Antidiabetic Treatments and Ischemic Cardiovascular Disease in Denmark: Risk and Outcome

PhD dissertation

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PREFACE

This PhD thesis was carried out during my employment at the Department of Clinical Epidemiology, Aarhus University Hospital and the Department of Pharmacology, University of Aarhus.

The work was made possible thanks to a number of persons. First of all, I wish to thank my supervisors: Jørgen Rungby, who introduced me to the field of research and who enthusiastically encouraged me to start this project and continuously supported me throughout the process, and Søren Paaske Johnsen for patiently teaching me clinical epidemiology, and for providing skilful and constructive feedback. To both of you, I am deeply grateful for your trust in me from the very beginning.

Also, I wish to thank the statisticians: Jacob Jacobsen, who helped me getting started and always was there with help and support, Flemming Søndergaard for the comprehensive work with data linkage and competent statistically assistance, and Frank Mehnert for his help, support and positive engagement. To all statisticians, I am thankful for good team work and advice.
I would also like to thank co-authors, Reimar W. Thomsen, Henrik T. Sørensen, and Ole Schmitz for great in-put in study III.

I am very grateful to all my colleagues and friends at the Department of Clinical Epidemiology for creating a pleasant and inspiring environment. I also want to thank everyone in the Department of Pharmacology for the many inspiring discussions and great company at conferences and seminars.

Finally, my warmest thanks go to my husband Morten and our son Lukas, for their love, support, and patience.

My work was possible through financial support from the University of Aarhus, Les Laboratories Servier, the Danish Medical Research Council, the Research Initiative of Aarhus University Hospital, and the Danish Diabetes Association.

Henriette Thisted Horsdal, January 2010

This PhD thesis is based on the following papers:

I. Horsdal HT, Søndergaard F, Johnsen SP, Rungby J. Antidiabetic treatments and risk of hospitalisation with myocardial infarction: a nationwide case-control study. Submitted to Diabetologia 2009.

II. Horsdal HT, Johnsen SP, Søndergaard F, Rungby J. Type of preadmission glucose-lowering treatment and prognosis among patients hospitalised with myocardial infarction: a nationwide follow-up study. Diabetologia 2008; 51: 567-574.

III. Horsdal HT, Johnsen SP, Søndergaard F, Jacobsen J, Thomsen RW, Schmitz O, Sørensen HT, Rungby J. Sulfonylureas and prognosis after myocardial infarction in patients with diabetes: a population-based follow-up study. Diabetes Metabolism Research and Reviews 2009; 25: 515-522.

IV. Horsdal HT, Mehnert F, Rungby J, Johnsen SP. Type of preadmission antidiabetic treatments and outcome among patients hospitalized with ischemic stroke: a nationwide follow-up study. In preparation.

CONTENTS

1. INTRODUCTION

1.1 Introduction to diabetes mellitus

1.1.1 Prevalence and incidence

The number of patients with diabetes mellitus is predicted to increase dramatically worldwide within the coming decades because of continued population growth, aging, urbanization, and the increasing prevalence of obesity and a sedentary lifestyle. Diabetes mellitus will thus be one of the most prominent threats to human health in the 21st century. Predicted estimates of the prevalence of patients with diabetes mellitus within the coming decades range up to more than 300 million, predominantly those with type 2 diabetes mellitus.[1,2] In Denmark, the prevalence of patients with diabetes mellitus is currently estimated to be approximately 240,000 (~ 4.1% of the Danish population).[3] The incidence rate of diabetes mellitus in Denmark has been increasing up until 2004 but has been stable over the last few years with about 22,000-24,000 new cases a year.[3,4]

1.1.2 Definition of diabetes mellitus

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia. Several distinct types of diabetes mellitus exist and are caused by a complex interaction between genetics and environmental factors. Diabetes mellitus is conventionally categorized into two major types designated as type 1 and type 2. Type 2 diabetes mellitus accounts for more than 90% of all patients with the disorder.[5]

Type 1 diabetes mellitus commonly develops before the age of 30 years and is the result of complete or near-total insulin deficiency arising from autoimmune-mediated destruction of the insulin-producing pancreatic β-cells.[5]

Type 2 diabetes mellitus is a heterogeneous group of disorders characterized by variable degrees of insulin resistance (a condition in which peripheral tissues show reduced sensitivity to the effects of insulin-stimulated glucose uptake), impaired insulin secretion, and increased glucose production. It is usually diagnosed in patients older than 30 years but also occurs in adolescents and children.[5] In the early stages of type 2 diabetes mellitus, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic β-cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. Impaired glucose tolerance,

characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes mellitus with fasting hyperglycaemia. Ultimately, β-cell failure may ensue.

1.1.3 Treatment of diabetes mellitus

Primary treatment goals for patients with diabetes mellitus include achievement of blood glucose levels that are as close to normal as possible to prevent diabetic complications. Both non-pharmacologic and pharmacologic therapies are used for achieving glycaemic control among patients with diabetes mellitus. Non-pharmacologic approaches include a healthy diet, exercise, and weight loss and are generally the first steps in treating type 2 diabetes mellitus. Later, patients will require drugs that stimulate β-cells to make more insulin and/or drugs that help insulin work better. Unlike patients with type 1 diabetes mellitus, those with type 2 diabetes mellitus are not dependent on exogenous insulin but may require it for glycaemic control if non-pharmacologic approaches alone or oral antidiabetic drug(s) do not achieve it.

Six types of antidiabetic drugs are approved for the treatment of diabetes mellitus: sulfonylureas, biguanides, alpha-glucosidase inhibitors, glitazones, meglitinides, and insulin.
In 2008, a total of 174,328 patients were treated with antidiabetic drugs in Denmark.[6] The most prescribed drugs in Denmark during the last decade have been sulfonylureas, metformin, and insulin, while only a few patients have been treated with alpha-glucosidase inhibitors, glitazones, and meglitinides. Novel antidiabetic treatments include combination pills (metformin+rosiglitazone, glimepiride+rosiglitazone, metformin+sitagliptin, and metformin+vildagliptin), incretin mimetic drugs (exenatide), and the dipeptidyl peptidase (DPP-4) inhibitors (sitagliptin and vildagliptin). Figure 1 shows the number of patients treated with the different antidiabetic drugs in Denmark from 1994-2008.[6]

