

**Evidence Based Diabetology –
Strategies to Prevent Macrovascular Disease and to Reduce Mortality**

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

Sabin Liliane Allemann

aus Welschenrohr (SO)

Basel, 2006

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät
auf Antrag von

Prof. Dr. Stephan Krähenbühl

Prof. Dr. Peter Diem

Prof. Dr. Matthias Egger

PD Dr. Christoph Meier

Basel, den 19. September 2006

Prof. Dr. Hans-Peter Hauri
Dekan

Table of contents

Table of contents	3
Summary	6
1. General Introduction	10
1.1 Clinical characteristics of diabetes mellitus and its role in the health care system	10
1.1.1 Classification of diabetes mellitus.....	10
1.1.2 Diagnosis of diabetes mellitus	11
1.1.3 Metabolic syndrome and the risk for type 2 DM	13
1.1.4 Diabetes control and the role of glycated haemoglobin (HbA _{1c})	13
1.1.5 Epidemiological data on diabetes mellitus.....	14
1.1.6 Impact of diabetes mellitus on health care costs	15
1.1.7 Prevention of diabetes mellitus.....	16
1.2 Late complications of diabetes mellitus	19
1.2.1 Microvascular complications.....	19
1.2.2 Macrovascular complications	20
1.2.3 The excess risk for macrovascular disease in patients with compared to patients without diabetes mellitus	21
1.3 Methods relevant to thesis	23
1.3.1 Systematic review and meta-analysis.....	23
1.3.1.1 Statistical methods used in meta-analysis	27
1.3.2 Survival analysis.....	30
1.3.2.1 Kaplan-Meier survival estimate	31
1.3.2.2 Nonparametric test comparing survival	32
1.3.2.3 Survival analysis adjusting for covariates.....	32

1.4 Aim of the thesis	34
1.4.1 Brief summary of studies	35
1.4.1.1 Study A: Glycaemic control and macrovascular disease in type 1 and type 2 diabetes mellitus: Meta-analysis of randomised controlled trials	35
1.4.1.2 Study B: Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: Meta-analysis of randomised trials.....	35
1.4.1.3 Study C: Efficacy of drug eluting stents in patients with and without diabetes mellitus: indirect comparison of controlled trials	36
1.4.1.4 Study D: QTc interval and resting heart rate as long-term predictors of mortality in type 1 and type 2 diabetes mellitus: a 23-year follow up.....	36
1.4.1.5 Study E: Apolipoprotein B as a long term predictor of mortality in type 1 diabetes mellitus: a 15-year follow up.....	37
2. Systematic reviews and meta-analyses on the effectiveness of specific treatment forms on macrovascular complications	38
2.1 Study A: Glycaemic control and macrovascular disease in type 1 and type 2 diabetes mellitus: Meta-analysis of randomised controlled trials	39
2.2 Study B: Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: Meta-analysis of randomised trials.....	52
2.3 Study C: Efficacy of drug eluting stents in patients with and without diabetes mellitus: indirect comparison of controlled trials.....	60
3. Survival analyses investigating the prognostic value of novel risk indicators	69
3.1 Study D: QTc interval and resting heart rate as long term predictors of mortality in type 1 and type 2 diabetes mellitus: a 23-year follow up	70
3.2 Study E: Apolipoprotein B as a long term predictor of mortality in type 1 diabetes mellitus: a 15-year follow up.....	80

4. General discussion & conclusions.....	.90
4.1 Comparison of patients with and without diabetes mellitus92
4.2 Within the patients with diabetes mellitus – comparison of type 1 and type 2.....	.92
4.3 Strengths and limitations of the thesis93
4.4 Conclusions.....	.94
5. References to general introduction & discussion.....	.95
6. Acknowledgements	108
7. Curriculum vitae.....	110

Summary

Diabetes mellitus (DM) is the most common metabolic disease worldwide and the number of newly diagnosed cases is increasing. DM is strongly associated with a number of devastating chronic late complications, including retinopathy, nephropathy and neuropathy (microvascular complications), as well as cardiac, cerebrovascular and peripheral vascular disease (macrovascular complications). Despite lots of progress in therapeutic possibilities during the last decades, mortality risk due to macrovascular complications is still increased in patients with DM when compared to non diabetic individuals. It has also been suggested that specific risk factors influence macrovascular risk differentially in persons with and without DM. In addition, there is still uncertainty whether the effectiveness of certain treatment forms differs between patients with and without DM, and in the patients with DM, between type 1 and type 2. The focus of my thesis was on prevention and therapy of macrovascular disease in patients with type 1 and type 2 DM, as well as on comparisons with patients without DM. Three studies (**Studies A-C**) investigated the effectiveness of specific treatment forms on macrovascular disease by means of systematic reviews and meta-analyses, whereas two studies (**Studies D and E**) evaluated novel risk indicators using survival analysis based on data from the 'Swiss Cohort of the World Health Organisation (WHO) Multinational Study of Vascular Disease in Diabetes'.

The aim of **Study A** (*published in Am Heart J 2006 Jul;152(1):27-38*) was to assess the effect of improved glycaemic control on cardiac, cerebrovascular and peripheral vascular complications in type 1 and type 2 DM. Outcomes included the incidence rate ratios (IRRs) for any macrovascular event, cardiac events, stroke, and peripheral arterial disease. Results showed a 62% (95% Confidence Interval (CI) 44-74%) and 19% (95% CI 9-27%) reduction in macrovascular risk for improved glycaemic control in type 1 and type 2 DM, respectively. In type 1 DM the effect was mainly based on a reduction of cardiac and peripheral vascular events. In type 2 DM it was due to reductions in stroke and peripheral vascular events. The effects appeared to be particularly important in younger patients with shorter duration of DM.

Study B (*published in Curr Med Res Opin 2006 Mar;22(3):617-23*) examined the effectiveness of fibrates (peroxisome proliferator activated receptor α -agonists) in the

prevention of coronary heart disease in type 2 DM. The primary outcome of this meta-analysis was the IRR for coronary heart disease (CHD) events (a combination of non fatal myocardial infarction and death due to CHD). Secondary endpoints were death due to CHD, fatal and non fatal myocardial infarction, and fatal and non fatal stroke. The results of **Study B** showed a 16% risk reduction for CHD events (95% CI 4-26%) in patients with type 2 DM when treated with fibrates compared to placebo. For the secondary endpoints a tendency towards reduction in risk was found, although this did not reach conventional levels of statistical significance.

Coronary stenting is established as a treatment of coronary heart disease. The aim of **Study C** (*published in Heart 2006 May;92(5):650-7*) was to indirectly compare the effects of polymer based sirolimus versus paclitaxel eluting coronary stents and to examine whether they are equally effective in the prevention of restenosis in patients with and without DM. The indirect comparisons were performed by calculating the ratio of incidence rate ratios (RIRR) of studies comparing sirolimus eluting stents versus conventional bare metal stents and studies comparing paclitaxel eluting versus bare metal stents. The overall study population and patients with and without DM were analysed separately. Outcomes included in-stent- and in-segment restenosis, target lesion revascularisation, and major adverse cardiac events. The results of this study showed that rates of revascularisation procedures are reduced by sirolimus as well as paclitaxel eluting stents when compared to bare metal stents independent of the study population. However, in persons without DM a superiority of the sirolimus eluting stent to the paclitaxel eluting stent was found for all endpoints under investigation. In contrast, for persons with DM no statistically significant differences between the two drug eluting stents were found. A meta-regression analysis confirmed a difference between individuals with and without DM.

Study D (*published in Diabetologia 2006, DOI 10.1007/s00125-006-0483-1*) evaluated the long-term association of two parameters with mortality, namely QT interval and resting heart rate (rHR) in patients with type 1 and type 2 DM. Based on the 23-year follow up of the 'Swiss Cohort of the WHO Multinational Study of Vascular Disease in Diabetes', the prognostic values of these two risk factors were examined on all-cause, cardiovascular and cardiac mortality and mortality due to ischaemic heart disease using a Cox proportional hazards model. Results showed an association of prolonged QT interval (corrected for heart rate, QTc) with an increased

mortality risk due to all causes, as well as cardiovascular and cardiac disease in type 1 DM, whereas no association was found for rHR. In contrast, in patients with type 2 DM elevated rHR but not QT_c was associated with an increased risk of all-cause mortality as well as death due to cardiovascular, cardiac and ischaemic heart disease.

Study E (*published in J Intern Med 2006 Sep;260(3):272-80*) was based on an 15-year follow up of the 'Swiss Cohort of the WHO Multinational Study of Vascular Disease in Diabetes'. This study evaluated the long-term association of apolipoprotein B (apo B) with mortality risk in patients with type 1 DM. Compared to Study D, follow up was shorter due to the fact that apo B was only measured later in the course of the study. Analyses were performed for all-cause and cardiac mortality and mortality due to ischaemic heart disease, using a parametric proportional hazards model based on the Weibull distribution. Apo B was found to be positively related to all-cause and cardiac mortality, and mortality due to ischaemic heart disease. An apo B ≥ 0.96 g/L translated into a doubling of overall mortality, and a sevenfold increase of mortality due to cardiac disease or ischaemic heart disease.

In conclusion, this thesis showed that:

- The incidence of macrovascular events is reduced by improved glycaemic control, both in type 1 and type 2 DM. Although effects on specific manifestations of macrovascular disease are different between the two types of DM, in absolute terms benefits are comparable.
- CHD events are substantially reduced in patients with type 2 DM when treated with fibrates. Nevertheless, their exact role in lipid lowering treatment needs to be investigated further.
- Compared to bare metal stents, sirolimus as well as paclitaxel eluting stents are effective in reducing the rates of revascularisation procedures. Based on indirect evidence, stents eluting sirolimus appear to be superior to paclitaxel eluting stents in patients without DM but not in patients with DM.

- Prolongation of QTc is related to an increased mortality risk in patients with type 1 DM, whereas elevated rHR is associated with higher mortality risk in patients with type 2 DM.
- Increased apo B levels are consistently associated with mortality risk in type 1 DM.

In addition to these conclusions, two general statements can be made:

- The effectiveness of therapeutic interventions may be different in persons with compared to persons without DM.
- Within the group of patients with DM, the effectiveness of specific interventions may vary between type 1 and type 2 DM.

1. General introduction

1.1 Clinical characteristics of diabetes mellitus and its role in the health care system

Diabetes Mellitus (DM) is characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Symptoms of marked hyperglycaemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycaemia. The four most common acute, life-threatening consequences of uncontrolled DM are hyperglycaemia with ketoacidosis, the nonketotic hyperosmolar syndrome as well as profound hypoglycaemia and lactate acidosis [1]. Characteristic chronic late complications of DM include retinopathy, nephropathy and neuropathy (microvascular complications) as well as cardiac, cerebrovascular and peripheral vascular disease (macrovascular complications).

1.1.1 *Classification of diabetes mellitus*

The aetiology and pathophysiology leading to metabolic defects and consequently to hyperglycaemia are markedly different among patients with DM. Consequently, different prevention strategies, diagnostic screening methods and treatments are needed. In June 1997, an international expert committee released a report with recommendations for the classification and diagnosis of DM [2]. These recommendations were the result of a collaboration over more than two years among experts from the American Diabetes Association (ADA) and the World Health Organisation (WHO). Based on this classification system, four major forms of DM are identified: type 1, type 2, other specific types, and gestational diabetes. Characteristically, in type 1 DM the pancreas is damaged by beta-cell destruction, usually leading to absolute insulin deficiency [3]. In contrast, in type 2 DM – the most common form – characteristics range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with or without insulin resistance [3]. An overview of all types of DM is given in [Table 1](#).

Table 1. Classification and characteristics of DM [3]

Type of Diabetes mellitus	Characteristics
I. Type 1	Destruction of β -cells (autoimmune or idiopathic), usually leading to absolute insulin deficiency
II. Type 2	Range of predominant insulin resistance with relative insulin deficiency to a predominantly secretory defect
III. Other specific types	<ul style="list-style-type: none"> A. Genetic defects of β-cell function B. Genetic defects of insulin action C. Diseases of the exocrine pancreas D. Endocrinopathies E. Destruction of pancreas by drugs or chemicals F. Infections G. Rare forms of immune-linked diabetes (e.g. Stiff-Person-Syndrome) H. Other syndromes, occasionally associated with diabetes (e.g. Down-Syndrome, Klinefelter-Syndrome, Turner-Syndrome, etc)
IV. Gestational diabetes	Operational classification identifying women who develop DM during gestation

1.1.2 *Diagnosis of diabetes mellitus*

The diagnosis of DM is based on guidelines constantly adapted by the WHO (World Health Organisation), the ADA (American Diabetes Association) and the IDF (International Diabetes Federation). To date, diagnosis of DM includes the following criteria [2]:

Table 2. Criteria for diagnosis of DM

1) Symptoms of DM plus casual plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of DM include polyuria, polydipsia, and unexplained weight loss.

or

2) Fasting Plasma Glucose > 126 mg/dl (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.

or

3) 2-h postload glucose ≥ 200 mg/dl (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT). The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycaemia, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

Based on these guidelines, there is an intermediate group with glucose levels not meeting criteria for DM, but too high to be considered normal. This group is defined as having fasting plasma glucose (FPG) levels ≥ 100 mg/dl (5.6 mmol/l) but ≤ 126 mg/dl (7.0 mmol/l) or 2-h values in the oral glucose tolerance test (OGTT) of ≥ 140 mg/dl (7.8 mmol/l) but ≤ 200 mg/dl (11.1 mmol/l). Thus, values for FPG or 2-h postload glucose, respectively, are considered as given in [Table 3](#):

Table 3. Criteria for fasting plasma glucose (FPG) or 2-h postload glucose, respectively

Fasting plasma glucose

FPG < 100 mg/dl (5.6 mmol/l)	Normal fasting glucose
FPG 100-125 mg/dl (5.6-6.9 mmol/l)	IFG (impaired fasting glucose)
FPG > 126 mg/dl (7.0 mmol/l)	Provisional diagnosis of DM (the diagnosis must be confirmed)

2-h postload glucose

2-h postload glucose < 140 mg/dl (7.8 mmol/l) in OGTT	Normal glucose tolerance
2-h postload glucose 140-199 mg/dl (7.8-11.1 mmol/l) in OGTT	IGT (impaired glucose tolerance)
2-h postload glucose ≥ 200 mg/dl (11.1 mmol/l) in OGTT	Provisional diagnosis of DM (the diagnosis must be confirmed)

Persons with IFG and IGT are at higher risk to develop DM compared to those with normal glucose values [4, 5]. In addition recent data suggest that individuals with IGT or IFG are predisposed to cardiovascular disease [6, 7]. Still, it is debated whether IFG and IGT are independent risk factors because they commonly coexist with other cardiovascular risk factors, as obesity (especially abdominal or visceral obesity), dyslipidaemia and hypertension, or, in general, with the metabolic syndrome [4, 5, 8].

1.1.3 Metabolic syndrome and the risk for type 2 DM

The metabolic syndrome is an important risk factor for cardiovascular disease and the development of type 2 DM [9]. Building on earlier definitions put forward by the World Health Organisation (WHO) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [10], a new definition for the metabolic syndrome has been proposed in 2005 by the International Diabetes Foundation [11]. Its specifications are easy to use in clinical practice and avoid the need for measurements that may only be available in research settings. The definition of the metabolic syndrome according to the IDF is given in [Table 4](#).

Table 4. Definition of the metabolic syndrome (based on IDF 2005) [11]

Abdominal obesity	Waist circumference for men ≥ 94 cm* Waist circumference for women ≥ 80 cm*
<i>in addition to 2 of the following risk factors</i>	
Hypertension	Systolic blood pressure ≥ 130 mm Hg or Diastolic blood pressure ≥ 85 mm Hg
Triglycerides	≥ 1.7 mmol/L
HDL-Cholesterol	Men < 1.03 mmol/L Women < 1.29 mmol/L
Fasting Plasma Glucose	≥ 5.6 mmol/L or diagnosis of DM

*values dependent on ethnicity, given data refer to Europeans

Due to the combination of several risk factors the metabolic syndrome is related to a high cardiovascular risk. Recent studies showed that cardiovascular risk was about doubled in persons with the metabolic syndrome compared to persons without risk factors [9, 12]. The causes of the metabolic syndrome are complex and have only been partially elucidated. Most individuals are obese and have some degree of insulin resistance. There is debate regarding whether obesity or insulin resistance is the pathogenetically relevant cause of the syndrome or a by-product of a more far-reaching metabolic derangement [13].

1.1.4 Diabetes control and the role of glycated haemoglobin (HbA_{1c})

The glycation of haemoglobin, estimated as HbA_{1c}, is increasingly described as the 'gold standard' to judge the effectiveness of glycaemic control and to set targets in clinical practice [14, 15]. Glycation describes the post-translational, non-enzymatic covalent chemical linkage of glucose onto proteins through amino groups (either N-terminal amino acids or ϵ -amino groups on lysine residues) [16]. Haemoglobin is predominantly glycosylated by attaching glucose to the N-terminal valine of the β -chain.

The extent of glycation is expressed as a percentage of total haemoglobin A, the predominant haemoglobin form after birth. Glycation of proteins is found in tissues exposed to glucose and is increased at higher levels of glucose [16]. Little is known about the chemistry of deglycation, a process also regulating the degree of glycation of proteins [16]. A recently identified enzymatic mechanism in erythrocytes involving fructosamine 3-kinase has been suggested to be responsible for deglycation and for the genetic variability in HbA_{1c} levels between individuals [17, 18]. At the time of measurement, the fraction of glycated haemoglobin depends on the average age of the erythrocytes; the older the cells the higher the percentage of HbA_{1c} [19, 20]. Therefore, it has been suggested that HbA_{1c} reflects the prevailing glycaemia over the previous six to eight weeks [21]. Values of a non diabetic population are generally between four to six percent [21]. Of note, it has been stated that there is a shortened red-cell life span in patients with compared to patients without DM [16]. In addition, HbA_{1c} values may differ markedly dependent on the applied assay or even the performing laboratory [16, 21]. When interpreting HbA_{1c} values, it is therefore important to be aware of the corresponding reference interval, potential assay interferences (e.g. haemoglobinopathies) and assay performances [21]. Microvascular complications have been clearly shown to increase with higher levels of HbA_{1c}, especially above seven percent [22-24], which has been established as a target level in the therapy of DM [21]. In contrast, the influence of glycaemia on macrovascular complications is still debated. A meta-analysis on observational studies found an association of higher levels of HbA_{1c} with the risk for cardiovascular disease [25]. In the context of glycaemic control within the clinical management of DM, postprandial hyperglycaemia has been shown to be more strongly related to macrovascular complications [26-28], thereby possibly reflecting a part of hyperglycaemia not detectable by HbA_{1c}. More research is needed in this context.

1.1.5 Epidemiological data on diabetes mellitus

It is suggested that about 194 million people in a wide range of ethnic groups have DM worldwide [29]. The European Region with 48 million and the Western Pacific Region with 43 million currently have the highest number of people with DM. However, the prevalence rate of 3.1% for the Western Pacific Region is lower than the 7.9% in the North American Region and 7.8% in the European Region [29].

Type 2 DM constitutes about 85-95% of the number of persons affected with DM in developed countries and accounts for an even higher percentage in developing countries [29]. Since human environment, behaviours and way-of-life have changed substantially over the last fifty years, rates of obesity and type 2 DM escalated globally. Therefore, the number of people with DM is expected to rise to almost 366 million by the year 2030 [30]. The combination of obesity and DM is recognised as one of the major threats in the 21st century and continues to affect ever-increasing numbers of people around the world. Moreover, not only the prevalence is increasing, also the age of onset of type 2 DM is falling: more and more type 2 DM is being reported in children and adolescents in many countries [29].

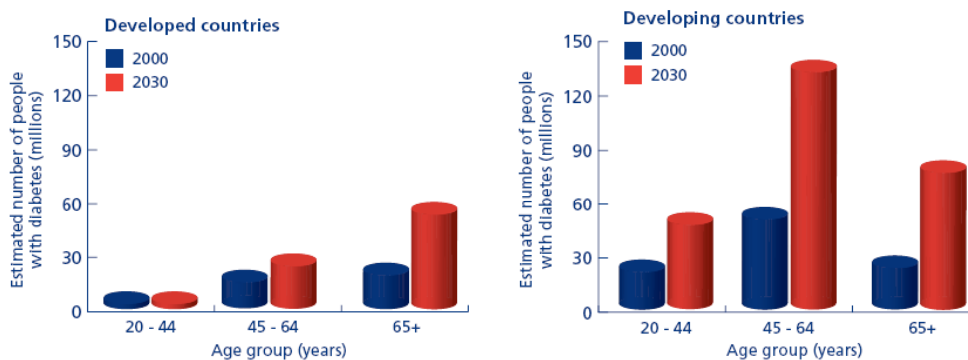


Figure 1. Number of adults with DM worldwide in 2000, and estimated number in 2030 (adapted from World Health Organisation, <http://www.who.int/diabetes/actionnow/en/diabprev.pdf>, accessed June 2006)

In contrast to type 2 DM, it is estimated that approximately 4.9 million people have type 1 DM, amounting to 0.09% of the world's population [29]. Europe has the highest estimated number of people with type 1 DM (1.27 million), followed by North America (1.04 million) and South East Asia (0.91 million) [29].

1.1.6 Impact of diabetes mellitus on health care costs

The annual direct healthcare costs of DM worldwide, for people in the 20-79 age bracket, is estimated to be at least 153 billion international dollars (hypothetical standardised unit of currency with the same purchasing power as the US dollar in the United States at a given point in time, allowing for comparisons between different countries over time) and may be as much as 286 billion, or even more. The economic

impact of DM is, therefore, considerable. If predictions of DM prevalence are fulfilled, total direct healthcare expenditure on DM will rise to about 213-396 billion international dollars in 2025, accounting for 7-13% or even more of the world's healthcare budget being spent in 2025 in high prevalence countries [29].

The costs affect health services, national productivity as well as individuals and families. Hospital in-patient costs for the treatment of complications are the largest single contributor to direct healthcare costs [29]. The total health care costs of a person with DM in the USA are between twice and three times those for people without the condition [31]. In Switzerland, direct costs have been estimated at around CHF 2,380 per year for a person with type 2 DM. If late complications are present, the amount is considerably higher [32, 33].

1.1.7 Prevention of diabetes mellitus

Regarding the health and economic burden of diabetes it is of great interest to delay or prevent the onset of the disease. To date, despite intensive efforts in research no successful methods have been documented to prevent type 1 DM. Though the availability of reliable and convenient screening tools (antibodies) allow to estimate the risk for development of type 1 DM, several studies failed to demonstrate an effective intervention regarding the prevention of type 1 DM. For example, the large Diabetes Prevention Trial-Type 1 (DPT-1) [34] or the European Nicotinamide Diabetes Intervention Trial (ENDIT) [35], investigating early administration of insulin or nicotinamide in high risk patients (i.e. first-degree relatives of a patient with type 1 DM), were unable to reproduce the promising results from animal research or small studies in humans.

For type 2 DM, where insulin resistance plays a fundamental role, the risk increases with age, obesity and lack of physical activity [36]. Several studies investigated the effect of either lifestyle or pharmacologic interventions on the onset of the disease in high risk patients (i.e. pre-existing IGT or IFG or increased body mass index). Lifestyle interventions in randomised controlled trials consisting of exercise and/or diet showed that the incidence of type 2 DM might be reduced by up to 58% [37, 38]. A meta-analysis investigating the effect of lifestyle education to prevent type 2 DM in high-risk individuals confirmed that lifestyle intervention is a useful tool in reducing the incidence of type 2 DM as well as lowering 2-h postload glucose levels [39].

Evaluations based on drug interventions were based on oral hypoglycaemic agents and a variety of other substances, as for example orlistat, verapamil, statins or estrogens [40]. Not all studies were able to report a meaningful reduction in risk for development of type 2 DM, but the different study designs make a solid comparability of all studies different (randomised controlled trials vs. post hoc analyses, different definitions of DM, etc.) [40]. However, the risk to develop type 2 DM was found to be significantly reduced in most of the prospective randomised trials as for example by 25% in the STOP-Noninsulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial [26, 27] using acarbose, by 31% in the Diabetes Prevention Program (DPP) [41,42] comparing metformin to placebo, and by 37% in the XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study [43], using orlistat. A short overview on randomised controlled trials investigating effects on the incidence of type 2 DM is given in [Table 5](#). Based on the findings of the large prevention studies, the American Diabetes Association (ADA) and the National Institute of Diabetes and Digestive and Kidney Diseases concluded that there is substantial evidence that type 2 DM can be prevented or at least delayed [44]. However, whether interventions will be cost-effective with respect to morbidity and mortality, is still an open question [45]. Due to the greatest reduction in the incidence of type 2 DM in high-risk patients in trials on lifestyle modification, the emphasis should be on these interventions in future prevention policies.

Table 5. Randomised controlled trials (RCTs) on the incidence of type 2 DM

Study	Intervention	Control	Inclusion criteria	Randomised patients	Follow-up [years]	Results
RCTs with lifestyle intervention						
DPP [46]	Diet + Exercise & Metformin§	Placebo	M & F, IFG, BMI \geq 24kg/m ² (Asian \geq 22), age \geq 25 years	3234	2.8	RR Diet + Exercise vs Placebo: 0.42 (95%CI 0.36-0.52) RR Metformin vs Placebo: 0.69 (95% CI 0.57-0.83)
Pan et al. [47]	Diet, Exercise, Diet + Exercise§	Conventional routine advice	M & F, IGT, age >25 years	577	6.0	RR Diet vs Control: 0.69 (p=0.028) RR Exercise vs Control: 0.54 (p<0.0005) RR Diet + Exercise vs Control: 0.58 (p=0.001)
Tuomilehto et al. [38]	Diet + Exercise	Conventional routine advice	M & F, IGT, BMI>25kg/m ² , age 40-64 years	522	3.2	HR: 0.4 (95% CI 0.3-0.7)
Wein et al. [48]	Diet + Exercise	Conventional routine advice	F with gestational DM, IGT	200	4.3	RR: 0.83 (95% CI 0.47-1.48)
RCTs with drug intervention						
BIGPRO [49]	Metformin	Placebo	M & F, high waist-to-hip ratio (men \geq 0.90, females \geq 0.80), age 35-65 years	457	1.0	Only 5 cases of DM in the placebo group [†]
Jarrett et al. [50]	Phenformin§	Placebo	M, IGT, age \geq 40 years	204	5.0	RR 0.90 (0.45-1.80) [†]
Li et al. [51]	Metformin	Placebo	M & F, IGT, age 30-60 years	70	1.0	RR 0.51 (0.14-1.9) [†]
STOP-NIDDM [26, 27]	Acarbose	Placebo	M & F, IGT & FPG 5.6-7.7 mmol/L, BMI 25-40kg/m ² , age 40-70 years	1429	3.3	RR 0.75 (0.63-0.90)
TRIPOD [52]	Troglitazone	Placebo	Hispanic women with gestational DM, age \geq 18 years	266	2.5	RR 0.45 (0.25-0.83)
XENDOS [43]	Orlistat + Lifestyle	Placebo	M & F, BMI \geq 30 kg/m ² , age 30-60 years	3305	4.0	HR 0.63 (0.46-0.86)

M, Males; F, Females; RR, Risk Ratio; HR, Hazard Ratio; IGT, Impaired glucose tolerance; IFG, Impaired fasting glucose; BMI, Body mass index; DPP, Diabetes Prevention Program; BIGPRO, BIGuanides and Prevention Risks in Obesity Study; STOP-NIDDM, STOP-Noninsulin-Dependent Diabetes Mellitus Trial; TRIPOD, Troglitazone In the Prevention Of Diabetes Study; XENDOS, XENical in the Prevention of Diabetes in Obese Subjects Study; § Study consisted of different intervention arms; †, data based on Padwal et al. [40] Note: For the RCTs with drug intervention only double-blind trials were included in this table where data on the incidence of type 2 DM was available from the publication and the control arm consisted of a placebo comparison

1.2. Late complications of diabetes mellitus

As stated above, all types of DM share similar chronic late complications. The high incidence and prevalence of these complications substantially increase morbidity and mortality associated with the disease, contributing to the high total health care costs, and reducing quality of life of individuals affected. Differences are made between micro- and macrovascular complications although they clinically often interact and relate to each other.

1.2.1 Microvascular complications

Microvascular complications include effects on small vessels, including arterioles, capillaries and venules. The development of these complications starts early in the pathogenesis of DM and accounts for morbidity in the form of retinopathy, nephropathy and neuropathy. There is clear evidence from several interventional studies that the progression of microvascular disease depends mainly on the quality of glycaemic control and the duration of the disease [22, 23, 53-59]. This was conclusively shown by the large Diabetes Control and Complications Trial (DCCT) [22] for patients with type 1 DM, and by the United Kingdom Prospective Diabetes Study (UKPDS) [23] and the Kumamoto Study [55] for patients with type 2 DM. All studies documented substantial reductions in microvascular complications in patients undergoing intensified glycaemic control (i.e. intensified insulin treatment) compared to patients with conventional treatment. Even in secondary prevention cohorts (i.e. patients with established retinopathy), progression of complications was reduced with decreasing blood glucose levels. Further epidemiological analyses of these studies confirmed the association between glycaemic control and the risk of development and/or progression of microvascular complications [25, 60]. Unfortunately, the incidence of severe hypoglycaemia in type 1 DM is approximately three times higher in intensively treated compared to conventionally treated patients [22, 61, 62]. It has also been shown that in this population intensive insulin therapy is associated with hypoglycaemia unawareness and severe hypoglycaemia, making iatrogenic hypoglycaemia a major limiting factor in the attempt to achieve optimal glycaemic control [63].

1.2.2 Macrovascular complications

Macrovascular disease is caused by atherosclerotic lesions of large vessels and includes cardiac, as well as cerebrovascular and peripheral vascular complications. Macrovascular disease is the leading cause of morbidity and mortality among persons with DM in developed countries [64]: a substantial proportion of premature deaths in patients with type 1 DM [65], and the majority of deaths in type 2 DM are related to macrovascular disease. Despite intensive efforts to improve treatment strategies in patients with DM, mortality is still increased when compared to the non-diabetic population [66, 67]. In contrast to the microvascular complications, the impact of optimal blood glucose levels on macrovascular complications is still debated. Trials of intensified blood glucose control showed a tendency towards a reduced risk of macrovascular disease with improved glycaemic control [22, 23, 59]. However, the question, whether improved glycaemic control could reduce the development and/or progression of macrovascular disease, has not been conclusively answered so far. Moreover, due to the fact that the beneficial effect of improved glycaemic control on microvascular complications has been documented, it would be unethical to perform further trials comparing intensified with conventional glycaemic control. In addition to chronic hyperglycaemia, several other factors have been found to contribute to the development or progression of macrovascular disease. Of these, especially important and commonly present in type 2 DM are hypertension and atherogenic dyslipidaemia. Atherogenic dyslipidaemia is characterised by small dense low density lipoprotein (LDL) particles, elevated very low density lipoprotein (VLDL) levels and low high density lipoprotein (HDL) cholesterol [68]. In addition, LDL cholesterol and triglycerides levels are often increased, which again is related to a higher cardiovascular risk [69]. Due to the accumulation of different risk factors within one individual, the risk of developing macrovascular complications is substantially increased. It is, therefore, of great importance to define optimal treatment strategies for these patients to reduce their macrovascular risk as much as possible.

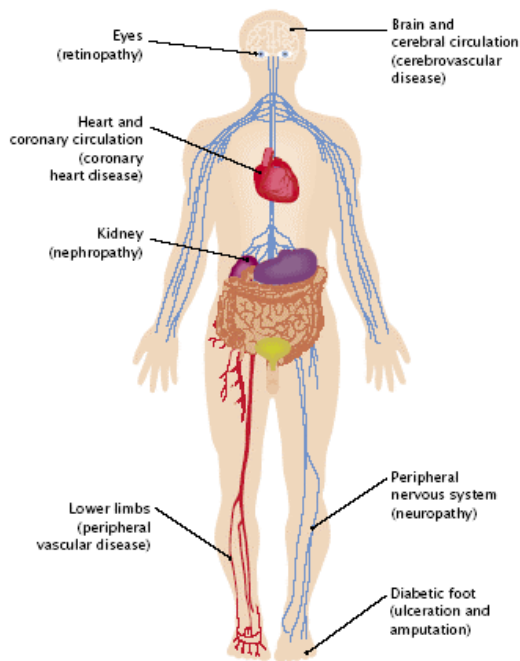


Figure 2. Locations of major diabetic complications. Figure based on http://www.eatlas.idf.org/webdata/img/diag_complications.gif, accessed June 2006.

1.2.3 The excess risk for macrovascular disease in patients with compared to patients without diabetes mellitus

The annual risk for death from cardiovascular disease has been found to be two to three times higher for persons with DM than for persons without DM [70]. Evidence suggests that even in the absence of pre-existing vascular disease, middle-aged people with type 2 DM exhibit a similar risk of coronary heart disease to those without DM who have had a myocardial infarction [71]. In this context, DM has been described as an independent risk factor for cardiovascular disease in both men and women [72-74]. In the Rancho Bernardo Study, women with DM had a probability to die from ischemic heart disease comparable to both men with and without DM, while women without DM had a considerably lower risk [75]. The inherent protection against developing cardiovascular disease seems, therefore, to be lost in women with DM [72-74]. Moreover, it has recently been speculated that the presence of DM might be the clinical equivalent of aging 15 years, putting men and women with the disease into a high-risk category for cardiovascular disease while still in middle age [76].

Due to autonomic neuropathy myocardial ischemia commonly occurs without symptoms in patients with DM, diagnosis of cardiovascular disease may be delayed, often leading to more advanced multivessel atherosclerosis at presentation, and consequently to a delay of the introduction of treatment [77]. Therefore, patients with DM and cardiovascular disease have worse prognosis for survival than patients

without DM [78-80]. Reliable risk indicators could help to identify patients at risk of late complications as early as possible, thereby improving prognosis and quality of life in these individuals. Since it has been shown that specific risk indicators may influence cardiovascular risk differently in individuals with and without DM [81-84], it is of interest to compare different risk markers in individuals with different underlying cardiovascular risk as patients with and without DM.

1.3 Methods relevant to thesis

1.3.1 Systematic review and meta-analysis

Over the last decades, the volume of the health care literature has increased enormously. It has, therefore, become almost impossible for health professionals to keep up with all publications relevant to an area of practice. In addition to the large volume, research results are often contradictory, which creates difficulties in interpreting the findings and corresponding conclusions while reading up on a specific topic. In this context, systematic reviews have emerged as essential tools to fulfil the need for accurate accounts of past research. These reviews summarise results and knowledge of current studies in a single document. While traditional narrative reviews tend to be subjective and therefore prone to bias [85], systematic reviews render the review process transparent. As a consequence, conclusions are based on the examined literature and should be replicable. Chalmers and Altman defined a systematic review as a review that has been prepared using a systematic approach to minimising biases and random errors, which is documented in a materials and methods section [86]. Even when the research evidence is limited or nonexistent, these systematic reviews summarise current best evidence on a specific topic. Furthermore, they can also help to determine future research needs.

A systematic review may, or may not, include a meta-analysis, which will be used to produce a single estimate of a treatment effect [87]. The distinction between systematic review and meta-analysis is made because it is always appropriate and desirable to systematically review a body of data, but it may sometimes be inappropriate, or even misleading, to statistically pool results from separate studies [87, 88]. The quality of the contributing studies has to be considered. If the material is flawed, the findings based on it will also be compromised [89]. Ideally the studies included in systematic reviews and meta-analyses should be of high methodological quality and free from bias to best guarantee that differences in outcomes observed between patient groups can be reliably attributed to the intervention under investigation [89]. Biases in trials can be observed in case of systematic differences in patients' characteristics at baseline (selection bias), unequal provision of care apart from the treatment under evaluation (performance bias), biased assessment of outcomes (detection bias), and bias due to exclusion of patients after they have been allocated to treatment groups (attrition bias) [90, 91]. For example, it has been shown

that the treatment effect was exaggerated in studies where treatment allocation was not concealed compared to studies, which reported adequately concealed treatment allocation [92]. Quality assessment of trials included in a systematic review is often hampered by the low quality of reporting of the respective studies. Thanks to the adoption of reporting guidelines such as the CONSORT (Consolidated Standards of Reporting Trials) recommendations [93] by an increasing number of journals, the situation is improving [94].

Another issue that has to be addressed when conducting a meta-analysis is the fact that the publication of research findings depends on the nature and direction of the results: statistically significant results, indicating that a treatment is beneficial, are more likely to be published [95-98], more likely to be published in English [99, 100], more likely to be published more than once, and more likely to be cited by others, than results showing no beneficial or even adverse effects of a treatment. It is also possible that outcomes are reported selectively, again depending on their properties and direction. Such reporting biases are listed in [Table 6](#).

Table 6. Reporting biases (adapted from Egger M et al. [89])

Type of reporting bias	Definition
Publication bias	The <i>publication</i> or <i>non-publication</i> of research findings, depending on the nature and direction of the results
Time lag bias	The <i>rapid</i> or <i>delayed</i> publication of research findings, depending on the nature and direction of the results
Multiple (duplicate) publication bias	The <i>multiple</i> or <i>singular</i> publication of research findings, depending on the nature and direction of the results
Citation bias	The <i>citation</i> or <i>non-citation</i> of research findings, depending on the nature and direction of the results
Language bias	The publication of research findings <i>in a particular language</i> , depending on the nature and direction of the results
Outcome reporting bias	The <i>selective reporting</i> of some outcomes but not others, depending on the nature and direction of the results

The combination of the results from different published trials may, therefore, lead to an exaggerated or even spurious beneficial effect of the treatment under investigation. This has been shown in trials on cancer chemotherapy, where pooled results of published studies were in favour of the treatment, in contrast to the findings

of an analysis based on the international trials registry [101, 102]. Nevertheless, it is debated if unpublished data should be included in systematic reviews and meta-analyses since this could introduce bias itself due to several reasons. First, the trials that can be identified may not be a representative sample of all unpublished studies. Second, unpublished trials may be of lower methodological quality than published trials [103]. A third problem is that investigators of identified unpublished studies may not be willing to provide their data. Finally, some editors express their concern if data that has not been peer reviewed is included in a meta-analysis, although the refereeing process does not guarantee the validity of published data [103]. Graphical as well as statistical methods exist to examine the presence and the impact of potential publication bias on overall treatment effects. One approach is to perform a scatter plot, a so called funnel plot, with the treatment effect of the individual studies on the horizontal axis against some measure of study size on the vertical axis (e.g. standard error of the logarithm of the odds ratio or relative risk). Effect estimates from small studies will be scattered more widely at the bottom of the graph, with the spread narrowing of larger studies. In the absence of bias, the plot will resemble a symmetrical funnel.

