Pharmacological Treatment in Patients with Type 2 Diabetes: Benefits and Risks

Epidemiological Studies from the Swedish National Diabetes Register

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"The world is governed by chance. Randomness stalks us every day of our lives."

Paul Auster

ABSTRACT

Background and Aims: A number of modifiable risk factors – including glycated haemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C) and blood pressure – are important for the prognosis of type 2 diabetes (T2D). Lifestyle changes and medications aimed at optimizing these risk factors are crucial components of diabetes care. The objective of this thesis was to assess the benefits and potential risks associated with pharmacological treatments in patients with T2D as part of routine clinical practice.

Patients and Methods: This thesis includes four observational studies based on data from the nationwide Swedish National Diabetes Register. Clinical characteristics and risk factor control were analysed in a cross-sectional study of an unselected sample of T2D patients (n=163,121) in 2009. The effectiveness and safety of various glucose-lowering agents were analysed in two cohort studies, including a sample of drug naive T2D patients (n=17,309) and a sample of T2D patients that were stratified according to renal function (n=51,675). Benefits and risks associated with aspirin treatment was analysed in T2D patients who were free of cardiovascular disease (CVD) (n=18,646).

Results: The majority of patients with T2D had not reached the treatment goals for HbA1c, LDL-C or blood pressure. New users of metformin showed a lower risk of requiring treatment intensification with add-on treatment with a second agent or a switch to a new agent than new users of sulphonylurea (SU) or meglitinide when followed for up to 5.5 years. Metformin showed lower risks for CVD, acidosis/serious infection and all-cause mortality than patients treated with insulin, as well as a lower risk of all-cause mortality than patients treated with other oral hypoglycaemic agents (OHAs) at 4 years follow-up. Similar beneficial effects of metformin were seen in patients with renal impairment (estimated glomerular filtration rate [eGFR] 45-60 ml/min/1.73 m^2); metformin was not associated with any increased risk of serious adverse events, even in patients with low renal function (eGFR 30-45 ml/min/1.73 m^2). Furthermore, there were no beneficial effects in terms of risks for CVD or mortality associated with aspirin treatment in T2D patients with no established CVD who were followed for 4 years.

Conclusions: The insufficient risk factor control that was seen in T2D patients highlights the importance of continuing efforts to reach treatment targets. Metformin was associated with superior glycaemic durability and lower risks for serious adverse events, even in patients with mild to moderate renal impairment, than other glucose-lowering agents. These results support the use of metformin

as a first-line agent and suggest that even more T2D patients could benefit from it. The absence of beneficial effects associated with aspirin in T2D patients with no established CVD supports more restrictive use for primary prevention of CVD in patients with T2D.

Key words: Type 2 diabetes, pharmacoepidemiology, glucose-lowering agents, aspirin, cardiovascular disease

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SAMMANFATTNING PÅ SVENSKA

Av de 382 miljoner personer som lever med diabetes runt om i världen beräknas ca 85-95 % ha typ 2-diabetes. Typ 2-diabetes är en multifaktoriellt orsakad sjukdom som karaktäriseras av flera olika rubbningar i kroppens fysiologi. Mest centralt är att kroppens celler utvecklar en minskad känslighet för insulin. Detta sker parallellt med att kroppens förmåga att producera insulin successivt försämras. Insulinbristen i kroppen resulterar bland annat i förhöjt blodsocker och en ogynnsam kolesterolsammansättning. Typ 2-diabetes har en tydlig koppling till livsstilsfaktorer så som övervikt och fetma, men genetik och andra miljöfaktorer bidrar också till att sjukdomen uppstår. Personer med typ 2-diabetes har en ökad risk för bland annat hjärt-kärlsjukdom och död jämfört med friska personer. Det beror delvis på att typ 2-diabetes ofta uppträder tillsammans med högt blodtryck, lipidrubbningar, övervikt och fetma som också ökar risken för hjärt-kärlsjukdom, men typ 2-diabetes i sig innebär också en ökad risk. En av de viktigaste uppgifterna för diabetesvården är att, med hjälp av livsstilsförändringar och läkemedel, minska risken för hjärt-kärlsjukdom och andra komplikationer.

Ett av målen med denna avhandling var att beskriva behandlingsresultaten för patienter med typ 2-diabetes i Sverige. Ytterligare ett mål var att utvärdera effekterna av olika läkemedelsbehandlingar som syftar till att förebygga komplikationer vid typ 2-diabetes. Detta gjordes genom att analysera information från Sveriges Nationella Diabetesregister (NDR). NDR är ett nationellt kvalitetsregister som startades 1996 i syfte att förbättra diabetesvården i Sverige. Antalet patienter med diabetes som är registrerade i registret har ökat kraftigt sedan starten. År 2009 beräknades registret innefatta ca 70 % av alla patienter med diabetes i Sverige, och 2013 hade siffran stigit till ca 90 %.

Vi fann att en majoritet av patienter med typ 2-diabetes inte uppfyllde de målvärden för blodsocker, blodtryck och kolesterol som anges i nationella behandlingsriktlinjer. Bland patienter som påbörjade behandling mot högt blodsocker var valet av det första läkemedlet relaterat till hur lång tid det tog innan behandlingen behövde trappas upp. De som fick behandling med läkemedlet metformin klarade sig längst utan tillägg av andra läkemedel eller byte till ett nytt läkemedel. Vilken typ av läkemedel som användes mot högt blodsocker var också relaterat till risken för hjärt-kärlsjukdom, död och andra allvarliga komplikationer under en 4-års period. De som fick behandling med läkemedlet metformin hade minskad risk för död och alvarliga sjukdomstillstånd, så som syraförgiftning och allvarliga infektioner, jämfört med de som behandlades med andra blodsockersänkande läkemedel. De fördelaktiga

effekterna med metformin sågs även hos patienter med en lätt till måttligt sänkt njurfunktion, patienter som i dagens behandlingsriktlinjer inte rekommenderas behandling med metformin. Bland patienter med typ 2-diabetes som inte tidigare drabbats av hjärt-kärlsjukdom var behandling med det blodpropps-förebyggande läkemedlet acetylsalicylsyra (trombyl) inte relaterat till några fördelaktiga effekter under en 4-års period. Behandling med acetylsalicylsyra hos dessa patienter var relaterat till en ökad risk för sjukhusvårdskrävande blödningar.

Sammantaget så visar resultaten att en stor andel patienter med typ 2-diabetes inte uppfyllde de målvärden för blodsocker, blodtryck och kolesterol som anges i nationella behandlingsriktlinjer. Bättre måluppfyllelse av dessa riskfaktorer skulle innebära betydande hälsovinster, bland annat genom minskad förekomst av hjärt-kärlsjukdom. Resultaten ger stöd åt dagens behandlingsriktlinjer, som förespråkar metformin som förstahandsval vid blodsockersänkande läkemedels-behandling vid typ 2-diabetes, och tyder på att även de med lätt till måttligt sänkt njurfunktion skulle ha nytta av läkemedlet. Resultaten ger också stöd åt ett mer restriktivt användande av acetylsalicylsyra i behandlingen av patienter med typ 2-diabetes som ännu inte drabbats av hjärt-kärlsjukdom.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by the corresponding Roman numerals.

I. Ekström N, Miftaraj M, Svensson AM, Andersson Sundell K, Cederholm J, Zethelius B, Gudbjörnsdottir S, Eliasson B. Glucose-lowering treatment and clinical results in 163 121 patients with type 2 diabetes: an observational study from the Swedish national diabetes register. Diabetes, obesity & metabolism. 2012;14(8):717-26.

II. Ekström N, Svensson AM, Miftaraj M, Andersson Sundell K, Cederholm J, Zethelius B, Eliasson B, Gudbjörnsdottir S. Durability of oral hypoglycaemic agents in drug naïve patients with type 2 diabetes: report from the Swedish National Diabetes Register – NDR. 2014. *Submitted.*

III. Ekström N, Schiöler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, Cederholm J, Eliasson B, Gudbjörnsdottir S. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open. 2012;2(4).

IV. Ekström N, Cederholm J, Zethelius B, Eliasson B, Fhärm E, Rolandsson O, Miftaraj M, Svensson AM, Gudbjörnsdottir S. Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register. BMJ Open. 2013;3(4).

TABLE OF CONTENTS

ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADOPT	A Diabetes Outcome Progression Trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AF	Atrial fibrillation
ANOVA	Analysis of variance
BMI	Body mass index
CABG	Coronary artery bypass grafting
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
DAI	Direct-acting insulin
DIGAMI	Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ETDRS	Early Treatment of Diabetic Retinopathy Study
GLM	General linear model
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GRADE Study	Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study
GWAS	Genome-wide association study
HbA1c	Glycated haemoglobin
HDL-C	High-density lipoprotein cholesterol
HMO	Health maintenance organization
HR	Hazard ratio
ITT	Intention to treat
JPAP	Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes
LDL-C	Low-density lipoprotein cholesterol
LISA	Longitudinal integration database for health insurance and labour market studies
MI	Myocardial infarction
NBHW	Swedish National Board of Health and Welfare

NDR	Swedish National Diabetes Register
NHANES	National Health and Nutrition Examination Survey
OHA	Oral hypoglycaemic agent
OLS	Ordinary least squares
OR	Odds ratio
PCI	Percutaneous coronary intervention
POPADAD	Prevention of Progression of Arterial Disease and Diabetes
PMI	Pre-mixed insulin
PROM	Patient reported outcome measure
PVD	Peripheral vascular disease
RCT	Randomized controlled trial
REACH	Reduction of Atherothrombosis for Continued Health
ROS	Reactive oxygen species
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SGLT-2	Sodium-glucose linked transporter-2
SU	Sulphonylurea
T1D	Type 1 diabetes
T2D	Type 2 diabetes
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
WHO	World Health Organization

INTRODUCTION

The prevalence of diabetes has increased rapidly over the past few decades. In 2013, 382 million people were estimated to have diabetes, corresponding to a prevalence of 8.3 % worldwide. Despite major efforts to combat the epidemic, the number of people living with the disease continues to rise and is set to increase by 55 % in less than 25 years. Type 2 diabetes (T2D) accounts for 85-95 % of the cases.[1] The burden of non-communicable diseases, including diabetes, is enormous. Such diseases represent the leading health challenge of today, causing two out of every three deaths worldwide in 2010.[2] The discovery and development of glucose-lowering drug classes has accelerated over the last few decades, stimulated by the growing prevalence of T2D and greater knowledge about its pathophysiology. The overall objective of this thesis was to investigate benefits and potential risks associated with pharmacological treatment in T2D patients as part of routine clinical care.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

β-cell function and insulin sensitivity

T2D is a multifactorial disease characterized by hyperglycaemia as a result of progressive insulin resistance and dysfunction of insulin-producing β-cells.[3] In the human body, a feedback loop between β-cells and insulin-sensitive tissues operates to closely regulate blood glucose levels.[4] The onset of T2D is preceded by the gradual development of insulin resistance, primarily in the normally insulin-sensitive hepatic, skeletal muscle and adipose tissues.[5, 6] As insulin resistance declines, β-cells are commanded via the feedback loop to increase their insulin secretion rate in order to maintain normal glucose tolerance. Eventually, when the β-cells can no longer produce such large quantities of insulin, hyperglycaemia occurs and the patient progresses to overt T2D.[5] The progression to β-cell failure, which is vital in the development of T2D, is a complex process involving many physiological pathways in various organs of the body (see Figure 1).[3, 6] This process typically continues for many years: at T2D onset, more than 80 % of the β-cell function has already been lost.[6] The development of T2D is closely related to obesity, whose exponential rise over the past few decades has paralleled the rapid increase in the prevalence of the disease. Lifestyle factors are essential to understanding this epidemic, but genetic variations are also important.

Genetic and environmental factors

The development of T2D is caused by a combination of genetic and environmental factors. A combination of common clinical risk factors, such as lipid profile, blood glucose, blood pressure and a family history of diabetes, has

been shown to effectively predict T2D risk in healthy individuals.[7] Genome-wide association studies (GWASs) have identified a number of genetic loci associated with T2D.[8] As expected, many of these genes are involved in physiological processes of insulin secretion and action.[9, 10] However, currently available genetic information adds only marginal value to diabetes risk prediction compared with knowledge of common clinical risk factors alone.[11-13]

DIAGNOSTIC CRITERIA

The World Health Organization (WHO) diagnostic criteria for diabetes mellitus are two consecutive values of fasting plasma glucose ≥7.0 mmol/L, or a 2-hour glucose value of ≥11.1 mmol/L after a 75 g oral glucose tolerance test, or a glycated haemoglobin (HbA1c) value ≥6.5 % (48 mmol/mol).[14, 15] WHO added HbA1c as a diagnostic criterion in 2011.[14] HbA1c, which is a measure of long-term glycaemic control, represents the average glycaemic level over the previous few weeks or months.[16]

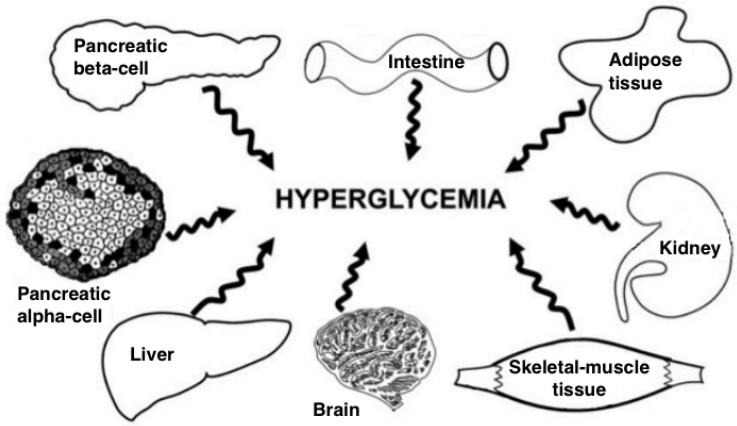


Figure 1. Schematic illustration of organs in the human body that are involved in the pathogenesis of type 2 diabetes (adapted from reference nr. 6).

DIABETES-RELATED COMPLICATIONS

T2D causes major morbidity and mortality, primarily as the result of long-term macrovascular and microvascular complications. Macrovascular complications, which are due to lesions in large vessels, include coronary heart disease (CHD), stroke and peripheral vascular disease (PVD) – the three conditions are collectively referred to as cardiovascular disease (CVD). Microvascular

complications, which are caused by lesions in small vessels, include retinopathy, nephropathy and neuropathy. Estimates based on data that are representative of the U.S. population in 2010, showed an age-adjusted increase in the risk of acute myocardial infarction (MI) by 2-fold, stroke by 1.5-fold, lower extremity amputation by 10-fold and end-stage renal disease by 6-fold in patients with diabetes compared to the general population [17] These results clearly demonstrate that T2D patients are at high risk of developing vascular complications.

Clustering of cardiovascular risk factors

In addition to the strong association between T2D and obesity,[18] clustering of other CVD risk factors in T2D patients has been known for quite some time.[19] In his Banting lecture of 1988, Reaven proposed a biological association between insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidaemia and hypertension, with insulin resistance and hyperinsulinemia as the underlying causes.[20] Clustering of these metabolic disturbances has received further attention in the scientific and clinical communities, and the clinical manifestation is now known as the metabolic syndrome.[21, 22] The clinical value of the metabolic syndrome construct has been questioned,[23] partly due to uncertainty about the presence of a single underlying cause. Still, clustering of these physiological disturbances helps explain the very high CVD risk among the T2D population. What is also important to remember is that T2D per se is a strong risk factor for CVD.

Type 2 diabetes: an independent risk factor

Even after adjustment for traditional CVD risk factors, diabetes is associated with a considerably increased risk of CHD,[24-28] indicating that T2D is an independent risk factor for CVD. Hyperglycaemia and insulin resistance appear to play important roles in the development of CVD. The activation of damaging signalling pathways via increased mitochondrial reactive oxygen species (ROS) production has been proposed as a possible way that insulin resistance participates in the development of CVD.[29, 30] Several studies have established a positive association between glycaemia and CVD risk in both the non-diabetic and diabetic populations.[31-33] Furthermore, recent Mendelian randomization studies[34] have shown both observational and genetic measures of glycaemia to be associated with increased risks for carotid intima media thickness and CHD,[35, 36] indicating a causal relationship between glycaemia and CVD. Similarly, several studies have reported a strong positive association between glycaemia and the risk of microvascular disease.[37-39] Activation of the damaging signalling pathways thought to be involved in the development of CVD, including increased ROS production, appears to be important in the development of microvascular disease as well. However, hyperglycaemia (rather

than insulin resistance) seems to be the key factor in triggering this process during the development of microvascular disease.[29, 30]

RISK FACTOR CONTROL

Optimization of modifiable CVD risk factors with lifestyle changes and pharmacological treatment is a key component of diabetes care. Lifestyle modifications have been shown to be efficacious in preventing the development of T2D in high-risk individuals.[40-43] More recently, the Look AHEAD (Action for Health in Diabetes) trial randomized 5,140 overweight or obese T2D patients to either intensive lifestyle changes aimed at weight loss or diabetes support and education. Despite less use of medication, the intensive lifestyle group achieved significantly greater weight loss and lower HbA1c levels, as well as initial improvements in blood pressure and lipid profile, than the control group during a mean follow-up period of 9.6 years.[44] Despite these beneficial effects, there was no significant difference in the incidence of CVD between the groups. In addition to lifestyle changes, pharmacological treatment is crucial to achieving good risk factor control and ultimately to preventing complications of T2D.

