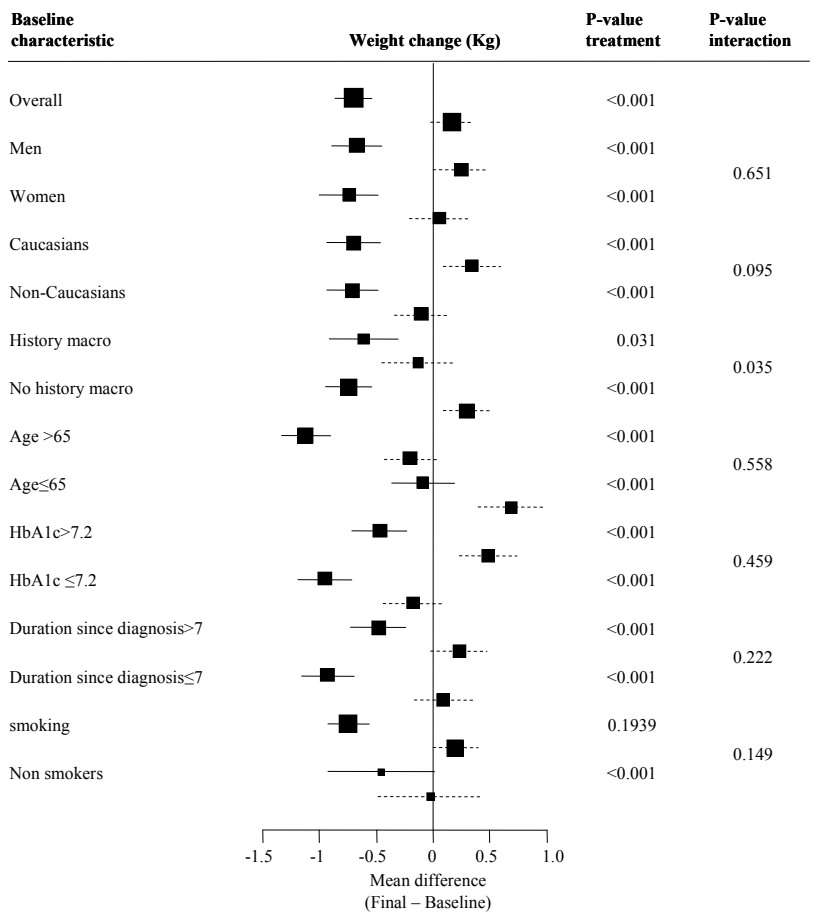


**Figure 2. Weight change by randomized treatment arm according to baseline characteristics.** The black boxes represent the effect sizes (mean weight change) and the horizontal lines represent the 95% confidence intervals, separately for the standard arm (solid line) and the intensive arm (broken line). The p-values represent the differences in effect sizes between randomized treatment arms and the heterogeneity across subgroups of baseline characteristics.

The patient characteristics that were associated with baseline weight were also associated with weight change during follow-up (Table 2). In addition, the number of oral glucose-lowering therapies used during follow-up was associated with weight change. Older age, female gender and smoking history were associated with weight loss. In contrast, a higher HbA1c level, the use of more oral medications and Caucasian ethnicity were associated with weight gain. In a sensitivity analysis examining, the baseline predictors of BMI change were broadly the same. In addition, baseline history of microvascular disease was associated with increase in BMI (Supplementary material Table 1).

**Table 2.** Baseline characteristics predicting weight change during follow-up

| Patient characteristics | Mean weight change (kg) (95% CI) | P-value |
|---|---|---|
| Age (Years) | -0.09 (-0.11 to -0.07) | <0.001 |
| Gender (Female) | -0.17 (-0.42 to 0.09) | 0.196 |
| Ethnicity (Caucasian) | 0.71 (0.45 to 0.97) | <0.001 |
| Smoking (current) | -0.39 (-0.75 to -0.04) | 0.029 |
| Duration since diagnosed diabetes (years) | 0.02 (-0.004 to 0.04) | 0.123 |
| $HbA_{1c}$ (%) | 0.27 (0.19 to 0.35) | <0.001 |
| Systolic blood pressure (10mmHg) | 0.09 (-0.14 to -0.02) | 0.004 |
| Number of oral medications at baseline | 0.48 (0.31 to 0.66) | <0.001 |

**Associations between glucose-lowering therapies and weight changes during follow-up**

The effects of glucose-control agents on weight change were assessed in two ways: (i) by entering indicator of each glucose lowering class in multivariable models without accounting for possible association of different agents in the same individual; and (ii) by creating mutually exclusive indicators for various glucose-lowering strategies including monotherapies and drug combination. Figure 3 represents the mean weight change for different blood glucose-lowering therapies used during follow-up (from non-mutually exclusive indicators), adjusted for age, sex, ethnicity, smoking, duration of diabetes, occurrence of hypoglycaemic events and HbA1c level. Allocation to intensive treatment arm *per se* was not independently associated with weight gain [0.018 kg (95% CI: −0.26 to 0.30)]. Insulin use was associated with a weight gain of 3.22 kg (2.92–3.52), thiazolidinedione use was

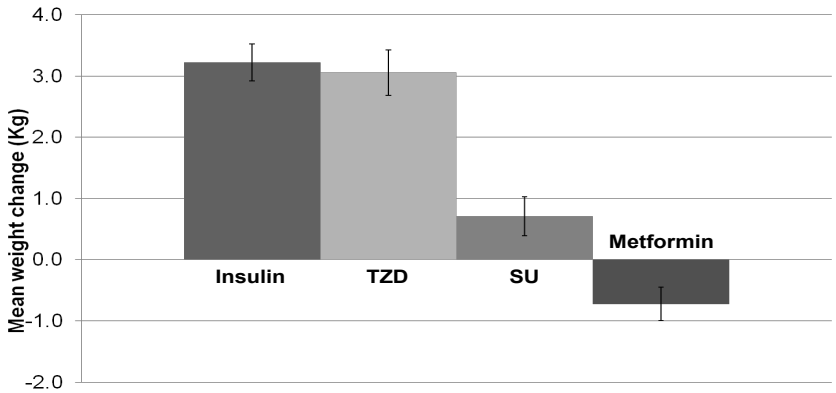


**Figure 3. Weight change by blood glucose lowering therapy during follow-up.** Estimates of mean weight change by insulin, thiazolidinedione (TZD), sulphonylurea (SU) and metformin, adjusted for age, sex , ethnicity, smoking, duration of diabetes, occurrence of hypoglycaemic events and HbA1c.

associated with a weight gain of 3.06 kg (2.69–3.43) and sulphonylurea use was associated with weight gain of 0.71 kg (0.39–1.03). In contrast, metformin use was associated with weight loss of 0.72 kg (0.45–1.00). In multivariable models based on mutually exclusive indicators of exposure to different glucose-lowering strategies, monotherapy with insulin was associated with significant weight gain and monotherapy with metformin associated with significant weight loss. Other monotherapies, based on small number of participants had no significant effect on weight during follow-up. All combinations of insulin and any other agents were associated with weight gain. In addition, combination of thiazolidinedione with sulphonylurea was associated with significant weight gain (Supplementary material Figure 1). The directions of effects were similar when change in BMI was examined in relation with glucose-lowering treatments (Supplementary material Figures 2 and Figure 3). A sensitivity analysis with a mixed model taking into consideration all medications used during follow-up and adjusted for the same baseline characteristics, gave similar results (data not shown).

## Discussion

The purpose of this study was to determine the patient characteristics and glucose-lowering pharmacotherapies associated with weight change in a contemporary cohort of patients with type 2 diabetes. More patients in the standard glucose-control arm lost weight, while more patients in the intensive glucose-control arm gained weight. Patient characteristics associated with weight loss were older age, current smoking and lower HbA1c level. Blood glucose-lowering therapies associated with the greatest weight gain were insulin and thiazolidinedione. Sulphonylureas were associated with less weight gain and metformin was associated with weight loss.

We observed that women tended to lose weight, although not significantly. In contrast, a trial of patients with type 1 diabetes showed that women were more likely to gain weight.[13] Additionally, Caucasian ethnicity and requirement for a greater number of oral medications were associated with weight gain. These observations are in line with an observational 12-month weight trajectory study of 4135 patients with newly diagnosed type 2 diabetes.[14]

Several trials of intensive glucose control have shown that most glucose-lowering strategies aggravate weight gain. In the United Kingdom Prospective Diabetes Study (UKPDS), intensification of therapy and improved glycaemic control were associated with substantial weight gain (6.0 kg vs. 3.0 kg in the intensive and conventional groups, respectively).[15] A similar pattern was observed in the ACCORD (3.5 kg compared to 0.4 kg)[9] and VADT trials (7.8 kg compared to 3.4 kg).[10] By contrast, in ADVANCE, patients in the intensive arm only gained 0.16 kg, while the patients in the standard arm actually lost 0.7 kg. The different patterns in these trials might be explained, at least in part, by the fact that considerably more patients received insulin in the intensive treatment arms of ACCORD and VADT compared to ADVANCE as well as the higher baseline HbA1c levels in these studies.

We observed that insulin and thiazolidinedione use resulted in a similar increase in body weight. This has also been reported by several other cohort studies.[5;16-18] Furthermore, metformin use in our trial was associated with weight loss, consistent with reports of other surveys.[5;14;16-19] An association between weight gain and sulphonylurea use has been reported by several studies.[14;16-19] In the UKPDS, sulphonylurea use was associated with a weight gain of 5.0–7.0 kg. A subsequent meta-analysis of the effects of a range of

oral glucose-lowering drugs has reported a more modest increase in body weight of 2.1 kg with sulphonylurea use;[5] however, this was in addition to metformin. In our study sulphonylurea use was associated with minimal weight gain. Possible explanations include that the sulphonylurea used in the intensive glucose-control arm of ADVANCE was gliclazide modified release. This third generation sulphonylurea has previously been reported to have a weight neutral impact.[18] In other studies, when gliclazide and glimepiride were compared with other sulphonylureas such as glyburide and tolbutamide, gliclazide and glimepiride have been shown to be associated with less weight gain.[20] It is also possible that the pragmatic stepwise up-titration of glucose-lowering therapy in conjunction with regular detailed review of dietary and lifestyle factors in the ADVANCE trial may have encouraged weight loss and limited weight gain. Furthermore, the entry glucose levels in the UKPDS trial were rather high resulting in more glycosuria at onset. With improvement of glycosuria more calories are kept in the body such that while calorie consumption stays the same, body weight increases.[21;22]

The Diabetes Prevention Program study[23] suggested that in obese patients with impaired glucose tolerance, reduction in body weight by lifestyle changes might be more effective in preventing progression to type 2 diabetes than some antidiabetic drugs. However, clinical practice shows that the reduction in weight is often not sustained over prolonged periods. It has been reported that weight gain is a psychological barrier to the initiation of insulin and sulphonylureas for both patients and general practitioners.[18] However, our data would suggest that use of the modified release sulphonylurea in this study has only a limited impact on weight gain compared to insulin and thiazolidinediones.

The strengths of our study are the large sample size, the inclusion of patients from 20 different countries and the use of several different glucose-lowering pharmacotherapies. However, some limitations need to be addressed. Several studies have shown that weight gain is greatest in the first year or two after the diagnosis of diabetes[17;19] but the average duration of diabetes before randomization in our study was 8 years. Furthermore, due to the inclusion criteria of our trial, weight change was only assessed in patients with moderate or high risk of cardiovascular disease.

In conclusion, this study shows that weight gain is not merely due to intensification of treatment, but is also related to HbA1c level and smoking status. Moreover, insulin and thiazolidinedione use was associated with substantial weight gain, while sulphonylurea use produced only minimal weight gain and metformin use minimal weight loss. It is important for clinicians to understand the differential effects on weight of different treatment strategies for type 2 diabetes. In this respect, our report of the patient characteristics and therapies associated with weight gain might assist clinicians in making treatment decisions that minimize weight gain.



## Acknowledgements

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## Supplementary materials

**Table 1.** Baseline characteristics predicting BMI change during follow-up

| Patient characteristics | Mean weight change (kg) (95% CI) | P-value |
|---|---|---|
| Age (Years) | -0.04 (-0.05 to -0.03) | <0.001 |
| Gender (Female) | -0.08 (-0.19 to 0.02) | 0.128 |
| Ethnicity (Caucasian) | 0.27 (0.16 to 0.39) | <0.001 |
| Duration since diagnosed diabetes (years) | 0.002 (-0.01 to 0.01) | 0.637 |
| History microvascular disease (yes) | 0.20 (0.02 to 0.39) | 0.030 |
| $HbA_{1c}$ (%) | 0.11 (0.07 to 0.15) | <0.001 |
| Number of oral diabetes medications at baseline | 0.24 (0.17 to 0.32) | <0.001 |

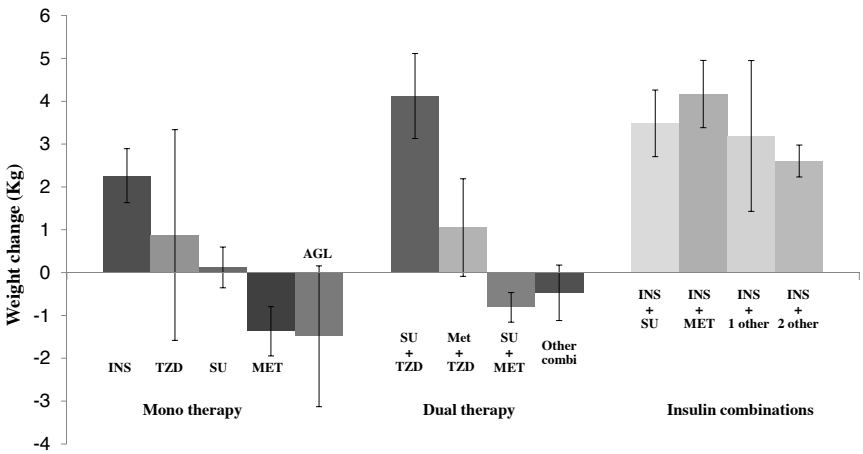
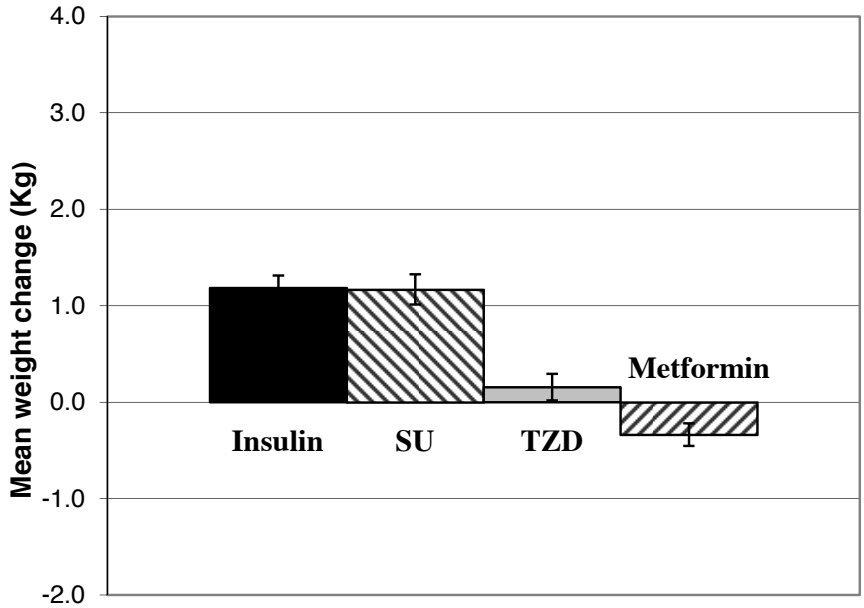



**Figure 1. Weight change (Kg) by mono and dual therapy and insulin combinations based on mutually exclusive indicators to different glucose lowering regimens.**
Adjusted for age, sex, ethnicity, smoking, duration of diabetes, $HbA_{1c}$ and treatment allocation.




**Supplementary material Figure 2. BMI by blood glucose lowering therapy during follow-up.** Estimates of body mass index change by insulin, thiazolidinedione (TZD), sulphonylurea (SU) and metformin, adjusted for age, sex , ethnicity, smoking, duration of diabetes and $HbA_{1c}$ and treatment allocation

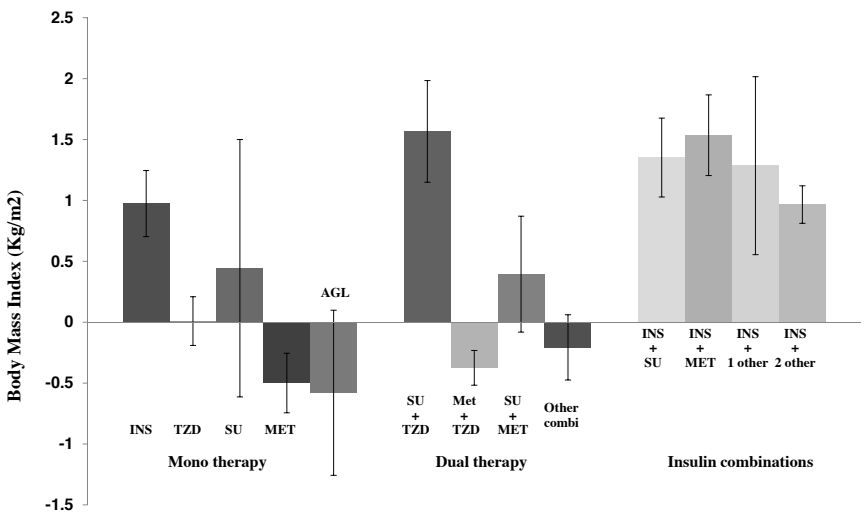



**Figure 3. BMI by mono and dual therapy and insulin combinations based on mutually exclusive indicators to different glucose lowering regimens.** Adjusted for age, sex, ethnicity, smoking, duration of diabetes, $HbA_{1c}$ and treatment allocation.

# Chapter 5

# Effect of blood pressure lowering on cardiovascular outcomes in different cardiovascular risk groups among participants with type 2 diabetes

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## Abstract

**Aims:**To assess differences in treatment effects of a fixed combination of perindopril–indapamide on major clinical outcomes in patients with type 2 diabetes across subgroups of cardiovascular risk.

**Methods:** 11,140 participants with type 2 diabetes, from the ADVANCE trial, were randomized to perindopril–indapamide or matching placebo. The Framingham equation was used to calculate 5-year CVD risk and to divide participants into two risk groups, moderate–high risk (<25% and no history of macrovascular disease), very high risk (>25% and/or history of macrovascular disease). Endpoints were macrovascular and microvascular events.

**Results:**The mean age of participants was 66 years (42.5% female). 1000 macrovascular and 916 microvascular events were recorded over follow-up of 4.3 years. Relative treatment effects were similar across risk groups, (all P-values for heterogeneity ≥0.38). Hazard ratios for combined macro- and microvascular events were 0.89 (0.77–1.03) for the moderate-high risk and 0.92 (0.81–1.03) for the very high risk. Absolute treatment effects tended to be greater in the high risk groups although differences were not statistically significant (P>0.05).

**Conclusions:** Relative effects of blood pressure lowering with perindopril–indapamide on cardiovascular outcomes were similar across risk groups whilst absolute effects trended to be greater in the high risk group.

## Introduction

People with type 2 diabetes are considered to be at high risk for developing cardiovascular disease (CVD).[1] Nevertheless, there is a gradation of CVD risk among people with type 2 diabetes as many factors contribute to this risk. Previous studies examining the effect of blood pressure lowering have focused on treatment effects according to single risk factors.[2-5] Recently, there has been a shift from focusing on individual risk factors to absolute cardiovascular risk based on a combination of risk factors.[6] Moreover, contemporary cardiovascular, diabetes and hypertension management guidelines recommend integrating several risk factors into total cardiovascular risk assessment by using prediction models.[7-9]

Several CVD prediction models have been developed over the past decade;[10] the most widely known and used models are Framingham and SCORE for primary prevention in the general population and the UKPDS risk engine for the population with diabetes.[11-13] The publicly available UKPDS risk engine only calculates the separate risk for either coronary heart disease or cerebrovascular disease.[14;15] While the Framingham risk equations are derived from general populations, free of prevalent disease, they do take diabetes into account and they calculate the risks for overall cardiovascular disease, including coronary heart disease and cerebrovascular disease.[11;12] As guidelines are increasingly recommending treatment according to absolute risk, it is important to define the absolute risks as well as the absolute effects of various interventions across cardiovascular risk groups, including those of blood pressure lowering in people with type 2 diabetes.

The recent Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study investigated the effects of routine administration of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in participants with type 2 diabetes.[16] The aim of the present study was to assess differences in absolute and relative treatment effects of blood pressure lowering across subgroups defined by initial absolute cardiovascular risk.

## Methods

### Study design and participants

ADVANCE was a factorial randomized controlled trial evaluating the effects of routine blood pressure lowering and intensive blood glucose control on vascular outcomes and death in participants with type 2 diabetes. Detailed descriptions of the design have been published previously.[16;17] In brief, 11,140 participants with type 2 diabetes, aged 55 years or older, with a history of major macrovascular or microvascular disease, or at least one other risk factor for vascular disease, were recruited from 215 centres in 20 countries. Patients were excluded if they had a definite indication for, or contraindication to, any of the study treatments, a definite indication for long-term insulin treatment or were participating in any other clinical trial. Approval for the trial was obtained from the institutional ethics committee of each centre and all participants signed an informed consent.

All potentially eligible participants entered a 6-week active run-in period during which they received a fixed combination of perindopril–indapamide (2 mg/0.625 mg). Participants who tolerated and were compliant with the run-in treatment were subsequently randomized to continued treatment with perindopril–indapamide (2 mg/0.625 mg) or matching placebo and to an intensive blood glucose control strategy aiming for a HbA1c ≤6.5% or a standard glucose therapy. The perindopril–indapamide dose was doubled to 4 mg/1.25 mg after three months. The use of concomitant treatments during follow-up, including blood pressure lowering therapy, remained at the discretion of the responsible physician with two exceptions, the use of thiazide diuretics was not allowed and open-label perindopril was the only ACE inhibitor allowed. Participants were seen at 2 pre-randomization visits, at 3, 4 and 6 months after randomization and subsequently every 6 months. The mean follow-up time was 4.3 years for the blood pressure arm of the study.

### Outcomes

The primary outcomes were composites of major macrovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) and microvascular events (new or worsening nephropathy or retinopathy). The secondary outcomes included all-cause mortality, cardiovascular death, all coronary events (death due to coronary heart disease, including sudden death, nonfatal myocardial infarction, silent myocardial infarction, coronary revascularization or hospital

admission for unstable angina), all cerebrovascular events (death from cerebrovascular events, nonfatal stroke, transient ischemic attack or subarachnoid haemorrhage) and new or worsening nephropathy. An independent adjudication committee reviewed and validated all suspected primary end-points and deaths.

**Cardiovascular risk assessment**

5-year cardiovascular disease risk was estimated using the Framingham Anderson equation for CVD,[12] which is based on age, gender, smoking status, systolic blood pressure, the ratio of total/HDL cholesterol, left ventricular hypertrophy and diabetes status.

CVD risk at baseline was calculated for all participants using the risk equation. For the 35 participants with missing values for one of the characteristics included in the equation, values were imputed using mean substitution. The median calculated 5-year CVD risk was 18.8% with an interquartile range of 13.6%–23.5%.

Participants were divided into two risk groups: moderate-high risk (a calculated CVD risk of ≤25% over 5 years) and very high risk (a calculated CVD risk of >25% over 5 years). Only 7.1% (n=789) of the patients had a calculated risk <10% and 10.8% (n = 85) of these participants had a major macrovascular or microvascular event. Combining this with the fact that guidelines classify all patients with type 2 diabetes to be at least at medium risk for a cardiovascular event,[8;18] we did not classify any patients into a low risk group. The Framing-ham risk equations do not take account of previous cardio-vascular event, therefore patients with a history of cardiovascular disease (n=3590) were all assigned to the very high risk group.

**Statistical analysis**

Follow-up time for each participant was calculated as time from registration date to date of event or date of censoring. The first event for each outcome was included in the analysis. Mean systolic and diastolic blood pressure were plotted split out by cardiovascular risk group and treatment arm. Change in blood pressure was calculated as blood pressure at registration minus blood pressure at the end of follow-up. The difference in blood pressure change between the moderate-high and very high risk groups was tested, stratified for treatment arm, using a mixed model. Hazard ratios and 95% confidence intervals for randomized treatment effects on study endpoints were estimated using unadjusted Cox proportional hazard models. Homogeneity of treatment effects between the risk subgroups was tested by adding interaction terms to the relevant Cox models.

Absolute risk reductions per 1000 persons and for both subgroups were calculated by subtracting the event rate of the perindopril–indapamide group from the event rate of the placebo group. Standard errors from the absolute risk reductions were obtained and used to calculate 95% confidence intervals following a normal distribution. Differences in absolute risk reduction between the moderate–high and very high risk groups were tested using a Wald test assuming a poisson distribution. Three sensitivity analyses were conducted: (1) using only those participants without a known history of cardiovascular disease at baseline; (2) by ranking participants according to their baseline 5-year coronary heart disease (CHD) risk estimated with the UKPDS coronary risk engine and dividing all participants into two groups: moderate–high risk, a predicted CHD risk of ≤15% in 5 years and no history of macrovascular disease, and very high risk, a predicted CHD risk of >15% in 5 years and/or a history of macrovascular disease); (3) by calculating 10-year CVD mortality risk using systematic coronary risk evaluation model (SCORE)[13] and dividing all participants into two groups: moderate–high (a calculated CVD mortality risk of ≤15% over 10 years) and very high risk (a calculated CVD mortality risk of >15% over 10 years). P-values<0.05 from two-tailed analysis were considered statistically significant. All analyses were performed using SAS Version 9.1.3.

## Results

Table 1 shows the baseline characteristics according to CVD risk group and treatment allocation. Baseline characteristics of participants were similar for perindopril–indapamide and placebo within each risk group. Only a difference in the number of participants who smoked was observed between the treatment arms in the very high risk group. Table 2a and b shows the medications at registration and at the end of follow-up in the moderate–high risk (Table 2a) and very high risk groups (Table 2b). Compared to the moderate–high risk group, the very high risk group received more calcium antagonists, aspirin and statins at the end of follow-up. Similar proportions of patients in each risk group received the other medications.

Figure 1 represents mean systolic and diastolic blood pressure during follow-up by risk group and treatment arm. The mean systolic and diastolic blood pressure during follow-up were higher in the very high risk group compared with the moderate–high risk group. In both arms of the study a significant difference in systolic blood pressure

between the risk groups was observed (138 mmHg vs 143 mmHg for the placebo arm and 132 mmHg vs 138 mmHg for the perindopril–indapamide arm for the moderate–high and very high risk groups respectively, both P-values <0.001). The mean changes in systolic blood pressure for the placebo and perindopril– indapamide treatment arms were -3.70 mmHg (95% CI:-4.47 to -2.93) and -4.42 mmHg (95%CI:-5.19 to -3.65) for the moderate–high risk group and -11.99 mmHg (95%CI:-12.95 to -11.04) and -11.29 mmHg (95%CI:-12.25 to -10.33) for the very high risk group respectively. The differences in diastolic blood pressure change during follow-up between the risk groups were also significant (P-value<0.001).

The event rate per year for macrovascular disease was 1.3% in the moderate–high CVD risk group and 2.9% in the very high risk group. For microvascular disease the event rate per year was 1.8% in the moderate–high risk group and 2.0% in the very high risk group. Relative treatment effects for the perindopril–indapamide arm compared with the placebo arm were similar across both risk groups for all endpoints including all-cause and cardiovascular mortality (Figure 2, all P-values for interaction ≥0.38). Hazard ratios for combined macrovascular and microvascular events were 0.89 (95%CI:0.77–1.03) for the moderate–high risk group and 0.92 (95%CI:0.81–1.03) for the very high risk group. Similar results were found when participants with a history of macrovascular disease at baseline were excluded (Supplementary material figure 1).

The absolute risk reductions for macrovascular events were greater in the very high risk group (11.7% (95%CI:-5.7 to 29.1)) compared to the moderate–high risk group (3.7% (95%CI:-8.2 to 15.7)), but did not achieve statistical significance (all P-values for difference >0.05) (Table 3). In contrast for microvascular events the absolute risk reduction in the perindopril–indapamide group tended to be greater in the very high risk group (9.4) compared to the very high risk group (4.3) (P for difference >0.05).

When patients with a history of macrovascular disease at baseline were excluded the absolute risk reductions were greater in the very high risk group compared to the moderate–high risk group for all endpoints except for nephropathy (Supplementary material table 1). Sensitivity analyses using the UKPDS risk engine produced similar results for both relative and absolute risk reductions (data not shown). Similar results were also obtained using the SCORE model to estimate the relative and absolute treatment effects for CVD mortality risk groups, as shown in the Supplementary material table 2 and figure 2.

**Table 1.** Baseline characteristics of the ADVANCE study population according to 5-year cardiovascular disease risk group and treatment allocation.

| | Moderate-high CVD risk | | Very high CVD risk | |
|---|---|---|---|---|
| Baseline characteristics | perindopril-indapamide (n=2775) | placebo (n=2821) | perindopril-indapamide (n=2794) | placebo (n=2750) |
| Age (years), mean (sd) | 64.8 (5.92) | 64.7 (6.00) | 66.8 (6.58) | 66.8 (6.73) |
| Female, n (%) | 1451 (52.3) | 1474 (52.3) | 915 (32.8) | 893 (32.5) |
| Age first diagnosis diabetes (years), mean (sd) | 56.8 (8.48) | 56.8 (8.64) | 58.9 (8.78) | 58.9 (8.71) |
| Diabetes duration (years), mean (sd) | 8.04 (6.31) | 7.91 (6.17) | 7.92 (6.50) | 7.88 (6.4) |
| **Previous vascular diseases** | | | | |
| History of major macrovascular disease, n (%) | n/a | n/a | 1798 (64.4) | 1792 (65.2) |
| History of myocardial infarction, n (%) | n/a | n/a | 678 (24.3) | 656 (23.9) |
| History of stroke, n (%) | n/a | n/a | 503 (18.0) | 520 (18.9) |
| History of major microvascular disease, n (%) | 276 (10.0) | 286 (10.1) | 294 (10.5) | 299 (10.9) |
| Blood pressure control | | | | |
| Systolic blood pressure (mmHg), mean (sd) | 139 (18.0) | 139 (17.6) | 151 (23.7) | 151 (23.0) |
| Diastolic blood pressure (mmHg), mean (sd) | 79.1 (10.2) | 78.9 (10.2) | 82.3 (11.6) | 82.2 (11.2) |
| History of currently treated hypertension, n (%) | 1709 (61.6) | 1748 (62.0) | 2093 (74.9) | 2105 (76.6) |
| **Other major risk factors** | | | | |
| Current smoking, n (%) | 296 (10.7) | 318 (11.3) | 508 (18.2)* | 560 (20.4)* |
| Left ventricular hypertrophy, n (%) | 45 (1.6) | 55 (2.0) | 356 (12.8) | 362 (13.2) |
| Serum haemoglobin $A_{1c}$ concentration (%), median (IQR) | 7.2 (6.4-8.2) | 7.2 (6.5-8.2) | 7.2 (6.5-8.2) | 7.2 (6.5-8.3) |
| Serum total cholesterol (mmol/l) , mean (sd) | 5.22 (1.13) | 5.16 (1.12) | 5.21 (1.23) | 5.21 (1.28) |
| Serum HDL cholesterol (mmol/l) , mean (sd) | 1.33 (0.37) | 1.32 (0.37) | 1.18 (0.31) | 1.19 (0.32) |
| Urinary albumin-creatinine ratio (µg/mg), median (IQR) | 13.8 (7-35) | 13.3 (7-32) | 16.0 (7-46) | 17.6 (8-49) |
| Body mass index ($kg^2$/m), mean (sd) | 28.2 (5.52) | 28.2 (5.39) | 28.5 (4.89) | 28.5 (4.89) |

*Indicates whether baseline characteristic is significantly different ($p<0.05$) between perindopril-indapamide and placebo arm

**Table 2a.** Treatment therapies of the ADVANCE study population according at registration and at the end of follow-up for the moderate-high CVD risk group.

| | Registration visit | | End of follow-up | |
|---|---|---|---|---|
| | perindopril-indapamide | placebo | perindopril-indapamide | placebo |
| **Blood pressure lowering drugs** | | | | |
| Perindopril, n (%) | 183 (7) | 170 (6) | 993 (40) | 1264 (51) |
| Other ACE-I n (%) | 789 (28) | 859 (30) | 93 (4) | 97 (4) |
| ARB, n (%) | 137 (5) | 153 (5) | 190 (8) | 290 (12) |
| B-blockers, n (%) | 460 (16) | 460 (17) | 594 (24) | 709 (28) |
| Calcium antagonists, n (%) | 714 (26) | 763 (27) | 669 (27) | 926 (37) |
| Thiazides, n (%) | 385 (14) | 388 (14) | 68 (3) | 101 (4) |
| Other diuretics, n (%) | 221 (8) | 218 (8) | 273 (11) | 307 (12) |
| Other BP lowering drugs, n (%) | 327 (12) | 337 (12) | 204 (8) | 310 (12) |
| **Other drugs** | | | | |
| Aspirin, n (%0 | 901 (32) | 881 (31) | 1220 (49) | 1192 (48) |
| Other antiplatelets, n(%) | 59 (2) | 70 (2) | 86 (3) | 87 (3) |
| Statins, n (%) | 600 (22) | 652 (23) | 975 (40) | 990 (40) |
| Other lipid modifying drugs, n (%) | 244 (9) | 238 (8) | 194 (8) | 161 (6) |
| Glicazide MR, n(%) | 169 (6) | 177 (6) | 1160 (47) | 1151 (46) |
| Other sulphonylurea, n (%) | 1771 (64) | 1797 (64) | 723 (29) | 776 (31) |
| Metformin, n (%) | 1770 (64) | 1768 (63) | 1727 (70) | 1828 (74) |
| Insulin, n (%) | 49 (2) | 38 (1) | 844 (34) | 774 (31) |

**Table 2b.** Treatment therapies of the ADVANCE study population according at registration and at the end of follow-up for the very high CVD risk group.

| | Registration visit | | End of follow-up | |
|---|---|---|---|---|
| | perindopril-indapamide | placebo | perindopril-indapamide | placebo |
| Blood pressure lowering drugs | | | | |
| Perindopril, n (%) | 307 (11) | 279 (10) | 1134 (49) | 1325 (60) |
| Other ACE-I n (%) | 1125 (40) | 1110 (40) | 138 (6) | 115 (5) |
| ARB, n (%) | 152 (5) | 167 (6) | 263 (11) | 330 (15) |
| B-blockers, n (%) | 884 (32) | 925 (34) | 900 (39) | 963 (43) |
| Calcium antagonists, n (%) | 955 (34) | 995 (36) | 861 (37) | 1118 (50) |
| Thiazides, n (%) | 400 (14) | 419 (15) | 88 (4) | 112 (5) |
| Other diuretics, n (%) | 375 (13) | 359 (13) | 401 (17) | 445 (20) |
| Other BP lowering drugs, n (%) | 373 (14) | 346 (13) | 259 (11) | 327 (15) |
| Other drugs | | | | |
| Aspirin, n (%) | 1544 (55) | 1569 (57) | 1463 (63) | 1383 (62) |
| Other antiplatelets, n(%) | 178 (6) | 199 (7) | 206 (9) | 183 (8) |
| Statins, n (%) | 938 (34) | 956 (35) | 1152 (50) | 1141 (51) |
| Other lipid modifying drugs, n (%) | 228 (8) | 226 (8) | 198 (9) | 147 (7) |
| Glicazide MR, n(%) | 264 (9) | 255 (9) | 1049 (45) | 1023 (46) |
| Other sulphonylurea, n (%) | 1800 (64) | 1723 (63) | 741 (32) | 705 (32) |
| Metformin, n (%) | 1630 (58) | 1584 (58) | 1595 (69) | 1554 (70) |
| Insulin, n (%) | 31 (1) | 41 (1) | 737 (32) | 657 (30) |

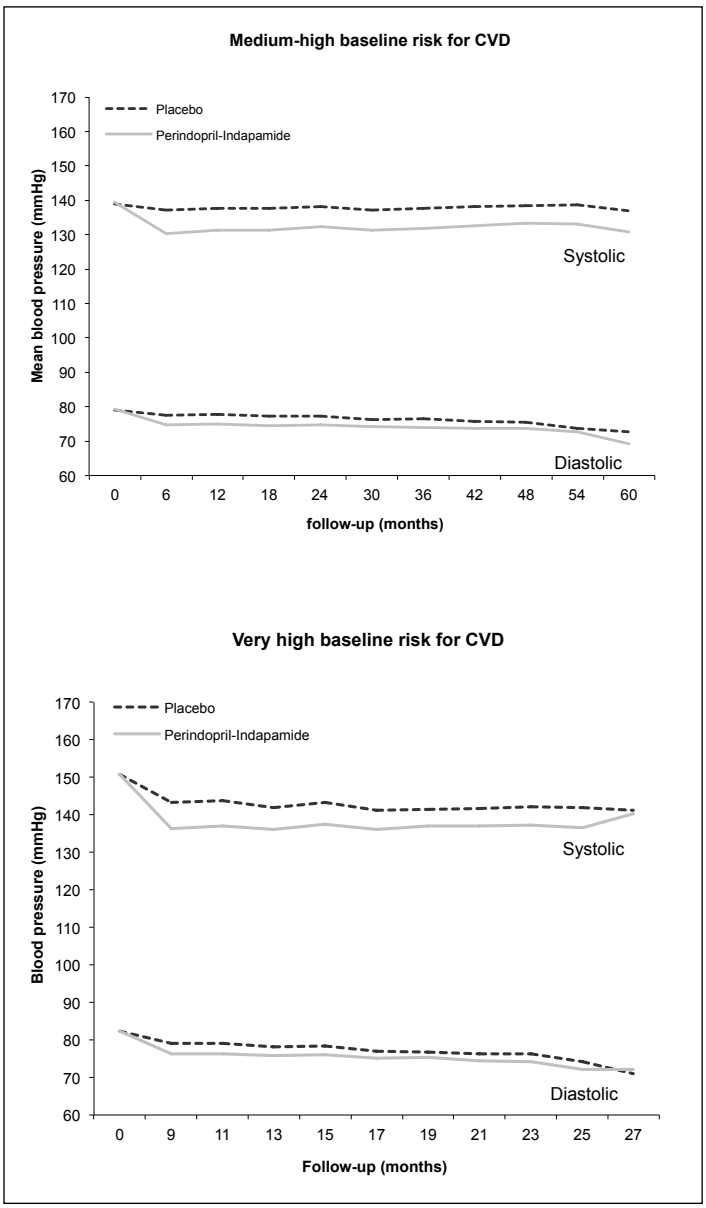


**Figure 1. Mean blood pressure split out by treatment arm and CVD risk. Systolic and diastolic blood pressure split out by 5-year CVD risk.** Grey solid lines represent the Perindopril-Indapamide group, while the black dashed lines represent the placebo arm.

| CVD Risk groups | N of events (%) | | Favours Perindopril-Indapamide | Favours Placebo | Hazard ratio (95% CI) | P for interaction |
|---|---|---|---|---|---|---|
| | Perindopril -Indapamide | Placebo | | | | |
| **Combined macro+micro** | | | | | | |
| Moderate-high | 333 (12.0) | 378 (13.4) | | | 0.89 (0.77 to 1.03) | 0.74 |
| Very high | 528 (18.9) | 560 (20.4) | | | 0.92 (0.81 to 1.03) | |
| Overall | 861 (15.5) | 938 (16.8) | | | 0.91 (0.83 to 1.00) | |
| **Macrovascular event** | | | | | | |
| Moderate-high | 148 (5.3) | 161 (5.7) | | | 0.93 (0.74 to 1.16) | 0.83 |
| Very high | 332 (11.9) | 359 (13.1) | | | 0.90 (0.78 to 1.05) | |
| Overall | 480 (8.6) | 520 (9.3) | | | 0.92 (0.81 to 1.04) | |
| **Microvascular event** | | | | | | |
| Moderate-high | 202 (7.3) | 232 (8.2) | | | 0.87 (0.72 to 1.06) | 0.57 |
| Very high | 237 (8.5) | 245 (8.9) | | | 0.94 (0.79 to 1.13) | |
| Overall | 439 (7.9) | 477 (8.6) | | | 0.91 (0.80 to 1.04) | |
| **All deaths** | | | | | | |
| Moderate-high | 125 (4.5) | 157 (5.6) | | | 0.80 (0.64 to 1.02) | 0.53 |
| Very high | 283 (10.1) | 314 (11.4) | | | 0.88 (0.75 to 1.03) | |
| Overall | 408 (7.3) | 471 (8.5) | | | 0.86 (0.75 to 0.98) | |
| **Cardiovascular death** | | | | | | |
| Moderate-high | 56 (2.0) | 74 (2.6) | | | 0.76 (0.54 to 1.08) | 0.70 |
| Very high | 155 (5.6) | 183 (6.7) | | | 0.83 (0.67 to 1.03) | |
| Overall | 211 (3.8) | 257 (4.6) | | | 0.82 (0.68 to 0.98) | |
| **Total coronary events** | | | | | | |
| Moderate-high | 132 (4.8) | 150 (5.3) | | | 0.89 (0.70 to 1.12) | 0.73 |
| Very high | 336 (12.0) | 385 (14.0) | | | 0.84 (0.73 to 0.98) | |
| Overall | 468 (8.4) | 535 (9.6) | | | 0.86 (0.76 to 0.98) | |
| **Total cerebrovascular events** | | | | | | |
| Moderate-high | 107 (3.9) | 110 (3.9) | | | 0.98 (0.75 to 1.28) | 0.64 |
| Very high | 179 (6.4) | 193 (7.0) | | | 0.90 (0.74 to 1.11) | |
| Overall | 286 (5.1) | 303 (5.4) | | | 0.94 (0.80 to 1.10) | |
| **Nephropathy** | | | | | | |
| Moderate-high | 74 (2.7) | 81 (2.9) | | | 0.92 (0.67 to 1.26) | 0.38 |
| Very high | 107 (3.8) | 135 (4.9) | | | 0.77 (0.59 to 0.99) | |
| Overall | 181 (3.3) | 216 (3.9) | | | 0.83 (0.68 to 1.01) | |

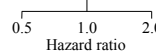


**Figure 2. Relative effects of blood pressure lowering across risk groups.**
Effects of randomized treatment on vascular disease and mortality events in subgroups according to 5-year predicted CVD risk. Solid boxes represent point estimates with the area proportional to number of events for the subgroups. The horizontal line represents the 95% CI. The diamonds are the overall effects for all endpoints.