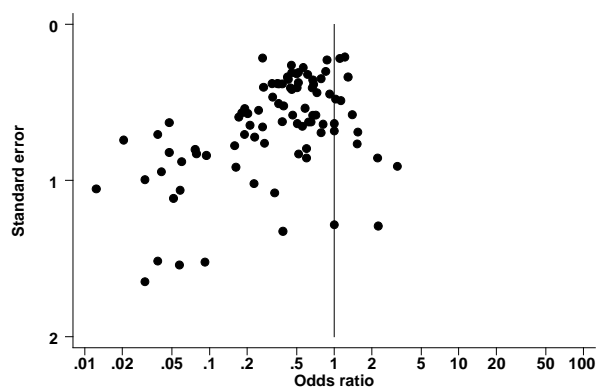


Figure 3. *Funnel plot of placebo-controlled trials of homoeopathy.* The plot is asymmetrical, suggesting the presence of publication bias. The solid line indicates the null effect (adapted from Egger M et al. [103])

An asymmetrical funnel plot may indicate publication bias. However, it can appear asymmetrical also for other reasons: In cases of true heterogeneity between the studies (e.g. intensity of intervention, differences in underlying risk), or of poor methodology of small studies leading to greater effect in these studies, graphs will also be asymmetrical. Furthermore, the symmetry may also depend on the choice of the effect measure (e.g. odds ratio versus risk ratio), on the choice of the measurements for the axis, or on chance. Therefore, the funnel plot should be seen as a means of examining differences in the results of smaller and larger trials rather

than a tool to determine specific types of bias. Together with the funnel plot, Egger's linear regression test [104] and Begg's rank correlation test [105] provide statistical tools to assess for potential bias in a meta-analysis. However, the power of all tests is limited, in particular, if the number of studies included in the meta-analysis is small.

Meta-analysis of randomised controlled trials is based on the assumption that each trial provides an unbiased estimate of the effect of the treatment under investigation, with the variability between the studies being attributed to random variation [89]. The combined overall effect of carefully identified representative studies will then provide an unbiased estimate of the treatment effect by increasing its precision. This is illustrated for example in trials of the effect of beta-blockers (Figure 4): the forest plot shows quite homogeneous results for all component trials with overlapping confidence intervals.

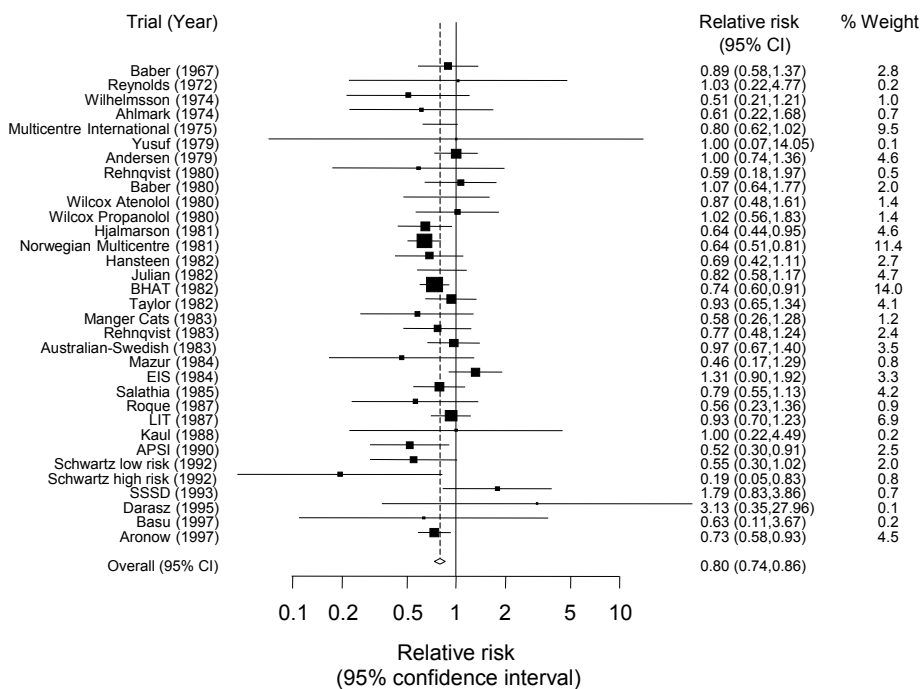


Figure 4. Forest plot of controlled trials of beta-blockers in secondary prevention of mortality after myocardial infarction. The centre of the square and the horizontal line correspond to the relative risk (RR) and 95% confidence intervals for each trial. The area of the square is proportional to the weight of the trial in the meta-analysis. The diamond at the bottom represents the combined estimate and its 95% confidence interval. The solid vertical line indicates no effect of treatment (RR=1.0), the dotted line the combined effect (RR=0.8) (adapted from Egger M et al. [89])

In other situations results of individual trials may be heterogenous, which precludes meaningful meta-analysis of the data. For example, as shown in [Figure 5](#), trials of the efficacy of BCG vaccination to prevent tuberculosis revealed fairly heterogeneous results with non compatible confidence intervals for all trials.

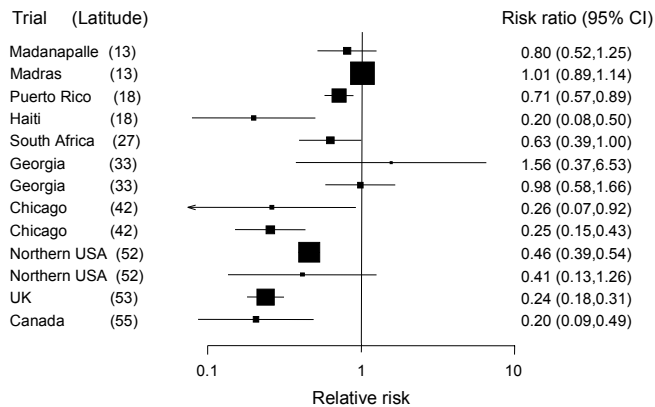


Figure 5. Forest plot of trials of BCG vaccine to prevent tuberculosis. Trials are ordered according to the latitude of the study location, expressed as degrees from the equator. No meta-analysis is shown (adapted from Egger M et al. [89])

Combining these study results would lead to a misleading overall finding of vaccine efficacy. In this situation, it is of interest why results differ. In the BCG example it can be shown that BCG vaccination appears to be effective at higher latitudes but not in warmer regions (possibly because exposure to certain environmental mycobacteria acts as a 'natural' BCG inoculation in warmer regions).

1.3.1.1 Statistical methods used in meta-analysis

Meta-analysis has been defined by Huque as a statistical analysis which combines the results of several independent studies considered by the analyst to be combinable' [106].

In situations where study results of the contributing trials are in agreement, a so-called fixed effects model will be used to combine the results of the different studies. It is thereby assumed that the observed variation in treatment effects is entirely due to sampling variation, and that the underlying true treatment effect is the same in all the studies [107].

The summary estimate of the treatment effect is calculated as a weighted average of the logarithm of the risk ratio or odds ratio or incidence rate ratio, etc:

$$\log(\text{odds ratio}) = \frac{\sum w_i \times \log(\text{odds ratio})}{\sum w_i}$$

There are several methods to define the weight of the individual studies. In the inverse variance method, the weight w_i for study i equals the inverse of the variance, v_i , of the estimated logarithm of the risk ratio in that study.

Inverse variance weights:

$$w_i = \frac{1}{v_i}$$

where $v_i = \frac{1}{d_1} + \frac{1}{h_1} + \frac{1}{d_0} + \frac{1}{h_0}$

d_1 : Number of patients with outcome in intervention arm
 d_0 : Number of patients with outcome in control arm
 h_1 : Number of patients without outcome in intervention arm
 h_0 : Number of patients without outcome in control arm

An alternative approach is to use Mantel-Haenszel weights to combine the results of the individual studies.

$$w_i = \frac{d_0 h_1}{n_i}$$

This method is preferable when data are sparse; in other situations Mantel-Haenszel methods give similar results to the inverse-variance weighting method.

In case of evidence of heterogeneity between studies, it is possible to calculate a summary estimate allowing for the heterogeneity by using a so-called random effects model. This can be seen as a last resort when heterogeneity cannot be explained. With this approach it is assumed that the true effect in each study derives from a normal distribution, whose mean equals the true overall effect and whose variance is usually denoted by τ^2 .

This between-study variance is estimated from the observed data and is used in calculation of the weights and thus in the calculation of the random effects summary estimate:

$$\log(\text{risk}) = \frac{\sum w_i^* \times \log(\text{risk}_i)}{\sum w_i^*}$$

$$w_i^* = \frac{1}{(v_i + \tau^2)}, \text{ where } v_i = \frac{1}{d_1} + \frac{1}{h_1} + \frac{1}{d_0} + \frac{1}{h_0}$$

d_1 : Number of patients with outcome in intervention arm
 d_0 : Number of patients with outcome in control arm
 h_1 : Number of patients without outcome in intervention arm
 h_0 : Number of patients without outcome in control arm

The commonly used method for calculating the between-study variance τ^2 was suggested by DerSimonian and Laird in 1986 [108]. Random effects weights are smaller and more similar across studies than their fixed effects counterparts. In a random effects meta-analysis smaller studies receive greater relative weight. The summary estimate will, therefore, be influenced by smaller studies more than in a fixed effects model. In addition, random effects model will reveal wider confidence intervals and a larger p-value. However, if heterogeneity of identified studies is present, it needs careful reflection whether a meta-analysis is appropriate at all. In case of apparent heterogeneity as illustrated in the example of BCG vaccination (Figure 5), stratifying of studies with similar inclusion criteria or other subgroup analyses might be more appropriate.

The investigation of sources of heterogeneity (such as study latitude in the BCG example) may yield important insights. To examine whether a particular characteristic of the trial or the study population (covariate), is related to the extent of the treatment effect, can be explored in so-called meta-regression models [109]. In this approach, it is postulated that the treatment effect is related in a linear manner to one or more study-level covariates. There are several statistical models to investigate such a relationship. A commonly used form uses assumptions as in the random effects model for meta-analysis – i.e. the observed treatment effects are normally distributed. The analysis is then based on a weighted regression model of the individual study estimates using the weights as described for the random effects meta-analysis.

The reporting of systematic reviews and meta-analyses is based on recommendations referred to as the Quality Of Reporting Of Meta-Analyses (QUOROM) statement [110]. The QUOROM statement consists of a checklist with 18 items referring primarily to the abstract, introduction, methods and results section of a report, pointing out the information that should be provided by the authors. Furthermore, the inclusion of a flow diagram showing details of the process of identifying potentially relevant trials and selecting eligible trials is also recommended.

1.3.2 Survival analysis

The time to an event of interest is one of the common major outcomes in clinical trials and cohort studies. This is also known as 'survival time' and indicates the time period from a well defined starting point, for example time of diagnosis of the disease or time of first clinical examination to the event of interest, for example death. In a time to event analysis information on the probability of survival following the predefined starting point is provided and also on the prognosis according to patient characteristics (sex, age, etc), disease characteristics (site, histology, etc) and methods of treatment. At the end of follow up not all individuals usually have had the event of interest, and thus their true time to event is unknown. Either a patient has not yet experienced the event of interest by the time of the close of the study or a patient is lost to follow up during the study period, or, a patient experiences a different event that makes further follow up impossible. In these situations the observation time is censored. Such censored survival times may underestimate the true (but unknown) time to event. Therefore, special methods of analysis are needed, including standard graphical methods of data exploration and presentation.

In general, survival data can be described and modelled in terms of two related functions, the survival and hazard functions, respectively. The survival probability (survival function) $S(t)$ is the probability that an individual survives from the time origin to a specified future time t . These values provide direct information on the survival experience of a study cohort. In contrast, the hazard function, usually denoted as $h(t)$ or $\lambda(t)$, specifies the instantaneous rate at which failures occur for individuals that are surviving at time t [111]. There are several possibilities to estimate the survival and

hazard function differing in the respective assumptions of each method. The calculations used in the present thesis are described in more detail as follows:

1.3.2.1 Kaplan-Meier survival estimate

In cases where the exact follow up time for each individual is known, survival probability can be estimated nonparametrically according to Kaplan-Meier [112]. The follow up times of all observations are arranged in increasing order of magnitude and time intervals are determined by the occurrences of the outcome of interest, as and when they occur. As events are assumed to occur independently of one another, the probabilities of surviving from one interval to the next may be multiplied together to give the cumulative survival probability. Therefore, the probability of being alive at time t_j , $S(t_j)$, is calculated from $S(t_{j-1})$ the probability of being alive at t_{j-1} , n_j the number of patients alive before t_j , and d_j the number of events at t_j , as follows:

$$S(t) = S(t_{j-1}) \left(1 - \frac{d_j}{n_j} \right), \text{ where } t_0 = 0 \text{ and } S(0) = 1$$

The value of $S(t_j)$ is constant between time of events, and, the estimated probability changes value only at the time of each event. The Kaplan-Meier survival curve, a plot of the Kaplan Meier survival probability against time, provides a useful summary of the data that can be used to estimate measures such as median survival time.

Figure 6 is based on data of the Swiss Cohort of the WHO Multinational Study of Vascular Disease in Diabetes and shows the survival probability at any given time point during the study follow up for the individuals under observation.

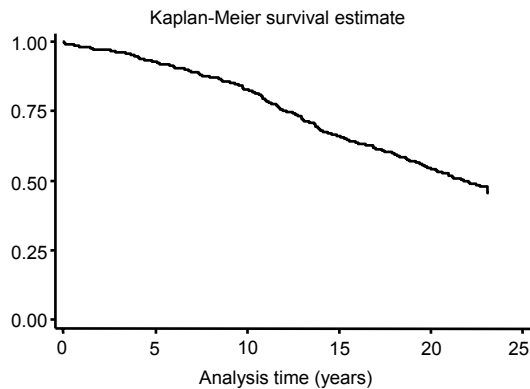


Figure 6. Example for Kaplan-Meier survival estimate, based on data of the Swiss Cohort of the WHO Multinational Study of Vascular Disease in Diabetes, showing survival probabilities for all subjects included in the cohort.

1.3.2.2 Nonparametric test comparing survival

Using a nonparametric test, survival rates in different groups can be compared. The most widely used method is the log rank test [113]. Groups may be defined for example by treatment or by demographic or prognostic criteria. For each group the number of events is calculated that would be expected if there were no differences between the groups. The number of observed events, O , in group i is then compared to the expected number, E , by calculating the test statistic

$$\chi^2 = \sum_{i=1}^g \frac{(O_i - E_i)^2}{E_i}$$

This value is compared to a χ^2 distribution with $(g-1)$ degrees of freedom, where g is the number of groups, and a p-value can be computed to calculate the statistical significance of the difference between the survival curves of different groups. When two groups are compared, the null hypothesis that the ratio of the hazard rates in the two groups equals to 1, is examined using the log rank test. In practise, it is often more powerful to estimate hazard ratios by multivariable regression modelling since several factors influencing survival can be taken into account in such models.

1.3.2.3 Survival analysis adjusting for covariates

Adjusting for subject-related factors (covariates or confounders) potentially affecting the survival time (i.e. age, gender) in time to event analyses, is performed by

multivariate modelling, using multiple regression. The Cox proportional hazard model is the most common multivariate approach. The relation between the event incidence, expressed by the hazard function and a set of covariates, is described as follows:

$$h(t) = h_0(t) \times \exp\{b_1x_1 + b_2x_2 + \dots + b_px_p\}$$

$h(t)$, hazard function; $h_0(t)$, baseline hazard (hazard if all covariates equal to zero, may vary with time t); x , covariate; b , regression parameter of the respective covariate; p , number of covariates

It is essentially a multiple linear regression of the logarithm of the hazard on all the included variables with the baseline hazard being an 'intercept' term that varies with time. The baseline hazard is estimated nonparametrically. Consequently, survival times in Cox regression models are not assumed to follow a particular statistical distribution.

As a key assumption of the Cox proportional model, the hazard of the event in any group is assumed to be a constant multiple of the hazard in any other. Therefore, plots of the hazard function should be proportional and curves should not cross. In contrast to the Cox model where no parametric assumptions are made for the distribution of the hazard, in parametric proportional models, the hazard is assumed to follow a specific statistical distribution. However, hazard ratios have the same interpretation, whether derived from a Cox model or a fully parametric regression model, and the proportionality of hazards is often assumed. Models commonly applied use the *exponential*, *Weibull* or *Gompertz* distribution. They take their names from the distribution that the survival times are assumed to follow, but the most distinguishing features between them are the hazard function. Although both, the Cox model and the parametric models, reveal comparable hazard ratios, the parametric approach allows for the calculation of predictions.

1.4 Aim of the thesis

The aim of this thesis was to critically synthesise the current knowledge in important clinical research areas focussing on prevention and reduction of macrovascular disease and consequently of mortality in patients with DM. For this purpose, five different studies were performed (**Studies A-E**).

According to the methodology, the studies can be grouped into two parts: **Studies A-C** include a systematic review and meta-analysis, focussing on treatment strategies in patients with type 1 and type 2 DM, and in comparison to individuals without DM:

- **Study A** investigated the effect of improved glycaemic control on macrovascular complications in type 1 and type 2 DM.
- **Study B** examined the efficacy of fibrates on coronary heart disease in patients with type 2 DM.
- **Study C** analysed the impact of two currently available coronary drug eluting stents on cardiovascular complications in individuals with compared to individuals without DM.

The second part of this thesis (**Studies D and E**) dealt with the definition of novel mortality risk indicators in patients with type 1 and type 2 DM using survival analyses. Both studies, **Studies D and E**, were based on data of the 'Swiss Cohort of the WHO Multinational Study of Vascular Disease in Diabetes'.

- **Study D** evaluated the prognostic value of the QT-interval corrected for heart rate (QT_c) and of resting heart rate (rHR) on mortality in type 1 and type 2 DM.
- In **Study E**, the impact of apolipoprotein B on mortality was assessed in type 1 DM.

1.4.1 Brief summary of studies

1.4.1.1 Study A: Glycaemic control and macrovascular disease in type 1 and type 2 diabetes mellitus: Meta-analysis of randomised controlled trials

Main causes of mortality in type 1 and type 2 DM are related to macrovascular disease. Although a beneficial effect of optimal glycaemic control has been documented in several randomised trials for microvascular complications, the impact on macrovascular disease is still uncertain. The aim of this project was to assess the effect of improved glycaemic control on cardiac, cerebrovascular and peripheral vascular complications. Analyses revealed a 62% reduction in the incidence of any macrovascular event (95% CI 44-74%) in type 1 and a 19% reduction (9-27%) in type 2 DM for treatment with improved glycaemic control. In type 1 DM, the effect was mainly based on reduction of cardiac and peripheral vascular events, whereas in type 2 DM it was related to reduced rates of stroke and peripheral vascular events. Effects appeared to be particularly important in younger patients with shorter duration of diabetes.

1.4.1.2 Study B: Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: Meta-analysis of randomised trials

Fibrates are well-known agonists of the peroxisome proliferator-activated receptor alpha (PPAR α), which is mainly expressed in liver, heart and skeletal muscle. Based on their mechanism of action, they have been shown to reduce triglyceride levels and increase HDL cholesterol, which is of particular interest for treatment of the characteristic dyslipidaemia of insulin resistance (increased concentrations of triglycerides and small dense low density lipoproteins, decreased levels of HDL cholesterol). In contrast to the documented lipid-lowering effect, there is still uncertainty about the role of fibrates in the prevention of cardiovascular disease. In this systematic review and meta-analysis the effectiveness of PPAR α -agonists in the prevention of cardiovascular disease was examined. Results showed a 16% reduction (95% CI 4-26%) in the risk for coronary events in patients with type 2 DM when treated with fibrates compared to placebo. Benefits were even larger when analyses were restricted to trials that were not confounded by unequal provision of additional lipid-lowering therapy.

1.4.1.3 Study C: Efficacy of drug eluting stents in patients with and without diabetes mellitus: indirect comparison of controlled trials

At the time of planning this study, two drug eluting stents have been approved by the Food and Drug Administration (FDA) for the treatment of coronary heart disease, a sirolimus and a paclitaxel eluting stent. Both have shown to effectively reduce the number of repeated revascularisations compared to uncoated bare metal stents. There is some evidence that sirolimus is superior to paclitaxel in reducing restenosis rates. However, results from head-to-head trials are conflicting. Open questions remain regarding the clinical benefits across patient groups with different underlying cardiovascular risk. Patients with DM tend to present with more advanced coronary artery disease, and outcomes after percutaneous intervention tend to be poorer than for patients without DM. The objective of this project was to indirectly compare the effects of polymer based sirolimus versus paclitaxel eluting stents, and to examine whether they are equally effective in the prevention of restenosis in patients with and without DM. Indirect comparisons were performed by calculating the ratio of the incidence rate ratios of the direct comparisons (sirolimus versus bare metal stents / paclitaxel versus bare metal stents) using meta-regression modelling. In patients without DM sirolimus eluting stents were superior to paclitaxel eluting stents with respect to in-stent- and in-segment restenosis, target lesion revascularisation, and major adverse cardiac events. In patients with DM the two drug eluting stents did not differ significantly in any of these end points. Meta-regression analysis confirmed a difference between patients with and without DM (tests for interaction for in-stent and insegment restenosis, $p = 0.036$ and $p = 0.016$).

1.4.1.4 Study D: QTc interval and resting heart rate as long term predictors of mortality in type 1 and type 2 diabetes mellitus: a 23-year follow up

In an effort to identify easily available and reliable predictors for cardiovascular risk and mortality in DM, the evaluation of parameters reflecting myocardial ventricular repolarisation has been of particular interest. In type 1 DM prolongation of the QT interval corrected for heart rate (QT_c) and heart rate variability have both been shown to be associated with increased risk of arrhythmia and death, whereas QT dispersion has been suggested to be less reliable. The association between QT_c and cardiovascular mortality in type 2 DM, however, is controversial: There have been

reports suggesting that QT_c is associated with increased cardiovascular mortality risk. Other studies have indicated that QT dispersion might more accurately predict cardiovascular mortality in this patient group. Based on data of the 'Swiss Cohort of the WHO Multinational Study of Vascular Disease in Diabetes', the long-term association of QT_c and resting Heart Rate (rHR) with mortality was evaluated in patients with type 1 and type 2 DM. Analyses showed that QT_c was associated with long-term mortality in patients with type 1 DM, whereas rHR was related to increased mortality risk in patients with type 2 DM.

1.4.1.5 Study E: Apolipoprotein B as a long term predictor of mortality in type 1 diabetes mellitus: a 15-year follow up

Apolipoprotein B (apo B) is an easily measurable clinical parameter and has been shown to be a valuable marker of cardiovascular risk in several prospective or cross-sectional clinical trials and a recent meta-analysis. However, these studies were either performed in a general population or in patients with type 2 DM. Data on the association of apo B with cardiovascular risk in type 1 diabetes is scarce, only one trial prospectively assessed its relationship. The aim of this project was to evaluate the long term association of apo B with mortality risk in patients with type 1 DM based on a 15-year follow up of the 'Swiss Cohort of the WHO Multinational Study of Vascular Disease in Diabetes'. Compared to Study D, follow up for this study was shorter due to the fact that measurement of apo B was available only later in the course of the study. Apo B was positively related to all cause and cardiac mortality as well as to mortality due to ischemic heart disease. An apo B ≥ 0.96 g L⁻¹ translated into a duplication of overall mortality hazard and a sevenfold increase of mortality because of cardiac disease or IHD.

2 Systematic reviews and meta-analyses on the effectiveness of specific treatment forms on macrovascular complications

2.1 Study A: Glycaemic control and macrovascular disease in type 1 and type 2 diabetes mellitus: Meta-analysis of randomised controlled trials

Christoph Stettler,¹ Sabin Allemann,^{1,2} Peter Jüni,^{1,3} Carole A. Cull,⁴
Rury R. Holman,⁴ Matthias Egger,^{1,3} Stephan Krähenbühl,⁵ Peter Diem²

- 1) Department of Social and Preventive Medicine, University of Bern, Switzerland
- 2) Division of Endocrinology and Diabetes, University of Bern, Switzerland
- 3) MRC Health Services Research Collaboration, Department of Social Medicine,
University of Bristol, United Kingdom
- 4) Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism,
University of Oxford, Oxford, United Kingdom
- 5) Department of Internal Medicine, University of Basel, Switzerland

Article published in:

Am Heart J 2006 Jul;152(1):27-38.

Abstract provided at:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16824829&query_hl=1&itool=pubmed_docsum

Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials

Christoph Stettler, MD,^a Sabin Allemann,^{a,b} Peter Jüni, MD,^{a,c} Carole A. Cull, PhD,^d Rury R. Holman, MD,^d Matthias Egger, MD, MSc,^{a,c} Stephan Krähenbühl, MD,^c and Peter Diem, MD^b *Bern, Switzerland; and Oxford, UK*

Background Uncertainty persists concerning the effect of improved long-term glycemic control on macrovascular disease in diabetes mellitus (DM).

Methods We performed a systematic review and meta-analysis of randomized controlled trials comparing interventions to improve glycemic control with conventional treatment in type 1 and type 2 diabetes. Outcomes included the incidence rate ratios for any macrovascular event, cardiac events, stroke, and peripheral arterial disease, and the number needed to treat intensively during 10 years to prevent one macrovascular event.

Results The analysis was based on 8 randomized comparisons including 1800 patients with type 1 DM (134 macrovascular events, 40 cardiac events, 88 peripheral vascular events, 6 cerebrovascular events, 11 293 person-years of follow-up) and 6 comparisons including 4472 patients with type 2 DM (1587 macrovascular events, 1197 cardiac events, 87 peripheral vascular events, 303 cerebrovascular events, 43 607 person-years). Combined incidence rate ratios for any macrovascular event were 0.38 (95% CI 0.26-0.56) in type 1 and 0.81 (0.73-0.91) in type 2 DM. In type 1 DM, effect was mainly based on reduction of cardiac and peripheral vascular events and, in type 2 DM, due to reductions in stroke and peripheral vascular events. Effects appear to be particularly important in younger patients with shorter duration of diabetes.

Conclusions Our data suggest that attempts to improve glycemic control reduce the incidence of macrovascular events both in type 1 and type 2 DM. In absolute terms, benefits are comparable, although effects on specific manifestations of macrovascular disease differ. (*Am Heart J* 2006;152:27-38.)

There is uncertainty about the place of improved glycemic control in the prevention of macrovascular disease in patients with diabetes mellitus (DM).^{1,2} The development of macrovascular complications, including cardiac, cerebrovascular, and peripheral vascular complications, is an important concern considering that a substantial proportion of premature deaths in patients with type 1 DM³ and most deaths in type 2 DM are related to macrovascular disease.⁴

The beneficial effects of improved glycemic control on microvascular complications, including retinopathy, nephropathy, and neuropathy, have been documented in several randomized studies published during the last 20 years. In patients with type 1 DM, this was conclusively shown by DCCT⁵ and, in patients with type 2 DM, by UKPDS.⁶ Although these and other studies^{5,7-13} prospectively recorded the occurrence of macrovascular complications, they did not conclusively answer the question whether improved glycemic control effectively reduces macrovascular complications. By pooling data from several studies, meta-analysis of the existing data could clarify this issue.¹⁴ In collaboration with the original investigators who provided additional information on macrovascular outcomes, we did a comprehensive systematic review and meta-analysis of all randomized controlled trials in patients with type 1 and type 2 DM.

Methods

Literature search and eligibility criteria

We aimed to identify all randomized controlled comparisons of improved glycemic control that assessed macrovascular disease in types 1 and 2 DM. Using Cochrane methodology,¹⁵

From the ^aDepartment of Social and Preventive Medicine, University of Bern, Switzerland, ^bDivision of Endocrinology and Diabetes, University of Bern, Switzerland, ^cMRC Health Services Research Collaboration Department of Social Medicine, University of Bristol, UK, ^dDiabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK, and ^eDepartment of Internal Medicine, University of Basel, Switzerland.

We declare that we have no conflict of interest. This study was supported by grants from Novo Nordisk, Künsnacht, Switzerland, Roche Diagnostics, Rotkreuz, Switzerland, and Glaxo Smith Kline, Münchenbuchsee, Switzerland.

Submitted July 5, 2005; accepted September 14, 2005.

Reprint requests: Peter Diem, MD, Division of Endocrinology and Diabetes, University of Bern-Inselspital, 3010 Bern, Switzerland.

E-mail: peter.diem@insel.ch

0002-8703/\$ - see front matter

© 2006, Published by Mosby, Inc.

doi:10.1016/j.ahj.2005.09.015

we searched MEDLINE, EMBASE, and the Cochrane Controlled Trials Register for relevant studies. We considered studies in any language. Electronic searches were supplemented by hand-searching of reference lists, reviews, relevant book chapters, conference abstracts, and specialist journals. We evaluated each study for inclusion in the meta-analysis on the basis of 6 criteria: (1) study design (randomized controlled trial), (2) target population (general population of patients with either type 1 or type 2 DM), (3) comparison of regimens aiming to improve glycemic control (subcutaneous insulin injections, insulin pump, oral antidiabetic agents, or a combination of the previous) with conventional treatments, (4) documentation of glycemic control by measurement of glycated hemoglobin (HbA_{1c}), (5) follow-up of at least 2 years, and (6) prospective recording of macrovascular events. Two reviewers (CS, SA) independently assessed publications for eligibility, with discrepancies being resolved in consultation with a third reviewer (PD).

Data extraction and outcome measures

Data on the characteristics of studies, patient populations, and interventions were extracted independently by 2 investigators (CS and SA), with disagreements resolved by a third reviewer (PD). This included the extraction of data on the distribution of cardiac risk factors at study end (blood pressure, lipid factors, body mass index, and smoking). All relevant publications from a study were considered, including, for example, early publications describing the study design. Authors from all studies were sent a standardized data extraction form and were asked to check the information extracted from published articles and, where necessary, to provide additional clinical and biochemical data. We defined macrovascular end points as (1) cardiac events, including fatal and nonfatal myocardial infarction (defined as evidence of acute myocardial infarction confirmed by electrocardiogram [ECG] and/or serum enzymes, confirmed nonacute myocardial infarction based on serial reading of baseline and biennial ECG and/or serum enzymes), any type of bypass graft and percutaneous transluminal angioplasty, angina pectoris (defined as evidence of ischemic heart disease confirmed by a new ECG abnormality or an ECG that becomes abnormal on exercise), congestive heart failure (based on clinical criteria, eg, Kerley's B lines, rales, raised jugular venous pressure, or third heart sound), and death due to cardiac disease or sudden death; (2) stroke (fatal and nonfatal, thrombotic or hemorrhagic); and (3) peripheral vascular disease, including intermittent claudication (defined as pain in leg(s) occurring with exercise, no pain at rest, no tissue necrosis, clinical impression combined with objective evidence [measurement of ankle blood pressure, examination of pulse rates, Doppler, angiography]), diabetes-related amputation of lower extremity, any type of peripheral artery bypass or angioplasty, and death due to peripheral arterial disease. The incidence of fatal or nonfatal macrovascular events of any type was the primary end point. Secondary outcomes included fatal or nonfatal cardiac events, stroke, peripheral arterial disease, and macrovascular deaths.

Assessment of methodological quality

Two of us (CS and SA) independently assessed the adequacy of the concealment of allocation of patients to treatment

groups, blinding of care providers and research staff ascertaining macrovascular outcomes, and the proportion of randomized patients included in analyses.¹⁶ Disagreements were resolved in discussion with a third reviewer (PJ).

Statistical analysis

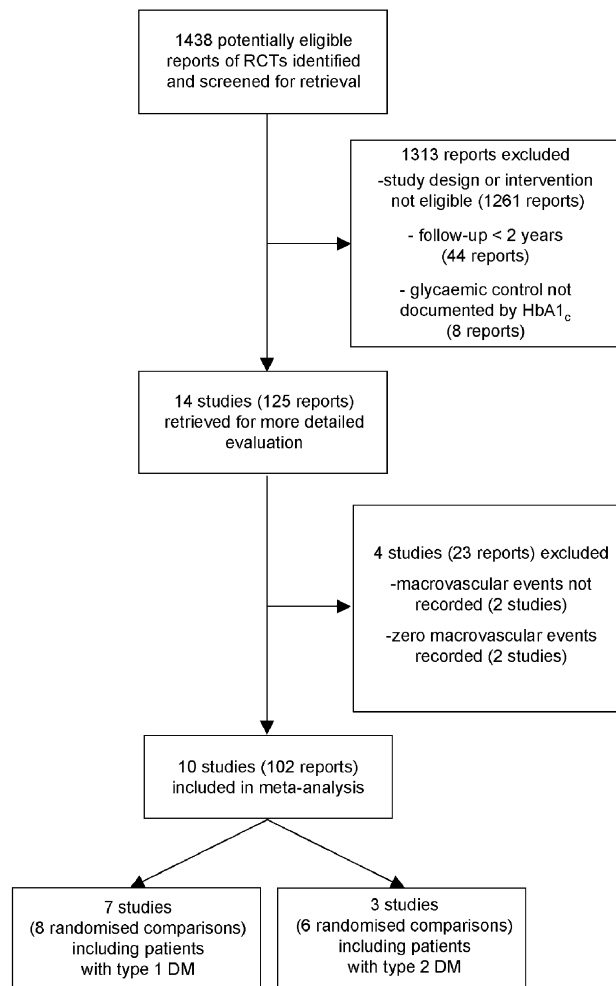
We calculated the incidence of macrovascular events separately for each treatment group by dividing the number of events by the number of person-years of follow-up. For each comparison and end point, the incidence rate ratio (IRR) was obtained by dividing the incidence in the intensified treatment group by the incidence in the control group. Comparisons with no outcome events in either group were excluded from the respective analysis. Comparisons with events only in one group were analyzed by adding one half to all cells. We combined IRRs in fixed-effects meta-analysis, assuming that the observed variation in treatment effects in the different studies is entirely due to sampling variation and that the underlying treatment effect is the same in all study populations. The weight for each study was calculated by using the inverse of the variance of the estimated log IRR in the corresponding study (inverse variance weighting). In addition, we calculated the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance: $I^2 = 100\% \times (Q - df) / Q$, where Q is the Cochran heterogeneity statistic and df is the degrees of freedom.¹⁷ Mild heterogeneity will account for <30% of the variation, and pronounced heterogeneity will account for substantially >50%. The number of patients that need to be treated intensively to prevent one macrovascular event¹⁸ was calculated by applying the combined IRRs to incidence rates typical for conventionally treated patients. In sensitivity analyses, we repeated calculations using random-effects models (attributing increased weight to smaller comparisons) and did tests of funnel plot asymmetry to assess for publication bias.^{19,20} The extent to which the effect of improved glycemic control was modified by study-level variables was explored in univariable meta-regression models.²¹ The following variables were considered: reduction of HbA_{1c} achieved with intensified treatment, duration of DM, mean age at baseline, proportion women, year of study begin, year of study reporting, and study quality (concealment of allocation, blinding, and the proportion of randomized patients included in analyses). Finally, we repeated analyses excluding one study²² where the prevalence of smoking was substantially higher in the intensive treatment group. Results are presented as IRRs with 95% CIs and numbers needed to treat (NNTs) to prevent one macrovascular event. All analyses were performed using Stata version 8.2 (Stata Corporation, College Station, TX).

Results

Identification of eligible studies and comparisons

We screened 1438 reports and excluded 1313. The remaining 125 reports, which reported on 14 different studies, were retrieved for detailed evaluation. Ten studies that included 14 randomized comparisons of intensified and conventional treatment were included (Figure 1). Eight comparisons had been performed in patients with type 1 DM^{5,7,8,10-12} and 6 in patients with type 2 DM.^{6,9,22,23} The DCCT in patients with

Figure 1



Identification of eligible randomized controlled trials. RCTs, Randomized controlled trials.

type 1 DM⁵ and the Kumamoto study in patients with type 2 DM⁹ included 2 parallel comparisons in patients with and without diabetic complications (secondary and primary prevention arms). The UKPDS contributed 3 comparisons: (1) comparison of an intensified regimen based on sulfonylurea or insulin with conventional treatment in nonoverweight patients (“UKPDS 1” in this article); (2) comparison of an intensified regimen based primarily on sulfonylurea or insulin with conventional treatment in overweight patients (>120% of ideal body weight, “UKPDS 2”); and (3) comparison of intensified metformin-based regimen with conventional treatment in overweight patients (“UKPDS 3”). There was overlap in groups receiving conventional treatment in UKPDS 2 and 3; this was

taken into account in the meta-analysis by reducing the weight of the respective groups.

Characteristics of trials, patients, and interventions

Nine comparisons were performed in Europe,^{6-8,10-12,23} 3 in North America,^{5,22} and 2 in Asia.⁹ Mean follow-up ranged from 2.0 to 8.0 years in patients with type 1 DM and from 2.3 to 10.7 years in type 2 DM. Appropriate methods of allocation concealment were described for 8 comparisons.^{5,8,11,12,24} For 7 comparisons, the degree of blinding of outcome assessors remained unclear.^{7-10,12} Eleven comparisons had been analyzed according to the intention-to-treat principle.^{5-7,9,12,22,23} In the remaining 3, the proportion of patients excluded from the analysis ranged from 5.4% to 13.6%.

The 14 randomized comparisons included a total of 6272 patients, 1800 patients with type 1 DM (11293 person-years of follow-up) and 4472 patients with type 2 DM (43607 person-years of follow-up). Study populations were heterogeneous, both in type 1 and type 2 DM, with a range of mean ages and durations of DM at baseline (Table D). In type 1 DM, intensified treatment typically consisted of multiple injection therapy or continuous subcutaneous insulin infusion using a pump, with intensive self-monitoring of blood glucose. Conventional treatment was based on 1 to 3 injections, with or without occasional blood glucose monitoring. In type 2 DM, attempts to improve glycemic control consisted of subcutaneous insulin injections or hypoglycemic agents combined with insulin injections, generally with blood glucose monitoring, whereas for conventional treatment, the number of insulin injections was either reduced or treatment was with hypoglycemic agents or diet alone, with less intensive blood glucose monitoring. Mean baseline HbA_{1c} ranged from 8.8% to 11.8% in patients with type 1 DM and from 7.0% to 9.5% in type 2 DM (Table II). At the conclusion of studies, differences in HbA_{1c} between intensified and conventional treatment groups ranged from -0.5% to -1.9% in type 1 and from -0.3% to -2.2% in type 2 DM. The prevalence of cardiac risk factors was similar between treatment groups (Table III), with one exception: in the Veterans Affairs study,²² smoking was more prevalent in the intensive group, 23% versus 13% at baseline and 21% versus 8% at study end.