Glucose control

Intensive glycaemic control aimed at achieving glucose levels near the normoglycaemic range reduces the risk of microvascular complications.[45-50] Whether intensive glycaemic control is also effective in reducing the risk of macrovascular complications is less clear.[51-53] In the United Kingdom Prospective Diabetes Study (UKPDS), launched in 1977, 4,209 newly diagnosed T2D patients were randomized to either intensive or conventional glucose control. At 10-year follow-up, patients who received intensive glucose control had a significantly lower risk of microvascular complications and a non-significant trend towards reduced risk of MI.[50] In a 10-year observational follow-up study, the beneficial effects of intensive glucose control on microvascular complications were shown to have been sustained. Patients randomized to intensive glucose control also showed reduced risks for MI and all-cause mortality, despite a rapid convergence of glucose levels in the two groups after the original trial.[47]

The results of the UKPDS spurred the launch of three new large randomized controlled trials (RCTs) to evaluate the effects of intensive glucose control: Action to Control Cardiovascular Risk in Diabetes (ACCORD),[54] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[48] and Veterans Affairs Diabetes Trial

(VADT).[55] None of the trials were able to confirm a beneficial effect of intensive glucose control on macrovascular events, as suggested in the UKPDS. In fact, the ACCORD study had to be discontinued early due to an increased risk of all-cause mortality and CVD mortality in the group assigned to intensive glucose control. Interestingly, MI was less frequent in the intensive therapy group both during the active treatment period and after another 1.2 years of post-trial follow-up in the ACCORD.[53] In contrast to the UKPDS, ACCORD, ADVANCE and VADT included patients with long diabetes duration and high percentages of established CVD. The results of these large trials indicate varying risk-benefit ratios of intensive glucose control among subgroups of the T2D population. As a result, Swedish and international treatment guidelines recommend a personalized treatment strategy that enables intensive glucose control in patients with relatively short diabetes duration and without established CVD, and less strict control in high-risk patients.[56, 57]

Other risk factor control

The results of several RCTs have demonstrated a clear benefit of blood pressure-lowering agents for the risk of CHD events, stroke and nephropathy in patients with T2D and hypertension regardless of the presence of CVD.[49, 58-62] Similarly, a number of RCTs have demonstrated beneficial effects of lipid-lowering treatment with statins on the risk of CVD events in T2D patients both with and without established CVD.[63-65] When it comes to prevention of CVD with antiplatelet agents, a low dose of aspirin has proven beneficial in T2D patients with established CVD, resulting in cardiovascular risk reductions that clearly outweigh the increased risk of bleeding.[66, 67] In T2D patients without established CVD, the evidence of a beneficial effect of aspirin is sparse[68] and current treatment guidelines vary in their recommendations.[69, 70] The trend during the past few years has been towards a more restrictive approach, either limiting the recommendation of primary prevention with aspirin to T2D patients at high risk or not suggesting it at all. The general view was different in 2008, when international treatment guidelines recommended the use of aspirin as a primary prevention strategy in all T2D patients over the age of 40.[71, 72] Despite the more restrictive approach these days, U.S. guidelines still recommend aspirin for primary prevention of CVD in patients at high estimated CVD risk; even approximately one-quarter of Swedish T2D patients without established CVD are treated with aspirin.[73]

Global risk factor control

In the STENO-2 study, patients with T2D and microalbuminuria were randomized to either conventional treatment or intensive multi-factorial interventions targeting multiple modifiable CVD risk factors simultaneously.

Interventions in the intensive arm included behavioural modification and pharmacological treatment targeting hyperglycaemia, hypertension, dyslipidaemia, microalbuminuria and secondary CVD prevention with aspirin. Patients who received intensive therapy had a significantly lower risk of CVD, nephropathy, retinopathy and autonomic neuropathy than patients who received conventional therapy.[74] After another 5.5 years of observational follow-up, the beneficial effects of the intensive therapy were shown to have been sustained, and patients who had originally been randomized to the intensive arm also showed significantly reduced risks for all-cause mortality and CVD mortality.[75]

GLUCOSE-LOWERING AGENTS

The discovery and development of glucose-lowering drug classes has accelerated over the past few decades (see Figure 2), stimulated by the growing prevalence of T2D and greater knowledge of its pathophysiology. All available drug classes effectively target hyperglycaemia, typically lowering HbA1c by 0.5-1.5 percentage points (5.5-16.5 mmol/mol).[57] However, because of the progressive nature of T2D,[76] treatment intensification such as adding a second glucose-lowering agent or switching to a more potent agent is often required to maintain acceptable HbA1c levels over time.[77, 78] This gradual decline in the effectiveness of glucose-lowering agents has been called secondary drug failure or monotherapy failure.[77, 79]

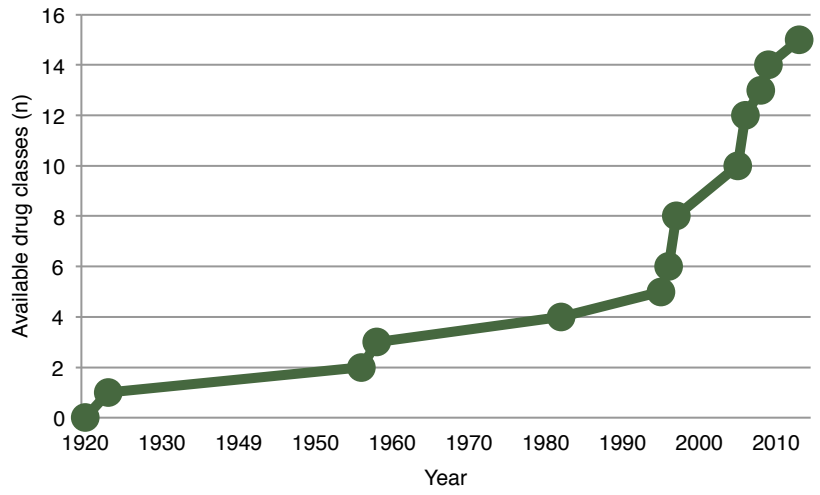


Figure 2. Number of available glucose-lowering drug classes.

Effects on complications

The mode of action of the various agents differs; aside from their glucose-lowering effects, they have distinct properties, including impact on body weight and risk of hypoglycaemia.[3, 57] This can translate into differing effects in terms of important clinical outcomes. Most of the large RCTs that investigate the effects of intensive glycaemic control have not been designed to compare individual glucose-lowering agents. As a result, knowledge about the comparative effectiveness of specific agents is sparse. However, in a sub-study of the UKPDS, 1,704 overweight or obese patients with newly diagnosed T2D were randomized to intensive therapy with metformin (n=342), insulin (n=409) or sulfonylurea (SU) (n=542), or to conventional therapy that focused on diet (n=411) with mean follow-up of 10.7 years. The results showed significantly greater risk reduction of any diabetes-related outcome, diabetes-related mortality and all-cause mortality for intensive therapy with metformin than for conventional therapy. Furthermore, intensive therapy with metformin showed significantly greater risk reduction of any diabetes-related outcome, all-cause mortality and stroke than with insulin or SU.[80]

Glycaemic durability

The gradual decline in the effectiveness of glucose-lowering agents over time has also attracted attention. A Diabetes Outcome Progression Trial (ADOPT) compared the incidence of monotherapy failure in 4,360 drug naive patients with T2D randomized to rosiglitazone, metformin or glyburide[77] Glycaemic durability differed significantly among the agents; the cumulative incidences of monotherapy failure at 5-year follow-up were 15 % for rosiglitazone, 21 % for metformin and 34 % for glyburide.

Treatment guidelines

In view of the above, Swedish and international treatment guidelines recommend metformin as the first-line agent in T2D patients. These recommendations are based on the results of a handful of clinical trials, primarily the UKPDS sub-study.[56, 57] Thus, international organisations have emphasized the need for comparative effectiveness research to evaluate and compare several different glucose-lowering agents.[57]

Metformin and risk of lactic acidosis

Metformin is thought to increase the risk of lactic acidosis, a potentially fatal condition. For that reason, metformin is contraindicated in patients at particular high risk of developing lactic acidosis, mainly those with impaired renal function.[56, 57, 69] Phenformin, a glucose-lowering drug in the same class as metformin, was pulled from the market because it was associated with a

substantially increased incidence of lactic acidosis. There is only sparse evidence of an increased risk of lactic acidosis due to metformin. In fact, a large meta-analysis of trials that compared metformin to non-metformin glucose-lowering drugs or placebo showed similar incidences of lactic acidosis in patients who were or were not treated with metformin.[81] However, the effects of metformin in patients at high risk of developing lactic acidosis have not been thoroughly studied.

COMPARATIVE EFFECTIVENESS RESEARCH

Comparative effectiveness research, in which two or more groups are weighed against each other, can be broken down into experimental studies and observational studies. In experimental studies, the investigator assigns exposure. This is the main difference between experimental studies and observational studies, for which exposure has already been assigned and the investigator observes only what happens to those with different exposure. An RCT is a type of experimental study in which exposure is assigned by randomization.[82] When scrupulously conducted, an RCT has very high internal validity, i.e. it measures what it set out to do, and is therefore regarded as the gold standard for clinical study design.[83, 84] Assuming that the study sample is large enough, randomization of participants to one of the various treatments balances both known and unknown covariates between the groups.[82] This is a unique advantage of RCTs over non-randomized trials and observational studies.

In observational studies, the groups that are being compared often differ in a number of ways beyond the exposure status, which may lead to confounding. Confounding, which is a mixing of effects, arises when one tries to relate an exposure to an outcome, but actually measures the effect of a third factor (a "confounding variable"). A confounding variable is defined as being associated with both exposure and outcome even though it is not an intermediate link in the chain of causation between the two (see Figure 3).[85] The very high internal validity of an RCT is related to strict selection criteria and close monitoring of participants. For that reason, RCTs have been criticised for having inadequate external validity: the extent to which the results can be generalized to routine clinical practice.[82] A recent study that investigated the generalizability of 7 large RCTs of glycaemic control found the external validity of the trials to be limited. The proportion of Scottish patients with T2D who met the eligibility criteria of the trials ranged from 3.5 % to 50.7 %.[86] It may also be impossible to conduct an RCT on ethical or financial grounds.[87] In view of these considerations, observational studies have been emphasized as an important compliment to RCTs.[88]

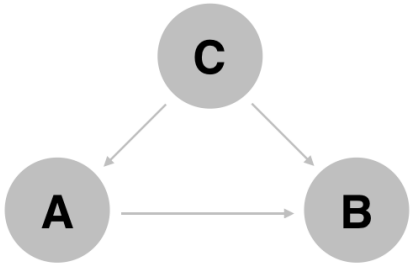


Figure 3. Schematic description of a confounding factor (C) in the relationship between variables A and B.

SUMMARY

To summarise the central arguments of this introduction, T2D is a multifactorial disease characterized by hyperglycaemia as the result of progressive insulin resistance and impaired β-cell function. T2D is an independent risk factor for CVD but is also associated with other important CVD risk factors, such as dyslipidaemia and hypertension. Thus, T2D patients are at high risk of developing CVD, as well as microvascular complications such as retinopathy, nephropathy and neuropathy. Lifestyle changes and medications aimed at optimizing these risk factors have proven effective and are fundamental components of diabetes care. For optimal drug utilisation, information obtained from RCTs – as well as data on the effectiveness and safety of various drugs and treatment strategies in a routine clinical setting – is needed.

AIMS

The overall objective of this thesis was to investigate benefits and potential risks associated with various pharmacological treatments and treatment strategies in T2D patients who are representative of routine clinical care. The specific aims included analysing:

- clinical characteristics, risk factor control and the prevalence of diabetes complications in an unselected nationwide sample of T2D patients (study I)

- durability of monotherapy with the most commonly used oral glucose-lowering agents in drug naive T2D patients (study II)

- effectiveness and safety of metformin in T2D patients with various levels of renal function (study III)

- benefits and risks associated with aspirin treatment in T2D patients with no established CVD (study IV)

PATIENTS AND METHODS

This chapter describes the data sources and methods that were used in the studies. The chapter is divided into five sections. The first section describes the data sources that were used. The second section discusses ethical considerations. The third and fourth sections review study design, participants, exposures and outcomes. The fifth section describes the statistical methods that were used. Methodology is not fully covered in this chapter. For a more comprehensive overview, refer to the material and methods sections in studies I-IV.

DATA SOURCES

All studies included information from the Swedish National Diabetes Register (NDR), the Hospital Discharge Register, the Cause of Death Register and the Prescribed Drug Register, all of which are kept by the Swedish National Board of Health and Welfare (NBHW). Study II also included information about educational level, which was obtained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) kept by Statistics Sweden.

SWEDISH NATIONAL DIABETES REGISTER

The Swedish Society for Diabetology launched the NDR in 1996 as a tool for local quality control of diabetes care and benchmarking against national treatment guidelines.[89] Doctors and nurses at participating primary health care centres and outpatient clinics report information about diabetes patients at least once a year, either online or by direct transmission of data from databases of medical records. The information includes patient clinical characteristics, results of laboratory analyses and the presence of complications. Reporting to the NDR is optional, but some regions encourage healthcare centres to do so. For example, Västra Götaland offers financial reimbursement. In 2004, the validity of data from the NDR was analysed from a sample of 1,017 patients treated at outpatient clinics using capture-recapture methodology. Verification against clinical records showed that 94 % of entries in the NDR were valid.[90]

Coverage in the National Diabetes Register

The number of healthcare units that report to the NDR has grown steadily since its establishment in 1996, which has led to a dramatic increase in the number of patients entered (see Figure 4). During the past few years, the increase has begun to level off. In the 2009 report on public health in Sweden, published by the NBHW, 365,000 Swedes were estimated to have diabetes.[91] This approximation yields a prevalence estimate of about 4 %. Similar prevalence estimates have been reported previously.[91-96] Assuming a diabetes prevalence of

4 %, the NDR included approximately 70 % in 2009 and 90 % in 2013. Similar estimates have been obtained when comparing all patients who filled a prescription for glucose-lowering agents during a specific period as entered in the Prescribed Drug Register with those entered in the NDR [73]

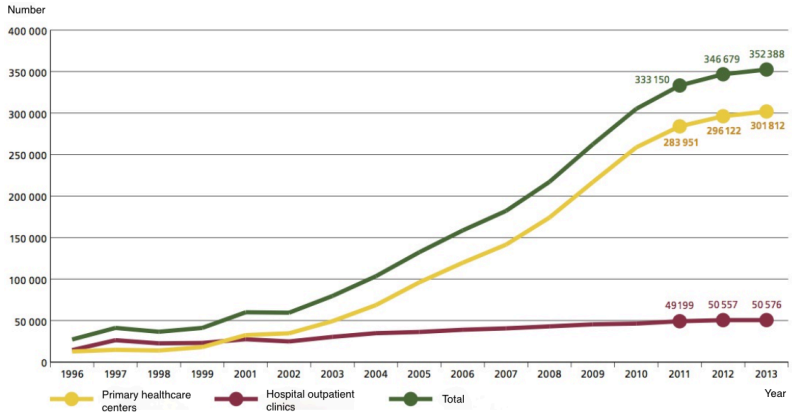


Figure 4. Number of patients entered in the Swedish National Diabetes Register between 1996 and 2013 by care provider (adapted from reference nr 71).

Diabetes diagnosis

In Sweden the WHO diagnostic criteria are used to diagnose diabetes;[14, 15] patients entered in the NDR have been diagnosed accordingly. However, HbA1c has been accepted as a diagnostic criterion only since January 2014. As a result, HbA1c has not been used in the diagnosis of patients included in the studies covered by this thesis. The epidemiological definition of T2D used in the studies was treatment with diet only, oral hypoglycaemic agents (OHAs) only or age of onset ≥ 40 and treatment with insulin alone or combined with OHA.