**Table 3.** Absolute risk reduction by subgroups of CVD risk.

| CVD risk groups | Cumulative incidence rate for study period | | ARR n per 1000 persons (95% CI) | P-value difference in ARR |
|---|---|---|---|---|
| | perindopril-indapamide | placebo | | |
| **Combined macro+micro** | | | | 0.962 |
| Moderate-high | 0.120 | 0.134 | 14.0 (-3.4 to 31.4) | |
| Very high | 0.189 | 0.204 | 14.7 (-6.3 to 35.6) | |
| **Macrovascular event** | | | | 0.459 |
| Moderate-high | 0.053 | 0.057 | 3.7 (-8.2 to 15.7) | |
| Very high | 0.119 | 0.131 | 11.7 (-5.7 to 29.1) | |
| **Microvascular event** | | | | 0.619 |
| Moderate-high | 0.073 | 0.082 | 9.4 (-4.6 to 23.5) | |
| Very high | 0.085 | 0.089 | 4.3 (-10.6 to 19.1) | |
| **All deaths** | | | | 0.822 |
| Moderate-high | 0.045 | 0.056 | 10.6 (-0.8 to 22.1) | |
| Very high | 0.101 | 0.114 | 12.9 (-3.4 to 29.2) | |
| **Cardiovascular death** | | | | 0.508 |
| Moderate-high | 0.020 | 0.026 | 6.1 (-1.8 to 13.9) | |
| Very high | 0.056 | 0.067 | 11.1 (-1.5 to 23.7) | |
| **Total coronary events** | | | | 0.189 |
| Moderate-high | 0.048 | 0.053 | 5.6 (-5.9 to 17.1) | |
| Very high | 0.120 | 0.140 | 19.7 (2.0 to 37.5) | |
| **Total cerebrovascular events** | | | | 0.503 |
| Moderate-high | 0.039 | 0.039 | 0.4 (-9.7 to 10.6) | |
| Very high | 0.064 | 0.070 | 6.1 (-7.1 to 19.3) | |
| **Nephropathy** | | | | 0.213 |
| Moderate-high | 0.027 | 0.029 | 2.0 (-6.6 to 10.6) | |
| Very high | 0.038 | 0.049 | 10.8 (0.0 to 21.6) | |

## Discussion

In this study of 11,140 participants with type 2 diabetes from the ADVANCE trial, relative treatment effects of routine blood pressure lowering with the fixed combination of perindopril and indapamide on CVD were consistent across subgroups defined by initial cardiovascular risk score. We also observed a trend toward greater absolute risk reductions in participants with very high initial cardiovascular risk compared to participants with moderate–high risk, though this was not significant. In contrast the reverse trend was observed for microvascular events, where the absolute treatment effects were non-significantly greater in the lower risk group.

Previous studies focusing on the ADVANCE trial have shown a consistency in relative treatment effect across risk groups defined by individual risk factors, such as albuminuria[19], age[20] and cognition.[21] We have now shown that the treatment effects of blood pressure lowering are consistent across CVD risk groups defined by a combination of risk factors, that is, by the total absolute cardiovascular risk.

Recently, there has been a shift from focusing on single risk factors to multiple risk factors for determining appropriate treatment strategies in routine clinical practice.[22] Observational studies have shown that several risk factors contribute to the cardiovascular disease risk.[23] People who are at low risk based on a single risk factor may be at high risk for developing cardiovascular disease when risk is calculated on the basis of multiple risk factors.[22] The absolute difference in risk may vary more than 20-fold in patients who have the same blood pressure and the same cholesterol levels.[24-26] Therefore guidelines now recommend multi-variable risk models to determine treatment strategies. However, the effects of such approaches have not been investigated in patients with type 2 diabetes. Our results show that although the relative risk reductions are very similar across CVD risk groups, the absolute risk reductions for the high risk group appear to be greater for macrovascular events and smaller for microvascular events. However the trend for microvascular events was reversed, which might be explained by competing risk. Since patients who are at a very high risk for developing cardiovascular disease might live longer and are therefore susceptible for microvascular disease. Another explanation is that the Framingham risk score, which was designed to predict major cardiovascular events, is not suitable for predicting microvascular events. The latter may also explain the lower magnitude absolute risk reduction observed for microvascular events within

risk groups as opposed to macrovascular events. It is also important to note that the ADVANCE blood pressure intervention as previously reported,[16] had no separately significant effect on eye events: one of the main components of the microvascular outcome in the trial.

Other studies have found comparable results. In a much smaller population with diabetes, the microHOPE study showed that relative risk reductions achieved by blood pressure lowering, were similar across higher risk subgroups (with a history of macrovascular disease and/or microalbuminuria) and lower risk subgroups (without a history of macrovascular disease and/or microalbuminuria).[25] The systolic hypertension in the elderly program (SHEP) study included elderly participants with normal glucose tolerance, but with systolic hypertension, and calculated their CVD risk using the global risk score, which is based on Framingham. They observed much higher CVD event rates in high risk groups, and the number-needed-to-treat (NNT) to prevent one cardiovascular event decreased progressively at higher predicted CVD risk.[27] A simulation study focusing on patients with diabetes found similar results.[28] Combining these results with our study suggests that similar relative benefits may be achieved by treating patients similarly regardless of their initial CVD risk, but absolute benefits will be greater in patients at highest risk.

The strengths of our study include the large sample size and the recruitment of participants from around the world. Another strength is the similarity of the results obtained with sensitivity analyses using a number of different risk equations such as the UKPDS and SCORE equations. Some limitations need to be highlighted. First, the ability of the Framingham equation to accurately predict CVD in participants with type 2 diabetes enrolled in the ADVANCE study was only moderate as previously reported.[29] However, as the Framingham equation is the most widely used prediction model in clinical practice, it was felt to be the most suitable model for use in this study. Second, the power of this study to detect small changes in relative risk across the broader risk groups was limited due to the study necessarily including patients with type 2 diabetes who are considered at increased risk for cardiovascular events. Third, the differences in absolute risk reduction between the two risk groups were not significant, reflecting at least in part limitations in statistical power due to the small number of events occurring in each group. Lastly the systematic coronary risk evaluation model,[13] derived from a broader population without accounting for diabetes status may be less suitable for application in people with diabetes.

In conclusion, relative effects of blood pressure lowering on macrovascular and microvascular outcomes were similar across cardiovascular risk groups among participants with type 2 diabetes. However, absolute risk reductions for macrovascular outcomes tended to be greater in the very high risk group compared to the moderate–high risk group, indicating that greater absolute benefits might be achieved in patients with diabetes at highest risk. It is therefore important to identify these patients and treat them intensively in order to improve their outcomes.

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## Supplementary materials

**Supplementary materials Table 1.** Absolute risk reduction by subgroups of CVD. Excluding patients with a history of macrovascular disease.

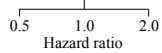
| CVD risk groups | cumulative incidence rate for study period | | Absolute risk reduction n per 1000 persons (95% CI) | P-value for difference in ARR |
|---|---|---|---|---|
| | perindopril-indapamide | placebo | | |
| Combined macro+micro | | | | 0.633 |
| Moderate-high | 0.120 | 0.134 | 14.0 (-3.4 to 31.4) | |
| Very high | 0.166 | 0.189 | 23.3 (-10.6 to 57.1) | |
| Macrovascular event | | | | 0.529 |
| Moderate-high | 0.053 | 0.057 | 3.7 (-8.2 to 15.7) | |
| Very high | 0.094 | 0.108 | 13.1 (-13.6 to 39.9) | |
| Microvascular event | | | | 0.824 |
| Moderate-high | 0.073 | 0.082 | 9.4 (-4.6 to 23.5) | |
| Very high | 0.084 | 0.097 | 12.7 (-12.7 to 38.2) | |
| All deaths | | | | 0.390 |
| Moderate-high | 0.045 | 0.056 | 10.6 (-0.8 to 22.1) | |
| Very high | 0.091 | 0.115 | 23.5 (-3.5 to 50.4) | |
| CVD death | | | | 0.703 |
| Moderate-high | 0.020 | 0.026 | 6.1 (-1.8 to 13.9) | |
| Very high | 0.041 | 0.051 | 10.0 (-8.6 to 28.6) | |
| Total coronary | | | | 0.316 |
| Moderate-high | 0.048 | 0.053 | 5.6 (-5.9 to 17.1) | |
| Very high | 0.080 | 0.100 | 19.9 (-5.5 to 45.3) | |
| Total CVA | | | | 0.681 |
| Moderate-high | 0.039 | 0.039 | 0.4 (-9.7 to 10.6) | |
| Very high | 0.047 | 0.052 | 5.0 (-14.3 to 24.3) | |
| Nephropathy | | | | 0.974 |
| Moderate-high | 0.027 | 0.029 | 2.0 (-6.6 to 10.6) | |
| Very high | 0.043 | 0.045 | 1.7 (-16.5 to 19.9) | |

**Supplementary materials Table 2.** Absolute risk reduction by subgroups of CVD mortality calculated using SCORE.

| CVD risk groups | Cumulative incidence rate for study period | | Absolute risk reduction n per 1000 persons (95% CI) | P-value for difference in ARR |
|---|---|---|---|---|
| | perindopril-indapamide | placebo | | |
| Combined macro+micro | | | | 0.778 |
| Moderate-high | 0.125 | 0.141 | 16.1 (-1.9 to 34.1) | |
| Very high | 0.183 | 0.195 | 12.1 (-8.2 to 32.5) | |
| Macrovascular event | | | | 0.492 |
| Moderate-high | 0.054 | 0.058 | 3.8 (-8.4 to 16.0) | |
| Very high | 0.117 | 0.128 | 11.1 (-5.9 to 28.2) | |
| Microvascular event | | | | 0.244 |
| Moderate-high | 0.077 | 0.090 | 13.0 (-1.7 to 27.6) | |
| Very high | 0.081 | 0.081 | 0.08 (-13.4 to 15.0) | |
| All deaths | | | | 0.512 |
| Moderate-high | 0.043 | 0.051 | 8.3 (-2.9 to 19.5) | |
| Very high | 0.102 | 0.117 | 14.9 (-1.4 to 31.1) | |
| CVD death | | | | 0.302 |
| Moderate-high | 0.020 | 0.024 | 4.5 (-3.3 to 12.3) | |
| Very high | 0.055 | 0.067 | 12.3 (-0.2 to 24.7) | |
| Total coronary | | | | 0.364 |
| Moderate-high | 0.045 | 0.053 | 7.5 (-4.0 to 18.9) | |
| Very high | 0.121 | 0.138 | 17.2 (-0.3 to 34.6) | |
| Total CVA | | | | 0.501 |
| Moderate-high | 0.039 | 0.039 | 0.3 (-10.1 to 10.6) | |
| Very high | 0.063 | 0.069 | 6.0 (-6.9 to 18.8) | |
| Nephropathy | | | | 0.210 |
| Moderate-high | 0.028 | 0.030 | 1.9 (-7.0 to 10.8) | |
| Very high | 0.037 | 0.048 | 10.6 (0.2 to 21.1) | |

Medium CVD mortality risk: defined as a risk of <10% calculated using the SCORE chart (n=5463). High CVD mortality risk: defined as a risk of >10% calculated using the SCORE chart (n=5677).

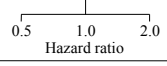
| CVD Risk groups | N of events (%) | | Favours Perindopril-Indapamide | Favours Placebo | Hazard ratio (95% CI) | P for interaction |
|---|---|---|---|---|---|---|
| | Perindopril -Indapamide | Placebo | | | | |
| **Combined macro+micro** | | | | | | |
| Moderate-high | 333 (12.0) | 378 (13.4) | | | 0.89 (0.77 to 1.03) | 0.73 |
| Very high | 165 (16.6) | 181 (18.9) | | | 0.85 (0.69 to 1.05) | |
| Overall | 498 (13.2) | 559 (14.8) | | | 0.88 (0.78 to 0.99) | |
| **Macrovascular event** | | | | | | |
| Moderate-high | 148 (5.3) | 161 (5.7) | | | 0.93 (0.74 to 1.16) | 0.69 |
| Very high | 94 (9.4) | 103 (10.8) | | | 0.86 (0.65 to 1.14) | |
| Overall | 242 (6.4) | 264 (7.0) | | | 0.91 (0.76 to 1.08) | |
| **Microvascular event** | | | | | | |
| Moderate-high | 202 (7.3) | 232 (8.2) | | | 0.87 (0.72 to 1.06) | 0.84 |
| Very high | 84 (8.4) | 93 (9.7) | | | 0.84 (0.63 to 1.13) | |
| Overall | 286 (7.6) | 325 (8.6) | | | 0.87 (0.74 to 1.02) | |
| **All deaths** | | | | | | |
| Moderate-high | 125 (4.5) | 157 (5.6) | | | 0.80 (0.64 to 1.02) | 0.90 |
| Very high | 91 (9.1) | 110 (11.5) | | | 0.78 (0.59 to 1.04) | |
| Overall | 216 (5.7) | 267 (7.1) | | | 0.80 (0.67 to 0.96) | |
| **CVD death** | | | | | | |
| Moderate-high | 56 (2.0) | 74 (2.6) | | | 0.76 (0.54 to 1.08) | 0.88 |
| Very high | 41 (4.1) | 49 (5.1) | | | 0.80 (0.53 to 1.20) | |
| Overall | 97 (2.6) | 123 (3.3) | | | 0.78 (0.60 to 1.02) | |
| **Total coronary events** | | | | | | |
| Moderate-high | 132 (4.8) | 150 (5.3) | | | 0.89 (0.70 to 1.12) | 0.52 |
| Very high | 80 (8.0) | 96 (10.0) | | | 0.78 (0.58 to 1.05) | |
| Overall | 212 (5.6) | 246 (6.5) | | | 0.85 (0.71 to 1.02) | |
| **Total cerebrovascular events** | | | | | | |
| Moderate-high | 107 (3.9) | 110 (3.9) | | | 0.98 (0.75 to 1.28) | 0.71 |
| Very high | 47 (4.7) | 50 (5.2) | | | 0.89 (0.60 to 1.33) | |
| Overall | 154 (4.1) | 160 (4.2) | | | 0.96 (0.77 to 1.19) | |
| **Nephropathy** | | | | | | |
| Moderate-high | 74 (2.7) | 81 (2.9) | | | 0.92 (0.67 to 1.26) | 0.94 |
| Very high | 43 (4.3) | 43 (4.5) | | | 0.93 (0.61 to 1.42) | |
| Overall | 117 (3.1) | 124 (3.3) | | | 0.93 (0.72 to 1.20) | |




**Supplementary materials Figure 1. Relative effects of blood pressure lowering across risk groups excluding patients with a history of macrovascular disease.**

Effects of randomized treatment on vascular disease and mortality events in subgroups according to 5-year predicted CVD risk, excluding patients with a history of macrovascular disease at baseline. Solid boxes represent point estimates with the area proportional to number of events for the subgroups. The horizontal line represents the 95% CI. The diamonds are the overall effects for all endpoints.

| Risk groups of CVD mortality | N of events (%) Perindopril -Indapamide | Placebo | Favours Perindopril-Indapamide | Favours Placebo | Hazard ratio (95% CI) | P for interaction |
|---|---|---|---|---|---|---|
| **Combined macro+micro** | | | | | | |
| Moderate-high | 339 (12.5) | 387 (14.1) | | | 0.88 (0.76 to 1.02) | 0.59 |
| Very high | 522 (19.5) | 522 (18.3) | | | 0.92 (0.81 to 1.03) | |
| Overall | 861 (15.5) | 938 (16.8) | | | 0.91 (0.83 to 1.00) | |
| **Macrovascular event** | | | | | | |
| Moderate-high | 147 (5.4) | 159 (5.8) | | | 0.93 (0.74 to 1.17) | 0.82 |
| Very high | 333 (11.7) | 361 (12.8) | | | 0.90 (0.78 to 1.05) | |
| Overall | 480 (8.6) | 520 (9.3) | | | 0.92 (0.81 to 1.04) | |
| **Microvascular event** | | | | | | |
| Moderate-high | 209 (7.7) | 247 (9.0) | | | 0.85 (0.70 to 1.02) | 0.26 |
| Very high | 230 (8.1) | 230 (8.1) | | | 0.98 (0.82 to 1.18) | |
| Overall | 439 (7.9) | 477 (8.6) | | | 0.91 (0.80 to 1.04) | |
| **All deaths** | | | | | | |
| Moderate-high | 116 (4.3) | 140 (5.1) | | | 0.83 (0.65 to 1.07) | 0.80 |
| Very high | 292 (10.2) | 331 (11.7) | | | 0.86 (0.74 to 1.01) | |
| Overall | 408 (7.3) | 471 (8.5) | | | 0.86 (0.75 to 0.98) | |
| **Cardiovascular death** | | | | | | |
| Moderate-high | 54 (2.0) | 67 (2.4) | | | 0.81 (0.57 to 1.16) | 0.99 |
| Very high | 157 (5.5) | 190 (6.7) | | | 0.81 (0.66 to 1.00) | |
| Overall | 211 (3.8) | 257 (4.6) | | | 0.82 (0.68 to 0.98) | |
| **Total coronary events** | | | | | | |
| Moderate-high | 123 (4.5) | 145 (5.3) | | | 0.85 (0.67 to 1.08) | 0.93 |
| Very high | 345 (12.1) | 390 (13.8) | | | 0.86 (0.74 to 0.99) | |
| Overall | 468 (8.4) | 535 (9.6) | | | 0.86 (0.76 to 0.98) | |
| **Total cerebrovascular events** | | | | | | |
| Moderate-high | 107 (3.9) | 109 (4.0) | | | 0.99 (0.76 to 1.29) | 0.60 |
| Very high | 179 (6.3) | 194 (6.9) | | | 0.90 (0.74 to 1.11) | |
| Overall | 286 (5.1) | 303 (5.4) | | | 0.94 (0.80 to 1.10) | |
| **Nephropathy** | | | | | | |
| Moderate-high | 76 (2.8) | 82 (3.0) | | | 0.92 (0.68 to 1.26) | 0.34 |
| Very high | 105 (3.7) | 134 (4.8) | | | 0.76 (0.59 to 0.98) | |
| Overall | 181 (3.3) | 216 (3.9) | | | 0.83 (0.68 to 1.01) | |




**Supplementary materials Figure 2. Relative effects of blood pressure lowering across risk groups of CVD mortality calculated using SCORE.**

Effects of randomized treatment of vascular disease and mortality events in subgroups according to 10-year predicted risk of CVD mortality. Solid boxes represent point estimates with the area proportional to number of events for the subgroups. The horizontal line represents the 95% CI. The diamonds are the overall effects for all endpoints.

# Chapter 6

## Non-fasting lipids and risk of cardiovascular disease in patients with diabetes mellitus

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*Diabetologia 2011; 54(1): 73-77*

## Abstract

**Aims:** The aim of this study was to examine the effect of postprandial time on the associations and predictive value of non-fasting lipid levels and cardiovascular disease risk in participants with diabetes.

**Methods:** This study was conducted among 1,337 participants with diabetes from the Dutch and German (Potsdam) contributions to the European Prospective Investigation into Cancer and Nutrition. At baseline, total cholesterol, LDL- and HDL-cholesterol and triacylglycerol concentrations were measured and the ratio of total cholesterol/HDL-cholesterol was calculated. Participants were followed for incidence of cardiovascular disease.

**Results:** Lipid concentrations changed minimally with increasing postprandial time, except for triacylglycerol which was elevated just after a meal and declined over time (1.86 at 0.1 h to 1.33 at >6 h, p for trend <0.001). During a mean follow-up of 8 years, 116 cardiovascular events were documented. After adjustment for potential confounders, triacylglycerol (HR for third tertile compared with first tertile ($HR_{t3\ to1}$), 1.73 [95% CI 1.04, 2.87]), HDL-cholesterol ($HR_{t3to1}$, 0.41 [95% CI 0.23, 0.72]) and total cholesterol/HDL-cholesterol ratio ($HR_{t3to1}$, 1.65 [95% CI 0.95, 2.85]) were associated with cardiovascular disease, independent of postprandial time. Cardiovascular disease risk prediction using the UK Prospective Diabetes Study risk engine was not affected by postprandial time.

**Conclusions:** Postprandial time did not affect associations between lipid concen-trations and cardiovascular disease risk in patients with diabetes, nor did it influence prediction of cardiovascular disease. Therefore, it may not be necessary to use fasting blood samples to determine lipid concentrations for cardiovascular disease risk prediction in patients with diabetes.

## Introduction

Guidelines recommend measuring fasting lipid profiles for cardiovascular disease (CVD) risk assessment.[1] The main reason for measurement of lipid concentrations during the fasting state is the possible increase in triacylglycerol levels up to 9 h after a meal. However, three different studies did not find a significant change in total cholesterol, HDL- or LDL-cholesterol or triacylglycerol over postprandial time.[2-4] This suggests that non-fasting lipid levels can be used to assess CVD risk in the general population. However, this may be different for patients with diabetes. Cholesterol and triacylglycerol concentrations differ between patients with diabetes and people with normal glucose tolerance. Patients with diabetes tend to have higher total cholesterol and triacylglycerol levels and lower HDL-cholesterol levels.[5] Furthermore, lipid responses after eating a meal by patients with diabetes are stronger compared to people with normal glucose tolerance.[5] So far, the effect of fasting time on the use of lipid levels for prediction of CVD risk in patients with diabetes has not been investigated.

Therefore, we examined the effect of time since last meal or drink on the associations of lipid levels and CVD risk in patients with diabetes. Furthermore, we assessed the effect of postprandial time on prediction of CVD risk in patients with diabetes using the UK Prospective Diabetes Study (UKPDS) risk engine.[6]

## Methods

The study population consisted of participants with diabetes from the Dutch and Potsdam (Germany) contributions to the European Prospective Investigation into Cancer and Nutrition (EPIC-NL and EPIC-Potsdam, n=67,627).[7;8] Both are observational cohort studies of the general population. Participants from EPIC-NL were all confirmed diagnosed type 2 diabetes patients (total n=387), verified through medical records of the general practitioner or pharmacist.[9] In EPIC-Potsdam 265 patients were confirmed with type 2 diabetes and 685 patients had an unspecified diabetes type (total n=950), verified through repeated self-report in follow-up questionnaires.

In total 1,337 participants with diabetes at baseline were used for the analyses. Exclusion criteria were history of CVD (n=239) and missing values on lipid concentrations (n=169). All participants gave written informed consent prior to study inclusion. Both cohorts were approved

by local ethical committees. At baseline, participants filled out a general questionnaire regarding demographic characteristics and presence of chronic diseases. Body weight, height and blood pressure were measured. Postprandial time was defined as time since last meal or drink, which was recorded when the participants provided a blood sample. Total cholesterol, HDL and LDL-cholesterol and triacylglycerol concentrations were measured with the automatic ADVIA 1650 analyser (Siemens Medical Solutions, Erlangen, Germany) in EPIC Potsdam and an auto-analyser (LX20; Beckman Coulter, Mijdrecht, the Netherlands) was used for the measurements of the cholesterol concentration for EPIC-NL participants. HbA1c concentrations were measured in frozen erythrocytes using an immunoturbidimetric latex test.

Participants were followed for incidence of CVD using registries in the Netherlands[9] and follow-up questionnaires with subsequent verification in Germany. Diagnosis of CVD was coded according to the International Classification of Diseases (ICD-9: ICD codes 410-414, 430-438; ICD-10: ICD codes I20-I25, I60-I67, I69).

Missing values for any of the confounders (ranging from 0.1% to 3.4%) were imputed using single imputation. Medians and interquartile ranges of lipid concentrations were examined across four categories of postprandial time (0–2, 2–4, 4–6 and >6 h) and plotted. Also categorical and continuous correlations between postprandial time and lipid concentrations were assessed. The HR and 95% CI were calculated for each tertile, with the lowest tertile as reference. Two different models were constructed. The first model was corrected for age, sex, smoking, systolic blood pressure, BMI, alcohol, HbA1c concentration, duration since diagnosis of diabetes, energy intake, physical activity, diabetes medication and cohort. The second model was further adjusted for postprandial time as a continuous variable. Furthermore, HRs for standard deviation increase in lipid concentration were calculated across tertiles of postprandial time. Models were not adjusted for statin use because only two patients were using statins.

To investigate the difference in CVD risk prediction over fasting time, patients were divided into two groups, according to their postprandial time. A cut-off time between the two groups of 3 h was used because most patients had a postprandial time up to 3 h and previous studies have shown that lipid concentrations after eating a normal meal might be elevated for 3–4 h.[3;4] The UKPDS risk engine was used to calculate 5 year CVD risk.[6] Discrimination was examined using the c-statistic. Calibration was examined using the Hosmer–Lemeshow $\chi 2$ test.

## Results

Baseline characteristics across tertiles of total cholesterol/HDL-cholesterol ratio have been examined. Higher total cholesterol/HDL-cholesterol ratio was associated with a low education level (first tertile, 34%; third tertile, 41%), higher mean BMI (kg/m$^{2)}$ (first, 28.0; third, 30.2), mean systolic blood pressure (mmHg; first, 139; third, 143) and percentage HbA1c (first, 7.74; third, 8.50). In total, 73.9% of the participants were receiving either oral diabetes medication or insulin. Only triacylglycerol concentrations declined over postprandial time, from 1.86 mmol/l at 0.1 h to 1.33 mmol/l at >6 h (p value for trend <0.001). While total cholesterol was 4.84 mmol/l at 0.1 h after a meal and 4.51 mmol/l after >6 h, HDL-cholesterol changed from 1.02 to 1.01 mmol/l and LDL-cholesterol from 2.83 to 2.79 mmol/l (Figure 1). Correlations between time since last meal or drink and lipid concentrations were only significant for triacylglycerols (p<0.001 for both continuous and



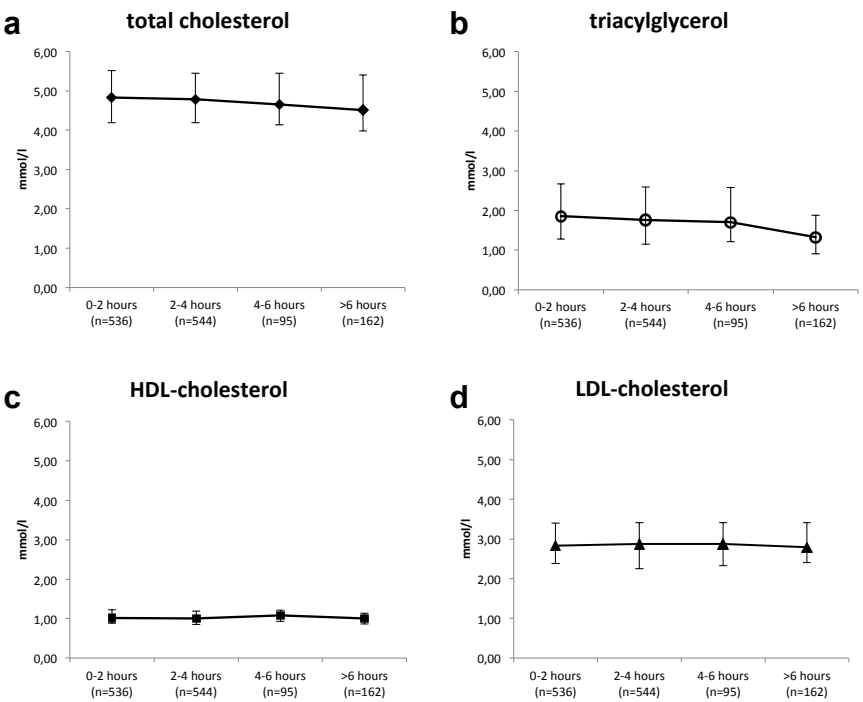


**Figure 1.** Median concentrations over postprandial time for concentrations of (**a**) total cholesterol, p-value=0.003; (**b**) triacylglycerol, p-value,0.001; (**c**) HDL cholesterol, p-value=0.23 and (**d**) LDL cholesterol, p-value=0.88. Error bars represent the interquartile range.

categorical correlations). Continuous correlations between total cholesterol and postprandial time were significant (p=0.04), while categorical correlations were not (p=0.23).
During a mean follow-up of 8 years, 116 incident cases of CVD were documented, of which 78 were coronary heart disease events. Increased triacylglycerol concentrations were associated with increased risk of CVD, while an inverse association was observed between levels of HDL-cholesterol and CVD risk (Table 1).

**Table 1.** Hazard ratios and 95% confidence intervals for cardiovascular disease by tertiles of lipid concentrations in 1,337 patients with diabetes mellitus.

| | | Model 1 | Model 2 |
|---|---|---|---|
| | Cases/n | HR (95%CI) | HR (95% CI) |
| **Total cholesterol** | | | |
| Tertile 1 (1.71-4.34) | 31/448 | 1.00 | 1.00 |
| Tertile 2 (4.35-5.21) | 40/442 | 1.15 (0.71-1.85) | 1.16 (0.72-1.87) |
| Tertile 3 (5.22-10.56) | 45/446 | 1.05 (0.64-1.73) | 1.05 (0.64-1.73) |
| P for trend | | 0.88 | 0.88 |
| **Triacylglycerols** | | | |
| Tertile 1 (0.22-1.36) | 25/443 | 1.00 | 1.00 |
| Tertile 2 (1.37-2.24) | 33/446 | 1.09 (0.64-1.87) | 1.11 (0.65-1.90) |
| Tertile 3 (2.25-11.91) | 58/447 | 1.73 (1.04-2.87) | 1.79 (1.07-2.98) |
| P for trend | | 0.01 | 0.01 |
| **HDL cholesterol** | | | |
| Tertile 1 (0.40-0.91) | 53/445 | 1.00 | 1.00 |
| Tertile 2 (0.92-1.14) | 44/438 | 0.96 (0.63-1.45) | 0.95 (0.62-1.45) |
| Tertile 3 (1.14-2.56) | 19/453 | 0.41 (0.23-0.72) | 0.41 (0.23-0.72) |
| P for trend | | 0.002 | 0.002 |
| **LDL cholesterol** | | | |
| Tertile 1 (0.54-2.48) | 37/458 | 1.00 | 1.00 |
| Tertile 2 (2.49-3.18) | 34/437 | 0.79 (0.49-1.28) | 0.79 (0.49-1.28) |
| Tertile 3 ( 3.19-6.62) | 45/441 | 0.89 (0.55-1.42) | 0.87 (0.55-1.40) |
| P for trend | | 0.65 | 0.61 |
| **Ratio total/HDL cholesterol** | | | |
| Tertile 1 (1.73-4.15) | 21/444 | 1.00 | 1.00 |
| Tertile 2 (4.16-5.27) | 42/446 | 1.76 (1.03-3.02) | 1.76 (1.03-3.02) |
| Tertile 3 (5.28-13.82) | 53/446 | 1.65 (0.95-2.85) | 1.65 (0.95-2.86) |
| P for trend | | 0.14 | 0.14 |

**Model 1** adjusted for age, sex, cohort, smoking, systolic blood pressure, BMI, alcohol, HbA1c level, duration since diagnosis of diabetes, energy intake, diabetes medication and physical activity.
**Model 2** adjusted for age, sex, cohort, smoking, systolic blood pressure, BMI, alcohol, HbA1c level, duration since diagnosis of diabetes, energy intake, diabetes medication, physical activity and postprandial time.

Ratio of total cholesterol/HDL-cholesterol was associated with an increased CVD risk. Further adjusting for postprandial time had no effect on the associations (model 2). CVD HR for a standard deviation increase in lipid concentrations did not differ across tertiles of postprandial time (data not shown). The p-value for trend was >0.08 for all lipid concentrations.
Prediction of 5-year CVD risk calculated using UKPDS risk engine did not differ significantly between patients who had their lipid levels measured after a postprandial time of >3 h (n=913) and ≤3 h (n=424). A discrimination of 0.71 (95% CI 0.57, 0.85) for >3 h was only slightly better than 0.67 (95% CI 0.59, 0.75) for ≤3 h. Calibration of the model was poor for both fasting-time durations (p value <0.01 for both time durations).