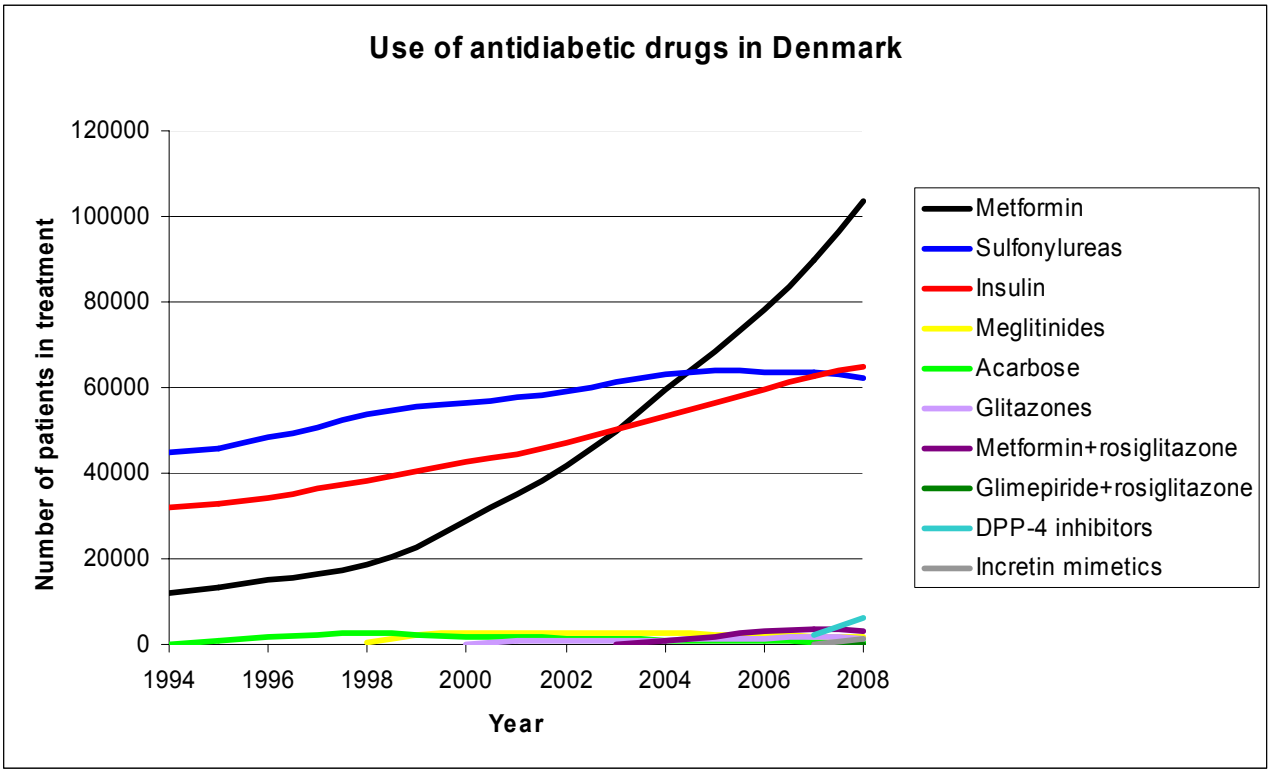

Figure 1. Use of antidiabetic drugs in Denmark, 1994-2008.

Sulfonylureas:

Sulfonylureas are insulin secretagogues and act by binding to an ATP-dependent K^+ (K_{ATP}) channel on the cell membrane of pancreatic β-cells, thus mediating an increase in insulin release from the β-cells.[7] Sulfonylureas therefore require functional pancreatic β-cells because they only stimulate insulin secretion if there is a sufficient mass of β-cells. Reduction in available β-cells with progression of type 2 diabetes mellitus results in inadequately stimulated insulin release.
In Denmark, five sulfonylureas are available: glibenclamide, glipizide, tolbutamide, glimepiride, and gliclazide.

Biguanides:

Metformin is the only available drug belonging to this class. It reduces blood glucose levels through suppression of gluconeogenesis, stimulation of peripheral glucose uptake in a number of tissues (mainly skeletal muscle) in the presence of insulin, and decreased absorption of glucose from the gastrointestinal tract. Metformin does not cause weight gain and appears to be the drug of choice in obese patients. Metformin is also used for the treatment of polycystic ovary syndrome.[8]

Alpha-glucosidase inhibitors:

The alpha-glucosidase inhibitor used to treat patients with type 2 diabetes mellitus in Denmark is acarbose. It works by slowing the action of enzymes that break down dietary carbohydrates to release glucose into the blood. It thus delays the breakdown of complex carbohydrates and disaccharides to the absorbable monosaccharides by inhibiting maltase, isomaltase, sucrase, and glucoamylase, thus keeping blood glucose from rising after meals.[9]

Glitazones:

This group of insulin sensitizers is also called thiazolidinediones and includes rosiglitazone and pioglitazone. They act by helping the body use the available amounts of insulin more effectively by increasing the insulin sensitivity, especially in adipocytes, muscle, and liver. They achieve this by binding to the peroxisome proliferator-activated receptor gamma, leading to increased transcription of various insulin-sensitive genes, including those encoding glucose transporters, lipoprotein lipase, and fatty acid transport protein.[10] An additional major effect is inhibition of hepatic gluconeogenesis.

Meglitinides:

Like the sulfonylureas, meglitinides are insulin secretagogues, and they too act by closing the K_{ATP}-channels. However, the binding sites for meglitinides on the β-cells are different from those of sulfonylureas,[11] leading to both specific and common cellular mechanisms. In Denmark, currently only repaglinide is available from this class, but during our study period, nateglinide also was available on the Danish market.

Insulin:

Insulin is taken via subcutaneous injection. A variety of insulin preparations are available that vary in their onset, peak, and duration of activity. Ideally, the use of exogenous insulin provides an insulin profile similar to that of a non-diabetic individual, with a continuous basal level of insulin availability augmented by increased availability following each meal. The injected insulin thus promotes glucose uptake and storage like endogenously produced insulin does.

Figure 2 summarizes the effect of different antidiabetic treatments.