REGISTERS KEPT BY THE NATIONAL BOARD OF HEALTH AND WELFARE AND STATISTICS SWEDEN

The Hospital Discharge Register, which is part of the National Patient Register, has had complete nationwide participation since 1987. It includes information about diagnoses, surgical and non-surgical procedures and length of hospitalization. Several validation studies, primarily by means of patient chart reviews, indicate reasonably valid data with positive predictive values of 85-95 % for most diagnoses.[97] The Cause of Death Register, which was established in 1961, contains information about causes of mortality and dates of death for

everyone in the population register.[98] The Prescribed Drug Register, which was established in 2005, contains information about all prescriptions that have been filled [99] LISA has kept annual registers since 1990 for everyone age 16 or older who was in the population register each year. LISA includes information about socioeconomic variables, such as educational level, and is kept by Statistics Sweden.[100]

LINKAGE OF NATIONAL REGISTER DATA

Sweden's unique 12-digit personal identity number was used to merge data from various national registers. Following approval by the Regional Ethical Review Board, a file containing NDR data was sent to the NBHW and Statistics Sweden. After they had each approved, data were merged by matching personal identity numbers. Once the process was complete, all of the data were sent back to us with a new unique but anonymous number for each patient (see Figure 5).

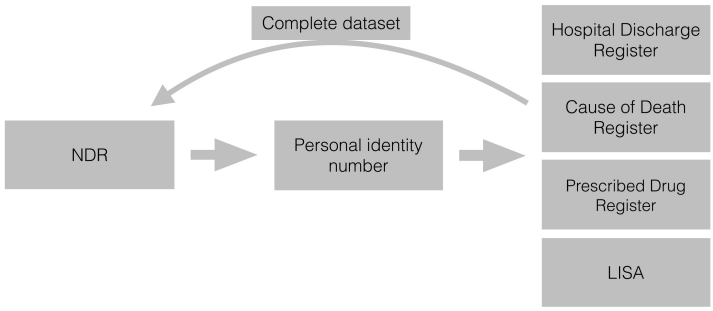


Figure 5. Schematic description of how data from the various national registers were linked using Sweden's unique personal identity number. Abbreviations: NDR: Swedish National Diabetes Register; LISA: Longitudinal integration database for health insurance and labour market studies

ETHICAL CONSIDERATIONS

The overall aim of this thesis was to gain a greater understanding of the benefits and risks associated with various drugs and treatment strategies for T2D. Such knowledge would enable more efficient use of available drugs and ultimately lead to improved health for the great majority of people with T2D. One could also speculate about potential social and economic benefits resulting from lower health care costs and less sick leave. We thought that the available data offered a unique opportunity to gain reliable knowledge about these important clinical questions. The primary potential risks were violation of personal privacy, as the

studies did not include any interventions that could be medically dangerous. All patients approved entry in the registers after being informed that their data could be used for research, but they did not give specific informed consent for these studies. However, all studies were conducted at the group level and patients were de-identified. Thus, the risk of violating personal privacy was considered very small. The studies included very large numbers of patients. Obtaining written informed consent from all of them would have required so much work as to render the studies impossible to conduct or seriously compromised their quality due to large dropout and non-response rates.

STUDY DESIGN

All studies included in this thesis are observational in nature. Study I has a cross-sectional design for which all information was collected in 2009, providing a snapshot of the T2D population at that point. Studies II–IV have a cohort design. Cohort studies are longitudinal and include information pertaining to more than one point in time. The occurrence of an outcome is measured in one or several cohorts over time.[101] Studies II-IV all have an exposure-based cohort design for which entry was based on exposure to various medications. To ensure that the medications under consideration had been taken on more than an occasional basis, prescriptions needed to have been filled repeatedly within a specific period of time for patients to be regarded as having been exposed. Covariates were assessed prior to cohort entry, and follow-up for outcome occurrence started after the requirements for entry had been fulfilled. In studies III and IV, an intention-to-treat (ITT) design, which retains the initial exposure status and disregards changes in treatment status over time,[102] was used. Thus, all outcomes during follow-up were attributed to the treatment initially intended even if it had changed prior to the outcome event. In study II, the outcome under consideration consisted of changes in treatment. Thus, follow-up of a particular patient was terminated when such a change occurred. This is sometimes referred to as an 'as-treated design'.[102]

PARTICIPANTS, EXPOSURE AND OUTCOME

This section describes the selection of participants, as well as the definitions of exposure and outcome in studies I-IV. An overview of the characteristics of studies I-IV can be found in Table 1.

STUDY I

This study was designed to analyse clinical characteristics, risk factor control and the prevalence of diabetes complications among Swedish T2D patients in 2009.

Participants

All T2D patients entered in the NDR in 2009 were eligible for inclusion in the study. Patients with non-pharmacological treatment and those on the 12 most common pharmacological regimens were included (n=163,121).

Exposure

The absence of pharmacological glucose-lowering treatment, or at least six months of a continuous pharmacological glucose-lowering regimen, during the study period (2009) was required for cohort entry. Six months of continuous use was defined as prescriptions having been filled on at least two occasions with a maximum of 125 days between them.

Outcome

The outcome was the probability of having an HbA1c level of ≤7.0 % (53.0 mmol/mol). Information about HbA1c was obtained from the NDR.

STUDY II

This study was designed to analyse glycaemic durability associated with various classes of OHAs.

Participants

Drug naive T2D patients age 18-85 who were entered in the NDR between 1 July 2005 and 31 December 2011 and started on an OHA in monotherapy between 1 July 2006 and 31 December 2010 were eligible for inclusion in the study cohort. The number of patients who had started on newer classes of glucose-lowering agents was small. Thus, this study was restricted to patients who were being treated with metformin (n=16,061), SU (n=1,026) or meglitinide (n=222), the most commonly used agents.

Exposure

At least 12 months of continuous use with the prescribed glucose-lowering agent was required for cohort entry. Twelve months of continuous use was defined as prescriptions having been filled on at least three occasions during the period. Once a patient was included in the cohort, having filled a prescription at least once every 180 days was required to be classified as a continuous user.

Outcomes

The included patients were followed from baseline until the occurrence of an outcome event, death or otherwise until end of the study period in 31 December 2011. The mean follow-up was 2.6 years. The primary outcome was time to monotherapy failure. Monotherapy failure was defined as

discontinuation of continuous use with the initial agent, switch to a new agent or add-on treatment with a second agent. Discontinuation was defined as a gap of >180 days between two prescription fills. This criterion was chosen on the basis of clinical experience, pharmacological knowledge and previous science. A period of 180 days corresponds to twice the daily supply of an ordinary prescription, which was considered to be a reasonable cut-off point for continuous treatment in a recent validation study of persistence and durability in diabetes treatment [103] Switch was defined as discontinuation of the initial agent while starting on a new glucose-lowering agent within 180 days after the last time that the prescription for the initial agent was filled. Add-on was defined as starting on a second glucose-lowering agent while treatment with the initial agent continued. Secondary outcomes were the individual components of monotherapy failure: discontinuation of continuous use of the initial agent, switch to a new agent and add-on of a second agent.

STUDY III

This study was designed to analyse the effectiveness and safety of metformin in patients with various degrees of renal function.

Participants

All T2D patients age 40-85 who were entered in the NDR between 1 July 2004 and 31 December 2007 and had started on pharmacological glucose-lowering treatment before 2007 were eligible for inclusion.

Exposure

At least 12 months of continuous use of the prescribed glucose-lowering agent were required for cohort entry. Twelve months of continuous use was defined as having filled prescriptions at least three times during the period.

Outcomes

The included patients were followed from baseline until the occurrence of an outcome event, or otherwise, until censor date of 31 December 2010. The mean follow-up was 3.9 years. Outcomes were time to an event of CVD, or an event of a composite of acidosis and serious infections or an event of all-cause mortality. Information about CVD events and events of acidosis/serious infection was obtained from the Hospital Discharge Register, while information about all-cause mortality was obtained from the Cause of Death Register. CVD was defined as MI, angina pectoris, intracerebral haemorrhage, cerebral infarction, unspecified stroke, PVD, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), whichever occurred first. Acidosis/serious infection was defined as acidosis, shock, serious infections or

acute renal failure. We constructed this composite endpoint since these conditions are frequently associated with lactic acidosis. The specificity of this measure, however, is probably low, and many events of the composite endpoint of acidosis and serious infections were probably not cases of lactic acidosis. A fatal event was defined as having been followed by death within 28 days.

STUDY IV

This study was designed to analyse benefits and risks associated with aspirin treatment in T2D patients with no established CVD.

Participants

All T2D patients age 30-85 who were entered in the NDR between 1 July 2005 and 30 June 2006 and had not been hospitalized for CVD, cancer or haemorrhages were eligible for inclusion. Five-year risk of CVD was estimated using the NDR risk model,[104] based on 12 predictors at baseline in 2006. All patients were assigned to one of two subgroups based on high (≥15 %) or low (<15 %) five-year CVD risk.

Exposure

The absence of aspirin treatment, or at least 12 months of continuous use of 75 mg of aspirin daily, was required for cohort entry. Twelve months of continuous use was defined as having filled prescriptions at least three times between 1 July 2005 and 30 June 2006.

Outcomes

The included patients were followed from baseline until the occurrence of an outcome event, or otherwise until censor date 31 December 2009. The mean follow-up was 3.9 years. Outcomes were time to an event of CVD, CHD or haemorrhages. Non-fatal CHD was defined as MI, PCI or CABG that did not lead to death. Fatal CHD was defined as ischaemic heart disease that led to death. Non-fatal or fatal stroke was defined as cerebral infarction or intracerebral haemorrhage. CVD was a composite of CHD or stroke, whichever occurred first. Outcomes of haemorrhages included non-fatal or fatal intracerebral haemorrhage, ventricular haemorrhage and other haemorrhage (a composite of unspecified and respiratory bleeding). The outcome of total haemorrhages, which included all three outcomes, was also constructed. Information about all events was obtained from the Hospital Discharge Register or the Cause of Death Register.

Table 1. Overview of the characteristics of studies I-IV

	Study I	**Study II**	**Study III**	**Study IV**
Study design	Cross-sectional	Cohort	Cohort	Cohort
Study period	2009	2005-2012	2005-2011	2005-2010
Exposure	Glucose-lowering treatment	Glucose-lowering treatment	Glucose-lowering treatment	Aspirin or no aspirin
Baseline variables	Age, gender, BMI, physical activity, smoking status, diabetes duration	Age, gender, BMI, physical activity, educational level, smoking status, diabetes duration	Age, gender, BMI, physical activity, smoking status, diabetes duration	Age, gender, BMI, physical activity, smoking status, diabetes duration
	HbA1c, blood lipids, BP, s-creatinine, eGFR, microalbuminuria	HbA1c, blood lipids, BP, s-creatinine, eGFR, microalbuminuria	HbA1c, blood lipids, BP, s-creatinine, eGFR, microalbuminuria	HbA1c, blood lipids, BP, s-creatinine, eGFR, microalbuminuria
	History of CVD or CHD	History of CVD, CHF or AF	Previous hospitalization and history of CVD, CHF or serious infections	Previous hospitalization
	Treatment with antihypertensive or lipid-lowering agents	Treatment with antihypertensive agents, lipid-lowering agents, aspirin or psychiatric agents or MDDD use	Treatment with antihypertensive agents, lipid-lowering agents, aspirin, cardiac glycosides or organic nitrates or MDDD use	Treatment with glucose-lowering agents, antihypertensive agents, lipid-lowering agents or oestrogen or MDDD use
Outcomes	HbA1c ≤ 7.0%	Monotherapy failure	Total mortality CVD Infections/acidosis	Total mortality CVD Haemorrhages
Statistics	GLM Generalized linear model	Student's t-test χ^2 test GLM Cox-regression propensity score	ANOVA Logistic regression OLS regression Cox-regression Propensity score	Student's t-test χ^2 test GLM Cox-regression Propensity score
Patients (n)	163,121	69,667	51,675	18,646
Mean follow-up (Years)	-	2.6	3.9	3.9
Person years (n)	-	181,134	201,533	72,719

Abbreviations: HbA1c: glycated haemoglobin; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; CVD: cardiovascular disease; CHD: coronary heart disease; CHF: congestive heart failure; MDDD: multi-dose drug dispensing; ANOVA: analysis of variance; GLM: general linear model; OLS regression: ordinary least squares regression

STATISTICAL METHODS

This section describes the statistical methods used in the studies. The methods employed specifically to control for confounding are described in general terms, followed by a more comprehensive review of the statistical analyses used in each study.

METHODS OF CONTROLLING FOR CONFOUNDING

The studies contained information about numerous covariates that described patients in terms of demographics, risk factors, laboratory results, comorbidity and treatment-related variables. In studies I-IV, multivariate techniques were used to control for confounding by all of the variables simultaneously.[85] Only patients with complete records of all covariates were included in the multivariate analyses. This is a way of handling missing data that is sometimes referred to as complete case analysis or available case analysis.[105]

Multivariate Cox proportional hazards models

Cox proportional hazards model is a semi-parametric test that describes the relationship between time to occurrence of an event and a set of covariates. Covariates are variables that may affect survival time. Cox proportional hazards models allow the simultaneous inclusion of several covariates and offer independent estimates of effect strength for each covariate.[106] Cox proportional hazards models were used in studies II-IV.

Propensity score

A propensity score can be used to balance numerous covariates in two groups. The propensity score, which is calculated for each individual in a particular study, is defined as the conditional probability of being exposed to a treatment, etc., given the individual's covariates. In order to estimate the score, the distribution of the exposure indicator variable must be modelled on the basis of observed covariates. Once estimated, the score can be used to balance covariates in the two groups through matching, stratification or regression adjustment.[107] Propensity scores were used for adjustment in studies II-IV.

Effects of unknown covariates

Unmeasured confounders may affect the results of observational studies if they are unrelated to, or not fully accounted for by, the covariates included in the regression model. The available model, including the exposure indicator variable and measured covariates but not unmeasured covariates, can be used to draw inferences about the true exposure effect. This is done by specifying the distribution of the unmeasured confounder in the exposed and unexposed

groups, along with the magnitude of effects of the unmeasured confounder on the outcome variable.[108] The effects of an unknown covariate were estimated in studies II and IV.

STATISTICAL METHODS IN THE STUDIES

All statistical analyses were performed using SAS statistical software version 9.2 or 9.3 (SAS Institute, Cary, NC, USA), JMP Version 11.0, SPSS V.18 (SPSS Inc.) or R (R Foundation for Statistical Computing). A two-sided p value <0.05 was considered statistically significant.

Baseline characteristics were compared among multiple groups using general linear model (GLM) (study I) or using analysis of variance (ANOVA) for continuous variables and logistic regression for categorical variables (study III). Baseline characteristics were compared between two groups using student's t-test for continuous variables and the χ^2 test for categorical variables (studies II, IV).

Propensity scores were estimated using boosted CART[109] (study III) and logistic regression (studies II, IV). Baseline characteristics were then compared using GLM (studies II, IV) or logistic regression and ordinary least squares (OLS) regression (study III) adjusted by stratification for quintiles (study II), octiles (study III) or deciles (study IV) of the propensity score. Variables included in the propensity score were age; gender; diabetes duration; HbA1c; body mass index (BMI); estimated glomerular filtration rate (eGFR); history of CVD, congestive heart failure (CHF) or (atrial fibrillation) AF; educational level; use of psychiatric agents; and multi-dose drug dispensing (study II); age, gender, diabetes duration; HbA1c; non-high-density lipoprotein cholesterol (HDL-C); BMI; smoking status; eGFR; multi-dose drug dispensation; previous hospitalization; history of CVD or CHF; microalbuminuria; and treatment with antihypertensive agents, lipid-lowering agents or cardiac glycosides (study III); age; gender; diabetes duration; previous hospitalization; HbA1c; BMI; systolic blood pressure; smoking; ratio of total-to-HDL-C; microalbuminuria; type of glucose-lowering treatment used; use of statins; other lipid-lowering agents; antihypertensive agents; oestrogen and multi-dose drug dispensation (study IV).

Cox regression models were used to estimate hazard ratios (HR) with 95 % confidence intervals (CI) for all outcomes (studies II-IV). Propensity scores were used for adjustment in the Cox regression analyses by stratification for quintiles (study II), octiles (study III) and deciles (study IV) of the score. In study III, HRs for all outcomes were also estimated in subgroups with various eGFR intervals, subject to conventional covariance adjustment with the

covariates that were included in the propensity score. Treatments with metformin, insulin or other OHAs in any combination were compared with all other glucose-lowering treatments.

The effect of various distributions of a hypothetical unmeasured confounder with HR 2.0 (study II) and HR 1.3 (study IV) for all outcomes in the exposed and unexposed groups was quantified.[108]

Odds ratios (ORs), not HR which was incorrectly stated in study I, of having HbA1c ≤7.0 % was analysed using generalized linear model, unadjusted and adjusted for age, gender, diabetes duration, BMI, eGFR, history of CVD, smoking status, physical activity ≥3 hours per week, and treatment with antihypertensive or lipid-lowering agents (study I).