## Discussion



In this cohort of 1,337 patients with diabetes, lipid concentrations did not change over postprandial time, except for triacylglycerols. Non-fasting lipid concentrations were associated with CVD risk independent of postprandial time. The associations between standard deviation of increase in lipid concentrations and CVD risk did not differ over postprandial time, which further strengthens the hypothesis that associations between lipid concentrations and CVD risk are not affected by postprandial time.
The strengths of this study are its relatively large sample size, validation of diabetes cases and geographical distribution of patients (from Germany and the Netherlands), but some limitations need to be addressed. First, the results may have been influenced by the limited number of patients with a postprandial time >8 h, which is the time limit for complete fasting. However, lipid concentrations did not change over postprandial time, therefore including more patients in complete fasting state would not have changed the results. Second, some differences in measurements between the cohorts may have occurred. However, the analyses were adjusted for the cohorts, and therefore it is unlikely that it affected the results.
Our findings among diabetes patients are in line with observations in the general population,[2-4] although no association between CVD risk and LDL-cholesterol was found, as has been observed in other studies. Associations between triacylglycerols and HDL-cholesterol and CVD were stronger in our study compared with an earlier study by Langsted et al.[3] These differences might be explained by differences in study

population—our study focuses on diabetes patients whereas other studies focused on the general population.
Several studies have suggested that non-fasting lipids might predict CVD risk similarly to or even better than fasting lipids,[2;10] which is now confirmed by our study. Therefore it may be unnecessary to measure fasting blood samples. Fasting requirements make blood sampling more burdensome for patients. It has been suggested that lipid levels might increase after a meal. Our study suggests that lipid levels do not change much in response to eating a normal meal, except for triacylglycerols. Moreover, postprandial time did not affect the ability to predict CVD risk in diabetes patients. This might be explained by the small contribution of lipids in CVD risk prediction models and therefore a slight increase in lipid concentrations after a meal may not substantially alter the risk.[6]
In conclusion, postprandial time did not influence the association of lipid concentrations with CVD in patients with diabetes, nor did it affect the prediction of CVD risk. Therefore it may be unnecessary to use fasting blood samples to determine lipid concentrations for CVD risk prediction in patients with diabetes.



## Acknowledgements

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# Part 2

## Prediction of cardiovascular complications among patients with type 2 diabetes

# Chapter 7

## Prediction models for the risk of cardiovascular disease in patients with type 2 diabetes: a systematic review

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*Heart 2012; 98(5): 360-369*

## Abstract

**Aims:** A recent overview of all CVD models applicable to diabetes patients is not available. The objective was to review the primary prevention studies that focused on the development, validation and impact assessment of a cardiovascular risk model, scores or rules that can be applied to patients with type 2 diabetes.
**Data sources:** Medline was searched from 1966 to 1 April 2011.
**Study selection:** A study was eligible when it described the development, validation or impact assessment of a model that was constructed to predict the occurrence of cardiovascular disease in people with type 2 diabetes, or when the model was designed for use in the general population and included diabetes as a predictor.
**Data extraction:** A standardized form was used to extract all data of the CVD models.
**Results:** 45 prediction models were identified, of which 12 were specifically developed for patients with type 2 diabetes. Only 31% of the risk scores has been externally validated in a diabetes population, with an area under the curve ranging from 0.61 to 0.86 and 0.59 to 0.80 for models developed in a diabetes population and in the general population, respectively. Only one risk score has been studied for its effect on patient management and outcomes. 10% of the risk scores are advocated in national diabetes guidelines.
**Conclusions:** Many cardiovascular risk scores are available that can be applied to patients with type 2 diabetes. A minority of these risk scores has been validated and tested for its predictive accuracy, with only a few showing a discriminative value of >0.80. The impact of applying these risk scores in clinical practice is almost completely unknown, but their use is recommended in various national guidelines.

## Introduction

People with type 2 diabetes have a two-fold increased risk of cardiovascular disease (CVD).[1;2] Guidelines for the management of type 2 diabetes advocate calculating CVD risk to guide the initiation of appropriate treatment.[3-5] Over the past decades many prediction models (or risk scores) have been developed to predict CVD, of which only a small number have been specifically developed for people with type 2 diabetes.[6] However, most prediction models developed for the general population take diabetes into account and can therefore be applied to the diabetes population. The performance of several prediction models has been examined in different populations for their discrimination (ability to discriminate between patients who will get the disease and those who will not) and calibration (ability to correctly quantify the absolute risk), but the outcomes have varied widely.[7-9]

A systematic review by Chamnan et al.[6] provides an overview of CVD prediction models that have been developed in diabetes populations, and prediction models for the general population that have been validated in a diabetes population. However, new prediction models for the diabetes population have been developed since this review, and many more prediction models exist that can be applied to people with diabetes. Moreover, it is unknown whether applying a certain prediction model in clinical practice affects the treatment of patients with diabetes and subsequently improves cardiovascular outcome.

Clinical prediction models need to provide accurate and validated estimates of the risk of the targeted outcome, in order to be useful for clinical decision making. Three stages of prediction modelling can be identified: (1) model development, which includes among other aspects determining the clinically relevant predictors, assigning the relative weights to these predictors and estimating the model's predictive performance, ideally after adjustment for overfitting or optimism with internal validation techniques; (2) assessment of the model's predictive performance in new patients (external validation studies); (3) quantifying whether the use of a prediction model in daily practice indeed improves decision-making and subsequently patient outcome as compared with not using the model (model impact studies).[10-15]

The aim of this study was to identify all CVD prediction models (or scores or rules) that can be applied to patients with type 2 diabetes, and subsequently to assess their status and compliance in relation to the three stages of prediction modelling.

## Methods

We started by systematically searching the literature for all CVD prediction models that can be applied to, or have been developed in, people with type 2 diabetes. Subsequently, we searched specifically for all studies that validated these models in patients with type 2 diabetes, followed by a search for all impact studies of these models and guidelines that incorporated these prediction models.

### Search strategy

*Existing CVD prediction models for patients with diabetes*
At 1 April 2011, Medline was searched using a mixture of MeSH terms and truncated words to identify all papers presenting a CVD prediction model developed in patients with diabetes or that can be applied to individuals with type 2 diabetes. The precise search query is available in the appendix 1 (search term 1).
To identify additional studies we searched our own literature files, previous reviews of cardiovascular prediction models and checked citations. A study was eligible when (1) the prediction model was either developed in people with diabetes or included diabetes as a predictor, (2) the outcome of the prediction model was CVD or a cardiovascular component (ie, coronary heart disease (CHD), heart failure or stroke) and (3) it presented a specific prediction rule/model with sufficient information on all variables to calculate the CVD risk in a different population (beta coefficients of the model or otherwise a scoring system/ graph/score card/nomogram was provided). Exclusion criteria were non-human studies, articles in languages other than English or Dutch, studies presenting a prediction model developed in patients with previous CVD or other vascular condition (eg, hypertensive patients) or studies focusing on the added predictive value of new risk factors to an existing prediction model. Furthermore, we checked the reference list of all retrieved development studies, to determine whether any studies presenting a risk score had been missed.

*External validation studies*
After retrieval of all developed prediction models, we performed a second search to identify all studies that evaluated these models in a new, independent patient sample (search term 2, appendix 1). The resulting studies were added to the validation studies obtained with search term 1. Again, to identify potentially missed studies we searched our own literature files, previous reviews of cardiovascular prediction models and checked citations.

*Impact studies*
To find any impact studies of the retrieved cardiovascular prediction models, we first searched among the publications that were identified through the first and second search strategy. Furthermore, we developed a specific search query for impact studies for each prediction model separately. This strategy was based on search strategy for impact studies developed by Reilly and Evans[16] (search term 3, appendix 1) combined with the specific prediction model's acronym, or if not available the name of the cohort in which the score was developed or first author of the paper.

**Data extraction**
Two authors (SVD and JWJB) independently reviewed all titles, followed by the abstract and full text of the studies. Any disagreements were resolved by a third (APK) and fourth (KGMM) reviewer. A standardized form was used for the data extraction, including outcome of the prediction model, number of events, specifics of the development population, presentation of the prediction model, type of model, results from an internal validation, selection procedure of, and variables included in, the prediction model.
For the data extraction of the external validation studies, a different data extraction sheet was used, including specifics of the validation population, number of events, type of outcome, statistical tests and measures of discrimination and calibration of the prediction model. From the retrieved impact studies additional data were extracted namely, number of subjects, type of intervention, prediction model used in the intervention, type of outcome, number of outcomes and statistical tests.

**Implementation of prediction models in guidelines**
Finally, we searched various guidelines for clinical practice written in English to examine the implementation of the prediction models in countries in which the prediction models have been developed. As there are no strategies available for these types of internet searches, we specifically searched among the guidelines developed by the following organizations that are known to deal with patients with diabetes: fourth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice,[17] the American Diabetes Association[18] National Institute for Health and Clinical Excellence (NICE),[4] Joint British Society (JBS2),[5] Canadian Diabetes Association,[19] the Australian National Vascular Disease Prevention Alliance[20] and International Diabetes Federation (IDF).[21]

## Results

Figure 1 describes the systematic selection process of studies presenting a CVD prediction model applicable to type 2 diabetes patients. After screening 6803 titles, 218 studies remained for abstract screening; main reasons for exclusion were 'etiological or therapeutic research' and 'outcome other than CVD'. After examining the full text, 45 studies remained, of which 12 studies presented a CVD prediction model specifically developed for the diabetes population, and 33 included diabetes as a factor in the model. The majority of these models were developed in a predominantly Caucasian population and 12 were developed in Asian countries (India, China and Japan). The development study samples ranged from 698 to 1.5 million participants.

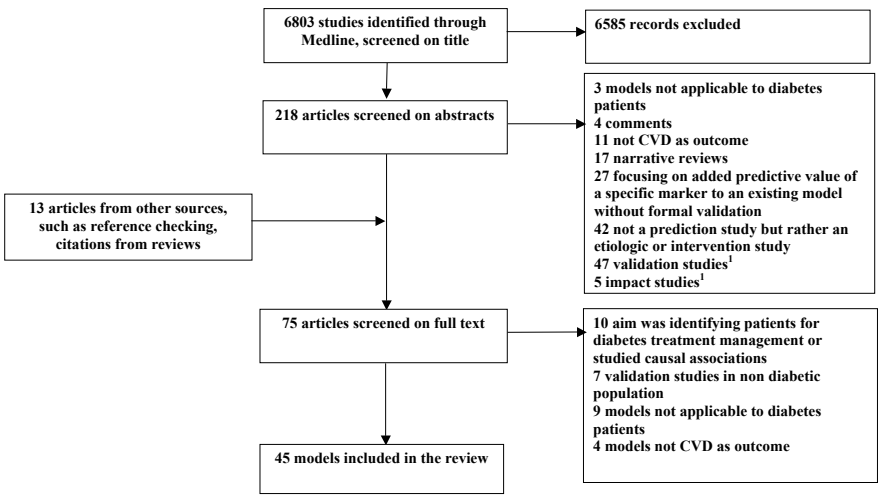


**Figure 1. Flow chart of systematic review of studies presenting a prediction model for cardiovascular disease which can be applied to individuals with type 2 diabetes.**
[1]Studies did not present a new risk score and were therefore excluded during the search for prediction models, but were included during the systematic search for validation studies or impact studies.

### Cardiovascular prediction models developed in diabetes patient populations

Only two prediction models were developed in patients with newly diagnosed diabetes (both from the UK Prospective Diabetes Study (UKPDS study)),[22;23] the other development populations were a mixture of people with varying duration of diagnosed diabetes (Table 1). Six of

these prediction models estimate CHD risk, while four estimate total CVD risk. The majority of the prediction models predicted 5-year risk with an average of eight predictors. The most commonly used predictors in these prediction models were age, sex, duration of diagnosed diabetes, HbA1c concentration and smoking (Supplementary material table 1).
Nine out of 12 studies reported the discrimination of their prediction model, with an area under receiver operating characteristic curve (AUC) ranging from 0.68 to 0.85. Eight studies also reported the calibration: all Hosmer-Lemeshow p values were >0.05, indicating no significant lack of calibration. Only half of these models examined the internal validation (performance of the model in the development population when the prediction model is corrected for overoptimism) using split samples or bootstrapping techniques. All studies reported the original model with the beta coefficients, and two studies additionally presented a risk chart.

**Cardiovascular prediction models developed in general populations including diabetes as predictor**

Prediction models derived from general populations which included diabetes as a predictor used a variety of cardiovascular outcomes: 14 had CHD as the endpoint, 12 had CVD, eight had stroke and three had myocardial infarction (Table 2). Most of these prediction models predicted 10-year risk using an average of eight predictors. The most commonly used predictors, in addition to diabetes, were age, sex, systolic blood pressure, smoking and cholesterol measurements (Supplementary material table 2).
Twenty of 33 studies gave a measure of validation, generally the AUC, which ranged from 0.65 to 0.86. Fourteen studies assessed calibration, with all Hosmer-Lemeshow p-values >0.05. Twelve of these prediction models were internally validated using either split sample, cross validation or bootstrapping techniques. There was a great variety in the way in which the prediction model was presented. The majority presented the original model with the beta coefficients, others presented a scoring chart, nomogram or produced a computerized software program that was available through a website.

**Table 1.** Cardiovascular prediction models specifically developed for patients with type 2 diabetes. Displayed the apparent (i.e. as quantified in the original development study) discrimination and calibration

| | Development population | n events/n total | Type of model | Outcome | Predicted years |
|---|---|---|---|---|---|
| Kengne 2011 (ADVANCE)[24] | NIDDM from 20 countries | 473/7168 | Cox | CVD | 4 |
| Davis 2010 (Fremantle)[25] | NIDDM from Australia | 185/1240 | Logistic | CVD | 5 |
| Elley 2010 (DCS)[26] | NIDDM from New Zealand | 6479/36127 | Cox | CVD and CHD | 5 |
| Cederholm 2008[27] | NIDDM from Sweden | 1482/11646 | Cox | CVD | 5 |
| Yang 2008[28] | NIDDM from China | 351/7067 | Cox | CHD | 5 |
| Yang 2008 (2)[29] | NIDDM from China | 274/7067 | Cox | Heart failure | 5 |
| Yang 2007[30] | NIDDM from China | 332/7209 | Cox | Stroke | 5 |
| Donnan 2006 (DARTS)[31] | NIDDM from Scotland | 243/4569 | Weibull | CHD | 5 |
| Folsom 2003 (ARIC)[32] | NIDDM from US | 128/1273 | Cox | CHD | 10 |
| Kothari 2002 (UKPDS risk engine)[22] | Newly diagnosed NIDDM from UK | 188/4549 | Gompertz | Stroke | Variable |
| | | | | | |
| Stevens 2001 (UKPDS risk engine)[23] | Newly diagnosed NIDDM from UK | NR/4540 | Gompertz | CHD | Variable |
| Yudkin 1999[33] | NIDDM from US | NR/2138 | NR | CHD | 10 |

[1]Discrimination after correction for over fitting, [2]Values of the simplified risk or sum score NIDDM: non-included in the models, see Supplementary material

are the type of model, the outcome, predicted risk period, population in which it has been developed and

| Number of predictors | Apparent discrimination (AUC) | Apparent Calibration (P-value Hosmer-Lemeshow) | Method of internal validation | Presentation of risk model |
|---|---|---|---|---|
| 10 | 0.70<br>0.70[1] | P=0.76 | bootstrapping | Original model and scoring chart |
| 7 | 0.80 | P=0.74 | n.a. | Original model |
| 10<br>9[2] | CVD: 0.68, 0.67[2]<br>CHD: 0.71, 0.71[2] | Good | n.a. | Original model |
| 6 | 0.70[1] | P=0.08[1] | Split sample | Original model |
| 7 | 0.70[1] | Good, p>0.05[1] | Split sample | Original model |
| 6 | 0.85[1] | Good, p>0.10[1] | Split sample | Original model |
| 4 | 0.75[1] | Good, p>0.05[1] | Split sample | Original model |
| 9 | 0.71 | P=0.54 | Split sample | Original model |
| 8<br>17[2] | 0.76 (men), 0.78 (women)<br>0.70 (men)[2], 0.72 (women)[2] | - | n.a. | Original model & simplified model |
| 7 | NR | NR | n.a. | Original model, risk software |
| | | | | |
| 7 | NR | NR | n.a. | Original model, risk software |
| 6 | NR | NR | n.a. | Scoring chart |

insulin dependent diabetes mellitus, NR: not reported, n.a.: not applicable, for details on risk factors

**Table 2.** Cardiovascular risk models developed in general populations with diabetes as risk factor. and the apparent (i.e. as quantified in the original development study) discrimination and calibration

| | Development population | n events/ n total | Type of model | Outcome | Predicted years |
|---|---|---|---|---|---|
| Chien 2010[34] | Chinese GP | 240/3,602 | Cox | Stroke | 10 |
| Hippisley-Cox 2010 (QRISK)[35] | British GP | 121,623/ 1,267,159 | Cox | CVD | Lifetime |
| McGorrian 2010 (IHMRS)[36] | GP | 12,438/ 27,043 | Logistic | MI | NR |
| Arima 2009[37] | Japanese GP | 216/2,742 | Cox | CVD | 14 |
| Ishikawa 2009 (JMS cohort study)[38] | Japanese GP | 255/12,276 | Cox | Stroke | 10 |
| Matsumoto 2009 (JMS cohort study)[39] | Japanese GP | 92/12,323 | Cox | MI | 10 |
| Pencina 2009 (Framingham)[40] | USA GP | 671/4,506 | Cox | CVD | 30 |
| D'Agostino 2008 (Framingham)[41] | USA GP | 641/8,491 | Cox | CVD | 10 |
| Hippisley-Cox 2008 (QRISK2)[42] | British GP | 140,115/ 1,535,583 | Cox | CVD | 10 |
| Assman 2007 (PROCAM)[43] | German GP | 596/35,100 | CHD: Weibull Stroke: Cox | CHD &stroke | 10 |
| Ridker 2007 (Reynolds risk score)[44] | USA GP | 504/24,558 | Cox | CVD | 10 |
| Woodward 2007 (ASSIGN)[45] GP from Scotland | 422/13,297 | Cox | CVD | 10 | 9 |
| Asia-Pacific Cohort Studies Collaboration 2006[46] | Asian GP | 2,265/ 364,566 | Cox | CHD mortality | 8 |
| Lee 2006 (Strong Heart Study)[47] | American Indian GP | 724/4372 | Cox | CHD | 10 |
| Mainous 2006 (Personal HEART)[48] | USA GP | 1,108/14,343 | Cox | CHD | 10 |

Displayed are the type of model, the outcome, predicted risk period, population in which it has been developed

| Number of predictors | Apparent discrimination (AUC) | Apparent Calibration (P-value Hosmer-Lemeshow) | Method of internal validation | Presentation of risk model |
|---|---|---|---|---|
| 8 | 0.77 | NR | Cross-validation | Original model, scoring chart, nomogram |
| 14 | Women: 0.84[1] Men: 0.83[1] | Good[1] | Split sample | Original model |
| 6 | 0.71 | P=0.0004 | Split sample | Original model |
| 7 | 0.81[1] | P=0.60[1] | Split sample | Original model, scoring chart |
| 5 | NR | NR | n.a. | Scoring chart |
| 6 | NR | NR | n.a. | Scoring chart |
| 8 | 0.80, 0.80[1] | P=0.913, P=0.894[1] | Cross-validation | Original model |
| 7 | Men: 0.76 Women: 0.79 Men: 0.75[2] women: 0.79[2] | P=0.14-0.56 | n.a. | Original model, simplified model, scoring chart |
| 14 | Women: 0.82 Men: 0.79 | Good[1] | Split sample | Original model |
| CHD: 8 Stroke: 5 | CHD: 0.81, Stroke: 0.71 | NR | n.a. | Original model, scoring chart |
| 9 | 0.81, 0.81[1] | P=0.38, P=0.62[1] | Split sample | Original model, simplified model |
| Men: 0.73 Women: 0.77 | NR | n.a. | Original model | |
| 6 | NR | NR | n.a. | Original model |
| 9 | Men: 0.73 Women: 0.71 Men: 0.70[1] Women: 0.72[1] | Men P=0.45 women P=0.51 | bootstrap | Original model |
| 9 | Men: 0.65[1] Women: 0.79[1] | NR | Split sample | Original model, scoring chart |

**Table 2.** Continued.

| | Development population | n events/ n total | Type of model | Outcome | Predicted years |
|---|---|---|---|---|---|
| Wu 2006[49] | Chinese GP | 742/9,903 | Cox | Ischemic CVD | 10 |
| Ferrario 2005 (CUORE)[50] | GP Italian men | 312/6,865 | Cox | CHD | 10 |
| Menotti 2005 (Riskard 2005)[51] | GP | 1,382/17,153 | Weibull | CVD | 5, 10 & 15 |
| Decode study Group 2004[52] | European GP | 791/25,413 | Cox | CVD death | 5 & 10 |
| Liu 2004 (CMCS)[53] | Chinese GP | 816/30,121 | Cox | CHD & mortality | 10 |
| Pignone 2004[54] | NR | NR | NR | CHD | 10 |
| Schau 2003[55] | NR | NR | NR | Stroke | NR |
| Assmann 2002 (PROCAM)[56] | German men | 325/5,345 | Cox | CHD | 10 |
| Lumley 2002 (CHS)[57] | GP of elderly | 399/5,888 | Cox | Stroke | 5 |
| Menotti 2002 (Riscard 2002)[58] | GP | 544/9771 | Weibull | CHD & CVA &CVD | 5 |
| Moons 2002 (EUROSTROKE)[59] | European GP | 219/698 | Logistic | Stroke | 7 |
| Thomsen 2001 (Copenhagen Risk Score)[60] | GP | 509/24,508 | Cox | MI | 5, 10, 20 |
| Knuiman 1998[61] | Australian GP | 519/2,258 | Cox | Mortality or CHD | 10 |
| Wilson 1998 (Framingham)[62] | USA GP | 610/5,345 | Cox | CHD | 10 |
| Wood 1998 (JBSRC)[63] | NR | NR | NR | CHD | 10 |
| Zodpey 1994[64] | Indian GP | 154/308 | Logistic | CHD | NR |
| Anderson 1991 (Framingham)[65] | USA GP | NR/5,573 | Weibull | CHD, stroke, CVD, CVD mortality | Variable |
| Anderson 1991(2) (Framingham)[66] | USA GP | 626/5,573 | Weibull | CHD | 5 & 10 |

[1]after correction, [2]Values of the simplified risk or sum score, GP: general population, NR: not reported, n.a.: not

| Number of predictors | Apparent discrimination (AUC) | Apparent Calibration (P-value Hosmer-Lemeshow) | Method of internal validation | Presentation of risk model |
|---|---|---|---|---|
| 7 | Men: 0.80<br>Women: 0.79 | Men: P=0.733<br>Women: P=0.274 | n.a. | Original model, simplified model, scoring chart |
| 8 | 0.75, 0.74[1] | p>0.05 | Bootstrap and split sample | Original model |
| 9 | NR | NR | n.a. | Original model, risk chart, risk software |
| 6 | NR | NR | n.a. | Original model |
| 6 | 0.73 | P=0.08 | n.a. | Original model |
| 8 | NR | NR | n.a. | Risk software |
| 8 | NR | NR | n.a. | Risk software |
| 8 | 0.83<br>0.82 scoring chart | P>0.03 | n.a. | Original model and scoring chart |
| 10 | 0.65 (men)[1]<br>0.77 (women)[1] | NR | Split sample, Bootstrap | Original model, scoring chart, risk software |
| 9 | CHD: 0.76<br>CVA: 0.86 | NR | n.a. | Original mode, risk software |
| 6 | 0.69[1] | p>0.50 | bootstrap | Original model |
| 9 | NR | NR | n.a. | Original model, risk software |
| 10 | NR | NR | n.a. | Original model |
| 7 | Men: 0.74<br>Women: 0.76<br>Men: 0.68[2]<br>Women:0.71[2] | NR | n.a. | Original model& Score sheet |
| 7 | NR | NR | n.a. | Risk chart |
| 5 | NR | NR | n.a. | Scoring chart |
| 7 | NR | NR | n.a. | Original model |
| 8 | NR | NR | n.a. | Original model<br>scoring chart |

applicable. For details on risk factors included in the models, see Supplementary material

**Validation studies of the CVD prediction models**

Thirty studies externally validated 14 different prediction models in patients with type 2 diabetes, nine studies validated two versions of the UKPDS risk engine,[22;23] 10 studies validated three versions of the Framingham Prediction model[24-27] and nine other prediction models were externally validated only once (Table 3). The UKPDS risk engine for stroke[22] was validated in two studies, which obtained very different results. One study observed an AUC of 0.61 and a poor calibration, while the other observed an AUC of 0.86 and good calibration. The UKPDS risk engine for CHD[23] was validated in eight studies. Discrimination ranged from 0.65 to 0.76, and most of these studies observed poor calibration with an overestimation of the risk.

The Framingham prediction models by D'Agostino et al.[24] and by Anderson et al.[26;27] were validated three times in diabetes populations and the prediction model developed by Wilson et al.[28] four times. The AUC varied widely, ranging between 0.56 and 0.80 and the calibration was poor ($p<0.001$). Of the prediction models that were externally validated once, the Fremantle prediction model had the best discrimination with an AUC of 0.84 and a good calibration ($p=0.85$).

**Impact studies of the CVD prediction models and incorporation in clinical guidelines**

Only three studies examined the impact of applying a prediction model in clinical practice. All three studies used a randomized controlled trial design and examined the impact of the Framingham prediction model[29-31] on treatment and prevention of CVD (Table 4). Two of these studies were restricted to patients with a history of hypertension and the other study consisted of patients with type 2 diabetes (n=323). Half of them were allocated to an intervention group for which the cardiovascular prediction model was noted on the patient's records, while in the control group it was not. No difference was observed in prescription of glucose control, blood pressure lowering and lipid-modifying treatments. However, restricting analysis to the high-risk group, patients in the intervention group were more likely to receive lipid-modifying or blood pressure-lowering prescriptions.[29]

Five out of seven guidelines recommended calculating cardiovascular risk in patients with type 2 diabetes with a prediction models that can be applied to the diabetes population (Table 4). The IDF[21] and NICE guidelines[4] recommended using the UKPDS risk engine,[23] as did the Canadian Diabetes Association,[19] although this guideline mentioned PROCAM[32] and the Strong Heart prediction model[33] as well. The EASD[3]

**Table 3.** Overview of the cardiovascular risk scores that have been externally validated in a diabetes population.

| | Number of studies | Validation study | Population | n events/ n total | Outcome | Predicted years | Discrimination (AUC) | Calibration (P-value Hosmer-Lemeshow) |
|---|---|---|---|---|---|---|---|---|
| Models for diabetes population | | | | | | | | |
| Kengne 2011 (ADVANCE)[24] | 1[24] | Kengne 2011[24] | NIDDM with microalbuminuria/ proteinuria from 16 countries | 183/1836 | CVD | 4 years | 0.69 | P=0.03 |
| Davis 2010 (Fremantle)[25] | 1[25] | Davis 2010[25] | NIDDM from Australia | 24/180 | CVD or death | 5 years | 0.84 | P=0.85 |
| Elley 2010 (DCS)[26] | 1[26] | Elley 2010[26] | NIDDM from New Zealand | NR/12598 | CVD | 5 years | 0.69 | good |
| Donnan 2006 (DARTS)[31] | 1[31] | Donnan 2006[31] | NIDDM from UK | NR/NR | CHD | 5 years | 0.69 | P=0.54 |
| Kothari 2002 (UKPDS risk engine)[23] | 2[67;68] | Kengne 2009[67] | NIDDM from 20 countries | 288/7502 | CVA | 4 years | 0.61 | P<0.001 |
| | | Davis 2009[68] | NIDDM from Australia | 23/791 | Stroke | 5 years | 0.86 | P>0.05 |
| Stevens 2001 (UKPDS risk engine)[22] | 9[7;9;67-73] | Kengne 2009[67]* | NIDDM from 20 countries | 407/7502 | CHD | 4 years | 0.66 | p<0.001 |
| Models for general population | | | | | | | | |

**Table 3.** Coninued I.

| | Number of studies | Validation study | Population | n events/ n total | Outcome | Predicted years | Discrimination (AUC) | Calibration (P-value Hosmer-Lemeshow) |
|---|---|---|---|---|---|---|---|---|
| McGorrian 2010 (IHMRS)[36] | 1[36] | McGorrian 2010[36] | IFG, IGT or NIDDM from 21 countries | 95/18838 | MI | 3.25 years | 0.69 | P=0.93 |
| D'Agostino 2008 (Framingham)[41] | 3[67;71;73] | Kengne 2009[67] | NIDDM from 20 countries | 1003/7502 | CVD | 4 years | 0.80 | P<0.001 |
| | | Simmons 2008[73] | NIDDM from UK | 69/272 | CVD | 10 years | 0.73 | P=0.02 |
| | | Guzder 2005[71] | Newly diagnosed NIDDM from UK | 98/428 | CVD | 10 years | 0.67 | P<0.001 |
| Ferrario 2005 (CUORE)[50] | 1[9] | Pellegrini 2010[9] | NIDDM | 228/1532 | CVD | 10 years | 0.64 | Risk underestimated |
| Decode study Group 2004[52] | 1[74] | Coleman 2007[74] | Newly diagnosed diabetes | NR/5102 | Fatal CVD/ fatal CHD | 10 years | 0.67 | Risk overestimated |
| Assmann 2002 (PROCAM)[56] | 1[7] | Stephens 2004[7] | NIDDM from UK | 332/798 | CVD and CHD | 10 years | CHD: 0.65 CVD: 0.67 | CHD: p=0.05 CVD: P=0.006 |
| Menotti 2002 (Riscard 2002)[58] | 1[9] | Pellegrini 2010[9] | NIDDM | 228/1532 | CVD | 10 years | 0.59 | good |
| Wilson 1998 (Framingham)[62] | 4[9; 68;72;75] | Pellegrini 2010[9] | NIDDM | 228/1532 | CVD | 10 years | 0.68 | Risk overestimated |

**Table 3.** Coninued II.

| | Number of studies | Validation study | Population | n events/ n total | Outcome | Predicted years | Discrimination (AUC) | Calibration (P-value Hosmer-Lemeshow) |
|---|---|---|---|---|---|---|---|---|
| | | Davis 2009[68] | NIDDM from Australia | 38/791 | CHD | 5 years | 0.59 | P<0.001 |
| | | Van der Heijden 2009[72] | NIDDM from the Netherlands | 28/125 | CHD | 10 years | 0.63 | Risk overestimated |
| | | Game 2001[76] | NIDDM from UK | NR/956 | CHD | 10 years | NR | High sensitivity, low specificity |
| Anderson 1991 (Framingham)[65 66] | 3[67;74;77] | Kengne 2009[67] | NIDDM from 20 countries | 1003/7502 | CVD | 4 years | 0.56 | P<0.001 |
| | | Coleman 2007[74] | Newly diagnosed diabetes | NR/5102 | Fatal CVD/ fatal CHD | 10 years | 0.76 | Risk underestimated |
| | | McEwan 2004[77] | NIDDM & IDMM from UK | 172/938 | CHD | 4 years | Men: 0.65 Women: 0.68 | NR |

*only the study with the greatest study population has been displayed, an overview of all validation studies of the UKPDS risk engine is available in the Supplementary material table 3

**Table 4.** Overview of the cardiovascular risk scores, that have been quantified for their impact on treatment and cardiovascular complications, and that are incorporated in national/clinical guidelines

| | Impact studies | Guidelines |
|---|---|---|
| Stevens 2001 (UKPDS risk engine)[22] | - | CDA[19], AU[20], IDF[21], NICE[4] |
| Decode study Group 2004[52] | - | EASD[3] |
| Wilson 1998 (Framingham)[62] | - | EASD[3] |
| Anderson 1991 (Framingham)[65;66] | 2 studies: change in medication[78;80]<br>1 study: No change[79] | AU[20], JBS2[5] |

AU: Australian National Vascular Disease Prevention Alliance, CDA: Canadian Diabetes Association, EASD: European Society of Cardiology and European Association for Study of Diabetes Guidelines, IDF: International Diabetes Federation, JBS2: Joint British Society, NICE: National Institute for Health and Clinical Excellence

recommends using Framingham[24] and DECODE[34] as the preferred prediction models for calculating CVD risk. The Australian National Vascular Disease Prevention Alliance[20] recommends using the Framingham prediction model[24] as well, but they also mention the UKPDS risk engine.[23] The JBS2[5] has developed risk charts based on the Framingham prediction model.[24]

## Discussion

This systematic review provides an overview of all CVD prediction models that are specifically developed for, or can be applied to, patients diagnosed with type 2 diabetes to calculate future cardiovascular risk. Twelve prediction models are specifically designed for patients with type 2 diabetes and 33 have been developed in the general population accounting for diabetes as a predictor in the model. Only 31% of these prediction models have been examined for their external validity, with varying results. Interestingly, the impact on treatment and prevention of CVD by applying a prediction model has only been examined for the most commonly known CVD prediction model-that is, the Framingham prediction model.[27] Nonetheless, several prediction models are incorporated in guidelines for the management of type 2 diabetes.

There are an extensive number of CVD prediction models with great variety in their quality and the methodology used to develop them. However, some of the older prediction models were developed when

the statistical analysis methods for constructing such models were not yet established. The discriminative ability of both diabetes-specific CVD prediction models and prediction models that account for diabetes in the datasets from which they were developed was mostly good, with a c-statistic often >0.70. However, the discriminative ability in new patients (validation studies) varied widely, as did the methods used to assess the performance in new patients. The discrimination of the prediction models designed for the general population was moderate (0.59 to 0.80) and the calibration mostly poor. This could be explained by a difference in incidence of CVD between the general and diabetes populations or that CVD prediction models developed in the general population do not account for diabetes-specific risk factors, as was suggested by Chamnan et al.[6] They argued that this problem could be overcome by using only diabetes-specific prediction models for patients with diabetes. However, when diabetes-specific CVD prediction models where tested in other diabetes patient samples, the calibration was also poor with a moderate to good discrimination.

The more contemporary models, like the DCS,[35] Fremantle[36] or DARTS[37] seem to have the best external validity, but these were validated in other patient populations only once. Therefore, more validation studies on the performance of these prediction models in different diabetes populations are needed. The moderate performance of most prediction models suggests that it is difficult to predict CVD in patients with type 2 diabetes. Many biomarkers for CVD are emerging and being tested for their added prognostic value by extending the prediction models with these biomarkers.[14;38]

Few studies have assessed the impact of applying a CVD prediction model in clinical practice. We found only one study that assessed the impact of a prediction model (ie, the Framingham risk model). Consequently, it is unknown if the use of prediction models will indeed change treatment of patients with diabetes and thus reduce the number of cardiovascular complications. Even though the effect of applying a prediction model in clinical practice has not been established, guidelines recommend using CVD prediction models to determine appropriate treatment of diabetes. Interestingly, these guidelines refer both to the Framingham prediction model, which was assessed for its impact, but also to other prediction models, many of which have not been comprehensively validated. For instance, the EASD refers to the DECODE prediction model, which has only been validated once, with moderate performance. Other guidelines refer to the UKPDS risk

engine, which indeed has been validated by several studies, but in most studies it showed poor calibration and severely overestimated the risk. Considering that the validation and impact of most prediction models has not been assessed, there is a great need for such studies to support their incorporation in clinical guidelines.

Prediction models which have been developed in the general population and do not correct for diabetes as a factor were excluded from this review. Therefore we did not include, for example, the Systematic COronary Risk Evaluation (SCORE).[39] This model predicts fatal CVD over 10 years based on five predictors-namely, sex, age, smoking, systolic blood pressure and either total cholesterol or ratio total/high-density lipoprotein-cholesterol. The predictive ability of SCORE in patients with type 2 diabetes, however, has been assessed by three studies and was similar to other CVD prediction models included in our review.[40-42]

In conclusion, three stages of constructing a good prediction model can be identified: (1) development and internal validation of a model; (2) external validation and (3) assessment of the impact of using the model in practice. Many studies exist that present a CVD prediction model that can be applied to the diabetes population. A minority of studies have externally validated this large number of clinical prediction models in a diabetes population. Assessment of the impact on diabetes treatment and complications has been made for only one prediction model. Nevertheless, several prediction models are incorporated in guidelines for the management of type 2 diabetes and prevention of cardiovascular complications. New studies investigating prediction of CVD among patients with type 2 diabetes should, in our view, focus on further validating the performance of existing prediction models in new patients,[10] improving the predictive performance of these existing models by adjusting them to local circumstances or adding new predictors[14;38;43] and assessing their impact on treatment and prevention of cardiovascular events instead of developing new prediction models.[16;44]

## APPENDIX 1

Search terms used in this study

**Search term 1**

The search term used for identification of prediction models that are devolved in, or can be applied to, diabetes individuals: ((Validat$ OR Predict$.ti. OR Rule$) OR (Predict$ AND (Outcome$ OR Risk$ OR Model$)) OR (Decision$ AND (Model$ OR Clinical$ OR Logistic

Models/)) OR (Prognostic AND (History OR Variable$ OR Criteria OR Scor$ OR Characteristic$ OR Finding$ OR Factor$ OR Model$)) OR ("risk score"[All fields] OR "prediction model"[All fields] OR "prediction rule"[All fields] OR "risk assessment" [All fields] OR "algorithm"[All fields])) AND (cardiovascular OR coronary OR cerebrovascular OR heart OR stroke) AND (diabetes OR "diabetes mellitus" OR "type 2 diabetes") NOT (Animals[MeSH] NOT Humans[MeSH]).

**Search term 2**
Additional search term used to identify all validation studies of the prediction models: (("diabetes"[All fields] OR "diabetes mellitus"[All fields] OR "type 2 diabetes"[All fields]) AND ("risk score"[All fields] OR "prediction model"[All fields] OR "risk model"[All fields] OR "predicting"[All fields] OR "predictive model"[All fields] OR "prediction tool"[All fields] OR "prediction rule"[All fields] OR "risk assessment"[All fields] OR "algorithm"[All fields] OR "validation"[All fields] or "discrimination"[All fields] OR "calibration"[All fields]) AND ("cardiovascular"[All fields] OR "coronary heart"[All fields] OR "heart"[All fields] OR stroke"[All fields] OR "cerebrovascular"[All fields]) AND (Humans[Mesh])).