Macrovascular events and mortality

Additional outcome data were obtained for 12 comparisons.^{5-10,12,22,23} A total of 134 macrovascular events of any type were recorded in type 1 DM and 1587 events in type 2 DM. The number of events and person-years of follow-up is shown in Table IV. The results from fixed-effects meta-analyses are shown in Figure 2 and Table V. Combined IRRs were 0.38

Table 1. Baseline characteristics of randomized trials comparing intensified blood glucose control with conventional control in patients with type 1 and type 2 DM

Study (year of publication)	n (intensified/conventional)	Female (%)	Mean age (y)	Mean duration of diabetes (y)	Mean follow-up (y)	Intervention in intensified group	Intervention in conventional group
Type 1 DM							
Holman et al (1983) ¹¹	36/38	36	42.4	18.7	2.0	2 daily injections, iSMBG	2 daily injections, SMBG
Verrillo et al (1988) ¹⁰	22/22	45	37.5	20.0	5.0	3 daily injections, iSMBG	1-2 daily injections, SMBG
Lauritzen (1991) ⁷	18/16	41	34.0	19.0	8.0	CSII, iSMBG	1-3 daily injections, SMBG
Feldt-Rasmussen et al (1992) ⁷	18/17	43	30.5	15.0	5.0	CSII, iSMBG	2-3 daily injections, SMBG
DCCT Primary Prevention (1993) ⁵	348/378	49	26.5	2.6	6.5	CSII, MIT, iSMBG	1-2 daily injections, SMBG
DCCT Secondary Intervention (1993) ⁵	363/352	47	27.0	8.8	6.5	CSII, MIT, iSMBG	1-2 daily injections, SMBG
SDIS (1993) ⁸	48/54	47	30.9	17.0	7.5	MIT, iSMBG	2-3 daily injections, SMBG
MCSG (1995) ¹²	36/34	27	37.0	19.5	5.0*	CSII, MIT, iSMBG	2 daily injections, SMBG
Type 2 DM							
Veterans Affairs (1997) ²²	75/78	0	60.2	7.9	2.3	Stepwise regimen (insulin, SU), iSMBG	1-2 daily injections, SMBG
UKPDS 1 (1998) ⁶	1433/589	26	53.7	0	10.3	Stepwise regimen beginning with SU or insulin (metformin, MIT if needed), iSMBG	Stepwise regimen beginning with diet (SU, metformin, insulin if needed), SMBG
UKPDS 2 (1998) ⁶	1296/549	53	52.7	0	9.7	Stepwise regimen beginning with SU or insulin (metformin, MIT if needed), iSMBG	Stepwise regimen beginning with diet (SU, metformin, insulin if needed), SMBG
UKPDS 3 (1998) ²³	342/411	54	52.9	0	10.7	Stepwise regimen beginning with metformin (SU, MIT if needed), iSMBG	Stepwise regimen beginning with diet (SU, metformin, insulin if needed), SMBG
Kumamoto Primary Prevention (2000) ⁹	28/27	49	48.0	6.6	8.0	MIT, iSMBG	1-2 daily injections, SMBG
Kumamoto Secondary Intervention (2000) ⁹	27/28	53	51.0	10.6	8.0	MIT, iSMBG	1-2 daily injections, SMBG

UKPDS 1, nonoverweight and sulfonylurea based; UKPDS 2, overweight and sulfonylurea based; UKPDS 3, overweight and metformin based. iSMBG, Intensive self-monitoring of blood glucose; SMBG, self-monitoring of blood glucose; CSII, continuous subcutaneous insulin infusion; MIT, multiple insulin injection therapy; SU, sulfonylurea.

*Median.

(95% CI 0.26-0.56) in type 1 and 0.81 (0.73-0.91) in type 2 DM, indicating a substantial risk reduction in type 1 DM and a smaller risk reduction in type 2 DM ($P < .001$ for difference between the 2 diabetes types). Thirteen comparisons contributed to the analysis of cardiac events. Forty events were recorded in type 1

and 1197 in type 2 DM. The combined IRRs were 0.41 (0.19-0.87) and 0.91 (0.80-1.03) ($P = .040$ for difference). The analysis of peripheral vascular events was based on 10 comparisons. Eighty-eight events were recorded in type 1 and 87 events in type 2 DM. The combined IRRs in type 1 DM were 0.39 (0.25-0.62)

Table II. Glycated hemoglobin levels at baseline and differences between intensified and conventional treatment groups at study end

Study (year of publication)	HbA _{1c} at baseline(%)		HbA _{1c} at study end(%)		Difference
	Intensified	Control	Intensified	Control	
Type 1 DM					
Holman et al (1983) ¹¹	11.7	11.8	9.5	10.2	-0.7
Verrillo et al (1988) ¹⁰	10.8	11.1	7.9	8.7	-0.8
Lauritzen (1991) ⁷	9.6	8.8	7.6	8.1	-0.5
Feldt-Rasmussen et al (1992) ⁷	9.5	9.3	7.3	9.2	-1.9
DCCT Primary Prevention (1993) ⁵	8.8	8.8	7.1	9.0	-1.9
DCCT Secondary Intervention (1993) ⁵	9.0	8.9	7.1	9.0	-1.9
SDIS (1993) ⁸	9.5	9.4	7.1	8.5	-1.4
MCSG (1995) ¹²	10.3	9.8	8.9	9.8	-0.9
Type 2 DM					
Veterans Affairs (1997) ²²	9.3	9.5	7.1	9.2	-2.1
UKPDS 1 (1998) ⁶	7.1	7.0	7.5	8.3	-0.8
UKPDS 2 (1998) ⁶	7.1	7.2	8.0	8.3	-0.3
UKPDS 3 (1998) ²³	7.2	7.0	8.0	8.3	-0.3
Kumamoto Primary Prevention (2000) ⁹	9.5	8.8	7.2	9.4	-2.2
Kumamoto Secondary Intervention (2000) ⁹	9.3	9.0	7.2	9.4	-2.2

UKPDS 1, nonoverweight and sulfonylurea based; UKPDS 2, overweight and sulfonylurea based; UKPDS 3, overweight and metformin based.

and 0.58 (0.38-0.89) in type 2 DM ($P = .22$ for difference). Six strokes were observed in type 1 and 303 in type 2 DM. Combined IRRs were 0.34 (0.05-2.57) and 0.58 (0.46-0.74), respectively ($P = .54$ for difference).

Figure 3 summarizes effect estimates for any macrovascular event and for cardiac, peripheral vascular, and stroke events by type of DM. In 3 studies^{7,10,11} (all in patients with type 1 DM), no macrovascular deaths occurred. Nine deaths occurred in type 1 DM and 441 in type 2 DM. Combined IRRs were comparable: 0.89 (0.27 to 2.98) and 0.88 (0.72 to 1.08) for type 1 and 2 DM, respectively.

Numbers needed to treat to prevent one macrovascular event

The incidence of macrovascular events in conventionally treated patients with type 1 DM ranged from 0.6 per 100 person-years in the MCSG trial¹² to 4.7 in the study of Feldt-Rasmussen et al.⁷ For calculation of NNTs, we assumed a typical incidence of 1 per 100 person-years. In conventionally treated patients with type 2 DM, incidences were more heterogeneous and ranged from 1.3 per 100 person-years in the Kumamoto secondary intervention arm⁹ to 13.7 in the Veterans Affairs study.²² We calculated NNTs assuming typical incidences of 4 per 100 person-years (lower risk) and 8 per 100 person-years (higher risk). Using the IRRs from our meta-analysis (0.38 for type 1 DM and 0.81 for type 2 DM), the numbers of patients that need to receive intensified treatment for 10 years to prevent one macrovascular event were 16 for type 1 DM, 14 for low-risk type 2 DM, and 7 for high-risk type 2 DM.

Sensitivity and meta-regression analyses

Combined IRRs from random-effects models were similar to those from the fixed-effects models. There was little evidence of funnel plot asymmetry in both types of DM ($P > .3$ for all end points). In type 1 DM, the reduction in the risk for macrovascular events associated with improved glycemic control was greater in studies that achieved larger reductions in HbA_{1c} levels ($P = .050$). No such interaction was evident for type 2 DM. In type 2 DM, the beneficial effect of improved glycemic control decreased with longer diabetes duration ($P = .040$). Similarly, older age of study populations was associated with smaller effect ($P = .024$). A comparable trend was found for type 1 DM, although it did not reach statistical significance. There was little evidence for associations with the proportion of women or dimensions of study quality and the inclusion of the year of study begin or reporting did not significantly influence the results. Finally, when excluding the Veterans Affairs study,²² the IRR for macrovascular event of any type was 0.79 (95% CI 0.71-0.88).

Discussion

In this systematic review and meta-analysis, we found that improved glycemic control translated into substantial reductions in macrovascular risk in type 1 DM while producing a smaller reduction in patients with type 2 DM. In type 1 DM, important beneficial effects were evident for cardiac and peripheral vascular events. In type 2 DM, substantial effects were observed for peripheral vascular disease and stroke, whereas cardiac events were not

Table III. Other cardiac risk factors at study end

Study	Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)		Total cholesterol (mmol/L)		HDL cholesterol (mmol/L)	
	Int	Conv	Int	Conv	Int	Conv	Int	Conv
Type 1 DM								
Holman et al (1983) ¹¹	129	133	79	85	4.8	5.1	1.4	1.4
Verrillo et al (1988) ¹⁰	142	140	96	94	na	na	na	na
Lauritzen (1991) ⁷	131	131	85	85	na	na	na	na
Feldt-Rasmussen et al (1992) ⁷	131	133	82	90	na	na	na	na
DCCT Primary Prevention (1993) ¹³	111	114	71	72	4.6	5.0	1.3	1.3
DCCT Secondary Intervention (1993) ¹³	111	114	71	72	4.6	4.7	1.2	1.2
SDIS (1993) ⁸	126	133	77	78	na	na	na	na
MCSG (1995) ¹²	130	127	79	73	na	na	na	na
Type 2 DM								
Veterans Affairs (1997) ²²	137	139	80	83	5.2	5.2	1.0	1.0
UKPDS 1 (1998) ⁶	137	137	76	76	5.0	5.0	1.1	1.1
UKPDS 2 (1998) ⁶	141	139	79	77	5.2	5.2	1.1	1.0
UKPDS 3 (1998) ²³	141	140	78	77	5.3	5.2	1.1	1.1
Kumamoto Primary Prevention (2000) ⁹	126	120	69	68	5.3	5.3	1.3	1.3
Kumamoto Secondary Intervention (2000) ⁹	132	139	72	75	5.3	5.3	1.3	1.3

UKPDS 1, nonoverweight and sulfonylurea based; UKPDS 2, overweight and sulfonylurea based; UKPDS 3, overweight and metformin based. HDL, High-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; Int, intensified treatment group; Conv, conventional treatment group; na, not applicable.

Table IV. Number of events and corresponding person-years

Study	Person-years		Any macrovascular event	
	Intensified	Conventional	Intensified	Conventional
Type 1 DM				
Holman et al (1983) ¹¹	72	76	0	1
Verrillo et al (1988) ¹⁰	110	110	4	3
Lauritzen (1991) ⁷	144	128	1	0
Feldt-Rasmussen et al (1992) ⁷	90	85	0	4
DCCT Primary Prevention (1993) ¹³	2262	2457	12	38
DCCT Secondary Intervention (1993) ¹³	2360	2288	15	46
SDIS (1993) ⁸	360	405	3	6
MCSG (1995) ¹²	178	168	0	1
Total	5576	5717	35	99
Type 2 DM				
Veterans Affairs (1997) ²²	169	176	35	24
UKPDS 1 (1998) ⁶	14760	6067	509	276
UKPDS 2 (1998) ⁶	12571	3126	423	116
UKPDS 3 (1998) ²³	3659	2199	105	88
Kumamoto Primary Prevention (2000) ⁹	224	216	0	4
Kumamoto Secondary Intervention (2000) ⁹	216	224	4	3
Total	31 599	12008	1076	511

UKPDS 1 and 2, in calculations, the number of events and the person-years in the placebo group were halved to prevent double counting. UKPDS 2 and 3, there was overlap in groups receiving conventional treatment and this was taken into account in the meta-analysis by reducing the weight of the respective groups to prevent double counting. UKPDS 1, nonoverweight and sulfonylurea based; UKPDS 2, overweight and sulfonylurea based; UKPDS 3, overweight and metformin based.

found to be reduced significantly. Of note, the number of patients that need to be treated to prevent one macrovascular event (NNT) was lower for type 2 DM compared with type 1 DM. This reflects a higher incidence of

macrovascular events in patients with type 2 DM and thereby a higher a priori risk. Interestingly, improved glycemic control was particularly beneficial in younger patients with shorter diabetes duration.

LDL cholesterol (mmol/L)		Triglycerides (mmol/L)		BMI (kg/m ²)		Percentage of smokers (%)	
Int	Conv	Int	Conv	Int	Conv	Int	Conv
2.7	2.9	1.6	1.8	24.9	24.8	na	na
na	na	na	na	na	na	na	na
na	na	na	na	na	na	na	na
na	na	na	na	na	na	na	na
2.8	3.1	1.1	1.2	26.2	25.1	28	23
2.9	3.0	1.1	1.1	27.2	25.3	27	21
na	na	na	na	23.9	23.3	na	na
na	na	na	na	na	na	na	na
3.4	3.3	2.0	2.0	31.9	32.7	21	8
3.2	3.2	1.6	1.5	26.0	25.4	29	36
3.4	3.4	2.0	2.0	33.0	32.4	30	25
3.4	3.4	2.2	2.0	31.7	32.2	27	27
na	na	1.1	1.2	21.5	21.3	na	na
na	na	1.1	1.2	21.5	21.3	na	na

Cardiac events		Peripheral vascular events		Cerebrovascular events	
Intensified	Conventional	Intensified	Conventional	Intensified	Conventional
0	1	0	0	0	0
2	0	1	0	1	1
1	0	0	0	0	0
0	0	0	0	0	4
1	11	11	27	0	0
3	12	12	34	0	0
3	5	0	0	0	0
0	1	0	0	0	0
10	30	24	64	1	5
26	18	4	4	5	2
401	184	17	12	91	80
327	87.5	20	10	76	18.5
84	64.5	8	9	13	14.5
0	1	0	1	0	2
3	1	1	1	0	1
841	356	50	37	185	118

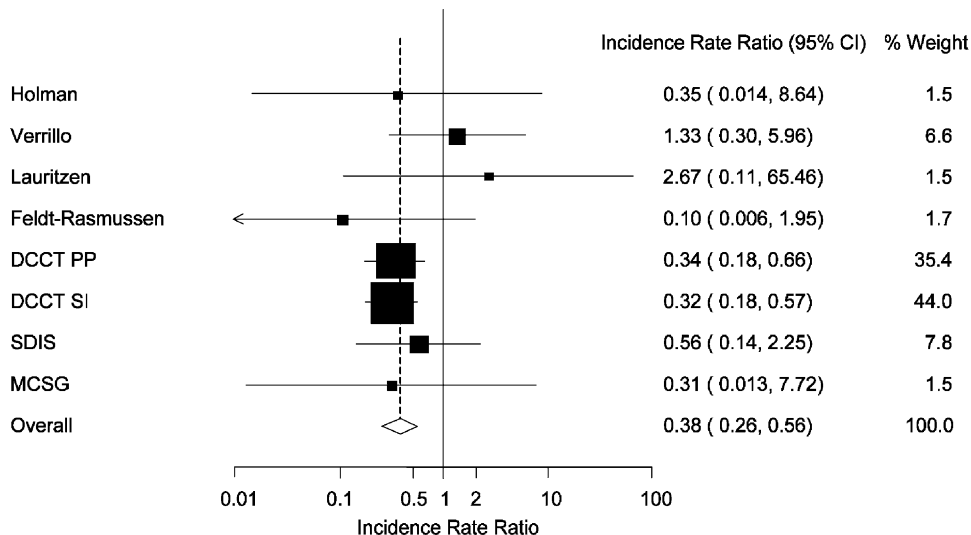
Strengths and limitations

This is the first systematic review and meta-analysis including all randomized controlled trials done in patients with type 1 and type 2 DM. The effects of

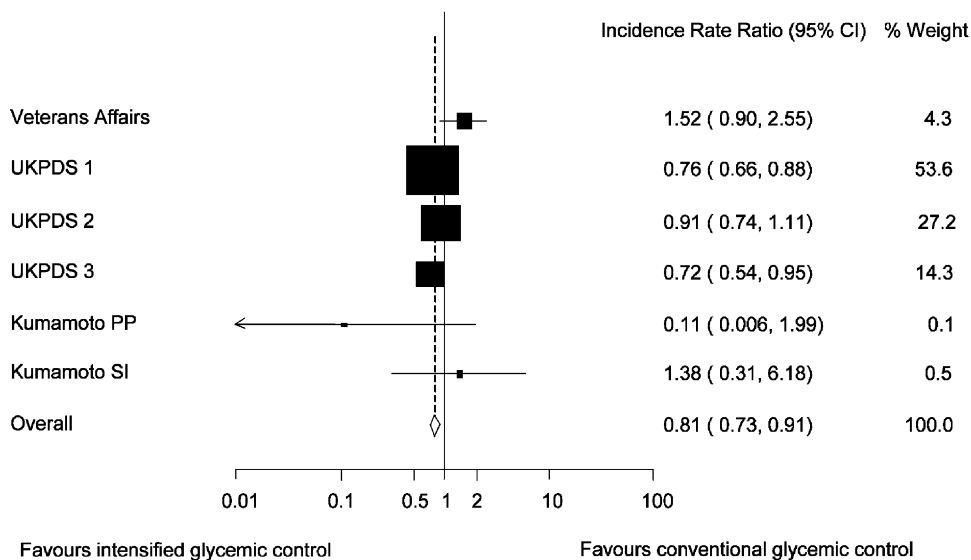
improved glycemic control could thus be compared between the 2 types of DM within the same review framework, using identical definitions and methodology. Previous reviews were restricted to one type of DM and

Figure 2

Trials in type 1 diabetes



Trials in type 2 diabetes



Effect of intensified glyceemic control on the risk for any type of macrovascular event in patients with type 1 and type 2 DM. Meta-analysis of randomized controlled trials.

not directly comparable.^{25,26} Our study was based on a comprehensive literature search. Original investigators checked the extracted data and contributed additional information. We acknowledge that the inclusion of large studies as DCCT in type 1 DM and UKPDS in type 2 DM could potentially have led to distortion of the results. As a consequence, whenever a study included several

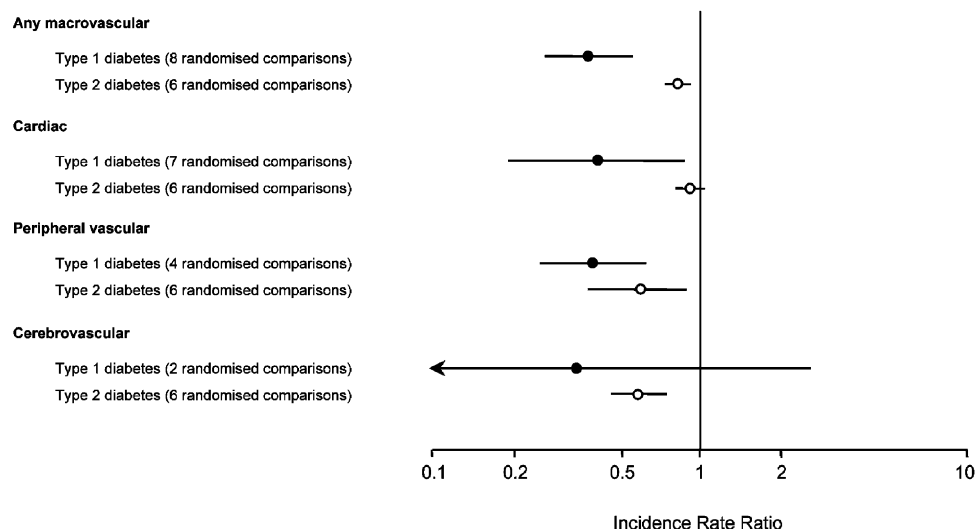
randomized comparisons, we included them separately to minimize individual weight and to maximize the power to identify factors that may modify the effect of improved glyceemic control. For example, the separate inclusion of the primary and secondary prevention cohorts from the DCCT⁵ and Kumamoto⁹ studies meant that the power to detect a possible interaction between

Table V. Incidence rate ratios (95% CI) for any macrovascular event and cardiac, peripheral vascular, and cerebrovascular events

Study	Any macrovascular	Cardiac	Peripheral vascular	Cerebrovascular
Type 1 DM				
Holman et al (1983) ¹¹	0.35 (0.014-8.64)	0.35 (0.014-8.64)	0 events	0 events
Verrillo et al (1988) ¹⁰	1.33 (0.30-5.96)	5.00 (0.24-104.15)	0.50 (0.05-5.51)	1.00 (0.06-15.99)
Lauritzen (1991) ⁷	2.67 (0.11-65.46)	2.67 (0.11-65.64)	0 events	0 events
Feldt-Rasmussen et al (1992) ⁷	0.10 (0.006-1.95)	0 events	0 events	0.10 (0.006-1.95)
DCCT Primary Prevention (1993) ¹³	0.34 (0.18-0.66)	0.10 (0.013-0.76)	0.44 (0.22-0.89)	0 events
DCCT Secondary Intervention (1993) ¹³	0.32 (0.18-0.57)	0.24 (0.07-0.86)	0.34 (0.18-0.66)	0 events
SDIS (1993) ⁸	0.56 (0.14-2.25)	0.68 (0.16-2.82)	0.38 (0.02-9.21)	0 events
MCSG (1995) ¹²	0.31 (0.013-7.72)	0.31 (0.013-7.72)	0 events	0 events
Combined IRR (fixed effect)	0.38 (0.26-0.56)	0.41 (0.19-0.87)	0.39 (0.25-0.62)	0.34 (0.05-2.57)
Heterogeneity (<i>I</i> ² , test of heterogeneity)	0.0%, <i>P</i> = .579	13.6%, <i>P</i> = .326	0.0%, <i>P</i> = .957	16.9%, <i>P</i> = .273
Type 2 DM				
Veterans Affairs (1997) ²²	1.52 (0.90-2.55)	1.50 (0.82-2.74)	1.04 (0.26-4.16)	2.60 (0.50-13.40)
UKPDS 1 (1998) ⁶	0.76 (0.66-0.88)	0.90 (0.75-1.07)	0.58 (0.28-1.22)	0.47 (0.35-0.63)
UKPDS 2 (1998) ⁶	0.91 (0.74-1.11)	0.93 (0.73-1.18)	0.50 (0.23-1.06)	1.02 (0.61-1.70)
UKPDS 3 (1998) ²³	0.72 (0.54-0.95)	0.78 (0.57-1.08)	0.60 (0.21-1.38)	0.54 (0.25-1.14)
Kumamoto Primary Prevention (2000) ⁹	0.11 (0.006-1.99)	0.32 (0.013-7.89)	0.32 (0.013-7.89)	0.19 (0.009-4.02)
Kumamoto Secondary Intervention (2000) ⁹	1.38 (0.31-6.18)	3.11 (0.32-29.91)	1.04 (0.06-16.58)	0.35 (0.014-8.49)
Combined IRR (fixed effect)	0.81 (0.73-0.91)	0.91 (0.80-1.03)	0.58 (0.38-0.89)	0.58 (0.46-0.74)
Heterogeneity (<i>I</i> ² , test of heterogeneity)	52.8%, <i>P</i> = .060	2.0%, <i>P</i> = .404	0.0%, <i>P</i> = .948	52.8%, <i>P</i> = .060

UKPDS 1, nonoverweight and sulfonylurea based; UKPDS 2, overweight and (SU) based; UKPDS 3, overweight and mefformin based.

Figure 3



Effect of intensified glycemic control on the risk for any type of macrovascular event and of cardiac, peripheral vascular, and cerebrovascular events in patients with type 1 and type 2 DM. Combined estimates from meta-analyses of randomized controlled trials.

diabetes duration and the effect of improved glycemic control was enhanced. Random-effects model, attributing increased weight to smaller comparisons, revealed very comparable IRRs.

Although our study represents the largest body of evidence from randomized trials ever assembled to

address this issue, the patients included in these trials may not be representative of patients with DM at large. Trials in type 1 DM enrolled young patients, most of them in their twenties and thirties, who were at low risk for macrovascular events. Trial participants with type 2 DM were also quite young, typically in their fifties.

Women were enrolled in all but one trial, but they generally were in the minority. The exclusion of women and older persons from trials has been documented previously, for example, in trials of statins.²⁷ It is difficult to judge whether the risk reductions observed in this meta-analysis are applicable to older patients and patients with longer duration of DM. We found that reductions in macrovascular risk tended to decrease with increasing age and duration of DM, particularly in type 2 DM, but in absolute terms, benefits may be as great or greater because of the increased macrovascular risk in the elderly. Finally, the duration of follow-up was generally <10 years, which may be insufficient if several years of treatment are required for effects to materialize fully.

Relation to other studies

Epidemiological studies have shown that the degree of blood glucose control achieved in patients with DM is associated with cardiac risk. Indeed, a recent meta-analysis of observational studies showed an increase in cardiac risk with increasing levels of HbA_{1c} both in patients with type 1 and type 2 DM.²⁸ Epidemiological analyses of the UKPDS showed a close relationship between HbA_{1c} and macrovascular risk.²⁹ In type 1 DM, the present analysis confirms an association of HbA_{1c} with macrovascular complications. Compared with a previous meta-analysis in patients with type 1 DM,²⁶ the present analysis included a larger number of studies and macrovascular events. In contrast to the aforementioned reports, metaregression analysis did not reveal a significant dependency of macrovascular risk on HbA_{1c} in type 2 DM. On one hand, this discrepancy could be due to statistical reasons in the present analysis and to the limitations of metaregression technique (analysis in type 2 DM only based on 6 comparisons, differences of HbA_{1c} lying in a close range). On the other hand, average changes in HbA_{1c} on study level might not entirely reflect efforts to improve glycemic control. The corresponding treatment strategies could nevertheless have beneficial effects on vascular end points not detected solely by measurement of HbA_{1c} (eg, reduction of postprandial hyperglycemia as a significant vascular risk factor as discussed hereinafter). In contrast to a broad analysis of interventions to prevent cardiac events in patients with type 2 DM,²⁵ we excluded the DIGAMI trial,³⁰ which showed that insulin-glucose infusion followed by a multidose insulin regimen improved prognosis in diabetic patients with acute myocardial infarction. The second DIGAMI trial³¹ did not confirm a positive effect of intensified glycemic control in the setting of acute myocardial infarction. Recently, a U-shaped relationship of glycemic control with outcomes in acute coronary syndrome and myocardial infarction has been shown.³² In contrast to these studies focusing on glycemic control in the setting of acute

myocardial infarction, the present meta-analysis investigated the effect of improved long-term glycemic control in a general diabetic population.

Possible mechanisms

What factors could explain the finding that, in type 2 DM, improved glycemic control leads to a more modest reduction of macrovascular events and does not appear to have a significant impact on cardiac events? First, the metabolic abnormalities typical for type 2 DM not only lead to insulin resistance and hyperglycemia but also to dyslipidemia, arterial hypertension, endothelial dysfunction, and increased platelet activity and coagulability.³³ Improving blood glucose control without also addressing the other abnormalities, most importantly hypertension, dyslipidemia, and platelet hyperactivity, may therefore produce only limited benefit. Indeed, recent randomized trials of multifactorial interventions, including the tight blood pressure control arm of the UKPDS, showed substantial reductions in cardiac events.^{29,34} Of note, in our analysis, the distribution of cardiac risk factors was similar both after randomization and at the conclusion of studies. One exception was the Veterans Affairs study²² where smoking was more prevalent in the intensive treatment group. This imbalance, combined with the long duration of diabetes in this study population, may explain the anomalous results of this trial. Interventions that reduce insulin resistance have been shown to have antiatherogenic effects,³⁵⁻³⁸ and this may have produced the somewhat larger benefits seen in overweight UKPDS patients randomized to metformin. In patients with type 1 DM, particularly younger patients, other macrovascular risk factors are less common and the nonenzymatic glycation of proteins and lipids, and the resulting formation of advanced glycation end products may thus be the predominant mechanism in the development of macrovascular and microvascular disease.^{39,40}

Second, in trials in type 1 DM, the intensified regimen generally included basal and prandial insulin (multiple insulin injections or continuous subcutaneous insulin injection), which will have reduced postprandial as well as basal hyperglycemia. Postchallenge hyperglycemia is strongly associated with macrovascular complications. For example, in the DECODE study,⁴¹ it was the postload blood glucose concentration that was independently associated with mortality. Furthermore, a post hoc analysis of the STOP-NIDDM trial⁴² showed that decreasing postprandial hyperglycemia with the α -glucosidase inhibitor acarbose reduced cardiac risk in patients with impaired glucose tolerance. Intensified treatment regimens in type 2 DM focused mainly on normalizing basal blood glucose. The better control of postprandial hyperglycemia in type 1 DM may thus have contributed to the differences observed between the 2 types of DM.

Implications and conclusions

Our results suggest that, in type 1 DM, glycemic control is the essential treatment strategy leading not only to the well-documented reduction of microvascular complications but also to a substantial reduction of macrovascular disease. In patients with type 2 DM, improved glycemic control is associated with a more modest reduction in macrovascular complications. In these patients, the prevention of cardiac events must be effected by means of a broader treatment strategy, including antihypertensive, lipid-lowering, and platelet-inhibiting measures. The improvement of glycemic control itself appears to be particularly effective in younger patients with shorter duration of the disease. Ongoing studies will help to better define the benefits and risks of improved blood glucose control in type 2 DM, including the large ACCORD trial.⁴³

We thank the original investigators who provided additional data and checked data extracted from the publications: Bo Feldt-Rasmussen, Per Reichard, Antonio Verrillo, Knut Dahl-Jorgensen, Carlos Abraira, Rebecca Martinez, Motoaki Shichiri, and Hideki Kishikawa. Special thanks to Michael Steffes and collaborators for help with extracting data from the DCCT trial, to Carol Lefebvre for providing assistance in literature search strategies, and to Emanuel R. Christ for valuable comments.

References

1. Haffner SJ, Cassells H. Hyperglycemia as a cardiovascular risk factor. *Am J Med* 2003;115(Suppl 8A):6S-11S.
2. Libby P, Plutzky J. Diabetic macrovascular disease: the glucose paradox? *Circulation* 2002;106:2760-3.
3. Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. I. Survival, causes of death, and complications. *Diabetologia* 1978;14:363-70.
4. Morrish NJ, Stevens LK, Head J, et al. A prospective study of mortality among middle-aged diabetic patients (the London Cohort of the WHO Multinational Study of Vascular Disease in Diabetics) I: causes and death rates. *Diabetologia* 1990;33:538-41.
5. 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* 1993;329:977-86.
6. 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* 1998;352:837-53.
7. Feldt-Rasmussen B, Mathiesen ER, Jensen T, et al. Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetic patients: an update of the Steno studies. *Diabetologia* 1991;34:164-70.
8. Reichard P, Pihl M. Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. *Diabetes* 1994;43:313-7.
9. Shichiri M, Kishikawa H, Ohkubo Y, et al. Long-term results of the Kumamoto study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 2000;23(Suppl 2):B21-9.
10. Verrillo A, de Teresa A, Martino C, et al. Long-term correction of hyperglycemia and progression of retinopathy in insulin dependent diabetes. A five-year randomized prospective study. *Diabetes Res* 1988;8:71-6.
11. Holman RR, Dornan TL, Mayon-White V, et al. Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. A two-year randomised prospective study. *Lancet* 1983;1:204-8.
12. Intensive therapy and progression to clinical albuminuria in patients with insulin dependent diabetes mellitus and microalbuminuria. Microalbuminuria Collaborative Study Group, United Kingdom. *BMJ* 1995;311:973-7.
13. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol* 1995;75:894-903.
14. Egger M, Davey Smith G. Meta-analysis: potentials and promise. *BMJ* 1997;315:1371-4.
15. Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *Int J Epidemiol* 2002;31:150-3.
16. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001;323:42-6.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.
18. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;317:1309-12.
19. Egger M, Davey Smith G, Minder C. Bias in meta-analysis detected by a simple, graphical test—authors reply. *BMJ* 1998;316:470-1.
20. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
21. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999;18:2693-708.
22. Abraira C, Colwell J, Nuttall F, et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. *Arch Intern Med* 1997;157:181-8.
23. Effect of intensive blood-glucose control with meformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854-65.
24. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. *Diabetologia* 1991;34:877-90.
25. Huang ES, Meigs JB, Singer DE. The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. *Am J Med* 2001;111:633-42.
26. Lawson ML, Gerstein HC, Tsui E, et al. Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes. A systematic review and meta-analysis. *Diabetes Care* 1999;22(Suppl 2):B35-9.
27. Bartlett C, Davey P, Dieppe P, et al. Women, older persons, and ethnic minorities: factors associated with their inclusion in randomised trials of statins 1990 to 2001. *Heart* 2003;89:327-8.
28. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;141:421-31.

29. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317:703-13.
30. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;26:57-65.
31. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;26:650-61.
32. Svensson AM, McGuire DK, Abrahamsson P, et al. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J* 2005;26:1255-61.
33. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002;287:2570-81.
34. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383-93.
35. Tan MH, Johns D, Strand J, et al. Sustained effects of pioglitazone vs. glibenclamide on insulin sensitivity, glycaemic control, and lipid profiles in patients with type 2 diabetes. *Diabet Med* 2004;21:859-66.
36. Nesto R. C-reactive protein, its role in inflammation, type 2 diabetes and cardiovascular disease, and the effects of insulin-sensitizing treatment with thiazolidinediones. *Diabet Med* 2004;21:810-7.
37. Dunn CJ, Peters DH. Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995;49:721-49.
38. Giugliano D, De Rosa N, Di Maro G, et al. Metformin improves glucose, lipid metabolism, and reduces blood pressure in hypertensive, obese women. *Diabetes Care* 1993;16:1387-90.
39. Brownlee M. Glycation products and the pathogenesis of diabetic complications. *Diabetes Care* 1992;15:1835-43.
40. Baynes JW. Role of oxidative stress in development of complications in diabetes. *Diabetes* 1991;40:405-12.
41. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. *Diabetes Epidemiology: collaborative analysis Of Diagnostic criteria in Europe*. *Lancet* 1999;354:617-21.
42. Chiasson JL, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003;290:486-94.
43. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, (<http://www.accordtrial.org/public/index.cfm>), accessed August 22, 2005.

Appendix A. Contributors

Christoph Stettler, Peter Diem, and Matthias Egger wrote the review protocol. Christoph Stettler and Sabin Allemann undertook the literature search, contacted trialists, performed data extraction, and assessed the methodological quality of trials. Rury R. Holman and Carole A. Cull performed data extraction on the UKPDS data. Matthias Egger, Peter Jüni, Sabin Allemann, and Christoph Stettler performed the statistical analyses. All authors contributed to the writing of the final draft of the manuscript.

2.2 Study B: Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised trials

Sabin Allemann¹, Peter Diem², Matthias Egger^{1,3}, Emanuel R. Christ², Christoph Stettler²

1) Department of Social and Preventive Medicine, University of Bern, Switzerland

2) Division of Endocrinology and Diabetes, University of Bern, Switzerland

3) MRC Health Services Research Collaboration Department of Social Medicine, University of Bristol, United Kingdom

Article published in:

Curr Med Res Opin 2006 Mar;22(3):617-23.

Abstract provided at:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16574044&query_hl=1&itool=pubmed_docsum

ORIGINAL ARTICLE

Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials

Sabin Allemann^a, Peter Diem^b, Matthias Egger^{a,c}, Emanuel R. Christ^b and Christoph Stettler^b

^a Department of Social and Preventive Medicine, University of Bern, Switzerland

^b Division of Endocrinology and Diabetes, University of Bern, Switzerland

^c MRC Health Services Research Collaboration Department of Social Medicine, University of Bristol, UK

Address for correspondence: Christoph Stettler, MD, Division of Endocrinology and Diabetes, University Hospital, 3011 Bern, Switzerland. Tel.: +41-31-632-40-72; Fax: +41-31-632-84-14; email: christoph.stettler@insel.ch

Key words: Coronary heart disease – Diabetes mellitus – Fibrates – Meta-analysis

ABSTRACT

Objective: To assess the impact of lipid lowering treatment with fibrates on cardiovascular endpoints in patients with type 2 diabetes mellitus.

Methods: MEDLINE (from inception to November 2005) and the Cochrane Controlled Trials Register (including Issue 3, 2005) were searched for randomised controlled trials comparing therapy with fibrates to placebo in patients with type 2 diabetes mellitus. Electronic searches were supplemented by manual searching of reference lists, reviews, conference abstracts and specialist journals. Incidence rate ratios (IRRs) were estimated using a fixed effects model. The primary endpoint was the IRR for coronary heart disease (CHD) events (a combination of non fatal myocardial infarction and death due to CHD). Secondary endpoints included: (1) death due to CHD; (2) fatal and non fatal myocardial infarction; and (3) fatal and non fatal stroke.

Results: Eight trials and 12249 patients with type 2 diabetes were included in the analyses.

A total of 924 CHD events (418 and 506 in the treatment and placebo groups, respectively) occurred during a follow up of 60395 person-years (30106 and 30289 in treatment and placebo groups). The combined IRR for CHD events was 0.84 (95% confidence interval [CI] 0.74–0.96, $p = 0.008$). The numbers needed to treat (NNTs) to prevent one CHD event over 10 years were nine and 26 for patients with and without pre-existing CHD, respectively. IRRs for death due to CHD, myocardial infarction and stroke were 0.96 (95% CI 0.77–1.20, $p = 0.73$), 0.88 (95% CI 0.69–1.12, $p = 0.30$) and 0.87 (95% CI 0.73–1.05, $p = 0.14$), respectively. Larger benefits were found when restricting the analysis to trials that were not confounded by unequal provision of additional lipid-lowering therapy.