RESULTS AND DISCUSSION

This chapter consists of four sections. In the first section the main findings of the studies are presented and discussed. The second section contains a general discussion about methodological aspects of the studies. In the third section, clinical implications of the findings are discussed. The fourth section covers future perspectives.

STUDY I

This is a nationwide cross-sectional study that analysed clinical characteristics, risk factor control and the prevalence of diabetes complications among T2D patients with non-pharmacological treatment, as well as the most commonly used pharmacological glucose-lowering treatment regimens.

Distribution of treatments

Of the 108,618 patients with the most commonly used pharmacological regimens, 38.5 % were treated with metformin alone, 6.4 % with SU alone, 15.5 % with metformin + SU, 3.4 % with metformin + meglitinide, 5.9 % with metformin + insulin NPH, 7.0 % with metformin + pre-mixed insulin (PMI), 2.1 % with SU + PMI, 2.2 % with metformin + SU + insulin NPH, 3.2 % with metformin + direct-acting insulin (DAI) + insulin NPH, 4.7 % with DAI + insulin glargine, and 6.3 % with PMI alone. In addition, 54,503 patients were treated non-pharmacologically.

Based on the results of clinical trials,[47, 80] Swedish and international treatment guidelines recommend metformin as the first-line agent in T2D patients without contraindications.[56, 57] The results of the present study showed that the vast majority of patients on pharmacological regimens (72.3 %) were treated with metformin alone or in combination with other agents. This indicates good penetration of treatment guidelines in routine clinical care. Data on glucose-lowering drug prescriptions for adults filled by U.S. retail pharmacies have shown a 97 % increase in metformin use between 2003 and 2013. Still, only half of American diabetes patients were prescribed metformin in 2012.[110]

Clinical characteristics

The results showed significant differences in both clinical characteristics and HbA1c levels achieved between the groups (Table 2). Patients with non-pharmacological treatment had the shortest diabetes duration, the lowest proportion of microalbuminuria and the least frequent use of antihypertensive and lipid-lowering agents. Patients on metformin, particularly in monotherapy, had shorter diabetes duration, higher eGFR and lower prevalence of CVD and CHD than the other groups with pharmacological treatment. Almost all groups

with insulin-based treatment regimens had mean diabetes duration longer than 10 years and relatively high HbA1c levels. The differences between the groups, including increased diabetes duration and higher HbA1c-levels as treatment regimens become more complex, reflect the progressive nature of T2D. As the disease progresses, the insulin-producing ability of the β-cells decreases and more complex treatment regimens are needed to maintain glycaemic control.[5, 6] In the UKPDS, which included newly diagnosed T2D patients, a gradual increase in hyperglycaemia and a decrease in β-cell function were seen in both conventional therapy and intensive therapy groups during six years of follow-up.[111] As a result, approximately 50 % of the patients who were randomized to intensive therapy required the addition of a second agent in order to maintain HbA1c <7.0 % at three years, whereas approximately 75 % required addition of a second agent at nine years.[78]

Table 2. Clinical characteristics of T2D patients in 2009

		NPT N=54503	Met N=41847	SU N=7003	Met+ SU N=16862	Met+ meg N=3698	Met+ NPH N=6361	Met+ PMI N=7657	SU+ PMI N=2298	Met+ SU+NPH N=2376	Met+ NPH+DAI N=3476	NPH+ DAI N=5054	Gla+ DAI N=5134	PMI N=6853
Age (years)	Mean± s.d.	68.8±12.4	65.4±11.2	75.6±10.6	68.5±10.9	65.8±10.7	66.2±9.9	69.1±9.2	72.3±9.8	68.7±9.4	65.1±9.4	67.3±10.3	65.4±10.6	74.4±9.5
Female gender	%	48.4	44.8	43.8	42.0	40.3	41.1	43.5	42.4	38.5	38.7	35.4	40.9	41.2
Diab dur (years)	Mean± s.d.	5.1±5.9	5.5±4.6	9.3±6.7	10.3±6.3	9.0±5.8	9.9±6.2	12.6±7.1	13.4±7.1	12.8±6.2	13.1±7.5	13.8±8.6	14.4±8.7	13.3±8.3
Smokers	%	15	17	12	15	17	17	15	13	16	15	16	16	13
BMI (kg/m^2)	Mean± s.d.	29.0±5.2	30.3±5.2	26.8±4.4	29.1±4.8	29.3±5.0	31.0±5.2	31.3±5.0	29.7±5.4	30.1±4.8	32.1±5.2	28.9±5.2	27.3±4.9	29.0±5.1
HbA1c (mmol/mol)	Mean± s.d.	6.4±0.9	6.8±0.9	6.9±0.9	7.2±1.0	7.1±1.0	7.4±1.1	7.5±1.2	7.9±1.2	7.7±1.2	7.7±1.2	7.5±1.2	7.8±1.2	7.4±1.1
Systolic BP (mmHg)	Mean± s.d.	136±17	136±16	138±18	138±16	136±16	137±16	137±16	138±17	138±16	136±15	136±17	134±16	137±18
Diastolic BP (mmHg)	Mean± s.d.	77±10	78±9	74±10	76±10	77±9	77±10	74±10	74±10	76±10	75±10	74±10	74±9	73±10
LDL-C (mmol/l)	Mean± s.d.	2.9±0.9	2.7±0.9	2.8±0.9	2.6±0.9	2.6±0.8	2.6±0.9	2.5±0.9	2.6±0.8	2.5±0.8	2.5±0.8	2.6±0.9	2.6±0.8	2.7±0.9
History of CVD	%	20.4	17.1	26.5	19.6	17.6	21.3	27.3	30.6	21.2	24.9	26.4	18.5	32.4

Abbreviations. NPT: non-pharmacological treatment; Met: metformin; SU: sulphonylurea; Meg: meglitinide; NPH: NPH insulin; PMI: premixed insulin; DAI: direct-acting insulin; Gla: insulin glargine; HbA1c: haemoglobin A1c; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; CVD: cardiovascular disease; T2D: type 2 diabetes

Glycaemic control

In the present study, the majority of patients with pharmacological treatment did not have an HbA1c-level <7.0 %, which is the target for most T2D patients recommended by Swedish and international treatment guidelines.[56, 57, 69, 112] The proportion of patients having HbA1c ≤7.0 % ranged from 70.1 % (metformin) to 25.0 % (SU in combination with PMI) among those with pharmacological treatment and was 84.8 % among those with non-pharmacological treatment. A gender comparison showed only minor differences in the proportions of patients having HbA1c ≤7.0 %; the clinical relevance was highly uncertain (see Figure 6).

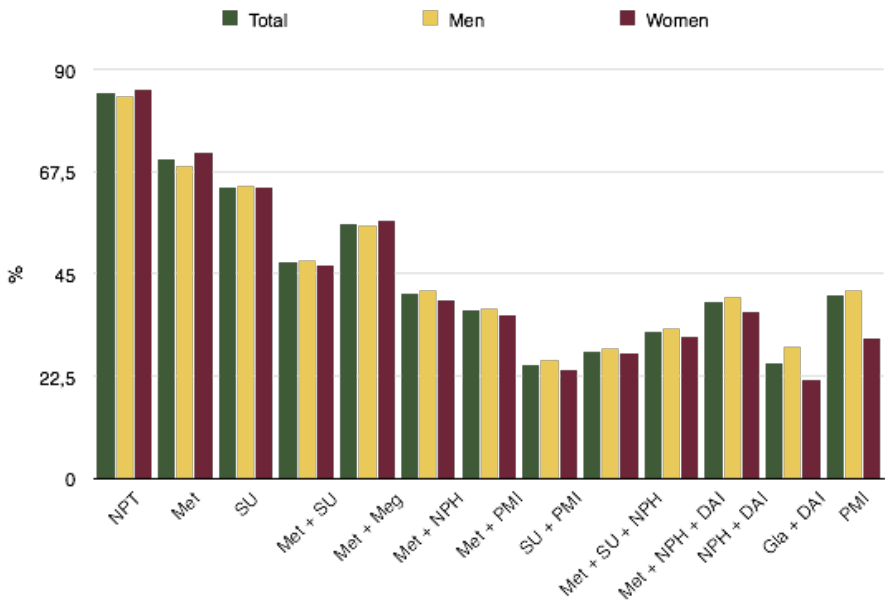


Figure 6. Proportions (%) of patients having HbA1c ≤7.0% (53.0 mmol/mol) in the total cohort and stratified by gender.

The highest proportions that did not reach HbA1c ≤7.0 % were in groups of patients with insulin-based treatment regimens. Such regimens were also associated with the lowest likelihood of having HbA1c ≤7 %, both unadjusted and after adjustment for covariates. These patients generally had a more advanced condition, long diabetes duration, high prevalence of complications and the likelihood of little remaining β-cell function, which could explain their low probability of having HbA1c ≤7 % even after adjustment for covariates.

Data from the National Health and Nutrition Examination Survey (NHANES), which is representative of the non-institutionalized U.S. population, have shown improved glycaemic control from 1999 to 2010. However, similar to our results, there were significant gaps between achieved glycaemic control and recommended treatment targets; approximately half of the patients did not reach HbA1c <7.0 %.[113, 114] As shown in our study of the Swedish population, the insufficient HbA1c control in NHANES applied to all treatment groups, including non-pharmacological treatment, although the largest proportion that did not reach the target was among patients with more complex treatment regimens.[114]

A meta-analysis of the four major trials that evaluated the effects of intensive glucose control showed that intensive glucose-lowering treatment was associated with a significant 9 % reduction in major cardiovascular events, caused primarily by a 15 % reduction in non-fatal and fatal MI at 4.4 years follow-ip.[51] Analyses of predetermined subgroups showed that patients without a history of macrovascular disease benefited the most from intensive glucose control, and also indicated that age younger than 65, diabetes duration of less than 5 years, and lower HbA1c-values were associated with more pronounced benefits from intensive treatment.[51] These results indicate differing risk-benefit ratios of intensive glucose control among various subgroups of the T2D population. As a result, treatment guidelines have increasingly emphasized the importance of individualized treatment goals. More stringent targets are recommended for patients with short diabetes duration, long life expectancy and no CVD if achievable without significant hypoglycaemia or other adverse effects. Less stringent targets are recommended for patients with a history of severe hypoglycaemia, limited life expectancy and extensive comorbidity.[69, 112]

Data from NHANES showed that the proportion of patients who achieved an individualized glycaemic target based on age and the presence or absence of pre-existing complications was considerably larger than the proportion that reached the target of HbA1c <7.0 %.[113] Thus, for some patients included in the present study, a less stringent treatment approach may have been justified. However, the majority of patients with pharmacological treatment did not reach the target of HbA1c ≤7.0 % in the present study. Even rather large proportions of newly diagnosed patients with non-pharmacological treatment (15.2 %) or metformin monotherapy (29.9 %) did not reach the target.

Other risk factor control

In the present study, levels of other risk factors also varied among the treatment groups. The proportions of patients who reached targets ranged from 35.3 % (metformin in combination with SU and NPH insulin) to 48.4% (insulin

glargine + DAI) for blood pressure and 35.3 % (non-pharmacological treatment) to 57.1 % (metformin in combination with NPH insulin + DAI) for LDL-C. Previous studies that included diabetes patients in the United States from 2007 to 2010 have shown similar achievement of blood pressure and LDL-C targets. It was also reported that less than 20 % of American diabetes patients achieved glycaemic, blood pressure and LDL-C targets at the same time.[113, 115] In the STENO-2 study, patients randomized to intensive multi-factorial interventions that simultaneously targeted multiple modifiable CVD risk factors showed an approximate 50 % reduction in CVD and an approximate 50 % reduction in long-term CVD mortality compared with those randomized to conventional therapy.[74, 75] The results of the STENO-2 study clearly demonstrate the importance of more stringent risk factor control.

STUDY II

This is a cohort study that analysed the durability of monotherapy with the most common OHAs in drug naive T2D patients. Time to monotherapy failure, defined as discontinuation of continuous use of the initial agent, switch to a new agent or add-on treatment with a second agent served as a measure of durability.

Treatment distribution

Of the 17,309 patients included in the study, 16,061 (93 %) started on metformin monotherapy, 1,026 (6 %) started on SU monotherapy and 222 (1 %) started on meglitidine monotherapy. Since very few started on monotherapy with newer OHAs (such as dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose linked transporter-2 [SGLT-2] inhibitors, glitazones or alpha glucosidase inhibitors) during the study period, the cohort was restricted to patients who started on metformin, SU and meglitinide. The fact that an overwhelming percentage started on metformin monotherapy indicates good adherence to treatment guidelines, which recommend metformin as the first-line agent.[56, 57] The low use of newer and often more expensive agents is also consistent with the guidelines, which recommend that these agents be reserved for patients who do not tolerate metformin or who do not achieve adequate glycaemic control with the highest dose of metformin. A cohort study of U.S. patients, who were members of a large health maintenance organization (HMO) network (SUPREME-DM) and diagnosed with diabetes in 2005-2010, investigated the choice of the initial glucose-lowering agent at the time of diagnosis. In line with our results, the majority (65.5 %) of patients who started on their initial glucose-lowering agent were prescribed metformin monotherapy. Lower age and normal serum creatinine level were associated with a greater

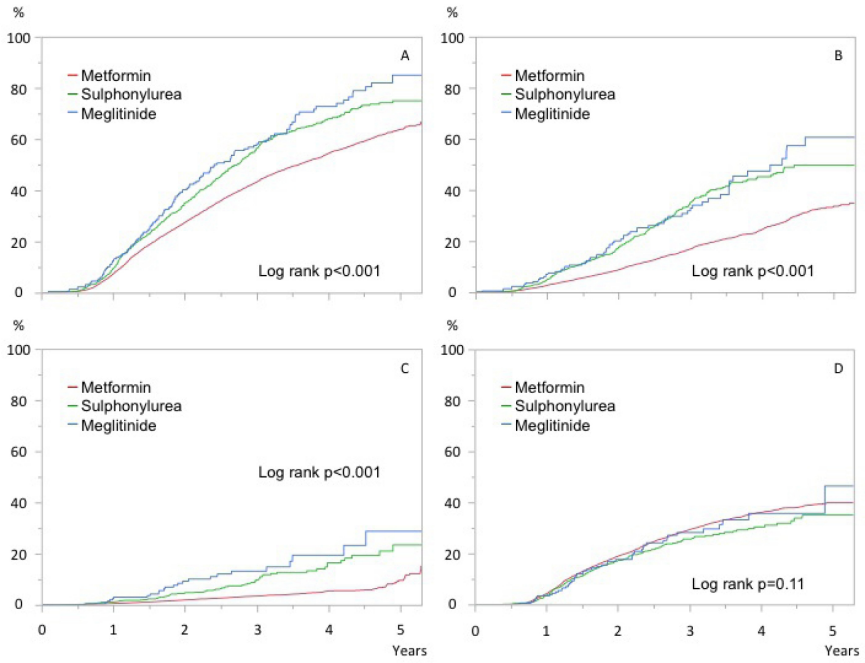
likelihood of starting on metformin monotherapy compared with SU monotherapy.[116]

Baseline clinical characteristics

Clinical characteristics differed significantly between the treatment groups at baseline. Mean ± s.d. age ranged between 65.9 ± 10.3 and 73.5 ± 10.3; diabetes duration between 3.6 ± 3.7 and 5.3 ± 4.8 years; HbA1c between 7.2 ± 1.0 % (54.8 ± 11.4 mmol/mol) and 7.3 ± 1.1 % (56.8 ± 11.2 mmol/mol); proportion of females between 31 % and 44 %; and the proportion with a history of CVD between 14 % and 21 %. Diabetes duration was remarkably long in all groups, though shorter in patients who started on metformin. Patients who started on metformin were also younger and less likely to have a history of CVD, CHF or AF than those who were started on SU or meglitinide. After adjustment by stratification with quintiles of propensity scores, the groups were balanced regarding all baseline variables. In line with our results, previous studies have shown that a rather small percentage of patients started on pharmacological glucose-lowering agents at the time of diagnosis.[116, 117] In a retrospective cohort study of Americans diagnosed with diabetes in 2003-2005, median time from diagnosis to initiation of a glucose-lowering agent was about one year in patients younger than 65 and more than 2 years in patients age 65 or older. The study found that advance age and several other variables were associated with longer time between diabetes diagnosis and starting on pharmacological treatment.[117]

Monotherapy failure

We found that almost half of the patients experienced monotherapy failure, (defined as add on of a second agent, switch to a new agent or discontinuation of the initial agent) when followed for up to 5.5 years. Figure 7 shows the unadjusted cumulative incidence of add-on treatment with a second agent, switch to a new agent and discontinuation of the initial agent when analysed separately and as a composite endpoint. The cumulative incidence of the composite endpoint of monotherapy failure was significantly higher for SU and meglitinide than for metformin ($p<0.001$); the curves diverged throughout the study period. When looking at the individual components of monotherapy failure, there were clear differences between the groups in terms of switch to a new agent ($p<0.001$) and add-on treatment with a second agent ($p<0.001$), but not for discontinuation ($p=0.11$).