**Search term 3**
Search term used to identify all impact studies, which is combined with each specific risk scores acronym, or if not applicable the name of the cohort in which the score was developed or first author:
(Effectiveness [tiab] OR Comparing [tiab] OR Compared [tiab]OR Evaluate [tiab]) AND (Algorithm [tiab] OR Strategy [tiab] OR Managed [tiab] OR Management [tiab] OR Decision [tiab]) AND (cardiovascular OR coronary OR cerebrovascular OR heart OR stroke) AND (diabetes OR "diabetes mellitus" OR "type 2 diabetes") NOT (Animals [MeSH] NOT Humans[MeSH]).



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## Supplementary materials

**Supplementary materials Table 1.** Overview of variables included (x) in the CVD prediction models for patients with type 2 diabetes

| | Kengne | Davis | Elley | Cederholm | Yang 2008 | Yang 2008 (2) | Yang 2007 | Donnan | Folsom | Kothari | Stevens | Yudkin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | x | x | x | x | x | - | - | x | x | x | x | x |
| Age | x | x | x | x | x | x | x | x | x | x | x | x |
| HbA1c | x | x | x | x | - | x | x | x | - | - | x | - |
| Duration of diabetes | x | - | x | x | x | - | - | x | - | x | x | - |
| Albuminuria | x | x | x | - | x | x | x | - | - | - | - | - |
| HDL cholesterol | - | x | - | - | - | - | - | - | x | - | - | - |
| nonHDL cholesterol | x | - | - | - | x | - | - | - | - | - | - | - |
| Total/HDL cholesterol | - | - | x | - | - | - | - | - | - | x | x | x |
| Total cholesterol | - | - | - | - | - | - | - | x | x | - | - | - |
| Atrial fibrillation | x | - | - | - | - | - | - | - | - | x | - | - |
| Systolic blood pressure | - | - | x | x | - | - | - | x | x | - | x | x |
| Pulse pressure | x | - | - | - | - | - | - | - | - | - | - | - |
| Antihypertensive medication | - | - | x | - | - | - | - | x | x | - | - | - |
| Retinopathy | x | - | - | - | - | - | - | - | - | - | - | - |
| History CVD | - | x | - | - | - | x | x | - | - | - | - | - |
| Ethnicity | - | x | x | - | - | - | - | - | x | x | x | - |
| Smoking | - | - | x | x | x | - | - | x | x | x | x | x |
| BMI | - | - | - | x | - | x | - | - | (x) | - | - | - |
| Height | - | - | - | - | - | - | - | x | - | - | - | - |
| Lipid lowering drug | - | - | - | x | - | - | - | - | - | - | - | - |

**Supplementary materials Table 1.** Overview of variables included (x) in the CVD prediction models for patients with type 2 diabetes

| | Kengne | Davis | Elley | Cederholm | Yang 2008 | Yang 2008 (2) | Yang 2007 | Donnan | Folsom | Kothari | Stevens | Yudkin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Blood haemoglobin | - | - | - | - | - | x | - | - | - | - | - | - |
| eGFR | - | - | - | - | x | - | - | - | - | - | - | - |
| Waist hip ratio | - | - | - | - | - | - | - | - | (x) | - | - | - |
| Sport activity | - | - | - | - | - | - | - | - | (x) | - | - | - |
| Keys score | - | - | - | - | - | - | - | - | (x) | - | - | - |
| Creatinine | - | - | - | - | - | - | - | - | (x) | - | - | - |
| Albumin | - | - | - | - | - | - | - | - | (x) | - | - | - |
| White blood cell count | - | - | - | - | - | - | - | - | (x) | - | - | - |
| Left ventricular hypertrophy | - | - | - | - | - | - | - | - | (x) | - | - | - |
| Intima-media thickness | - | - | - | - | - | - | - | - | (x) | - | - | - |

**Supplementary materials Table 2.** Overview of variables included (x) in CVD prediction models developed from data of a general population with diabetes as predictor

| | Chien | Hippisley-Cox 2010 | McGorrian | Ridker | Woodward | Arima | Ishikawa | Matsumoto | Pencina | D'Agostino | Hippisley-Cox 2008 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | x | x | x | x | x | x | x | x | x | x | x |
| Sex | x | x | x | - | x | x | x | x | x | x | x |
| Diabetes | x | x | x | x | x | x | x | x | x | x | x |
| Systolic blood pressure | x | x | - | x | x | x | x | x | x | x | x |
| Diastolic blood pressure | x | - | - | - | - | - | - | - | - | - | - |
| Total cholesterol | (x) | - | - | (x) | x | - | - | x | x | x | - |
| HDL cholesterol | - | - | - | (x) | x | x | - | - | x | x | - |
| nonHDL cholesterol | - | - | - | - | - | - | - | - | - | - | - |
| LDL cholesterol | - | - | - | - | - | x | - | - | - | - | - |
| Total/HDL cholesterol | - | x | - | - | - | - | - | - | - | - | x |
| Triglycerides | - | - | - | - | - | - | - | - | - | - | - |
| Smoking | - | x | x | x | x | x | x | - | x | - | x |
| Hypertensive medication | - | x | - | - | - | - | - | - | x | x | x |
| Family history CHD | - | x | - | x | - | - | - | - | - | - | x |
| Family history CVD | - | - | - | - | x | - | - | - | - | - | - |
| LVH | - | - | - | - | - | - | - | - | - | - | - |
| Education level | - | - | - | - | - | - | - | - | - | - | - |
| History of stroke | - | - | - | - | - | - | - | x | - | - | - |
| History of hypertension | - | - | x | - | - | - | - | x | - | - | - |
| Fasting plasma glucose | x | - | - | - | - | - | x | - | - | - | - |

**Supplementary materials Table 2.** Continued I.

| | Chien | Hippisley-Cox 2010 | McGorrian | Ridker | Woodward | Arima | Ishikawa | Matsumoto | Pencina | D'Agostino | Hippisley-Cox 2008 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BMI | (x) | x | - | - | - | - | - | - | - | - | x |
| Heart rate | (x) | - | - | - | - | - | - | - | - | - | - |
| History CHD | - | - | - | - | - | - | x | - | - | - | - |
| Creatinine | - | - | - | - | - | - | x | - | - | - | - |
| Albuminuria | - | - | - | - | - | - | - | - | - | - | - |
| 15ft walktime | - | - | - | - | - | - | x | - | - | - | - |
| Atrial fibrilation | - | x | - | - | - | - | x | - | - | - | x |
| France region | - | - | - | - | - | - | - | - | - | - | - |
| Family history stroke | x | - | - | - | - | - | - | - | - | - | - |
| White blood cell count | x | - | - | - | - | - | - | - | - | - | - |
| Ethnicity | - | x | - | - | - | - | - | - | - | - | x |
| Social economic status | - | x | - | - | x | - | - | - | - | - | x |
| Reumatoid arthritis | - | x | - | - | - | - | - | - | - | - | x |
| Chronic renal disease | - | x | - | - | - | - | - | - | - | - | x |
| Apolipoprotein A | - | (x) | x | - | - | - | - | - | - | - | - |
| Apolipoprotein B | - | (x) | x | - | | - | - | - | - | - | - |
| hsCRP | - | x | - | - | - | - | - | - | - | - | - |
| Physical activity | - | - | - | - | - | - | - | - | - | - | - |
| hypercholesterolemia | - | - | - | - | - | - | - | - | - | - | - |

**Supplementary materials Table 2.** Continued II.

| | Assmann | Asia Pacific cohort study | Lee | Mainous | Wu | Ferrario | Menotti | Decode | Liu | Pignone | Schau |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | x | x | x | x | x | x | x | x | x | x | x |
| Sex | x | x | x | x | x | - | x | x | x | x | x |
| Diabetes | x | x | x | x | x | x | x | x | x | x | x |
| Systolic blood pressure | x | x | x | - | x | x | x | x | x | x | - |
| Diastolic blood pressure | - | - | - | - | - | - | - | - | - | - | - |
| Total cholesterol | - | x | (x) | - | x | x | x | x | x | x | - |
| HDL cholesterol | (x) | - | x | - | - | x | (x) | - | x | x | - |
| nonHDL cholesterol | - | - | - | - | - | - | (x) | - | - | - | - |
| LDL cholesterol | (x) | - | (x) | - | - | - | - | - | - | - | - |
| Total/HDL cholesterol | - | - | - | - | - | - | - | - | - | - | - |
| Triglycerides | (x) | - | - | - | - | - | - | - | - | - | - |
| Smoking | x | x | x | x | x | x | - | x | - | x | x |
| Hypertensive medication | - | - | x | - | - | x | - | - | - | - | - |
| Family history CHD | - | - | - | x | - | x | - | - | - | - | - |
| Family history CVD | - | - | - | - | - | - | - | - | - | - | - |
| LVH | - | - | - | - | - | - | - | - | - | x | - |
| Education level | - | - | - | - | - | - | - | - | - | - | - |
| History of stroke | - | - | - | - | - | - | - | - | - | - | - |
| History of hypertension | - | - | - | x | - | - | - | - | - | - | x |
| Fasting plasma glucose | - | - | - | - | - | - | - | x | - | - | - |

**Supplementary materials Table 2.** Continued III.

| | Assmann | Asia Pacific cohort study | Lee | Mainous | Wu | Ferrario | Menotti | Decode | Liu | Pignone | Schau |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BMI | - | - | - | x | x | - | (x) | - | - | - | - |
| Heart rate | - | - | - | - | - | - | (x) | - | - | - | - |
| History CHD | - | - | - | - | - | - | - | - | - | - | x |
| Creatinine | - | - | - | - | - | - | - | - | - | - | - |
| Albuminuria | - | - | x | - | - | - | - | - | - | - | - |
| 15ft walktime | - | - | - | - | - | - | - | - | - | - | - |
| Atrial fibrilation | - | - | - | - | - | - | - | - | - | - | x |
| France region | - | - | - | - | - | - | - | - | - | - | - |
| Family history stroke | - | - | - | - | - | - | - | - | - | - | - |
| WBC | - | - | - | - | - | - | - | - | - | - | - |
| Ethnicity | - | - | - | - | - | - | - | - | - | - | x |
| Social economic status | - | - | - | - | - | - | - | - | - | - | - |
| Reumatoid arthritis | - | - | - | - | - | - | - | - | - | - | - |
| Chronic renal disease | - | - | - | - | - | - | - | - | - | - | - |
| Apolipoprotein A | - | - | - | - | - | - | - | - | - | - | - |
| Apolipoprotein B | - | - | - | - | - | - | - | - | - | - | - |
| hsCRP | - | - | - | - | - | - | - | - | - | - | - |
| Physical activity | - | - | - | x | - | - | - | - | - | - | - |
| hypercholesterolemia | - | - | - | x | - | - | - | - | - | - | - |

**Supplementary materials Table 2.** Continued IV.

| | Assmann 2002 | Lumley | Menotti 2002 | Moons | Thomsen | Knuiman | Wilson | Wood | Zodpey | Anderson 1991 | Anderson 1991(updated) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | x | x | x | x | - | x | x | x | - | x | x |
| Sex | - | x | x | - | x | x | x | x | - | x | x |
| Diabetes | x | x | x | x | x | x | x | x | x | x | x |
| Systolic blood pressure | x | x | x | - | x | x | x | x | - | (x) | x |
| Diastolic blood pressure | - | - | x | x | - | x | - | x | - | (x) | - |
| Total cholesterol | - | - | - | - | x | - | (x) | x | x | - | x |
| HDL cholesterol | x | - | x | - | x | - | x | - | - | - | x |
| nonHDL cholesterol | - | - | x | - | - | - | - | - | - | - | - |
| LDL cholesterol | x | - | - | - | - | - | (x) | - | - | - | - |
| Total/HDL cholesterol | - | - | - | - | - | x | - | - | - | x | - |
| Triglycerides | x | - | - | - | - | - | - | - | - | - | - |
| Smoking | x | - | x | x | x | x | x | x | - | x | x |
| Hypertensive medication | - | - | - | - | - | x | - | - | - | - | - |
| Family history CVD | - | - | - | - | - | - | - | - | - | - | - |
| Family history CHD | x | - | - | - | x | - | - | - | - | - | - |
| LVH | - | x | - | - | - | x | - | - | - | x | x |
| History of stroke | - | - | - | x | - | - | - | - | - | - | - |
| History of hypertension | - | - | - | x | - | - | - | - | x | - | - |
| Fasting plasma glucose | - | - | - | - | - | - | - | - | - | - | - |
| BMI | - | x | x | - | x | - | - | - | - | - | - |

**Supplementary materials Table 2.** Continued V.

| | Assmann 2002 | Lumley | Menotti 2002 | Moons | Thomsen | Knuiman | Wilson | Wood | Zodpey | Anderson 1991 | Anderson 1991(updated) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Heart rate | - | - | x | - | - | - | - | - | - | - | - |
| History CHD | - | - | - | - | x | x | - | - | - | - | - |
| Creatinine | - | x | - | - | - | - | - | - | - | - | - |
| albuminuria | - | - | - | - | - | - | - | - | - | - | - |
| 15ft walktime | - | x | - | - | - | - | - | - | - | - | - |
| Atrial fibrilation | - | x | - | - | - | - | - | - | x | - | - |
| France region | - | x | - | - | - | - | - | - | - | - | - |
| Family history stroke | - | - | - | - | - | - | - | - | - | - | - |
| WBC | - | - | - | - | - | - | - | - | - | - | - |
| Ethnicity | - | - | - | - | - | - | - | - | - | - | - |
| Social economic status | - | - | - | - | - | - | - | - | x | - | - |
| Reumatoid arthritis | - | - | - | - | - | - | - | - | - | - | - |
| Chronic renal disease | - | - | - | - | - | - | - | - | - | - | - |
| Apolipoprotein A | - | - | - | - | - | - | - | - | - | - | - |
| Apolipoprotein B | - | - | - | - | - | - | - | - | - | - | - |
| hsCRP | - | - | - | - | - | - | - | - | - | - | - |
| Physical activity | - | - | - | - | - | - | - | - | - | - | - |
| hypercholesterolemia | - | - | - | - | - | - | - | - | - | - | - |

**Supplementary materials Table 3.** Overview of all external validation studies of the UKPDS risk engine

| | Number of studies | Validation study | Validation population | n events/ total n | Outcome | Predicted years | Discrimination (AUC) | Calibration (P-value Hosmer-Lemeshow) |
|---|---|---|---|---|---|---|---|---|
| Stevens 2001 (UKPDS risk engine) | 9 | Kengne 2009 | NIDDM from 20 countries | 407/7502 | CHD | 4 years | 0.66 | p<0.001 |
| | | Stephens 2004 | NIDDM from UK | 332/798 | CVD and CHD | 10 years | CVD: 0.74 CHD: 0.76 | P<0.001 |
| | | Pellegrini 2010 | NIDDM from Italy | 100/1532 | CHD | 10 years | 0.68 | Risk overestimated |
| | | Davis 2009 | NIDDM from Australia | 38/791 | CHD | 5 years | 0.68 | P<0.001 |
| | | Van Dieren 2011 | NIDDM from the Netherlands and Germany | 99/1622 | CHD | 5 years | 0.65 | P<0.001 |
| | | Song 2004 | NIDDM from UK | NR/700 | CHD | 10 years | NR | P<0.001 |
| | | Guzder 2005 | Newly diagnosed NIDDM from UK | 60/428 | CHD | 10 years | 0.67 | P=0.029 |
| | | Van der heijden 2009 | NIDDM from the Netherlands | 28/125 | CHD | 10 years | 0.66 | Risk overestimated |
| | | Simmons 2009 | NIDDM from UK | 69/272 | CVD | 10 years | 0.72 | Good sensitivity, poor specificity |

# Chapter 8

# External validation of the UK prospective diabetes study (UKPDS) risk engine in patients with type 2 diabetes

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## Abstract

**Aims:** Treatment guidelines recommend the UK Prospective Diabetes Study (UKPDS) risk engine for predicting cardiovascular risk in patients with type 2 diabetes, although validation studies showed moderate performance. The methods used in these validation studies were diverse, however, and sometimes insufficient. Hence, we assessed the discrimination and calibration of the UKPDS risk engine to predict 4, 5, 6 and 8 year cardiovascular risk in patients with type 2 diabetes

**Methods:** The cohort included 1,622 patients with type 2 diabetes. During a mean follow-up of 8 years, patients were followed for incidence of CHD and cardiovascular disease (CVD). Discrimination and calibration were assessed for 4, 5, 6 and 8 year risk. Discrimination was examined using the c-statistic and calibration by visually inspecting calibration plots and calculating the Hosmer–Lemeshow $Chi^2$ statistic.

**Results:** The UKPDS risk engine showed moderate to poor discrimination for both CHD and CVD (c-statistic of 0.66 for both 5 year CHD and CVD risks), and an overestimation of the risk (224% and 112%). The calibration of the UKPDS risk engine was slightly better for patients with type 2 diabetes who had been diagnosed with diabetes more than 10 years ago compared with patients diagnosed more recently, particularly for 4 and 5 year predicted CVD and CHD risks. Discrimination for these periods was still moderate to poor.

**Conclusions:** We observed that the UKPDS risk engine overestimates CHD and CVD risk. The discriminative ability of this model is moderate, irrespective of various subgroup analyses. To enhance the prediction of CVD in patients with type 2 diabetes, this model should be updated.

## Introduction

Cardiovascular disease (CVD) is a major cause of death in patients with type 2 diabetes, with risk for developing CHD increased two- to fourfold.[1] Practice guidelines recommend calculating CVD risk for treatment of cardiovascular complications. Several risk equations are available to estimate CVD risk, such as the Systematic Coronary Risk Evaluation (SCORE)[2] and Framingham Risk Score (FRS)[3] for the general (non-diabetic) population. The ability of SCORE and FRS to distinguish between those at low and high risk (discrimination) is only moderate and the ability to correctly quantify the observed absolute risks (calibration) is poor in patients with type 2 diabetes.[4;5]

A few prediction scores have been developed specifically for diabetes patients, either newly detected patients or those already receiving treatment,[6-10] of which the UK Prospective Diabetes Study (UKPDS) risk engine is most widely known and used. It estimates absolute CHD risk using traditional risk factors such as BMI, age, sex, smoking, systolic blood pressure and ratio of total cholesterol to HDL-cholesterol, plus the diabetes-specific factors duration of diabetes and HbA1c (Supplementary material text 1 and Supplementary material Table 1).[8]

Several studies have validated the UKPDS risk engine with inconsistent results, as shown in a recent systematic review.[4;6;7;11;12] In general, the discrimination of the model was moderate and calibration poor. The methods used in the validation studies were diverse, with different study populations and different endpoints (e.g. CHD vs CVD), and the calculated time period varied. Furthermore, the methods of these validation studies could be improved. For example, none of the studies calculating a 10 year risk accounted for loss to follow-up or endpoints registered for a shorter duration than 10 years, which probably biased results.

Nonetheless, guidelines promoted and funded by the National Institute for Health and Clinical Excellence, British Canadian guidelines and Dutch general practitioner guidelines advocate using the UKPDS risk engine among other risk models for risk quantification in clinical practice.[13-15]

Therefore, the aim of our study was to quantify the discrimination and calibration of the UKPDS risk engine in a large cohort of patients with type 2 diabetes. We studied the risk engine's performance in prediction of cardiovascular risk over various time intervals, including 4, 5, 6 and 8 years. Furthermore, we investigated whether the duration of diabetes or the choice of disease endpoint (CVD or CHD) has any impact on the performance of the UKPDS risk engine.

## Methods

### Study population and design

The study population consisted of patients with type 2 diabetes from the Dutch and Potsdam (Germany) contributions to the European Prospective Investigation into Cancer and Nutrition (EPIC-NL and EPIC-Potsdam, respectively). Both cohorts have been described in more detail by Beulens et al. and Boeing et al.[16;17] In brief, EPIC-NL consists of the Prospect cohort and the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) cohort. Prospect is a prospective population-based cohort of 17,357 women, aged 49–70 years, who participated in breast cancer screening between 1993 and 1997. The MORGEN cohort consists of 22,654 men and women, aged 20–59 years, recruited from three Dutch towns (Amsterdam, Maastricht and Doetinchem). From 1993 to 1997 each year a new random sample of about 5,000 participants was examined. The EPIC-Potsdam cohort recruited 27,548 participants between 1994 and 1998 and was based on general population registries. In total, 1,861 individuals with type 2 diabetes were identified at baseline; 239 patients had a history of CVD or missing endpoint measurements and were excluded. This resulted in 1,622 patients with type 2 diabetes for inclusion in the current analyses. Participants from EPIC-NL were all patients with a confirmed diagnosis of type 2 diabetes. For EPIC-Potsdam 322 patients were confirmed as having type 2 diabetes; for 845 patients the diabetes type was unspecified. Diabetes cases in the EPIC-NL cohort were verified through medical records of the general practitioner or pharmacist, while diabetes cases in EPIC-Potsdam were verified through repeated self-report in follow-up questionnaires. All participants gave written informed consent prior to study inclusion. Both cohorts were approved by the local ethics committee. All information from EPIC-NL and EPIC-Potsdam was compared, recoded and merged into one uniform database.

*Predictors and measurements*

At baseline, a general questionnaire containing questions on demographic characteristics, smoking, presence of chronic diseases and other potential risk factors was filled out by all participants. Body weight and height were measured. Smoking was recoded into current smokers and non-smokers (former or nonsmokers). Blood pressure was measured twice for the participants in EPIC-NL and three times for EPIC-Potsdam participants. The measurement was performed on the left arm while the participant was in a supine position. The mean of

these measurements was used in the analyses. In the EPIC-Potsdam and Prospect cohorts systolic and diastolic blood pressure was measured using a Boso oscillomat (Bosch and Sohn, Jungingen, Germany). In the MORGEN cohort a random zero sphygmomanometer (Hawksley and Sons, Lancing, UK) was used, which slightly underestimated the blood pressure compared with the Boso oscillomat.
Blood, 30 ml, was collected from all participants to obtain plasma, serum and erythrocytes. Total cholesterol, HDL- and LDL-cholesterol, and triacylglycerol levels were measured in frozen serum samples and HbA1c was measured in frozen erythrocytes.

*Endpoints*
Participants were followed for two primary outcomes: coronary events, defined as myocardial infarction and ischaemic heart disease (International Classification of Diseases [ICD]-9 codes 410–414; ICD-10 codes I20–I25) and cardiovascular events, defined as myocardial infarction, ischaemic heart disease or stroke (ICD-9 codes 430–438; ICD-10 codes I60–I67,I69). In EPIC-NL, incident morbidity cases were obtained through linkage with the Dutch National Medical Registry, which holds a standardised computerised database of all hospital discharge diagnoses throughout the country. In the Netherlands it is mandatory to fill out a hospital discharge diagnosis whenever a patient leaves the hospital. The vital status of EPIC-NL participants was obtained through linkage with the municipal population registries. The records of this database were linked to the EPIC-NL cohort with a validated probabilistic method.[18]
In EPIC-Potsdam the major source of data on incident cases was questionnaires that were mailed to all participants every 2 years. Of these questionnaires, 95% were returned. Mortality data for EPIC-Potsdam participants were collected through cooperation with the local health offices of Potsdam and the state office of statistics of Brandenburg.[19]

*Data analysis*
Years at risk for developing the endpoints were calculated as the time between enrolment in the study and the diagnosis of one of the two endpoints (CHD or CVD), the date of death or the end of follow-up.
Missing values occurred on various predictor variables ranging from 4.2% (for systolic blood pressure) to 19.0% (for HDL-cholesterol). As missing values seldom occur completely at random, simply leaving those patients out of the analysis yields biased results. Accordingly, it is

widely recommended to impute missing values rather than performing a complete subject analysis.[20] We used multiple imputation (MI) for our missing data on predictor variables using the MI by chained equations procedure, assuming that after correction for measured variables the patterns of 'missingness' can be considered to be at random.

The 4, 5, 6 and 8 year predicted risks for CHD and CVD were calculated using the UKPDS risk engine (Supplementary material 1). The measurements of HbA1c, blood pressure and lipid ratio were less precise than the estimates of the UKPDS. Therefore, in order to prevent overestimation of the risk, we used the beta values from the appendix of the paper as suggested by Stevens et al.[8]

Not all participants had a follow-up of 8 years; therefore, two types of analysis were conducted. The first analysis included only patients with type 2 diabetes who were followed up for at least the corresponding time; participants with follow-up shorter than the calculated risk period were excluded. The second analysis included all patients, with patients with a follow-up shorter than the calculated risk period included as non-cases.

Model performance was assessed by measuring discrimination (the ability to discriminate between participants with or without an event) and calibration (the ability to quantify the observed absolute risk). The discriminative ability of the model was examined by calculating the c-statistic with 95% CI for each time period (4, 5, 6 and 8 year risk). The calibration of the model was assessed through visually inspecting the calibration plots and by calculating the Hosmer–Lemeshow $Chi^2$ statistic (HL $Chi^2$). Estimates for the c-statistic and HL $Chi^2$ were pooled using Rubin's rule, in order to correct for the MI.

To take into account the time-to-event structure of our data, we analysed the data and assessed the discrimination of the UKPDS risk engine using Harrell's c-statistic for censored data.[21] The calibration was examined by plotting predicted survival probabilities against right-censored failure times (using the R program, val.surv function, developed by F. E. Harrell Jr). As a longer duration of diagnosed diabetes is modelled in the survival part of the risk equation rather than in the linear predictor, each year longer duration results in a much higher predicted CVD risk. We examined whether performance of the UKPDS risk engine was affected by duration of diagnosed diabetes. Separate analyses were performed for patients who had had diabetes for over 10 years and patients who had had diabetes for up to and including 10 years. All statistical analyses were performed using R-2.10.1 for Windows (http://cran.r-project.org/).

## Results

During a mean exposure time of 8 years, 146 CVD cases were identified, of which 99 were cases of CHD. Baseline characteristics according to cohort are shown in Table 1, together with the characteristics of the UKPDS cohort. In EPIC-NL there were more smokers and participants had a higher total cholesterol/HDL-cholesterol ratio, but a shorter duration of diabetes compared with EPIC-Potsdam participants. Compared with the participants from the UKPDS population in which the risk equation was developed, EPIC-NL and EPIC-Potsdam included fewer smokers and participants were older and had higher levels of HbA1c.

**Table 1.** Baseline characteristics by country of 1622 participants next to baseline characteristics of UKPDS cohort[8]

| Characteristics | EPIC-NL (n=455) | EPIC-Potsdam (n=1167) | UKPDS (n=4540) |
|---|---|---|---|
| Age at recruitment, years (sd) | 58.2 (6.7) | 57.7 (6.5) | 52.0 (8.8) |
| Male participants % (n) | 17.8 (81) | 54.4 (639) | 58.2 (2643) |
| Systolic blood pressure, mmHg (sd) | 144 (21.0) | 141 (18.6) | 136 (19.3) |
| Current smoking, % (n) | 23.3 (106) | 18.7 (219) | 30.2 (1372) |
| Ratio total/HDL cholesterol | 5.36 (1.75) | 4.57 (1.19) | 5.2 (1.4) |
| $HbA_{1c}$ level, % (sd) | 8.13 (1.79) | 8.27 (2.34) | 6.7 (1.4) |
| Duration of diabetes , years (sd) | 6.7 (6.7) | 7.6 (7.3) | 0 |

Using the UKPDS risk engine the mean predicted 8 year risk was 15.9% while the observed 8 year CHD risk was 4.9%, resulting in an overestimation of 224%. For 8 year CVD risk, the UKPDS risk engine overestimated the CVD risk by 112%, as the observed 8 year CVD risk was 7.5%.

**Performance of the model for CHD outcome**

In the first analysis (excluding participants with a shorter follow-up than the predicted duration) the c-statistic was 0.66 (95% CI 0.51–0.81) for 5 year risk (Table 2). The calibration was poor (HL $Chi^2$=61.9, $p<0.001$ for 5 year risk) with a severe overestimation of the risk (Figure 1a). Discrimination and calibration were similar for other calculated risk periods. In the second analysis (including patients with a shorter follow-up than predicted duration), the discrimination was the same as for the first analysis (c-statistic 0.65 [95% CI 0.50–0.80]), and the calibration was similarly poor (HL $Chi^2$=77.4, $p<0.001$).

**Table 2.** Discrimination and calibration of the UKPDS risk engine for 4, 5, 6 & 8 calculated risk years with CHD as outcome.

| Calculated risk period (years) | First analysis | | | Second analysis | | |
|---|---|---|---|---|---|---|
| | Cases/n | c-statistic | $\chi^2$ statistic | Cases/n | c-statistic | $\chi^2$ statistic |
| 4 | 48/1508 | 0.65 (0.49-0.82) | 44.6 (p<0.001) | 48/1622 | 0.65 (0.48-0.81) | 53.2 (p<0.001) |
| 5 | 55/1476 | 0.66 (0.51-0.81) | 61.9 (p<0.001) | 55/1622 | 0.65 (0.50-0.80) | 77.4 (p<0.001) |
| 6 | 63/1438 | 0.66 (0.52-0.80) | 78.5 (p<0.001) | 63/1622 | 0.65 (0.51-0.79) | 104.1 (p<0.001) |
| 8 | 80/1094 | 0.66 (0.53-0.78) | 71.7 (p<0.001) | 80/1622 | 0.65 (0.53-0.77) | 169.8 (p<0.001) |

First analysis: participants with shorter follow up than calculated risk period excluded. Second analysis: participants with shorter follow up than calculated risk period included.

Taking into account the time-to-event structure of the data, the overall discrimination was similar; Harrell's c-statistic was 0.65 (95% CI 0.53–0.76). The overall calibration was similarly poor, showing a severe overestimation, comparable with the plots of the first and second analyses.

The discrimination of the model for patients with a duration of diabetes >10 years was similar to the discrimination of the model for patients with a duration of <10 years (Supplementary material tables 1 and 2). However, the calibration was better for 4 and 5 year risk prediction for patients with diabetes for >10 years, as the HL $Chi^2$ statistics were 15.2 (p=0.347) for 4 year risk and 20.8 (p=0.098) for 5 year risk, which indicates that the observed and predicted risks did not differ significantly. For other calculated risk periods the calibration was similarly poor for both patient groups with up to and over 10 years of diagnosed diabetes.

**Performance of the model for CVD outcome**

In the first analysis, discrimination for 5 year risk prediction was moderate to poor, with a c-statistic of 0.66 (95% CI 0.53-0.79) (Table 3). The calibration was poor (HL $Chi^2$=35.2, p=0.002) with a severe overestimation (Figure 1b). Again, similar results were obtained for the other calculated risk periods. For the second analysis the discrimination

for 5 year risk prediction was similar to the first analysis (c-statistic 0.65 [95% CI 0.53–0.79]). The calibration was also poor (HL $Chi^2$=48.1, p<0.001), but the overestimation was greater than for the first analysis. Overall discrimination for CVD, taking into account the time-to-event structure of the data, yielded similar results; Harrell's c-statistic was 0.65 (95% CI 0.55–0.74). The calibration plot for right censored data was similarly poor, showing a severe overestimation comparable with the plots of the first and second analysis.

Overall, the performance of the model for predicting CVD was about the same as for predicting CHD. The discriminative ability of the model was similar for patients with up to and over 10 years of diagnosed diabetes (Supplementary material tables 3 and 4).

Consistent with the results for CHD risk, the calibration was better for patients who had diabetes for >10 years compared with patients with diabetes <10 years for 4 and 5 year calculated risk periods. The HL $Chi^2$ test was not significant, meaning there was no significant difference between observed and predicted risks.

**Table 3. Discrimination and calibration of the UKPDS risk engine for 4, 5, 6 & 8 calculated risk years with CVD as outcome.** First analysis: participants with shorter follow up than calculated risk period excluded. Second analysis: participants with shorter follow up than calculated risk period included.

| Calculated risk period | First analysis | | | Second analysis | | |
|---|---|---|---|---|---|---|
| (years) | Cases/n | c-statistic | $\chi^2$ statistic | Cases/n | c-statistic | $\chi^2$ statistic |
| 4 | 67/1510 | 0. 66 (0.52-0.80) | 25.2 (p =0.023) | 67/1622 | 0.65 (0.52-0.79) | 32.1 (p =0.002) |
| 5 | 78/1479 | 0.66 (0.53-0.79) | 35.2 (p =0.002) | 78/1622 | 0.65 (0.53-0.79) | 48.1 (p <0.001) |
| 6 | 94/1442 | 0.66 (0.55-0.77) | 41.6 (p <0.001) | 94/1622 | 0. 65 (0.54-0.77) | 62.2 (p <0.001) |
| 8 | 122/1100 | 0.65 (0.55-0.76) | 29.7 (p=0.008) | 122/1622 | 0.64 (0.54-0.74) | 106.0 (p <0.001) |

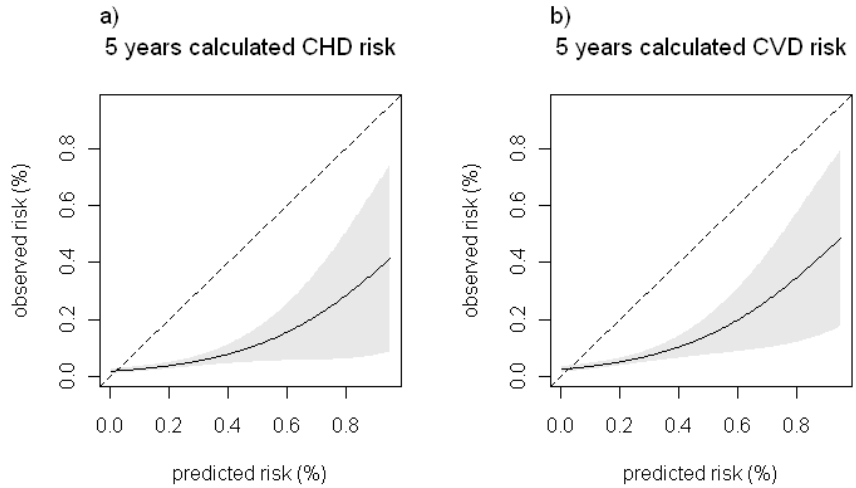


**Figure 1. Calibration plots for 5-year calculated CHD (a) and CVD (b) risk.**
Values depict observed and predicted risk with 95% confidence interval. The dotted 45° line denotes ideal agreement between predicted risk and observed risk. Results based on first analysis (censored cases excluded).

## Discussion

This study shows that the discriminative ability of the UKPDS risk engine is moderate and the calibration poor, with a severely overestimated CHD risk prediction. The performance was similar for prediction of CVD. The calibration of the UKPDS risk engine for 4 and 5 year prediction was better for patients who had been diagnosed with diabetes for >10 years compared with patients who had been diagnosed with type 2 diabetes <10 years ago. But this difference must be interpreted with caution because the number of patients in these subgroup analyses was much smaller, making it difficult to detect differences between observed and predicted risks.

The strengths of this study are its large sample size of patients with type 2 diabetes, the verification of diabetes cases and the variety of patients (from Germany and the Netherlands), which enhances the generalisability of the results. However, some limitations need to be addressed. First, the mean follow-up time was 8 years; therefore, we could not validate 10 year CVD and CHD risks. However, the UKPDS risk engine is, in principle, designed for all risk periods, including periods shorter than 10 years.[8] Second, our population consisted of all diabetes cases, not just individuals newly diagnosed with diabetes.

Therefore, we could only validate the use of the UKPDS risk engine for patients who have been diagnosed with diabetes for some time. Finally, we had some missing values in the baseline factors, but we addressed this limitation using MI.

There are several explanations for the poor to moderate performance of the UKPDS risk engine to predict CHD and CVD risk in this population. First, the UKPDS risk engine was developed from a cohort that started including patients in 1977.[8] Treatment of type 2 diabetes and prevention of CVD has improved since 1977 and the risk of developing CVD has declined with better treatment of type 2 diabetes.[22] Also, as diabetes is now detected at an earlier stage, therapeutic intervention can be initiated earlier, reducing CVD risk even further. Altogether, this is likely to explain the large differences in predicted and observed absolute risks that have led to poor calibration.

To further investigate the difference between the study populations, the model was fitted on our data and the regression coefficients were compared with the original values of the UKPDS risk engine. The greatest difference was observed for sex, with women having a slightly greater risk compared with men in our population, which is opposite to the original UKPDS model. This difference might be explained by different lifestyles between men and women in 1977 and nowadays. More men tended to smoke in 1977 which, combined with starting smoking at an earlier age, may have increased the CVD risk in men at this time.[23]

The current cohort was established between 1993 and 1997 and differences in lifestyle between men and women may have changed over time, probably resulting in the observed change in the regression coefficient for sex. Furthermore, to some extent it can be explained by the high number of women in our population. When only the German cohort, which has equal numbers of men and women, was analysed, this difference in the CVD risk for women between our cohort and the UKPDS was eliminated.

The results of this study are comparable with those of other validation studies. Two studies observed a modest discrimination (c-statistics 0.74, 0.67) and an underestimation[5;6] of CHD risk instead of an overestimation as we and others observed.[4;7;11] Yet, the number of diabetes patients in these studies was small (n=125, n=428). Furthermore, one of these studies estimated 10 year CVD and CHD risk, while the follow-up of their cohort was only 4 years.[5] A validation study in the EPIC-Norfolk population observed a good discrimination and an overestimation

of the 10 year CVD risk.[4] However, a slightly different version of the UKPDS risk engine was validated, which was designed to calculate CVD risk instead of CHD risk.[4] Therefore, their results might not be directly comparable with the results of our study. Combining our results with the previous studies mentioned, we can conclude that the performance of the UKPDS risk engine for predicting CVD and CHD risks is only moderate to poor. Nonetheless, Dutch, Canadian and UK guidelines recommend using the UKPDS risk engine to calculate CHD risk in general practice.[13-15] The UKPDS risk engine is also used in large trials to calculate initial CHD risk.[24] It may not be advisable to use the UKPDS risk engine to calculate absolute risk as a basis to initiate treatment or to use risk ranking based on the outcome of the UKPDS risk engine, as performance of the UKPDS is moderate to poor.