Conclusions: Fibrates are associated with a substantial reduction of CHD events, but their exact role in lipid lowering treatment of patients with type 2 diabetes mellitus remains to be defined.

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus¹. The characteristic dyslipidaemia of insulin resistance, i.e. increased concentrations of triglycerides, decreased high density lipoprotein (HDL) cholesterol levels and increased 'small dense' low density lipoproteins (LDLs) contribute to the increased cardiovascular risk². Fibrates are well established agonists of the peroxisome proliferator-activated receptors alpha (PPAR α), which are mainly expressed in liver, heart and skeletal muscle³. They have been shown to stimulate the expression of genes involved in fatty acid and lipoprotein metabolism, resulting in a shift from hepatic fat synthesis to fat oxidation^{4,5}. This leads to a substantial reduction in serum triglycerides and an increase in HDL cholesterol concentrations⁶⁻⁸.

Despite well documented lipid lowering effects, there is still uncertainty about the role of fibrates in the prevention of cardiovascular disease. A recent meta-analysis of trials comparing fibrates with placebo showed little evidence for a reduced cardiac mortality with fibrate treatment, but the analysis did not distinguish between patients with and without type 2 diabetes mellitus⁹. In patients with type 2 diabetes, several randomised controlled trials failed to demonstrate a significant reduction of coronary heart disease (CHD) with fibrates^{6,7,11}. In contrast, a subgroup analysis of the Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT) suggested a beneficial effect of fibrate therapy on CHD in patients with type 2 diabetes⁸. The recent Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, which included 9795 patients with diabetes, showed a 11% reduction of CHD, which failed to reach statistical significance ($p = 0.16$)¹². We performed a systematic review and meta-analysis of randomised controlled trials in order to assess the effectiveness of fibrates in the prevention of CHD in this patient group.

Materials and methods

Literature search and eligibility criteria

We aimed to identify all randomised controlled trials of lipid lowering treatment by fibrates that prospectively assessed cardiovascular outcomes in patients with type 2 diabetes mellitus. Using Cochrane methodology¹³ we searched MEDLINE (from inception to November 2005) and the Cochrane Controlled Trials Register (issue 3, 2005) for relevant studies in any language. Electronic searches were supplemented by manual searching of reference lists, reviews, conference

abstracts and specialist journals. We evaluated each study for inclusion in the meta-analysis on the basis of five criteria: (1) study design (randomised controlled trial); (2) comparison of lipid lowering therapy with a fibrate to placebo; (3) inclusion of patients with type 2 diabetes mellitus; (4) follow-up of at least 2 years; and (5) prospective recording of cardiovascular events.

Data extraction and outcome measures

Two reviewers independently assessed publications for eligibility and extracted data, with discrepancies being resolved in consultation with a third reviewer. All relevant publications from a trial were considered, including, for example, early publications describing the study design. The primary endpoint was the incidence of CHD events (defined as a combination of non fatal myocardial infarction or death due to CHD). Secondary endpoints were: (1) death due to CHD (e.g. fatal myocardial infarction, death due to congestive heart failure, sudden death); (2) fatal and non fatal myocardial infarction; and (3) fatal and non fatal stroke. If data on the predefined outcomes were not reported for patients with type 2 diabetes separately, original investigators were asked for additional information.

Assessment of methodological quality

Two investigators independently assessed the adequacy of the concealment of allocation of patients to treatment groups and blinding of care providers and research staff ascertaining cardiovascular outcomes. Disagreements were resolved in discussion with a third reviewer.

Statistical analysis

Incidence rate ratios (IRRs) were combined in a fixed-effects meta-analysis. We calculated the *I*-squared statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance, and applied standard tests of heterogeneity. In sensitivity analyses, we repeated analyses using random effects models and did tests of funnel plot asymmetry¹⁴.

Separate analyses were performed for trials assessing the effect of fibrates in patients without pre-existing CHD (primary prevention) and in patients with known CHD (secondary prevention). The extent to which the effect of treatment with fibrates was modified by study-level variables was explored in univariable meta-regression models¹⁵. The following variables were considered: mean age at baseline, duration of diabetes, body mass index, proportion of smokers, proportion of women, mean total cholesterol at baseline and at study follow up, mean LDL cholesterol at baseline

and at study follow up, mean HDL cholesterol at baseline and at study follow up, mean triglyceride level at baseline and at study follow up and parameters of methodological quality. The number of patients that need to be treated (NNT) in order to prevent one CHD event, or one death due to CHD, was calculated by applying the combined IRRs to incidence rates typical for placebo groups. Finally, analyses were repeated after the exclusion of trials that allowed additional lipid modifying treatment in the fibrate and control groups. All analyses were performed using Stata version 8.2 (Stata Corporation, College Station, TX, USA).

Results

We screened 226 potentially eligible reports and identified 11 trials fulfilling the inclusion criteria (Figure 1). Five trials were performed in patients with type 2 diabetes^{6,7,11,12,16} and six trials included patients with and without diabetes^{10,17-21}. For three of these trials separate data for diabetic patients were unavailable and these trials were therefore excluded^{18,19,21}. Eight trials were included in the analysis^{6-8,10-12,16,22}. Trials were of high methodological quality; appropriate methods of concealment of allocation of patients to treatment group were described in all trials, and all but one trial¹¹ reported analyses according to the intention-to-treat principle. For one trial the degree of blinding of outcome assessors remained unclear¹¹. The characteristics of trials and patients are shown in Table 1.

Coronary heart disease

All trials contributed to the analysis of the primary endpoint. During a follow up of 60 395 person-years (30 106 and 30 289 in the treatment and placebo group,

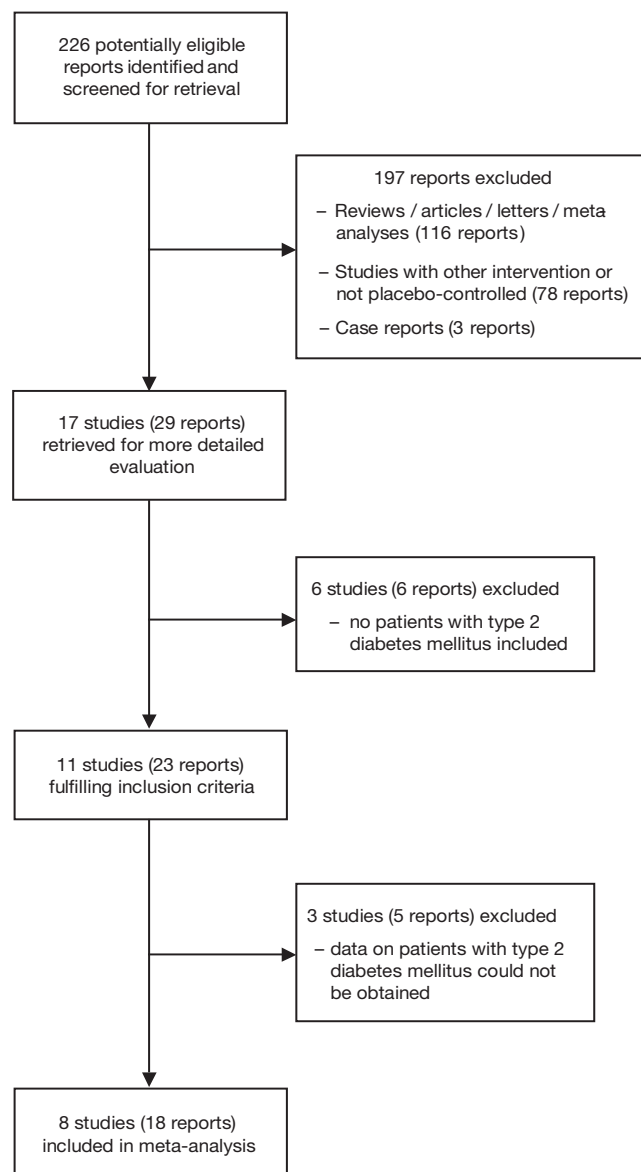


Figure 1. Identification of randomised controlled trials comparing fibrates with placebo for the prevention of coronary heart disease in patients with type 2 diabetes mellitus

Table 1. Baseline characteristics of patients with type 2 diabetes mellitus enrolled in eight randomised controlled trials comparing fibrates with placebo for the prevention of cardiovascular disease in patients with type 2 diabetes mellitus

Trial (year of first publication)	Treatment group, n	Control group, n	Females, %	Mean age, years	Current smokers, %	Mean diabetes duration, years	Mean follow up, years	Drug	Intervention
Cullen <i>et al.</i> (1974) ¹¹	20	20	60	51	NR	10.6	2.0	Clofibrate	PP
Helsinki (1987) ^{20,22}	59	76	NR	49	27	NR	5.0	Gemfibrozil	PP
DIS (1991) ⁶	379	382	44	46	34	0.0	5.0	Clofibric acid	PP
SENDCAP (1998) ¹⁶	81	83	29	51	18	5.1	3.0	Bezafibrate	PP
VA-HIT (1999) ^{8,17}	309	318	0	65	15	NR	5.1*	Gemfibrozil	SP
BIP (2000) ¹⁰	155	154	13	61	NR	NR	6.2	Bezafibrate	SP
DAIS (2001) ⁷	207	211	27	57	15	8.6	3.0	Fenofibrate	SP
FIELD (2005) ¹²	4895	4900	37	62	9	5.0*	5.0*	Fenofibrate	Mixed: 78% PP 22% SP

*Median

NR = not reported; PP = primary prevention; SP = secondary prevention; Helsinki = Helsinki Heart Study; DIS = Diabetes Intervention Study; SENDCAP = St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention Study; VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial; BIP = Bezafibrate Infarction Prevention Study; DAIS = Diabetes Atherosclerosis Intervention Study; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes Trial

respectively) a total of 924 CHD events (418 and 506 in the treatment and placebo group, respectively) were recorded. The IRR was 0.84 (95% confidence interval [CI] 0.74–0.96), indicating a 16% risk reduction of CHD events with therapy by fibrates compared to placebo ($p = 0.008$) (Table 2, Figure 2).

Death due to coronary heart disease

The analysis for this endpoint was based on seven trials^{6,7,8,10,11,12,16} and 327 deaths due to CHD (159 and 168 in the treatment and placebo group, respectively) during a follow up of 59 720 person-years (29 811 and 29 909 in the treatment and placebo group,

respectively). The IRR was 0.96 (95% CI 0.77–1.20), indicating a risk reduction of 4% for death due to CHD after treatment with fibrates ($p = 0.73$) (Table 2).

Myocardial infarction and stroke

Five trials were included in each of the analyses of myocardial infarction^{6,7,8,10,16} and stroke^{7,8,10,12,16}. A total of 268 fatal and nonfatal myocardial infarctions (124 and 144 in the treatment and placebo group, respectively), during a follow up of 10 665 person-years (5296 and 5369 in the treatment and placebo group, respectively), and 461 fatal and nonfatal strokes (214 and 247 in the treatment and the placebo group, respectively), during

Table 2. Meta-analysis of results from eight randomised controlled trials comparing fibrates with placebo for the prevention of cardiovascular disease and stroke in patients with type 2 diabetes mellitus

Trial (year of first publication)	Incidence rate ratio (95% confidence interval)			
	CHD events	Death due to CHD	Myocardial infarction	Stroke
Cullen <i>et al.</i> (1974) ¹¹	0.33 (0.014–8.18)	0.33 (0.014–8.18)	NR	NR
Helsinki (1987) ^{20,22}	0.32 (0.07–1.52)	NR	NR	NR
DIS (1991) ⁶	1.07 (0.55–2.07)	1.01 (0.06–16.11)	1.07 (0.55–2.07)	NR
SENDCAP (1998) ¹⁶	0.26 (0.03–2.29)	0.34 (0.014–8.38)	0.34 (0.04–3.28)	0 events
VA-HIT (1999) ^{8,17}	0.70 (0.54–0.91)	0.60 (0.40–0.92)	0.79 (0.58–1.08)	0.66 (0.42–1.04)
BIP (2000) ¹⁰	1.06 (0.65–1.73)	1.09 (0.46–2.57)	1.22 (0.69–2.14)	0.99 (0.53–1.88)
DAIS (2001) ⁷	0.75 (0.34–1.63)	0.76 (0.17–3.42)	0.74 (0.30–1.84)	1.19 (0.40–3.54)
FIELD (2005) ¹²	0.89 (0.75–1.05)	1.18 (0.90–1.56)	NR	0.90 (0.73–1.12)
Combined incidence rate ratio (fixed effect)	0.84 (0.74–0.96)	0.96 (0.77–1.20)	0.88 (0.69–1.12)	0.87 (0.73–1.05)
Combined incidence rate ratio (random effect)	0.84 (0.74–0.96)	0.89 (0.64–1.25)	0.88 (0.69–1.12)	0.87 (0.73–1.05)
Heterogeneity (<i>I</i> -squared, <i>p</i> from test of heterogeneity)	0%, <i>p</i> = 0.47	23.5%, <i>p</i> = 0.25	0%, <i>p</i> = 0.58	0%, <i>p</i> = 0.56

CHD = coronary heart disease; NR = not reported; Helsinki = Helsinki Heart Study; DIS = Diabetes Intervention Study; SENDCAP = St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention Study; VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial; BIP = Bezafibrate Infarction Prevention Study; DAIS = Diabetes Atherosclerosis Intervention Study; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes Trial

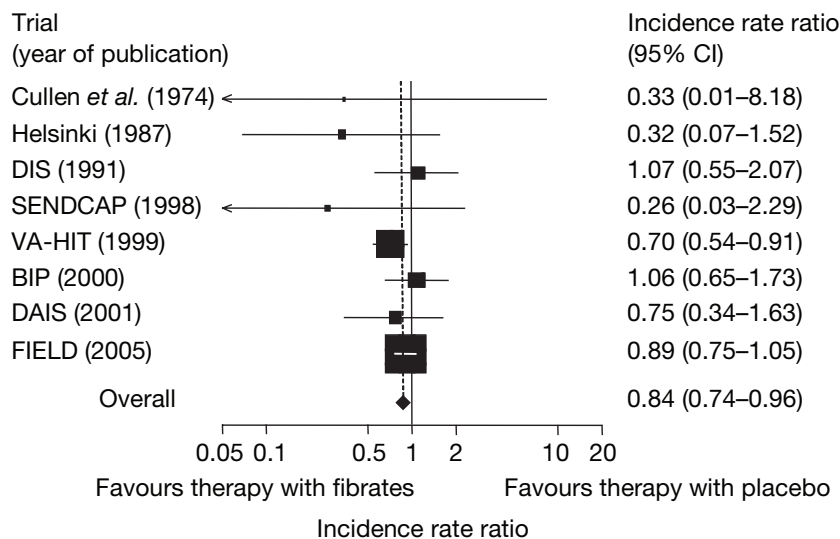


Figure 2. Meta-analysis of randomised controlled trials comparing fibrates with placebo for the prevention of coronary heart disease in patients with type 2 diabetes mellitus. The size of the squares is proportional to the trial's weight in the fixed-effects meta-analysis; horizontal lines indicate 95% confidence intervals

a follow up of 55 343 person-years (27 633 and 27 710 in the treatment and placebo group, respectively), were recorded. The corresponding IRRs were 0.88 (95% CI 0.69–1.12, $p = 0.30$) and 0.87 (95% CI 0.73–1.05, $p = 0.14$), respectively (Table 2).

Sensitivity analyses

The combined IRRs from random effects models were identical or similar to those from the fixed effects models (Table 2). There was little evidence of funnel plot asymmetry ($p > 0.3$ for all endpoints). In meta-regression analysis, there was a positive association between the lowering of triglyceride levels and the reduction in CHD events ($p = 0.036$). This was not the case for total cholesterol, LDL cholesterol and HDL cholesterol. Moreover, there was little evidence for an association with mean age, body mass index, the proportion of women, smoking prevalence or diabetes duration. The IRRs did not materially change when the study with unclear blinding of endpoint assessors was excluded from the analysis¹¹. Two trials were confounded by unequal provision of additional lipid modifying therapy and re-analysis of the data, excluding the Bezafibrate Infarction Prevention (BIP)¹⁰ and FIELD¹² trials, gave an IRR of 0.72 (95% CI 0.57–0.90, $p = 0.004$) for CHD events and 0.61 (95% CI 0.41–0.91, $p = 0.014$) for death due to CHD. Analyses of trials assessing the effect of fibrates in patients without pre-existing CHD (primary prevention)^{6,11,16,22} and in patients with known CHD (secondary prevention)^{7,8,10} gave similar results, with non-significant tests of interaction; IRRs for CHD events were 0.79 and 0.77 ($p = 0.93$ by test of interaction), IRRs for death due to CHD were 0.52 and 0.68, ($p = 0.77$). The IRR from the overall analysis was therefore used in the calculation of NNTs.

Number needed to treat in primary and secondary prevention settings

Based on the mean of the incidences observed in the placebo groups, we assumed a typical incidence of 1.67 CHD events per 100 person-years for patients without pre-existing CHD (primary prevention) and 4.79 CHD events per 100 person-years for patients with pre-existing CHD (secondary prevention). When the corresponding IRRs were applied to these rates, we found that in the primary prevention setting 26 patients needed to be treated over 10 years to prevent one CHD event. The NNT for patients with pre-existing CHD was lower (nine over 10 years), due to the higher baseline risk. Similarly, the NNTs to prevent one death due to CHD were 32 and 18 over 10 years for primary and secondary prevention, respectively.

Discussion

We found that in patients with type 2 diabetes mellitus, lipid-lowering therapy with fibrates reduced the rate of CHD. The numbers needed to treat over 10 years to prevent one CHD event were 9 and 26 for patients with and without pre-existing CHD, respectively. There was a tendency towards reduction of myocardial infarction and stroke, but this did not reach conventional levels of statistical significance. More pronounced effects, including a reduction of CHD mortality, were found when restricting the analysis to trials that were not confounded by unequal provision of additional lipid-lowering therapy.

Relation to other studies and possible mechanisms

PPAR α agonists may be of particular benefit in patients with type 2 diabetes. This may be due to the fact that the increased risk for cardiovascular disease in patients with type 2 diabetes is related to their characteristic dyslipidaemia, consisting of low HDL cholesterol, high triglyceride and 'small dense' LDL concentrations²³. Fibrates specifically lower triglyceride and increase HDL-cholesterol concentrations, thereby improving the atherogenic lipid profile in these patients^{6–8,24}. In addition to dyslipidaemia, type 2 diabetes has been related to a pro-inflammatory and pro-atherogenic state, with endothelial dysfunction, increased platelet activity and coagulability, further promoting atherosclerosis²⁵. Fibrates are known to have an anti-inflammatory, antioxidant and antithrombotic effect^{5,24,26}. Furthermore, in patients with type 2 diabetes it has been shown that endothelial function improves in the fasting and postprandial state following fibrate therapy, which may contribute to explaining our findings²⁷. Our meta-analysis of eight trials, which included the recently published, large Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial¹², showed a more pronounced beneficial effect of fibrates on the risk of CHD than the FIELD trial alone. Of note, a considerable proportion of patients in the FIELD trial, particularly in the placebo group, received additional, non-study lipid-lowering therapy (17% in the placebo group and 8% in the fenofibrate group). In almost all cases the additional drug was a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin)¹². Statins have been consistently shown to reduce cardiac mortality in patients with and without type 2 diabetes²⁸. As discussed by the FIELD investigators, this unequal provision of statin treatment will have introduced confounding, and reduced the difference in CHD events between the two study arms¹². This is in-line with the comparably low incidence of

CHD events in the placebo group of FIELD (1.17 per 100 person-years) compared to the primary and secondary intervention trials included in this meta-analysis (1.67 and 4.79 per 100 person-years, respectively). Additional, open-label lipid-lowering therapy was allowed in a further trial, and uptake was again higher in the placebo group¹⁰. When excluding these two trials, the reduction in CHD events and deaths associated with fibrates became more pronounced.

Meta-regression analysis revealed a significant association between the reduction in triglyceride levels and the reduction of CHD events, which is consistent with the pharmacological profile of fibrates^{6-8,24}. Unfortunately, the present meta-analysis was not based on individual patient data and we were therefore unable to further characterise the patients most likely to benefit from treatment with fibrates. The results from a recent individual patient data meta-analysis of the effect of statins in type 2 diabetes suggested a 22% risk reduction of major CHD events per mmol/L decrease of LDL cholesterol²⁸. Based on these findings the median reduction of LDL cholesterol in the present analysis (0.24 mmol/L) would correspond to a risk reduction of about 5% for CHD events, leaving another 11% reduction in risk, which may be explained by favourable changes in levels of HDL cholesterol and triglycerides. Important data on the effect of adding fibrates to statins will be provided by the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial²⁹.

Strengths and limitations

This is the first systematic review and meta-analysis investigating the effect of fibrates in patients with type 2 diabetes mellitus. Our study was based on a comprehensive literature search and original investigators checked the extracted data and provided additional information. We acknowledge that our analysis was to some extent dominated by the FIELD and Veterans Affairs High-Density Lipoprotein Intervention (VA-HIT) trials. However, the inclusion of a further six trials increased the precision of effect estimates and allowed subgroup analyses by trial and average patient characteristics. Most of these analyses were planned *a priori*, with the exception of the analysis excluding the two trials that allowed additional lipid-lowering therapy. Unfortunately, separate data for patients with type 2 diabetes were not available for three trials^{18,19,21}, despite repeated attempts to contact the study authors, and these studies had to be excluded from our analysis. However, funnel plot analysis suggests that the included studies are a representative sample, indicating that the exclusion of these studies did not introduce substantial bias. We could not examine the influence of glycaemic

control on the rate of CHD events; although a protective effect of optimised glycaemic control in patients with diabetes has been shown³⁰, detailed information on glycated haemoglobin A1c (HbA_{1c}) was available only for a small number of trials^{12,16,31}. Different fibrates were used in the trials under investigation. Fibrates reduce triglycerides and increase HDL cholesterol levels but they may differ in their effects on other cardiovascular risk factors, for example fibrinogen³². Furthermore, it is clear that trials included in the present analysis are heterogeneous in terms of patient characteristics³³. However, in the present analysis risk ratios did not differ significantly in primary prevention and secondary prevention trials, respectively. Accordingly, there was a small degree of heterogeneity between trials in this meta-analysis, indicating that the effects of fibrates on cardiovascular disease might be due to a class effect of PPAR α -agonists.

Conclusions

In conclusion, this systematic review and meta-analysis shows that, in patients with type 2 diabetes mellitus, fibrates reduce CHD events. Larger benefits were found when restricting the analysis to trials that were not confounded by unequal provision of additional lipid-lowering therapy. More data are needed to better define the role of fibrate therapy in type 2 diabetes. An individual patient data meta-analysis of existing trials might be useful in this context.

Acknowledgements

Declaration of interest: SA was supported by unrestricted grants from Novo Nordisk, Roche Diagnostics and Glaxo Smith Kline.

We thank the original investigators who provided additional data and checked data extracted from the publications: Shlomo Behar, George Steiner, Mikko Syvanne, Jean Claude Ansquer, Markolf Hanefeld, Robert S. Elkeles, Judith Diamond, Hanna Bloomfield Rubins and Dorothea Collins.

References

1. 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* 1998;352:837-53
2. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia* 2003;46:733-49
3. Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator-activated receptor agonists. *Diabetes* 2005;54:2460-70
4. Despres JP, Lemieux I, Robins SJ. Role of fibric acid derivatives in the management of risk factors for coronary heart disease. *Drugs* 2004;64:2177-98

5. Elisaf M. Effects of fibrates on serum metabolic parameters. *Curr Med Res Opin* 2002;18:269-76
6. Hanefeld M, Fischer S, Schmechel H, et al. Diabetes Intervention Study. Multi-intervention trial in newly diagnosed NIDDM. *Diabetes Care* 1991;14:308-17
7. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 2001;357:905-10
8. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med* 2002;162:2597-604
9. Studer M, Briel M, Leimenstoll B, et al. Effect of different antilipidemic agents and diets on mortality: a systematic review. *Arch Intern Med* 2005;165:725-30
10. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation* 2000;102:21-7
11. Cullen JF, Town SM, Campbell CJ. Double-blind trial of Atromid-S in exudative diabetic retinopathy. *Trans Ophthalmol Soc U K* 1974;94:554-62
12. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849-61
13. Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *Int J Epidemiol* 2002;31:150-3
14. Egger M, Davey SG, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34
15. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999;18:2693-708
16. Elkeles RS, Diamond JR, Poulter C, et al. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. *Diabetes Care* 1998;21:641-8
17. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410-8
18. Meade T, Zuhrie R, Cook C, et al. Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. *BMJ* 2002;325:1139
19. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;231:360-81
20. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237-45
21. Acheson J, Hutchinson EC. Controlled trial of clofibrate in cerebral vascular disease. *Atherosclerosis* 1972;15:177-83
22. Koskinen P, Manttari M, Manninen V, et al. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 1992;15:820-5
23. Verges B. Diabetic dyslipidemia: insights for optimising patient management. *Curr Med Res Opin* 2005;21:S29-40
24. Tsimihodimos V, Miltiadous G, Daskalopoulou SS, et al. Fenofibrate: metabolic and pleiotropic effects. *Curr Vasc Pharmacol* 2005;3:87-98
25. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002;287:2570-81
26. Fruchart JC, Staels B, Duriez P. The role of fibric acids in atherosclerosis. *Curr Atheroscler Rep* 2001;3:83-92
27. Evans M, Anderson RA, Graham J, et al. Ciprofibrate therapy improves endothelial function and reduces postprandial lipemia and oxidative stress in type 2 diabetes mellitus. *Circulation* 2000;101:1773-9
28. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78
29. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Available from <http://www.accordtrial.org/public/index.cfm> [Accessed 5 December 2005]
30. Stettler C, Allemann S, Jüni P, et al. Glycemic control and macrovascular disease in type 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J* [in press]
31. Steiner G. The Diabetes Atherosclerosis Intervention Study (DAIS): a study conducted in cooperation with the World Health Organization. The DAIS project group. *Diabetologia* 1996;39:1655-61
32. Branchi A, Rovellini A, Sommariva D, et al. Effect of three fibrate derivatives and of two HMG-CoA reductase inhibitors on plasma fibrinogen level in patients with primary hypercholesterolemia. *Thromb Haemost* 1993;70:241-3
33. Rizos E, Mikhailidis DP. Are high-density lipoprotein and triglyceride levels important in secondary prevention: impressions from the BIP and VA-HIT trials. *Int J Cardiol* 2002;82:199-207

CrossRef links are available in the online published version of this paper:
<http://www.cmrojournal.com>
 Paper CMRO-3285_3, Accepted for publication: 17 January 2006
 Published Online: 15 February 2006
 doi:10.1185/030079906X89865

2.3 Study C: Efficacy of drug eluting stents in patients with and without diabetes mellitus: indirect comparison of controlled trials

Christoph Stettler,¹ Sabin Allemann,^{1,2} Peter Diem,¹ Stephan Windecker,³
Bernhard Meier,³ Matthias Egger^{2,4}

1) Division of Endocrinology and Diabetes, University Hospital Bern, Switzerland

2) Department of Social and Preventive Medicine, University of Bern, Switzerland

3) Department of Cardiology, University Hospital Bern, Switzerland

4) MRC Health Services Research Collaboration Department of Social Medicine, University
of Bristol, United Kingdom

Article published in:

Heart 2006 May;92(5):650-7. Epub 2005 Oct 26.

Abstract provided at:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16251229&query_hl=1&itool=pubmed_docsum

Efficacy of drug eluting stents in patients with and without diabetes mellitus: indirect comparison of controlled trials

C Stettler, S Allemann, M Egger, S Windecker, B Meier, P Diem



Heart 2006;92:650–657. doi: 10.1136/hrt.2005.070698

See end of article for authors' affiliations

Correspondence to: Professor Matthias Egger, Department of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, 3012 Bern, Switzerland; egger@isp.m.unibe.ch

Accepted 17 October 2005
Published Online First 26 October 2005

Objective: To examine whether polymer based coronary stents eluting sirolimus or paclitaxel are equally effective in patients with and without diabetes.

Methods: Systematic review and meta-analysis by indirect comparison of randomised controlled trials comparing stents eluting sirolimus or paclitaxel with conventional bare metal stents. The overall study population and patients with and without diabetes were analysed separately by using the ratio of incidence rate ratios (RIRR).

Results: The analysis was based on 10 trials (six with sirolimus, four with paclitaxel), 4513 patients (1146 patients with diabetes), 5755 years of follow up, and 2464 events. In patients without diabetes sirolimus eluting stents were superior to paclitaxel eluting stents with respect to in-stent (RIRR 0.21, 95% confidence interval (CI) 0.10 to 0.48, $p < 0.001$) and in-segment restenosis (RIRR 0.47, 95% CI 0.24 to 0.92, $p = 0.027$), target lesion revascularisation (RIRR 0.54, 95% CI 0.30 to 0.99, $p = 0.045$), and major adverse cardiac events (RIRR 0.46, 95% CI 0.26 to 0.83, $p = 0.010$). In patients with diabetes the two drug eluting stents did not differ significantly in any of these end points. Meta-regression analysis showed a significant difference between patients with and without diabetes (tests for interaction for in-stent and in-segment restenosis, $p = 0.036$ and $p = 0.016$).

Conclusion: Indirect evidence indicates that sirolimus eluting stents are superior to paclitaxel eluting stents in patients without diabetes but not in patients with diabetes.

Two drug eluting stents are approved by the US Food and Drug Administration (FDA), a sirolimus and a paclitaxel eluting stent. Both drug eluting stents share a similar stent platform consisting of a stainless steel stent and a non-biodegradable polymer for controlled drug release. Several randomised controlled trials and meta-analyses have shown that both drug eluting stents reduce restenosis and the need for repeated revascularisation procedures compared with bare metal stents.^{1–11}

More recently, two large randomised head to head comparisons and a meta-analysis have shown that sirolimus is superior to paclitaxel in the prevention of restenosis.^{12–14} Open questions remain, however. In particular, it is unclear whether the clinical benefits of these two drug eluting stents are similar across patient groups who differ in terms of underlying cardiovascular risk. Diabetes mellitus is a common and a major risk factor for cardiovascular disease.^{15–16} Patients with diabetes tend to present with more advanced coronary artery disease, and outcomes after percutaneous coronary intervention (PCI) tend to be poorer than for patients without diabetes.^{17–19} The beneficial effect of drug eluting stents appears attenuated in patients with diabetes compared with patients without diabetes, most probably due to more severe neointimal hyperplasia.^{20–21} The objective of the present study was to indirectly compare the effects of polymer based sirolimus versus paclitaxel eluting stents and to evaluate whether they are equally effective in the prevention of restenosis in patients with and without diabetes.

METHODS

Literature search and eligibility criteria

We identified all randomised clinical trials that compared the two commercially available, polymer based drug eluting stent

systems (the Cypher stent, Cordis, Miami Lakes, Florida, USA, which elutes sirolimus; and the Taxus stent, Boston Scientific, Natick, Massachusetts, USA, which elutes paclitaxel) with bare metal stents. By using Cochrane methods we searched Medline, Embase, and the Cochrane controlled trials register (from inception to April 2004) for relevant studies in any language. Electronic searches were supplemented by manual searching of reference lists, reviews, relevant book chapters, conference abstracts, and specialist journals. We also scrutinised the proceedings of the relevant FDA advisory panels.

We evaluated each trial for inclusion in the meta-analysis on the basis of five criteria: (1) study design (randomised controlled trial); (2) study population (patients with stable or unstable angina as defined elsewhere^{22–23} and signs of myocardial ischaemia—patients had to have a new target lesion in a native coronary artery); (3) intervention group (sirolimus or paclitaxel polymer based stent systems); (4) control group (bare metal stent); and (5) length of follow up (at least four months). Two reviewers (CS, SA) independently assessed publications for eligibility, with discrepancies being resolved in consultation with a third reviewer (PD, BM).

Data extraction and outcome measures

Two investigators (CS and SA) independently extracted data, with disagreements resolved by a third reviewer (PD or BM). All relevant publications from a trial were considered, including, for example, early publications describing the

Abbreviations: BENESTENT II, Belgian Netherlands stent II; CI, confidence interval; FDA, Food and Drug Administration; IRR, incidence rate ratio; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; RIRR, ratio of incidence rate ratios

study design. Authors from all studies were contacted and asked to check the information extracted from published articles and, where necessary, to provide additional data. Study end points were defined as follows: (1) in-stent restenosis (stenosis of 50% or greater of the target lesion, confirmed by coronary angiography or intravascular ultrasound); (2) in-segment restenosis (stenosis of 50% or greater of the target segment, confirmed by coronary angiography or intravascular ultrasound); (3) target lesion revascularisation (coronary artery bypass grafting or repeat PCI procedure at the original lesion site, including the area inside the stent and the 5 mm vessel segments adjacent to it); (4) major adverse cardiac events (MACE) (Q wave and non-Q wave myocardial infarction, surgical revascularisation (coronary artery bypass graft), percutaneous revascularisation (PCI), or death).

Assessment of methodological quality

Two of us (CS and SA) independently assessed the adequacy of the concealment of allocation of patients to treatment groups and blinding of care providers and research staff ascertaining cardiovascular outcomes. Disagreements were resolved in discussion with a third reviewer (ME).

Statistical analysis

We calculated the incidence rate by dividing the number of events by the number of person years of follow up and separately analysed all patients, patients with diabetes, and patients without diabetes. For each comparison and end point the incidence rate ratio (IRR) was obtained by dividing the incidence in the drug eluting stent group by the incidence in the bare metal stent group. Studies with no outcome events in either group were excluded from the respective analysis. Comparisons with events in only one group were analysed by adding one half to all cells. We combined IRRs in fixed effects meta-analysis by using inverse variance

weighting and calculated the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. We also did standard tests of heterogeneity.²⁴ The numbers of patients needed to be treated with drug eluting rather than bare metal stents to prevent one adverse event was calculated by applying the combined IRRs to the median incidence rate in the bare metal stent group of patients with or without diabetes. In sensitivity analyses we repeated calculations by using random effects models and did tests of funnel plot asymmetry.²⁵ For comparisons between the two drug eluting stent systems we calculated the ratio of IRRs (RIRR) by using a random effects meta-regression model.²⁶

Crude and adjusted indirect comparisons were performed by fitting random effects meta-regression models.²⁶ Variables entered in the model were the drug (sirolimus versus paclitaxel), stent strut thickness, study characteristics (dimensions of trial quality and length of angiographic and clinical of follow up), angiographic parameters (length of target lesion, reference vessel diameter, proportion of patients with angiographic follow up, mean duration of use of clopidogrel or ticlopidine, proportion of patients receiving glycoprotein IIb/IIIa antagonists, target artery, American College of Cardiology/American Heart Association lesion classification, proportion of patients with multivessel disease, proportion of patients with stable and unstable angina, and use of direct stenting), and the characteristics of study populations at baseline (mean age, proportion of women, proportion of patients with hypertension or dyslipidaemia, and proportion of smokers). A recent analysis of data from the BENESTENT II (Belgian Netherlands stent) study showed that the inclusion of angiographic follow up increased the number of repeat revascularisations by a factor of 1.6.^{27, 28} In a sensitivity analysis we reanalysed the data with this factor to correct for angiography driven revascularisations. Results are presented as IRRs with 95% confidence intervals (CIs) and numbers needed to treat and 95% CIs. All analyses were performed with Stata version 8.2 (Stata Corporation, College Station, Texas, USA).

RESULTS

Identification of eligible studies

We screened the titles and abstracts of 233 potentially eligible reports, examined the full text of 57 articles reporting on 29 different studies, and identified 10 studies that met our inclusion criteria (fig 1). Additional, unpublished data were obtained for seven trials.^{1-3 5 6 29 30}

Characteristics of trials and patients

Six trials^{1-4 8 30} examined the sirolimus and four^{5-7 31} the paclitaxel eluting stent. Trials were of high methodological quality: appropriate methods of allocation concealment were described for all trials and most trials reported analyses according to the intention to treat principle. For one trial the degree of blinding of outcome assessors was unclear.³ In all trials patients with recent acute myocardial infarction or a stenosis of 50% or greater in the left main coronary artery and patients with heart failure were excluded. In all studies except one patients with diabetes constituted a subgroup of the study population.³⁰ Stratified randomisation of patients with and without diabetes was reported in two trials.^{4 7} Five trials were performed in Europe^{1 5 8 30 31} and three in North America,^{3 4 7} and two were multicentre trials performed in Europe and North, Central, and South America.^{2 6}

The 10 trials included a total of 4513 patients, 1146 (25%) patients with and 3367 (75%) patients without diabetes. Table 1 shows the characteristics of the study participants. Patient characteristics were generally comparable across trials.^{1-8 29-33} The mean age of patients at baseline ranged

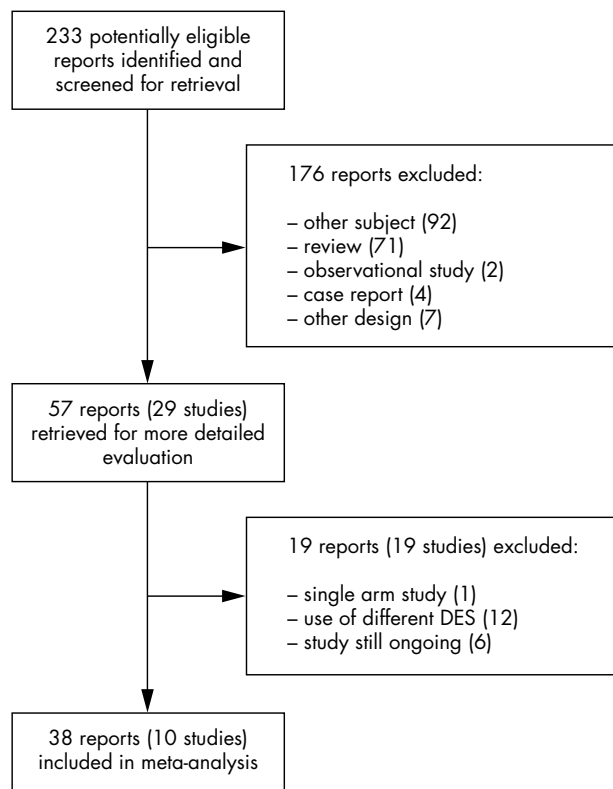


Figure 1 Identification of eligible randomised controlled trials. DES, drug eluting stents.