No. at risk per year	1st	2nd	3rd	4th	5th	6th
Metformin	16061	14693	7774	3717	1446	290
Sulphonylurea	1026	923	517	245	104	28
Meglitinide	222	191	114	64	24	4

Figure 7. Unadjusted cumulative incidence of secondary monotherapy failure in each treatment group, when followed for up to 5.5 years. A: All failure; B. Add-on; C. Switch; D. Discontinuation. All graphs with log-rank test p<0.001, except D with log-rank test non-significant.

Similar results were obtained from multivariate Cox proportional hazards models, adjusted for differences in baseline demographics and patient characteristics. SU and meglitinide were associated with a greater risk of overall monotherapy failure than metformin (HR 1.59, 95 % CI 1.45 to 1.75 and HR 1.74, 95 % CI 1.47 to 2.07 for SU and meglitinide, respectively). The increased risk of overall monotherapy failure associated with SU and meglitinide was caused by a substantially increased risk of add on of a second agent (HR 2.78, 95 % CI 2.42 to 3.18 and HR 2.75, 95 % CI 2.14 to 3.53 for SU and meglitinide, respectively) and of switch to a new agent (HR 2.17, 95 % CI 1.65 to 2.86 and HR 3.13, 95 % CI 2.04 to 4.79 for SU and meglitinide, respectively). The risk of discontinuation did not differ significantly from one group to another (Figure 8).

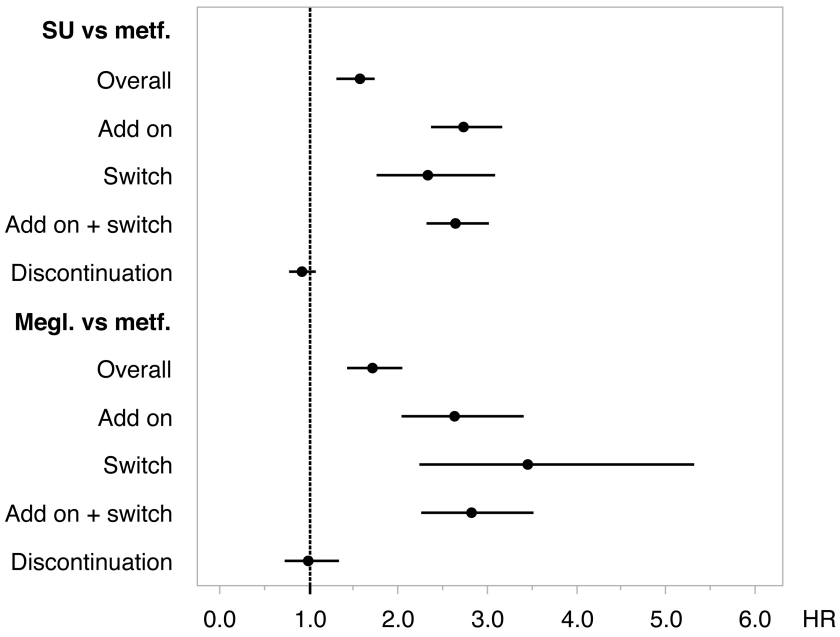


Figure 8. Hazard ratio (HR) with 95 % confidence intervals (CI) for overall monotherapy failure and its individual components, comparing SU (n=1026) with metformin (n=16061) and meglitinide (n=222) with metformin during mean follow-up of 2.6 years. A HR of >1.0 favours metformin. Adjustments were made by stratification with quintiles of propensity scores including the following variables: age, gender, diabetes duration, HbA1c, BMI, eGFR, change in eGFR, previous cardiovascular disease, congestive heart failure and atrial fibrillation, educational level, use of psychiatric medications and multi-dose drug dispensing.

Patients who remained on their initial monotherapy throughout the study showed improved HbA1c levels of approximately 10 % regardless of the type of OHA used, whereas patients who switched agents or received add-on of a second agent showed stable or slightly increased HbA1c levels. The improved HbA1c levels among patients who remained on their initial monotherapy confirm that they represented responders to treatment. More surprisingly, patients who discontinued their initial OHA showed similar improvement in glycaemic control. This is most certainly a highly heterogeneous group of patients, with a wide range of underlying reasons for discontinuation. Patients who received add-on of a second agent or switched to a new agent showed unchanged or slightly increased HbA1c levels prior to these events, indicating that deterioration of glycaemic control was the primary underlying cause.

Our results are in line with those of ADOPT. In ADOPT, initial monotherapy with metformin provided better glycaemic durability than with glyburide (a member of the SU drug class),[77] caused by a faster decline in β-cell function and insulin sensitivity in patients who started on glyburide.[118] Despite similar results, the present study and ADOPT revealed important differences. The present study was observational in design and reported the durability of various OHAs in routine clinical care. ADOPT was an RCT that reported effects of protocol-driven treatments in a selected group of motivated patients who were closely followed with frequent visits.

A few observational studies have compared the durability of metformin and SU in real life. They also reported better durability with metformin than with SU. These studies, however, either lacked information about important variables – such as diabetes duration, HbA1c and BMI – or had short follow-up periods.[103, 119] Both HbA1c and BMI have been shown to be associated with progression from prediabetes to overt T2D;[120, 121] diabetes duration is related to remaining β-cell function. As a result, these variables are crucial covariates for estimating the risk of monotherapy failure. ADOPT showed that glyburide had better effects on β-cell function and glycaemic control than metformin or rosiglitazone during the first 6 months. However, patients on glyburide had a faster decline in β-cell function and loss of glycaemic control after that time. This resulted in significantly lower glycaemic durability with glyburide than with metformin or rosiglitazone when analysed over a median period of 4 years.[77] Thus, a reasonably long follow-up period is also important in studies that evaluate the durability of glucose-lowering agents.

The results of the present study suggest that metformin also has better glycaemic durability than meglitinides. Meglitinides are agents that – along with SU, etc. – add a therapeutic option among patients who have contraindications for metformin or require a second agent in order to achieve glycaemic control.[57]

STUDY III

This is a cohort study that analysed the benefits and risks of metformin for T2D patients with various degrees of renal function. Risks for all-cause mortality, CVD and a composite endpoint of acidosis and serious infection were analysed in a cohort of 51,675 T2D patients treated with metformin and other glucose-lowering agents. Analyses were also performed in subgroups with various degrees of renal function.

Treatment distribution and clinical characteristics

Of the 51,675 patients included in the study, 14,697 (28 %) were treated with metformin alone, 5,171 (10 %) with other OHA alone, 12,291 (24 %) with insulin alone, 8,807 (17 %) with metformin + other OHA, 7,109 (14 %) with metformin + insulin, 1,365 (2.6 %) with other OHA + insulin and 2,235 (4.3 %) with metformin + other OHA + insulin. Other OHA included all OHAs with the exception of metformin, but approximately 80 % were SU.

The total population had a mean ± s.d. age of 65.3 ± 9.8; diabetes duration of 9.4 ± 8.0 years; HbA1c of 7.3 ± 3.3 % (56.3 ± 36.1 mmol/mol); BMI of 29.5 ± 5.1 kg/m^2; systolic blood pressure of 140 ± 17 mmHg and non-HDL-C of 3.5 ± 1.0 mmol/l. A total of 42 % were women, 14 % were smokers and 21 % had a history of CVD. There were significant differences in clinical characteristics between the groups. Patients on insulin-based treatments had longer diabetes duration, higher HbA1c and a greater likelihood of microalbuminuria or history of hospitalization for CVD, CHF and serious infections than the population in general. Patients on metformin monotherapy were the youngest, had the shortest diabetes duration and had relatively low HbA1c. They also less often had a history of hospitalization for CVD, CHF or serious infections. Patients treated with other OHA monotherapy were the oldest and had relatively low HbA1c and BMI. After adjustment by stratification with octiles of propensity scores, the treatment groups were balanced in terms of the baseline variables.

Outcomes in the total cohort

We found that metformin monotherapy was associated with lower risk of all-cause mortality, CVD and the composite endpoint of acidosis and serious infection than insulin monotherapy. Borderline significant risk reduction of all-cause mortality was also shown compared with other OHA monotherapy or SU monotherapy. The analyses were adjusted for differences in baseline characteristics by stratification with propensity scores (Figure 9).

These results are in line with previous studies. In the UKPDS sub-study, 1,704 overweight or obese patients with newly diagnosed T2D were randomized to intensive therapy with metformin (n=342), insulin (n=409) or sulfonylurea (n=542), or to conventional therapy that focused on diet alone (n=411) and were followed for 10.7 years.[80] The results showed significantly greater risk reductions for any diabetes-related outcome, all-cause mortality and stroke in patients randomized to metformin than to insulin or sulfonylurea. Another small RCT showed beneficial effects of metformin in insulin-treated T2D patients who were followed for 4.3 years. Among the 390 participants, those

who received add-on treatment with metformin had a lower risk of CVD than those who received placebo.[122]

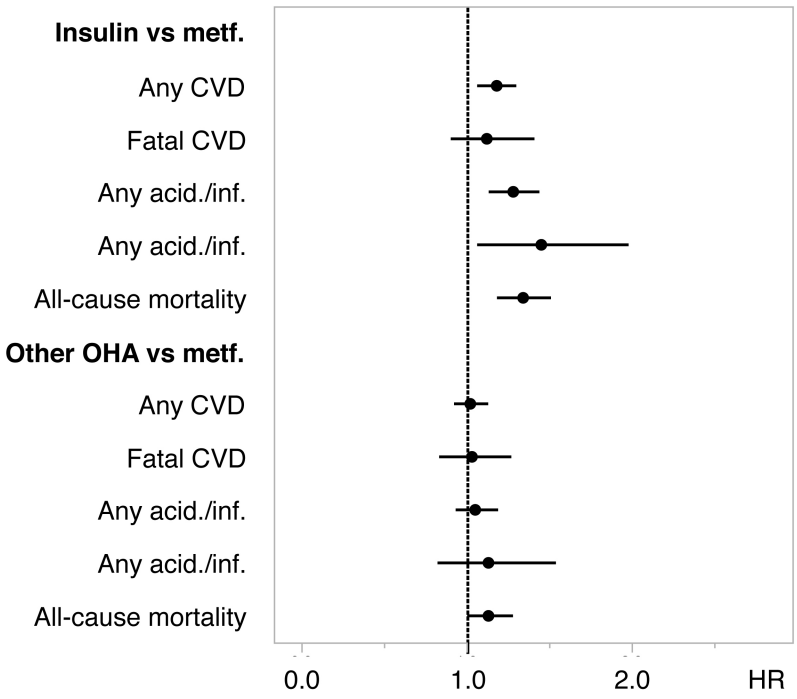


Figure 9. Hazard ratio (HR) with 95% confidence interval (CI) for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection and all-cause mortality comparing insulin monotherapy with metformin monotherapy and other OHA monotherapy with metformin monotherapy at 4 years follow-up. A HR of >1.0 favours metformin. Adjustments were made by stratification for octiles of propensity scores. The following variables were included in the propensity scores: age, gender, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose drug dispensing, previous hospitalization, history of CVD and CHF and microalbuminuria, as well as treatment with antihypertensive agents, lipid-lowering agents and cardiac glycosides.

Previous observational studies, for example epidemiological analyses of data from the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI)-2 trial, have reported similar results. The DIGAMI-2 trial randomized 1253 T2D patients with suspected myocardial infarction to long-term, insulin-based or standard glucose control. Post hoc epidemiological

analyses showed significantly lower risks for non-fatal CVD and all-cause mortality associated with metformin than with any other glucose-lowering agent.[123-125] Other observational studies have also reported lower risks for all-cause mortality and CVD with metformin than with any other glucose-lowering agent,[126-128] or SU.[129-134] As opposed to many other glucose-lowering agents, metformin is weight-neutral and does not increase the risk of hypoglycaemia. Furthermore, metformin has been suggested to protect against malignancies;[135] experimental studies on mice have shown beneficial effects of metformin on myocardial function regardless of glucose levels.[136, 137] Such beneficial properties may explain why metformin seems to have better protective effects than other glucose-lowering agents even though glucose levels are similar.

Several observational studies have reported associations between insulin treatment and greater risk of all-cause mortality and CVD than other glucose-lowering agents.[32, 123-127, 138-141] This has led to concerns about the safety of insulin treatment.[142] Most of these studies compared the effects of insulin with other glucose-lowering drugs including metformin. Therefore it is possible that the differences seen in those studies and in the present study were due to beneficial effects of metformin rather than harmful effects of insulin. The fact that large RCTs have not found convincing signs of adverse events with insulin militates against such serious harmful effects.[47-50, 54, 55, 143]

Outcomes in subgroups based on renal function

We found that the beneficial effects of metformin were also present in patients with mild to moderate renal impairment (Figure 10). Among patients with eGFR between 45 and 60 ml/min/1.73m^2, metformin was associated with 13 % lower risk of all-cause mortality and 15 % lower risk of the composite endpoint of acidosis and serious infection at 3.9 years follow-up. Looking at patients with moderate to severe renal impairment (eGFR 30-45), we did not find any difference in risks for all-cause mortality, CVD or the composite endpoint of acidosis and serious infections.

Only a handful of studies have evaluated the effects associated with metformin in patients who have various degrees of renal function. An observational study based on the international Reduction of Atherothrombosis for Continued Health (REACH) registry examined the effects associated with metformin in 19,691 patients with diabetes and advanced CVD who were followed for 2 years.[128] In line with our results, the study found metformin to be associated with a lower risk of all-cause mortality than other glucose-lowering agents in patients with eGFR of 30-60. However, as opposed to our results, the study found the greatest risk reduction in patients with eGFR of 30-45. Significant limitations of the study based on the REACH registry include a short follow-up

period and missing information about important covariates, such as HbA1c and diabetes duration. Our study – which included more than 50,000 patients, a longer follow-up period (4 years) and complete data on many important covariates – adds strength to evidence of the beneficial effects of metformin in patients with mild to moderate renal impairment.

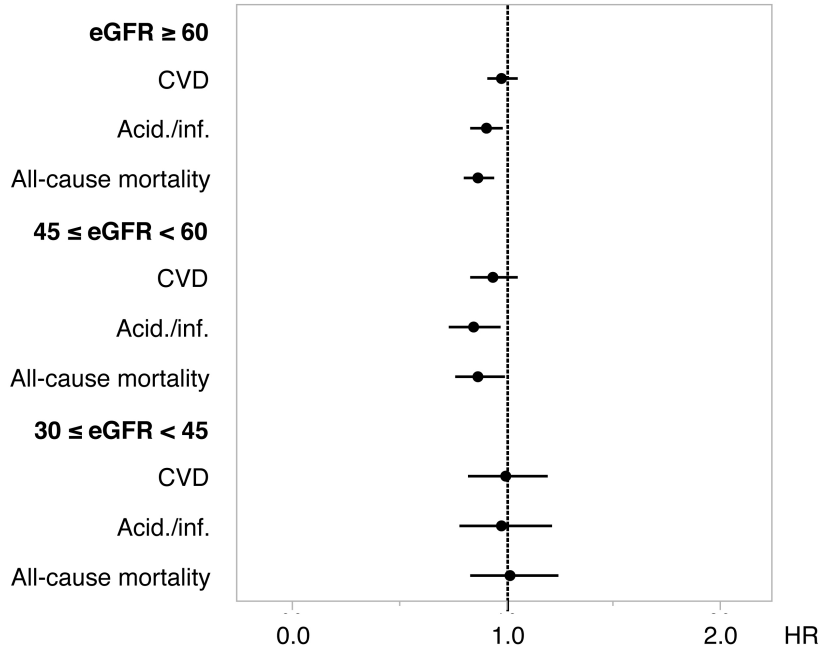


Figure 10. Hazard ratio (HR) with 95% confidence interval (CI) for fatal/non-fatal CVD, fatal/non-fatal acidosis/serious infection and all-cause mortality with metformin compared with any other glucose-lowering medication at 4 years follow-up. A HR of <1.0 favours metformin. Covariate adjustment was made for the following variables: age, gender, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose drug dispensing, previous hospitalization, history of CVD and CHF and microalbuminuria, as well as treatment with antihypertensive agents, lipid-lowering agents and cardiac glycosides.