Constructing a new diabetes-specific CVD risk model might enhance accurate risk prediction, particularly if using a more contemporary population. As treatment of diabetes has improved over time, CVD risk has been lowered. Furthermore, modifiable risk factors have changed over time: smoking is less common and there are better treatments for hypertension and to lower HbA1c concentrations. These developments have impacted on the associated risk for a cardiovascular event.

In summary, we observed that the UKPDS risk engine severely overestimated CHD and CVD risks in patients with type 2 diabetes. The discriminative ability was only moderate to poor. The results from various subgroup analyses were not substantially different. To enhance prediction of CVD and CHD in patients with type 2 diabetes, there is a need to update or construct a new and improved diabetes-specific model with better performance and, more importantly, better external validity.[25;26]



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# Supplementary materials

## Supplementary material text 1

### Model description UKPDS risk engine

$R(t) = 1\text{-}\exp(-qd^{T}((1-d^{t})/(1-d)))$

R: predicted risk
t: calculated risk years
$d^{T}$: duration since diagnosis of diabetes

Linear predictor:

$$q = q_0 ß_1^{\text{age-55}} ß_2^{\text{sex}} ß_3^{\text{ac}} ß_4^{\text{smoke}} ß_5^{\text{HbA1c-6.72}} ß_6^{\text{(sbp-135.7)/10}} ß_7^{\text{ln (LR)-1.59}}$$

| Estimates for the model | |
|---|---|
| Intercept ($q_0$) | 0.0112 |
| Age ($ß_1$) | 1.059 |
| Sex ($ß_2$) | 0.525 |
| Ethnicity ($ß_3$) | 0.390 |
| Smoking ($ß_4$) | 1.350 |
| HbA1c ($ß_5$) | 1.144 |
| Systolic blood pressure ($ß_6$) | 1.073 |
| Lipid ratio ($ß_7$) | 3.11 |
| Duration of diabetes (d) | 1.078 |

**Supplementary materials Table 1.** Discrimination and calibration of the UKPDS risk engine for 4, 5, 6 & 8 calculated risk years with CHD as outcome for patient group with diagnoses of diabetes up to 10 years. First analysis: censored cases excluded, second analysis: censored cases included.

| Calculated risk period | First analysis | | | Second analysis | | |
|---|---|---|---|---|---|---|
| (Years) | Cases/n | c-statistic | $\chi^2$ statistic | Cases/n | c-statistic | $\chi^2$ statistic |
| 4 | 30/1093 | 0.64 (0.45-0.85) | 33.2 (p<0.001) | 30/1170 | 0.64 (0.44-0.84) | 37.9 (p<0.001) |
| 5 | 30/1066 | 0.66 (0.48-0.84) | 46.6 (p<0.001) | 33/1170 | 0.65 (0.47-0.84) | 56.0 (p<0.001) |
| 6 | 36/1037 | 0.66 (0.48-0.83) | 60.6 (p<0.001) | 36/1170 | 0.65 (0.47-0.83) | 77.2 (p<0.001) |
| 8 | 49/802 | 0.65 (0.50-0.80) | 56.5 (p<0.001) | 49/1170 | 0.64 (0.49-0.79) | 118.8 (p<0.001) |

**Supplementary materials Table 2.** Discrimination and calibration of the UKPDS risk engine for 4, 5, 6 & 8 calculated risk years with CHD as outcome for patient group with diagnosed diabetes for over 10 years. First analysis: censored cases excluded, second analysis: censored cases included.

| Calculated risk period | First analysis | | | Second analysis | | |
|---|---|---|---|---|---|---|
| (Years) | Cases/n | c-statistic | $\chi^2$ statistic | Cases/n | c-statistic | $\chi^2$ statistic |
| 4 | 18/415 | 0.65 (0.35-0.94) | 15.2 (p=0.347) | 18/452 | 0.64 (0.34-0.94) | 18.2 (p=0.174) |
| 5 | 22/410 | 0.63 (0.37-0.89) | 20.8 (p=0.098) | 22/452 | 0.63 (0.37-0.88) | 25.6 (p=0.031) |
| 6 | 27/401 | 0.63 (0.39-0.86) | 25.3 (p=0.018) | 27/452 | 0.62 (0.39-0.85) | 32.2 (p=0.005) |
| 8 | 31/292 | 0.63 (0.42-0.84) | 23.3 (p=0.028) | 31/452 | 0.63 (0.42-0.84) | 55.3 (p<0.001) |

**Supplementary materials Table 3.** Discrimination and calibration of the UKPDS risk engine for 4, 5, 6 & 8 calculated risk years with CVD as outcome for patient group with diagnoses of diabetes up to 10 years. First analysis: censored cases excluded, second analysis: censored

| Calculated risk period | First analysis | | | Second analysis | | |
|---|---|---|---|---|---|---|
| (Years) | Cases/n | c-statistic | $\chi^2$ statistic | Cases/n | c-statistic | $\chi^2$ statistic |
| 4 | 46/1094 | 0.66 (0.50-0.82) | 16.0 (p=0.232) | 46/1170 | 0.65 (0.49-0.81) | 20.3 (p=0.065) |
| 5 | 51/1068 | 0.67 (0.52-0.82) | 24.0 (p=0.026) | 51/1170 | 0.66 (0.51-0.81) | 32.1 (p=0.002) |
| 6 | 60/1040 | 0.67 (0.53-0.80) | 29.6 (p=0.005) | 60/1170 | 0.66 (0.52-0.80) | 43.0 (p<0.001) |
| 8 | 81/807 | 0.65 (0.53-0.78) | 22.1 (p=0.009) | 81/1170 | 0.64 (0.52-0.76) | 70.3 (p<0.001) |

**Supplementary materials Table 4.** Discrimination and calibration of the UKPDS risk engine for 4, 5, 6 & 8 calculated risk years with CVD as outcome for patient group with diagnosed diabetes for over 10 years. First analysis: censored cases excluded, second analysis: censored cases included.

| Calculated risk period | First analysis | | | Second analysis | | |
|---|---|---|---|---|---|---|
| (years) | Cases/n | c-statistic | $\chi^2$ statistic | Cases/n | c-statistic | $\chi^2$ statistic |
| 4 | 21/416 | 0.66 (0.39-0.93) | 13.0 (p=0.456) | 21/452 | 0.66 (0.39-0.93) | 15.5 (p=0.290) |
| 5 | 27/411 | 0.63 (0.40-0.87) | 16.6 (p=0.260) | 27/452 | 0.63 (0.39-0.86) | 20.3 (p=0.083) |
| 6 | 34/402 | 0.63 (0.42-0.84) | 19.3 (p=0.049) | 34/452 | 0.62 (0.41-0.83) | 25.0 (p=0.023) |
| 8 | 41/293 | 0.63 (0.45-0.82) | 15.1 (p=0.395) | 41/452 | 0.64 (0.46-0.82) | 39.8 (p<0.001) |

# Chapter 9

# The validation of cardiovascular risk scores in people with type 2 diabetes mellitus

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## Abstract

**Introduction:** Several cardiovascular prediction models have been developed for application in patients with type 2 diabetes. Their predictive performance in a new set of patients is mostly lacking. We validated the cardiovascular prediction models, identified by a recent systematic review, in two different cohorts of patients with type 2 diabetes.

**Methods:** Data from five years follow-up of 455 diabetes patients of the prospective EPIC-NL cohort and 1,175 diabetes patients of the prospective EPIC-Potsdam cohort were used to validate 9 prediction models to predict cardiovascular disease (CVD) or coronary heart disease (CHD) (EPIC-NL) and myocardial infarction (EPIC-Potsdam) among patients with type 2 diabetes. Discrimination was assessed by the c-statistic for survival data. Calibration was assessed by calibration plots before and after recalibration of the prediction models, and tested by the Hosmer-Lemeshow (H-L) test.

**Results:** During 5-year follow-up, patients were followed for incidence of CVD and CHD. All nine prediction models showed a moderate discrimination, with c-statistics ranging from 0.55 (95% CI: 0.46 to 0.70) for the Fremantle risk score to 0.71 (95% CI: 0.61 to 0.80) for the UKPDS risk score. Most prediction models severely overestimated the risk between 23% to 189%, except for the ADVANCE risk score, which underestimated the risk. After recalibration of the models, the calibration of all models was good, (all H-L test p-values>0.05), with only a slight overestimation of the risk.

**Conclusion:** After appropriate recalibration of the models, most of the models provided accurate CVD risk estimates. However, discrimination for almost all models between type 2 diabetes patients who did and those who did not develop CVD or CHD was only moderate. Before using these prediction models in clinical practice performance, especially discrimination, should be improved.

## Introduction

The global population of patients with type 2 diabetes (T2D) is rapidly growing. The number of people living with diabetes is expected to rise from 366 million people in 2011 to 552 million by 2030.[1] One of the major complications of type 2 diabetes is cardiovascular disease (CVD). People with type 2 diabetes are at a 2-4 fold increased risk for developing CVD compared to people without diabetes.[2]

In order to prevent CVD and initiate appropriate treatment it is important to stratify patients into groups based on their risk of developing CVD, as recommended by several guidelines.[3-5] In the past decades many prediction models for estimating cardiovascular risk have been developed. In a recent systematic review, we identified 45 cardiovascular prediction models, of which 12 were designed specifically for patients with type 2 diabetes.[6] Interestingly, only a few of these prediction models were evaluated in independent patient populations.[6] The older and more commonly used prediction models such as the UKPDS risk engine[7] have been externally validated, and turned out to have moderate discrimination (ability to distinguish between patients at low and high risk) and often poor calibration (ability to correctly quantify the observed risk).[8-10] Nevertheless, this risk engine, has been included in several national guidelines.[4;11;12] Since the publication of these prediction models, diabetes treatment has changed considerably; statin use is widespread among T2D patients and both HbA1c and blood pressure targets have decreased. Over the past two years three new cardiovascular prediction models have been developed for diabetes patients: the ADVANCE, DCS, and the Fremantle risk score, respectively.[13-15] These contemporary prediction models have rarely been validated.[13-15] With so many prediction models available, it is important to know whether they have a good performance in a new set of patients before including them in guidelines.[16] The aim of this study is to quantify the predictive performance of all cardiovascular prediction models developed specifically for CVD risk prediction in diabetes patients.



## Methods

### Selected Cardiovascular risk models

For the comparison in this study all risk scores for diabetes patients that predict either coronary heart disease (CHD) or CVD, identified by our previous systematic review[6], were eligible. Of the thirteen models

identified, three were excluded because the outcome of the risk score was stroke or heart failure.[17-19] One model was excluded because the paper did not provide sufficient information to recalculate the model in our patient data.[20] As one model was developed in two separate versions (the DCS risk score)[15] to predict either coronary heart disease (CHD) or cardiovascular disease (CVD), in total nine models were tested in our analyses.

The prediction models for CVD included: the Action in Diabetes and Vascular Disease: preterax and Diomicron-MR controlled Evaluation (ADVANCE) risk score[13], the Fremantle risk score,[14] the Swedish National Diabetes Registry (NDR) risk score,[21] and the New Zealand Diabetes Cohort Study (DCS) risk score[15] (Table 1). The prediction models for CHD were: the DCS risk score,[15] Diabetes Audit and Research in Tayside Scotland (DARTS) risk score,[22] Hong Kong Diabetes Register (HKDR) risk score,[23] Atherosclerosis Risk in Communities (ARIC) risk score[24] and the United Kingdom Prospective Diabetes Study (UKPDS) risk engine.[7]

Seven out of the nine prediction models predict 5-year risk, whereas the ARIC risk score predicts 10 year risk and the ADVANCE risk score predicts 4-year risk. Most of the prediction models were initially based on a Cox proportional hazard model, except the DARTS risk score (Weibull model) and the UKPDS risk engine (Gompertz model). Table 1 gives an overview of the predictors used in each of the models.

**Study population and design**

The study population consisted of patients with type 2 diabetes from the Dutch and German contributions to the European Prospective Investigation into Cancer and Nutrition (EPIC-NL and EPIC-Potsdam). Both cohorts are described in more detail elsewhere.[25;26] In brief, EPIC-NL consists of two sub-cohorts, the Prospect cohort and the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) cohort. Prospect is a prospective population-based cohort of 17,357 women, aged 49-70 years, living in Utrecht and vicinity, who participated in breast cancer screening between 1993 and 1997. The MORGEN cohort consists of 22,654 men and women, aged 20-59 years, recruited from three Dutch towns (Amsterdam, Maastricht and Doetinchem). From 1993 to 1997 each year a new random sample of about 5,000 participants was examined. Between 1994 and 1998 the EPIC-Potsdam cohort recruited 27,548 participants, aged 35 to 65 years, living in Potsdam, Germany and surrounding communities. The recruitment population was based on general population registries.

**Table 1.** Description of cardiovascular prediction models for patients with type 2 diabetes

| Risk score | ADVANCE[13] | Fremantle[14] | DCS[15] | NDR[21] | HKDR[23] | DARTS[22] | ARIC[24] | UKPDS 56[7] |
|---|---|---|---|---|---|---|---|---|
| First author, publication year | Kengne 2011 | Davis 2010 | Elley 2010 | Cederholm 2008 | Yang 2008 | Donnan 2006 | Folsom 2001 | Stevens 2001 |
| Outcome | CVD | CVD | CVD/ CHD | CVD | CHD | CHD | CHD | CHD |
| Cohort size | 7168 | 1240 | 36127 | 11646 | 7067 | 4569 | 1273 | 4540 |
| Incidence (%) | 6.6 (473) | 14.9 (185) | 17.9 (6479)/n.a. | 12.7 (1482) | (5.0) 351 | 5.3 (243) | 10.1(128) | n.a. |
| Predicted time period (years) | 4 | 5 | 5 | 5 | 5 | 5 | 10 | Variable |
| Model type Predictors | Cox | Cox | Cox | Cox | Cox | Weibull | Cox | Gompertz |
| Sex | yes | yes | yes | yes | yes | yes | yes | yes |
| Age | yes | yes | yes | yes | yes | yes | yes | yes |
| HbA1c | yes | yes | yes | yes | no | yes | no | yes |
| Duration of diabetes | yes | no | yes | yes | yes | yes | no | yes |
| Albuminuria | yes | no | yes | no | no | no | no | no |
| AC ratio | no | yes | no | no | yes | no | no | no |
| HDL cholesterol | no | yes | no | no | no | no | yes | no |
| Non-HDL cholesterol | yes | no | no | no | yes | no | no | no |
| Total/HDL cholesterol | no | no | yes | no | no | no | no | yes |
| Total cholesterol | no | no | no | no | no | yes | yes | no |
| Pulse pressure | yes | no | no | no | no | no | no | yes |
| Systolic blood pressure | no | no | yes | yes | no | yes | yes | no |
| Hypertensive medication | yes | no | yes | no | no | yes | yes | no |
| History CVD | no | yes | no | no | no | no | no | no |

**Table 1.** Continued.

| Risk score | ADVANCE[13] | Fremantle[14] | DCS[15] | NDR[21] | HKDR[23] | DARTS[22] | ARIC[24] | UKPDS 56[7] |
|---|---|---|---|---|---|---|---|---|
| First author, publication year | Kengne 2011 | Davis 2010 | Elley 2010 | Cederholm 2008 | Yang 2008 | Donnan 2006 | Folsom 2001 | Stevens 2001 |
| Ethnicity | no | yes | yes | no | no | no | yes | yes |
| Smoking | no | no | yes | yes | yes | yes | yes | yes |
| BMI | no | no | no | yes | no | no | no | no |
| Height | no | no | no | no | no | yes | no | no |
| Lipid lowering medication | no | no | no | yes | no | no | no | no |
| eGFR | no | no | no | no | yes | no | no | no |
| Retinopathy | yes | no | no | no | no | no | no | no |
| Atrial fibrillation | yes | no | no | no | no | no | no | no |

In total, 536 prevalent type 2 diabetes cases were identified at baseline in EPIC-NL and 1332 diabetes cases were identified in EPIC-Potsdam. Patients with a history of cardiovascular disease (EPIC-NL n=71, EPIC-Potsdam n=157) and patients with missing endpoints (EPIC-NL n=10, EPIC-Potsdam n=1) were excluded from the analyses. This resulted in 455 patients with type 2 diabetes in EPIC-NL and 1174 diabetes patients in EPIC-Potsdam for the current analyses. Participants from EPIC-NL were all confirmed diagnosed type 2 diabetes patients. For EPIC-Potsdam 322 patients were confirmed type 2 diabetes patients and for 852 patients the diabetes type was unspecified. Diabetes cases of the EPIC-NL cohort were verified through medical records of the general practitioner or pharmacist,[27] while participants of the EPIC-Potsdam were verified through repeated self-report in follow-up questionnaires.[28] All participants gave written informed consent prior to study inclusion. Both studies were approved by the local ethical committee.

**Predictors and Measurements**

At baseline, a general questionnaire containing questions on demographic characteristics, smoking, presence of chronic diseases and other potential risk factors was filled out by all participants in both cohorts. Body weight and height were measured. Smoking was recoded into current smokers and non-smokers. For participants of EPIC-NL blood pressure was measured twice and for EPIC-Potsdam thrice. The measurement was performed on the left arm while the participant was in a supine position. The mean of these measurements was used in the analyses. In EPIC-Potsdam and the Prospect study systolic and diastolic blood pressure was measured using a Boso oscillomat (Bosch & Sohn, Jungingen, Germany). In the MORGEN cohort a random zero Sphygmomanometer (Hawksley & Sons, Lancing, UK) was used. Thirty millilitres of blood was collected from all participants to obtain plasma, serum and erythrocytes and stored at -196°C. Total, HDL and LDL cholesterol and triacylglycerol levels were measured in frozen serum samples and HbA1c was measured in erythrocytes.

**Endpoints**

Participants were followed-up for CVD and CHD in both cohorts, although different definitions for these endpoints in EPIC-NL and EPIC-Potsdam were used. CHD was defined as acute myocardial infarction in EPIC-Potsdam [ICD-9 codes: 410, ICD-10 codes: I21], whereas it was defined as a combination of acute myocardial infarction and ischemic

heart disease in EPIC-NL [ICD-9 codes: 410-414, ICD-10 codes: I20-I25]. Cardiovascular events were defined as myocardial infarction, ischemic heart disease or stroke in EPIC-NL [ICD-9 codes: 410-414, 430-434, 436, ICD-10 codes: I20-I25, I60-I67, I69] and as acute myocardial infarction or stroke in EPIC-Potsdam [ICD-9 codes: 410, 430-434, ICD-10 codes: I21, I60-I64]. Vital status of EPIC-NL participants was obtained through linkage with the municipal population registries. In EPIC-NL incident morbidity cases were obtained through linkage with the Dutch National Medical Registry, which holds a standardized computerized database of all hospital discharge diagnoses throughout the country, using a validated probabilistic method. In EPIC-Potsdam the major source of incident cases was obtained through questionnaires that were mailed to all participants every two years. Mortality data for EPIC-Potsdam participants was collected through cooperation with the local health offices of Potsdam and the state office of statistics of Brandenburg. Follow-up was 95% complete.

**Statistical analysis**

Time at risk was calculated as time between enrolment in the study and diagnosis of one of the two endpoints (CHD or CVD), date of death or end of follow-up. Means, standard deviation and percentages were used to compare the baseline characteristics between the two country cohorts.

Most of the variables included in the prediction models were available in both EPIC-NL and EPIC-Potsdam cohort. Data on age and sex were available for all participants. If a variable was missing in some patients, these values were imputed using single imputation. Simply excluding these participants would have provided biased results, since missing data did not occur completely at random.[29] In EPIC-NL missing values ranged from 0.4% (for smoking) to 13.6% (for cholesterol). In EPIC-Potsdam missing values ranged from 0.1% (for age at diabetes diagnosis) to 21.6% (for HbA1c). The variable albumin-creatinin ratio (AC ratio) (used in the ADVANCE[13] and DCS[15] models) was missing in all patients and was replaced by a proxy based on estimated glomerular filtration rate (eGFR), which was calculated using serum creatinine. If eGFR<60ml then AC ratio was defined as 300µg/mg, if eGFR was between 60 and 90ml then AC ratio was set to 165µg/mg if eGFR>90ml then AC ratio was set to 15µg/mg. Using these AC ratios macroalbuminuria was defined as an AC ratio ≥300µg/mg, microalbuminuria was defined as AC ratio between 30-300µg/mg. To validate this proxy we explored the association with CVD, which showed a HR for macroalbuminuria of 1.83

(95% CI: 0.75-4.46) and for microalbuminria of 1.27 (95% CI: 0.88-185). Retinopathy and atrial fibrillation (used in the ADVANCE prediction model) were also missing for all patients, since no appropriate proxy could be defined, all patients were assigned the value of zero for these variables.

Performance of all 9 models was examined by discrimination (ability to distinguish between patients who will get the disease and patients who will not get the disease) and calibration (the agreement between observed and predicted risk). Discrimination was assessed by Harrell's c-statistic, which is comparable to the area under receiver operator characteristic, adapted for time-to-event data.[30] To further examine the discrimination, patients were divided according to low medium and high risk as calculated by the prediction models and percentage with outcome was calculated for each category. Based on the cardiovascular incidence in the cohorts, low, medium and high risk groups for CVD were defined as <5%, 5-10%, >10% for EPIC-NL and <4%, 4-8%, >8% for EPIC-Potsdam. For CHD the risk groups were defined as <5%, 5-10%, >10% for EPIC-NL and <2%, 2-4%, >4% for EPIC-Potsdam.

For the predicted probabilities either 4-, 5- or 10-year risk was used, depending on the predicted time period of the individual prediction models.

The calibration of the prediction models was assessed by the Hosmer-Lemeshow chi-square test as well as calibration plots. Since calibration is strongly influenced by the incidence of the outcome in the population of interest, the prediction models were recalibrated to the incidence in our study population. Using this approach, differences between the models due to differences in incidence between the development populations are eliminated, thereby mimicking the process one would follow when implementing a prediction model in practice.[16;31] All prediction models were recalibrated to 5-year risks for both cohorts separately. Recalibration was performed by replacing the baseline hazard with the baseline 5-year hazard of our cohorts and by recalculating the risk for a mean patient in our cohorts and subtracting this mean from the linear predictor in the prediction models. After recalibration, calibration was re-assessed by Hosmer-Lemeshow and calibration plots.

A sensitivity analyses was conducted with a longer prediction horizon by using all follow-up years and endpoints in order to have more endpoints for sufficient power. A second sensitivity analysis

was performed to examine the influence of the missing values of retinopathy and atrial fibrillation in which these predictors were set as being present. To estimate the effects of using a proxy for AC ratio, we performed a third sensitivity analysis in which AC ratio was set to a very low value (i.e. 0.01).
All statistical analyses were performed using R-2.15.1 for windows (http://cran.r-project.org/).

## Results

In EPIC-NL 35 CVD events were documented during 5 years of follow-up, of which 32 were CHD. In EPIC-Potsdam 41 CVD events were documented of which 23 were CHD.
Table 2 displays the baseline characteristics of EPIC-NL and EPIC-Potsdam. The EPIC-NL cohort consisted of more women compared with EPIC-Potsdam. Patients in the EPIC-NL cohort were diagnosed with type 2 diabetes for a mean of 6.9 (SD: 6.8) years, while patients in EPIC-Potsdam had diabetes for 7.6 (SD: 7.4) years. Diabetes patients from EPIC-Potsdam were slightly healthier than diabetes patients from EPIC-NL; they smoked less, had a lower systolic blood pressure and

**Table 2.** Baseline characteristics of diabetes patients from EPIC-NL (n=455) and EPIC-Potsdam (n=1174)

| Variable | EPIC-NL | EPIC-Potsdam | P-value |
|---|---|---|---|
| Sex (male), n (%) | 82 (17.6) | 639 (54.4) | <0.001 |
| Age at recruitment (years), m (SD) | 58.1 (6.69) | 57.7 (6.46) | 0.207 |
| Age at diagnosis of diabetes (years), m (SD) | 51.3 (9.23) | 50.1 (9.22) | 0.015 |
| Diabetes duration (years), m (SD) | 6.85 (6.84) | 7.62 (7.36) | 0.045 |
| BMI ($Kgm^{-2}$), m (SD) | 29.6 (5.06) | 29.4 (5.01) | 0.420 |
| Smoking (current), n (%) | 107 (23.0) | 219 (18.7) | 0.028 |
| Systolic blood pressure (mmHg), n (%) | 143 (21.0) | 141 (18.5) | 0.033 |
| HbA1c (%), m (SD) | 8.10 (1.72) | 8.28 (2.34) | 0.094 |
| Total cholesterol (mmol/l), m (SD) | 5.31 (1.19) | 4.69 (0.94) | <0.001 |
| HDL cholesterol (mmol/l), m (SD) | 1.05 (0.28) | 1.07 (0.28) | 0.147 |
| LDL cholesterol (mmol/l), m (SD) | 3.22 (0.84) | 2.71 (0.82) | <0.001 |

lower cholesterol levels.

**Discrimination**

Table 3 describes the discrimination of the nine prediction models. All prediction models predicting either CVD or CHD showed a similar moderate discrimination. In EPIC-NL the c-statistics ranged from 0.55 to 0.61, while the discrimination in EPIC-Potsdam was slightly better than in EPIC-NL for most of the models. The c-statistics ranged from 0.67 to 0.71 for almost all models except for the DARTS risk score which showed a lower discrimination of 0.57 (95% CI:0.43-0.70).

The NDR and Fremantle prediction models showed a slightly better discrimination according to risk categories of low, medium and high CVD risk in both EPIC-NL and EPIC-Potsdam (Supplementary material table 2 and table 3). According to percentages of patients with CHD classified as low, medium or high risk several risk scores showed a better discrimination, which were the HKDR and DARTS in EPIC-NL and the DCS HKDR and UKPDS in EPIC-Potsdam compared to the other prediction models (Supplementary material table 4 and table 5).

The sensitivity analysis using all follow-up years showed a similar discrimination for all prediction models for both EPIC-NL and EPIC-Potsdam. Discrimination in EPIC-NL ranged from 0.55 to 0.60 and in EPIC-Potsdam from 0.66 to 0.69, with DARTS showing a lower

**Table 3.** Discrimination of the prediction models in Epic-NL and Epic-Potsdam

| Risk score | Epic-NL | Epic-Potsdam |
|---|---|---|
| CVD prediction models | | |
| Kengne 2011 (ADVANCE)[13] | 0.58 (0.46-0.70) | 0.66 (0.58-0.75) |
| Davis 2010 (Fremantle)[14] | 0.55 (0.46-0.65) | 0.68 (0.61-0.76) |
| Elley 2010 (DCS)[15] | 0.60 (0.50-0.70) | 0.68 (0.60-0.75) |
| Cederholm 2008 (NDR)[21] | 0.60 (0.51-0.70) | 0.67 (0.59-0.75) |
| CHD prediction models | | |
| Elley 2010 (DCS)[15] | 0.59 (0.48-0.69) | 0.68 (0.59-0.78) |
| Yang 2008 (HKDR)[23] | 0.61 (0.52-0.71) | 0.69 (0.59-0.80) |
| Donnan 2006 (DARTS)[22] | 0.60 (0.51-0.70) | 0.57 (0.43-0.70) |
| Folsom 2003 (ARIC)[24] | 0.56 (0.49-0.64) | 0.67 (0.60-0.74) |
| Stevens 2001 (UKPDS risk engine)[7] | 0.59 (0.48-0.70) | 0.71 (0.61-0.80) |

All prediction models calculate a 5-year predicted risk except the ADVANCE risk score (4 years) and the ARIC risk score (10 years) and similar time periods from our cohorts where used to estimate the discrimination

discrimination of 0.56.

**Calibration**

The observed 5-year CVD risk was 8.1% in EPIC-NL and 3.5% in EPIC-Potsdam. Before recalibration the calibration was poor (all p-values for the HL statistic were <0.001). The risk estimated by the prediction models ranged from considerable under prediction (estimated risk: 2.03%) to severe over prediction (estimated risk: 21.7%) for both EPIC-NL and EPIC-Potsdam (Supplementary material table 1 & Figure 1). Table 4 shows the predicted risk by each of the prediction models after recalibration. The mean estimated risk by the prediction models was only slightly overestimated and varied between 8.9% for the NDR risk score and 9.5% for the ADVANCE risk score in EPIC-NL.

The overestimation of the risk varied between 4.1% for the DCS risk score and 4.6% for the ADVANCE risk score in EPIC-Potsdam. After recalibration all prediction models showed a good calibration (all p-values>0.05; Figure 1, Table 4). Only for the Fremantle risk score in EPIC-NL a significant difference between the observed and predicted risk was observed (HL-$\chi^2$: 17.92, p-value=0.036).

The observed 5-year CHD risk was 7.3% in EPIC-NL, while this was 2.0% in EPIC-Potsdam. All prediction models showed a poor calibration, except the DCS risk score in EPIC-NL (Supplementary material table 1 & Figure 2). After recalibration the estimated risk was still slightly overestimated and calibration was good for three out of five CHD prediction models (Table 4 & Figure 2).

In the sensitivity analysis using all follow-up years, a poorer calibration was observed, which is to be expected since the predicted time period was then up to 14 years while the prediction models are designed to predict for 5 years. The sensitivity analysis in which all patients were assigned as having retinopathy and atrial fibrillation or setting AC ratio

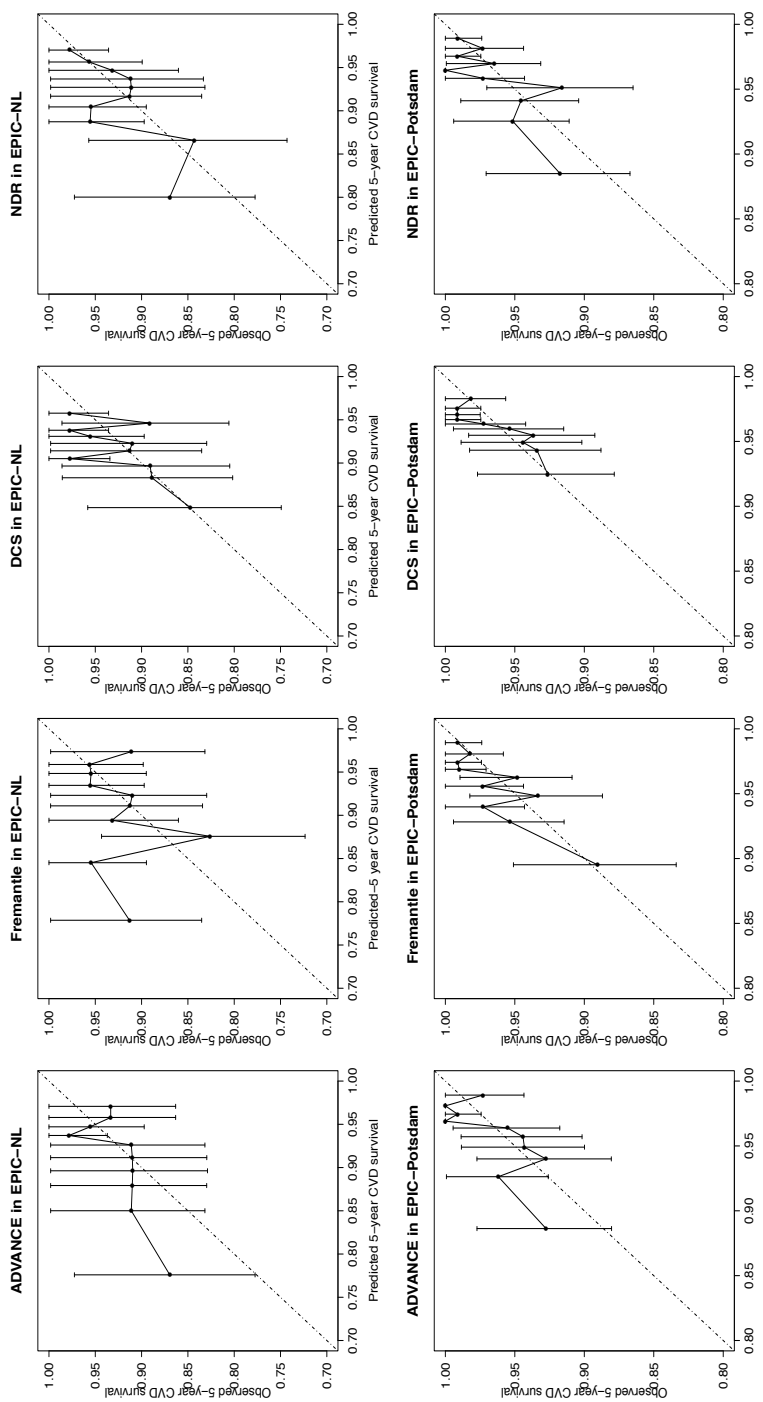


**Figure 1. Calibration plots after recalibration of the CVD prediction models in EPIC-NL and EPIC-Potsdam.** The plots display the CVD free 5-year survival (1 minus 5-year CVD risk). The observed survival (y-axes) is plotted against the predicted survival by the prediction models (x-axes).

**Table 4.** Mean estimated risk and Hosmer-Lemeshow chi-square after recalibration of the prediction models

| Risk score | EPIC-NL | | EPIC-Potsdam | |
|---|---|---|---|---|
| | Estimated risk (%), mean (SD)[1] | Hosmer-Lemeshow Chi-square | Estimated risk (%), mean (SD)[2] | Hosmer-Lemeshow Chi-square |
| CVD prediction models | | | | |
| Kengne 2011 (ADVANCE) | 9.5 (5.88) | 8.40 (p=0.494) | 4.6 (3.11) | 15.3 (p=0.083) |
| Davis 2010 (Fremantle) | 9.6 (5.77) | 17.92 (p=0.036) | 4.6 (2.78) | 9.29 (p=0.411) |
| Elley 2010 (DCS) | 8.6 (3.21) | 8.09 (p=0.525) | 4.1 (1.70) | 6.35 (p=0.704) |
| Cederholm 2008 (NDR) | 8.9 (4.99) | 5.84 (p=0.756) | 4.6 (3.19) | 12.3 (p=0.195) |
| CHD prediction models | | | | |
| Elley 2010 (DCS) | 8.0 (3.36) | 13.8 (p=0.130) | 2.4 (1.15) | 6.96 (p=0.641) |
| Yang 2008 (HKDR) | 8.1 (3.87) | 5.35 (p=0.802) | 2.4 (1.31) | 20.2 (p=0.017) |
| Donnan 2006 (DARTS) | 8.9 (5.75) | 9.71 (p=0.374) | 2.7 (1.80) | 28.2 (p<0.001) |
| Folsom 2001 (ARIC) | 8.8 (5.62) | 17.9 (p=0.037) | 2.5 (1.70) | 8.52 (p=0.483) |
| Stevens 2001 (UKPDS) | 10.0 (8.86) | 20.7 (p=0.014) | 3.5 (5.66) | 14.28 (p=0.113) |

[1]The observed risk in EPIC-NL was 8.1% and 7.3% for CVD and CHD respectively.
[2]The observed risk in EPIC-Potsdam was 3.5% and 2.0% for CVD and CHD respectively.

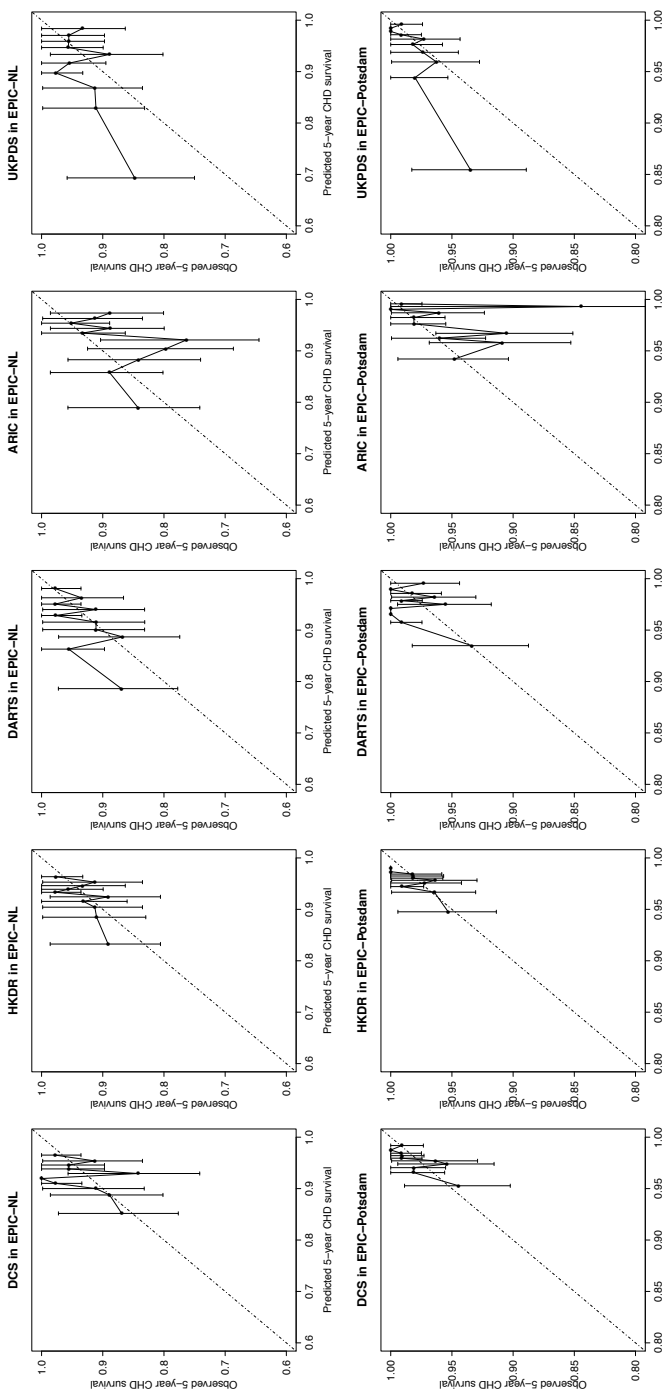


**Figure 2. Calibration plots after recalibration of the CHD prediction models in EPIC-NL and EPIC-Potsdam.** The plots display the CHD free 5-year survival (1 minus 5-year CHD risk). The observed survival (y-axes) is plotted against the predicted survival by the prediction models (x-axes).

to a low value yielded similar results.