Table 1 Characteristics of randomised trials comparing drug eluting stents with bare metal stents

Study	Diabetes mellitus		Mean age at baseline (years)	Women (%)	Hypertension (%)	Dyslipidaemia (%)	Smoking (%)	Mean follow up (months)	
	Yes	No						Angiographic	Clinical
Sirolimus eluting stents									
SIRIUS (2003) ⁶	279	778	62.3	29.0	68.0	74.0	20.0	8	9
E-SIRIUS (2003) ¹	81	271	62.3	29.3	64.0	74.0	33.0	8	9
C-SIRIUS (2004) ³	24	76	60.5	31.0	52.0	85.0	37.0	8	9
DIABETES (2005) ³⁰	160		66.6	37.5	66.3	61.3	47.5	9	9
RAVEL (2002) ²	44	194	60.7	24.0	61.0	40.0	30.0	6	12
SES-SMART (2004) ⁸	64	193	63.6	28.4	64.7	63.0	16.3	8	8
Paclitaxel eluting stents									
TAXUS I (2003) ⁵	11	49	64.9	11.4	63.9	80.3	50.8	6	12
TAXUS II (2003) ^{6, 32, 33}	76	453	60.1	24.4	61.5	76.6	24.8	6	24
TAXUS IV (2004) ^{7, 29}	318	996	62.5	27.9	69.8	65.3	21.8	9	24
TAXUS VI (2005) ³¹	89	357	62.6	23.7	57.8	71.9	NA	9	12

C-SIRIUS, Canadian sirolimus coated balloon expandable stent in the treatment of patients with de novo coronary artery lesions; DIABETES, diabetes and sirolimus eluting stent trial; E-SIRIUS, European sirolimus coated balloon expandable stent in the treatment of patients with de novo coronary artery lesions; NA, not available; RAVEL, randomised study with the sirolimus eluting velocity balloon expandable stent; SES-SMART, randomised comparison of a sirolimus eluting stent and a standard stent in the prevention of restenosis in small coronary arteries; SIRIUS, sirolimus coated balloon expandable stent in the treatment of patients with de novo coronary artery lesions.

from 60–67 years. The proportions of women, smokers, and patients with hypertension or dyslipidaemia varied somewhat. Indications for PCI were similar across trials (table 2). There was a tendency towards a smaller mean reference vessel diameter in trials with sirolimus. Mean angiographic follow up and clinical follow up ranged from six to nine months and eight to 24 months, respectively.

Outcomes

Table 3 shows IRRs from individual trials for the four outcomes analysed and combined rate ratios from meta-analyses. Table 4 and table 5 show the same data for patients with and without diabetes. Figure 2 presents combined results from meta-analyses for all patients, and fig 3 shows these results separately for patients with and without diabetes. For some trials and outcomes separate data on patients with and without diabetes were not available, which meant that the number of trials that contributed to a given analysis varied. Crude and adjusted RIRR comparing sirolimus versus paclitaxel eluting stents were closely similar, and crude results are therefore presented throughout.

Restenosis

Overall, analyses were based on 604 episodes of in-stent restenosis and 657 episodes of in-segment restenosis. Compared with bare metal stents, drug eluting stents were associated with substantial reductions in the risk of restenosis in all trials reporting this outcome, but reductions were more pronounced with sirolimus than with paclitaxel eluting stents. The combined IRRs for in-stent and in-segment restenosis were 0.10 (95% CI 0.07 to 0.14) and 0.20 (95% CI 0.15 to 0.26), respectively, with sirolimus eluting stents, and 0.27 (95% CI 0.20 to 0.37) and 0.29 (95% CI 0.22 to 0.39) with paclitaxel eluting stents. Of note, heterogeneity between study results in these two meta-analyses was entirely attributable to random variation ($I^2 = 0\%$). These results translated into an RIRR of 0.35 (95% CI 0.21 to 0.57) for in-stent restenosis indicating that, compared with paclitaxel, sirolimus eluting stents led to a reduction in incidence by 65%. The corresponding RIRR for in-segment restenosis was 0.68 (95% CI 0.45 to 1.01). These differences in the efficacy of preventing restenosis between the two stent systems were attributable to lower rates of restenosis with sirolimus compared with paclitaxel eluting stents in patients without diabetes, whereas results were comparable in patients with diabetes (tables 4 and 5, fig 3). Meta-regression analysis showed a significant difference between patients

with and without diabetes (tests for interaction for in-stent and in-segment restenosis, $p = 0.036$ and $p = 0.016$).

Revascularisation

Overall, analyses were based on 522 target lesion revascularisations. Compared with bare metal stents, drug eluting stents were associated with a substantial reduction in the risk of revascularisation, but reductions were more pronounced with sirolimus than with paclitaxel eluting stents (RIRR 0.71, 95% CI 0.46 to 1.09). This difference was also more pronounced in patients without diabetes (RIRR 0.54, 95% CI 0.30 to 0.99) than in patients with diabetes (RIRR 0.86, 95% CI 0.40 to 1.86), although the formal test for interaction did not reach conventional levels of significance ($p = 0.36$). Results were closely similar when correcting for angiography driven revascularisations.

Major adverse cardiac events

Analyses were based on 681 MACE, including 148 myocardial infarctions, and 41 deaths. The TAXUS trialists included stent thrombosis in their definition of MACE (17 events). Reductions were also more pronounced with sirolimus eluting stents than with paclitaxel stents (RIRR 0.54, 95% CI 0.39 to 0.76), and the difference between the two types of drug eluting stents was more pronounced in patients without diabetes (RIRR 0.46, 95% CI 0.26 to 0.83) than in patients with diabetes (RIRR 0.60, 95% CI 0.21 to 1.71, test for interaction $p = 0.68$).

Numbers needed to treat to prevent one event

Table 6 shows the estimated numbers of patients needed to treat with drug eluting rather than bare metal stents to prevent one outcome event. Numbers needed to treat were lowest for sirolimus eluting stents in patients with diabetes, followed by paclitaxel eluting stents in patients with diabetes, sirolimus eluting stents in patients without diabetes, and paclitaxel eluting stents in patients without diabetes. For one end point (MACE) the CI for the IRR of paclitaxel eluting stents was compatible with benefit and harm. We accounted for this by calculating numbers needed to benefit (corresponding to the lower limit of the CI) and numbers needed to harm (corresponding to the upper limit of the CI).³⁴

DISCUSSION

The indirect comparisons presented here indicate that sirolimus eluting stents are superior to paclitaxel eluting

Table 2 Angiographic parameters for studies with sirolimus eluting stents

Study	Indications for PCI	Mean RVD (mm)	Mean lesion length (mm)	Target artery (%)			ACC/AHA class (%)				Multivessel disease (%)	AP (%)		
				LAD	RCA	LCX	A	B1	B2	C		Previous MI (%)	Stable	Unstable
Sirolimus trials														
SIRIUS (2003) ⁴	Stable or unstable AP, signs of myocardial ischaemia	2.80	14.40	44	31	25	8	36	33	23	42	31	58	53
E-SIRIUS (2003) ¹	Stable or unstable AP, silent ischaemia	2.55	15.00	56	21	23	NA	NA	NA	NA	36	42	NA	33
C-SIRIUS (2004) ³	Stable or unstable AP, silent ischaemia	2.63	13.60	36	41	23	NA	NA	59	40	40	42	12	51
DIABETES (2005) ³⁰	Symptoms or objective evidence of ischaemia	2.34	15.00	41	37	22	NA	NA	80	65	65	37	NA	NA
RAVEL (2002) ²	Stable or unstable AP, silent ischaemia	2.62	9.58	50	27	23	6	37	57	0	NA	36	39	50
SES-SMART (2004) ⁸	ACS, stable AP, silent myocardial ischaemia as shown by exercise stress test	2.20	11.84	28	16	30	2.5	47	24	4	65	NA	NA	NA
Paclitaxel trials														
TAXUS I (2003) ⁵	Stable or unstable AP or silent ischaemia	2.97	11.30	40	30	30	23	41	36	0	NA	28	NA	NA
TAXUS II (2003) ^{6, 32}	Stable or unstable AP or silent ischaemia	2.75	10.48	45	36	19	NA	NA	NA	NA	NA	40	60	34
TAXUS IV (2004) ^{7, 29}	Stable or unstable angina or provokable ischaemia	2.75	13.40	41	31	28	NA	NA	NA	NA	NA	30	NA	34
TAXUS VI (2005) ³¹	Stable or unstable AP or silent ischaemia	2.78	20.62				NA	NA	28	56	NA	NA	NA	NA

ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; AP, angina pectoris; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; RVD, reference vessel diameter.

stents, and that the difference in the effectiveness between the two drug eluting stent systems is clearly evident in patients without diabetes but less certain in patients with diabetes. Calculations of numbers needed to treat show that, compared with sirolimus eluting stents, about 10 additional patients without diabetes have to be treated with paclitaxel eluting stents to prevent one MACE.

Strengths and limitations

Our review was based on a comprehensive literature search and included assessments of trial quality and a substantial amount of additional information supplied by the original investigators. Although most trials included in this analysis were not designed to examine the effectiveness of drug eluting stents in patients with and without diabetes, randomisation was stratified according to the presence or absence of diabetes in some studies,^{4, 31} and all studies prospectively recorded outcomes according to standardised definitions. Indirect comparisons between sirolimus and paclitaxel eluting stents were appropriate because trials were of high methodological quality and had enrolled similar patient populations. Indeed, results were robust when adjusted for study characteristics and patient characteristics at baseline. We acknowledge that such comparisons are observational in nature and therefore have to be interpreted with caution. Only 10 trials were identified and average follow up was relatively short, which means that there was limited power to detect or exclude differences in effectiveness for rarer but clinically relevant end points, including myocardial infarction, stent thrombosis, and death.

The effect of drug eluting stents on MACE was mainly due to a reduction of revascularisation procedures. As Babapulle *et al*⁹ pointed out, the clinical significance of these additional revascularisation procedures is unclear because angiography was done routinely in these trials, at least in a proportion of the study population. Angiographic follow up may influence the rate of revascularisation, especially in patients with diabetes and autonomic neuropathy.³⁵ The impact of angiography on revascularisation rates has recently been quantified.²⁸ When we used these estimates to correct incidences for angiography driven revascularisation, results were not materially altered. We could not examine the influence of glycaemic control on the rate of restenosis and revascularisation; although a protective effect of optimised glycaemic control in patients with diabetes has been shown, no detailed information on glycaemic control was available for the trials we analysed.³⁶

Results in context with other studies

Two meta-analyses have shown that the presence of diabetes is a risk factor for restenosis, both with drug eluting and bare metal stents.^{21, 37} Our findings confirm these results: diabetes clearly remains a risk factor for restenosis in the drug eluting stent era. Methodological research has shown that indirect comparisons adjusted at the aggregate level usually agree with the results of head to head randomised trials.³⁸ In this study overall results were indeed closely similar to those reported in a recent meta-analysis of six head to head trials.¹⁴ Data from head to head comparisons in patients with diabetes are, however, more limited, and results are more heterogeneous. The large REALITY trial showed no overall difference in restenosis rates between the two stent systems, although sirolimus eluting stents appeared to be superior in patients without diabetes.³⁹ The SIRTAX trial, in contrast, found the sirolimus eluting stent to be superior overall, with a more pronounced reduction of the rate of restenosis and revascularisation in patients with diabetes than in patients without diabetes.¹² In both trials the number of patients with diabetes was relatively small, and formal tests of interaction

Table 3 Incidence rate ratios (IRRs) from trials of sirolimus and paclitaxel eluting stents and ratio of incidence rate ratios (RIRR) comparing sirolimus with paclitaxel in all patients

Study	IRR (95% confidence interval)			
	In-stent restenosis	In-segment restenosis	TLR	MACE
Sirolimus trials				
SIRIUS (2003) ⁴	0.09 (0.05 to 0.16)	0.24 (0.16 to 0.36)	0.24 (0.15 to 0.39)	0.38 (0.26 to 0.55)
E-SIRIUS (2003) ¹	0.09 (0.04 to 0.22)	0.14 (0.07 to 0.28)	0.19 (0.09 to 0.43)	0.35 (0.19 to 0.65)
C-SIRIUS (2004) ³	0.02 (0.001 to 0.40)	0.04 (0.01 to 0.32)	0.22 (0.05 to 1.03)	0.22 (0.05 to 1.03)
DIABETES (2005) ³⁰	0.15 (0.06 to 0.39)	0.22 (0.10 to 0.47)	0.24 (0.10 to 0.59)	0.31 (0.15 to 0.66)
RAVEL (2002) ²	0.02 (0.001 to 0.26)	0.02 (0.001 to 0.26)	0.02 (0.001 to 0.29)	0.20 (0.09 to 0.44)
SES-SMART (2004) ⁸	0.10 (0.04 to 0.23)	0.18 (0.10 to 0.34)	0.33 (0.16 to 0.70)	0.30 (0.16 to 0.57)
Combined IRR	0.10 (0.07 to 0.14)	0.20 (0.15 to 0.26)	0.24 (0.17 to 0.33)	0.33 (0.25 to 0.42)
Heterogeneity*	0.0%, p=0.63	33.6%, p=0.18	0.0%, p=0.51	0.0%, p=0.78
Paclitaxel trials				
TAXUS I (2003) ⁵	0.14 (0.01 to 2.67)	NA	0.14 (0.01 to 2.77)	0.25 (0.03 to 2.24)
TAXUS II (2003) ^{6, 32, 33}	0.33 (0.19 to 0.55)	0.18 (0.09 to 0.36)	0.27 (0.13 to 0.53)	0.58 (0.38 to 0.86)
TAXUS IV (2004) ^{7, 29}	0.23 (0.13 to 0.39)	0.30 (0.19 to 0.47)	0.32 (0.22 to 0.46)	0.56 (0.41 to 0.78)
TAXUS VI (2004) ³¹	0.28 (0.17 to 0.46)	0.35 (0.22 to 0.54)	0.42 (0.25 to 0.72)	0.73 (0.48 to 1.12)
Combined IRR	0.27 (0.20 to 0.37)	0.29 (0.22 to 0.39)	0.33 (0.25 to 0.44)	0.60 (0.48 to 0.75)
Heterogeneity*	0.0%, p=0.77	16.3%, p=0.30	0.0%, p=0.67	0.0%, p=0.65
RIRR (sirolimus v paclitaxel)	0.35 (0.21 to 0.57) p<0.001	0.68 (0.45 to 1.01) p=0.057	0.71 (0.46 to 1.09) p=0.120	0.54 (0.39 to 0.76) p<0.001

*I², test of heterogeneity.

MACE, major adverse cardiac events; TLR, target lesion revascularisation.

were non-significant. Lastly, the ISAR-DIABETES trial in 250 patients with diabetes showed larger reductions in angiographic restenosis ($p = 0.03$) and target lesion revascularisation ($p = 0.13$) with sirolimus than with paclitaxel.¹³

Possible mechanisms

In-stent restenosis results from neointimal hyperplasia, and the pharmacological inhibition of vascular smooth muscle proliferation by local drug delivery has proved effective in reducing restenosis and thus repeat revascularisation procedures.⁴⁰⁻⁴¹ The biological mechanisms of action differ between paclitaxel and sirolimus: paclitaxel treated cells form abnormally stable and non-functional microtubules, which inhibit cellular replication and proliferation.⁴² In contrast, sirolimus is a macrocyclic lactone that inhibits cytokine mediated and growth factor induced proliferation of smooth muscle cells and has immunoregulatory and anti-inflammatory properties.⁴³⁻⁴⁵ One would expect these properties to be particularly beneficial in diabetic atherosclerosis, which is characterised by increased inflammatory markers.⁴⁶ On the other hand, treatment of human platelets with sirolimus has

been shown to result in enhanced agonist induced platelet aggregation and secretion.⁴⁷ The more complex and advanced nature of lesions in patients with diabetes may interact with the biological mechanisms of action of both drugs but hamper effects of sirolimus more than effects of paclitaxel. Differences in local drug concentrations may also have a role: both drugs are highly lipophilic but different protein binding characteristics mean that sirolimus is distributed evenly through the vessel wall, whereas paclitaxel remains primarily subintimal.⁴⁸ These distribution patterns and tissue residence time may be modified in atherosclerotic lesions of patients with diabetes. It is also possible that differences in the doses of the two drugs or differences in concomitant medications have a role.

Stents with thinner struts elicit less angiographic and clinical restenosis than stents with thicker struts.⁴⁹⁻⁵⁰ Differences in strut thickness can therefore have affected indirect comparisons. This is, however, unlikely because differences were small (140 and 130 μm for the sirolimus and the paclitaxel eluting stent, respectively). Event rates tended to be somewhat higher in the bare metal stent groups of the

Table 4 IRRs from trials of sirolimus and paclitaxel eluting stents and RIRR comparing sirolimus with paclitaxel in patients without diabetes

Study	IRR (95% confidence interval)			
	In-stent restenosis	In-segment restenosis	TLR	MACE
Sirolimus trials				
SIRIUS (2003) ⁴	0.05 (0.02 to 0.14)	0.20 (0.11 to 0.34)	0.21 (0.11 to 0.40)	0.39 (0.25 to 0.62)
E-SIRIUS (2003) ¹	0.09 (0.03 to 0.24)	0.13 (0.05 to 0.30)	0.20 (0.08 to 0.52)	0.42 (0.20 to 0.85)
C-SIRIUS (2004) ³	0.04 (0.002 to 0.68)	0.03 (0.002 to 0.54)	0.13 (0.02 to 1.00)	0.13 (0.02 to 1.00)
RAVEL (2004) ²	0.02 (0.001 to 0.37)	0.02 (0.001 to 0.37)	0.02 (0.001 to 0.41)	0.20 (0.08 to 0.53)
SES-SMART (2002) ⁸	NA	0.11 (0.04 to 0.28)	NA	NA
Combined IRR	0.06 (0.03 to 0.12)	0.15 (0.10 to 0.22)	0.19 (0.11 to 0.31)	0.35 (0.25 to 0.50)
Heterogeneity*	0.0%, p=0.77	8.8%, p=0.36	0.0%, p=0.52	0.0%, p=0.44
Paclitaxel trials				
TAXUS I (2003) ⁵	NA	NA	0.16 (0.01 to 3.13)	0.28 (0.03 to 2.53)
TAXUS II (2003) ^{6, 32, 33}	NA	0.08 (0.02 to 0.24)	0.29 (0.14 to 0.61)	NA
TAXUS IV (2004) ^{7, 29}	0.25 (0.13 to 0.47)	0.35 (0.20 to 0.59)	0.30 (0.19 to 0.48)	NA
TAXUS VI (2004) ³¹	0.30 (0.17 to 0.53)	0.39 (0.24 to 0.64)	0.49 (0.27 to 0.88)	0.80 (0.49 to 1.29)
Combined IRR	0.28 (0.18 to 0.42)	0.32 (0.23 to 0.45)	0.35 (0.25 to 0.48)	0.76 (0.48 to 1.22)
Heterogeneity*	0.0%, p=0.67	69.2%, p=0.04	0.0%, p=0.53	0.0%, p=0.37
RIRR (sirolimus v paclitaxel)	0.21 (0.10 to 0.48) p<0.001	0.47 (0.24 to 0.92) p=0.027	0.54 (0.30 to 0.99) p=0.045	0.46 (0.26 to 0.83) p=0.010

*I², test of heterogeneity.

Table 5 IRRs from trials of sirolimus and paclitaxel eluting stents and RIRR comparing sirolimus with paclitaxel in patients with diabetes

Study	IRR (95% confidence interval)			
	In-stent restenosis	In-segment restenosis	TLR	MACE
Sirolimus trials				
SIRIUS (2003) ⁴	0.17 (0.08 to 0.37)	0.35 (0.20 to 0.62)	0.31 (0.15 to 0.64)	0.37 (0.19 to 0.70)
E-SIRIUS (2003) ¹	0.13 (0.03 to 0.57)	0.19 (0.06 to 0.64)	0.21 (0.05 to 0.91)	0.27 (0.08 to 0.94)
C-SIRIUS (2004) ³	0.06 (0.003 to 1.02)	0.13 (0.02 to 1.00)	1.00 (0.06 to 15.99)	1.00 (0.06 to 15.99)
DIABETES (2005) ³⁰	0.15 (0.06 to 0.39)	0.22 (0.10 to 0.47)	0.24 (0.10 to 0.59)	0.31 (0.15 to 0.66)
RAVEL (2002) ²	0.06 (0.003 to 0.97)	0.06 (0.003 to 0.97)	0.07 (0.004 to 1.19)	0.22 (0.05 to 0.98)
SES-SMART (2004) ⁸	NA	0.39 (0.17 to 0.91)	NA	NA
Combined IRR	0.15 (0.09 to 0.25)	0.28 (0.20 to 0.41)	0.27 (0.16 to 0.45)	0.33 (0.21 to 0.51)
Heterogeneity*	(0.0%, p=0.92)	(0.0%, p=0.59)	(0.0%, p=0.73)	(0.0%, p=0.89)
Paclitaxel trials				
TAXUS I (2003) ⁵	NA	NA	0 events	0 events
TAXUS II (2003) ^{6, 32, 33}	NA	0.07 (0.004 to 1.17)	0.16 (0.02 to 1.25)	NA
TAXUS IV (2004) ^{7, 29}	0.16 (0.05 to 0.48)	0.18 (0.07 to 0.49)	0.36 (0.19 to 0.70)	NA
TAXUS VI (2005) ³¹	0.20 (0.05 to 0.68)	0.23 (0.08 to 0.66)	0.20 (0.04 to 0.90)	0.55 (0.21 to 1.43)
Combined IRR	0.18 (0.08 to 0.40)	0.19 (0.09 to 0.38)	0.31 (0.18 to 0.56)	0.55 (0.21 to 1.43)
Heterogeneity*	0.0%, p=0.80	0.0%, p=0.73	0.0%, p=0.62	NA
RIRR (sirolimus v paclitaxel)	0.82 (0.31 to 2.18) p=0.694	1.51 (0.68 to 3.33) p=0.312	0.86 (0.40 to 1.86) p=0.703	0.60 (0.21 to 1.71) p=0.336

*I², test of heterogeneity.

sirolimus trials than in the corresponding groups of the paclitaxel trials. If the relative reduction in restenosis risk strongly depended on the control group risk, this can partly explain the superior efficacy observed for sirolimus eluting stents. This is unlikely for several reasons. Recent head to head trials in patient populations that differed in terms of underlying risk consistently showed that sirolimus is superior to paclitaxel.¹⁴ Moreover, methodological research has shown that the relative reductions in risk associated with medical interventions tend to be constant across patient populations with different underlying risks.⁵¹

Conclusions

This systematic review and meta-analysis shows substantial reductions in restenosis and revascularisation rates with the two widely used polymer based drug eluting stents, in both patients with and patients without diabetes. Sirolimus eluting stents appear more effective than paclitaxel eluting

stents in patients without diabetes, whereas efficacy appears to be comparable in patients with diabetes. We submit that a collaborative meta-analysis based on individual patient data

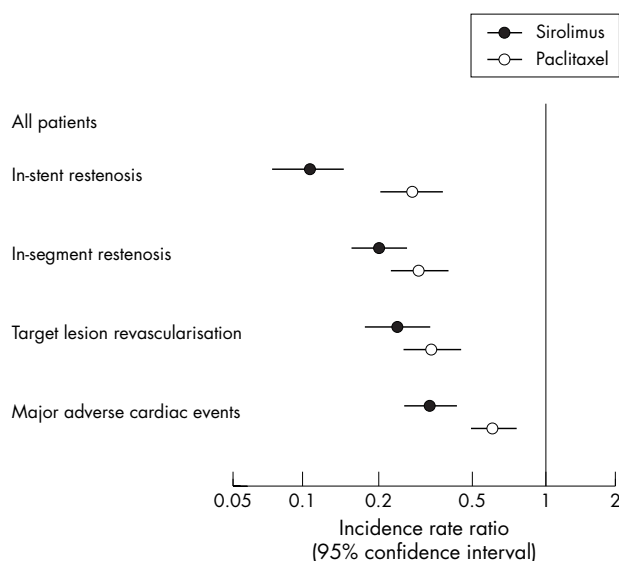


Figure 2 Effect of DES with sirolimus and paclitaxel compared with bare metal stents on the risks of restenosis, revascularisation, or adverse events. Combined estimates from meta-analyses of randomised controlled trials.

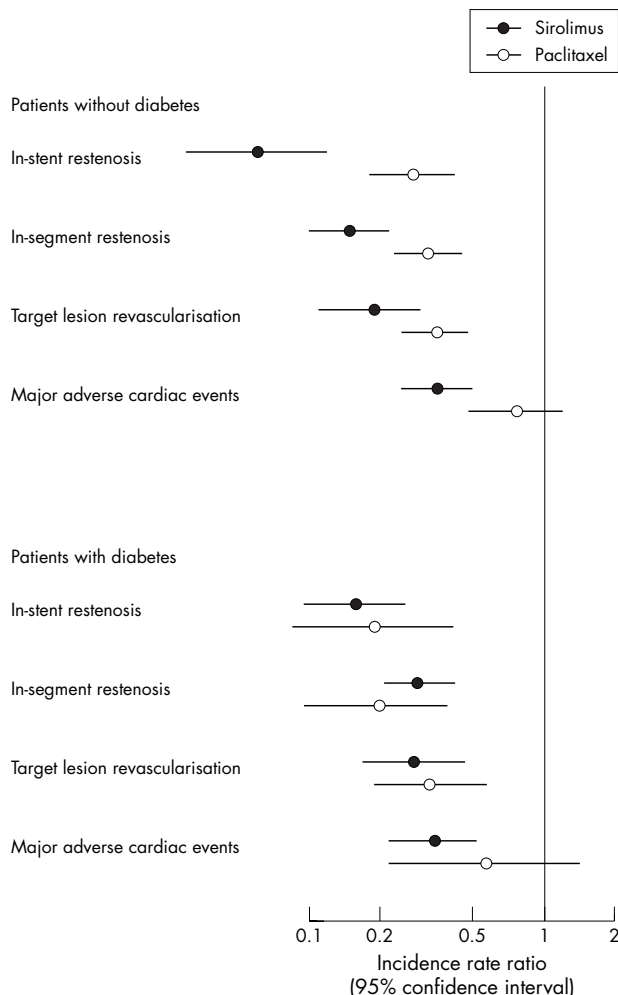


Figure 3 Effect of DES with sirolimus and paclitaxel in patients with and without diabetes.

Table 6 Number of patients needed to treat during one year to prevent one adverse event

	Number needed to treat (95% confidence interval)			
	In-stent restenosis	In-segment restenosis	TLR	MACE
Sirolimus eluting stent				
Patients without diabetes	2.4 (2.3 to 2.6)	2.6 (2.5 to 2.9)	6.5 (5.9 to 7.6)	6.2 (5.3 to 8.0)
Patients with diabetes	1.6 (1.5 to 1.9)	1.9 (1.7 to 2.3)	5.5 (4.8 to 7.3)	4.0 (3.4 to 5.5)
Paclitaxel eluting stent				
Patients without diabetes	3.2 (2.8 to 3.9)	3.3 (2.9 to 4.0)	8.1 (7.0 to 10.1)	16.7 (NNTB 7.7 to NNTH 18.2)*
Patients with diabetes	1.7 (1.5 to 2.3)	1.7 (1.5 to 2.2)	5.8 (4.9 to 9.1)	6.0 (NNTB 3.4 to NNTH 6.3)*

*95% confidence interval includes benefit and harm (number of patients needed to treat to prevent one event (NNTB); number of patients needed to treat to harm one patient (NNTH)).³⁴

should be performed, which addresses the question whether the effectiveness of the two stents differs across patient groups with and without diabetes and, more in general, between patients at higher or lower risk of complications.

ACKNOWLEDGEMENTS

SA is supported by grants from Novo Nordisk, Roche Diagnostics, and GlaxoSmithKline. We are grateful to the trialists who provided additional data and checked the data we extracted from their publications.

Authors' affiliations

C Stettler, S Allemann*, M Egger†, Department of Social and Preventive Medicine, University of Bern, Bern, Switzerland

P Diem, Division of Endocrinology and Diabetes, University Hospital Bern, Bern, Switzerland

S Windecker, B Meier, Department of Cardiology, University Hospital Bern, Bern, Switzerland

*Also the Division of Endocrinology and Diabetes, University Hospital Bern, Bern, Switzerland

†Also the MRC Health Services Research Collaboration Department of Social Medicine, University of Bristol, Bristol, UK

Contributors: PD, CS, and ME conceived the study and wrote the protocol with help from SA. CS and SA searched the literature, contacted trialists, extracted data, and assessed the methodological quality of trials. CS, SA, and ME performed the statistical analyses. All authors contributed to the writing of the final draft of the manuscript. ME is the guarantor of this study.

Competing interests: none declared.

REFERENCES

- Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003;**362**:1093–9.
- Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;**346**:1773–80.
- Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004;**43**:1110–5.
- Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;**349**:1315–23.
- Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation* 2003;**107**:38–42.
- Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003;**108**:788–94.
- Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;**350**:221–31.
- Ardissino D, Cavallini C, Bramucci E, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. *JAMA* 2004;**292**:2727–34.
- Babapulle MN, Joseph L, Belisle P, et al. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet* 2004;**364**:583–91.
- Hill RA, Dunder Y, Bakhai A, et al. Drug-eluting stents: an early systematic review to inform policy. *Eur Heart J* 2004;**25**:902–19.
- Indolfi C, Pavia M, Angelillo IF. Drug-eluting stents versus bare metal stents in percutaneous coronary interventions (a meta-analysis). *Am J Cardiol* 2005;**95**:1146–52.
- Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005;**353**:653–62.
- Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005;**353**:663–70.
- Kastrati A, Dibra A, Eberle S, et al. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. *JAMA* 2005;**294**:819–25.
- Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979;**241**:2035–8.
- Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. *Diabetes Care* 1993;**16**:434–44.
- Carrozza JP Jr, Kuntz RE, Fishman RF, et al. Restenosis after arterial injury caused by coronary stenting in patients with diabetes mellitus. *Ann Intern Med* 1993;**118**:344–9.
- Stein B, Weintraub WS, Gebhart SP, et al. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. *Circulation* 1995;**91**:979–89.
- Detre KM, Guo P, Holubkov R et al. Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the bypass angioplasty revascularization investigation (BARI). *Circulation* 1999;**99**:633–40.
- Scheen AJ, Warzee F. Diabetes is still a risk factor for restenosis after drug-eluting stent in coronary arteries. *Diabetes Care* 2004;**27**:1840–1.
- Scheen AJ, Warzee F, Legrand VM. Drug-eluting stents: meta-analysis in diabetic patients. *Eur Heart J* 2004;**25**:2167–8.
- Campeau L. Grading of angina pectoris [letter]. *Circulation* 1976;**54**:522–3.
- Hamm CW, Braunwald E. A classification of unstable angina revisited. *Circulation* 2000;**102**:118–22.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–58.
- Egger M, Davey SG, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.
- Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999;**18**:2693–708.
- Serruys PW, van Hout B, Bonnier H, et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998;**352**:673–81.
- Van Hout BA, Serruys PW, Lemos PA, et al. One year cost effectiveness of sirolimus eluting stents compared with bare metal stents in the treatment of single native de novo coronary lesions: an analysis from the RAVEL trial. *Heart* 2005;**91**:507–12.
- Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 2004;**109**:1942–7.
- Sabate M, Jimenez-Quevedo P, Angiolillo DJ, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. *Circulation* 2005;**112**:2175–83.
- Dawkins KD, Grube E, Guagliumi G, et al. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. *Circulation* 2005;**112**:3306–13.
- Serruys PW, Degertekin M, Tanabe K, et al. Vascular responses at proximal and distal edges of paclitaxel-eluting stents: serial intravascular ultrasound analysis from the TAXUS II trial. *Circulation* 2004;**109**:627–33.
- Tanabe K, Serruys PW, Degertekin M, et al. Chronic arterial responses to polymer-controlled paclitaxel-eluting stents: comparison with bare metal stents

- by serial intravascular ultrasound analyses: data from the randomized TAXUS-II trial. *Circulation* 2004;**109**:196–200.
- 34 **Altman DG**. Confidence intervals for the number needed to treat. *BMJ* 1998;**317**:1309–12.
 - 35 **Finn AV**, Palacios IF, Kastrati A, *et al*. Drug-eluting stents for diabetes mellitus: a rush to judgment? *J Am Coll Cardiol* 2005;**45**:479–83.
 - 36 **Corpus RA**, George PB, House JA, *et al*. Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. *J Am Coll Cardiol* 2004;**43**:8–14.
 - 37 **Gilbert J**, Raboud J, Zinman B. Meta-analysis of the effect of diabetes on restenosis rates among patients receiving coronary angioplasty stenting. *Diabetes Care* 2004;**27**:990–4.
 - 38 **Song F**, Altman DG, Glenny AM, *et al*. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;**326**:472.
 - 39 **Morice MC**. Eight-month outcome of the REALITY study: a prospective randomized multi-center head-to-head comparison of the sirolimus-eluting stent (Cypher) and the paclitaxel-eluting stent (Taxus) [video]. American College of Cardiology, Annual Scientific Session 2005, Orlando, 6–9 March 2005. www.acc05online.acc.org/highlights/keyLectures.aspx?sessionId=7890&ddate=6 (accessed 8 September 2005).
 - 40 **Hoffmann R**, Mintz GS, Dussaillant GR, *et al*. Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. *Circulation* 1996;**94**:1247–54.
 - 41 **Farb A**, Heller PF, Shroff S, *et al*. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. *Circulation* 2001;**104**:473–9.
 - 42 **Schiff PB**, Horwitz SB. Taxol stabilizes microtubules in mouse fibroblast cells. *Proc Natl Acad Sci U S A* 1980;**77**:1561–5.
 - 43 **Gallo R**, Padurean A, Jayaraman T, *et al*. Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. *Circulation* 1999;**99**:2164–70.
 - 44 **Burke SE**, Lubbers NL, Chen YW, *et al*. Neointimal formation after balloon-induced vascular injury in Yucatan minipigs is reduced by oral rapamycin. *J Cardiovasc Pharmacol* 1999;**33**:829–35.
 - 45 **Poon M**, Marx SO, Gallo R, *et al*. Rapamycin inhibits vascular smooth muscle cell migration. *J Clin Invest* 1996;**98**:2277–83.
 - 46 **Kornowski R**, Mintz GS, Lansky AJ, *et al*. Paradoxical decreases in atherosclerotic plaque mass in insulin-treated diabetic patients. *Am J Cardiol* 1998;**81**:1298–304.
 - 47 **Babinska A**, Markell MS, Salifu MO, *et al*. Enhancement of human platelet aggregation and secretion induced by rapamycin. *Nephrol Dial Transplant* 1998;**13**:3153–9.
 - 48 **Levin AD**, Vukmirovic N, Hwang CW, *et al*. Specific binding to intracellular proteins determines arterial transport properties for rapamycin and paclitaxel. *Proc Natl Acad Sci U S A* 2004;**101**:9463–7.
 - 49 **Kastrati A**, Mehilli J, Dirschinger J, *et al*. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STERO) trial. *Circulation* 2001;**103**:2816–21.
 - 50 **Pache J**, Kastrati A, Mehilli J *et al*. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STERO-2) trial. *J Am Coll Cardiol* 2003;**41**:1283–8.
 - 51 **Deeks JJ**. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Stat Med* 2002;**21**:1575–600.

3 Survival analyses investigating the prognostic value of novel risk indicators

3.1 Study D: QTc interval and resting heart rate as long term predictors of mortality in type 1 and type 2 diabetes mellitus: a 23-year follow up

Christoph Stettler,^{1,2} Andrea Bearth,¹ Sabin Allemann,^{1,2} Marcel Zwahlen,² Leonardo Zanchin,³ Marcus Deplazes,¹ Emanuel R. Christ,¹ Arthur Teuscher¹ and Peter Diem¹

- 1) Division of Endocrinology and Diabetes, University of Bern, Switzerland
- 2) Division of Epidemiology and Biostatistics, Department of Social and Preventive Medicine, University of Bern, Switzerland
- 3) Division of Cardiology, SRO, Langenthal, Switzerland

Article published in:

Diabetologia 2006 Nov; Epub ahead of print; DOI 10.1007/s00125-006-0483-1.

Abstract provided at:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17096116&query_hl=1&itool=pubmed_docsum

QT_c interval and resting heart rate as long-term predictors of mortality in type 1 and type 2 diabetes mellitus: a 23-year follow-up

C. Stettler · A. Bearth · S. Allemann · M. Zwahlen ·
L. Zanchin · M. Deplazes · E. R. Christ · A. Teuscher ·
P. Diem

Received: 24 July 2006 / Accepted: 31 August 2006
© Springer-Verlag 2006

Abstract

Aims/hypothesis We evaluated the association of QT interval corrected for heart rate (QT_c) and resting heart rate (rHR) with mortality (all-causes, cardiovascular, cardiac, and ischaemic heart disease) in subjects with type 1 and type 2 diabetes.

Methods We followed 523 diabetic patients (221 with type 1 diabetes, 302 with type 2 diabetes) who were recruited between 1974 and 1977 in Switzerland for the WHO Multinational Study of Vascular Disease in Diabetes. Duration of follow-up was 22.6±0.6 years. Causes of death were obtained from death certificates, hospital records, post-mortem reports, and additional information given by treating physicians.

Results In subjects with type 1 diabetes QT_c, but not rHR, was associated with an increased risk of: (1) all-cause mortality (hazard ratio [HR] 1.10 per 10 ms increase in QT_c, 95% CI 1.02–1.20, *p*=0.011); (2) mortality due to cardiovascular (HR 1.15, 1.02–1.31, *p*=0.024); and (3) mortality due to cardiac disease (HR 1.19, 1.03–1.36, *p*=0.016). Findings for subjects with type 2 diabetes were

different: rHR, but not QT_c was associated with mortality due to: (1) all causes (HR 1.31 per 10 beats per min, 95% CI 1.15–1.50, *p*<0.001); (2) cardiovascular disease (HR 1.43, 1.18–1.73, *p*<0.001); (3) cardiac disease (HR 1.45, 1.19–1.76, *p*<0.001); and (4) ischaemic heart disease (HR 1.52, 1.21–1.90, *p*<0.001). Effect modification of QT_c by type 1 and rHR by type 2 diabetes was statistically significant (*p*<0.05 for all terms of interaction).