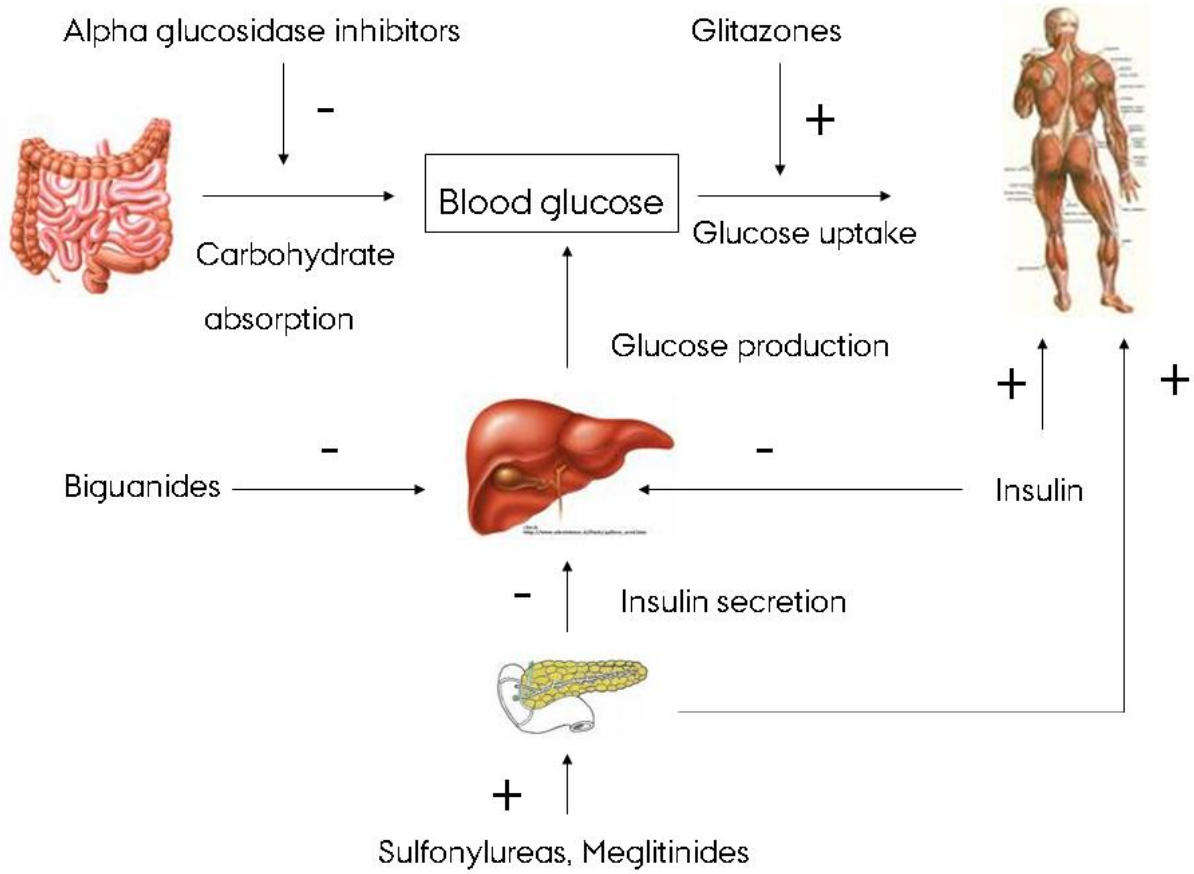

Figure 2. Antidiabetic treatments and their effects.

1.2 Diabetes mellitus and cardiovascular disease

The metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiologic changes in multiple organ systems. Some of these changes increase the risk and worsen the prognosis of atherosclerotic diseases. Hence, patients with diabetes mellitus have an increased risk of these diseases (including myocardial infarction) compared with non-diabetic patients and a poorer prognosis compared with non-diabetic patients who do develop atherosclerotic diseases, including myocardial infarction and stroke.[12] Factors associated with an increased risk are not necessarily the same as those that confer a poorer prognosis, but diabetes mellitus is nevertheless a well-recognized risk factor for myocardial infarction as well as a prognostic factor after myocardial infarction (Figure 3).

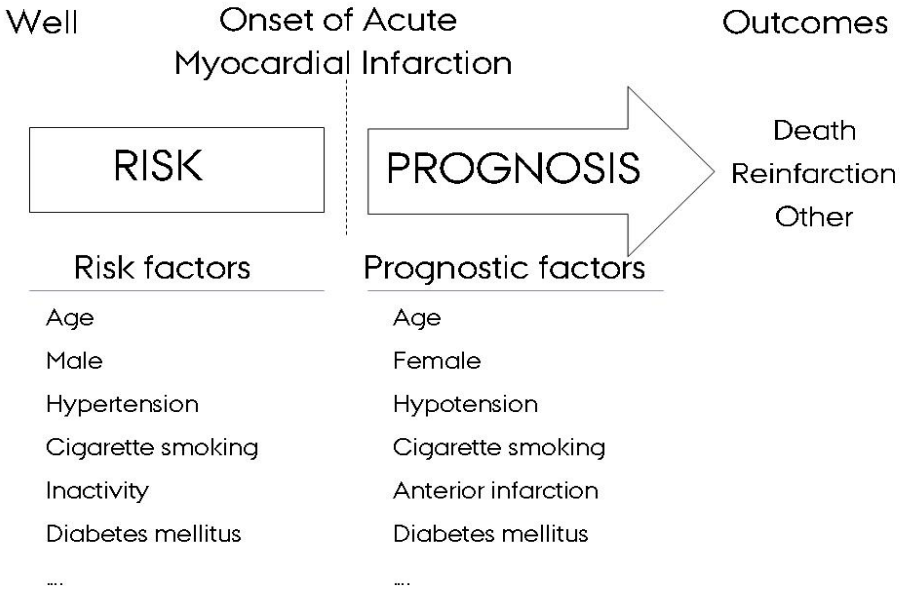

Figure 3. Risk and prognosis. Modified from *Clinical Epidemiology - The Essentials*.[13]

1.2.1 Risk of atherosclerotic disease

The increased risk of atherosclerotic disease among patients with diabetes mellitus was first demonstrated in epidemiological data originating from the Framingham Study in 1979. In this cohort, a total of 5,209 men and women were followed for 20 years and clinical cardiovascular endpoints were assessed. Diabetes mellitus was associated with an almost two-fold increased risk of coronary heart disease (including myocardial infarction) and stroke.[14]

The large INTERHEART case-control study of 12,461 cases with myocardial infarction found diabetes mellitus to be a significant risk factor for the occurrence of myocardial infarction.[15] In addition, it has been suggested that patients with diabetes mellitus without previous myocardial infarction carry the same risk of myocardial infarction as non-diabetic patients with previous myocardial infarction.[16,17]

Finally, in a 12-year follow-up study of 690 patients with diabetes mellitus and 6,908 non-diabetic patients enrolled in the Honolulu Heart Program, diabetes mellitus was also associated with an almost two-fold increase in the incidence of stroke.[18]

1.2.2 Outcome after atherosclerotic disease

Patients with diabetes mellitus have an adverse prognosis after atherosclerotic disease when compared to their non-diabetic counterparts. The adverse prognosis includes increased mortality rate and increased risk of readmission. In the Finnish Monitoring Trends and Determinants in Cardiovascular Diseases (FINMONICA) Myocardial Infarction Register Study, patients with diabetes mellitus had increased short- and long-term mortality rates after first-time myocardial infarction compared with non-diabetic patients,[19] and a 5-year follow-up study of 787 patients with myocardial infarction in the Göteborg Metoprolol Trial showed that diabetes mellitus was an independent determinant of long-term reinfarction and mortality.[20]

Diabetes mellitus affects stroke outcome as well. Among 1,135 patients with acute stroke in the Copenhagen Stroke Study, mortality was significantly increased in patients with diabetes mellitus.[21] A Swedish cohort study followed 121 patients with diabetes mellitus and 584 non-diabetic patients for up to 10 years after they had suffered a stroke and found that diabetes mellitus was associated with an increased risk of death after stroke and an increased risk of recurrent stroke and myocardial infarction among stroke survivors.[22]

1.3 Antidiabetic treatments and cardiovascular disease

Maintaining blood glucose levels as close as possible to the normal range (*i.e.*, haemoglobin A_{1c} (HbA_{1c}) level <6.0%) among patients with type 2 diabetes mellitus is one way to lower the risk of macrovascular diseases. Each 1% reduction in HbA_{1c} has been associated with a 14% decrease in risk of myocardial infarction and a 21% decrease in any endpoint related to diabetes mellitus.[23]

1.3.1 Potential cardiovascular effects of different antidiabetic drugs

Because different antidiabetic drugs lower blood glucose through different mechanisms, their effect on the cardiovascular system may differ. Several potential cardiovascular effects of different antidiabetic drugs have been postulated to explain how they may influence cardiovascular risk and outcome among patients with type 2 diabetes mellitus.