## Discussion

In this study we tested the predictive accuracy of cardiovascular prediction models developed for patients with type 2 diabetes in two different countries. Overall the discrimination was moderate with a c-statistic between 0.55 and 0.71. Most prediction models showed an overestimation of the risk, while the ADVANCE risk score underestimated the risk before recalibration. After recalibrating the models, calibration was good for most models, with only a slight overestimation of the risk. The main strengths of this study are the inclusion of almost all existing cardiovascular prediction models that have been developed specifically for patients with type 2 diabetes and testing of the models in two independent cohorts with different incidences of CVD. In addition, we did not only assess the calibration of the original models, as differences between the models would then have been influenced strongly by incidence differences in the development cohorts. Rather, we also provided a comparison of the models after a simple recalibration, a procedure one would commonly apply before implementing a risk score in practice[16;31] to address the question which model would yield the best risk estimates. Nevertheless some limitations need to be addressed. First, not all predictors included in the prediction models (ADVANCE, Fremantle and DCS) were available in our cohorts (albumin-creatinin ratio, retinopathy and atrial fibrillation were missing). We addressed this issue by assigning a value of zero to atrial fibrillation and retinopathy. For albumin-creatinin ratio we used an unconventional proxy, but exclusion of these models because of missing predictors would lead to an incomplete validation. We do not expect that these missing predictors have largely influenced our results, since similar performance was shown for prediction models that only included variables that were all available in our cohorts and sensitivity analyses for these predictors yielded similar results. A second issue is the small number of outcomes occurring in the cohorts over the first 5 years of follow-up (CVD: n=35 for EPIC-NL and n=41 for EPIC-Potsdam). This is due to the fact that most prediction models predicted 5-year risk, while most cardiovascular events occurred after 5 years in our cohorts. It has been shown that a number of 100 events is required to validate existing prediction model in other cohorts. [32] However, a sensitivity analysis using all follow-up data from our cohorts provided more than 100 endpoints and showed similar discrimination. Therefore we expect

that this issue did not influence our results. Slightly different endpoints were used in the two cohorts, in EPIC-Potsdam patients were followed for myocardial infarction, while in EPIC-NL patients were followed for coronary heart disease, including myocardial infarction. These differences in endpoints lead to differences in calibration, however recalibration of the risk scores solves this issue.

In this study we observed that most prediction models to predict CVD among diabetes patients performed only moderately in identifying patients at risk, while after recalibration they were able to accurately quantify the risk. The moderate discrimination might be explained by the complicated disease pattern and the many factors involved resulting in a heterogeneous population. Furthermore patients at an increased cardiovascular risk take medication for modifiable cardiovascular risk factors, although drug therapy is beneficial for patients, it might make prediction of cardiovascular disease more difficult. According to risk categories of low, medium and high risk several models were identified that were the most promising in discriminating between low, medium and high risk patients. These were the NDR and Fremantle for CVD in both EPIC-NL and EPIC-Potsdam, while there was less consistency among the CHD prediction models.

The ADVANCE,[13] Fremantle,[14] DCS[15] and DARTS[22] prediction models have been externally tested for their predictive accuracy once before. The discrimination observed was similar to the results obtained in our study, except for the discrimination of the Fremantle risk score[14] which showed a much better discrimination of 0.84 in the validation reported than was reported in the development paper. This difference might be explained by the small validation cohort that was used (n=180) or a difference in baseline characteristics (lower HbA1c, higher age) between the original validation set and our cohorts. The calibration observed in the above mentioned validation studies was mostly good which is in line with the calibration we observed after recalibrating the models. The previous validation of the ADVANCE risk score[13] showed a moderate underestimation of the risk, similar to what we observed before recalibrating this risk score. This underestimation of the risk might be explained by the fact that ADVANCE is a randomized trial in which the patients received a stringent treatment by either blood pressure lowering or blood glucose lowering or standard therapy. The UKPDS risk engine[7] has been extensively validated by nine studies with varying results,[9;10;33-39] the observed discrimination varied from 0.65 to 0.76. In a previous external validation study of the UKPDS risk

engine in a combined cohort of diabetes patients of EPIC-Potsdam and EPIC-NL, we observed a discrimination of 0.65 and a poor calibration, which is comparable to the results of this study where a c-statistic of 0.59 in EPIC-NL and 0.71 in EPIC-Potsdam was observed. Most validation studies showed a poor calibration and the UKPDS risk engine mostly overestimated the risk while in some studies the risk was underestimated. An overestimation of the risk might be explained by the fact that the UKPDS trial is an older study where the incidence of cardiovascular disease was among diabetes patients was much higher than nowadays. After recalibrating the UKPDS risk engine, it showed a good calibration in our cohorts.

In general, clinical prediction models are increasingly used to guide treatment and inform patients of their risk. Dutch guidelines[40] but also international guidelines[41] advocate to use prediction models for guiding treatment of type 2 diabetes patients and prevention of cardiovascular events. In order to be useful in clinical practice prediction models should be externally validated.[42] However a relative small number of studies tested these prediction models in independent samples, which is also observed for cardiovascular prediction models applicable to diabetes patients.[6] While the most used risk score for diabetes patients, the UKPDS risk engine, has been extensively tested,[8] the more contemporary models have only been tested once. In this study we externally evaluated all cardiovascular prediction models designed for diabetes patients. Even though the more contemporary prediction models might be more applicable to diabetes patients nowadays, since treatment might have changed over time and diabetes patients are detected at an earlier stage, the performance of contemporary and older prediction models were similar in both of our validation cohorts. Only after recalibration of the prediction models, they provided a good estimate of the risk. As prediction models should provide accurate and validated estimates to be useful in clinical practice,[42] it is questionable whether the prediction models are applicable for guiding treatment and useful for clinical decision making.

In conclusion, all prediction models for CVD among type 2 diabetes patients showed only moderate performance in discrimination. For cardiovascular disease the NDR and Fremantle showed a slightly better discrimination according to risk categories of low, medium and high risk. Only after appropriate recalibration the prediction models showed a good estimate of the cardiovascular risk. Before using

these prediction models in clinical practice performance, especially discrimination, should be improved.

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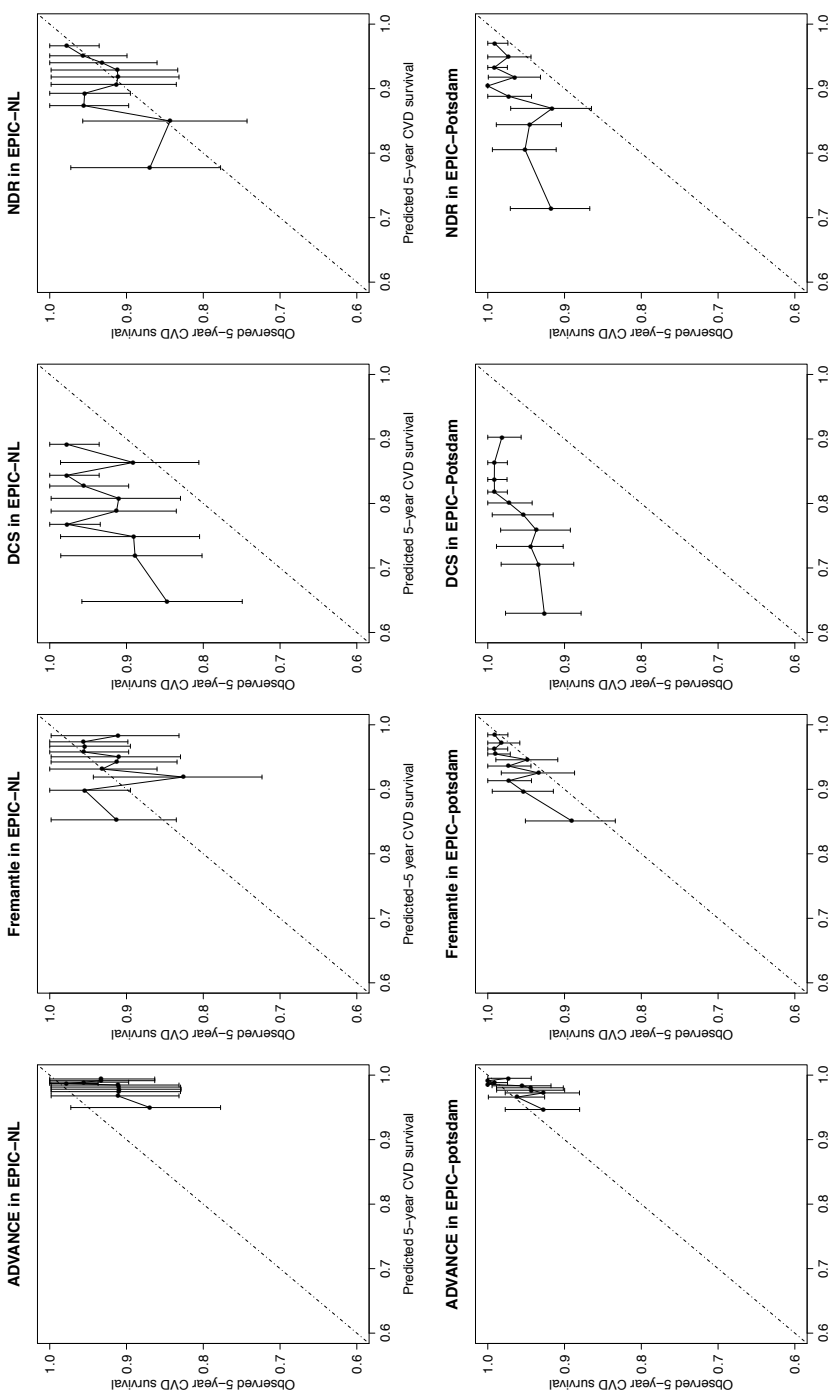
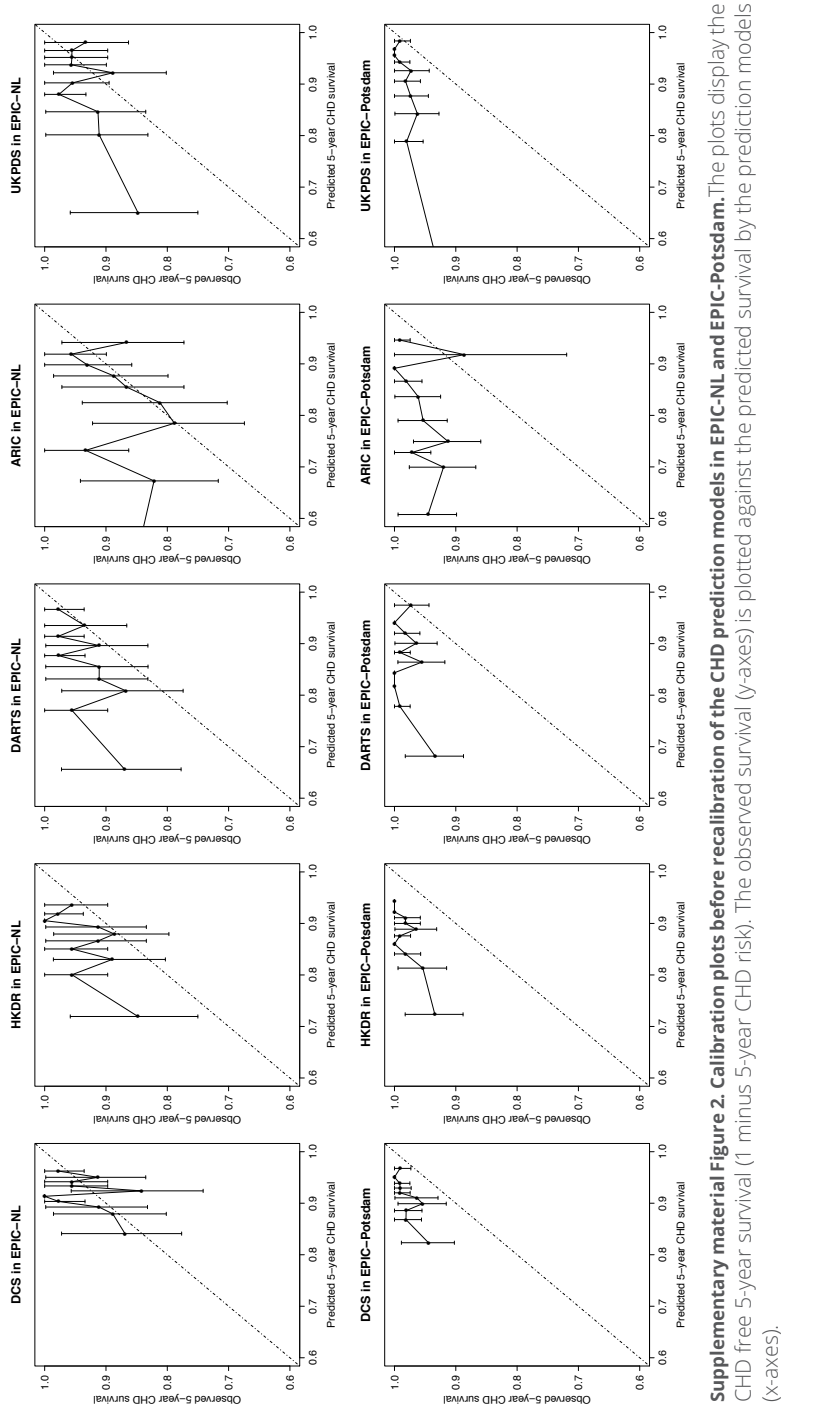
## Supplementary materials




**Supplementary material Figure 1. Calibration plots before recalibration of the CVD prediction models in EPIC-NL and EPIC-Potsdam.** The plots display the CVD free 5-year survival (1 minus 5-year CVD risk). The observed survival (y-axes) is plotted against the predicted survival by the prediction models (x-axes).




**Supplementary material Figure 2. Calibration plots before recalibration of the CHD prediction models in EPIC-NL and EPIC-Potsdam.** The plots display the CHD free 5-year survival (1 minus 5-year CHD risk). The observed survival (y-axes) is plotted against the predicted survival by the prediction models (x-axes).

**Supplementary material Table 1.** Mean estimated risk and Hosmer-Lemeshow chi-square before recalibration of the risk scores

| Risk score | EPIC-NL | | EPIC-Potsdam | |
|---|---|---|---|---|
| | Estimated risk (%), mean (SD) | Hosmer-Lemeshow Chi-square | Estimated risk (%), mean (SD) | Hosmer-Lemeshow Chi-square |
| **CVD risk scores** | | | | |
| Kengne 2011 (ADVANCE) | 2.0 (1.35) | 76.7 (p<0.001) | 2.1 (1.48) | 25.4 (p=0.003) |
| Davis 2010 (Fremantle) | 6.3 (3.86) | 24.9 (p=0.003) | 6.6 (3.94) | 22.9 (p=0.006) |
| Elley 2010 (DCS) | 21.0 (7.14) | 53.4 (p<0.001) | 21.7 (7.87) | 238.9 (p<0.001) |
| Cederholm 2008 (NDR) | 10.0 (5.54) | 7.31 (p=0.605) | 12.1 (7.68) | 90.1 (p<0.001) |
| **CHD risk scores** | | | | |
| Elley 2010 (DCS) | 8.6 (3.60) | 13.8 (p=0.130) | 9.1 (4.21) | 75.1 (p<0.001) |
| Yang 2008 (HKDR) | 13.9 (6.29) | 23.7 (p=0.004) | 13.2 (6.59) | 135.5 (p<0.001) |
| Donnan 2006 (DARTS) | 14.9 (9.07) | 29.5 (p<0.001) | 14.0 (8.50) | 156.8 (p<0.001) |
| Folsom 2001 (ARIC) | 19.4 (11.8) | 35.1 (p<0.001) | 19.7 (10.4) | 219.3 (p<0.001) |
| Stevens 2001 (UKPDS) | 11.6 (10.0) | 24.5 (p=0.003) | 12.4 (13.0) | 142.3 (p<0.001) |

**Supplementary material Table 2.** Participants with and without CVD split out by calculated risk for EPIC-NL

| Risk | NDR | | | Fremantle | | |
|---|---|---|---|---|---|---|
| | No CVD | CVD | % | No CVD | CVD | % |
| Low | 94 | 3 | 3.09 | 104 | 6 | 5.45 |
| Medium | 196 | 17 | 7.98 | 156 | 12 | 7.14 |
| High | 120 | 15 | 11.11 | 160 | 17 | 9.60 |
| | DCS | | | ADVANCE | | |
| | No CVD | CVD | % | No CVD | CVD | % |
| Low | 40 | 1 | 2.44 | 95 | 7 | 6.86 |
| Medium | 266 | 18 | 6.34 | 173 | 10 | 5.46 |
| High | 114 | 16 | 12.31 | 152 | 18 | 10.59 |

**Supplementary material Table 3.** Participants with and without CVD split out by calculated risk for EPIC-Potsdam

| Risk | NDR | | | Fremantle | | |
|---|---|---|---|---|---|---|
| | No CVD | CVD | % | No CVD | CVD | % |
| Low | 610 | 10 | 1.61 | 564 | 10 | 1.74 |
| Medium | 390 | 20 | 4.88 | 456 | 19 | 4.00 |
| High | 133 | 11 | 7.64 | 113 | 12 | 9.60 |
| | DCS | | | ADVANCE | | |
| | No CVD | CVD | % | No CVD | CVD | % |
| Low | 631 | 11 | 1.71 | 589 | 10 | 1.67 |
| Medium | 474 | 29 | 5.77 | 413 | 23 | 5.28 |
| High | 29 | 1 | 3.33 | 131 | 8 | 5.76 |

**Supplementary material Table 4.** Participants with and without CHD split out by calculated risk for EPIC-NL

| Risk | DCS | | | HKDR | | | DARTS | | | ARIC | | | UKPDS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No CHD | CHD | % | No CHD | CHD | % | No CHD | CHD | % | No CHD | CHD | % | No CHD | CHD | % |
| Low | 83 | 5 | 5.68 | 87 | 5 | 5.43 | 110 | 4 | 3.51 | 4 | 0 | 0.00 | 139 | 8 | 5.44 |
| Medium | 242 | 14 | 5.47 | 246 | 18 | 6.82 | 171 | 13 | 7.07 | 83 | 7 | 7.78 | 136 | 8 | 5.56 |
| High | 98 | 13 | 11.71 | 90 | 9 | 9.09 | 142 | 15 | 9.55 | 336 | 25 | 6.93 | 148 | 16 | 9.76 |

**Supplementary material Table 5.** Participants with and without CHD split out by calculated risk for EPIC-potsdam

| | DCS | | | HKDR | | | DARTS | | | ARIC | | | UKPDS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Risk | No CHD | CHD | % | No CHD | CHD | % | No CHD | CHD | % | No CHD | CHD | % | No CHD | CHD | % |
| Low | 505 | 3 | 0.59 | 543 | 5 | 0.91 | 473 | 9 | 1.87 | 380 | 1 | 0.26 | 558 | 5 | 0.89 |
| Medium | 559 | 16 | 2.78 | 524 | 14 | 2.60 | 480 | 6 | 1.23 | 287 | 15 | 4.97 | 310 | 8 | 2.52 |
| High | 87 | 4 | 4.40 | 84 | 4 | 4.55 | 198 | 8 | 3.88 | 484 | 17 | 3.39 | 283 | 10 | 3.41 |

# Chapter 10

## Associations and risk prediction of heart-type fatty acid-binding protein with cardiovascular disease among patients with type 2 diabetes

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## Abstract

**Aims:** The aim of this study was to examine the associations of heart-type fatty acid-binding protein (H-FABP) with CVD and assess the added prognostic value of H-FABP to the prediction of CVD among patients with type 2 diabetes.

**Methods:** 524 patients with type 2 diabetes from the prospective EPIC-NL cohort were followed for a mean period of 10 years. Baseline characteristics and H-FABP were measured. Cox proportional hazard regression was used to examine the association between H-FABP and CVD. The Swedish NDR risk score was used to predict 10-year cardiovascular risk and the added prognostic value of H-FABP to the NDR risk score was calculated using the NRI and IDI.

**Results:** 172 cardiovascular events were documented during 10 years of follow-up. After multivariable adjustment a trend towards a positive association between H-FABP and CVD was observed (p trend=0.09), but this did not reach significance. A HR of 1.10 (95%CI: 0.96-1.27) was observed for a continuous association between H-FABP and CVD. The c-statistic improved from 0.597 (95%CI: 0.553-0.641) to 0.615 (95%CI: 0.572-0.659) when H-FABP was added to the risk score. The improvement with the IDI was small (0.0121) but significant (P=0.015), while it was not with the NRI (0.062, p=0.121).

**Conclusions:** High concentrations of H-FAPB may be associated with an increased risk of CVD. A small improvement of cardiovascular risk prediction was observed by the addition of H-FABP to the NDR risk score on a continuous scale (IDI), but not on a categorical scale (NRI). The small improvement with the discrimination has limited clinical value for cardiovascular risk assessment.

## Introduction

Patients with type 2 diabetes have a 2- to 4-fold increased risk of cardiovascular diseases (CVD).[1] In order to prevent CVD and initiate appropriate treatment it is important to stratify patients into groups based on their cardiovascular risk. Several prediction models have been developed to estimate this risk. In a recent systematic review, 45 cardiovascular risk scores applicable to diabetes patients were identified, of which 12 were designed specifically for patients with type 2 diabetes.[2] We examined all risk scores predicting either CVD or CHD specifically designed for diabetes patients in an external validation study. These risk scores showed only moderate discrimination (ability to distinguish between patients at low and high risk) and a poor calibration (ability to correctly quantify the observed risk), which was improved after recalibration of the prediction models.[3] The performance of these cardiovascular prediction models for patients with type 2 diabetes might be improved by adding novel biomarkers to the original risk scores.

Heart-type fatty acid-binding protein (H-FABP or FABP3) is a novel plasma marker for the detection of myocardial tissue injury. This small unbound cytoplasmic protein is present in high concentrations in the myocardial cell and released into the circulation within minutes of myocardial ischemia.[4] H-FABP is primarily investigated as a biomarker for the early diagnosis of acute myocardial infarction.[4] However, several studies have also investigated H-FABP as prognostic marker for cardiac events or for adverse outcome in patients with already present CVD, such as congestive heart failure or pulmonary embolism.[5-10] These studies indeed all showed a strong positive association between H-FABP and cardiac events, mortality or adverse outcome.[5-10] However, most of these studies were performed in patients in the acute phase of the cardiac event, with short follow-up periods, generally less than 1.5 years. Among diabetes patients and patients with impaired glucose tolerance a higher concentrations of H-FABP was observed compared to control subjects. However associations with cardiovascular disease or the added prognostic value of H-FABP has not been inverstigated.[11;12] We therefore aimed to investigate the etiologic associations of H-FABP with CVD among type 2 diabetes patients and whether H-FABP added prognostic value to an existing prediction model to predict 10-year CVD risk among patients with type 2 diabetes.

## Methods

### Study population

The study population consists of patients with type 2 diabetes from the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition (EPIC-NL), which is described in more detail elsewhere.[13] In brief, EPIC-NL consists of Prospect cohort and Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) cohort. Prospect is a prospective population-based cohort of 17,357 women, aged 49-70 years, living in Utrecht, Netherlands and vicinity, who participated in breast cancer screening between 1993 and 1997. The MORGEN cohort consists of 22,654 men and women, aged 20-59 years, recruited from three Dutch towns (Amsterdam, Maastricht and Doetinchem). From 1993 to 1997 each year a new random sample of about 5,000 participants was examined.

In total, 536 type 2 diabetes cases from EPIC-NL were identified at baseline. Patients with missing endpoints (n=12) were excluded from the analyses. This resulted in 524 patients with confirmed type 2 diabetes for the current analyses. All participants gave written informed consent prior to study inclusion. Both studies were approved by the local ethical committee.

At baseline, a general questionnaire containing questions on demographic characteristics, presence of chronic diseases and other potential risk factors was filled out by all participants. Body weight and height were measured. Smoking was coded into current smokers and non-smokers (former- or non-smokers). Blood pressure was measured twice on the left arm while the participant was in a supine position. The mean of these measurements was used in the analyses. In the Prospect study systolic and diastolic blood pressure was measured using a Boso oscillomat (Bosch & Sohn, Jungingen, Germany), while in the MORGEN cohort a random zero Sphygmomanometer (Hawksley & Sons, Lancing, UK) was used. Thirty millilitres of blood was collected from all participants to obtain plasma, serum and erythrocytes and stored in liquid nitrogen for future use. H-FABP was measured in plasma using a one step enzyme-linked immunosorbent assay and HbA1c was measured in erythrocytes with an immunoturbidimetric latex test.

Participants were followed-up from baseline to end of follow-up (31 December 2007), first incident CVD event or death. CVD was defined as ischemic heart disease, heart failure, sudden death, pulmonary

embolism, transient ischemic attack, cerebrovascular disease or atherosclerosis [ICD-10 codes: I20-I26, I46, R96, G45, I60-I67, I69-I74, I50). Incident morbidity cases were obtained through linkage with the Dutch National Medical Registry, which holds a standardized computerized database of all hospital discharge diagnoses throughout the country. Vital status of the participants was obtained through linkage with the municipal population registries.

**Statistical analyses**

Since H-FABP was not normally distributed it was divided in tertiles (0-1.17, 1.18-1.77, 1.78-8.54). Baseline characteristics were examined across the H-FABP tertiles using means and standard deviations for continuous variables and percentages for categorical values. P for trend for baseline predictors over H-FABP tertiles was calculated using a generalized linear model. Missing values for any of the baseline characteristics were imputed using single imputation. Hazard ratios and 95% confidence intervals were calculated for each H-FABP tertile versus the lowest tertile as reference using Cox regression. Model 1 was adjusted for age and sex, while model 2 was further adjusted for BMI, cohort, smoking, systolic blood pressure, HDL-cholesterol, diabetes duration and HbA1c. Since established cardiovascular disease is strongly associated with H-FABP model 3 was further adjusted for hypertensive medication and history of CVD. An interaction between H-FABP and previous myocardial infarction was assessed by including the interaction term in the models.

Since the Swedish National Diabetes Registry (NDR) risk score[14] performed best in our validation study of all cardiovascular risk scores for diabetes patients[3] this prediction model was used to calculate future cardiovascular risk. This prediction model estimates cardiovascular risk based on nine predictors: age at diabetes diagnosis, sex, duration of diabetes, HbA1c level, BMI, systolic blood pressure, current smoking, antihypertensive medication and lipid-lowering drugs as follows; CVD risk=1-exp(-$q_5$ x $\beta_1^{\text{age-duration}}$ x $\beta_2^{\text{sex}}$ x $\beta_3^{\text{duration}}$ x $\beta_4^{\text{HbA1c}}$ x $\beta_5^{\text{BMI}}$ x $\beta_6^{\text{antihypertensive drugs}}$ x $\beta_7^{\text{systolic blood pressure}}$ x $\beta_8^{\text{lipid-lowering drugs}}$ x $\beta_9^{\text{smoker}}$)).

The betas for the linear predictor are as follows: $\beta_1$:1.066, $\beta_2$:1.538, $\beta_3$:1.087, $\beta_4$:1.117, $\beta_5$:1.017, $\beta_6$:1.278, $\beta_7$:1.007, $\beta_8$:1.314, $\beta_9$:1.492. The baseline hazard($q_5$) was replaced with the baseline hazard of the EPIC-NL cohort and the linear predictor of a mean patient from EPIC-NL was subtracted from the original linear predictor in order to recalibrate the risk score to the incidence in our population.[15]

To examine the added prognostic value of H-FABP, H-FABP was added to the linear predictor of the NDR model.
Discrimination of the models without and with H-FABP was assessed using Harrel's c-statistic.[16] Calibration was assessed using the Hosmer-Lemeshow Chi square test. Since the c-statistic is not sensitive enough to examine the added prognostic value, the Nett Reclassification Index was calculated using cut-offs of 0-20%, 21-30%, >30% and for continuous improvement in discrimination the Integrated Discrimination Index was calculated. All statistical analyses were performed using R-2.15.1 for Windows (http://cran.r-project.org/).

## Results

During a mean follow-up of 10 years 172 cardiovascular events were documented. Baseline characteristics associated with a higher H-FABP were increasing age, higher BMI, prevalence of smoking, higher blood pressure, longer diabetes duration, lower HDL cholesterol, anti-hypertensive medication usage and a history of cardiovascular events (Table 1). The mean predicted cardiovascular risk by the NDR risk score increased with higher H-FABP, from 30.4% for the first tertile to 35.5% for the third tertile.
An association between H-FABP and CVD was observed with a hazard ratio (HR) of 1.93 (95%CI: 1.33-2.81) for the third tertile compared to the first tertile adjusted for age and sex. The association was still significant when multivariable adjusted for age, sex, BMI, cohort, smoking, systolic blood pressure, HDL-cholesterol, diabetes duration and HbA1c (HR third tertile: 1.59 [95%CI: 1.08-2.33]). However when further adjusted for history of cardiovascular disease or using anti-hypertensive medications the association attenuated to borderline significance, with a HR of 1.33 (95%CI: 0.90-1.97) for the third tertile compared to the first tertile. Similar results were observed when H-FABP was modelled continuously (Table 2). No interaction was observed between previous cardiovascular disease and H-FABP (P for interaction=0.331)
The discrimination of the NDR was moderate (c-statistic=0.597, 95%CI: 0.553-0.641) and increased slightly when H-FABP was added to the risk score (c-statistic-0.615, 95%CI: 0.572-0.659). After recalibration of the risk score the calibration was good and remained good when H-FABP was added to the model (Both p-values>0.05). Using the Nett reclassification index, 12 participants who experienced a cardiovascular event were correctly reclassified into a higher risk category when H-FABP was added to the risk score, while 17 patients who experienced

**Table 1** Baseline characteristics of type 2 diabetes patients from the EPIC-NL cohort across tertiles of H-FABP

| Baseline characteristic | h-FABP | | | P for trend |
|---|---|---|---|---|
| | T1 (0-1.17 ng/ml) | T2 (1.18-1.77 ng/ml) | T3 (1.78-8.54 ng/ml) | |
| Participants (n) | 175 | 175 | 174 | |
| H-FABP (ng/ml) | 0.75 (0.34) | 1.44 (0.16 | 2.56 (0.96) | <0.001 |
| Age (years) | 57.0 (7.05) | 58.6 (6.34) | 59.5 (6.45) | <0.001 |
| Sex (men), n (%) | 33 (18.9) | 26 (14.9) | 35 (20.1) | 0.762 |
| BMI Kg/m$^2$) | 28.9 (4.94) | 29.7 (5.05) | 30.4 (5.00) | 0.006 |
| Smoke (current), n (%) | 35 (20.0) | 45 (25.7) | 46 (26.4) | 0.050 |
| Systolic blood pressure (mmHg) | 141 (20.5) | 143 (21.2) | 147 (22.4) | 0.008 |
| Diastolic blood pressure (mmHg) | 82.0 (10.6) | 81.7 (10.2) | 83.4 (10.7) | 0.192 |
| Diabetes duration (years) | 6.53 (6.03) | 6.63 (6.72) | 8.11 (8.07) | 0.036 |
| HbA1c (%) | 8.07 (1.72) | 8.06 (1.76) | 8.17 (1.65) | 0.582 |
| Total cholesterol (mmol/l) | 5.39 (1.16) | 5.33 (1.25) | 5.24 (1.14) | 0.239 |
| HDL cholesterol (mmol/l) | 1.08 (0.29) | 1.02 (0.28) | 0.99 (0.28) | 0.002 |
| Hypertensive medication, n (%) | 77 (44.0) | 84 (48.0) | 112 (64.4) | <0.001 |
| History of CVD, n (%) | 8 (4.6) | 25 (24.3) | 38 (21.7) | <0.001 |
| Mean cardiovascular risk (%) | 30.4 (8.24) | 32.6 (8.15) | 35.5 (8.05) | <0.001 |

**Table 2.** Hazard ratios and 95% confidence intervals for the association between H-FABP and cardiovascular risk

| | h-FABP | | | | P for trend |
|---|---|---|---|---|---|
| | T1 (0-1.17) | T2 (1.18-1.77) | T3 (1.78-8.54) | Continuous | |
| Cases (n) | 46 (26.3%) | 52 (29.7%) | 74 (42.5%) | 172 (32.8%) | - |
| Model 1 | 1.00 | 1.22 (0.82-1.82) | 1.93 (1.33-2.81) | 1.25 (1.10-1.41) | <0.001 |
| Model 2 | 1.00 | 1.09 (0.73-1.64) | 1.59 (1.08-2.33) | 1.17 91.02-1.35) | 0.009 |
| Model 3 further adjusted for CVD factors | 1.00 | 1.00 (0.66-1.51) | 1.33 (0.90-1.97) | 1.10 (0.96-1.27) | 0.089 |

Model 1 age, sex adjusted
Model 2 age, sex, BMI, cohort, smoke, systolic blood pressure, HDL cholesterol, diabetes duration, HbA1c
Model 3 age, sex, BMI, cohort, smoke, systolic blood pressure, HDL cholesterol, diabetes duration, HbA1c, hypertensive medication, prevalent CVD

**Table 3.** Nett Reclassification table of the NDR risk score with and without H-FABP

| Model without h-FABP | Model with h-FABP | | | Total |
|---|---|---|---|---|
| Frequency (Row %) | Risk (0-20%) | Risk (21%-30%) | Risk (>30%) | |
| Participants who experience a CVD event | | | | |
| 0-20% | 7 (87.5) | 1 (12.5) | 0 (0.0) | 8 |
| 21-30% | 3 (7.3) | 27 (65.9) | 11 (26.8) | 41 |
| >30% | 0 (0.0) | 14 (11.4) | 109 (88.6) | 123 |
| Total | 10 | 42 | 120 | 172 |
| Participants who do not experience a CVD event | | | | |
| 0-20% | 21 (84.0) | 4 (16.0) | 0 (0.0) | 25 |
| 21-30% | 11 (9.0) | 93 (76.2) | 18 (14.8) | 122 |
| >30% | 0 (0) | 43 (21.0) | 162 (79.0) | 205 |
| Total | 32 | 140 | 180 | 352 |

a CVD event were wrongly reclassified to a lower risk category. Among participants who did not experience a cardiovascular event, 53 patients were correctly reclassified into a lower risk group, while 22 participants were wrongly reclassified to a higher risk group (Table 3). The NRI was not significant (0.062, p=0.121), while the IDI showed a small, but significant improvement of classification (0.0121, p=0.015).

## Discussion

This study showed that H-FABP tended to be associated with an increased risk of CVD among patients with type 2 diabetes. Although addition of adding H-FABP to an existing risk score to predict 5-year CVD did not improve the c-statistic, however, a small improvement of classification as measured by the IDI was observed.

Strengths of our study include its prospective design with long follow-up. However, certain limitations need to be addressed. Thus far, most studies on H-FABP have measured H-FABP concentrations in the time window directly after a cardiac event.[8;10;17-19] However, we investigated H-FABP in type 2 diabetes patients from a general population cohort that had not yet experienced a cardiac event. Our samples may therefore have not captured the most appropriate time-window to measure H-FABP, which may have led to attenuation of the observed associations. However, a previous study has shown that H-FABP is already increased in pre-diabetic patients compared to controls.[11] Our study further supports the evidence on associations between H-FABP and CVD in high risk patients. In addition, our sample size may have been slightly small to detect such weaker associations of H-FABP with CVD risk. Nevertheless, our main objective was to investigate the added prognostic value of H-FABP beyond an existing risk score. Although sample size requirements to study added prognostic value are unknown, previous studies have shown that at least 100 events are required to validate an existing risk score.[20] With 172 events, our sample size therefore appears to be sufficient for the primary aim of our study.

Previous studies generally observed a strong positive association of H-FABP with cardiac events, mortality or other outcomes. We only observed a borderline positive association of H-FABP with CVD risk. This smaller effect size could be due to the fact that our study measured H-FABP among patients with type 2 diabetes who did not suffer a cardiac event recently, while the other studies measured H-FABP on admission to the emergency department or before discharge from

the hospital after an CVD event.[8;10;17-19] This may also have affected the H-FABP concentrations, since the concentrations observed in our study were 2- to 5-fold lower than those in other studies. However, concentrations in our study were higher than those reported among patients with pre-diabetes and controls.[11;12] Another study examining H-FABP concentrations among diabetes metabolic syndrome patients (24.0 ng/ml) and controls (7.9 ng/ml) observed larger differences ($p<0.05$) in H-FABP concentrations however they did not assess the associations with cardiovascular disease.[12] In line with these results, we also observed that H-FABP concentrations were higher (around 2 ng/ml) among those experiencing a previous CVD event. A study measuring H-FABP both at admission and discharge from the hospital showed that H-FABP concentrations declined from 7.4 ng/ml to 4.9 ng/ml during a mean follow-up of 20 days.[21] In addition, the association of H-FABP at discharge also appeared slightly weaker, although relative risks were not provided.