What about the risk of lactic acidosis? A pooled analysis of 347 clinical trials and cohort studies of metformin treatment did not find any cases of fatal or nonfatal lactic acidosis in 70,490 patient-years among metformin users or in 55,451 patients-years among non-metformin users. Furthermore, there was no difference in lactate levels, either as mean treatment levels during the study periods or as a net change from baseline, between metformin and non-

metformin therapies.[81] A recent observational study that used the Clinical Practice Research Datalink (CPRD) database in the UK explored the incidence of lactic acidosis among metformin-treated T2D patients with various degrees of kidney function.[144] The study found 35 events of lactic acidosis in 337,590 person-years, with no significant difference in incidence among patients with normal, mildly reduced, moderately reduced or severely reduced renal function. Of the 35 cases of lactic acidosis in the study in the UK, a majority were associated with conditions that could have increased the risk for lactic acidosis, independent of metformin use.

Another observational study that used data from the same register (CPRD) explored the risk of lactic acidosis or elevated lactate levels (>5 mmol/L) with metformin compared with other non-insulin glucose-lowering agents.[145] The study found a higher risk of lactic acidosis or elevated lactate level in metformin-treated patients with impaired renal function than in patients who had never used metformin. These findings are inconsistent with previous studies for which metformin concentration did not have any prognostic value in cases of lactic acidosis.[146, 147] The authors concluded that the results support adequate monitoring of renal function in metformin users and that the dose of metformin should be adjusted, if necessary, when GFR falls below 60. However, they also emphasised the risk of bias due to differential misclassification of outcome events as a limitation of their study.[145] Because of the established belief that metformin may be linked to lactic acidosis, lactate concentrations in metformin users may have been measured and recorded more selectively, particularly when renal function was impaired. This would introduce bias by overestimating the risk in metformin users and conceivably underestimating the risk in non-metformin users.

STUDY IV

This is a cohort study that analysed the benefits and risks associated with aspirin treatment in T2D patients with no established CVD. Risks for CVD, CHD, stroke, all-cause mortality and bleeding associated with aspirin compared with no aspirin were analysed in the total cohort of 18,646 T2D patients and in subgroups by gender and estimated CVD risk.

Treatment distribution and baseline characteristics

Among the 18,646 patients, 4,608 (25 %) received low-dose (75 mg) aspirin treatment and 14,038 (75 %) did not receive any aspirin treatment. In both groups, there were approximately 55 % men and 15 % smokers. Mean HbA1c was approximately 7 % (53 mmol/mol), mean BMI was approximately

30 kg/m², mean systolic blood pressure was approximately 140 mmHg and mean total cholesterol was approximately 5 mmol/l. There were, however, important differences between the groups. Patients who received aspirin were older, had longer diabetes duration and were more likely to have microalbuminuria than patients who did not receive any aspirin. They were also more likely to be on glucose-lowering regimens with multiple drug combinations, lipid-lowering regimens and blood pressure-lowering regimens, indicating that they required more advanced treatment to achieve roughly the same risk factor control. After adjustment by stratification with a propensity score, the groups were balanced in terms of baseline variables.

Risks of cardiovascular events and all-cause mortality

The results of our study did not show any significant difference in risk for CVD or all-cause mortality between the groups, except for a borderline significant 19 % increased risk for any CHD associated with aspirin treatment at 4-year follow-up (Figure 11.). The increased risk of any CHD associated with aspirin was confirmed in women but not in men. There was also a borderline significant 28 % increased risk of any CVD associated with aspirin treatment in women that was not seen in men. There was no significant difference in risk for CVD or all-cause mortality between aspirin treatment and absence of aspirin treatment in patients with high estimated CVD risk (5-year CVD risk ≥15 %) or low estimated CVD risk (5-year CVD risk <15 %).

Previous studies have reported inconsistent findings regarding the risk-to-benefit ratio for the use of low-dose aspirin in primary CVD prevention among patients with T2D. Three RCTs have evaluated the effects of aspirin for primary prevention of CVD exclusively in patients with diabetes.[148-150] In line with our results, they did not find convincing beneficial effects of such treatment. The Early Treatment of Diabetic Retinopathy Study (ETDRS) randomized 3,711 patients with type 1 diabetes (T1D) or T2D (half of them with previous CVD) to treatment with 650 mg aspirin daily or placebo. The results showed a non-significant 17 % lower risk of non-fatal or fatal MI in the aspirin group after 5 years.[148] The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial of 1,276 patients with T1D or T2D with no previous CVD presented similar results for two primary composite endpoints after a median of 7 years of follow-up – fatal or non-fatal CVD or amputation above the ankle (HR 0.98, 95 % CI 0.76 to 1.26), and fatal CVD (HR 1.23, 95 % CI 0.79 to 1.93) – in comparing the aspirin to the placebo groups.[149] In the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial among 2,539 patients with T2D and no CVD at baseline who were followed for a mean of 4 years, aspirin (81–100 mg daily) had no significant effect compared with placebo on the primary composite endpoint of fatal or non-fatal CHD, fatal or

non-fatal stroke and peripheral arterial disease. Only one of the several secondary endpoints (fatal CHD and stroke) showed a significantly lower risk with aspirin.[150] Meta-analyses of the available trials have consistently indicated modest but not statistically significant reductions in the risk of CVD with aspirin in T2D patients.[68, 151, 152]

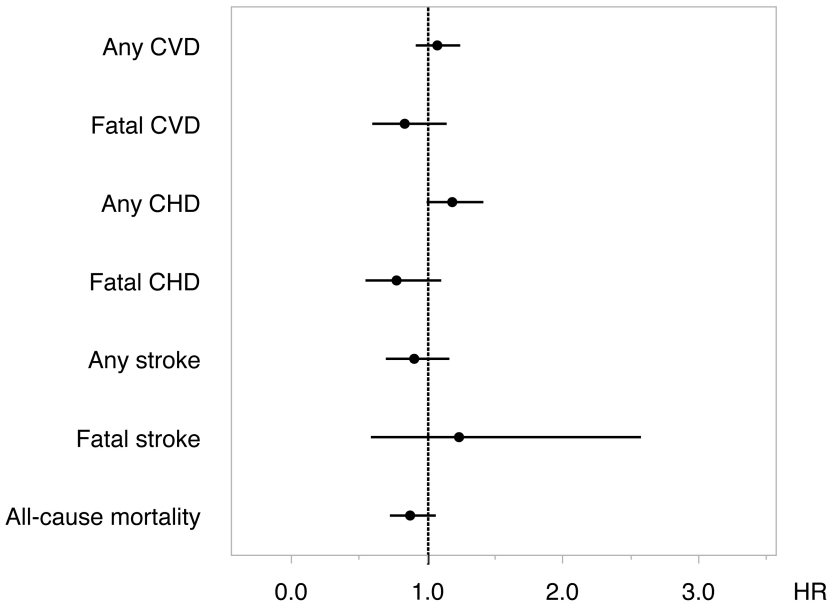


Figure 11. HR with 95 % CI for outcomes in T2D patients with aspirin treatment (n=4,608) compared with absence of aspirin treatment (n=14,038) who were followed for 4 years. A HR of <1.0 favours aspirin treatment. Adjustment was made by stratification with deciles of a propensity score. The following variables were included in the propensity score: age, gender, diabetes duration, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio of total-to-HDL cholesterol, albuminuria >20 μg/min, antihypertensive drugs, statins, other lipid-lowering drugs, oestrogen, multi-dose drug dispensing and previous hospitalization.

Clinical trial knowledge of the effects of aspirin treatment for primary prevention in patients with diabetes is based largely on subgroup analyses in trials designed to evaluate its impact on a general population, which increases the risk of bias.[68] The few available RCTs that have evaluated the effects of aspirin for primary prevention of CVD exclusively in patients with diabetes also suffer from significant limitations. The ETDRS included both T1D and T2D patients; even more importantly, half of the participants had established CVD.

In fact the ETDRS was not a true primary prevention study. Both the POPADAD and JPAD trials were rather small, and concerns have been expressed about insufficient power.[68] Our study contributes important information to this controversial question. We included T2D patients only, and the results are representative of routine clinical care. Furthermore, the study had sufficient power to evaluate benefits and risks associated with aspirin for primary prevention of CVD in subgroups based on gender or estimated CVD risk.

In line with our results, previous observational studies have reported a lack of beneficial effects from primary CVD prevention with aspirin in T2D patients. A Swedish study analysed the association between aspirin treatment, mortality and serious bleeding in 58,465 diabetes patients with and without established CVD at baseline.[153] in fact, the results showed a statistically significant 17-29 % increased risk of all-cause mortality in patients receiving primary prevention with aspirin who were followed for up to 1.5 years. The analysis was adjusted for age, gender and comorbidity. A recent prospective observational study in Italy evaluated the effect of aspirin on the risk of CVD events in a cohort of 564 T2D patients with nephropathy but free of CVD at baseline.[154] In the Italian study, all patients were screened with anamnesis, resting ECG and stress ECG to ensure the absence of CVD at baseline. The results did not show any significant difference in the occurrence of major cardiovascular events between patients who received 100 mg of aspirin daily and patients who did not receive any aspirin after average follow-up of 8 years. The analyses were adjusted for age, gender, smoking habits, GFR, albumin excretion rate, HbA1c, systolic blood pressure, BMI and total cholesterol.

Risk of bleeding

The results of the present study did not show any significant difference in the risk of intracerebral or ventricular haemorrhages between the groups. There was a borderline statistically significant 41 % increased risk of total haemorrhages ($p=0.05$) and a borderline statistically significant 2.5-fold increased risk of other haemorrhages ($p=0.05$) associated with aspirin treatment. Other haemorrhages included unspecified and respiratory bleeding. total haemorrhages was a composite endpoint that included intracerebral, ventricular and other haemorrhages. A large population-based cohort study in Italy analysed the association between aspirin use and major haemorrhages.[155] Similar to our results, the study did not find any significant difference in the risk of ventricular or intracerebral haemorrhage between aspirin treatment and the absence of aspirin treatment among patients with diabetes. Unfortunately, the study did not analyse the risk of haemorrhage from other locations and thus could not confirm our findings of a likely increased risk for other haemorrhages.

METHODOLOGICAL CONSIDERATIONS

Results of RCTs are considered the highest level of evidence when comparing alternative management strategies or interventions.[83, 84] The reason is the high internal validity of RCTs. Internal validity is a property of a scientific study that reflects the extent to which it measures what it's set out to measure. The high internal validity of RCTs is a result of random assignment of patients to various exposures, strict selection criteria for inclusion and close monitoring during follow-up. Assuming that the study sample is large enough, the randomization process reduces bias by making the groups as equal as possible with respect to all patient characteristics that can have an impact on outcomes. In theory, the process makes the groups identical except for the kinds of treatment to which they are assigned.

Observational studies, on the other hand, do not randomly assign patients to various exposures but observe differences in outcomes after treatment decisions have been made on the basis of clinical assessment by a doctor, etc. As a result, the groups that are compared in observational studies may differ with respect to characteristics other than the particular treatment to which they have been assigned, which may lead to biased results and low internal validity. However, observational studies often reflect results from routine clinical practice and thus have high external validity. External validity is a property of scientific studies that reflects the extent to which the results can be generalized to routine clinical practice. Because of strict selection criteria for inclusion of participants and close monitoring during follow-up, RCTs often have limited external validity.[156] These general pros and cons for the various study designs is an important argument for why RCTs and observational studies can be used synergistically to obtain more and better information about the relative merits of alternative management strategies or interventions. However, despite these general differences between RCTs and observational studies, they tend to arrive at highly similar results.[157, 158]

Even though RCTs generally have superior internal validity and observational studies often have superior external validity, the presence of important limitations in study design can offset such dynamics.[156] Grading of Recommendations Assessment, Development, and Evaluation (GRADE) is a widely used and accepted approach for rating quality of evidence in systematic reviews and guidelines.[159] In the GRADE approach, RCTs start off as the highest quality of evidence and observational studies as a lower quality of evidence. However, both RCTs and observational studies can be up-rated or down-rated based on strengths and limitations of study design.[83] When evaluating the quality of evidence in any epidemiologic study, whether RCT or

observational, it is crucial to be aware of the various errors that may have arisen. There are two types of errors that affect epidemiologic studies: random and systematic. Random errors, which are a result of variability in the data, can be reduced by increasing the sample size. Systematic errors (also called bias), on the other hand, are not affected by sample size.[101]

Random errors

Random errors are a result of variability in the data. For example, errors may arise randomly in a particular measurement. This would lead to inconsistent values if the measurement were to be repeated. Because of this random variability, there is a risk that any finding of an epidemiologic study is due to chance and does not reflect the real world. One key role of statistics in the analysis of epidemiologic data is to assess the role of chance. This can be done by estimating a confidence interval or p-value. The confidence interval is an area around the point estimate that provides an estimate of statistical variability in the data. A small confidence interval indicates little variability and a wide confidence interval indicates a great deal of variability. The p-value is based on the null hypothesis, which states that there is no relationship between exposure and outcome. The p-value is a measure of the consistency between the results and the null hypothesis; a small value indicates little consistency. A p-value of <0.05 is often used as the threshold for rejection of the null hypothesis and acceptance of the observed difference as statistically significant. A large study is less affected by random variability and thus not as susceptible to random error. This is reflected in the confidence interval and p-value. For example, confidence intervals narrow as the study becomes larger.[101] One major strength of the studies included in this thesis is the large number of patients that they included.

Systematic errors

Systematic errors, also called biases, are not affected by the size of the study. Biases are usually assigned to one of three broad categories: selection bias, information bias and confounding.[101]

Selection bias

There are several different types of selection bias, all of which are related to the procedures used to select study participants.[101] The samples that were selected for the studies in this thesis were derived from patients entered in the NDR during the study periods. Despite the rapidly increasing coverage of the NDR, it does not include all Swedish T2D patients. Healthcare units that reported to the NDR may not have been fully representative. This is mainly a concern in cross-sectional studies such as study I. In 2009, when study I was conducted, approximately 70% of all Swedish T2D patients had been entered in the NDR

and participating health care units represented all geographical areas. This indicates that the patients included were representative of the overall T2D population.

Of more concern is another type of selection bias, sometimes referred to as indication bias.[101] It arises when severity of disease, comorbidity and other factors influence the treatment a doctor prescribes for a particular patient. This is relevant in all the studies included in this thesis – especially studies I-III, which evaluated various glucose-lowering agents. As T2D progresses, the insulin-producing ability of the β-cells decreases and more complex treatment regimens are needed to maintain glycaemic control. As a result, patients treated with multiple drug combinations or insulin had more advanced disease with longer diabetes duration and a greater propensity for complications. Many of these characteristics, such as the presence of vascular complications, are also associated with the outcomes that were used in the studies covered by this thesis. This may lead to biased results due to confounding. This 'confounding by indication'[102] is discussed in more detail under the heading of Confounding.

We used complete case analysis in the included studies. In other words, only patients with complete records of all covariates were included in the analyses. If the fact of a missing observation was unrelated to both the unobserved value and the data that were available, the cause could be regarded as entirely random. If so, the use of complete case analysis would reduce the power of the study but would not introduce any biases. If the cause was not entirely random, the use of complete case analysis could introduce a selection bias.[105, 160] The clinics that reported to the NDR did not intend to selectively exclude certain data. Instead, data were likely to have been missed by chance because certain variables happened not to have been measured in individual patients when reporting to the NDR. In studies II and III, sensitivity analyses were performed for which missing data were managed differently. In study II, all analyses were performed among an additional, larger group of patients with complete records on a selection of variables that did not suffer from missing observations. In study III, the analyses were performed after multiple imputations of missing values.[160] Both sensitivity analyses yielded the same results as the main analyses, which indicates that the risk of bias due to management of missing data is of little concern.

Finally, Protopathic bias, also known as reversed causality, may occur in observational studies if early manifestations of the outcomes under consideration influence the selection of medication.[102] In such cases, medication may erroneously appear to have caused the outcome. In studies II-IV, there was

a lag time between the commencement of medication and the start of follow-up for outcome occurrence, which reduced the risk of this bias.[102]

Information bias

Information bias occurs when information about study participants is erroneous. Information bias can be classified as differential or non-differential. Misclassification is non-differential if it is unrelated to other study variables, whereas differential misclassification is related to the value of other study variables. Non-differential misclassification usually leads to dilution of differences between the groups, perhaps disguising a beneficial or harmful effect of a medication. Differential misclassification is less predictive and can lead to either underestimating or overestimating an effect.[101]

Because the studies in this thesis are based on data from registers, there is a risk that some variables were incorrectly reported. However, validation studies have shown that the data in the Hospital Discharge Register and the NDR are reasonably valid.[90, 97] Routines for reporting data to the NDR have improved over the years, and a growing percentage are transmitted directly from medical records. These improvements have presumably increased the validity of the data even further. Furthermore, exposure to various treatments was classified on the basis of prescription fills. It is possible that some patients have been misclassified because they filled prescriptions without actually taking the medications. Furthermore, the ITT approach used in studies III and IV, which carries forward the initial exposure status and disregards changes in treatment status over time, will by definition misclassify the exposure status in patients who switch treatment during follow-up. This misclassification tends to produce overly conservative results by reducing the effects of a medication but does not create bias in a particular direction.[102] Finally, we used an epidemiological definition of type 2 diabetes. This definition has been employed in several publications based on data from the NDR. Similar definitions have been used in publications from other large registers and have been widely accepted.[126, 133] However, some patients with other types of diabetes, such as latent autoimmune diabetes in adults, may have been misclassified as having T2D. There is no reason to believe that such misclassification was differential. The expected consequence of misclassification in the included studies would be a small dilution of differences in outcomes between the groups under comparison.