Sulfonylureas:

Binding of the sulfonylureas to K_{ATP}-channels in extra-pancreatic tissues may have a number of physiologic consequences. In cardiac myocytes, ischemia results in K_{ATP} opening, K^+ efflux,

reduced Ca^{++} influx, and via these mechanisms a reduced contractility and consequently a decreased need for oxygen. Further, activation of K_{ATP} channels in the heart during ischemia is thought to minimize cardiac damage by "ischemic preconditioning". In vascular cells, K_{ATP} opening decreases muscular tone, resulting in increased flow. In the brain, opening of the K_{ATP} channels under metabolic stress has been suggested to protect against neuronal damage and neurodegeneration.[24] Thus, sulfonylureas could at least theoretically be harmful by closing K_{ATP} channels.

The impairment of ischemic preconditioning by some sulfonylureas (glibenclamide, glipizide) has been described both in experimental models[25-27] and in patients undergoing coronary angiography.[28-30] A similar effect has not been seen with other sulfonylureas (glimepiride, gliclazide).[26-29,31]

The extra-pancreatic K_{ATP} channels are structurally different from the pancreatic isoform, giving a potentially different effect of sulfonylureas as their affinity for the different receptors differs.

Sulfonylureas can also block the $N_{Cca\text{-}ATP}$ channel, which is expressed in the central nervous system only under conditions of injury or ischemia. In a rodent model of ischemic stroke, this channel was upregulated, and post-event block by glibenclamide reduced mortality, cerebral oedema and infarct volume by half.[32]

In addition, gliclazide may enhance fibrinolysis and reduce platelet activity and oxidative stress,[33] properties that might reduce myocardial ischemic damage. Glibenclamide may reduce arrhythmias during ischemia.[34] Finally, glimepiride improves the lipid profile by reducing total and low-density lipoprotein (LDL) cholesterol and triglycerides and increasing high-density lipoprotein (HDL) cholesterol.[35]

Biguanides:

Metformin decreases total and LDL cholesterol, plasma free fatty acids, and triglycerides, giving a beneficial effect with regard to the lipid profile. Metformin also decreases concentrations and activity of the antifibrinolytic factor plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA) antigen, von Willebrand factor, and platelet aggregation and adhesion, and increases

tPA activity, each of which improves hypercoagulability. Metformin further improves vasoreactivity.[8]

However, metformin may cause gastrointestinal disturbances such as nausea and diarrhoea, and during chronic therapy, it will impair the intestinal absorption of group B vitamins (mainly vitamin B12) and folate. This effect leads to increased serum homocysteine, which may accelerate the risk for cardiovascular disease by adverse effects on platelets, clotting factors, and endothelium.[8] Finally, metformin may also lead to lethal lactic acidosis,[8] but this is a rare complication.

Alpha-glucosidase inhibitors:
Acarbose has been shown to lower triglyceride levels, total and LDL cholesterol levels, and blood pressure.[9]

Glitazones:
Glitazones improve endothelial function and markedly increase circulating concentrations of the adipokine adiponectin, which may have antiatherogenic properties. Glitazones increase HDL cholesterol and reduce triglycerides, free fatty acids, PAI-1, tumour necrosis factor-α, and the inflammatory markers C-reactive protein (CRP) and CD40 ligand.[10,36]

Meglitinides:
Because of their shared mechanism of action, meglitinides may exert effects similar to those of sulfonylureas on the extra-pancreatic K_{ATP} channels. They have also shown beneficial effects on cardiovascular risk factors by reducing total and LDL cholesterol, triglycerides, free fatty acids, PAI-1, CRP, fibrinogen, and thrombin-antithrombin complexes.[35]

Insulin:
Insulin treatment has been shown to decrease PAI-1 activity.[37] It may also restore impaired platelet function and correct the disturbed lipoprotein pattern after myocardial infarction.

The clinical importance of the potential cardiovascular effects of the different antidiabetic treatments is unclear. It is not certain that beneficial/harmful physiological and biochemical effects translate into beneficial/harmful clinical effects. In the following sections, the literature on the

association of different antidiabetic treatments and clinical outcomes is described; however, the literature overview has been restricted to clinical outcomes that are important to this thesis, *i.e.*, risk of myocardial infarction and outcomes after myocardial infarction and stroke.

1.3.2 Antidiabetic treatment and risk of myocardial infarction

PubMed was searched to identify articles on the association between antidiabetic treatments and risk of myocardial infarction, using the following search strategy:
"Myocardial Infarction"[Mesh] AND ("Diabetes Mellitus, Type 2/diet therapy"[Mesh] OR "Diabetes Mellitus, Type 2/drug therapy"[Mesh] OR "Diabetes Mellitus, Type 2/therapy"[Mesh])) AND "Risk"[Mesh]
The search was limited to include only English- and Danish-language studies in humans. Additional studies were found by searching the reference lists from the identified publications. Table 1 shows the relevant studies on antidiabetic treatment and risk of myocardial infarction.

Table 1. Studies on antidiabetic treatments and risk of myocardial infarction

Author, year, country	N	Study design	Outcome	Study population	Results
Boyle *et al.* 1972, Northern Ireland[38]	Diet: 115 Tablets: 71	Cohort	Myocardial infarction	Newly diagnosed adult-onset diabetes, age 35-75	Diet: 9.5% Tablets: 19.7% p<0.05
Hadden *et al.* 1972, Northern Ireland[39]	670 (5,659 patient-years) Diet: 2,436 patient-years Tablets: 2,475 patient-years Insulin: 748 patient-years	Cohort	Myocardial infarction	Maturity-onset female patients with diabetes mellitus	Diet: 1.52 per 100 patient-year Tablets: 3.06 per 100 patient-year Insulin: 2.14 per 100 patient-year
UKPDS Study Group 1998, UK[40]	Glibenclamide: 615 Chlorpropamide: 619 Insulin: 911 Diet: 896	RCT	Myocardial infarction	Newly diagnosed type 2 diabetes mellitus, age 25-65	Diet: RR 1.00 (ref.) Chlorpropamide: RR 0.87 (0.68-1.12) Glibenclamide: RR 0.78 (0.60-1.01) Insulin: RR 0.87 (0.70-1.09) Glibenclamide+chlorpropamide+insulin: RR 0.84 (0.71-1.00)
UKPDS Study Group 1998, UK[41]	Glibenclamide: 277 Chlorpropamide: 265 Insulin: 409 Diet: 411 Metformin: 342	RCT	Myocardial infarction	Newly diagnosed type 2 diabetes mellitus, age 25-65, overweight (>120% ideal bodyweight)	Diet: RR 1.00 (ref.) Metformin: RR 0.61 (0.41-0.89), Glibenclamide+chlorpropamide+insulin: RR 0.79 (0.60-1.05)
UKPDS Study Group 1998, UK[41]	Sulfonylurea: 269 Sulfonylurea+metformin: 268	RCT	Myocardial infarction	Newly diagnosed type 2 diabetes mellitus on max. sulfonylurea therapy	Sulfonylurea: RR 1.00 (ref.) Sulfonylurea+metformin: RR 1.09 (0.67-1.78)
Holman *et al.* 2008, UK[42]	Glibenclamide+chlorpropamide+insulin: 2,118	RCT-post-trial	Myocardial infarction	Newly diagnosed type 2 diabetes mellitus, age	Diet: RR 1.00 (reference) Glibenclamide+chlorpropamide+insulin: RR 0.85 (0.74-0.97)