Since many studies investigated association with events occurring within 1.5 years, but mostly even shorter periods, this may have led to stronger associations, while the follow-up time in our study was much longer (mean of 10 years). Two studies had a longer follow-up period of approximately 4 years.[22;23] One study showed a relative risk of death, lung transplantation or persistent pulmonary hypertension of 1.10 with each ng/ml increment of H-FABP, which is identical to our results.[22] The other, however, reported a relative risk of 7.5 for cardiac events with each ng/ml increment.[23] This suggests that a longer follow-up does not necessarily explain the strength of the association. Finally, the choice of endpoint and level of adjustment may also be involved, since certain studies have shown substantial differences in strength of the association depending on the endpoint studied.[5]

In addition, our study showed that adding H-FABP to an existing risk score to predict 10-year CVD risk among patients with type 2 diabetes did not improve discrimination, while it only showed a small, albeit statistically significant improvement of classification as measured by the IDI. Although other studies have investigated prognostic value of H-FABP using c-statistics, none of them have studied added prognostic value beyond an existing risk score including established predictors of CVD or another outcome. These studies generally showed high c-statistics ranging from 0.73 to 0.78.[10;24;25] However, these cannot be directly compared to our results, since these studies did not account for established risk factors. Finally, the small improvement of the IDI

probably has limited clinical value. Since reclassification based on the NRI was not significant, treatment decisions will not be affected by including H-FABP in prediction of CVD among patients with type 2 diabetes.

Other markers have shown similar improvements in discrimination. For instance NT-proBNP is another biomarker associated with stress or cardiovascular injury has a clear association with incidence of CVD and generally yielded modest improvements in risk discrimination, ranging from 0.01 to 0.1, that appeared slightly smaller in general population based studies.[26]

In conclusion, this study showed that elevated levels of H-FABP may be associated with a modestly increased risk of CVD among patients with type 2 diabetes. Although adding H-FABP to an existing risk score to predict CVD among type 2 diabetes patients did not improve discrimination, a small improvement on a continuous scale was observed. However, this probably has limited clinical value for cardiovascular risk assessment.

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# Chapter 11

## The use of repeated measurements in clinical prediction models

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## Abstract

**Aims:** It is unknown how to incorporate repeated predictor information into the development of clinical prediction models. Therefore we assessed how to incorporate repeated predictor measurements in clinical prediction models and how this affected the predictive performance of the model.

**Methods:** To estimate the effect of repeated predictor measurements in clinical prediction models a simulation study based on available data was performed. A cohort of 536 diabetes patients from EPIC-NL were used to bootstrap 10.000 samples. Repeated measurements over 5-years of follow-up and the outcome were simulated. Predictors were kept constant over time, except for a random variation. Diabetes duration increased with each year of follow-up and a change in one predictor (total/HDL cholesterol) was based on trial data of statin therapy effects. A baseline logistic model without inclusion of repeated predictor measurements was compared with three types of models including repeated measurements: 1) A model constructed using baseline data, which was used at each consecutive time point to recalculate the predicted risk based on repeated measurements of consecutive years. 2) A new model was fitted each consecutive year using the repeated predictor measurement at new time points. 3) Change in repeated predictor measurement from baseline to each time point was added to the model. Differences in predictive performance of the models was assessed by discrimination and calibration. For the discrimination the c-statistic and NRI and IDI were used, while for the calibration the Hosmer-Lemeshow chi-square test was used.

**Results:** The beta for total/HDL cholesterol in the logistic prediction model changed over time in model 2 and model 3. No difference was observed between the discrimination of the baseline model and models including repeated measurements. The c-statistics of the 3 models including repeated predictor measurements were identical and the NRI of model 2 and model 3 showed no significant improvement in discrimination compared to model 1. However small improvements were observed with the IDI for the first follow-up years ranging from 0.003 to 0.012, whereas the calibration decreased over time for model 1, although not significantly. The calibration of model 2 and model 3 was the same for all follow-up years.

**Conclusions:** This study suggests that the use of a baseline model without inclusion of repeated predictor measurements or recalculating

of the risk at new time points is almost as predictive as fitting a new model each year. Only small changes in discrimination were observed for models using updated information. However, it should be examined if the change in multiple predictors or a different way to include repeated measurements in prediction models do show an improvement in performance.

## Introduction

To estimate risk for certain diseases (e.g. cardiovascular risk), a risk score or prediction model is often used. These prediction models are used to obtain a predicted absolute risk of a certain outcome over time, which is used to guide disease management, adjust medication and inform patients of their risk.[1;2] Most prediction models include several variables measured only at one certain time point to predict an outcome over several years (i.e. 5-year or 10-year risk).

Many predictors will change over time due to natural course or interventions such as medication use. Nevertheless, prediction model development mostly focuses on risk scores including only baseline predictors and changes in predictors are often ignored. The predicted risk may therefore be less accurate, particularly when predicted over a longer time period.[3] Furthermore, disease management is increasingly guided by predicted risk and type and dose of medication are sometimes based on predicted risk.[4]. An interaction between medication and predictors might have a great effect on the accuracy of risk prediction. Even though patients, especially with chronic diseases, repeatedly visit their physician and certain predictors are measured at each visit, prediction models do not include the measurements of these follow-up visits.

Despite the fact that many studies have examined how to incorporate repeated measurements or trajectories of covariates in etiologic studies,[5-7] almost no studies have assessed how to incorporate longitudinal data in prediction models. One study examined the difference in follow-up time to predict the outcome of coronary heart disease and observed that updated measurements improved the prediction, although they only examined the overall performance of the models by the variation explained, and did not specifically examine the often desired discriminative ability and calibration of the models.[8] A second study examined trajectories for smoke cravings to predict smoking cessation and observed an improvement of the AUC of 0.72 to 0.82, however this was a trajectory over a short period (weeks instead of years).[9] Nonetheless, there is no standardized approach on how to incorporate updated measurements into prediction models, nor is it known how different methods perform in terms of predictive ability.

Therefore we assessed how to incorporate repeated predictor measurements in clinical prediction models and how this affected the predictive performance of the model.

## Methods

### Data description

Data for this simulation study were based on diabetes patients from the EPIC-NL cohort. The baseline characteristics of 536 patients diagnosed with type 2 diabetes and the outcome of cardiovascular disease (n=145) during a mean of 10 years follow-up were used to simulate repeated measurements of physiological parameters and the outcome. The model used to predict occurrence of cardiovascular disease was a logistic model based on common cardiovascular repeated predictor measurements for diabetes patients: age at diabetes diagnoses, sex, smoking, systolic blood pressure, ratio total/HDL cholesterol, previous cardiovascular event and anti-hypertensive medication.[10-13]

### Description of models

Assume a situation in which we predict the outcome of a patient at time point *n* and predictors have been measured at time points 0 (baseline), 1, 2, …, up to *n*. In this study we compared the use of a baseline model with a model including repeated predictor measurements. Three options for inclusion of repeated predictor measurements were examined: Option 1) Computing a baseline model and recalculate risk using this baseline model at each yearly measurement. Option 2) refit the model at each yearly measurement, re-estimate betas and computing a new model each year and calculate the risk using the updated predictor measurements. Model 3) Use baseline measurements and add change in predictors between baseline and current time point to the model and use this model to calculate risk.

### Simulation of repeated measurements

Follow-up measurements were not available, therefore the repeated measurements for the predictors were simulated.

The repeated measurements were simulated using 2 scenarios.

1. In this scenario the changes in the physiological variables are not directly influenced by medication use, i.e. the same change will occur for all patients.
2. The changes in physiological variables are directly influenced by medication use. Based on current guidelines all patients with a certain risk factor above a certain threshold will be prescribed medication, which in turn lowers the predictor and has a direct decreasing effect on the observed risk.

Repeated measurements of predictors for year 1 to 5 were based on the baseline characteristics. These simulated measurements were kept constant over time with a small random factor, except for duration of diagnosed diabetes, which increased with 1 year for each repeated measurement, and total cholesterol, which changed over time according to the two scenarios by the use of statin therapy. The effect of statin therapy in diabetes patients, as has been shown in several statin trials, is a reduction of total cholesterol of 1 mmol/l and a relative cardiovascular risk reduction of 20%.[14-16] For scenario 1 it was simulated that all patients received a statin during the first year, which lowers the total cholesterol with 1 mmol/l for year 1. The risk factor total/HDL cholesterol is therefore lowered due to the statin therapy for the first year and kept constant with a random factor for the next 4 years (year 2 to year 5).
For scenario 2 all patients with a total cholesterol above 6.5 mmol/l or an LDL cholesterol above 3.0 mmol/l received statin therapy reducing the total cholesterol by 1 mmol/l. Each year the patients were checked for the above described thresholds for statin therapy, if the patient was above the threshold, it was simulated that medication was up titrated and total cholesterol was further reduced by 1 mmol/l. If the patient is below the threshold, the total cholesterol is kept constant with a random factor for the next simulated years.
A sensitivity analysis with greater changes was performed in which all patients were put on a statin during the first year and up-titrated each year, reducing the total cholesterol by 1 mmol/l each year.

**Simulation of outcome**
After simulation of the repeated predictor measurements for the follow-up years, the means over year 0 to year 5 were calculated. The means of the predictors and the original outcome were used to obtain estimated risks using a logistic model. These estimated risks were then corrected for the 20% relative risk reduction due to statin therapy when applicable (Scenario 1: all patients, Scenario 2: each patients that received a statin at any time point during follow-up). These risks were then used as a probability in a binomial distribution to simulate the outcome.
In total 10.00 bootstrap samples of the original baseline dataset were drawn. For each sample the patient characteristics for consecutive years and outcomes were simulated and the three types of models described above were fitted at each bootstrap sample.

**Data analysis**
All three models were logistic regression models predicting cardio-vascular outcome over 5 years. Age at diagnosis, duration of diagnosed

diabetes, HbA1c concentration, systolic blood pressure and total/HDL cholesterol ratio were included as continuous predictors. Sex, current smoking, past smoking and treatment with antihypertensive medication were included as categorical predictors.
The baseline model and three different options to include repeated measurements in the prediction models were compared for the discrimination (ability to distinguish between patients who will get the outcome from those who will not) and calibration (agreement between observed and predicted risk) of the model over 5 years of follow-up. Discrimination was assessed by the c-statistic. The calibration was assessed by computing the Hosmer-Lemeshow Chi-square test. The models used in option 2 (refitting of model using the patient characteristics at each year) and in option 3 (inclusion of change in patient characteristics from year 0) were compared with option 1 (recalculating the risk at each year using the baseline model). For the comparison of model 2 and model 3 with model 1 the Nett Reclassification Improvement (NRI) and the Integrated Discrimination Improvement (IDI) were calculated. For the NRI cut-offs of 20% and 30% risk were used. Moreover we compare the models over 5 years of follow-up from year 0 to year 5. The three models at year 0 (baseline) are all the same model and only include baseline factors to predict the outcome and are thus the same as standard prediction models without inclusion of repeated measurements. All simulations and analyses were performed using R-2.15.1 for Windows.

## Results

### Baseline model without inclusion of repeated predictor measurements

The baseline model without including repeated measurements was similar for scenario 1 and scenario 2 (Table 1). Age at diagnosed diabetes, current smoking, HbA1c concentration, systolic blood pressure, diabetes duration and treatment with antihypertensive medication were associated with an increased risk for cardiovascular disease. Female sex and past smoking were associated with a decreased risk for cardiovascular disease. The predictors that were included in the risk scores showed similar betas for all follow-up years, and the three different models (Supplementary material table 1 to table 3). The discrimination was moderate (c-statistic=0.682) and the calibration was good in both scenarios.

**Table 1.** Predictors and betas for baseline model in Scenario 1 and Scenario 2

| Predictor | Scenario 1 | Scenario 2 |
|---|---|---|
| Intercept | -4.186 | -4.174 |
| Age at diagnosis of diabetes (year) | 0.020 | 0.023 |
| Sex (Female) | -0.302 | -0.282 |
| Past smoker | -0.239 | -0.250 |
| Current smoker | 0.623 | 0.657 |
| HbA1c concentration (%) | 0.098 | 0.103 |
| Systolic blood pressure (mmHg) | 0.001 | 0.000 |
| Total/HDL cholesterol ratio | 0.127 | 0.121 |
| Diabetes duration (year) | 0.057 | 0.063 |
| Antihypertensive medication | 0.251 | 0.261 |
| c-statistic (95% CI) | 0.682 (0.630-0.733) | 0.682 (0.632-0.732) |
| HL chi-square (p-value) | 7.893 (0.545) | 7.950 (0.539) |

**Models including repeated measurement of predictors in scenario 1**

Scenario 1 was modelled as if all patients received statin therapy during the first year, reducing the total cholesterol by 1 mmol/l and cardiovascular risk by 20%. Total/HDL cholesterol was associated with an increased risk for cardiovascular disease with a beta of 0.127 for model 1 (Supplementary material table 1). In model 2 total/HDL cholesterol ratio was refitted at each follow-up year and the beta increased from 0.127 to 0.143 at year 1 and was the same thereafter (Supplementary material table 2). In model 3 total/HDL cholesterol was modelled as change from baseline for each follow-up year and total/HDL cholesterol at baseline. The beta for baseline cholesterol increased from 0.127 to 0.144 in the first year and was the same for the consecutive years. The beta for change in total/ HDL cholesterol from baseline was 0.135 at year 1 and decreased slightly over the years to 0.107 for year 5 (Supplementary material table 3).

The discrimination for models including repeated predictor measurements by recalculating the risk at follow-up years (model 1) or refitted using follow-up data (model 2) or including change in cholesterol ratio (model 3), was the same as for the baseline model (Table 2). When examining the difference in discrimination for follow-up measurements for model 2 and model 3 compared to model 1 no significant effect was observed with the NRI (all-p-values>0.05) (Table 3).

**Table 2.** C-statistic and 95% Confidence interval for model 1, model 2 and model 3 for the two scenarios at all follow-up years

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| Scenario 1 | | | |
| Year 1 | 0.682 (0.630-0.733) | 0.682 (0.631-0.733) | 0.684 (0.633-0.735) |
| Year 2 | 0.682 (0.630-0.733) | 0.682 (0.631-0.733) | 0.684 (0.633-0.735) |
| Year 3 | 0.682 (0.630-0.733) | 0.682 (0.631-0.733) | 0.684 (0.632-0.735) |
| Year 4 | 0.682 (0.630-0.733) | 0.682 (0.631-0.733) | 0.684 (0.632-0.735) |
| Year 5 | 0.682 (0.630-0.733) | 0.682 (0.631-0.733) | 0.684 (0.632-0.735) |
| Scenario 2 | | | |
| Year 1 | 0.686 (0.636-0.736) | 0.687 (0.637-0.737) | 0.693 (0.644-0.742) |
| Year 2 | 0.687 (0.637-0.737) | 0.689 (0.639-0.738) | 0.693 (0.643-0.742) |
| Year 3 | 0.687 (0.637-0.737) | 0.689 (0.639-0.739) | 0.692 (0.643-0.742) |
| Year 4 | 0.687 (0.637-0.737) | 0.689 (0.639-0.739) | 0.692 (0.643-0.742) |
| Year 5 | 0.687 (0.637-0.737) | 0.689 (0.639-0.738) | 0.692 (0.643-0.742) |

**Table 3.** NRI and IDI for model 2 and model 3 compared to model 1 for scenario 1 and scenario 2 at all follow-up years.

| | Model 2 | | | | Model 3 | | | |
|---|---|---|---|---|---|---|---|---|
| | NRI | P-value | IDI | P-value | NRI | P-value | IDI | P-value |
| Scenario 1 | | | | | | | | |
| Year 1 | 0.002 | 0.951 | 0.004 | <0.001 | 0.008 | 0.803 | 0.007 | 0.003 |
| Year 2 | 0.004 | 0.888 | 0.003 | 0.005 | 0.009 | 0.756 | 0.005 | 0.029 |
| Year 3 | 0.009 | 0.750 | 0.001 | 0.371 | 0.015 | 0.650 | 0.003 | 0.174 |
| Year 4 | 0.018 | 0.594 | -0.001 | 0.431 | 0.024 | 0.523 | 0.001 | 0.555 |
| Year 5 | 0.030 | 0.443 | -0.002 | 0.042 | 0.036 | 0.393 | 0.000 | 0.930 |
| Scenario 2 | | | | | | | | |
| Year 1 | 0.006 | 0.777 | 0.005 | 0.005 | 0.025 | 0.486 | 0.012 | 0.003 |
| Year 2 | 0.020 | 0.487 | 0.006 | 0.012 | 0.032 | 0.357 | 0.011 | 0.005 |
| Year 3 | 0.036 | 0.290 | 0.005 | 0.061 | 0.046 | 0.221 | 0.009 | 0.018 |
| Year 4 | 0.055 | 0.161 | 0.003 | 0.219 | 0.064 | 0.123 | 0.007 | 0.057 |
| Year 5 | 0.076 | 0.084 | 0.002 | 0.508 | 0.084 | 0.064 | 0.005 | 0.141 |

However small improvements in the IDI were observed for the first two follow-up years for model 2 (IDI: 0.004 and 0.003) and model 3 (IDI: 0.007 and 0.005) compared to model 1, although for follow-up year 5 refitting of the baseline model (model 1) was significantly better compared to model 2 with a small significant change in IDI (IDI: 0.002) . The calibration was good for the baseline model without inclusion of follow-up measurements (HL $\chi^2$=7.893, p-value=0.545) (table 1). Although not significant, the calibration of the baseline model decreased over time when predicted risk was re-estimated. The Hosmer-Lemeshow chi square statistic increased to 12.095 (p-value=0.208) at year 5, while the calibration for the models in model 2 and model 3 was good for all follow-up years (Table 4).

**Table 4.** Hosmer-Lemeshow Chi-square test and P value for all models at scenario and scenario 2 for all follow-up years.

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | HL Chi-square | P-value | HL Chi-square | P-value | HL Chi-square | P-value |
| Scenario 1 | | | | | | |
| Year 1 | 9.263 | 0.413 | 7.890 | 0.545 | 7.830 | 0.551 |
| Year 2 | 8.725 | 0.463 | 7.879 | 0.546 | 7.883 | 0.546 |
| Year 3 | 9.045 | 0.433 | 7.845 | 0.550 | 7.875 | 0.547 |
| Year 4 | 10.138 | 0.339 | 7.869 | 0.547 | 7.884 | 0.546 |
| Year 5 | 12.095 | 0.208 | 7.887 | 0.546 | 7.864 | 0.548 |
| Scenario 2 | | | | | | |
| Year 1 | 8.214 | 0.513 | 7.908 | 0.543 | 7.912 | 0.543 |
| Year 2 | 8.512 | 0.483 | 7.888 | 0.545 | 7.947 | 0.540 |
| Year 3 | 9.535 | 0.389 | 7.900 | 0.544 | 7.951 | 0.539 |
| Year 4 | 11.542 | 0.240 | 7.883 | 0.546 | 7.908 | 0.543 |
| Year 5 | 14.587 | 0.103 | 7.904 | 0.544 | 7.889 | 0.545 |

**Models including repeated measurement of predictors in scenario 2**

Total/HDL cholesterol was associated with an increased risk for cardiovascular disease with a beta of 0.121 in model 1 (Supplementary material table 1). In model 2 the beta for total/HDL cholesterol ratio increased with each follow-up year from 0.121 to 0.188 in year 3 and stayed at the same level for year 4 and year 5 (Supplementary material table 2). In model 3, baseline total/HDL cholesterol increased from 0.12 to 0.20 for year 1 to year 5. The beta for change in total/HDL

cholesterol from baseline decreased from 0.503 in year 1 to 0.311 in year 5 (Supplementary material table 3).
When follow-up measurements were included the discrimination increased very slightly from year 0 (c-statistic 0.68 (95%CI 0.63-0.73) to year 1 (c-statistic of 0.69 (95%CI 0.64-0.74) for all models. For the consecutive years the discrimination was the same (Table 2). When examining the difference in discrimination for follow-up measurements for models 2 and 3 compared with model 1 no significant improvement was observed for all follow-up years with the NRI (all p-values>0.05). However, for model 2 a small improvement in the IDI was observed for the first 2 follow-up years (IDI: 0.005 and 0.006) compared to the model 1. While model 3 showed a small improvement with the IDI compared to model 1 for all follow-up years except year 5 (table 3). The calibration for the baseline model without inclusion of follow-up measurements was good (HL $\chi^2$=7.950, p-value=0.539). Also in scenario 2 the calibration of model 1 decreased over time, although not significantly. The Hosmer-Lemeshow chi square statistic increased from 7.950 (p-value=0.539) at year 0 to 14.587 (p-value=0.103) at year 5. In model 2 and 3 the calibration did not change over all follow-up years (Table 4).
A sensitivity analysis in which total cholesterol was reduced by 1 mmol/l each year and thus a greater change in risk factor was simulated, showed similar results for the c-statistic. However a greater significant difference in IDI for model 2 and 3 compared to model 1 was observed. The IDIs for both model 2 and model 3 compared to model 1 were significant for all follow-up years. For model 2 the IDI increased from 0.004 for year 1 to 0.016 for year 5 and for model 3 from 0.007 at year 1 to 0.021 for year 5.

## Discussion

In this study we have assessed the discrimination and calibration of a model using baseline information only and three models for inclusion of repeated predictor measurements. It was shown that the discrimination as well as the calibration for a model including baseline information only was as predictive as the inclusion of repeated predictor measurements. The discrimination and calibration of models including repeated measurements was similar. Moreover, we observed that the predictive ability of recalculating risk of the outcome using updated patient characteristics at 5 years of follow-up is almost similar to re-estimating a new model or including change in updated information at new time points.

**Scenario 1**

In this scenario the same change in predictor was simulated for all patients (a reduction in total cholesterol of 1 mmol/l). In this scenario the calibration declined over time when the baseline model (model 1) was used to recalculate the risk, although this was not statistically significant. Only small improvements using the IDI were observed for the first follow-up years for models 2 and 3 compared to refitting the baseline model at new follow-up years (model 1), with smaller improvements at increased follow-up years and even reversed for model 2. This means that recalculating the risk with the baseline model using updated information from year 5 showed a better discrimination than refitting a new model. This change is probably due to the combination of the duration of diagnosed diabetes, which increased every year, and the manner of simulating the outcome. For simulation of the outcome the mean of the predictors over all follow-up years was used, also for diabetes duration leading to a mean of duration of diabetes in the range of the first follow-up years and less comparable to the last follow-up years. Moreover in this scenario the change in the predictor total cholesterol/HDL cholesterol was very small and the difference in diabetes duration had probably a greater impact on the discrimination than the ratio total/HDL cholesterol. Furthermore the cardiovascular risk for each patient changed by a similar amount leading to small changes in reclassifying the patients.

**Scenario 2**

In Scenario 2 the change in total cholesterol was based on cholesterol level in each patient, leading to a different reduction of this risk factor between patients. Some concerns have been voiced over predicting an outcome using baseline risk. Modifiable risk factors can be treated with medications, which influence the risk factors and reduce their effect on the outcome.[17] Even without medications some risk factors, especially cardiovascular risk factors, show considerable change over time, which decreases the correlations between initial and updated values with increasing follow-up.[8] While some studies showed that baseline predictors change over time and the association with certain outcomes (e.g. coronary heart disease) decrease[4;18], other studies have shown that repeated predictor measurements have a regular and monotonic relation with the outcome.[19;20] However these were all observational etiologic studies or randomized controlled trials and predictive performance by discrimination and calibration was not assessed. In scenario 2 we assessed the effect of medication on the

predictive performance of a baseline model and models including repeated predictor measurements.
In this scenario we have shown that recalculating the risk is almost as predictive as fitting a new model (model 1) using updated information when one drug (i.e. statins) decreases a risk factor (i.e. total cholesterol), which is used for estimating the risk. In contrast, a previous study has shown that the use of trajectories (change in predictor) might be more predictive than a naïve approach using baseline information.[9] They observed an improvement in the AUC from 0.72 for models without trajectories to an AUC of 0.82 for a model including trajectories. In this study they only assessed the discrimination while the calibration was ignored and the trajectory included in this study was over weeks instead of years as was the case in our study.

The fact that we observed almost no difference in predictive ability between the models might be explained by several factors. First, the non-significant outcome of the study might be due to the fact that only one variable was changed, while in clinical practice often multiple therapies are used to treat diabetes patients and therefore multiple repeated predictor measurements change over time. Secondly, the change in total/HDL cholesterol ratio was small and a greater change in this risk factor might have a greater impact on the performance of the three models over time. In the sensitivity analysis, we therefore simulated a greater change in ratio total/HDL cholesterol and indeed observed greater differences between the models in both the discrimination and the calibration, although the improvements remained modest. Moreover, in this study we have simulated the outcome based on the mean values of predictors over 5 years. However, it might be more realistic to assume that predictor levels at year 5 are more correlated with the outcome than at year 0, since they are closer to the outcome. The main reason for the decision to weight repeated predictor measurements at all follow-up years similarly in this study was to reduce the risk of favouring updated models over the baseline model. This way of simulation may, however, explain why the study by Maruyama et al. showed significant improvements in discrimination while we did not. It should therefore be assessed if the same results are obtained if repeated predictor measurements at years closer to the outcome weight more than repeated predictor measurements closer to baseline. Furthermore, current analyses should be repeated using clinical data in order to obtain conclusive results on the way to handle repeated measurements in clinical prediction models.

There is a need for improvement of the prediction of cardiovascular disease among diabetes patients, and although inclusion of change in predictors or recalculating risk according to updated predictor measurements seem a good way to improve prediction, the current analyses showed that cardiovascular risk prediction among diabetes patients might not be enhanced by inclusion of updated repeated predictor measurements.
In conclusion, the current study suggests that the use of a prediction model including baseline information only is as predictive as recalculating the risk of a certain outcome at a later time point using repeated predictor measurements or re-estimating new risk scores at new time points using the updated repeated predictor measurements. However, it should be examined if the change in multiple predictors or a different way to include repeated measurements in prediction models do show an improvement in performance.

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**Supplementary materials Table 1.** Betas for predictors in model 1

| | Intercept | Age diabetes | Sex(F) | Smoke past | Smoke current | Hba1c | Systolic Blood pressure | Chol/ HDL ratio | Diabetes duration | Treatment hypertensive medication |
|---|---|---|---|---|---|---|---|---|---|---|
| Scenario 1 | | | | | | | | | | |
| Year 0 | -4.186 | 0.02 | -0.302 | -0.239 | 0.623 | 0.098 | 0.001 | 0.127 | 0.057 | 0.251 |
| Year 1 | -4.186 | 0.02 | -0.302 | -0.239 | 0.623 | 0.098 | 0.001 | 0.127 | 0.057 | 0.251 |
| Year 2 | -4.186 | 0.02 | -0.302 | -0.239 | 0.623 | 0.098 | 0.001 | 0.127 | 0.057 | 0.251 |
| Year 3 | -4.186 | 0.02 | -0.302 | -0.239 | 0.623 | 0.098 | 0.001 | 0.127 | 0.057 | 0.251 |
| Year 4 | -4.186 | 0.02 | -0.302 | -0.239 | 0.623 | 0.098 | 0.001 | 0.127 | 0.057 | 0.251 |
| Year 5 | -4.186 | 0.02 | -0.302 | -0.239 | 0.623 | 0.098 | 0.001 | 0.127 | 0.057 | 0.251 |
| Scenario 2 | | | | | | | | | | |
| Year 0 | -4.174 | 0.023 | -0.282 | -0.250 | 0.657 | 0.103 | 0.000 | 0.121 | 0.063 | 0.261 |
| Year 1 | -4.174 | 0.023 | -0.282 | -0.250 | 0.657 | 0.103 | 0.000 | 0.121 | 0.063 | 0.261 |
| Year 2 | -4.174 | 0.023 | -0.282 | -0.250 | 0.657 | 0.103 | 0.000 | 0.121 | 0.063 | 0.261 |
| Year 3 | -4.174 | 0.023 | -0.282 | -0.250 | 0.657 | 0.103 | 0.000 | 0.121 | 0.063 | 0.261 |
| Year 4 | -4.174 | 0.023 | -0.282 | -0.250 | 0.657 | 0.103 | 0.000 | 0.121 | 0.063 | 0.261 |
| Year 5 | -4.174 | 0.023 | -0.282 | -0.250 | 0.657 | 0.103 | 0.000 | 0.121 | 0.063 | 0.261 |

**Supplementary materials Table 2.** Betas for predictors in model 2

| | Intercept | Age diabetes | Sex(F) | Smoke past | Smoke current | Hba1c | Systolic Blood pressure | Chol/HDL ratio at T=Year | Diabetes duration | Treatment hypertensive medication |
|---|---|---|---|---|---|---|---|---|---|---|
| Scenario 1 | | | | | | | | | | |
| Year 0 | -4.186 | 0.020 | -0.302 | -0.239 | 0.623 | 0.098 | 0.001 | 0.127 | 0.057 | 0.251 |
| Year 1 | -4.223 | 0.020 | -0.291 | -0.240 | 0.627 | 0.099 | 0.001 | 0.143 | 0.058 | 0.253 |
| Year 2 | -4.280 | 0.020 | -0.291 | -0.240 | 0.627 | 0.099 | 0.001 | 0.143 | 0.058 | 0.253 |
| Year 3 | -4.338 | 0.020 | -0.291 | -0.240 | 0.627 | 0.099 | 0.001 | 0.143 | 0.058 | 0.253 |
| Year 4 | -4.394 | 0.020 | -0.291 | -0.239 | 0.627 | 0.099 | 0.001 | 0.143 | 0.058 | 0.253 |
| Year 5 | -4.450 | 0.020 | -0.291 | -0.239 | 0.627 | 0.099 | 0.001 | 0.143 | 0.058 | 0.253 |
| Scenario 2 | | | | | | | | | | |
| Year 0 | -4.174 | 0.023 | -0.282 | -0.250 | 0.657 | 0.103 | 0.000 | 0.121 | 0.063 | 0.261 |
| Year 1 | -4.365 | 0.023 | -0.267 | -0.246 | 0.646 | 0.101 | 0.000 | 0.164 | 0.064 | 0.255 |
| Year 2 | -4.472 | 0.022 | -0.284 | -0.247 | 0.644 | 0.102 | 0.001 | 0.186 | 0.063 | 0.253 |
| Year 3 | -4.546 | 0.022 | -0.285 | -0.250 | 0.644 | 0.101 | 0.001 | 0.188 | 0.063 | 0.255 |
| Year 4 | -4.608 | 0.022 | -0.285 | -0.250 | 0.643 | 0.101 | 0.001 | 0.188 | 0.063 | 0.255 |
| Year 5 | -4.667 | 0.022 | -0.284 | -0.249 | 0.643 | 0.101 | 0.001 | 0.188 | 0.063 | 0.254 |

**Supplementary materials Table 3.** Betas for predictors in model 3

| | Intercept | Age diabetes | Sex(F) | Smoke past | Smoke current | Hba1c | Systolic Blood pressure | Chol/ HDL ratio | Diabetes duration | Treatment hypertensive medication | Change in Chol/ HDL ratio From T=0 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Scenario 1 | | | | | | | | | | | |
| Year 0 | -4.186 | 0.020 | -0.302 | -0.239 | 0.623 | 0.098 | 0.001 | 0.127 | 0.057 | 0.251 | n.a. |
| Year 1 | -4.238 | 0.020 | -0.291 | -0.239 | 0.627 | 0.099 | 0.001 | 0.144 | 0.058 | 0.253 | 0.135 |
| Year 2 | -4.296 | 0.020 | -0.291 | -0.239 | 0.627 | 0.099 | 0.001 | 0.144 | 0.058 | 0.253 | 0.131 |
| Year 3 | -4.355 | 0.020 | -0.291 | -0.239 | 0.626 | 0.099 | 0.001 | 0.143 | 0.058 | 0.252 | 0.124 |
| Year 4 | -4.415 | 0.020 | -0.291 | -0.239 | 0.626 | 0.099 | 0.001 | 0.142 | 0.058 | 0.252 | 0.115 |
| Year 5 | -4.474 | 0.020 | -0.292 | -0.239 | 0.626 | 0.099 | 0.001 | 0.141 | 0.058 | 0.252 | 0.107 |
| Scenario 2 | | | | | | | | | | | |
| Year 0 | -4.174 | 0.023 | -0.282 | -0.250 | 0.657 | 0.103 | 0.000 | 0.121 | 0.063 | 0.261 | n.a. |
| Year 1 | -4.326 | 0.021 | -0.287 | -0.230 | 0.668 | 0.103 | 0.001 | 0.191 | 0.061 | 0.256 | 0.503 |
| Year 2 | -4.418 | 0.020 | -0.321 | -0.240 | 0.665 | 0.105 | 0.001 | 0.202 | 0.060 | 0.255 | 0.355 |
| Year 3 | -4.495 | 0.020 | -0.319 | -0.247 | 0.663 | 0.103 | 0.001 | 0.199 | 0.061 | 0.258 | 0.324 |
| Year 4 | -4.556 | 0.020 | -0.316 | -0.247 | 0.661 | 0.103 | 0.001 | 0.198 | 0.061 | 0.258 | 0.316 |
| Year 5 | -4.614 | 0.021 | -0.315 | -0.246 | 0.660 | 0.102 | 0.001 | 0.197 | 0.061 | 0.258 | 0.311 |

# Chapter 12

## General discussion

## Early intensification and weight gain among patients with type 2 diabetes

The number of patients with type 2 diabetes is increasing worldwide, which leads to an increase in the economic and social burden this disease puts on society.[1] Hence it is important that diabetes and diabetes related complications are managed adequately. Over the last decades the effects of intensive glycaemic control were examined by many large randomized controlled trials (i.e. UKPDS, ADVANCE, VADT and ACCORD).[2-5] Intensive glycaemic control has been associated with substantial benefits on microvascular outcomes,[2;5] but individually these studies have not shown a clear benefit on macrovascular outcomes.[2-4]

Observational studies based on trial data have, however, shown that HbA1c concentrations are directly related to macrovascular complications among diabetes patients.[6;7] Near to normal blood glucose concentrations should be aimed for, in order to reduce the risk of long-term complications.[8;9] The progressive nature of type 2 diabetes and the declining beta-cell function make it difficult to reach and maintain near normal HbA1c targets in patients with type 2 diabetes.[8;9] In the UKPDS trial beta-cell function seemed to decline despite intensive glycaemic control. However, in more recent trials like the ADVANCE, VADT and also ACCORD, a stable near to normal HbA1c concentration was observed.[2-4] In chapter 3 we have shown that early intensification of treatment by either an oral agent or insulin is associated with effective glycaemic control. Moreover, even when a patient is already treated with an oral medication addition of an extra oral agent or commencement of insulin was associated with effective glycaemic control. This is consistent with the recommendations of guidelines which advocate to increase the dose or number of oral agents to achieve near normal glucose levels.[10;11]

Nevertheless, these recommendations also discourage to use a stringent approach to attain near normal glucose levels among patients with high cardiovascular risk or with long-standing diabetes. Intensive glycaemic control might be less effective in reducing blood glucose concentrations among these patients compared to patients with shorter duration of type 2 diabetes.[12] Moreover, patients with long-standing diabetes and at higher cardiovascular risk might be more susceptible for hypoglycaemia.[10] However in our study, which included patients with long-standing diabetes and at an increased

cardiovascular risk, an effective glycaemic control was observed with increasing number of oral agents. The prevalence of hypoglycaemia was only 2.7% in the intensive glucose arm and 1.5% in the standard arm. A second reason to advocate a less stringent approach by treatment guidelines is the uncertainty of possible increased all-cause mortality observed in one trial (ACCORD),[4] which was however not observed in ADVANCE.[2] One of the theories to explain this increased all-cause mortality is the high number of combinations of many drugs used. In ACCORD the target of the intensive glucose arm (HbA1c<6.0%) required the use of multiple combination of glucose-lowering therapies. 42% of the participants in the intensive treatment group were receiving three or more classes of oral agents either alone or even in combination with insulin, whereas this was only 19% in the standard arm.[13] In ADVANCE, where the target of the intensive arm was HbA1c<6.5%, no increased mortality was observed and effective glycaemic control was achieved by early intensification by addition of an oral agent or commencement of insulin, the overall number of combinations of drugs used by participants was much lower. Nonetheless, 27% of the participants in the intensive glucose-lowering arm were on three or more oral agents after 5 years and 11% of the participants in the standard arm were on three or more oral agents after 5 years. Hence it seems that use of three or more oral agents does not necessarily increase all-cause mortality. However, side effects of different combinations of therapies or dose might be responsible for the increased all-cause mortality and this should be further investigated.

General practitioners are still hesitant to adopt an intensified glycaemic treatment strategy by either prescribing an extra oral glucose lowering agent or commencement of insulin therapy.[14;15] The main reason for this hesitation by the general practitioner as well as diabetes patients is fear of weight gain. Although weight gain has been associated with intensified glycaemic control in some trials[16;17], in the ADVANCE trial there was no substantial weight gain in the intensified glucose control group. The mean weight change was +0.16kg in the intensive glycaemic control group and -0.70kg in the standard glycaemic control group. Both weight gain and weight loss were observed in both the standard arm and intensive glucose control arm.[2] Therefore in chapter 4 we examined which patient characteristics and therapies were associated with weight gain. A higher HbA1c level and number of oral medications at baseline were associated with weight gain. The combination of these factors reflects disease progression and beta cell deterioration. Particularly

patients on treatment combinations that included insulin gained the most weight in the ADVANCE trial, both in the intensive glucose arm and standard arm. At the end of the study 42% of the intensive glucose control arm and 24% of the participants in the standard arm were receiving a therapy including insulin. The rates of participants on insulin were much higher in other trials where participants gained more weight. In ACCORD 77% of the participants in the intensive glucose arm were on insulin at the end of the study, whereas this was 55% in the standard glucose control arm. The mean weight gain in this study was 3.5kg and 0.4kg for the intensive and standard arm respectively.[4] In the VADT trial 89% and 74% of the participants were on insulin for the intensive glucose control and standard control arm. The weight gain was 7.8 kg and 3.4 kg, respectively.[3] Combining this information from other trials with the results from chapter 4 we can conclude that intensive treatment is directly related to the percentage of patients who end up on insulin therapy and gain weight. Despite this fact we have shown in chapter 4 that intensive glucose control does not necessarily lead to weight gain, but depends mostly on the types of medication prescribed and on patient characteristics like ethnicity and duration of diagnosed diabetes. However it should be assessed if a difference in weight gain also shows a difference in cardiovascular complications.