A special type of information bias that may occur in observational studies is referred to as immortal time bias. Immortal time bias may occur if the study design produces a period of observation during which the outcome under study could not have occurred.[161] This bias usually arises due to study designs in which exposure status is classified on the basis of information that is not yet known at

the time of cohort entry. For all studies included in this thesis, clear definitions ensured that covariates were assessed prior to cohort entry and that follow-up for outcome occurrence started after the requirements for cohort entry had been met. All of these study characteristics reduce the potential for immortal time bias.[102]

Confounding

Confounding, which is a mixing of effects, occurs if predictors of the outcomes under consideration are unevenly distributed between the groups being compared.[101] For the studies in this thesis, confounding by indication is of particular concern. This occurs when disease severity, the presence of comorbidity and other characteristics associated with the outcome affect the treatment that doctors prescribe.[102] In studies II and III, patients who received multiple drug combinations or insulin treatment had more severe disease than others. The effects of confounding can be limited by adjusting for known and probable confounding factors in the statistical analysis. This eliminates bias due to the variables that have been adjusted for. For the studies in this thesis, we had extensive information about risk factors, complications, comorbidity, use of medication and demographics, for which we were able to adjust in the analyses. This is a major strength of the studies in this thesis. However, statistical adjustment can never eliminate bias that is due to unknown or unmeasured confounding factors. In studies II and IV, analyses were performed to estimate the effects of a hypothetical unknown confounder. A strong predictor of the outcomes had to be much more present in one group than the other in order to invalidate the findings.

CLINICAL IMPLICATIONS

Several findings of the research presented in this thesis have direct relevance to the everyday care of T2D patients. The findings of study I highlight the importance of continuing efforts to achieve good risk factor control in T2D patients. Even a rather large percentage of newly diagnosed patients with non-pharmacological treatment or metformin monotherapy did not reach HbA1c <7.0 %. Hypertension and dyslipidaemia were also insufficiently controlled in a large percentage of the patients. There is strong evidence of beneficial effects of intensive glucose control in newly diagnosed T2D patients;[50, 51, 80] results of the UKPDS suggest that management of glucose control in the early stages of the disease has consequences for a long time.[47] Thus, good glycaemic control from the beginning is of major importance. The results of the STENO-2 study clearly demonstrated the benefits of simultaneous intensive control of multiple modifiable CVD risk factors.[74, 75] Despite concerted efforts in the management

of T2D patients, the results of study I indicate that improvements are still possible in order to help even more patients reach multiple risk factor targets.

The results of studies II and III support the use of metformin as a first-line agent in T2D patients. ADOPT showed that metformin has better glycaemic durability than SU;[77] the results of the UKPDS showed a reduction in mortality with metformin compared with SU, insulin or diet.[80] Studies II and III strengthen the evidence of such beneficial effects of metformin by confirming the results of ADOPT and the UKPDS in large cohorts representing T2D patients in routine clinical practice. The results of study II indicated that the superiority in glycaemic durability of metformin over other frequently used glucose-lowering agents is even more pronounced in routine clinical care than in an RCT setting. In study III, we found that patients with mildly to moderately reduced renal function (eGFR 60-45) also benefited from metformin treatment. In these patients, metformin was associated with a significant 15% lower risk of mortality than with other glucose-lowering agents at 4-year follow-up. These results support a less restrictive approach to the use of metformin in patients with mildly to moderately reduced renal function. However, it is important to emphasise that we did not have any detailed information about metformin doses. Since metformin is not metabolized and is eliminated by the kidneys,[162] the dosage should be adjusted on the basis of renal function. Furthermore, most of the reported cases of metformin-associated lactic acidosis have been linked to other conditions, such as infections, dehydration and CVD, which are associated per se with increased risks for lactic acidosis.[144, 162] This underscores the importance of terminating metformin treatment in cases of acute illness. A less restrictive approach to metformin treatment would set higher requirements for adequate dosage adjustments based on renal function. If this could be achieved without sacrificing a conscientious effort to inform patients that treatment needs to be terminated in cases of acute illness and dehydration, significant improvements in health outcomes would ensue.

Previous studies have shown highly uncertain net benefits of aspirin treatment among T2D patients without established CVD.[68, 151, 152, 154, 163] In study IV, there were no beneficial effects associated with aspirin for primary prevention of CVD in a large cohort of T2D patients in routine clinical practice. Aspirin was instead associated with increased risk of bleeding. The lack of beneficial effects also held true for patients at particular high estimated CVD risk. These findings militate against the treatment guidelines of the American Diabetes Association (ADA), which recommend aspirin for primary prevention of CVD in T2D patients with an estimated 10-year CVD risk of >10 %.[69] Large RCTs concerning the benefits and risks of aspirin treatment in diabetes patients without established CVD are ongoing and will provide additional information in

coming years.[164] In the meantime, our results support a more restrictive approach to the use of aspirin for primary prevention of CVD in T2D patients.

FUTURE PERSPECTIVES

What comes after metformin?

One important question is what glucose-lowering agent to add when metformin fails to achieve or maintain glycaemic targets. The available evidence is sparse, and there is a great need for studies to evaluate the relative effectiveness and safety of several different glucose-lowering agents when added to metformin. This question will be addressed by using real-world data from the NDR in the near future. The ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) study, scheduled for completion in 2020, will provide additional information.[165]

Personalized medicine

The results of large trials of glycaemic control have indicated differing risk-benefit ratios of intensive glucose control in various T2D subpopulations.[51] As a result, there has been a growing focus on a personalized approach to managing T2D.[166, 167] Factors such as patient preferences, life expectancy, disease duration, comorbidity and cognitive ability already play an important role in the selection of optimal therapeutic agents and treatment targets.[57] A great deal of research is currently being conducted in the field of personalized medicine. For example, pharmacogenetic studies have indicated differing effects of glucose-lowering agents on incident diabetes and glycaemic control due to genetic variation.[168] Knowledge of the complex pathophysiology of T2D is also growing;[6] a more pathophysiologic approach to T2D management in order to target key pathophysiologic disturbances, such as β-cell failure, is increasingly encouraged.[169-171] As knowledge of genetics, pathophysiology and patient preferences/needs increase, treatment for T2D will have to be customised in a much more sophisticated and effective manner.

Observational research: a key player

Observational research will play an import role in the development of personalized medicine. Beyond their major strength of providing real-world data, observational studies enable analyses of large cohorts during long follow-up periods, enabling evaluation of the effects associated with differing treatments in various T2D subpopulations. The availability of high-quality register data has increased rapidly over the past decade. Along with this evolution, the emergence of new statistical and epidemiological methods has improved the reliability and effectiveness of observational analyses.[107, 108, 172, 173]

An excellent example of this trend is the development of registry RCTs, which have been conducted using the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).[172, 173] The NDR is constantly working on becoming better. The next big step is to introduce patient reported outcome measures (PROMs). The goal is a register that focuses more on patient-oriented concerns and outcomes. The availability of PROMs will enable analyses of patient perceptions, needs, preferences and concerns, all of which are important components of personalized medicine.

Early interventions to tackle the epidemic

At the time of diagnosis, T2D patients are maximally insulin-resistant and have lost about 80 % of their β-cell function.[169] This highlights the need for early interventions. Screening is an appealing way to detect T2D, possibly facilitating early interventions. However, a cluster-randomized trial in eastern England did not find any beneficial effects on mortality from population-based screening for T2D.[174] Furthermore, among screening-detected T2D patients in the UK, the Netherlands and Denmark, intensive treatment of multiple risk factors was associated with only a small, non-significant reduction in the incidence of cardiovascular events and death compared with routine care.[175] Thus, population-based screening for diabetes may not result in large benefits for mortality, at least among some populations. The benefits of screening might be greater in populations with a higher prevalence of undiagnosed diabetes and lower quality of care. As opposed to these negative results, early intervention with intensive lifestyle measures or glucose-lowering medication has been shown to prevent conversion to T2D in patients with impaired glucose tolerance.[41-43] Ongoing efforts to identify effective interventions that can be implemented early in the natural history of T2D in order to prevent progressive β-cell failure and reduce the burden of T2D are crucial to tackling the growing epidemic.

CONCLUSIONS

- Observational studies serve as important complements to RCTs by providing valuable knowledge obtained from routine clinical care and enabling analyses of large cohorts that represent the entire T2D population.

- The NDR offers a unique source of information. Both society in general and patients in particular deserve optimal use of this information with the overall aim of improving diabetes care.

- Treatment targets for HbA1c, blood pressure and lipids were insufficiently reached in all groups, regardless of the glucose-lowering treatment regimen that was used. Even a fairly large percentage of newly diagnosed patients did not reach HbA1c <7.0%. These results highlight the importance of ongoing efforts to achieve good risk factor control from the beginning.

- SU and meglitinide were associated with a substantially higher risk of switching to a new agent or adding a second agent than metformin. These results indicate better glycaemic durability with metformin than with SU and meglitinide, supporting the current recommendation of metformin as the first-line agent for T2D.

- Metformin was associated with a smaller risk of all-cause mortality and acidosis/serious infection than other glucose-lowering treatments for patients with renal impairment (eGFR 45-60), and there was no increased risk of all-cause mortality, CVD or acidosis/serious infection, even in patients with low renal function (eGFR 30-45). These results suggest that even more patients could benefit from metformin.

- There were no beneficial effects associated with aspirin for primary prevention of CVD in T2D patients. The results indicated a lack of beneficial effects regardless of whether the CVD risk was estimated to be high or low, supporting more restrictive use of aspirin for T2D patients without established CVD.

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REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, update 2013. 6th edn. http://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf (accessed October 12, 2014).
2. Lozano, R. et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**, 2095-128 (2012).
3. Kahn, S.E., Cooper, M.E. & Del Prato, S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* **383**, 1068-83 (2014).
4. Kahn, S.E. et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes* **42**, 1663-72 (1993).
5. DeFronzo, R.A. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* **37**, 667-87 (1988).
6. Defronzo, R.A. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* **58**, 773-95 (2009).
7. Wilson, P.W. et al. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. *Arch Intern Med* **167**, 1068-74 (2007).
8. Morris, A.P. et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet* **44**, 981-90 (2012).
9. Ingelsson, E. et al. Detailed physiologic characterization reveals diverse mechanisms for novel genetic Loci regulating glucose and insulin metabolism in humans. *Diabetes* **59**, 1266-75 (2010).
10. Dimas, A.S. et al. Impact of type 2 diabetes susceptibility variants on quantitative glycemic traits reveals mechanistic heterogeneity. *Diabetes* **63**, 2158-71 (2014).
11. Vassy, J.L. et al. Polygenic type 2 diabetes prediction at the limit of common variant detection. *Diabetes* **63**, 2172-82 (2014).
12. Meigs, J.B. et al. Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med* **359**, 2208-19 (2008).
13. Lyssenko, V. et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med* **359**, 2220-32 (2008).
14. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. WHO 2011.
15. World Health Organization. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/ IDF Consultation. WHO 2006

16. Koenig, R.J., Peterson, C.M., Kilo, C., Cerami, A. & Williamson, J.R. Hemoglobin AIc as an indicator of the degree of glucose intolerance in diabetes. *Diabetes* **25**, 230-2 (1976).
17. Gregg, E.W. et al. Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med* **370**, 1514-23 (2014).
18. Wilson, P.W., D'Agostino, R.B., Sullivan, L., Parise, H. & Kannel, W.B. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med* **162**, 1867-72 (2002).
19. Wingard, D.L., Barrett-Connor, E., Criqui, M.H. & Suarez, L. Clustering of heart disease risk factors in diabetic compared to nondiabetic adults. *Am J Epidemiol* **117**, 19-26 (1983).
20. Reaven, G.M. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* **37**, 1595-607 (1988).
21. Miranda, P.J., DeFronzo, R.A., Califf, R.M. & Guyton, J.R. Metabolic syndrome: evaluation of pathological and therapeutic outcomes. *Am Heart J* **149**, 20-32 (2005).
22. Miranda, P.J., DeFronzo, R.A., Califf, R.M. & Guyton, J.R. Metabolic syndrome: definition, pathophysiology, and mechanisms. *Am Heart J* **149**, 33-45 (2005).
23. Kahn, R., Buse, J., Ferrannini, E. & Stern, M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **28**, 2289-304 (2005).
24. Folsom, A.R. et al. A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes. The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* **20**, 935-42 (1997).
25. Hu, F.B. et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch Intern Med* **161**, 1717-23 (2001).
26. Huxley, R., Barzi, F. & Woodward, M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *Bmj* **332**, 73-8 (2006).
27. Lotufo, P.A. et al. Diabetes and all-cause and coronary heart disease mortality among US male physicians. *Arch Intern Med* **161**, 242-7 (2001).
28. Vilbergsson, S., Sigurdsson, G., Sigvaldason, H. & Sigfusson, N. Coronary heart disease mortality amongst non-insulin-dependent diabetic subjects in Iceland: the independent effect of diabetes. The Reykjavik Study 17-year follow up. *J Intern Med* **244**, 309-16 (1998).
29. Brownlee, M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* **54**, 1615-25 (2005).

30. Laakso, M. & Kuusisto, J. Insulin resistance and hyperglycaemia in cardiovascular disease development. *Nat Rev Endocrinol* **10**, 293-302 (2014).
31. Coutinho, M., Gerstein, H.C., Wang, Y. & Yusuf, S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* **22**, 233-40 (1999).
32. Eeg-Olofsson, K. et al. New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR). *J Intern Med* **268**, 471-82 (2010).
33. Sarwar, N. et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* **375**, 2215-22 (2010).
34. Lawlor, D.A., Harbord, R.M., Sterne, J.A., Timpson, N. & Davey Smith, G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med* **27**, 1133-63 (2008).
35. Benn, M. et al. Nonfasting glucose, ischemic heart disease, and myocardial infarction: a Mendelian randomization study. *J Am Coll Cardiol* **59**, 2356-65 (2012).
36. Rasmussen-Torvik, L.J. et al. Association of a fasting glucose genetic risk score with subclinical atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) study. *Diabetes* **60**, 331-5 (2011).
37. Bash, L.D., Selvin, E., Steffes, M., Coresh, J. & Astor, B.C. Poor glycemic control in diabetes and the risk of incident chronic kidney disease even in the absence of albuminuria and retinopathy: Atherosclerosis Risk in Communities (ARIC) Study. *Arch Intern Med* **168**, 2440-7 (2008).
38. Klein, R. Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* **18**, 258-68 (1995).
39. Stratton, I.M. et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *Bmj* **321**, 405-12 (2000).
40. Gillies, C.L. et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *Bmj* **334**, 299 (2007).
41. Knowler, W.C. et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* **346**, 393-403 (2002).
42. Knowler, W.C. et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* **374**, 1677-86 (2009).