	Diet: 880 (411 overweight) Metformin: 279			25-65	Metformin: RR 0.67 (0.51-0.89)
Belcher *et al.* 2004, UK[43]	Pioglitazone: 1,857 Non-pioglitazone (metformin+gliclazide): 1,856	RCT	Myocardial infarction	Type 2 diabetes mellitus, no prior myocardial infarction	Pioglitazone: 10 (0.5%) Non-pioglitazone: 7 (0.4%) p>0.05
Kahn *et al.* 2006, USA[44]	Rosiglitazone:1,456 Metformin: 1,454 Glibenclamide: 1,441	RCT	Myocardial infarction	Recently diagnosed type 2 diabetes mellitus	Fatal: Rosiglitazone: 2 (0.1%) Metformin: 2 (0.1%) Glibenclamide: 3 (0.2%) p>0.05 Nonfatal: Rosiglitazone: 25 (1.7%) Metformin: 21 (1.4%) Glibenclamide: 15 (1.0%) p>0.05
Hanefeld *et al.* 2004, Germany[45]	Placebo: 932 Acarbose: 1,248	Meta-analysis	Cardiovascular events, including myocardial infarction	RCTs with minimum treatment duration of 52 weeks and at least 50 patients.	Placebo: HR 1.00 (ref.) Acarbose: HR 0.36 (0.16-0.80)
Evans *et al.* 2006, UK[46]	Metformin (mono): 2,286 Sulfonylurea (mono): 3,331 Metformin+sulfonylurea later: 985 Sulfonylurea+metformin later: 1,252 Metformin+sulfonylurea similar start: 113	Cohort	Cardiovascular admission	Type 2 diabetes mellitus, newly treated with oral antidiabetic drugs	Metformin (mono): RR 1.00 (ref.) Sulfonylurea (mono): RR 1.30 (0.71-2.40) Metformin+sulfonylurea: RR 1.86 (1.03-3.35) Sulfonylurea+metformin: RR 2.24 (1.26-3.99) Both: RR 1.52 (0.84-2.77)
McAfee *et al.*	Rosiglitazone: 8,977	Matched	Myocardial	Initiators of	Metformin: HR 1.00 (ref.)

2007, USA[47]	Metformin: 8,977 Sulfonylurea: 8,977 Rosiglitazone+metformin: 1,362 Rosiglitazone+sulfonylurea: 1,362 Metformin+sulfonylurea: 1,362 Rosiglitazone+insulin: 1,173 Other+insulin: 1,173	cohorts	infarction	rosiglitazone, metformin, or sulfonylureas	Rosiglitazone: HR 1.19 (0.84-1.68) Sulfonylurea: HR 1.00 (ref.) Rosiglitazone: HR 0.79 (0.58-1.07) Rosiglitazone+metformin: HR 1.00 (ref.) Metformin+sulfonylurea: HR 0.41 (0.16-1.04) Rosiglitazone+sulfonylurea: HR 1.00 (ref.) Metformin+sulfonylurea: HR 1.45 (0.76-2.75) Other+insulin: HR 1.00 (ref.) Rosiglitazone+insulin: HR 0.79 (0.46-1.36)
Johnson *et al.* 2005, Canada[48]	Sulfonylurea: 2,138 Metformin: 923 Sulfonylurea+metformin:1,081	Cohort	Fatal and nonfatal cardiovascular events	New users of antidiabetic medicin (metformin or sulfonylurea)	Sulfonylurea: HR 1.00 (ref.) Metformin: HR 0.81 (0.68-0.97) Sulfonylurea+metformin: HR 0.97 (0.84-1.13)
Sauer *et al.* 2006, USA[49]	Sulfonylureas: 75 cases/83 controls Glitazones: 7/19 Metformin: 38/87 Diet: 83/119	Case-control	Myocardial infarction	First myocardial infarction, age 40-75, type 2 diabetes mellitus	Sulfonylurea: OR 1.00 (ref.) Metformin: OR 0.48 (0.27-0.82) Glitazones: OR 0.33 (0.12-0.92) Glitazones+sulfonylurea: OR 0.35 (0.13-0.95) Metformin+sulfonylurea: OR 0.69 (0.40-1.20) Diet: OR 1.00 (ref.) Sulfonylurea: OR 1.15 (0.73-1.83) Metformin: OR 0.59 (0.34-0.98) Glitazones: OR 0.43 (0.16-1.18)
Singh *et al.* 2007, USA[50]	Control therapy: 7,870 Rosiglitazone: 6,421	Meta-analysis	Myocardial infarction	Rosiglitazone trials	Control therapy: RR 1.00 (ref.) Rosiglitazone: RR 1.42 (1.06-1.91)
Nissen & Wolski	Control group: 11,635	Meta-	Myocardial	Rosiglitazone trials	Control group: OR 1.00 (ref.)

2007, USA[51]	Rosiglitazone: 14,376	analysis	infarction	with study duration of more than 24 weeks	Rosiglitazone: OR 1.43 (1.03-1.98)
Lincoff *et al.* 2007, USA[52]	Control therapy: 7,836 Pioglitazone: 8,554	Meta-analysis	Myocardial infarction	Pioglitazone trials	Control therapy: HR 1.00 (ref.) Pioglitazone: HR 0.81 (0.64-1.02)
Johnsen *et al.* 2006, Denmark[53]	Glimepiride: 35 cases/205 controls Gliclazide: 21/117 Glibenclamide: 206/889 Glipizide: 72/317 Tolbutamide: 27/100 Other oral antidiabetic drugs: 31/177 Insulin: 235/737 Any combination: 51/183 No pharmacotherapy: 189/423	Case-control	Myocardial infarction	First myocardial infarction, age >18	Non-diabetic patients: OR 1.00 (ref.) Glimepiride: OR 1.36 (0.93-1.99) Gliclazide: OR 1.37 (0.84-2.22) Glibenclamide: OR 2.08 (1.77-2.45) Glipizide: OR 1.97 (1.50-2.58) Tolbutamide: OR 2.32 (1.48-3.64) Other oral antidiabetic drugs: OR 1.38 (0.90-2.11) Insulin: OR 2.56 (2.16-3.03) Any combination: OR 1.02 (0.70-1.47) No pharmacotherapy: OR 3.51 (2.92-4.22)

HR = hazard ratio, OR = odds ratio, RCT = randomized controlled trial, ref. = reference, RR = relative risk

Uncertainty regarding the cardiovascular safety of sulfonylureas arose in 1970 when the University Group Diabetes Program (UGDP), on the basis of epidemiological data, concluded that treatment with the sulfonylurea tolbutamide for 5-8 years increased cardiovascular mortality in comparison with treatment with insulin (both a fixed and a variable dose) or placebo.[54] The observation generated much controversy, and the study has been heavily criticized for perceived methodological shortcomings.[55,56] However, several other studies have also found increased cardiovascular risk among users of sulfonylureas. Two studies from Northern Ireland found a higher risk of myocardial infarction in patients treated with tablets (carbutamide, tolbutamide, chlorpropamide, tolazamide, acetohexamide, glibenclamide, phenformin, and/or metformin) than in patients treated with diet.[38,39]