Combining the post-hoc analyses we have performed in chapter 3 and 4 and the literature of other trials we can conclude that early intensification by oral medication has a positive effect on glycaemic control, also in diabetes patients with increased cardiovascular risk. However, the combination of drugs should be chosen carefully in order to prevent weight gain, which might have a harmful effect on cardiovascular complications.

## Individualized therapy and guidelines

Studies examining the cardiovascular risk of diabetes patients have shown that risk for a cardiovascular death in diabetes patients is the same as for people with normal glucose tolerance who suffered a myocardial infarction.[18;19] However, other studies have shown that this risk among diabetes patients is much lower.[20-22] Diabetes patients have a wide range of classical cardiovascular factors like age, systolic blood pressure, blood glucose level and smoking, which individually may lead to differences in cardiovascular risk among diabetes patients.[23] Treatment guidelines are generally focusing more on

personalized treatment, either by treating diabetes patients with a high cardiovascular risk or by treatment of the different contributing cardiovascular risk factors.
Current guidelines have no consensus on whether or not a risk score should be used to estimate cardiovascular risk among diabetes patients and use this to guide preventive treatment. The ADA[10] and WHO[24] regard all diabetes patients as high risk individuals and advocate to treat individual risk factor components. In contrast, the IDF[25] and also the Dutch national guidelines[26] recommend applying a risk score, either the UKPDS risk engine[27] or a modification of the SCORE risk chart[28] and use the outcome of this risk score to guide treatment. The general idea of the latter approach is that treatment might be more effective for those at the highest risk. One risk factor that should be controlled to prevent occurrence of CVD is blood pressure. In chapter 5 we have examined if blood pressure control has a different effect among high cardiovascular risk individuals compared to medium cardiovascular risk individuals. Notwithstanding the fact that the relative effects of blood pressure lowering therapy were similar for the patients from the different groups of cardiovascular risk, the absolute beneficial effects were greater among the highest risk individuals. Although treatment of high risk individuals would lead to the greatest benefit in a small subset of the patients and might prove to be the most cost-effective,[29] it could be argued that treatment of the medium risk groups would reduce the absolute numbers of cardiovascular incidences to the greatest extent. In order to treat either the medium or highest risk individuals it is necessary to correctly discriminate between high risk and low risk individuals.

## Current risk prediction of cardiovascular disease among diabetes patients

Risk prediction models are used to discriminate between high and low risk patients and to estimate the absolute probability that an outcome will occur within a specified time frame.[30] Prognostic studies use a multivariable approach to determine the important predictors of a particular outcome. Although some clear similarities between etiologic research and prognostic research exist, distinctions should be made. While in etiologic research the aim is to explain whether an outcome is causally related to a particular factor, in prognostic research the aim is to use multiple variables to estimate as accurately as possible the

absolute risk of a particular outcome. All potential predictors, causal or not, can be considered in a prognostic study. Although causal factors are often predictors, it is not necessary for predictors to have a causal relation with the outcome.[30]

Over the past decades interest in risk prediction and prognostic modelling has substantially increased. The number of risk scores for the same particular disease has expanded rapidly over the last decade, making it hard for general practitioners to determine which model to use.[31] Many prediction models have been developed, however the number of studies that examine their performance in a new set of patients (external validation) of these risk scores is limited.[32] The potential impact of these prediction models has hardly been examined at all.[33]

In the cardiovascular domain many risk scores have been developed, with the most commonly known and important ones being SCORE[28] in Europe and the Framingham Risk Score[34-36] in the USA. Over 100 cardiovascular risk scores have been developed, but only 15 of these risk scores have been externally validated.[37] The most extensively validated risk scores are the Framingham Risk Score[36], SCORE[28] and PROCAM.[38] Discrimination of cardiovascular risk scores is moderate and calibration is often poor.[37]

To predict cardiovascular complications among diabetes patients the number of risk scores available is much smaller, but still many risk scores exist. In chapter 7 we provide an overview of all cardiovascular risk scores applicable to diabetes patients. We identified 12 prediction models specifically designed for diabetes patients and 33 models applicable to diabetes patients since they include diabetes as a factor. Only 14 of these risk scores have been externally validated among diabetes patients. In chapter 8 and 9 we therefore examined the performance of different cardiovascular risk scores for diabetes patients, and also observed a moderate discrimination and a poor calibration among diabetes patients. While the predictive performance of cardiovascular risk scores among diabetes patients need improvements, the prediction of the occurrence of diabetes itself is much better. A systematic review of diabetes risk scores showed that most risk scores showed a good discrimination between 0.7 to 0.8.[39] This difference in performance of prediction of diabetes and cardiovascular complications among diabetes patients might be explained by several factors. Cardiovascular disease is a complex disease and many factors contribute to the cardiovascular profile.[40;41] The population at risk for cardiovascular disease is heterogeneous, many risk factors and pathogenic pathways are involved in the occurrence of cardiovascular

disease.[42] Moreover cardiovascular disease is a composite endpoint, consisting of ischemic heart disease and stroke with even subgroups among these diseases. Different endpoints might have a different frequency and combining them may lead to a discrepancy in calibration.[43] In chapter 9 we also observed a difference in calibration of cardiovascular prediction models between the EPIC-NL cohort which used a broader definition of cardiovascular risk compared to the calibration in the EPIC-Potsdam cohort. However simple recalibration of the prediction models can solve this issue. Furthermore patients at an increased cardiovascular risk take medication for modifiable cardiovascular risk factors, eg statins, anti-hypertensive medication and glycaemic control medication. Although drug therapy is beneficial for patients, it might make prediction of cardiovascular disease more difficult. Patients using drugs may fare better than patients not taking drugs.[42] Especially patients with type 2 diabetes often use several drugs to control their blood glucose and other cardiovascular risk factors. Hence multiple pathogenic pathways are drug treated making it harder to predict cardiovascular disease.

The occurrence of type 2 diabetes might be easier to predict, considering that patients at risk for development of type 2 diabetes are all relatively healthy and not taking many medications. Additionally no preventive strategies have yet been adopted to prevent the incidence of type 2 diabetes from occurring in high risk but healthy individuals. Moreover one main risk factor exists for the occurrence of diabetes which is obesity or large weight gain, while diabetes patients at risk for CVD often have several risk factors. However it is possible that the poor performance of cardiovascular prediction models among diabetes patients in our cohorts (EPIC-NL and EPIC-Potsdam) might be due to the fact that these cohorts consists of diabetes patients from the general population. Therefore no clinical data is available, while some risk scores include factors like retinopathy, left ventricular hypertrophy or microalbuminuria. Thus, for the validation of the prediction scores including these factors, we had to use a proxy for these factors, which may have affected the calibration of the models. However models not including these risk factors had a similar low calibration. Another limitation that might have an impact on the validation of the prediction models is that the baseline data of EPIC-NL is documented nearly 20 years ago. However, this is inherent to many prediction studies, since 10 years of follow-up are required to predict 10 year risk of a certain disease.

## Can we improve the prediction of cardiovascular disease among diabetes patients?

Several options for increasing the prediction of cardiovascular disease among patients with type 2 diabetes should be considered. The easiest way to improve cardiovascular risk prediction among diabetes patients might be found in systematic improvement of risk prediction by recalibrating existing models. Intercept recalibration as we have shown in chapter 9 can increase the agreement between observed cardiovascular risk and predicted cardiovascular risk, but does not affect discrimination. Furthermore a full refitting of existing cardiovascular models can enhance the prediction when the model is used in a new set of patient with different characteristics.[32] However systematic improvements like recalibration and refitting of the predictors in existing models might only improve the prediction in the current cohort in which the improvement is performed. Generally, applying the updated risk score in a different set of patients often leads again to disappointing results. Consequently we should examine other ways to improve risk prediction.

The addition of new biomarkers to existing prediction models has attracted considerable attention over the past decade. Many studies have assessed the effect of circulating, genetic and imaging biomarkers on prediction of cardiovascular disease either as single marker or addition of multiple markers[44-51], all with only modest enhancements in risk prediction.[49-51] One of the most examined biomarkers for added prognostic value in cardiovascular risk prediction is c-reactive protein (CRP). Despite a robust association between CRP and future cardiovascular risk, the added predictive value is only moderate.[52] Whereas CRP reflects the inflammation pathway, a second pathway associated with cardiovascular events is stress or cardiovascular injury. A biomarker associated with this pathway is NT-proBNP which is synthesized when cardiac myocytes are stretched. This is one of the few biomarkers showing a clear association with incidence of cardiovascular disease and leads to a small improvement in the discrimination of patients who will develop cardiovascular disease from those who will not among the general population.[53] Notwithstanding the added predictive effect in the general population, among diabetes patients it has yet to be established, and this biomarker is currently being measured among diabetes patients from the EPIC-NL cohort in order to test its added prognostic value.

In chapter 10 we examined the associations between heart-type fatty acid-binding protein (H-FABP) and cardiovascular risk and the added prognostic value of this biomarker among diabetes patients. Although a modest etiologic association between H-FABP and cardiovascular disease was observed among patients with type 2 diabetes, the added predictive value was limited.

Other markers that have been recently examined for their added value to cardiovascular risk prediction by other studies are adiponectin, lipoprotein-associated phospholipase $A_2$ and carotid-intima media thickness.[46-48;54] Addition of multiple biomarkers simultaneously showed only a modest improvement, leading to the question if biomarkers can improve the prediction of cardiovascular disease. Considering the fact that a key determinant for improvement in discrimination by multiple markers is the correlation between the markers, the answer to this question is yes. A set of moderately correlated markers (r=0.4) need more than 50 markers to increase the c-statistic by 0.05, but weakly correlated markers (r=0.05) need less than 10 markers for the same increase in discrimination.[46] Therefore it is possible to increase the discrimination for predicting cardiovascular disease with only a small set of biomarkers provided that they are weakly correlated with each other and weakly correlated with established risk factors included in the model. This means that biomarkers examined for their added value should come from different pathways leading to cardiovascular disease.

Hence biomarkers outside of established pathways should be explored. Uncorrelated biomarkers outside of already established pathways can be found using an untargeted approach in which global panels of biomarkers are compared between patients with and without cardiovascular disease. Metabolomics are small substrates and products from metabolic pathways which can be assessed using mass spectrometry or nuclear magnetic resonance with both a targeted and untargeted approach.[55] They can either quantitatively screen predefined metabolites (targeted) or can aim at global detection of metabolites reflecting a difference between cardiovascular patients and patients without cardiovascular disease (untargeted).[48] While the use of metabolomics for prediction is still a relatively new area of research, it might be promising for providing new insights and markers for added predictive accuracy.[46]

Inclusion of patient history might improve prediction as well. Diabetes patients often visit their physician regularly providing updated information of their modifiable risk factors. However, none of the risk scores to predict cardiovascular risk among diabetes patients include such updated information, nor is it known what the best way would be to model such information. In chapter 11 we observed that inclusion of this updated information led to only a modest improvement in reclassification of patients. However this was examined using a simulation study which has certain limitations. It is impossible to exactly simulate clinical practice. Furthermore in this chapter we have focused on a single predictor whereas in clinical practice often multiple treatments and risk factors are modified leading to greater differences in risk. The influence of differences in multiple factors on risk prediction should therefore be further investigated.

## Conclusion and future perspectives

In conclusion, earlier identification of high cardiovascular risk patients can reduce the burden and economic costs diabetes puts on society. Hence the research to improve cardiovascular prediction among type 2 diabetes patients should continue. One of the most promising ways to improve risk prediction is through the addition of new biomarkers by establishing new risk factors though profiling of metabolomics and proteomics on a large scale. If we can identify new pathways with metabolomics and proteomics, we might be able to improve cardiovascular risk prediction among diabetes patients. Furthermore the impact of the use of prediction models has not been examined intensively. Therefore future perspective should focus on examining the effects the use of different cardiovascular risk scores have on cardiovascular prevention compared to the traditional way general practitioners are treating patients with type 2 diabetes. Lastly to further examine if inclusion of data from repeated visits by diabetes patients to the general practitioner might improve the prediction, we should assess the effects the change in multiple variables have on risk prediction. If over time many factors change and a pattern can be modelled it might lead to the much needed improvement of cardiovascular risk prediction among diabetes patients.

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# Chapter 13

**Summary**

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In part 1 the burden of diabetes on society was introduced, and the management of type 2 diabetes was described. Several post-hoc analyses of the ADVANCE trial data were conducted. ADVANCE is a study that examines the effects of perindopril-indapamide and intensive glucose lowering on cardiovascular outcomes. Moreover, in this part of the thesis non-fasting lipid levels among diabetes patients were examined for associations and prediction of cardiovascular disease.

Chapter 2 provided an overview of the burden of diabetes and its complications on the society. The number of patients with type 2 diabetes is increasing rapidly worldwide. It is projected that the number of people with type 2 diabetes will double by 2030 compared to the number of patients in 2000. Most of this growth will be in developing countries and will be attributable to changes in average ages of the population of countries like China and India. In 2007 there was an estimated 308 million people with impaired glucose tolerance with the majority of these patients living in developing countries. Progression of impaired glucose tolerance to diabetes is not inevitable, but about 30% of these patients will progress to diabetes. Cardiovascular disease is the leading complication of type 2 diabetes and approximately half of the patients with type 2 diabetes will die of a cardiovascular cause. Patients with type 2 diabetes have a 2-4 fold increased risk for coronary heart disease compared to the general population. Moreover patients with type 2 diabetes might suffer other complications, like nephropathy, retinopathy or lower extremity amputations. Diabetes is one of the world's most important causes of expenditure, mortality, disability and economic loss. Therefore it is important that diabetes is managed adequately either by reducing several risk factors or intensive glycaemic control.

Chapter 3 described the effects on glycaemic control of intensified treatment by either an additional oral glucose lowering agent or commencement of insulin among the 11,140 patients enrolled in the ADVANCE trial. Patients were classified as either effective glycaemic control (an HbA1c≤7.0 or a reduction in HbA1c of ≥10%) or ineffective glycaemic control (HbA1c>7.0% and <10% reduction). Therapy intensification through both an oral agent or insulin was associated with effective glycaemic control. This association was independent of the number of oral glucose lowering agents a patients was already receiving. Furthermore a low HbA1c at time of treatment intensification was associated with effective glycaemic control, meaning that early treatment intensification has a beneficial effect on glycaemic control

regardless of disease stage.
Some trials have shown that intensified glucose treatment is associated with weight gain however this pattern was not observed in the ADVANCE trial. Therefore in chapter 4 we examined the baseline characteristics and glucose lowering therapies associated with weight gain among patients with type 2 diabetes. This was assessed using patients enrolled in the ADVANCE trial, patients were either enrolled in the intensive glycaemic control arm or the standard arm. Weight was measured every 6 months. The mean weight decreased by 0.70 kg in the standard arm and non-significantly increased in the intensive arm. Baseline characteristics associated with weight gain were younger age, higher HbA1c, Caucasian ethnicity and number of oral medications at baseline. Treatment combinations including insulin or thiazolidinedione were associated with a weight gain of 3 kg, while sulphonylurea or metformin were weight neutral.
Chapter 5 focused on the effects of blood pressure lowering among diabetes patients on cardiovascular risk. Differences in treatment effects of a fixed combination of perindopril-indapamide on major cardiovascular outcomes across subgroups of cardiovascular risk were assessed. Patients from the ADVANCE trial were divided in two cardiovascular risk groups according to their 5-year cardiovascular risk calculated using the Framingham risk score (moderate-high risk: ≤25% cardiovascular risk; or very high risk group: >25% risk or a history of cardiovascular events). Cox regression was used to obtain hazard ratios for the relative blood pressure lowering effects on cardiovascular outcomes. Absolute risk reductions were obtained by subtracting the event rates for the blood pressure lowering group from the event rate of the placebo group. No difference in relative effect for blood pressure lowering was observed between the moderate-high risk group and the very high risk group (all p-values for heterogeneity≥0.38). Absolute treatment effects tended to be different between the two risk groups with greater absolute risk reduction for the very high risk group, but this did not reach significance.
Patients with type 2 diabetes often have dyslipidemia and cholesterol levels might be differently associated with cardiovascular risk compared to the general population. Therefore in chapter 6 the associations between non-fasting lipid levels and cardiovascular risk among diabetes patients were examined. Moreover cardiovascular risk prediction using non-fasting lipid levels was assessed. In this study 1337 diabetes patients from EPIC-NL and EPIC-Potsdam were included. At baseline

total, HDL and LDL cholesterol and triacylglycerol were measured and postprandial time was documented. Hazard ratios for cardiovascular events across tertiles for lipid concentrations were obtained. After adjustment for potential confounders a higher triacylglycerol and ratio total/HDL cholesterol were associated with cardiovascular disease. To examine the risk prediction using non-fasting lipid levels, patients were divided according to their postprandial time (>3hours or ≤3 hours). No difference in cardiovascular risk prediction was observed between both groups for either the discrimination or the calibration. Therefore it might not be necessary to use fasting blood samples to determine lipid concentrations for cardiovascular risk prediction among diabetes patients.

Part 2 focused on cardiovascular risk prediction among patients with type 2 diabetes by examining the existing prediction models and their predictive value and examine possibilities to increase cardiovascular risk prediction among diabetes patients.
Chapter 7 provided an overview of all cardiovascular prediction models applicable to patients with type 2 diabetes. Performing a systematic review of the literature 12 cardiovascular risk scores specifically designed for diabetes patients and 33 prediction models applicable to diabetes patients which included diabetes as a factor were identified. Thirty studies externally validated 14 different prediction models among patients with type 2 diabetes of which nine studies examined the external validation of the UKPDS risk engine and 10 studies examined the external validation of the Framingham risk score. Most risk scores showed a moderate discrimination with a c-statistic between 0.60 to 0.70 and a poor calibration. Even though many risk scores have not been validated or only with a moderate to poor performance, several risk scores have been included in clinical guidelines.
The most frequently used risk score for patients with type 2 diabetes is the UKPDS risk engine. In Chapter 8 the external performance of this risk engine among 1,622 diabetes patients from EPIC-NL and EPIC-Potsdam was described. The UKPDS risk engine was used to calculate 4-,5-,6- and 8-year cardiovascular risk. Patients were followed for incidence of coronary heart disease and cardiovascular disease during a mean period of 8 years. The UKPDS risk engine showed a poor calibration and overestimated the risk for both cardiovascular disease and coronary heart disease for all predicted risk periods. The discrimination was moderate with a c-statistic of 0.65. Calibration was slightly better for

patients being diagnosed with type 2 diabetes for more than 10 years. A complete assessment of all risk scores designed specifically for diabetes patients that predicted cardiovascular risk was conducted and described in chapter 9. The external validation of nine cardiovascular risk scores that were identified in chapter 7 was assessed in both EPIC-NL and EPIC-Potsdam separately. Discrimination was assessed using the c-statistic and calibration was assessed using the Hosmer-Lemeshow chi square statistic and calibration plots. To compensate for differences in incidence between the validation cohorts and the development cohorts all risk scores were recalibrated after which calibration was re-assessed. All nine risk scores showed a poor to moderate discrimination, with c-statistics ranging from 0.55 for the Fremantle risk score to 0.71 for the UKPDS risk score. After recalibration, the calibration of all models was good, (all p-values>0.05) with a slight overestimation of the risk. The model with the best calibration in our cohort was the Swedish NDR risk score which was then used to assess the added prognostic value of Heart-type Fatty Acid-Binding Protein (H-FABP) for the prediction of cardiovascular disease among diabetes patients, which is described in chapter 10. Moreover in this chapter etiologic associations between H-FABP and cardiovascular risk were also examined. A positive association between H-FABP and CVD was observed, but this attenuated to not significant after multivariable adjustments (HR 1.10 (95%CI:0.96-1.27)). The discrimination increased slightly and was significant with the IDI (0.0121, P=0.015), but not with the NRI (0.062, p=0.121). The small improvement in the discrimination has only little clinical value for cardiovascular risk assessment.

Patients with type 2 diabetes visit their physician regularly. In chapter 11 it was assessed how to incorporate repeated measurements in clinical prediction models and if this affected the predictive performance using cardiovascular risk assessment among diabetes patients as an example. A cohort of 536 diabetes patients from EPIC-NL was used to obtain 10.000 bootstrap samples and for each sample 5 years of follow-up measurements were simulated in which one predictor was changed using 2 scenarios. In scenario 1 all patients had the same change in this predictor while in scenario 2 this predictor was changed according to the value of this predictor. As an example a logistic model predicting cardiovascular events among diabetes patients was used, simulating the effect of statin therapy on one risk factor (total/HDL cholesterol ratio). The inclusion of repeated measurements were compared to a standard baseline model in which no repeated

measurements were included. Three types of models for inclusion of repeated measurements were compared: 1) A model constructed using baseline data, which was used at each consecutive time point to recalculate the risk. 2) A new model was fitted each year using the updated information at new time points. 3) Change in predictor from baseline to each time point was added to the model and risk was calculated using this model. The c-statistics of the baseline model and the 3 models including repeated measurements were identical. The NRI of model 2 and model 3 showed no significant improvement in discrimination compared to model 1. However small improvements were observed with the IDI for the first follow-up years ranging from 0.003 to 0.012, whereas the calibration decreased over time for model 1, although not significantly. The calibration of model 2 and model 3 was the same for all follow-up years. This study suggests that the use of a baseline model is as predictive as recalculating the risk at new time points or fitting a new model using repeated measurements. Only small changes in discrimination were observed for models using updated information.

In conclusion this thesis shows that it is of great importance that patients with a high risk of developing cardiovascular diseases are detected at an early stage, in order to initiate appropriate treatment. To identify these patients it is important that research of cardiovascular risk prediction is continued.

# Chapter 13

Summary

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Deel 1 van dit proefschrift richtte zich op de impact die diabetes heeft op de samenleving en op management van type 2 diabetes. In dit deel van het proefschrift worden verschillende post-hoc analyses van de ADVANCE studie beschreven. ADVANCE is een gerandomiseerde studie waarbij het effect van perindopril-indapamide en een intensieve bloedglucose behandeling op hart- en vaatziekten risico is onderzocht. Daarnaast is in dit deel van het proefschrift de waarde van niet-nuchtere lipiden waarden voor associaties met en voorspelling van hart- en vaatziekten bij diabetes patiënten bepaald.

Hoofdstuk 2 gaf een overzicht van de impact van diabetes en de bijbehorende complicaties op de samenleving. Het aantal patiënten met type 2 diabetes neemt wereldwijd in snel tempo toe. Verwacht wordt dat het aantal personen met type 2 diabetes in 2030 verdubbeld zal zijn ten opzichte van het aantal patiënten in 2000. Het grootste deel van deze groei zal plaatsvinden in de ontwikkelingslanden en is toe te schrijven aan veranderingen in de gemiddelde leeftijd van de bevolking van landen als China en India. In 2007 waren er naar schatting 308 miljoen mensen met een verstoorde glucosetolerantie, waarvan de meerderheid in ontwikkelingslanden. Progressie van verminderde glucosetolerantie naar diabetes is niet onvermijdelijk, ongeveer 30% van deze patiënten zal uiteindelijk diabetes ontwikkelen.

Hart- en vaatziekten is de belangrijkste complicatie van type 2 diabetes en ongeveer de helft van deze patiënten sterft aan hart- en vaatziekten. Patiënten met type 2 diabetes hebben een 2-4 maal verhoogd risico op coronaire hartziekten in vergelijking met de algemene bevolking. Tevens lijden patiënten met type 2 diabetes vaak aan andere complicaties, zoals nefropathie, retinopathie of amputatie van de onderste extremiteiten. Diabetes is wereldwijd één van de belangrijkste oorzaken van sterfte, invaliditeit en economische schade. Daarom is het belangrijk dat diabetes adequaat behandeld wordt, hetzij door verschillende risicofactoren te verlagen, danwel door een intensieve bloedglucose verlagende behandeling.

Hoofdstuk 3 beschreef de effecten van een intensieve behandeling op de glykemische waarde, door ofwel een extra orale glucose verlagend medicijn toe te dienen of de start van insuline. Dit is onderzocht onder 11,140 patiënten die deelnamen aan de ADVANCE studie. Patiënten werden geclassificeerd als effectieve glykemische controle (met een HbA1c ≤ 7.0 of een vermindering in HbA1c van ≥ 10%) of als niet-effectieve glykemische controle (met een HbA1c> 7.0% en <10% reductie in HBA1c). Intensivering van therapie door middel van zowel orale glucose verlagende middelen als toediening van insuline

zijn geassocieerd met effectieve glykemische controle. Deze effecten waren onafhankelijk van het aantal orale glucose verlagende middelen die een patiënt al neemt. Daarnaast was een lage HbA1c waarde op het moment van intensivering van therapie geassocieerd met effectieve glykemische behandeling, ongeacht de status en progressie van diabetes.
Een aantal studies hebben aangetoond dat intensieve behandeling gepaard gaat met gewichtstoename, maar dit patroon werd niet waargenomen in de ADVANCE trial. In hoofdstuk 4 was onderzocht welke patiënt karakteristieken en bloedglucose verlagende middelen geassocieerd zijn met gewichtsverandering bij diabetes patiënten. Dit is onderzocht in patiënten die deelnamen aan de ADVANCE trial, waarbij patiënten werden ingedeeld in de intensieve glykemische behandelgroep (HbA1c<6.5%) of de standaard behandelgroep. Gewicht werd elke 6 maanden gemeten. Het gemiddelde gewichtsverlies was 0.70 kg in de standaard groep en niet significant verhoogd in de intensieve groep. Patiënt karakteristieken geassocieerd met gewichtstoename waren een jongere leeftijd, een hogere HbA1c, kaukasische etniciteit en het aantal orale glucose verlagende medicijnen bij de start van de studie. Behandelingscombinaties met insuline of thiazolidinedione waren geassocieerd met een gewichtstoename van 3 kg, terwijl sulfonylureum derivaten of metformine gewicht-neutraal waren.
Hoofdstuk 5 richt zich op de effecten van bloeddrukverlagende middelen op hart- en vaatziekten risico bij diabetes patiënten. Verschillen in behandelingseffecten door een combinatie van perindopril-indapamide op belangrijke hart- en vaatziekten uitkomsten werd onderzocht in verschillende cardiovasculaire subgroepen. Patiënten uit de ADVANCE studie werden verdeeld in twee cardiovasculair risicogroepen op basis van hun 5-jaars hart- en vaatziekten risico, dat werd berekend met de Framingham risicoscore (gemiddeld-hoog risico groep: ≤ 25% risico, en de zeer hoog risico groep:> 25% risico of een voorgeschiedenis van hart- en vaatziekten). Cox regressie werd gebruikt om hazard ratio's voor de relatieve bloeddrukverlagende effecten op de hart- en vaatziekten te bepalen. Absolute risicoreductie werd bepaald door het verschil in incidentie tussen de bloeddrukverlagende groep en de placebogroep. Er werd geen verschil in relatief effect tussen de gemiddeld-hoog risico groep en de zeer hoog risicogroep waargenomen (alle p-waarden voor de heterogeniteit ≥ 0.38). Absolute behandeleffecten waren iets verschillend tussen de twee risicogroepen, waarbij het grootste absolute effect werd gemeten in de zeer hoog risicogroep, maar dit effect was niet significant.

Patiënten met type 2 diabetes hebben vaak dyslipidemie en het cholesterolgehalte zou daardoor anders geassocieerd kunnen zijn met hart- en vaatziekten risico dan in de normale populatie. In hoofdstuk 6 waren de associaties tussen niet-nuchtere lipiden waarden en hart- en vaatziekten risico bij diabetes patiënten onderzocht. Tevens is er gekeken naar de voorspelling van hart- en vaatziekten met niet nuchtere lipiden waarde bij diabetes patiënten. Deze studie is uitgevoerd onder 1,337 patiënten met diabetes uit EPIC-NL en EPIC-Potsdam. Bij de start van de studie werden totaal, HDL- en LDL-cholesterol en triacylglycerol gemeten en de postprandiale tijd bepaald. Hazard ratio's voor hart- en vaatziekten werden vergeleken tussen tertielen van lipiden concentraties. Na correctie voor potentiële confounders waren een verhoogde triacylglycerol concentratie en de ratio totaal/HDL-cholesterol geassocieerd met hart- en vaatziekten. Om het effect van niet nuchtere lipiden concentraties op de voorspelling van het hart- en vaatziekten risico te bepalen werden patiënten ingedeeld volgens hun postprandiale tijd (>3 uur of ≤ 3 uur). Er werd geen verschil gevonden in de voorspelling van het cardiovasculair risico tussen de groepen, voor zowel de discriminatie als de kalibratie. Daarom is het wellicht niet nodig om nuchtere bloedmonsters te gebruiken voor de bepaling van lipiden concentraties om het hart- en vaatziekten risico te voorspellen bij diabetes patiënten.

Deel 2 van dit proefschrift richtte zich op het voorspellen van hart- en vaatziekten bij patiënten met type 2 diabetes door het analyseren van de voorspellende waarde van bestaande risicomodellen en het onderzoeken of de risicovoorspelling verbeterend kan worden. In hoofdstuk 7 was een overzicht gegeven van alle hart- en vaatziekten modellen die toepasbaar zijn voor patiënten met type 2 diabetes. In een systematische review van de literatuur werden 12 hart- en vaatziekten risicoscores gevonden die specifiek ontwikkeld zijn voor diabetes patiënten en 33 modellen die toepasbaar zijn voor mensen met diabetes omdat diabetes als factor in het model is opgenomen. Dertig studies hebben 14 verschillende risicomodellen gevalideerd in patiënten met type 2 diabetes, waarvan negen studies de UKPDS risk engine hebben gevalideerd en 10 studies de Framingham risicoscore. De meeste risicoscores hebben een matige discriminatie met een c-statistiek tussen 0.60 en 0.70 en een slechte kalibratie. Ondanks dat veel risicoscores niet zijn gevalideerd of slechts met een matige tot slechte prestatie, zijn een aantal van deze risicoscores in klinische richtlijnen opgenomen.

De meest gebruikte risicoscore voor patiënten met type 2 diabetes is de UKPDS risk engine. In Hoofdstuk 8 was de externe validatie van dit risicomodel bij 1,622 diabetes patiënten van EPIC-NL en EPIC-Potsdam onderzocht. De UKPDS risk engine werd gebruikt om 4-, 5-, 6- en 8-jaar hart- en vaatziekten risico te voorspellen. Patiënten werden gevolgd voor hart- en vaatziekten en coronaire hartziekten apart gedurende een gemiddelde periode van 8 jaar. De UKPDS risk engine had een slechte kalibratie en overschatte het risico voor zowel hart- en vaatziekten als coronaire hartziekte voor alle voorspelde risico periodes. De discriminatie was matig met een c-statistiek van 0.65. De kalibratie was iets beter voor patiënten die meer dan 10 jaar geleden gediagnosticeerd waren met type 2 diabetes.
Een complete studie van de externe validatie van alle hart- en vaatziekten risicomodellen speciaal ontwikkeld voor patiënten met diabetes was beschreven in hoofdstuk 9. Negen hart- en vaatziekten risicoscores die werden geïdentificeerd in hoofdstuk 7 werden extern gevalideerd in EPIC-NL en EPIC-Potsdam afzonderlijk. De discriminatie werd berekend met de c-statistiek en kalibratie werd bepaald met behulp van de Hosmer-Lemeshow chi kwadraat test en kalibratieplots. Om te corrigeren voor verschillen in incidentie tussen de validatie cohorten en de cohorten waarin de modellen ontwikkeld zijn, werden alle risicoscores opnieuw gekalibreerd en werd de kalibratie vervolgens opnieuw getoetst. Alle negen risicomodellen vertoonden een slechte tot matige discriminatie met c-statistieken, variërend van 0.55 voor de Fremantle risicoscore tot 0.71 voor de UKPDS risicoscore. Nadat de modellen opnieuw gekalibreerd waren was de kalibratie goed (alle p-waarden> 0.05) met een kleine overschatting van het risico. Het model met de beste kalibratie in het EPIC-NL cohort was de Zweedse NDR risicoscore dat vervolgens werd gebruikt om de toegevoegde prognostische waarde van het myocardiale vetzuur bindend eiwit (H-FABP) te berekenen voor het voorspellen van hart- en vaatziekten bij diabetes patiënten, dit was beschreven in hoofdstuk 10. Daarnaast is in dit hoofdstuk de etiologische associatie tussen H-FABP en cardiovasculair risico onderzocht. Er werd een positieve associatie tussen H-FABP en hart- en vaatziekten waargenomen, maar na multivariabele correctie was deze niet meer significant (HR 1.10 (95% CI: 0.96-1.27)). De toevoeging van H-FABP zorgde voor een toename in de discriminatie en was significant volgens de IDI (0.0121, P=0.015), maar niet met de NRI (0.062, P=0.121). De kleine verbetering in de discriminatie heeft slechts weinig klinische waarde voor hart- en vaatziekten voorspelling.

Patiënten met type 2 diabetes bezoeken regelmatig hun huisarts. In hoofdstuk 11 werd onderzocht hoe de herhaalde metingen in klinische voorspelregels kunnen worden opgenomen en of dit het hart- en vaatziekten risico van diabetes patiënten beter kan inschatten. Een cohort van 536 diabetes patiënten van EPIC-NL werd gebruikt om 10.000 bootstrap samples te verkrijgen. Voor elk van deze samples werden 5 jaar follow-up metingen gesimuleerd, waarin steeds 1 predictor veranderd werd volgens 2 scenario's. In scenario 1 werd dezelfde verandering in de predictor gebruikt voor alle patiënten. In scenario 2 was de verandering in deze predictor afhankelijk van de waarde van de predictor. Als voorbeeld is er gebruik gemaakt van een logistisch model dat hart- en vaatziekten voorspelt bij diabetes patiënten waarbij het effect van statines op de predictor totaal/HDL cholesterol ratio is gesimuleerd. De toevoeging van herhaalde metingen werd vergeleken met een standaard basismodel waarin geen herhaalde metingen werden geïncludeerd. Drie verschillende modellen voor de toevoeging van herhaalde metingen werden onderzocht: 1) een vast model dat werd gebruikt om voor elk opeenvolgende tijdstip het risico opnieuw te berekenen; 2) een model dat gebruik maakt van de bijgewerkte informatie op nieuwe tijdstippen en elk jaar opnieuw gefit word; 3) een model waarbij de verandering in de predictor tussen baseline en elk jaar werd toegevoegd aan het model en het risico werd berekend op basis van dit model. De c-statistieken van het basismodel en de 3 modellen, die herhaalde metingen includeren waren gelijk. De NRI van model 2 en model 3 vertoonden geen significante verbetering in discriminatie ten opzichte van model 1. Maar kleine verbeteringen werden waargenomen met de IDI voor het eerste follow-up jaar, de IDI varieerde van 0.003 tot 0.012. De kalibratie van model 1 nam niet significant af naarmate de tijd verstreek, terwijl de kalibratie van model 2 en 3 gelijk was voor alle follow-up jaren. Deze studie suggereert dat een model dat alleen baseline informatie gebruikt even goed voorspelt als een model waarbij het risico elk jaar opnieuw berekend wordt of een nieuw model gefit word voor elk tijdstip. Slechts kleine veranderingen in discriminatie werden waargenomen voor modellen met herhaalde metingen.

Dit proefschrift laat zien dat het van groot belang is dat patiënten met een hoog risico op hart en vaatziekten in een eerder stadium worden gedetecteerd, zodat een adequate behandeling kan worden ingezet. Om deze patiënten zo goed mogelijk te kunnen identificeren, is het belangrijk dat het onderzoek naar voorspelling hart- en vaatziekten risico wordt voortgezet.

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De weg van promoveren komt tot een eind met dit proefschrift. Dit mooie resultaat had ik nooit kunnen behalen zonder de hulp van velen. Ik wil graag iedereen bedanken die heeft bij gedragen aan het tot stand komen van dit proefschrift. Een aantal mensen wil ik graag in het bijzonder bedanken.

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During my PhD I had the opportunity to go to the George Institute in Sydney Australia. I have worked on several papers under the supervision of Professor John Chalmers, dr. Sophia Zoungas and dr. Andre Pascal Kengne. Thank you for your hospitality during my stay, I loved being in Sydney and working with the ADVANCE database.

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Susan van Dieren was born on 4 march 1981 in Nieuwegein. In 2003 she started her training in biological sciences and obtained her Master in Science degree at the University of Utrecht in 2008. Subsequently she started her work presented in this thesis under supervision of Prof. dr. Y.T. van der Schouw, Dr.ir. J.W.J. Beulens and Dr. L.M. Peelen at the Julius Center for Health Sciences and Primary Care at the UMC Utrecht. Her research is part of the CTMM-PREDICCt project and focuses on optimizing the prediction of cardiovascular disease among patients with type 2 diabetes. During her PhD training Susan worked as a visiting PhD candidate at the George Institute for Global Health at the University of Sydney, under supervision of Prof. dr. J. Chalmers and Dr. S. zoungas, where her research focused on management of type 2 diabetes. In 2012 Susan obtained her Master in Science degree in Epidemiology. Currently she is working as a post-doctoral researcher at the Julius Center for Health Sciences and Primary Care, UMC Utrecht.

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