Conclusions/interpretation QT_c is associated with long-term mortality in subjects with type 1 diabetes, whereas rHR is related to increased mortality risk in subjects with type 2 diabetes.

Keywords Cardiovascular disease · Diabetes mellitus · Heart rate · Mortality · QT interval · Risk factors

Abbreviations

bpm beats per min
HR hazard ratio
QT_c QT interval corrected for heart rate
rHR resting heart rate
V ventral

C. Stettler · A. Bearth · S. Allemann · M. Deplazes · E. R. Christ ·
A. Teuscher · P. Diem (✉)
Division of Endocrinology and Diabetes, University of Bern,
Inselspital, CH-3010 Bern, Switzerland
e-mail: peter.diem@insel.ch

C. Stettler · S. Allemann · M. Zwahlen
Division of Epidemiology and Biostatistics,
Department of Social and Preventive Medicine,
University of Bern,
Bern, Switzerland

L. Zanchin
Division of Cardiology, SRO Hospital,
Langenthal, Switzerland

Introduction

Compared with the non-diabetic population, subjects with type 1 and type 2 diabetes mellitus are reported to have an increase in all-cause mortality [1]. Cardiovascular disease has been found to be the main reason for this excess mortality [1–4]. In an effort to identify easily available and reliable predictors for cardiovascular risk and mortality in diabetes mellitus, the evaluation of parameters reflecting myocardial ventricular repolarisation has been of particular

interest. In subjects with type 1 diabetes, prolongation of the QT interval corrected for heart rate (QT_c) and heart rate variability have both been shown to be associated with increased risk of arrhythmia and death, whereas QT dispersion has been suggested to be less reliable [5]. However, the association between QT_c and cardiovascular mortality in type 2 diabetes is controversial. Some reports suggest that QT_c correlates with an increase in cardiovascular mortality [6–9]. Others have indicated that QT dispersion might more accurately predict cardiovascular mortality in this patient group [10–12].

Increased resting heart rate (rHR), which is easily measurable in clinical practice, has been shown to be an independent risk factor for cardiovascular death in a non-diabetic population [13–16]. Recently, rHR has also been shown to be valuable in estimating the risk of cardiovascular death in patients with type 2 diabetes [8, 10]. However, data directly comparing the role of QT_c and rHR in subjects with type 1 and type 2 diabetes are lacking. Based on a 23-year follow-up of the Swiss cohort of the WHO Multinational Study of Vascular Disease in Diabetes [17], the present study aimed to evaluate the long-term association of QT_c and rHR with mortality in patients with type 1 and type 2 diabetes within the same study framework.

Subjects and methods

Study population The WHO Multinational Study of Vascular Disease in Diabetes is a multicentre international study with a central protocol applied by 14 centres in 13 countries [18]. For the original study, each centre recruited stratified samples of 250 men and 250 women with a clinical diagnosis of diabetes, aged between 35 and 54 years at time of recruitment. The present analysis was based on the Swiss cohort of this study [17], which included 533 subjects randomly selected according to the central protocol by 231 local practitioners [17, 18]. The sample was representative of a large area including almost the entire country. The diagnosis of diabetes mellitus was made on a clinical basis. Subjects were eligible if diabetes had been diagnosed at least 1 year prior to study entry and anti-diabetic treatment (diet, oral glucose-lowering drugs, insulin) had been initiated by their physicians. If insulin was needed for treatment within 1 year of diagnosis, subjects were considered to have type 1 diabetes [18], the remaining subjects were classified as having type 2 diabetes. These comparably simple clinical definitions with acknowledged inadequacies were used because of the constraints on information available and the need for consistency with earlier reports [19–21]. At baseline, a standardised clinical examination was performed, including

a detailed questionnaire with information on diabetes diagnosis, the duration and treatment, as well as on symptoms of vascular and cardiac disease. Previous medical history also included the use of other medication (including diuretics, lipid-lowering drugs and blood pressure-lowering drugs). Central randomisation to the cohort was stratified according to sex, age (35–41 years, 42–48 years, 49–54 years) and duration of diabetes (1–6 years, 7–13 years, 14 years and more). In addition, height and weight were recorded, and blood pressure was measured after 30 min of rest; hypertension being defined as a systolic blood pressure of ≥ 160 mmHg, and/or a diastolic blood pressure ≥ 95 mmHg, and/or the use of antihypertensive medication including diuretics. Urine was tested semiquantitatively for proteinuria using the salicylsulfonic acid method, blood samples were drawn to measure fasting plasma glucose, cholesterol, triacylglycerol and creatinine, and a 12-lead ECG was recorded. These baseline investigations were carried out between February 1974 and May 1977. All subjects gave informed consent. Analyses were carried out in accordance with the Declaration of Helsinki and the Swiss laws regarding data security. Data used were made fully anonymous before the analyses.

ECG recordings Standard 12-lead resting ECGs were recorded with the patient supine and resting for at least 30 min. Analyses were performed according to the Minnesota code [22]. All tracings were evaluated by the same two experienced readers. The following items were derived from the ECG code results: ‘ECG coronary probable’ consisting of code 1.1, 1.2 and 7.1; ‘ECG coronary possible’ consisting of codes 1.3, 4.1, 4.2, 4.3, 5.1, 5.2 and 5.3; all other recordings were rated as ‘ECG coronary unlikely’ [22]. QT and RR intervals were measured by an experienced cardiologist, blinded to the diagnosis and outcome of the individual patients. QT interval length was usually measured in the ventral (V)2 and V3 leads using a digitiser (CalComp, Newbury, Berks, UK). Measurements in V2 and V3 were chosen, since they provide a close approximation of maximal QT [23]. QT interval length was measured from the onset of the QRS to the end of the T wave. In the presence of U waves, the end of the QT interval was set at the nadir of the curve between T and U wave. Maximal QT interval was corrected for the respective heart rate using the Bazett formula [24] ($QT_{c\text{Bazett}} = QT/RR^{1/2}$). In addition, the formulas suggested by Fridericia ($QT_{c\text{Fridericia}} = QT/RR^{1/3}$) [25] and the Framingham formula derived by linear regression [$QT_{c\text{Sagie}} = QT + 0.154(1 - RR)$] were used [26].

Follow-up and outcome definition The status (alive/dead) and date of death of each subject were ascertained as per 1 January 1998 on the basis of data obtained from population

registries. In deceased patients, the underlying cause of each death was determined from a copy of the death certificate, hospital records, post-mortem reports (where available), and additional information given by the treating physicians. Causes of death were coded according to the International Classification of Disease (ICD-9). Cardiovascular mortality included codes 390 to 459 and 798.1, cardiac mortality codes 390 to 429 and 798.1, and mortality due to ischaemic heart disease codes 410 to 414.

Statistical analysis Statistical assessment of potential differences in baseline characteristics between patients with type 1 and type 2 diabetes mellitus was carried out using the two-tailed unpaired Student's *t* test for continuous variables and the Pearson's chi-squared test for proportions. The impact of QT_c interval and rHR on mortality rates was assessed by time-to-event analysis using Cox proportional hazards models. Date of last clinical contact or documented date of leaving Switzerland was used for censored subjects, and exact date of death for subjects who had died. Analyses were conducted separately for subjects with type 1 and type 2 diabetes respectively, regarding all-cause, cardiovascular and cardiac mortality, and death due to ischaemic heart disease. Univariable analyses were performed before adjusting the regression model for age and sex. Then a 'full model' was fitted including the following explanatory variables: age, sex, BMI, duration of diabetes, total cholesterol, triacylglycerol, fasting plasma glucose, presence of hypertension/antihypertensive medication, history of coronary heart disease, history of microvascular disease, smoking, alcohol consumption, treatment with insulin (subjects with type 2 diabetes) and treatment with diuretics. QT_c was included in the analysis of rHR and vice versa. The model's assumptions (proportionality) were regularly checked. Analyses were then repeated using cut-off values corresponding to the lower limits of the upper quartiles (QT_c interval ≥ 450 ms or < 450 ms in type 1, rHR ≥ 90 beats per min [bpm] or < 90 bpm in type 2 diabetes). Comparable cut-off values have been suggested in earlier reports [13, 27, 28]. Based on these cut-off values, Kaplan–Meier survival analyses were performed for the main endpoint (overall mortality) and differences were statistically assessed using log-rank test. To formally assess effect modification of QT_c and rHR by diabetes type a confirmatory analysis was performed including terms of interaction in an analysis by Cox regression. Finally, regression models using the Bazett formula for QT_c were compared with models using the formula suggested by Fridericia [25] and by Sagie [26]. All analyses were performed using Stata version 8.2 (Stata Corporation, College Station, TX, USA). Results are given as mean \pm SD and as hazard ratio (HR) with 95% CI. *p* values < 0.05 were considered statistically significant.

Results

Study characteristics The entire cohort comprised 533 patients and baseline ECGs were available in 523 patients (221 type 1 diabetes, 302 type 2 diabetes). During follow-up 18 patients left the country and were censored accordingly. This translated into a drop-out rate of 3.4%. Baseline ECG was normal in more than three-quarters of all patients (85% and 77% for types 1 and 2 diabetes, respectively). The mean difference of repeated determinations of QT_c was 2.8%. Mean follow-up was 22.6 ± 0.6 years corresponding to a total of 11,815 person-years. Baseline characteristics are shown in Table 1. The proportion of women in the type 1 diabetes group was 54%, that for type 2 diabetes was lower (44%). Overall there were slightly more men than women (278, 255). Subjects with type 1 diabetes were generally younger, but had a longer duration of diabetes and a higher prevalence of retinopathy as well as higher mean values for fasting glucose at baseline. In contrast, subjects with type 2 diabetes showed higher values for BMI, blood pressure, and lipids, with coronary heart disease reported more frequently. Only a minority of subjects with type 2 diabetes were being treated with diet alone; two-thirds were using oral glucose-lowering drugs (e.g. sulfonylureas and/or biguanides), and less than one-third were being treated with insulin. In contrast, all patients with type 1 diabetes used insulin, with a minority also receiving oral glucose-lowering drugs (e.g. biguanides). While the proportion of subjects treated with antihypertensive drugs other than diuretics as well as with lipid-lowering drugs was comparable for the two types of diabetes, the use of diuretics was more frequent in subjects with type 2 diabetes. At baseline rHR tended to be higher and QT_c interval was significantly longer in patients with type 1 diabetes than in those with type 2 diabetes.

All-cause mortality During the study period 107 subjects with type 1 diabetes and 158 subjects with type 2 diabetes died. In subjects with type 1 diabetes, QT_c was positively associated with overall mortality. The unadjusted HR was 1.07 per 10 ms increase of QT_c (95% CI 1.01–1.15, $p=0.033$). This was not substantially altered when the model was adjusted for age and sex (HR 1.10, 95% 1.02–1.18, $p=0.009$). The association persisted after additional inclusion of further explanatory variables as stated in Subjects and methods ('full model', HR 1.10, 1.02–1.20, $p=0.011$). In contrast, no association of rHR with this endpoint was detected in type 1 diabetes ($p=0.924$) (Fig. 1, Tables 2 and 3). Subjects with type 2 diabetes revealed a strong positive association between rHR and mortality due to all causes. The unadjusted HR was 1.27 per 10 bpm (95% CI 1.14–1.41, $p<0.001$). Again, adjustment for age and sex revealed a similar HR (1.28, 1.16–1.42, $p<0.001$),

Table 1 Study characteristics

	Type 1 diabetes	Type 2 diabetes
Demographic		
Total number of patients (<i>n</i>)	225	308
Age (years)	43±6	46±6 ^b
Female patients (<i>n</i>)	121 (54%)	134 (44%) ^a
Clinical		
BMI (kg/m ²)	24±4	28±5 ^b
Duration of diabetes (years)	15±10	9±6 ^b
Systolic blood pressure (mmHg)	136±20	141±21 ^a
Diastolic blood pressure (mmHg)	86±11	89±11 ^b
Nicotine consumption (no. cigarettes per day)	4±8	4±8
Alcohol consumption (g/day)	8±17	12±28
ECG performed	221 (98%)	302 (98%)
ECG normal	187 (85%)	234 (77%)
Resting heart rate (bpm)	79±13	77±14
QT _c (ms)	433±30	426±32 ^a
Biochemical		
Total cholesterol (mmol/l)	6.1±1.4	6.5±1.4 ^a
Triacylglycerol (mmol/l)	1.4±1.2	2.4±2.7 ^b
Fasting glucose (mmol/l)	11.7±6.5	10±4.1 ^b
Serum creatinine (μmol/l)	91.9±43.3	86.6±27.4
Micro- and macrovascular disease		
Presence of retinopathy	117 (52%)	68 (22%) ^b
Presence of proteinuria	51 (23%)	75 (24%)
Presence of coronary heart disease	45 (20%)	96 (31%) ^a
Medication		
Diet alone as glucose-lowering treatment	0 (0%)	27 (9%) ^b
Use of oral glucose-lowering drugs	27 (12%)	188 (62%) ^b
Use of insulin	225 (100%)	90 (29%) ^b
Use of any antihypertensive drug*	33 (15%)	68 (22%)
Use of lipid-lowering drugs	4 (2%)	15 (5%)
Use of diuretics	22 (10%)	60 (20%) ^a

Data are mean values±SD

QT_c QT interval corrected for heart rate according to the formula suggested by Bazett

*Diuretics excluded

^a*p*<0.05 for difference between type 1 and type 2 diabetes

^b*p*<0.001 for difference between type 1 and type 2

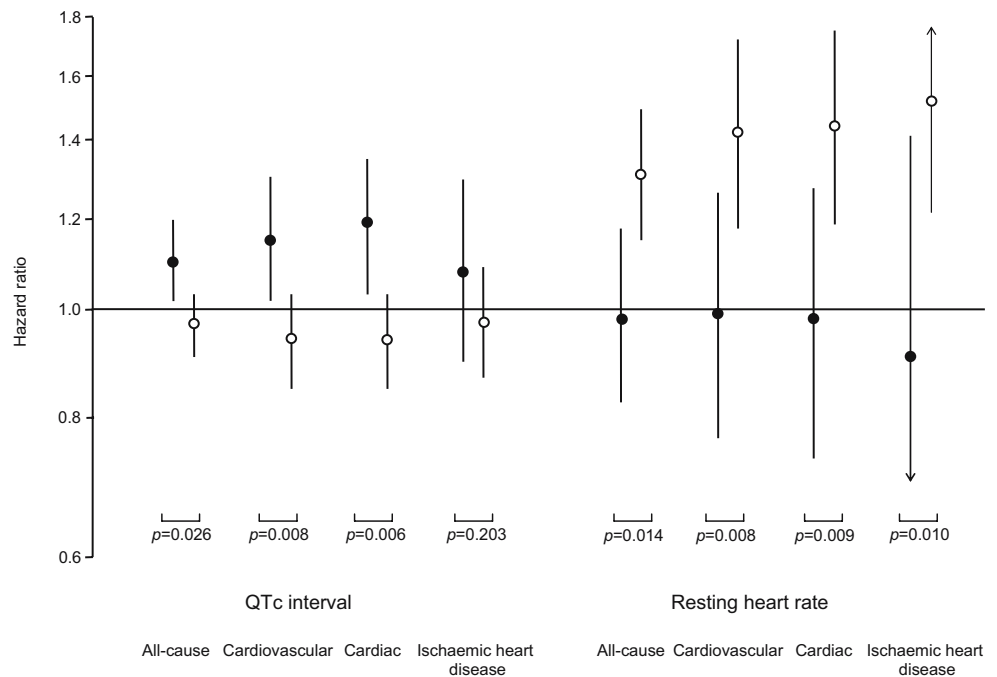
which was not substantially altered in the fully adjusted model (HR 1.31, 1.15–1.50, *p*<0.001). A comparable effect was not detected for QT_c in these patients (*p*=0.380). The analysis of an effect modification of QT_c and rHR by diabetes type revealed a statistically significant association between QT_c and type 1 diabetes and between rHR and type 2 diabetes (*p*=0.026 and *p*=0.014 for terms of interaction; Fig. 1), thereby underscoring the differences between the two types of diabetes. Subjects with type 1 diabetes and a QT_c ≥450 ms had a twofold increased mortality risk compared with those with a QT_c <450 ms (HR 2.04, 95% CI 1.27–3.25, *p*=0.003). In type 2 diabetes, a comparable increase in risk was observed when subjects with a rHR ≥90 bpm were compared with those with rHR <90 bpm (HR 2.23, 95% CI 1.43–3.46, *p*<0.001). Results of Kaplan–Meier survival analysis are shown in Fig. 2 (*p* values for log-rank test 0.019 and 0.001 for type 1 and type 2 diabetes, respectively).

Cardiovascular mortality In 50 subjects with type 1 and in 76 subjects with type 2 diabetes, death was classified as due to cardiovascular disease. As for all-cause mortality, QT_c

but not rHR was positively associated with cardiovascular mortality in type 1 diabetes (Fig. 1, Table 2). HRs for QT_c tended to be lower in the unadjusted model and after inclusion of age and sex when compared with the fully adjusted model, although conventional levels of significance were reached only in the latter (Table 3). Inverse findings were observed in subjects with type 2 diabetes, where rHR but not QT_c was related to this endpoint (Fig. 1, Table 2). Again, the HR in the unadjusted model was similar to those after adjustment for age and sex and to the ‘full model’ (Table 3). Confirmatory analysis using interaction terms revealed that the differences between the two types of diabetes were unlikely to be a chance finding (*p*=0.008 and *p*=0.008 for interaction, respectively; Fig. 1). In type 1 diabetes, mortality risk for a QT_c ≥450 ms was again increased twofold compared with a QT_c <450 ms (HR 2.34, 95% CI 1.16–4.71, *p*=0.018). In type 2 diabetes a rHR ≥90 bpm was even associated with a threefold increased risk (HR 3.27, 95% CI 1.76–6.09, *p*<0.001).

Cardiac mortality Cardiac mortality was confirmed in 43 type 1 and 71 type 2 diabetic patients. In the former, QT_c

Fig. 1 Hazard ratios for mortality due to all causes, cardiovascular disease, cardiac disease, and ischaemic heart disease per incremental 10 ms prolongation of QT_c interval and per 10 bpm increase in resting heart rate, respectively. *p* values are for effect modification by type of diabetes (closed circles, type 1 diabetes; open circles, type 2 diabetes)



but not rHR was significantly associated with cardiac mortality (Fig. 1, Table 2). HRs tended to be slightly higher in the fully adjusted model compared with the unadjusted analysis (Table 3). In type 2 diabetes, rHR was found to predict cardiac mortality, whereas QT_c was not (Fig. 1, Table 2). Adjustment for age and sex and inclusion of further explanatory variables did not affect HRs (Table 3). Again, effect modification showed that QT_c was related to type 1 and rHR to type 2 diabetes ($p=0.006$ and $p=0.009$ for interaction, respectively; Fig. 1). HR for subjects with type 1 diabetes and QT_c ≥ 450 ms was 2.90 (95% CI 1.36–6.16, $p=0.006$). In subjects with type 2 diabetes, risk of cardiac mortality was comparably increased for those with a rHR ≥ 90 bpm (HR 3.51, 95% CI 1.86–6.64, $p<0.001$).

Death due to ischaemic heart disease There were 25 and 52 deaths due to ischaemic heart disease in subjects with type 1 and type 2 diabetes, respectively. In the former, no statistically significant association was found for either QT_c nor rHR (Fig. 1, Tables 2 and 3). In subjects with type 2 diabetes, a strong positive association persisted for rHR but not for QT_c ($p=0.010$ for interaction; Fig. 1, Tables 2 and 3). Type 2 diabetic subjects with a rHR of ≥ 90 bpm had a more than threefold increased risk of dying from ischaemic heart disease (HR 3.33, 95% CI 1.63–6.77, $p=0.001$).

Different formulas for correcting QT interval for heart rate Similar results were obtained using the formulas proposed by Fridericia [25] or Sagie [26] when compared with Bazett's formula [24]. For example, in subjects with type 1 diabetes, HR for all-cause mortality was 1.10 using

Bazett's model. Applying Fridericia's or Sagie's approach the corresponding values were 1.12 and 1.13, respectively (Table 2). The same additional explanatory variables were used for all three analyses. The current literature is mainly based on Bazett's formula. In order to compare the present findings with previous reports, the formula suggested by Bazett was included in the final model.

Discussion

The main finding of this 23-year follow-up was a difference in the prognostic value of rHR and QT_c between the two types of diabetes. In subjects with type 1 diabetes QT_c, but not rHR was associated with an increased risk of all-cause mortality and mortality due to cardiovascular and cardiac disease. In contrast, in type 2 diabetes rHR, but not QT_c was consistently related to mortality due to all causes, cardiovascular, cardiac, and ischaemic heart disease. Interestingly, in type 1 diabetes a QT_c interval ≥ 450 ms translated into a twofold increase in all-cause mortality and a threefold increase in cardiac mortality. In subjects with type 2 diabetes a comparable increase in mortality risk was found for a rHR of ≥ 90 bpm compared with a rHR < 90 bpm.

To our knowledge, this is the first study to prospectively assess the role of QT_c and rHR in both types of diabetes within the same study framework. Its findings confirm the prognostic value of QT_c as an independent risk factor for all-cause mortality in type 1 diabetes [5, 28–30]. In addition to the results of Rossing et al. [5], the present

Table 2 Hazard ratios (95% CI) for mortality due to all causes, cardiovascular, cardiac, and ischaemic heart disease

	Type 1 diabetes		Type 2 diabetes	
All-cause mortality				
QT _c Bazett (model with rHR)	1.10 (1.02–1.20)	<i>p</i> =0.011	0.97 (0.91–1.03)	<i>p</i> =0.380
rHR (model with QT _c Bazett)	0.98 (0.83–1.18)	<i>p</i> =0.924	1.31 (1.15–1.50)	<i>p</i> <0.001
QT _c Fridericia (model with rHR)	1.12 (1.03–1.21)	<i>p</i> =0.011	0.97 (0.91–1.03)	<i>p</i> =0.343
rHR (model with QT _c Fridericia)	1.09 (0.93–1.28)	<i>p</i> =0.307	1.28 (1.13–1.46)	<i>p</i> <0.001
QT _c Sagie (model with rHR)	1.13 (1.03–1.23)	<i>p</i> =0.012	0.97 (0.90–1.04)	<i>p</i> =0.366
rHR (model with QT _c Sagie)	1.10 (0.94–1.30)	<i>p</i> =0.241	1.28 (1.13–1.46)	<i>p</i> <0.001
Cardiovascular mortality				
QT _c Bazett (model with rHR)	1.15 (1.02–1.31)	<i>p</i> =0.024	0.94 (0.85–1.03)	<i>p</i> =0.160
rHR (model with QT _c Bazett)	0.99 (0.77–1.27)	<i>p</i> =0.917	1.43 (1.18–1.73)	<i>p</i> <0.001
QT _c Fridericia (model with rHR)	1.16 (1.02–1.32)	<i>p</i> =0.026	0.93 (0.84–1.02)	<i>p</i> =0.140
rHR (model with QT _c Fridericia)	1.12 (0.88–1.42)	<i>p</i> =0.346	1.35 (1.12–1.63)	<i>p</i> =0.002
QT _c Sagie (model with rHR)	1.18 (1.02–1.36)	<i>p</i> =0.023	0.91 (0.82–1.02)	<i>p</i> =0.100
rHR (model with QT _c Sagie)	1.14 (0.90–1.46)	<i>p</i> =0.272	1.34 (1.11–1.61)	<i>p</i> =0.002
Cardiac mortality				
QT _c Bazett (model with rHR)	1.19 (1.03–1.36)	<i>p</i> =0.016	0.94 (0.85–1.03)	<i>p</i> =0.182
rHR (model with QT _c Bazett)	0.98 (0.74–1.28)	<i>p</i> =0.865	1.45 (1.19–1.76)	<i>p</i> <0.001
QT _c Fridericia (model with rHR)	1.19 (1.03–1.38)	<i>p</i> =0.018	0.93 (0.84–1.03)	<i>p</i> =0.163
rHR (model with QT _c Fridericia)	1.13 (0.88–1.46)	<i>p</i> =0.336	1.37 (1.13–1.66)	<i>p</i> =0.001
QT _c Sagie (model with rHR)	1.21 (1.03–1.42)	<i>p</i> =0.017	0.92 (0.82–1.02)	<i>p</i> =0.115
rHR (model with QT _c Sagie)	1.16 (0.90–1.51)	<i>p</i> =0.256	1.36 (1.12–1.66)	<i>p</i> =0.002
Death due to ischaemic heart disease				
QT _c Bazett (model with rHR)	1.08 (0.90–1.30)	<i>p</i> =0.397	0.97 (0.87–1.09)	<i>p</i> =0.617
rHR (model with QT _c Bazett)	0.91 (0.58–1.42)	<i>p</i> =0.678	1.52 (1.21–1.90)	<i>p</i> <0.001
QT _c Fridericia (model with rHR)	1.09 (0.90–1.32)	<i>p</i> =0.399	0.97 (0.86–1.09)	<i>p</i> =0.581
rHR (model with QT _c Fridericia)	0.98 (0.64–1.49)	<i>p</i> =0.914	1.48 (1.18–1.85)	<i>p</i> =0.001
QT _c Sagie (model with rHR)	1.09 (0.89–1.34)	<i>p</i> =0.401	0.96 (0.84–1.09)	<i>p</i> =0.531
rHR (model with QT _c Sagie)	0.99 (0.64–1.51)	<i>p</i> =0.946	1.47 (1.18–1.84)	<i>p</i> =0.001

Data are given per incremental 10 ms prolongation of QT_c interval and 10 bpm increase in rHR, respectively. Formulas for calculation of QT_c: Bazett [24], Fridericia [25], Sagie [26], as indicated by subscript. All models adjusted for age, sex, BMI, duration of diabetes, total cholesterol, triacylglycerol, fasting plasma glucose, presence of hypertension, history of coronary heart disease, history of microvascular disease, smoking, alcohol consumption, treatment with insulin (subjects with type 2 diabetes) and treatment with diuretics.

analysis found QT_c to be associated not only with overall mortality but also with cardiovascular and cardiac mortality. Moreover, it also reproduced the findings of Sawicki and colleagues, which were made in subjects with nephropathy [28] in a more general sample of subjects with type 1 diabetes. The HR for overall mortality found in the present analysis was comparable to that in Rossing's report [5], but tended to be lower than the risk ratio found in subjects with overt nephropathy [28] (1.10 and 1.47 per 10 ms, respectively). Earlier reports have suggested that the association between QT_c and cardiovascular disease was stronger in male than in female subjects with type 1 diabetes [30]. The present study had slightly more female subjects in the group with type 1 diabetes, thereby potentially underestimating the prognostic value of QT_c for this patient group.

An increased rHR has been found to be related to all-cause mortality and cardiovascular death in several trials of non-diabetic subjects [13, 31–34], and in subjects with type 2 diabetes [8, 10]. Our analysis confirmed the role of rHR

as an easily measurable factor for risk assessment of all-cause and cardiovascular mortality in subjects with type 2 diabetes, and had comparable HRs. In addition to findings of previous reports, we also observed a relation between elevated rHR and both cardiac mortality and mortality due to ischaemic heart disease. On the other hand, the present analysis did not confirm an association between QT_c and any of the endpoints in type 2 diabetes as has been reported previously [6, 7, 9, 10, 35]. Given previous hypotheses that prolongation of QT_c as a marker of cardiac autonomic neuropathy could be of greater importance in type 1 than in type 2 diabetes [5], our findings on this count are intriguing, and it can only be speculated on the underlying mechanisms.

In subjects with type 1 diabetes an increased prevalence of prolonged QT_c has been reported before [30, 36], in particular in subjects with autonomic neuropathy [36–38]. This may indicate that increased QT_c relates to diabetic autonomic neuropathy [39]. QT_c prolongation has been suggested to result from a reduction in vagal activity and an

Table 3 Hazard ratios (95% CI) for mortality due to all causes, and to cardiovascular, cardiac and ischaemic heart disease

		All-cause mortality		Cardiovascular mortality		Cardiac mortality		Death due to ischaemic heart disease	
Type 1 diabetes									
QTc	Crude/unadjusted	1.07 (1.01–1.15)	$p=0.033$	1.08 (0.99–1.19)	$p=0.098$	1.10 (0.99–1.22)	$p=0.084$	1.04 (0.91–1.19)	$p=0.610$
	Adjusted for age and sex	1.10 (1.02–1.18)	$p=0.009$	1.10 (1.00–1.22)	$p=0.057$	1.12 (1.00–1.25)	$p=0.055$	1.06 (0.92–1.23)	$p=0.410$
	Full model*	1.10 (1.02–1.20)	$p=0.011$	1.15 (1.02–1.31)	$p=0.024$	1.19 (1.03–1.36)	$p=0.016$	1.08 (0.90–1.30)	$p=0.397$
Type 2 diabetes									
rHR	Crude/unadjusted	1.27 (1.14–1.41)	$p<0.001$	1.35 (1.15–1.57)	$p<0.001$	1.36 (1.16–1.60)	$p<0.001$	1.42 (1.18–1.70)	$p<0.001$
	Adjusted for age and sex	1.28 (1.16–1.42)	$p<0.001$	1.36 (1.18–1.57)	$p<0.001$	1.37 (1.18–1.59)	$p<0.001$	1.41 (1.19–1.68)	$p<0.001$
	Full model*	1.31 (1.15–1.50)	$p<0.001$	1.43 (1.18–1.73)	$p<0.001$	1.45 (1.19–1.76)	$p<0.001$	1.52 (1.21–1.90)	$p<0.001$

Results are shown from a three-step approach in regression modelling (unadjusted, adjusted for age and sex, and ‘full model’). Data are given per incremental 10 ms prolongation of QT_c interval for type 1 and 10 bpm increase in rHR for type 2 diabetes, respectively.

*Full model adjusted for: age, sex, BMI, diabetes duration; levels of fasting glucose, triacylglycerol and cholesterol; presence or absence of microvascular disease, hypertension, coronary heart disease; treatment with diuretics, insulin (for type 2 diabetes); alcohol consumption, smoking. QT_c was included in the analysis of rHR and vice versa.

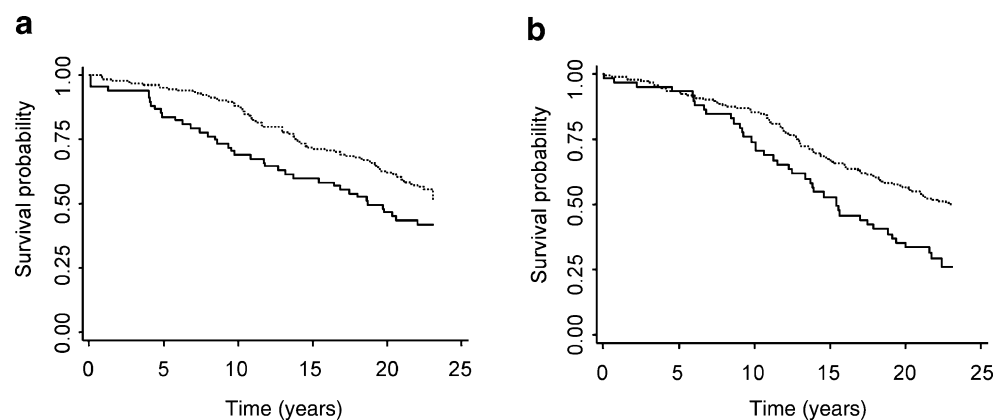
increased sympathetic tonus, thereby reflecting myocardial autonomic instability and an increased risk of arrhythmia and cardiac death [9, 28, 36, 40]. Compared with previous publications reporting an association of QT_c with mortality in type 2 diabetes [9, 10, 35], subjects with type 2 diabetes were substantially younger in the present study. It should also be noted that some earlier reports revealing an association between QT_c and mortality were cross-sectional [35] or based on a case–control design [9] and in the case of prospective trials [6, 7, 10] had a considerably shorter follow-up.

In type 2 diabetes hyperglycaemia is often associated with a pro-inflammatory state including obesity, dyslipidaemia and hypertension, thereby promoting the development of atherosclerosis [41]. Interestingly, impaired myocardial oxygen supply has also been shown to influence QT interval [28, 30]. As has been pointed out

before [6, 10], QT_c is possibly a composite marker, reflecting abnormal ventricular repolarisation due to ischaemia, fibrosis, left ventricular hypertrophy and dilatation, autonomic neuropathy, and vascular damage, conditions frequently present in diabetic myocardium. Although the models used in this analysis were adjusted for the pre-existence of coronary heart disease, we could not fully rule out a potential interference due to silent heart disease in subjects with diabetes, since invasive cardiac procedures were not performed.

The strength of the present study lies in the long follow-up period, the well-defined cohort of diabetic subjects (Swiss cohort [17] of the WHO Multinational Study of Vascular Disease in Diabetes [18, 22]), the evaluation of pre-specified endpoints, and the small drop-out rate. Considerable efforts were undertaken to adjust for relevant factors known to affect cardiovascular risk and/or myocar-

Fig. 2 Kaplan–Meier estimation of survival probabilities for overall mortality. **a** The survival probabilities for type 1 diabetes, comparing patients with a QT_c interval ≥ 450 ms (solid line) with those with a QT_c interval < 450 ms (dotted line). $p=0.019$ for difference by log-rank test. **b** Survival probabilities for type 2 diabetes comparing patients with a resting heart rate ≥ 90 bpm (solid line) with those with rHR < 90 bpm (dotted line). $p=0.001$ for difference by log-rank test



dial ventricular repolarisation. This allowed inclusion of parameters that earlier reports had not been adjusted for, despite their known influence on mortality (e.g. alcohol consumption) [42]. Moreover, as the use of Bazett's formula [24] to calculate QT_c has been questioned before [8, 26, 43], possible differences in effect were taken into account by performing sensitivity analyses using the formulas suggested by Fridericia [25] and by Sagie [26]. In contrast to earlier reports [8], inclusion of different calculations of QT_c did not substantially alter our results (Table 2). As a consequence, Bazett's formula was included in the final model to allow for comparisons with other reports.

Nevertheless, we must acknowledge some limitations to our findings. Thus rHR was determined from ECG recordings, whereas in clinical practice it is usually measured by pulse palpation, rendering it subject to variation due to circumstantial factors (medical setting, circadian rhythm, body position etc.). In addition, QT_c and rHR can potentially be influenced by specific medication. Although the use of antihypertensive medication and diuretics was recorded in the present trial, data did not allow to specifically adjust for the use of beta blockers. Since it is known that treatment with these agents can influence both QT_c [44], and rHR, a potential interfering effect on the present findings cannot be fully excluded. It should, however, be noted that at the time of study entry only a limited number of beta blockers was available in Switzerland. Moreover, in another study [9] adjustment for use of beta blockers only modestly attenuated the association between QT_c and the risk of primary cardiac arrest. Another known factor to influence rHR is physical training [45]. Tachycardia may be a marker of decreased physical fitness, which in turn may be associated with an increased risk of mortality [46]. Interestingly, increased rHR was found to be an independent prognostic factor of cardiovascular mortality in studies controlling for energy expenditure as an indicator of physical fitness [31].

In deceased patients, the underlying cause of death was determined from a copy of the death certificate, hospital records, post-mortem reports, and additional information given by the treating physicians. Despite intensive efforts to collect comprehensive data, the cause of death may, in some cases, have been misclassified, especially if based only on death certificates, which are a comparatively unreliable source of information. Thus, our findings regarding all-cause mortality are clearly more robust than those for cause-specific mortality.

Glycaemic control has been shown to be related to macrovascular complications [47, 48], and was, therefore, included in the present analysis. Importantly, information on glycaemic control had to be based on fasting glucose, since HbA_{1c} was not available at the time of study entry,

thereby potentially limiting the accuracy of adjustment. With regard to this, however, Veglio et al. did not report a significant influence of HbA_{1c} levels on QT_c [35].

In summary, this study, performed in a large, diabetic cohort followed over 23 years, confirms that in subjects with type 1 diabetes prolonged QT_c is associated with an increased mortality risk due to all causes, and to cardiovascular and cardiac disease, whereas no association was found for rHR. In contrast, in subjects with type 2 diabetes, elevated rHR, but not QT_c , is associated with an increased risk of all-cause mortality as well as risk of death due to cardiovascular, cardiac and ischaemic heart disease. The underlying pathophysiological mechanisms are probably complex and remain to be fully elucidated.

Acknowledgements We are indebted to the study participants, their treating physicians, and to the Federal Office of Statistics, Neuchâtel (Th. Spuler), as well as to the various community-based population registries throughout the country. We thank E. Hurni, R. Fajfr, P. P. Studer, H. Schnell, St. Suter and K. Diem for help with data collection and verification.

Duality of interest The authors declare that they have no duality of interest.