The United Kingdom Prospective Diabetes Study (UKPDS) group followed 3,867 newly diagnosed patients with type 2 diabetes mellitus randomly assigned to intensive treatment or conventional treatment and found a non-significant risk reduction for myocardial infarction with intensive treatment with chlorpropamide, glibenclamide, or insulin.[40] In an analysis of overweight patients with type 2 diabetes mellitus the use of metformin was associated with reduced risk of myocardial infarction compared with diet therapy.[41] However, addition of metformin to sulfonylurea therapy did not reduce the risk of myocardial infarction compared with sulfonylurea monotherapy.[41] A recent follow-up study on the UKPDS trial found a reduced post-trial risk of myocardial infarction among users of sulfonylureas and/or insulin and also confirmed the reduced risk of myocardial infarction among users of metformin compared with diet therapy.[42]

Metformin has also been associated with reduced risk of hospitalization with fatal and nonfatal cardiovascular events (including myocardial infarction) compared with sulfonylurea.[48] A case-control study also demonstrated a statistically significant reduction in the risk of myocardial infarction associated with use of metformin or glitazones (pioglitazone, rosiglitazone, and troglitazone) compared with sulfonylurea (glibenclamide and glipizide) among patients with type 2 diabetes mellitus.[49] Like the UKPDS trial, this study also found a reduced risk of myocardial infarction among those using metformin compared with diet therapy.[49] Also consistent with the UKPDS findings, the risk of myocardial infarction among users of metformin and sulfonylurea was not lower than that among users of sulfonylurea alone.[49]

In contrast, a Scottish cohort study of patients newly treated with oral antidiabetic drugs reported similar risks of being hospitalized with cardiovascular disease among users of metformin and sulfonylureas, however, a combination of these (either sulfonylurea added to metformin or metformin added to sulfonylurea) was associated with an increased risk of being hospitalized with cardiovascular disease compared with metformin monotherapy.[46]
In A Diabetes Outcome Progression Trial (ADOPT), a total of 4,360 patients without previous pharmacologic treatment for their newly diagnosed type 2 diabetes mellitus were randomized to rosiglitazone, metformin, or glibenclamide, and they had a similar risk of admissions with fatal and nonfatal myocardial infarction.[44]

Recently, the cardiovascular safety of glitazones has been debated. Meta-analyses suggest that rosiglitazone is associated with increased risk of myocardial infarction compared with control therapy (placebo or other antidiabetic treatments),[50,51] while pioglitazone is associated with a decreased risk of myocardial infarction (although not statistically significant) compared with control therapy.[52] On the other hand, results from four randomized trials in patients with type 2 diabetes mellitus after one year of treatment with pioglitazone or non-pioglitazone (metformin, gliclazide) showed a similar risk of myocardial infarction in the groups,[43] and in a propensity score-matched cohort study, rosiglitazone users had the same risk of myocardial infarction as users of sulfonylureas and metformin.[47]

A meta-analysis including seven randomized double-blind placebo-controlled trials showed that treatment with the α-glucosidase inhibitor acarbose may reduce the risk of myocardial infarction in patients with type 2 diabetes mellitus.[45]

We have previously examined the association between the use of antidiabetic treatment and the risk of myocardial infarction in a population-based case-control study including 6,738 cases and 67,374 age- and gender-matched population controls. The risk of myocardial infarction appeared higher among users of glibenclamide, glipizide or tolbutamide compared with users of glimepiride or gliclazide.[53] The risk of myocardial infarction among users of insulin was higher than for users of oral antidiabetic drugs. Patients with diabetes mellitus without antidiabetic pharmacotherapy had the highest risk estimates for myocardial infarction.[53]

Comparison of the different studies in Table 1 is complicated because they compare different antidiabetic treatments, use different outcomes (some studies include myocardial infarction in a combined cardiovascular endpoint),[45,46,48] and adjust for different sets of covariates.
In addition, because antidiabetic treatment changes over time as the diabetes progresses, it is important to consider the severity of diabetes mellitus when comparing different antidiabetic treatments, but several of the existing studies did not include these data.[38,39,47-49,53] The lack of information on other important covariates, including other diseases[38,39] and the use of cardiovascular drugs,[38,39] also makes results interpretation difficult.
Finally, the majority of the existing studies did not distinguish between antidiabetic treatments (biguanides and sulfonylureas)[38,39,43] and certainly not between sulfonylureas[38,39,46-49]. Combining the effect of different medical treatments may lead to over- or underestimation of the effect of one treatment by another.

In conclusion, because the prevalence of type 2 diabetes mellitus is rising and patients are permanently dependent on their antidiabetic treatment, it is important to clarify whether any of these antidiabetic treatments is a risk factor for myocardial infarction.

1.3.3 Antidiabetic treatment and outcome after myocardial infarction

PubMed was searched to identify articles on the association between antidiabetic treatments and outcome after myocardial infarction, using the following terms:
("Myocardial Infarction"[Mesh] AND ("Diabetes Mellitus, Type 2/diet therapy"[Mesh] OR "Diabetes Mellitus, Type 2/drug therapy"[Mesh] OR "Diabetes Mellitus, Type 2/therapy"[Mesh])) AND "Prognosis"[Mesh]
The search was limited to include only English- and Danish-language studies in humans. Additional studies were found by searching the reference list from the identified publications.
Table 2 shows the relevant studies on antidiabetic treatment and clinical outcome after myocardial infarction.

Table 2. Studies on antidiabetic treatments and clinical outcome after myocardial infarction

Author, year, country	N	Study design	Inclusion criteria	Outcome	Results
Rytter *et al.* 1985, Denmark[57]	Diet: 8 Tablets+diet: 54 Insulin: 11	Cohort	Myocardial infarction	Mortality	Diet: 25% Tablets+diet: 50% Insulin: 9.1% Tablets+diet vs. insulin: $p<0.02$ Diet vs. tablets+diet: $0.05<p<0.1$
Soler *et al.* 1974, UK[58]	Diet: 27 Oral antidiabetic drugs: 90 Insulin: 67	Cohort	Myocardial infarction	Mortality	Diet: 4 (15%) Oral antidiabetic drugs: 36 (40%) Insulin: 25 (37%)
Soler *et al.* 1975, UK[59]	Diet: 31 Oral antidiabetic drugs: 129 Insulin: 125	Cohort	Myocardial infarction	Mortality	Diet: 15% Oral antidiabetic drugs: 40% Insulin: 37%
Ulvenstam *et al.* 1985, Sweden[60]	Diet: 21 Sulfonylurea and/or metformin: 37 Insulin: 15	Cohort	First-time myocardial infarction, men	Mortality	Diet: 9 (42.9%) Sulfonylurea/metformin: 24 (64.9%) Insulin: 5 (33.3%) Sulfonylurea/metformin vs. insulin: p=0.077
Brady *et al.* 1998, USA[61]	Insulin: 56 Sulfonylurea: 46	Cohort	Myocardial infarction	Mortality	Insulin: 20 Sulfonylurea: 24 p=0.79
Malmberg *et al.* 1995, Sweden[62]	Control: 314 Insulin: 306	RCT	Myocardial infarction	Mortality and morbidity	3-month mortality: Control: 15.6% Insulin: 12.4%