43. Tuomilehto, J. et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* **344**, 1343-50 (2001).
44. Wing, R.R. et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* **369**, 145-54 (2013).
45. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* **329**, 977-86 (1993).
46. Nathan, D.M. et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* **353**, 2643-53 (2005).
47. Holman, R.R., Paul, S.K., Bethel, M.A., Matthews, D.R. & Neil, H.A. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**, 1577-89 (2008).
48. Patel, A. et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* **358**, 2560-72 (2008).
49. Zoungas, S. et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* **371**, 1392-406 (2014).
50. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* **352**, 837-53 (1998).
51. Turnbull, F.M. et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* **52**, 2288-98 (2009).
52. Hemmingsen, B. et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev* **11**, Cd008143 (2013).
53. Gerstein, H.C. et al. Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. *Lancet* (2014).
54. Gerstein, H.C. et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* **358**, 2545-59 (2008).
55. Duckworth, W. et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* **360**, 129-39 (2009).
56. The National Board of Health and Welfare. National Guidelines for Diabetes Care. NBHW 2010
57. Inzucchi, S.E. et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **35**, 1364-79 (2012).
58. Adler, A.I. et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes

(UKPDS 36): prospective observational study. *Bmj* **321**, 412-9 (2000).
59. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *Bmj* **317**, 703-13 (1998).
60. Hansson, L. et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* **351**, 1755-62 (1998).
61. Patel, A. et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* **370**, 829-40 (2007).
62. Cederholm, J. et al. Blood pressure and risk of cardiovascular diseases in type 2 diabetes: further findings from the Swedish National Diabetes Register (NDR-BP II). *J Hypertens* **30**, 2020-30 (2012).
63. Mihaylova, B. et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* **380**, 581-90 (2012).
64. Kearney, P.M. et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* **371**, 117-25 (2008).
65. Colhoun, H.M. et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* **364**, 685-96 (2004).
66. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Bmj* **324**, 71-86 (2002).
67. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *Bmj* **308**, 81-106 (1994).
68. Pignone, M. et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Diabetes Care* **33**, 1395-402 (2010).
69. Standards of medical care in diabetes--2014. *Diabetes Care* **37 Suppl 1**, S14-80 (2014).
70. Perk, J. et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task

Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* **33**, 1635-701 (2012).
71. Standards of medical care in diabetes--2008. *Diabetes Care* **31 Suppl 1**, S12-54 (2008).
72. Buse, J.B. et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* **30**, 162-72 (2007).
73. Swedish National Diabetes Register, Annual Report 2013. http://www.ndr.nu/pdf/Annual_Report_NDR_2013.pdf (accessed October 13, 2014).
74. Gaede, P. et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* **348**, 383-93 (2003).
75. Gaede, P., Lund-Andersen, H., Parving, H.H. & Pedersen, O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* **358**, 580-91 (2008).
76. Fonseca, V.A. Defining and characterizing the progression of type 2 diabetes. *Diabetes Care* **32 Suppl 2**, S151-6 (2009).
77. Kahn, S.E. et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* **355**, 2427-43 (2006).
78. Turner, R.C., Cull, C.A., Frighi, V. & Holman, R.R. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *Jama* **281**, 2005-12 (1999).
79. Groop, L.C., Pelkonen, R., Koskimies, S., Bottazzo, G.F. & Doniach, D. Secondary failure to treatment with oral antidiabetic agents in non-insulin-dependent diabetes. *Diabetes Care* **9**, 129-33 (1986).
80. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* **352**, 854-65 (1998).
81. Salpeter, S.R., Greyber, E., Pasternak, G.A. & Salpeter, E.E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*, Cd002967 (2010).
82. Grimes, D.A. & Schulz, K.F. An overview of clinical research: the lay of the land. *Lancet* **359**, 57-61 (2002).
83. Balshem, H. et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* **64**, 401-6 (2011).
84. Guyatt, G. et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* **64**, 383-94 (2011).

85. Grimes, D.A. & Schulz, K.F. Bias and causal associations in observational research. *Lancet* **359**, 248-52 (2002).
86. Saunders, C. et al. External validity of randomized controlled trials of glycaemic control and vascular disease: how representative are participants? *Diabet Med* **30**, 300-8 (2013).
87. Black, N. Why we need observational studies to evaluate the effectiveness of health care. *Bmj* **312**, 1215-8 (1996).
88. Ligthelm, R.J. et al. Importance of observational studies in clinical practice. *Clin Ther* **29 Spec No**, 1284-92 (2007).
89. Gudbjornsdottir, S., Cederholm, J., Nilsson, P.M. & Eliasson, B. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. *Diabetes Care* **26**, 1270-6 (2003).
90. Swedish National Diabetes Register, Annual Report 2005.
91. The National Board of Health and Welfare. Folhälsorapport 2009. http://www.socialstyrelsen.se/publikationer2009/2009-126-71/Documents/7_Overvikt.pdf (accessed October 13, 2014).
92. Ringborg, A. et al. Prevalence and incidence of Type 2 diabetes and its complications 1996-2003--estimates from a Swedish population-based study. *Diabet Med* **25**, 1178-86 (2008).
93. Jansson, S.P., Andersson, D.K. & Svardsudd, K. Prevalence and incidence rate of diabetes mellitus in a Swedish community during 30 years of follow-up. *Diabetologia* **50**, 703-10 (2007).
94. Eliasson, M., Lindahl, B., Lundberg, V. & Stegmayr, B. No increase in the prevalence of known diabetes between 1986 and 1999 in subjects 25-64 years of age in northern Sweden. *Diabet Med* **19**, 874-80 (2002).
95. Berger, B., Stenstrom, G. & Sundkvist, G. Incidence, prevalence, and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry. *Diabetes Care* **22**, 773-8 (1999).
96. Berger, B., Stenstrom, G., Chang, Y.F. & Sundkvist, G. The prevalence of diabetes in a Swedish population of 280,411 inhabitants. A report from the Skaraborg Diabetes Registry. *Diabetes Care* **21**, 546-8 (1998).
97. Ludvigsson, J.F. et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* **11**, 450 (2011).
98. Merlo, J. et al. Comparison of different procedures to identify probable cases of myocardial infarction and stroke in two Swedish prospective cohort studies using local and national routine registers. *Eur J Epidemiol* **16**, 235-43 (2000).
99. Wettermark, B. et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* **16**, 726-35 (2007).

100. Statistics Sweden. Longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym). http://www.scb.se/en_/Services/Guidance-for-researchers-and-universities/SCB-Data/Longitudinal-integration-database-for-health-insurance-and-labour-market-studies-LISA-by-Swedish-acronym/ (accessed October 13, 2014).
101. Rothman, K.J. Epidemiology - An Introduction, 2nd edition. (2012).
102. Patorno, E. et al. Observational studies of the association between glucose-lowering medications and cardiovascular outcomes: addressing methodological limitations. *Diabetologia* **57**, 2237-50 (2014).
103. Greevy, R.A., Jr. et al. Comparisons of persistence and durability among three oral antidiabetic therapies using electronic prescription-fill data: the impact of adherence requirements and stockpiling. *Clin Pharmacol Ther* **90**, 813-9 (2011).
104. Zethelius, B. et al. A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). *Diabetes Res Clin Pract* **93**, 276-84 (2011).
105. Altman, D.G. & Bland, J.M. Missing data. *Bmj* **334**, 424 (2007).
106. Bradburn, M.J., Clark, T.G., Love, S.B. & Altman, D.G. Survival analysis part II: multivariate data analysis--an introduction to concepts and methods. *Br J Cancer* **89**, 431-6 (2003).
107. D'Agostino, R.B., Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* **17**, 2265-81 (1998).
108. Lin, D.Y., Psaty, B.M. & Kronmal, R.A. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* **54**, 948-63 (1998).
109. Lee, B.K., Lessler, J. & Stuart, E.A. Improving propensity score weighting using machine learning. *Stat Med* **29**, 337-46 (2010).
110. Hampp, C., Borders-Hemphill, V., Moeny, D.G. & Wysowski, D.K. Use of antidiabetic drugs in the U.S., 2003-2012. *Diabetes Care* **37**, 1367-74 (2014).
111. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes* **44**, 1249-58 (1995).
112. Garber, A.J. et al. AACE comprehensive diabetes management algorithm 2013. *Endocr Pract* **19**, 327-36 (2013).
113. Ali, M.K. et al. Achievement of goals in U.S. diabetes care, 1999-2010. *N Engl J Med* **368**, 1613-24 (2013).
114. Selvin, E., Parrinello, C.M., Sacks, D.B. & Coresh, J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. *Ann Intern Med* **160**, 517-25 (2014).
115. Stark Casagrande, S., Fradkin, J.E., Saydah, S.H., Rust, K.F. & Cowie, C.C. The prevalence of meeting A1C, blood pressure, and

LDL goals among people with diabetes, 1988-2010. *Diabetes Care* **36**, 2271-9 (2013).
116. Raebel, M.A. et al. Initial antihyperglycemic drug therapy among 241 327 adults with newly identified diabetes from 2005 through 2010: a surveillance, prevention, and management of diabetes mellitus (SUPREME-DM) study. *Ann Pharmacother* **47**, 1280-91 (2013).
117. Zhang, Q. et al. Time to treatment initiation with oral antihyperglycaemic therapy in US patients with newly diagnosed type 2 diabetes. *Diabetes Obes Metab* **14**, 149-54 (2012).
118. Kahn, S.E. et al. Effects of rosiglitazone, glyburide, and metformin on beta-cell function and insulin sensitivity in ADOPT. *Diabetes* **60**, 1552-60 (2011).
119. Eurich, D.T., Simpson, S.H., Majumdar, S.R. & Johnson, J.A. Secondary failure rates associated with metformin and sulfonylurea therapy for type 2 diabetes mellitus. *Pharmacotherapy* **25**, 810-6 (2005).
120. de Mello, V.D. et al. Insulin secretion and its determinants in the progression of impaired glucose tolerance to type 2 diabetes in impaired glucose-tolerant individuals: the Finnish Diabetes Prevention Study. *Diabetes Care* **35**, 211-7 (2012).
121. Defronzo, R.A. et al. Prediction of diabetes based on baseline metabolic characteristics in individuals at high risk. *Diabetes Care* **36**, 3607-12 (2013).
122. Kooy, A. et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med* **169**, 616-25 (2009).
123. Aas, A.M., Ohrvik, J., Malmberg, K., Ryden, L. & Birkeland, K.I. Insulin-induced weight gain and cardiovascular events in patients with type 2 diabetes. A report from the DIGAMI 2 study. *Diabetes Obes Metab* **11**, 323-9 (2009).
124. Mellbin, L.G., Malmberg, K., Norhammar, A., Wedel, H. & Ryden, L. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur Heart J* **29**, 166-76 (2008).
125. Mellbin, L.G., Malmberg, K., Norhammar, A., Wedel, H. & Ryden, L. Prognostic implications of glucose-lowering treatment in patients with acute myocardial infarction and diabetes: experiences from an extended follow-up of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study. *Diabetologia* **54**, 1308-17 (2011).
126. Currie, C.J., Poole, C.D., Evans, M., Peters, J.R. & Morgan, C.L. Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. *J Clin Endocrinol Metab* **98**, 668-77 (2013).

127. Margolis, D.J., Hoffstad, O. & Strom, B.L. Association between serious ischemic cardiac outcomes and medications used to treat diabetes. *Pharmacoepidemiol Drug Saf* **17**, 753-9 (2008).
128. Roussel, R. et al. Metformin use and mortality among patients with diabetes and atherothrombosis. *Arch Intern Med* **170**, 1892-9 (2010).
129. Tzoulaki, I. et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *Bmj* **339**, b4731 (2009).
130. Schramm, T.K. et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. *Eur Heart J* **32**, 1900-8 (2011).
131. Roumie, C.L. et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann Intern Med* **157**, 601-10 (2012).
132. Pantalone, K.M. et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. *Diabetes Obes Metab* **14**, 803-9 (2012).
133. Morgan, C.L., Mukherjee, J., Jenkins-Jones, S., Holden, S.E. & Currie, C.J. Association between first-line monotherapy with sulphonylurea versus metformin and risk of all-cause mortality and cardiovascular events: a retrospective, observational study. *Diabetes Obes Metab* **16**, 957-62 (2014).
134. Li, Y., Hu, Y., Ley, S.H., Rajpathak, S. & Hu, F.B. Sulfonylurea Use and Incident Cardiovascular Disease Among Patients With Type 2 Diabetes: Prospective Cohort Study Among Women. *Diabetes Care* (2014).
135. Zhang, P., Li, H., Tan, X., Chen, L. & Wang, S. Association of metformin use with cancer incidence and mortality: a meta-analysis. *Cancer Epidemiol* **37**, 207-18 (2013).
136. Yin, M. et al. Metformin improves cardiac function in a nondiabetic rat model of post-MI heart failure. *Am J Physiol Heart Circ Physiol* **301**, H459-68 (2011).
137. Cittadini, A. et al. Metformin prevents the development of chronic heart failure in the SHHF rat model. *Diabetes* **61**, 944-53 (2012).
138. Gamble, J.M., Simpson, S.H., Eurich, D.T., Majumdar, S.R. & Johnson, J.A. Insulin use and increased risk of mortality in type 2 diabetes: a cohort study. *Diabetes Obes Metab* **12**, 47-53 (2010).
139. Currie, C.J. et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. *Lancet* **375**, 481-9 (2010).

140. Colayco, D.C., Niu, F., McCombs, J.S. & Cheetham, T.C. A1C and cardiovascular outcomes in type 2 diabetes: a nested case-control study. *Diabetes Care* **34**, 77-83 (2011).
141. Roumie, C.L. et al. Association between intensification of metformin treatment with insulin vs sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes. *Jama* **311**, 2288-96 (2014).
142. Currie, C.J. & Johnson, J.A. The safety profile of exogenous insulin in people with type 2 diabetes: justification for concern. *Diabetes Obes Metab* **14**, 1-4 (2012).
143. Gerstein, H.C. et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* **367**, 319-28 (2012).
144. Richy, F.F., Sabido-Espin, M., Guedes, S., Corvino, F.A. & Gottwald-Hostalek, U. Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: a retrospective cohort study. *Diabetes Care* **37**, 2291-5 (2014).
145. Eppenga, W.L. et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care* **37**, 2218-24 (2014).
146. Kajbaf, F. & Lalau, J.D. The prognostic value of blood pH and lactate and metformin concentrations in severe metformin-associated lactic acidosis. *BMC Pharmacol Toxicol* **14**, 22 (2013).
147. Lalau, J.D. & Race, J.M. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf* **20**, 377-84 (1999).
148. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. *Jama* **268**, 1292-300 (1992).
149. Belch, J. et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *Bmj* **337**, a1840 (2008).
150. Ogawa, H. et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *Jama* **300**, 2134-41 (2008).
151. Baigent, C. et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* **373**, 1849-60 (2009).
152. De Berardis, G. et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *Bmj* **339**, b4531 (2009).
153. Welin, L., Wilhelmsen, L., Bjornberg, A. & Oden, A. Aspirin increases mortality in diabetic patients without cardiovascular

disease: a Swedish record linkage study. *Pharmacoepidemiol Drug Saf* **18**, 1143-9 (2009).
154. Sasso, F.C. et al. Lack of effect of aspirin in primary CV prevention in type 2 diabetic patients with nephropathy: results from 8 years follow-up of NID-2 study. *Acta Diabetol* (2014).
155. De Berardis, G. et al. Association of aspirin use with major bleeding in patients with and without diabetes. *Jama* **307**, 2286-94 (2012).
156. Hannan, E.L. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. *JACC Cardiovasc Interv* **1**, 211-7 (2008).
157. Benson, K. & Hartz, A.J. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* **342**, 1878-86 (2000).
158. Concato, J., Shah, N. & Horwitz, R.I. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* **342**, 1887-92 (2000).
159. Atkins, D. et al. Grading quality of evidence and strength of recommendations. *Bmj* **328**, 1490 (2004).
160. Sterne, J.A. et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj* **338**, b2393 (2009).
161. Suissa, S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* **167**, 492-9 (2008).
162. Lalau, J.D., Arnouts, P., Sharif, A. & De Broe, M.E. Metformin and other antidiabetic agents in renal failure patients. *Kidney Int* (2014).
163. Cleland, J.G. Is aspirin useful in primary prevention? *Eur Heart J* **34**, 3412-8 (2013).
164. De Berardis, G. et al. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. *Trials* **8**, 21 (2007).
165. Nathan, D.M. et al. Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). *Diabetes Care* **36**, 2254-61 (2013).
166. Cefalu, W.T. et al. Beyond metformin: safety considerations in the decision-making process for selecting a second medication for type 2 diabetes management: reflections from a diabetes care editors' expert forum. *Diabetes Care* **37**, 2647-59 (2014).
167. Raz, I. et al. Personalized management of hyperglycemia in type 2 diabetes: reflections from a Diabetes Care Editors' Expert Forum. *Diabetes Care* **36**, 1779-88 (2013).
168. Maruthur, N.M. et al. The pharmacogenetics of type 2 diabetes: a systematic review. *Diabetes Care* **37**, 876-86 (2014).

169. DeFronzo, R.A., Eldor, R. & Abdul-Ghani, M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. *Diabetes Care* **36 Suppl 2**, S127-38 (2013).
170. Del Prato, S., Penno, G. & Miccoli, R. Changing the treatment paradigm for type 2 diabetes. *Diabetes Care* **32 Suppl 2**, S217-22 (2009).
171. Vetere, A., Choudhary, A., Burns, S.M. & Wagner, B.K. Targeting the pancreatic beta-cell to treat diabetes. *Nat Rev Drug Discov* **13**, 278-89 (2014).
172. Frobert, O. et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* **369**, 1587-97 (2013).
173. Lagerqvist, B. et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med* **371**, 1111-20 (2014).
174. Simmons, R.K. et al. Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial. *Lancet* **380**, 1741-8 (2012).
175. Griffin, S.J. et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. *Lancet* **378**, 156-67 (2011).