References

1. Waernbaum I, Blohme G, Ostman J et al (2006) Excess mortality in incident cases of diabetes mellitus aged 15 to 34 years at diagnosis: a population-based study (DISS) in Sweden. *Diabetologia* 49:653–659
2. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM (2006) All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992–1999. *Diabetologia* 49:660–666
3. Nathan DM, Cleary PA, Backlund JY et al (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353:2643–2653
4. Ford ES, DeStefano F (1991) Risk factors for mortality from all causes and from coronary heart disease among persons with diabetes. Findings from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Am J Epidemiol* 133:1220–1230
5. Rossing P, Breum L, Major-Pedersen A et al (2001) Prolonged QT_c interval predicts mortality in patients with Type 1 diabetes mellitus. *Diabet Med* 18:199–205
6. Naas AA, Davidson NC, Thompson C et al (1998) QT and QT_c dispersion are accurate predictors of cardiac death in newly diagnosed non-insulin dependent diabetes: cohort study. *Br Med J* 316:745–746
7. Christensen PK, Gall MA, Major-Pedersen A et al (2000) QT_c interval length and QT dispersion as predictors of mortality in patients with non-insulin-dependent diabetes. *Scand J Clin Lab Invest* 60:323–332
8. Linnemann B, Janka HU (2003) Prolonged QT_c interval and elevated heart rate identify the type 2 diabetic patient at high risk for cardiovascular death. The Bremen Diabetes Study. *Exp Clin Endocrinol Diabetes* 111:215–222
9. Whitsel EA, Boyko EJ, Rautaharju PM et al (2005) Electrocardiographic QT interval prolongation and risk of primary cardiac arrest in diabetic patients. *Diabetes Care* 28:2045–2047

10. Cardoso CR, Salles GF, Deccache W (2003) Prognostic value of QT interval parameters in type 2 diabetes mellitus: results of a long-term follow-up prospective study. *J Diabetes Complications* 17:169–178
11. Rana BS, Band MM, Ogston S, Morris AD, Pringle SD, Struthers AD (2002) Relation of QT interval dispersion to the number of different cardiac abnormalities in diabetes mellitus. *Am J Cardiol* 90:483–487
12. Sawicki PT, Kiwitt S, Bender R, Berger M (1998) The value of QT interval dispersion for identification of total mortality risk in non-insulin-dependent diabetes mellitus. *J Intern Med* 243:49–56
13. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA (1987) Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 113:1489–1494
14. Palatini P, Julius S (1997) Heart rate and the cardiovascular risk. *J Hypertens* 15:3–17
15. Palatini P, Casiglia E, Julius S, Pessina AC (1999) High heart rate: a risk factor for cardiovascular death in elderly men. *Arch Intern Med* 159:585–592
16. Mensink GB, Hoffmeister H (1997) The relationship between resting heart rate and all-cause, cardiovascular and cancer mortality. *Eur Heart J* 18:1404–1410
17. Teuscher A, Herman JB, Studer PP (1983) Vascular diseases in 534 Swiss diabetics within the scope of a multinational study. *Klin Wochenschr* 61:139–149 (in German)
18. Jarrett RJ, Keen H, Grabauskas V (1979) The WHO multinational study of vascular disease in diabetes: 1. General description. *Diabetes Care* 2:175–186
19. Lee ET, Keen H, Bennett PH, Fuller JH, Lu M (2001) Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: general description and morbidity. *Diabetologia* 44 (Suppl 2):S3–S13
20. Fuller JH, Stevens LK, Wang SL (2001) Risk factors for cardiovascular mortality and morbidity: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 44(Suppl 2): S54–S64
21. Miki E, Lu M, Lee ET, Keen H, Bennett PH, Russell D (2001) The incidence of visual impairment and its determinants in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 44(Suppl 2):S31–S36
22. No authors listed (1985) Prevalence of small vessel and large vessel disease in diabetic patients from 14 centres. The World Health Organisation Multinational Study of Vascular Disease in Diabetics. Diabetes Drafting Group. *Diabetologia* 28(Suppl):615–640
23. Cowan JC, Hilton CJ, Griffiths CJ et al (1988) Sequence of epicardial repolarisation and configuration of the T wave. *Br Heart J* 60:424–433
24. Bazett HC (1920) An analysis of time relation of electrocardiograms. *Heart* 7:353–370
25. Fridericia LS (1920) Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. *Acta Med Scand* 53:469–486
26. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D (1992) An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol* 70:797–801
27. Fujiura Y, Adachi H, Tsuruta M, Jacobs DR Jr, Hirai Y, Imaizumi T (2001) Heart rate and mortality in a Japanese general population: an 18-year follow-up study. *J Clin Epidemiol* 54:495–500
28. Sawicki PT, Dahne R, Bender R, Berger M (1996) Prolonged QT interval as a predictor of mortality in diabetic nephropathy. *Diabetologia* 39:77–81
29. Veglio M, Sivieri R, Chinaglia A, Scaglione L, Cavallo-Perin P (2000) QT interval prolongation and mortality in type 1 diabetic patients: a 5-year cohort prospective study. Neuropathy Study Group of the Italian Society of the Study of Diabetes, Piemonte Affiliate. *Diabetes Care* 23:1381–1383
30. Veglio M, Borra M, Stevens LK, Fuller JH, Perin PC (1999) The relation between QTc interval prolongation and diabetic complications. The EURODIAB IDDM Complication Study Group. *Diabetologia* 42:68–75
31. Gillum RF, Makuc DM, Feldman JJ (1991) Pulse rate, coronary heart disease, and death: the NHANES I Epidemiologic Follow-up Study. *Am Heart J* 121:172–177
32. Fuller JH, McCartney P, Jarrett RJ et al (1979) Hyperglycaemia and coronary heart disease: the Whitehall study. *J Chronic Dis* 32:721–728
33. Dyer AR, Persky V, Stamler J et al (1980) Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. *Am J Epidemiol* 112:736–749
34. Filipovsky J, Ducimetiere P, Safar ME (1992) Prognostic significance of exercise blood pressure and heart rate in middle-aged men. *Hypertension* 20:333–339
35. Veglio M, Bruno G, Borra M et al (2002) Prevalence of increased QT interval duration and dispersion in type 2 diabetic patients and its relationship with coronary heart disease: a population-based cohort. *J Intern Med* 251:317–324
36. Sivieri R, Veglio M, Chinaglia A, Scaglione P, Cavallo-Perin P (1993) Prevalence of QT prolongation in a type 1 diabetic population and its association with autonomic neuropathy. The Neuropathy Study Group of the Italian Society for the Study of Diabetes. *Diabet Med* 10:920–924
37. Ewing DJ, Boland O, Neilson JM, Cho CG, Clarke BF (1991) Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. *Diabetologia* 34:182–185
38. Veglio M, Chinaglia A, Borra M, Perin PC (1995) Does abnormal QT interval prolongation reflect autonomic dysfunction in diabetic patients? QTc interval measure versus standardized tests in diabetic autonomic neuropathy. *Diabet Med* 12:302–306
39. Vinik AI, Maser RE, Mitchell BD, Freeman R (2003) Diabetic autonomic neuropathy. *Diabetes Care* 26:1553–1579
40. Ewing DJ, Neilson JM (1990) QT interval length and diabetic autonomic neuropathy. *Diabet Med* 7:23–26
41. Schwartz CJ, Valente AJ, Sprague EA, Kelley JL, Cayatte AJ, Rozek MM (1992) Pathogenesis of the atherosclerotic lesion. Implications for diabetes mellitus. *Diabetes Care* 15:1156–1167
42. Diem P, Deplazes M, Fajfr R et al (2003) Effects of alcohol consumption on mortality in patients with Type 2 diabetes mellitus. *Diabetologia* 46:1581–1585
43. Ahnve S (1991) Is QT interval prolongation a strong or weak predictor for cardiac death? *Circulation* 84:1862–1865
44. Molgaard H, Mickley H, Pless P, Bjerregaard P, Moller M (1993) Effects of metoprolol on heart rate variability in survivors of acute myocardial infarction. *Am J Cardiol* 71:1357–1359
45. Somers VK, Conway J, Johnston J, Sleight P (1991) Effects of endurance training on baroreflex sensitivity and blood pressure in borderline hypertension. *Lancet* 337:1363–1368
46. Palatini P (1999) Need for a revision of the normal limits of resting heart rate. *Hypertension* 33:622–625
47. Selvin E, Marinopoulos S, Berkenblit G et al (2004) Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 141:421–431
48. Stettler C, Allemann S, Jüni P et al (2006) Glycemic control and macrovascular disease in type 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J* 152:27–38

3.2 Study E: Apolipoprotein B as a long term predictor of mortality in type 1 diabetes mellitus: a 15-year follow up

Christoph Stettler,^{1,2} Yves Suter,¹ Sabin Allemann,^{1,2} Marcel Zwahlen,²
Emanuel R. Christ,¹ and Peter Diem¹

- 1) Division of Endocrinology and Diabetes, University of Bern, Switzerland
- 2) Division of Epidemiology and Biostatistics, Department of Social and Preventive Medicine, University of Bern, Switzerland

Article published in:

J Intern Med 2006 Sep;260(3):272-80.

Abstract provided at:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16918825&query_hl=1&itool=pubmed_docsum

Apolipoprotein B as a long-term predictor of mortality in type 1 diabetes mellitus: a 15-year follow up

C. STETTLER^{1,2}, Y. SUTER¹, S. ALLEMANN^{1,2}, M. ZWAHLEN², E. R. CHRIST¹ & P. DIEM¹
From the Divisions of¹Endocrinology and Diabetes; and ²Epidemiology and Biostatistics, Department of Social and Preventive Medicine; University of Bern, Bern, Switzerland

Abstract. Stettler C, Suter Y, Allemann S, Zwahlen M, Christ ER, Diem P (University of Bern, Bern, Switzerland). Apolipoprotein B as a long-term predictor of mortality in type 1 diabetes mellitus: a 15-year follow up. *J Intern Med* 2006; doi: 10.1111/j.1365-2796.2006.01690.x

Objectives. To evaluate the association of apolipoprotein B (apo B) with mortality due to all causes, to cardiac disease and to ischaemic heart disease (IHD) in subjects with type 1 diabetes mellitus.

Subjects. 165 subjects with type 1 diabetes included in the Swiss Cohort of the WHO Multinational Study of Vascular Disease in Diabetes were followed for 14.7 ± 0.45 years.

Methods. Causes of death were obtained from death certificates, hospital records and postmortem reports. Using a parametric proportional hazards model the association of apo B with mortality rates was assessed by time-to-event analysis, including the absolute cumulative mortality risk over time for various apo B levels at baseline.

Results. Apo B was positively associated with all-cause mortality [hazard ratio (HR) 2.65 per g L⁻¹ increase of apo B, 95% CI: 1.11–6.36, $P = 0.029$], cardiac mortality (HR 11.64, 1.03–131.11, $P = 0.047$) and IHD mortality (HR 9.36, 1.26–69.66, $P = 0.029$). An apo B ≥ 0.96 g L⁻¹ translated into a duplication of overall mortality hazard (HR 1.93, 1.00–3.72, $P = 0.050$), and a sevenfold increase of mortality because of cardiac disease or IHD (HR 7.44, 1.44–38.42, $P = 0.017$ and HR 7.38, 0.78–69.82, $P = 0.081$). A baseline apo B of 1.5 g L⁻¹ predicted an absolute cumulative risk to die over the next 10 years of 12.1% (5.2–31.7) for male and of 10.4% (4.7–26.1) for female subjects whereas risks were 6.3% (1.8–21.4) and 5.4% (0.8–15.8) for an apo B of 0.8 g L⁻¹.

Conclusion. Apo B is consistently associated with an increased mortality in type 1 diabetes.

Keywords: apolipoproteins, cardiovascular risk factors, mortality, type 1 diabetes mellitus.

Introduction

Apolipoprotein B (apo B) has recently been suggested an easily measurable and valuable estimate of cardiovascular risk [1–4]. In contrast, current guidelines in the United States [5, 6] as well as in Europe [7, 8] recommend the use of low-density lipoprotein (LDL) cholesterol as the primary target risk factor. The main advantage of apo B has been related to the fact that its levels correspond to the number of atherogenic particles thereby improving the estimate of total atherogenic burden [1, 4]. Several prospective clinical trials [9–13] and a recent meta-analysis [14] have underscored the

value of apo B in the assessment of cardiovascular risk in the general population. Similar results have been found in multiple cross-sectional [15–19] and prospective [20–23] trials in subjects with type 2 diabetes mellitus or the metabolic syndrome.

In contrast to the evidence of the value of apo B in nondiabetic subjects or in subjects with type 2 diabetes, comparably little is known about its role in type 1 diabetes. Although accounting for only 5–10% of all diabetic subjects type 1 diabetes remains a serious chronic disorder with important short-term and long-term complications [24]. Despite all efforts to improve treatment strategies recent reports showed that cardiovascular mortality in type 1

diabetes is still increased when compared with healthy subjects [25]. The precise underlying pathophysiological abnormalities are currently ill defined [25]. Dyslipidaemia is a well-established cardiovascular risk factor in the general population and in subjects with type 2 diabetes. It has been suggested to contribute to the increased risk in subjects with type 1 diabetes as well [26, 27]. However, epidemiological data have indicated a stronger association of apo B with microvascular complications than with cardiovascular disease in type 1 diabetes [28–30]. Only one prospectively conducted trial in subjects with type 1 diabetes has reported an association of apo B with cardiovascular disease but not with mortality [31]. Taken together, in type 1 diabetes there is uncertainty about the association of apo B with cardiovascular disease. In particular, little is known on the prognostic value of apo B on mortality in these subjects. Based on a 15-year follow up of the Swiss Cohort of the WHO Multinational Study of Vascular Disease in Diabetes [32] we, therefore, assessed the long-term association of apo B with mortality because of different causes.

Subjects and methods

Study population

In 1972, the 'WHO multinational study of vascular disease in diabetes' was planned to assess the frequency of microvascular and macrovascular morbidity in subjects with diabetes mellitus in different countries and to examine the relationship with potential influencing factors, as for example, race, diet or therapy. Overall, 6695 subjects with diabetes mellitus with an age between 35 and 54 years were recruited in 14 countries [33]. In Switzerland, 225 subjects with type 1 diabetes mellitus were examined by local practitioners between February 1974 and May 1977, according to a standardized protocol [32, 33]. For the purpose of this study type 1 diabetes was diagnosed if insulin was needed for treatment within 1 year of diagnosis [33]. Randomization to the cohort was stratified according to gender, age and duration of diabetes. The sample was representative of a large area including almost the entire country. Between March 1982 and February 1985 a second clinical visit was performed in a subset of the entire cohort. At this time-point a second blood sample was drawn in 165 subjects with type 1 diabetes.

Data recording and blood sampling

At baseline and at the second visit, a standardized clinical examination was performed, including a detailed questionnaire with information on the diagnosis of diabetes, the duration and treatment as well as on symptoms of vascular and cardiac disease. In addition, height, weight and blood pressure were recorded; proteinuria was measured semiquantitatively using the salicylsulphonic acid method. Blood samples were drawn to measure fasting plasma glucose, cholesterol, triglycerides and creatinine concentrations, and a 12-lead electrocardiogram was recorded. The concentration of apo B was measured by radioimmunoassay (Behring, Germany). Analyses were carried out in accordance with the Declaration of Helsinki and the Swiss laws regarding data safety. The data were rendered anonymous before the analyses.

Follow up and outcome definition

The primary outcome was overall mortality, secondary outcomes included death due to cardiac disease and ischaemic heart disease (IHD). The status (alive/dead) and date of death of each subject was ascertained as per 1 January 1998 based on data obtained from population registries. In deceased patients, the underlying cause of each death was determined from a copy of the death certificate, hospital records, postmortem reports (where available) and additional information given by the treating doctors. Causes of death were coded according to the International Classification of Disease (ICD-9). Cardiac mortality included codes 390–429 and 798.1 and mortality due to ischaemic heart disease (IHD) codes 410–414.

Statistical analysis

The impact of apo B on mortality was assessed by time-to-event analysis. Date of last clinical contact or documented date of leaving Switzerland was used for censored subjects, whereas exact date of death was included for deceased subjects. Analyses were conducted separately for all end-points. Using a cut-off value based on the upper limit of the lowest quartile (0.96 g L^{-1}), subjects with an apo B level $<0.96 \text{ g L}^{-1}$ were compared to those with an apo B level $\geq 0.96 \text{ g L}^{-1}$ in a Kaplan–Meier survival

analysis, and differences were statistically assessed using log-rank test. To assess prognostic variables, multivariable parametric proportional hazards models of the Weibull family were fitted [34]. Univariable analyses were performed before adjusting the regression model for age and gender. Then a 'full model' was fitted including the following explanatory variables: age, gender, body mass index (BMI), duration of diabetes, cholesterol, triglycerides, fasting plasma glucose, presence of hypertension (defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or treatment with antihypertensive drugs), history of microvascular disease, treatment with diuretics, treatment with antihypertensive drugs and alcohol consumption.

Finally, to illustrate the prognostic value of apo B, the cumulative absolute mortality risk over time was computed for various values of baseline concentration of apo B. For this analysis all explanatory variables as specified above were taken into account and the covariate pattern for continuous variables was set to the average covariate of the study population. A separate analysis was performed for male and female subjects to assess potential gender differences. Confidence intervals (CI) were obtained using bootstrapping (300 replications). All analyses were performed using STATA version 8.2 (Stata Corporation, College Station, TX, USA). Results are given as mean \pm SD and as hazard ratio (HR) with 95% CI. *P*-values of <0.05 were considered statistically significant.

Results

Study characteristics

Measurement of apo B was performed in 165 subjects with type 1 diabetes between March 1982 and February 1985. Mean follow up was 14.7 ± 0.45 years corresponding to a total of 2424 person-years. No subject was lost to follow up. Baseline characteristics are shown in Table 1. The study population consisted of slightly more females than males. Subjects had a mean age of about 50 years, weight was generally normal but blood pressure tended to be elevated although only about a quarter of the subjects used antihypertensive drugs. Total cholesterol levels were comparably high whereas triglycerides were in the normal range. Less than 4% of subjects were under lipid-

Table 1 Study characteristics

	All subjects (<i>n</i> = 165)
Demographic	
Age (years)	51.0 \pm 6.3
Males/females	72/93
Clinical	
Body mass index (kg m ⁻²)	24.3 \pm 3.9
Duration of diabetes (years)	23.5 \pm 9.2
Systolic blood pressure (mmHg)	143.5 \pm 22.4
Diastolic blood pressure (mmHg)	86.7 \pm 11.6
Alcohol consumption (dL day ⁻¹) ^a	1.3 \pm 2.3
Biochemical	
Fasting glucose (mmol L ⁻¹)	10.2 \pm 5.3
Serum creatinine (mmol L ⁻¹)	103.6 \pm 70.9
Total cholesterol (mmol L ⁻¹)	7.5 \pm 6.2
Triglycerides (mmol L ⁻¹)	1.6 \pm 0.8
Apo B (g L ⁻¹)	1.2 \pm 0.3
Medications [<i>n</i> (%)]	
Diuretics	43 (26)
Antihypertensive drugs	39 (24)
Lipid-lowering drugs	6 (4)
Microvascular disease [<i>n</i> (%)]	
Retinopathy	108 (66)
Proteinuria	49 (30)

Data are given as mean \pm SD or as numbers (percentage) of subjects.

^aIncludes consumption of wine, beer and all types of liquors.

lowering therapy. In two-thirds of the study population evidence of diabetic retinopathy was found whereas nephropathy was less frequently documented. Apo B levels ranged from 0.6 to 2.9 g L⁻¹ with a mean of 1.2 g L⁻¹.

All-cause mortality

During the study period 72 subjects died. Apo B levels were positively associated with an increased mortality risk. The unadjusted HR was 2.78 per g L⁻¹ increase of apo B (95% CI: 1.35–5.75, *P* = 0.006). This was not substantially altered when the model was adjusted for age and gender (HR 2.62 per g L⁻¹, 95% CI: 1.17–5.83, *P* = 0.019; Table 2). The association persisted after additional inclusion of further explanatory variables as stated in the Subjects and Methods section ('full model'; HR 2.65 per g L⁻¹, 95% CI: 1.11–6.36, *P* = 0.029; Table 2). Of note, the fully adjusted model revealed no association of total cholesterol levels with all-cause mortality (HR 0.96 per g L⁻¹, 95% CI 0.81–1.13, *P* = 0.598). The levels of triglycerides were positively associated with overall mortality, although

Table 2 Hazard ratios per g L⁻¹ increase in apo B

	All-cause mortality; <i>P</i> -value	Cardiac mortality; <i>P</i> -value	Death due to ischaemic heart disease; <i>P</i> -value
Crude/univariate	2.78 (1.35–5.75); 0.006	3.07 (0.99–9.49); 0.051	5.76 (1.37–24.31); 0.017
Adjusted for age and gender	2.62 (1.17–5.83); 0.019	3.17 (0.85–11.92); 0.087	6.85 (1.26–37.38); 0.026
Full Model ^a	2.65 (1.11–6.36); 0.029	11.64 (1.03–131.11); 0.047	9.36 (1.26–69.66); 0.029

^aFull Model: adjusted for age, gender, body mass index, diabetes duration; levels of fasting glucose, triglycerides, and cholesterol; presence or absence of microvascular disease, hypertension; antihypertensive treatment, treatment with diuretics; alcohol consumption.

the HR per g L⁻¹ increase was lower than for apo B and association did not reach conventional levels of statistical significance (HR 1.35 per g L⁻¹, 95% CI: 0.99–1.84, *P* = 0.054). Subjects in the lowest quartile for apo B (<0.96 g L⁻¹) had a significantly lower risk of mortality when compared with the remainders of this cohort. Unadjusted Kaplan–Meier survival analysis for this cut-off value is illustrated in Fig. 1 (*P* = 0.020 by log-rank test). The increased mortality of subjects with an apo B ≥0.96 g L⁻¹ persisted after adjusting for all explanatory variables (HR 1.93, 95% CI: 1.00–3.72, *P* = 0.050).

Cardiac mortality

A death due to cardiac disease was confirmed in 28 subjects. Again, apo B was significantly associated with this outcome for all models that were tested (Table 2). However, whilst the univariate model revealed a HR that was very similar to the model adjusted for age and gender (HR 3.07 and 3.17, respectively) the fully adjusted model resulted in a considerably higher HR of 11.64 (95% CI: 1.03–131.11). In contrast, no association was found for total cholesterol and cardiac mortality (HR 0.55, 95% CI: 0.18–1.71, *P* = 0.300) whereas the HR for triglycerides was again lower than for apo B (HR 1.89, 95% CI: 1.14–3.14, *P* = 0.014). In Kaplan–Meier survival analysis subjects in the lowest quartile (apo B <0.96 g L⁻¹) differed significantly from those with an apo B level >0.96 g L⁻¹ (*P* = 0.011, Fig. 1). The HR after adjustment for all explanatory variables was seven times lower for subjects in the lowest quartile compared to subjects with apo B ≥0.96 g L⁻¹ (HR 7.44, 95% CI: 1.44–38.42, *P* = 0.017).

Death due to ischaemic heart diseases

Fifteen deaths were related to IHD. As for overall mortality and mortality due to cardiac disease apo B

was consistently associated with this outcome, too (Table 2). Hazard ratios were again very similar for the crude model and after adjustment for age and gender (HR 5.76 and 6.85, respectively). Fully adjusting for explanatory variables resulted into a higher HR of 9.36 (95% CI: 1.26–69.66) that was still statistically significant (*P* = 0.029). In contrast, neither total cholesterol nor triglycerides were found to be related to death due to IHD (HR for total cholesterol 0.99, 0.63–1.56, *P* = 0.960; HR for triglycerides 1.66, 0.87–3.15, *P* = 0.123). Comparable with the analysis of cardiac mortality an apo B level >0.96 g L⁻¹ was associated with a sevenfold increase in mortality (HR 7.38, 95% CI 0.78–69.82) although this did not reach conventional levels of statistical significance (*P* = 0.081).

Prediction of cumulative absolute mortality risk over time for different apo B levels

Figure 2 shows the predicted cumulative absolute mortality risk over time for two specific baseline levels of apo B (0.8 and 1.5 g L⁻¹, representing typical values of the lowest and the highest quartiles, respectively). Results are separated according to gender status. For example, the overall cumulative risk to die in the next 10 years was found to be 12.1% (95% CI: 5.2–31.7) for a male subject with type 1 diabetes and an apo B level of 1.5 g L⁻¹ at baseline. In contrast, the cumulative mortality risk over the same time period was about halved (6.3%, 1.8–21.4) when considering a male subject having an apo B level of 0.8 g L⁻¹. This indicated an excess mortality of about six of 100 male subjects with type 1 diabetes over 10 years for the high when compared with the low apo B level. Female subjects revealed a lower absolute cumulative mortality risk over time than males. However, after 10 years the absolute predicted mortality in a female subject with an apo B level of 1.5 g L⁻¹ was again about doubled

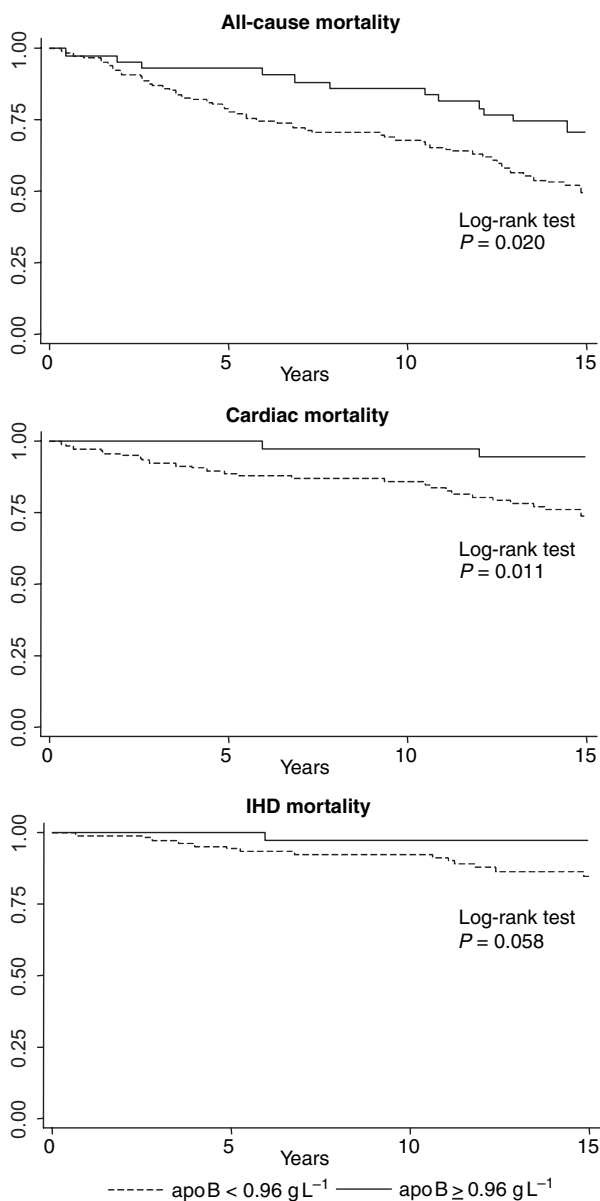


Fig. 1 Kaplan-Meier estimation of survival probabilities for all-cause mortality, cardiac mortality and mortality due to ischaemic heart disease (IHD). Subjects with an apolipoprotein B (apo B) level <0.96 g L⁻¹ were compared to subjects with an apo B level ≥0.96 g L⁻¹.

when compared with the same subject having an apo B of 0.8 g L⁻¹ at baseline (10.4%, 95% CI: 4.7–26.1 and 5.4%, 0.8–15.8).

Discussion

This 15-year follow up showed that in type 1 diabetes apo B is consistently associated with a

significantly increased risk of mortality due to all causes as well as to cardiac disease and to IHD. An apo B level ≥0.96 g L⁻¹ translated into a duplication of overall mortality risk and a sevenfold increase of mortality due to cardiac disease or IHD. When the absolute cumulative mortality risk over time was calculated based on different apo B levels a considerable excess mortality was predicted for higher apo B values in male and female subjects.

To the best of our knowledge this is the first study that has prospectively assessed the association of apo B with overall mortality and mortality due to cardiac disease and IHD in type 1 diabetes. The findings of the present analysis are in accordance with results of recent reports showing an association of apo B and cardiovascular risk in nondiabetic subjects [9–14] as well as in subjects with type 2 diabetes [16–22] and in those with the metabolic syndrome [15, 23]. In type 1 diabetes there is conflicting evidence of the association of apo B and cardiovascular disease or mortality. Several cross-sectional trials showed an association of apo B with microvascular complications but there is a lack of consistent evidence with regard to cardiovascular disease or mortality [28–30]. In contrast, one prospective trial reported that apo B content of modified lipoproteins was related to progression of carotid intima-media thickness [35], a surrogate marker of atherosclerosis. So far, only one prospective trial investigated the association of apo B with a combined end-point of cardiovascular morbidity and mortality in subjects with type 1 diabetes [31]. The authors reported a limited prognostic value of apo B on the development of coronary artery disease whereas no association was found with overall mortality. They concluded that the measurement of apo B was of limited value in subjects with type 1 diabetes [31]. In contrast to these findings, the present study revealed a consistent and positive association of apo B levels with overall mortality as well as with mortality due to IHD and cardiac disease. These differences may be due to the fact that the subjects of the current study were generally older (51 vs. 32 years) and tended to have more microvascular complications at baseline thereby implicating an increased *a priori* cardiovascular risk. This is underscored by the higher absolute mortality rate in the present trial (72 of 165 vs. 28 of 147). Of note, the odds ratio of 65.5 per g L⁻¹ of apo B for cardiovascular disease found by Weis *et al.* [31] was

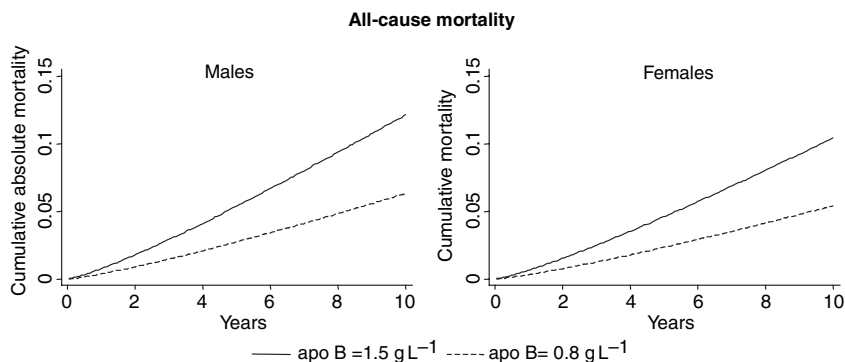


Fig. 2 Cumulative absolute mortality risk over time for subjects with an apolipoprotein B (apo B) level of 0.8 and 1.5 g L⁻¹. Separate analyses for female and male subjects.

substantially higher than the HRs for mortality due to cardiac disease or IHD as well as for overall mortality in the present analysis. Whilst direct comparability is limited by differences in outcome definitions as stated above the present analysis did also include more explanatory variables. Of interest, the present study suggests that in subjects with type 1 diabetes apo B is a stronger risk factor for mortality than total cholesterol or triglycerides. This is in full accordance with previous studies in the general population showing that total cholesterol was predictive for cardiovascular disease in univariate analyses but not when corrected for apo B and triglycerides [13, 36].

The strength of the present study lies in the well-defined cohort of diabetic subjects (Swiss cohort [32] of the 'WHO Multinational Study of Vascular Disease in Diabetes' [33]), the comparably long follow up with no drop-out cases for this analysis, and the evaluation of prespecified end-points. Considerable efforts were undertaken to adjust for relevant factors known to affect cardiovascular risk. This allowed us to adjust not only for age and gender as in an earlier report in type 1 diabetes [31], but also for further parameters with known influence on mortality (e.g. alcohol consumption) [37]. In addition, a direct comparison of the prognostic values of apo B, total cholesterol and triglycerides was enabled. Measurement of apo B was performed in one central laboratory, thereby limiting potential variation.

Still, there are some limitations to our findings. First, although the present study included the largest number of subjects with type 1 diabetes for a prospective analysis of apo B and mortality the absolute number of participants is comparably small. Secondly, in deceased patients, the underlying

cause of each death was determined from a copy of the death certificate, hospital records, postmortem reports and additional information given by the treating doctors. Despite intensive efforts to collect comprehensive data in some cases, the cause of death may have been misclassified, especially if it was only based on death certificates, which are a comparatively unreliable source of information. Thus, our findings regarding all-cause mortality are clearly more robust than cause-specific mortality. Thirdly, information on glycaemic control had to be based on fasting glucose since HbA_{1c} was not available at the time of study entry. As glycaemic control has been related to macrovascular complications [38, 39] this fact could potentially have limited the accuracy of adjustment for this parameter. Finally, no statement can be drawn on the prognostic values of LDL, high-density lipoprotein (HDL) and non-HDL cholesterol because of the fact that only total cholesterol and triglycerides were measured when the study was initiated.

Current guidelines are based on LDL cholesterol concentration as a principal factor in the assessment of cardiovascular risk as well as a main target in the treatment of dyslipidaemia in subjects with and without diabetes mellitus [5–8]. However, the measurement of apo B has recently been suggested to offer a useful alternative [1–4]. As lipid composition of all atherogenic lipoprotein particles can considerably vary between subjects, the measurement of LDL cholesterol concentration may not adequately reflect atherogenic risk. Due to the fact that each particle of very low-density lipoprotein (VLDL), IDL, LDL and Lp(a) contains one molecule of apo B100 and chylomicrons and its remnant form contain one molecule of apo B48 the sum of total

apo B was stated to represent a better estimate of atherogenic risk [1–4].

The present study emphasizes the value of apo B as a prognostic factor for mortality end-points and extends its validity to subjects with type 1 diabetes mellitus. In contrast to the considerable amount of studies in type 2 diabetes and the metabolic syndrome comparably little is known on the metabolism of lipoproteins in type 1 diabetes. Lipid profiles in well-controlled subjects with type 1 diabetes tend to be similar to those seen in nondiabetic controls but altered lipoprotein composition has consistently been demonstrated despite normal lipoprotein metabolism in these subjects [26, 27]. The finding of an increased secretion of triglyceride-rich VLDL associated with an increased number of small-dense LDL particles – a constellation known to be highly prevalent in premature coronary artery disease in nondiabetic subjects as well as in type 2 diabetes [4, 40, 41] – was also suggested to be associated with accelerated atherosclerosis in type 1 diabetes [27]. Of note, it has been shown before that improved metabolic control positively influenced lipoprotein composition in type 1 diabetes [42].

However, the role of apo B as a prognostic risk factor must be separated from its potential role as a therapeutic target. Lipid-lowering treatment with statins has been shown to lower apo B in a general population [43–46] as well as in type 2 diabetes [47] and subjects with type 1 diabetes are likely to behave similarly. Whilst apo B still appeared to be a useful parameter under lipid-lowering therapy, the value of LDL cholesterol has been questioned under these conditions [3, 41, 45]. In type 1 diabetes lipid-lowering therapy is also becoming more frequent in clinical practice. The importance of apo B as a risk marker might be even greater under these circumstances. Recent guidelines for a general population recommend a lowering of apo B below 0.9 g L^{-1} , in high-risk situations even lower [48, 49]. The observational nature of the present study precludes a solid statement on therapeutic effects and goals. It may be of interest, though, that in the present analysis subjects with apo B levels in the lowest quartile ($<0.96 \text{ g L}^{-1}$) had a significantly lower mortality risk than the rest of the cohort. Absolute cumulative mortality risk over 10 years was 50% lower for a subject with an apo B of 0.8 g L^{-1} compared with a level of 1.5 g L^{-1} thereby implicating that lowering apo B to comparable levels as suggested above could

be beneficial in type 1 diabetes, too. However, this has to be confirmed by prospective interventional trials.

Apo B has been shown to have several advantages when compared with conventional lipid parameters [1, 4, 49]. First, it can be measured in a nonfasting sample. Secondly, methods are standardized and automated thereby minimizing interferences by methodological or biological factors. Thirdly, the measurement of apo B is comparably simple, inexpensive and widely available.

Conclusion

In conclusion, this study confirms that in subjects with type 1 diabetes apo B is consistently associated with an increased risk of mortality due to all causes as well as due to cardiac disease and IHD. Due to the fact that the measurement of apo B is accurate and easily obtainable in clinical practice its use should be encouraged in the risk assessment of subjects with type 1 diabetes.

Conflict of interest statement

No conflict of interest was declared.

Acknowledgements

We are indebted to the study participants, their relatives as well as their treating physicians and staff for their participation, help and support throughout the study. We are also grateful for the support we received from the Federal Office of Statistics, Neuchatel (Dr Th. Spuler) and the various community-based population registries throughout the country. We thank Prof. W. Riesen for the biochemical analyses of apo B and Prof. A. Teuscher, E. Hurni, Dr P.P. Studer and Dr H. Schnell for help with the collection of the baseline data.

References

- 1 Barter PJ, Ballantyne CM, Carmena R *et al*. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med* 2006; **259**: 247–58.
- 2 Faergeman O. Introduction: apolipoproteins and guidelines for prevention of cardiovascular disease. *J Intern Med* 2006; **259**: 434–6.

- 3 Charlton-Menys V, Durrington P. Apolipoproteins AI and B as therapeutic targets. *J Intern Med* 2006; **259**: 462–72.
- 4 Marcovina S, Packard CJ. Measurement and meaning of apolipoprotein AI and apolipoprotein B plasma levels. *J Intern Med* 2006; **259**: 437–46.
- 5 Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106**: 3143–421.
- 6 Grundy SM, Cleeman JI, Merz CN *et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **110**: 227–39.
- 7 De Backer G, Ambrosioni E, Borch-Johnsen K *et al.* European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003; **24**: 1601–10.
- 8 Erhardt LR, Gotto A Jr. The evolution of European guidelines: changing the management of cholesterol levels. *Atherosclerosis* 2006; **185**: 12–20.
- 9 St-Pierre AC, Cantin B, Dagenais GR *et al.* Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Quebec Cardiovascular Study. *Arterioscler Thromb Vasc Biol* 2005; **25**: 553–9.
- 10 Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation* 2005; **112**: 3375–83.
- 11 Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA* 2005; **294**: 326–33.
- 12 Shai I, Rimm EB, Hankinson SE *et al.* Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women: potential implications for clinical guidelines. *Circulation* 2004; **110**: 2824–30.
- 13 Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 2001; **358**: 2026–33.
- 14 Thompson A, Danesh J. Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. *J Intern Med* 2006; **259**: 481–92.
- 15 Lind L, Vessby B, Sundstrom J. The apolipoprotein B/AI ratio and the metabolic syndrome independently predict risk for myocardial infarction in middle-aged men. *Arterioscler Thromb Vasc Biol* 2006; **26**: 406–10.
- 16 Al-Bahrani AI, Bakhiet CS, Bayoumi RA, Al-Yahyaee SA. A potential role of apolipoprotein B in the risk stratification of diabetic patients with dyslipidaemia. *Diabetes Res Clin Pract* 2005; **69**: 44–51.
- 17 Sattar N, Williams K, Sniderman AD, D'Agostino R Jr, Haffner SM. Comparison of the associations of apolipoprotein B and non-high-density lipoprotein cholesterol with other cardiovascular risk factors in patients with the metabolic syndrome in the Insulin Resistance Atherosclerosis Study. *Circulation* 2004; **110**: 2687–93.
- 18 Wagner AM, Perez A, Zapico E, Ordóñez-Llanos J. Non-HDL cholesterol and apolipoprotein B in the dyslipidemic classification of type 2 diabetic patients. *Diabetes Care* 2003; **26**: 2048–51.
- 19 Sniderman AD, Lamarche B, Tilley J, Secombe D, Frohlich J. Hypertriglyceridemic hyperapoB in type 2 diabetes. *Diabetes Care* 2002; **25**: 579–82.
- 20 Bruno G, Merletti F, Biggeri A *et al.* Effect of age on the association of non-high-density-lipoprotein cholesterol and apolipoprotein B with cardiovascular mortality in a Mediterranean population with type 2 diabetes: the Casale Monferrato study. *Diabetologia* 2006; **49**: 937–44.
- 21 Schulze MB, Shai I, Manson JE *et al.* Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes. *Diabetologia* 2004; **47**: 2129–36.
- 22 Jiang R, Schulze MB, Li T *et al.* Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. *Diabetes Care* 2004; **27**: 1991–7.
- 23 Corsetti JP, Zareba W, Moss AJ, Sparks CE. Apolipoprotein B determines risk for recurrent coronary events in postinfarction patients with metabolic syndrome. *Atherosclerosis* 2004; **177**: 367–73.
- 24 Daneman D. Type 1 diabetes. *Lancet* 2006; **367**: 847–58.
- 25 Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992–1999. *Diabetologia* 2006; **49**: 660–6.
- 26 Duvillard L, Florentin E, Lalanne-Mistrich ML *et al.* Normal metabolism of apolipoprotein B100-containing lipoproteins despite qualitative abnormalities in type 1 diabetic men. *Diabetologia* 2005; **48**: 1366–72.
- 27 Christ ER, Carroll PV, Albany E *et al.* Normal VLDL metabolism despite altered lipoprotein composition in type 1 diabetes mellitus. *Clin Endocrinol (Oxf)* 2001; **55**: 777–87.
- 28 Chaturvedi N, Fuller JH, Taskinen MR. Differing associations of lipid and lipoprotein disturbances with the macrovascular and microvascular complications of type 1 diabetes. *Diabetes Care* 2001; **24**: 2071–7.
- 29 Jenkins AJ, Lyons TJ, Zheng D *et al.* Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. *Kidney Int* 2003; **64**: 817–28.
- 30 Lyons TJ, Jenkins AJ, Zheng D *et al.* Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort. *Invest Ophthalmol Vis Sci* 2004; **45**: 910–8.
- 31 Weis U, Turner B, Gibney J *et al.* Long-term predictors of coronary artery disease and mortality in type 1 diabetes. *QJM* 2001; **94**: 623–30.
- 32 Teuscher A, Herman JB, Studer PP. Vascular diseases in 534 Swiss diabetics within the scope of a multinational study. *Klin Wochenschr* 1983; **61**: 139–49.
- 33 Jarrett RJ, Keen H, Grabauskas V. The WHO multinational study of vascular disease in diabetes: 1. General description. *Diabetes Care* 1979; **2**: 175–86.
- 34 Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis: Part II. Multivariate data analysis – an introduction to concepts and methods. *Br J Cancer* 2003; **89**: 431–6.
- 35 Lopes-Virella MF, McHenry MB, Lipsitz S *et al.* Immune complexes containing modified lipoproteins are related to the progression of internal carotid intima-media thickness in

- patients with type 1 diabetes. *Atherosclerosis* 2006; Epub ahead of print.
- 36 Talmud PJ, Hawe E, Miller GJ, Humphries SE. Nonfasting apolipoprotein B and triglyceride levels as a useful predictor of coronary heart disease risk in middle-aged UK men. *Arterioscler Thromb Vasc Biol* 2002; **22**: 1918–23.
 - 37 Diem P, Deplazes M, Fajfr R *et al.* Effects of alcohol consumption on mortality in patients with type 2 diabetes mellitus. *Diabetologia* 2003; **46**: 1581–5.
 - 38 Selvin E, Marinopoulos S, Berkenblit G *et al.* Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; **141**: 421–31.
 - 39 Stettler C, Allemann S, Jüni P *et al.* Glycemic control and macrovascular disease in type 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J* 2006; **152**: 27–38.
 - 40 Sniderman AD, Scantlebury T, Cianflone K. Hypertriglyceridemic hyperapob: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. *Ann Intern Med* 2001; **135**: 447–59.
 - 41 Sniderman AD, Furberg CD, Keech A *et al.* Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *Lancet* 2003; **361**: 777–80.
 - 42 James RW, Pometta D. Differences in lipoprotein subfraction composition and distribution between type I diabetic men and control subjects. *Diabetes* 1990; **39**: 1158–64.
 - 43 Pedersen TR, Olsson AG, Faergeman O *et al.* Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998; **97**: 1453–60.
 - 44 Simes RJ, Marschner IC, Hunt D *et al.* Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? *Circulation* 2002; **105**: 1162–9.
 - 45 Gotto AM Jr, Whitney E, Stein EA *et al.* Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation* 2000; **101**: 477–84.
 - 46 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7–22.
 - 47 Colhoun HM, Betteridge DJ, Durrington PN *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* 2004; **364**: 685–96.
 - 48 Genest J, Frohlich J, Fodor G, McPherson R. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. *CMAJ* 2003; **169**: 921–4.
 - 49 Grundy SM. Low-density lipoprotein, non-high-density lipoprotein, and apolipoprotein B as targets of lipid-lowering therapy. *Circulation* 2002; **106**: 2526–9.
- Correspondence:* Christoph Stettler MD, Division of Endocrinology and Diabetes, University of Bern, Inselspital, CH-3010 Bern, Switzerland.
(fax: 0041 31 632 8414; e-mail: christoph.stettler@insel.ch).

4. General discussion & conclusions

The five studies of this thesis focussed on the prevention and therapy of macrovascular complications and on the definition of prognostic factors for mortality in type 1 and type 2 diabetes mellitus (DM). An approach from two sides was used. The first part of the thesis consisted of three studies (**Studies A-C**) evaluating specific treatment strategies in type 1 and type 2 DM. In this context, **Study A** investigated the effect of improved glycaemic control on macrovascular complications in type 1 and type 2 DM. Focussing on type 2 DM, **Study B** examined the role of fibrates in the prevention of coronary heart disease in this type of DM. **Study C** aimed at analysing outcomes after coronary stenting using drug-eluting stents in patients with and without DM.

The second part of the thesis included two studies (**Studies D and E**), focussing on the definition of novel mortality risk indicators for patients with DM. In **Study D** the prognostic value of two parameters (QT interval and resting heart rate) on mortality risk was assessed in type 1 and type 2 DM, respectively. **Study E** examined the role of apolipoprotein B (apo B) in the mortality risk assessment of patients with type 1 DM. A brief summary of the results is given in [Table 6](#).

Taken together, this thesis demonstrated potential differences in the effectiveness of specific treatment forms in patients with compared to patients without DM. In addition, the effectiveness of treatment forms may vary between type 1 and type 2 DM despite hyperglycaemia being a common factor.

Table 6. Brief summary of all studies of the thesis

	Study	Aim	Main Results
Systematic reviews and meta-analyses	A	To assess the effect of improved glycaemic control on cardiac, cerebrovascular and peripheral vascular complications in type 1 and type 2 DM	<p><i>Any macrovascular event:</i></p> <p>Type 1 DM: 62% reduction in incidence (95% CI 44-74%)</p> <p>Type 2 DM: 19% reduction in incidence (95% CI 9-27%)</p> <ul style="list-style-type: none"> - Type 1 DM: effect mainly based on reductions of cardiac and peripheral vascular events - Type 2 DM: effect based on reductions in stroke and peripheral vascular events - Effects particularly important in younger patients with shorter duration of diabetes
	B	To examine the effectiveness of fibrates (PPAR α -agonists) in the prevention of coronary heart disease in type 2 DM	<p><i>Coronary events:</i></p> <p>16% risk reduction (95% CI 4-26%) with fibrate therapy compared to placebo</p> <ul style="list-style-type: none"> - Benefits even larger when analyses restricted to trials not confounded by unequal provision of additional lipid-lowering therapy
	C	To indirectly compare the effects of polymer based sirolimus versus paclitaxel eluting stents and to examine whether they are equally effective in the prevention of restenosis in patients with and without DM	<p><i>Patients without DM:</i></p> <p>Superiority of sirolimus eluting stents to paclitaxel eluting stents for all end points (in-stent- and in-segment restenosis, target lesion revascularisation, major adverse cardiac events)</p> <p><i>Patients with DM:</i></p> <p>No significant difference of the two drug eluting stents in any of the end points</p>
Survival analyses	D	To evaluate the long-term association of QT interval corrected for heart rate (QT _c) and resting Heart Rate (rHR) with mortality in patients with type 1 and type 2 DM	<p><i>Type 1 DM:</i></p> <p>QT_c associated with long-term mortality, but not rHR</p> <p><i>Type 2 DM:</i></p> <p>rHR related to increased mortality risk, but not QT_c</p>
	E	To evaluate the long term association of apo B with mortality risk in patients with type 1	<ul style="list-style-type: none"> - Apo B positively related to all cause and cardiac mortality, and mortality due to ischemic heart disease - Apo B >0.96 g L⁻¹ translated into a doubling of overall mortality hazard and a sevenfold increase of mortality because of cardiac disease or IHD

4.1 Comparison of patients with and without diabetes mellitus

As patients with DM have a higher cardiovascular risk compared to non diabetic patients [81, 114, 115], DM has been considered as an independent risk factor [72, 73]. In contrast to patients without DM, heart disease in patients with DM appears earlier in life, affects women almost as often as men, and is more often fatal [78-80]. Patients with DM also tend to present with more advanced coronary artery disease, and outcomes after percutaneous interventions consequently tend to be poorer in these individuals [116-118]. The fact that the more severe neointimal hyperplasia in diabetic patients may lead to a different effectiveness of these interventions in patients with compared to patients without DM, was also reflected in the results of **Study C** on coronary stenting. In non-diabetic persons the sirolimus eluting stent was superior to the paclitaxel eluting stent in all end points under investigation. In contrast, this superiority disappeared in the analyses of patients with DM. In addition to the results of **Study C**, the findings of **Study B** demonstrated a potential difference in the effectiveness of treatments between patients with and without DM: A substantial reduction of coronary heart disease was found in this study when patients with type 2 DM were treated with fibrates compared to placebo. This was in contrast to a recent meta-analysis that showed little evidence for a reduction in cardiac mortality with fibrate treatment in a general population not distinguishing between patients with and without type 2 DM [119].

4.2 Within the patients with diabetes mellitus – comparison of type 1 and type 2

Concerning the therapy of macrovascular complications within the group of DM, again possible differences in the effectiveness of specific treatment forms have to be considered [2]. While hyperglycaemia represents the predominant abnormality in patients with type 1 DM, patients with type 2 DM exhibit additional cardiovascular risk factors, as hypertension, dyslipidaemia and central obesity. In type 2 DM, cardiovascular risk is, therefore, influenced by several risk factors at the same time leading to differences in the process of developing late complications when compared to type 1 DM [120]. The results of **Study A** emphasise this difference of the underlying diseases in type 1 and type 2 DM by a difference in the efficacy of improved glycaemic control. Relative effects appeared to be more modest in type 2 DM, probably due to the fact that with improving glycaemic control not all risk factors

are considered. In this context, it has been suggested that cardiovascular risk in type 2 DM can be best reduced by a multifactorial therapy [121].

Regarding the evaluation of mortality risk, again a potentially different impact of certain risk indicators has to be considered in the two types of DM. While the findings of **Study D** revealed a discrepancy in the prognostic values of parameters reflecting myocardial ventricular repolarisation between the two types of DM, the results of **Study E**, performed in type 1 DM, were in accordance with earlier studies performed in type 2 and non diabetic individuals. **Studies D and E**, therefore, underscore the need to differentiate between the two types of DM.

4.3 Strengths and limitations of the thesis

For the first part of the thesis (**Studies A-C**), work was based on a comprehensive literature search and efforts were undertaken to include all relevant trials in the respective field. Whenever data was not available from the publication, attempts were made to contact the principle investigators to obtain the information. All three studies were performed according to the QUOROM guidelines [110], thereby fulfilling widely accepted quality criteria for systematic reviews and meta-analyses. All studies were planned using a predefined study protocol. The three studies, therefore, provide a summary of all the currently available evidence in the respective research field in one review framework. Nevertheless, some limitations have to be acknowledged. First, despite a good collaboration with many of the principle investigators of the original studies, it was not always possible to obtain all the lacking information. Still, funnel plot analysis suggested that the available data illustrated a representative sample, and that no substantial bias was introduced. Second, due to the fact that these meta-analyses were not based on individual patient data, no statement could be made on sub-categories of patients most likely to benefit. For example, research based on individual patient data could examine, whether drug eluting stents are equally effective in patients with DM and long coronary lesions compared to those with shorter lesions. In **Studies D and E** the prognostic value of specific risk indicators was assessed prospectively allowing inclusion of almost all patients of the cohort. Furthermore, the analyses could be adjusted for additional parameters potentially influencing the outcome compared to previous studies. Despite attempts to include all relevant parameters, not always all the desired information had been collected when

the study was initiated. Since the studies were based on data of the Swiss arm of the cohort exclusively, no statement can be made on effects in other areas.

4.4 Conclusions

In conclusion, this thesis showed that:

- Attempts to improve glycaemic control reduce the incidence of macrovascular events both in type 1 and type 2 DM. In absolute terms benefits are comparable, although effects on specific manifestations of macrovascular disease differ between the two types of DM.
- Fibrates are associated with a substantial reduction of CHD events in patients with type 2 DM. Their exact role in lipid lowering treatment, however, remains to be defined.
- Sirolimus as well as paclitaxel eluting stents reduce the rates of revascularisation procedures when compared to bare metal stents. Based on indirect evidence, stents eluting sirolimus appear to be superior to paclitaxel eluting stents in patients without DM but not in patients with DM.
- Prolonged QT_c is associated with long-term mortality in patients with type 1 DM, whereas elevated rHR is related to increased mortality risk in patients with type 2 DM.
- Higher apo B levels are consistently associated with an increased mortality in type 1 DM.

In addition to these conclusions, two general statements can be made:

- The effectiveness of therapeutic interventions may be different in patients with compared to patients without DM.
- Within the group of patients with DM, the effectiveness of interventions may vary between type 1 and type 2 DM. Furthermore, in the evaluation of macrovascular risk, specific risk indicators may play a different role in the two types of DM.

5. References to general introduction & discussion

- [1] Mehnert H, Standl E, Usadel K-H. *Diabetologie in Klinik und Praxis*. Würzburg, Thieme Verlag 1998.
- [2] Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; 20(7):1183-1197.
- [3] National Diabetes Data Group. Diabetes in America. 2d ed. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, *NIH publication 1995*, 95-1468.
- [4] Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 2002; 19(9):708-723.
- [5] Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004; 27 Suppl 1:S5-S10.
- [6] Rewers M, Shetterly SM, Baxter J, Marshall JA, Hamman RF. Prevalence of coronary heart disease in subjects with normal and impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a biethnic Colorado population. The San Luis Valley Diabetes Study. *Am J Epidemiol* 1992; 135(12):1321-1330.
- [7] Coutinho M, Gerstein HC, 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* 1999; 22(2):233-240.
- [8] Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care* 1999; 22(6):920-924.
- [9] Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR *et al*. Impact of the metabolic syndrome on mortality from coronary heart disease,

- cardiovascular disease, and all causes in United States adults. *Circulation* 2004; 110(10):1245-1250.
- [10] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; 285(19):2486-2497.
- [11] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; 23(5):469-480.
- [12] Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M *et al.* Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; 24(4):683-689.
- [13] Ferrannini E. Is insulin resistance the cause of the metabolic syndrome? *Ann Med* 2006; 38(1):42-51.
- [14] American Diabetes Association Clinical Practice Recommendations 2001. *Diabetes Care* 2001; 24 Suppl 1:S1-133.
- [15] American Diabetes Association: clinical practice recommendations 2002. *Diabetes Care* 2002; 25 Suppl 1:S1-147.
- [16] Jeffcoate SL. Diabetes control and complications: the role of glycated haemoglobin, 25 years on. *Diabet Med* 2004; 21(7):657-665.
- [17] Delpierre G, Rider MH, Collard F, Stroobant V, Vanstapel F, Santos H *et al.* Identification, cloning, and heterologous expression of a mammalian fructosamine-3-kinase. *Diabetes* 2000; 49(10):1627-1634.
- [18] Delpierre G, Collard F, Fortpied J, Van Schaftingen E. Fructosamine 3-kinase is involved in an intracellular deglycation pathway in human erythrocytes. *Biochem J* 2002; 365(Pt 3):801-808.
- [19] Bunn HF, Gabbay KH, Gallop PM. The glycosylation of hemoglobin: relevance to diabetes mellitus. *Science* 1978; 200(4337):21-27.

- [20] Fitzgibbons JF, Koler RD, Jones RT. Red cell age-related changes of hemoglobins Ala+b and Alc in normal and diabetic subjects. *J Clin Invest* 1976; 58(4):820-824.
- [21] Stettler C, Mueller B, Diem P. [What you always wanted to know about HbA1c]. *Schweiz Med Wochenschr* 2000; 130(26):993-1005.
- [22] 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* 1993; 329(14):977-986.
- [23] 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* 1998; 352(9131):837-853.
- [24] Skyler JS. Diabetic complications. The importance of glucose control. *Endocrinol Metab Clin North Am* 1996; 25(2):243-254.
- [25] Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR *et al.* Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; 141(6):421-431.
- [26] Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. *Diabetes Care* 1998; 21(10):1720-1725.
- [27] Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; 359(9323):2072-2077.
- [28] Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes

- Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet* 1999; 354(9179):617-621.
- [29] International Diabetes Foundation (IDF) homepage, [<http://www.eatlas.idf.org/>], accessed June 2006.
- [30] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27(5):1047-1053.
- [31] World Health Organisation (WHO) homepage, [<http://www.who.int/mediacentre/factsheets/fs236/en/>], accessed June 2006.
- [32] Szucs T, Schwenkglens M, Spinass G. Typ 2 Diabetes mellitus in der Schweiz, Verbreitung, Ressourcenverbrauch und Kosten. Eine Bevölkerungsstudie. Universitätsspital Zürich 2000.
- [33] Palmer AJ, Roze S, Valentine WJ, Ray JA, Frei A, Burnier M *et al.* Health economic implications of irbesartan plus conventional antihypertensive medications versus conventional blood pressure control alone in patients with type 2 diabetes, hypertension, and renal disease in Switzerland. *Swiss Med Wkly* 2006; 136(21-22):346-352.
- [34] Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 2002; 346(22):1685-1691.
- [35] Gale EA, Bingley PJ, Emmett CL, Collier T. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet* 2004; 363(9413):925-931.
- [36] Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest* 2000; 106(4):473-481.
- [37] Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX *et al.* Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997; 20(4):537-544.

- [38] Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344(18):1343-1350.
- [39] Yamaoka K, Tango T. Efficacy of lifestyle education to prevent type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Care* 2005; 28(11):2780-2786.
- [40] Padwal R, Majumdar SR, Johnson JA, Varney J, McAlister FA. A systematic review of drug therapy to delay or prevent type 2 diabetes. *Diabetes Care* 2005; 28(3):736-744.
- [41] The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care* 1999; 22(4):623-634.
- [42] The Diabetes Prevention Program: baseline characteristics of the randomized cohort. The Diabetes Prevention Program Research Group. *Diabetes Care* 2000; 23(11):1619-1629.
- [43] Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; 27(1):155-161.
- [44] Sherwin RS, Anderson RM, Buse JB, Chin MH, Eddy D, Fradkin J *et al.* Prevention or delay of type 2 diabetes. *Diabetes Care* 2004; 27 Suppl 1:S47-S54.
- [45] Hernan WH, Brandle M, Zhang P, Williamson DF, Matulik MJ, Ratner RE *et al.* Costs associated with the primary prevention of type 2 diabetes mellitus in the diabetes prevention program. *Diabetes Care* 2003; 26(1):36-47.
- [46] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346(6):393-403.

- [47] Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX *et al.* Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997; 20(4):537-544.
- [48] Wein P, Beischer N, Harris C, Permezel M. A trial of simple versus intensified dietary modification for prevention of progression to diabetes mellitus in women with impaired glucose tolerance. *Aust N Z J Obstet Gynaecol* 1999; 39(2):162-166.
- [49] Fontbonne A, Charles MA, Juhan-Vague I, Bard JM, Andre P, Isnard F *et al.* The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. BIGPRO Study Group. *Diabetes Care* 1996; 19(9):920-926.
- [50] Jarrett RJ, Keen H, Fuller JH, McCartney M. Worsening to diabetes in men with impaired glucose tolerance ("borderline diabetes"). *Diabetologia* 1979; 16(1):25-30.
- [51] Li CL, Pan CY, Lu JM, Zhu Y, Wang JH, Deng XX *et al.* Effect of metformin on patients with impaired glucose tolerance. *Diabet Med* 1999; 16(6):477-481.
- [52] Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J *et al.* Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 2002; 51(9):2796-2803.
- [53] Feldt-Rasmussen B, Mathiesen ER, Jensen T, Lauritzen T, Deckert T. Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetic patients: an update of the Steno studies. *Diabetologia* 1991; 34(3):164-170.
- [54] Reichard P, Pihl M. Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. *Diabetes* 1994; 43(2):313-317.
- [55] Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 2000; 23 Suppl 2:B21-B29.

- [56] Verrillo A, de Teresa A, Martino C, Verrillo L, di Chiara G. Long-term correction of hyperglycemia and progression of retinopathy in insulin dependent diabetes. A five-year randomized prospective study. *Diabetes Res* 1988; 8(2):71-76.
- [57] Holman RR, Dornan TL, Mayon-White V, Howard-Williams J, Orde-Peckar C, Jenkins L *et al*. Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. A two-year randomised prospective study. *Lancet* 1983; 1(8318):204-208.
- [58] Intensive therapy and progression to clinical albuminuria in patients with insulin dependent diabetes mellitus and microalbuminuria. Microalbuminuria Collaborative Study Group, United Kingdom. *BMJ* 1995; 311(7011):973-977.
- [59] Abaira C, Colwell J, Nuttall F, Sawin CT, Henderson W, Comstock JP *et al*. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. *Arch Intern Med* 1997; 157(2):181-188.
- [60] Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998; 317(7160):703-713.
- [61] Diabetes Control and Complications Trial (DCCT): results of feasibility study. The DCCT Research Group. *Diabetes Care* 1987; 10(1):1-19.
- [62] Egger M, Davey SG, Stettler C, Diem P. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 1997; 14(11):919-928.
- [63] Cryer PE. Banting Lecture. Hypoglycemia: the limiting factor in the management of IDDM. *Diabetes* 1994; 43(11):1378-1389.
- [64] Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001; 104(22):2746-2753.

- [65] Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. I. Survival, causes of death, and complications. *Diabetologia* 1978; 14(6):363-370.
- [66] Waernbaum I, Blohme G, Ostman J, Sundkvist G, Eriksson JW, Arnqvist HJ *et al.* Excess mortality in incident cases of diabetes mellitus aged 15 to 34 years at diagnosis: a population-based study (DISS) in Sweden. *Diabetologia* 2006; 49(4):653-659.
- [67] Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992-1999. *Diabetologia* 2006; 49(4):660-666.
- [68] Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia* 2003; 46(6):733-749.
- [69] National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994; 89(3):1333-1445.
- [70] Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B *et al.* A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 1991; 151(6):1141-1147.
- [71] Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; 339(4):229-234.
- [72] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97(18):1837-1847.
- [73] Wilson PW. Diabetes mellitus and coronary heart disease. *Am J Kidney Dis* 1998; 32(5 Suppl 3):S89-100.

- [74] McGill HC, Jr., McMahan CA. Determinants of atherosclerosis in the young. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Am J Cardiol* 1998; 82(10B):30T-36T.
- [75] Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 1991; 265(5):627-631.
- [76] Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet* 2006; 368(9529):29-36.
- [77] Wingard DL, Barrett-Connor EL, Scheidt-Nave C, McPhillips JB. Prevalence of cardiovascular and renal complications in older adults with normal or impaired glucose tolerance or NIDDM. A population-based study. *Diabetes Care* 1993; 16(7):1022-1025.
- [78] Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB *et al*. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. The MILIS Study Group. *J Am Coll Cardiol* 1989; 14(1):49-57.
- [79] Singer DE, Moulton AW, Nathan DM. Diabetic myocardial infarction. Interaction of diabetes with other preinfarction risk factors. *Diabetes* 1989; 38(3):350-357.
- [80] Smith JW, Marcus FI, Serokman R. Prognosis of patients with diabetes mellitus after acute myocardial infarction. *Am J Cardiol* 1984; 54(7):718-721.
- [81] Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979; 241(19):2035-2038.
- [82] Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16(2):434-444.

- [83] Lehto S, Ronnema T, Haffner SM, Pyorala K, Kallio V, Laakso M. Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. *Diabetes* 1997; 46(8):1354-1359.
- [84] Rosengren A, Welin L, Tsipogianni A, Wilhelmsen L. Impact of cardiovascular risk factors on coronary heart disease and mortality among middle aged diabetic men: a general population study. *BMJ* 1989; 299(6708):1127-1131.
- [85] Teagarden JR. Meta-analysis: whither narrative review? *Pharmacotherapy* 1989; 9(5):274-281.
- [86] Chalmers I, Altman DG. Systematic reviews. London: BMJ Publishing Group, 1995.
- [87] Egger M, Smith GD, O'Rourke K. Rationale, potentials, and promise of systematic reviews. In: Egger M, Smith DG, Altman DG (eds). *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2001:3-19.
- [88] O'Rourke K, Detsky AS. Meta-analysis in medical research: strong encouragement for higher quality in individual research efforts. *J Clin Epidemiol* 1989; 42(10):1021-1024.
- [89] Egger M, Smith GD, Sterne JA. Uses and abuses of meta-analysis. *Clin Med* 2001; 1(6):478-484.
- [90] Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. In: Egger M, Smith DG, Altman DG (eds). *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2001:87-108.
- [91] Altman DG. Practical statistics for medical research. London: Chapman and Hall, 1991.
- [92] Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; 273(5):408-412.

- [93] Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; 357(9263):1191-1194.
- [94] Moher D. CONSORT: an evolving tool to help improve the quality of reports of randomized controlled trials. Consolidated Standards of Reporting Trials. *JAMA* 1998; 279(18):1489-1491.
- [95] Begg CB, Berlin JA. Publication bias and dissemination of clinical research. *J Natl Cancer Inst* 1989; 81(2):107-115.
- [96] Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991; 337(8746):867-872.
- [97] Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. *JAMA* 1992; 267(3):374-378.
- [98] Dickersin K. How important is publication bias? A synthesis of available data. *AIDS Educ Prev* 1997; 9(1 Suppl):15-21.
- [99] Gregoire G, Derderian F, Le Lorier J. Selecting the language of the publications included in a meta-analysis: is there a Tower of Babel bias? *J Clin Epidemiol* 1995; 48(1):159-163.
- [100] Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997; 350(9074):326-329.
- [101] Simes RJ. Confronting publication bias: a cohort design for meta-analysis. *Stat Med* 1987; 6(1):11-29.
- [102] Simes RJ. Publication bias: the case for an international registry of clinical trials. *J Clin Oncol* 1986; 4(10):1529-1541.
- [103] Egger M, Smith DG, Altman DG (eds). *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2001.

- [104] Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315(7109):629-634.
- [105] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50(4):1088-1101.
- [106] Huque MF. Experiences with meta-analysis in NDA submissions. Proceedings of the Biopharmaceutical Section of the American Statistical Association 1988;2:28-33.
- [107] Kirkwood BR SJ. Systematic reviews and meta-analysis. In: Kirkwood BR, Sterne JAC. *Essential Medical Statistics*, London: Blackwell Publishing Ltd. 2003:371-387.
- [108] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7(3):177-188.
- [109] Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999; 18(20):2693-2708.
- [110] Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. QUOROM Group. *Br J Surg* 2000; 87(11):1448-1454.
- [111] Kalbfleisch JD, Prentice RL. In: *The Statistical Analysis of Failure Time Data*. Wiley Series in probability and statistics. Hoboken, NJ, 1980.
- [112] Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457-481.
- [113] Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV *et al*. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *Br J Cancer* 1977; 35(1):1-39.
- [114] Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. *Circulation* 1979; 59(1):8-13.
- [115] Pyorala K, Laakso M, Uusitupa M. Diabetes and atherosclerosis: an epidemiologic view. *Diabetes Metab Rev* 1987; 3(2):463-524.

- [116] Carrozza JP, Jr., Kuntz RE, Fishman RF, Baim DS. Restenosis after arterial injury caused by coronary stenting in patients with diabetes mellitus. *Ann Intern Med* 1993; 118(5):344-349.
- [117] Detre KM, Guo P, Holubkov R, Califf RM, Sopko G, Bach R *et al.* Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the Aypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1999; 99(5):633-640.
- [118] Stein B, Weintraub WS, Gebhart SP, Cohen-Bernstein CL, Grosswald R, Liberman HA *et al.* Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. *Circulation* 1995; 91(4):979-989.
- [119] Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality: a systematic review. *Arch Intern Med* 2005; 165(7):725-730.
- [120] Rudofsky G, Jr., Isermann B, Schilling T, Schiekofer S, Andrassy M, Schneider JG *et al.* A 63bp deletion in the promoter of rage correlates with a decreased risk for nephropathy in patients with type 2 diabetes. *Exp Clin Endocrinol Diabetes* 2004; 112(3):135-141.
- [121] Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *NEJM* 2003; 348(5):383-393.

6. Acknowledgements

This work resulted from a collaboration of the Institute of Clinical Pharmacy (University of Basel) with the Division of Endocrinology and Diabetology and the Institute of Social and Preventive Medicine (both University of Bern) under the supervision of Prof. Dr. Stephan Krähenbühl, Prof. Dr. Peter Diem, and Prof. Dr. Matthias Egger.

I would like to thank Prof. Dr. Stephan Krähenbühl for assuming the reference of this thesis and for always supporting this work.

I am deeply thankful to Prof. Dr. Peter Diem and Prof. Dr. Matthias Egger for giving me the opportunity to accomplish this PhD thesis and for their unrestricted support in conducting my work. I am very grateful for the useful discussions, all the valuable ideas and inputs and the outstanding scientific help.

Sincere thanks go to Dr. Christoph Stettler for his excellent support during the whole time. I would like to thank for the managing of all our projects, the great collaboration, the numerous fruitful discussions and the well substantiated help. I am very grateful for his untiring dedication, his encouragement and patience at all times.

I would also like to thank PD Dr. Christoph Meier for assuming the co-reference of my thesis, and to Prof. Dr. Matthias Hamburger for accepting the function of representative of the Faculty.

I am grateful to the Swiss Diabetes Foundation, Novo Nordisk, Roche Diagnostics and Glaxo Smith Kline for their unrestricted financial support.

Special thanks go to Dr. Marcel Zwahlen from the Institute of Social and Preventive Medicine for all the help in statistical topics. In addition, I would like to thank PD Dr. Peter Jüni for the help in conducting the meta-analyses, as well as to PD Dr. Emanuel Christ from the Division of Endocrinology and Diabetology for his support in medical questions.

Many thanks go to all the colleagues at the Institute of Social and Preventive Medicine and in the Division of Endocrinology and Diabetology for the pleasant working atmosphere. Especially, I would like to thank Dr. Martin Schneider, Heidi Gafner, Fabienne Zurbriggen and Adriane Martine Hilber, who shared the office with me, for their friendly attitudes and all the enjoyable conversations. In addition, I would like to thank Dr. Stefan Jenni and Yves Suter for the great collaboration in some parts of the projects.

Finally, I would like to thank all my friends and my family for their everlasting support and motivation during my studies.

7. Curriculum Vitae

Personal Data

Name	Allemann
First name	Sabin Liliane
Address	Hornusserstrasse 1, 4600 Olten
Date of Birth	11 February 1977
Place of Birth	Rheinfelden (AG)
Place of Origin	Welschenrohr (SO)

Education

1984-1989	Primary School, Aarburg
1989-1993	Secondary School, Aarburg
1993-1997	High School, Kantonsschule Zofingen, Typus B, Zofingen
1997-2002	Studies in pharmacy, University of Basel, Basel
1999-2000	Practical year in the pharmacy 'Apotheke Aarburg', B. and M. Hostettler, Aarburg
April 2000	Analytical practical in the pharmacy of the cantonal hospital 'Kantonsspital' Luzern, Dr. X. Schorno, Luzern
February-July 2002	Diploma Thesis ' <i>in vitro</i> Modell für topische Arzneiformen' at Novartis Animal Health, under supervision of Dr. S. Wieland-Berghausen and Prof. Dr. H. Leuenberger
November 2002	Swiss federal diploma in pharmacy
April 2003-current	PhD Thesis under supervision of Prof. S. Krähenbühl, (University of Basel), in collaboration with Prof. P. Diem, Prof. M. Egger, and Dr. C. Stettler (University of Bern): 'Evidence Based Diabetology – Strategies to Prevent Macrovascular Disease and to Reduce Mortality'

Professional exercise

2000-2002	Occasional work Apotheke Murgenthal, M. Fidel, Murgenthal and Apotheke Aarburg, B. und M. Hostettler, Aarburg
2000-current	Continuous work Careland Apotheke & Drogerie, E. Kaiser, Aarau

Scientific Publications

Trepp R, Everts R, Stettler C, Fischli S, Allemann S, Webb SM, Christ ER. Assessment of quality of life in patients with uncontrolled vs. controlled acromegaly using the Acromegaly Quality of Life Questionnaire (AcroQoL). *Clin Endocrinol (Oxf)* 2005;63:103-10.

Stettler C, Allemann S, Egger M, Windecker S, Meier B, Diem P. Efficacy of drug eluting stents in patients with and without diabetes mellitus: indirect comparison of randomised controlled trials. *Heart* 2006;92:650-7. Epub 2005 Oct 26.

Stettler C, Jenni S, Allemann S, Steiner R, Hoppeler H, Trepp R, Christ ER, Zwahlen M, Diem P. Exercise capacity in subjects with type 1 diabetes mellitus in eu- and hyperglycaemia. *Diabetes Metab Res Rev* 2006;22:300-6.

Allemann S, Diem P, Egger M, Christ ER, Stettler C. Fibrates in the Prevention of Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus: Meta-Analysis of Randomised Controlled Trials. *Curr Med Res Opin* 2006;22:617-23.

Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, Krähenbühl S, Diem P. Glycemic Control and Macrovascular Disease in Type 1 and 2 Diabetes Mellitus: Meta-Analysis of Randomized Trials. *Am Heart J* 2006;152:27-38.

Stettler C, Suter Y, Allemann S, Zwahlen M, Christ ER, Diem P. Apolipoprotein B as a Long-Term Predictor of Mortality in Type 1 Diabetes Mellitus: A 15-year Follow-Up. *J Intern Med* 2006;260:272-80.

Stettler C, Bearth A, Allemann S, Zwahlen M, Zanchin L, Deplazes M, Christ ER, Teuscher A, Diem P. QTc Interval and Resting Heart Rate as Long-Term Predictors of Mortality in Type 1 and Type 2 Diabetes Mellitus: A 23-year Follow-Up. *Diabetologia* 2006, DOI 10.1007/s00125-006-0483-1.

Chappuis B, Braun M, Stettler C, Allemann S, Diem P, Lumb J, Wierzbicki S, James R, Christ ER. Differential effect of pioglitazone (PGZ) and rosiglitazone (RGZ) on

postprandial glucose and lipid metabolism in patients with type 2 diabetes mellitus: A prospective, randomised cross-over study. *Diabetes Metab Res Rev* 2006, in press.

Scheidegger U, Allemann S, Scheidegger K, Diem P. Continuous Subcutaneous Insulin Infusion Therapy: Effects on Quality of Life. *Swiss Med Wkly* 2006, submitted.

Poster Presentations

Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, Krähenbühl S, Diem P. Glycemic Control and Macrovascular Disease in Type 1 and 2 Diabetes Mellitus: Meta-Analysis of Randomized Trials. Annual Meeting of the Swiss Society of Endocrinology and Diabetology, November 2003, Bern.

Stettler C, Allemann S, Jenni S, Diem P, Christ ER. Evaluation of growth hormone deficiency: prognostic value of DHEA-S and IGF-1. Annual Meeting of the Swiss Society of Endocrinology and Diabetology, November 2004, Bern.

Stettler C, Allemann S, Jenni S, Diem P, Christ ER. Evaluation of hypothalamic-pituitary-adrenal function: prognostic value of DHEA-S and fasting cortisol. Annual Meeting of the Swiss Society of Endocrinology and Diabetology, November 2004, Bern.

Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, Krähenbühl S, Diem P. Glycemic Control and Macrovascular Disease in Type 1 and 2 Diabetes Mellitus: Meta-Analysis of Randomized Trials. Pharma Day University of Basel, April 2005, Basel.

Stettler C, Jenni S, Allemann S, Steiner R, Hoppeler H, Trepp R, Christ ER, Zwahlen M, Diem P. Exercise capacity in Subjects with Type 1 Diabetes Mellitus in Eu- and Hyperglycaemia. 41st Annual Meeting of the European Association for the Study of Diabetes, September 2005, Athens, Greece.

Stettler C, Jenni S, Allemann S, Steiner R, Hoppeler H, Trepp R, Christ ER, Zwahlen M, Diem P. Exercise capacity in Subjects with Type 1 Diabetes Mellitus in Eu- and Hyperglycaemia. Annual Meeting of the Swiss Society of Endocrinology and Diabetology, November 2005, Bern.

Stettler C, Allemann S, Diem P, Windecker S, Meier B, Egger M. Efficacy of drug eluting stents in patients with and without diabetes mellitus: Indirect comparison of randomised controlled trials. Annual Meeting of the Swiss Society of Endocrinology and Diabetology, November 2005, Bern.

Oral Presentations

Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, Krähenbühl S, Diem P. Glycemic Control and Macrovascular Disease in Type 1 and 2 Diabetes Mellitus: Meta-Analysis of Randomized Trials. Forschungstage Institute for Social and Preventive Medicine, June 2004.

Stettler C, Allemann S, Diem P, Windecker S, Meier B, Egger M. Efficacy of drug eluting stents in patients with and without diabetes mellitus: Indirect comparison of randomised controlled trials. Forschungstage Institute for Social and Preventive Medicine, September 2005.

Additional Training / Courses

April-June 2003	'Statistische Prinzipien für medizinische Projekte', University of Bern
July 2003	'Einführung in die Statistiksoftware STATA™', University of Bern
December 2003	'Advanced Methods in Epidemiology: Meta-Analysis', University of Bern
2004-2005	Monthly, Books Club 'Essential Medical Statistics', University of Bern
February 2004	'Advanced Methods in Epidemiology: Applied Regression Modelling', University of Bern
April 2004	'Working efficiently with STATA™', University of Bern
March 2005	'Tim Albert Training: Writing a journal article – and getting it published', University of Bern
August/September 2006	'Biostatistics I', University of Bern