					Mortality reduction: 21%, p>0.05 1-year mortality: Control: 26.1% Insulin: 18.6% Mortality reduction: 29%, p=0.0273 (with the Cox model: 31% (4%-51%)) Hospital reinfarction: Control: 4% Insulin: 5% p>0.05
Malmberg *et al.* 1996, Sweden[63]	Insulin: 306 Control: 314	RCT	Myocardial infarction	Morbidity and mortality	1-year mortality: Control: 26% Insulin: 19% Mortality reduction: 29%, p=0.0273 In-hospital reinfarction: Control: 4% Insulin: 5% p>0.05 1 year reinfarction: Control: 55 Insulin: 53 p>0.05
Malmberg *et al.* 1997, Sweden[64]	Insulin: 306 Control: 314	RCT	Myocardial infarction	Mortality	Control: 44% Insulin: 33% Mortality reduction with the Cox model:

					28% (8%-45%), RR 0.72 (0.55-0.92)
Malmberg *et al.* 2005, Europe[65]	Group 1: Insulin-glucose infusion followed by insulin-based long-term glucose control: 474 Group 2: Insulin-glucose infusion followed by standard glucose control: 473 Group 3: Routine metabolic management according to local practice: 306	RCT	Myocardial infarction	Mortality and morbidity	2-year mortality: Group 2: HR 1.00 (ref.) Group 1: HR 1.03 (0.79-1.34) Group 3: HR 1.00 (ref.) Group 1: HR 1.26 (0.92-1.72) Group 2: HR 1.23 (0.89-1.69). Reinfarction: Group 2: HR 1.00 (ref.) Group 1: HR 1.34 (0.94-1.90) Group 3: HR 1.00 (ref.) Group 1: HR 1.36 (0.91-2.03)
Melbin *et al.* 2008, Sweden[66]	Sulfonylurea: 268 Metformin: 200 Insulin: 690 Acarbose: 9 Diet: 176 Combination: 173	Sub-analysis in RCT	Myocardial infarction	Mortality and morbidity	All-cause mortality: No insulin: HR 1.00 (ref.) Insulin: HR 1.12 (0.83-1.51) No metformin: HR 1.00 (ref.) Metformin: HR 0.91 (0.61-1.34) No sulfonylurea: HR 1.00 (ref.) Sulfonylurea: HR 1.08 (0.78-1.50) Cardiovascular mortality: No insulin: HR 1.00 (ref.) Insulin: HR 1.05 (0.75-1.46) No metformin: HR 1.00 (ref.) Metformin: HR 0.93 (0.60-1.43) No sulfonylurea: HR 1.00 (ref.)

					Sulfonylurea: HR 1.15 (0.80-1.64), Nonfatal reinfarction or stroke: No insulin: HR 1.00 (ref.) Insulin: HR 1.73 (1.26-2.37) No metformin: HR 1.00 (ref.) Metformin: HR 0.63 (0.42-0.95) No sulfonylurea: HR 1.00 (ref.) Sulfonylurea: HR 0.81 (0.57-1.14),
Mak *et al.* 1997, UK[67]	Non-diabetic: 34,888 Insulin: 1,643 Non-insulin: 4,301	Cohort	Myocardial infarction	Mortality and morbidity	30-day mortality: Non-insulin: OR 1.00 (ref.) Insulin: OR 1.32 (1.10-1.57) 1-year mortality: Non-insulin: 13.1% Insulin: 17.8% p=0.0001 30-day reinfarction: Non-insulin: 4.2% Insulin: 4.6% p>0.05 30-day stroke: Non-insulin: OR 1.00 (ref.) Insulin: OR 1.59 (1.07-2.36)
Jollis *et al.* 1999, USA[68]	Sulfonylurea: 25,035 Insulin: 18,935 Sulfonylurea+insulin: 2,340	Cohort	Myocardial infarction	Mortality and morbidity	Neither: OR 1.00 (ref.) Sulfonylurea: OR 0.95 Insulin: OR 1.02

	Neither: 17,861				
Danchin *et al.* 2003, France[69]	Sulfonylurea: 215 No sulfonylurea: 272	Cohort	Myocardial infarction	Mortality	No sulfonylurea: RR 1.00 (ref.) Sulfonylurea: RR 0.37 (0.16-0.86)
Berger *et al.* 2001, USA[70]	Non-diabetic: 80,832 Diet: 9,862 Oral antidiabetic drugs: 14,664 Insulin: 12,241	Cohort	Myocardial infarction	Mortality	30-day mortality: Non-diabetic: OR 1.00 (ref.) Diet: OR 1.09 (1.03-1.16), Oral antidiabetic agents: OR 1.14 (1.08-1.20) Insulin: OR 1.14 (1.08-1.20) 1-year mortality: Non-diabetic: OR 1.00 (ref.) Diet: OR 1.26 (1.19-1.32) Oral antidiabetic agents: OR 1.28 (1.22-1.34) Insulin: OR 1.48 (1.41-1.55)
Davis *et al.* 1998, Australia[71]	Admission/discharge Diet: 229/0 Glibenclamide: 111/103 Gliclazide: 111/82 Insulin: 136/76 Metformin: 40/46	Cohort	Myocardial infarction	Mortality	28-day mortality: Glibenclamide: OR 1.00 (ref.) Gliclazide: OR 0.7 (0.3-1.4) Insulin: OR 0.8 (0.4-1.7) Diet: OR 1.00 (ref.) Metformin: OR 0.4 (0.1-1.3) Long-term mortality: Glibenclamide: HR 1.00 (ref.) Gliclazide: HR 1.6 (0.8-3.2) Insulin: HR 1.1 (0.5-2.4) Metformin: HR 2.6 (0.8-8.0)
Fisman *et al.*	Diet: 990	Cohort	Myocardial	Mortality	Diet: RR 1.00 (ref.)

1999, Israel[72]	Sulfonylurea: 1,041 Metformin (alone or in combination with sulfonylurea): 344		infarction and/or stable anginal syndrom		Metformin: RR 1.42 (1.10-1.85) Sulfonylurea: RR 1.11 (0.90-1.36)
Fisman *et al.* 2001, Israel[73]	Diet: 990, Glibenclamide: 953 Metformin:79 Glibenclamide+metformin: 253	Cohort	Myocardial infarction and/or stable anginal syndrom	Mortality	Diet: RR 1.00 (ref.) Glibenclamide: RR 1.21 (1.02-1.44) Metformin: RR 1.19 (0.76-1.84) Glibenclamide+metformin: RR 1.53 (1.20-1.95)
Garratt *et al.* 1999, USA[74]	Sulfonylurea: 67 Non-sulfonylurea: 118	Cohort	Direct coronary angioplasty for treatment for myocardial infarction	Mortality and morbidity	Mortality: Non-sulfonylurea: OR 1.00 (ref.) Sulfonylurea: OR 2.53 (1.13-5.67) 5-year reinfarction: Non-sulfonylurea: 23.1% Sulfonylurea: 19.9% p>0.05
Gustafsson *et al.* 2000, Denmark[75]	Non-diabetic: 5957 Diet: 206 Tablets: 372 Insulin: 140	Cohort	Myocardial infarction	Mortality	Non-diabetic: RR 1.00 (ref.) Diet: RR 1.05 (0.87-1.27) Tablets: RR 1.49 (1.30-1.70) Insulin: RR 1.71 (1.40-2.10)
Gustafsson *et al.* 2001, Denmark[76]	Non-diabetic: 5957 Diet: 206 Tablets: 372 Insulin:140	Cohort	Myocardial infarction	Mortality	Non-diabetic: RR 1.00 (ref.) Diet: RR 1.05 (0.87-1.27) Tablets: RR 1.49 (1.30-1.70) Insulin: RR 1.71 (1.40-2.10)
Halkin *et al.*	Sulfonylurea: 121	Cohort	Myocardial	Mortality	30-day mortality:

2001, Israel[77]	Other oral antidiabetic drugs: 17 Insulin: 28 Diet: 79		infarction	and morbidity	Diet: OR 1.00 (ref.) Sulfonylurea: OR 1.4 (0.5-4.6) Other oral antidiabetic drugs: OR 3.7 (0.7-17.7) Insulin: OR 4.5 (1.17-18.3) 1-year mortality: Diet: OR 1.00 (ref.) Sulfonylurea: OR 1.8 (0.7-5.0) Other oral antidiabetic drugs: OR 2.4 (0.5-10.5) Insulin: OR 5.2 (1.16-17.7) 1-month composite endpoint (mortality, cardiogenic shock, reinfarction, stroke): Diet: OR 1.00 (ref.) Sulfonylurea: OR 1.39 (0.6-5.0) Other oral antidiabetic drugs: OR 2.94 (0.7-11.6) Insulin: OR 3.17 (0.96-10.4)
Klamann *et al.* 2000, Germany[78]	Non-diabetic: 357 Glibenclamide: 76 Non-sulfonylurea: 89	Cohort	Myocardial infarction	Mortality	Difference in non-diabetic Glibenclamide: 12.4% (1.8-23.0) Non-sulfonylurea: 12.7% (1.4-24.1) p=0.97
Alserius *et al.* 2006, Sweden[79]	No diabetes: 5,871 Insulin: 246 Oral antidiabetic drugs: 393 Diet: 161	Cohort	Primary isolated coronary artery bypass grafting	Mortality	30-days mortality: Non-diabetic: OR 1.00 (ref.) Insulin: OR 4.6 (2.5-8.4) Oral antidiabetic drugs: OR 2.0 (1.0-3.8) Diet: OR 1.3 (0.4-4.2) 10-year mortality:

					Non-diabetic: RR 1.00 (ref.) Insulin: RR 2.1 (1.6-2.6) Oral antidiabetic drugs: RR 1.6 (1.3-1.9) Diet: RR 1.1 (0.8-1.6)
Meier *et al.* 2003, Germany[80]	Glibenclamide: 77 Non-sulfonylurea: 75	Cohort	Myocardial infarction	Mortality	p=0.53
Kao *et al.* 2004, USA[81]	Non-insulin-sensitizing therapy (sulfonylureas and/or insulin): 1,110 Metformin (alone or in combination): 887	Cohort	Percutaneous coronary interventions	Mortality and morbidity	Mortality: Non-insulin-sensitizing therapy: OR 1.00 (ref.) Metformin: OR 0.39 (0.19-0.77) Myocardial infarction: Non-insulin-sensitizing therapy: OR 1.00 (ref.) Metformin: OR 0.31 (0.15-0.66)
Johnsen *et al.* 2006, Denmark[53]	Non-diabetic: 66,839 Glimepiride: 35 Gliclazide: 21 Glibenclamide: 206 Glipizide: 72 Tolbutamide: 27 Other oral antidiabetic drugs: 31 Insulin: 235 Any combination: 51 No pharmacotherapy: 189	Cohort study	First-time myocardial infarction	Mortality	Non-diabetic patients: OR 1.00 (ref.) Glimepiride: OR 1.65 (0.78-3.47) Gliclazide: OR 0.30 (0.07-1.32) Glibenclamide: OR 1.32 (0.96-1.80) Glipizide: OR 1.30 (0.79-2.15) Tolbutamide: OR 1.20 (0.53-2.72) Other oral antidiabetic drugs: OR 0.69 (0.27-1.76) Insulin: OR 1.27 (0.92-1.74) Any combination: OR 1.34 (0.67-2.68) No pharmacotherapy: OR 1.04 (0.73-1.49)
Aronow *et al.* 2001, USA[82]	Sulfonylurea: 278 Insulin: 272 Metformin: 9	Cohort	Myocardial infarction	Coronary event	Non-sulfonylurea: RR 1.00 (ref.) Sulfonylurea: RR 1.35 (1.13-1.63) Sulfonylureas vs. insulin: p=0.0003

	Diet: 77				Sulfonylureas vs. diet: p=0.022
Inzucchi *et al.* 2005, USA[83]	Glitazones: 819 Metformin: 1,273 Glitazones+metformin: 139 No insulin sensitizer (sulfonylurea, non-sulfonylurea insulin secretagogues, α-glucosidase inhibitors, or insulin): 6,641	Cohort	Myocardial infarction	Mortality and morbidity	<u>Mortality</u>: No insulin sensitizer: HR 1.00 (ref.) Metformin: HR 0.92 (0.81-1.06) Glitazones: HR 0.92 (0.80-1.05) Glitazones+metformin: HR 0.52 (0.34-0.82) <u>Reinfarction</u>: No insulin sensitizer: HR 1.00 (ref.) Metformin: HR 1.02 (0.86-1.20) Glitazones: HR 0.92 (0.77-1.10) Glitazones+metformin: HR 0.88 (0.56-1.37) <u>Heart failure readmission</u>: No insulin sensitizer: HR 1.00 (ref.) Metformin: HR 1.06 (0.95-1.18) Glitazones: HR 1.17 (1.05-1.30) Glitazones+metformin: HR 1.24 (0.94-1.63)
McGuire *et al.* 2004, USA[84]	Insulin providing (insulin, sulfonylurea, alone or in combination): 1,473 Insulin-sensitizing (glitazones, metformin, alone or in combination): 100 Diet: 372 Sulfonylurea: 1,018 Insulin: 1,200	Cohort	Acute coronary syndrome	Mortality and morbidity	Insulin-sensitizing: OR 1.00 (ref.) Insulin providing: OR 2.1 (1.2-3.7), Diet: OR 1.00 (ref.) Insulin: OR 1.8 (1.3-2.4) Sulfonylurea: OR 1.1 (0.8-1.5) Metformin: OR 0.8 (0.5-1.2) Glitazones: OR 0.7 (0.3-1.8)

	Metformin: 454 Glitazones: 58				
Murcia *et al.* 2004, USA[85]	Insulin: 168 Non-insulin: 328	Subgroup analysis in RCT	Myocardial infarction with left ventricular dysfunction	Mortality and morbidity	Mortality: Non-insulin: HR 1.00 (ref.) Insulin: HR 1.66 (1.20-2.31) Cardiovascular mortality/morbidity: Non-insulin: HR 1.00 (ref.) Insulin: HR 1.38 (1.06-1.80)
Erdmann *et al.* 2007, Europe[86]	Pioglitazone: 1,230 Placebo: 1,215	Sub-analysis in RCT among patients with myocardial infarction	Myocardial infarction	Mortality and morbidity	Fatal/nonfatal myocardial infarction: Placebo: RR 1.00 (ref.) Pioglitazone: RR 0.72 (0.52-0.99) Nonfatal myocardial infarction, coronary revascularization, acute coronary syndrome or cardiac death: Placebo: RR 1.00 (ref.) Pioglitazone: RR 0.85 (0.69-1.03)

HR = hazard ratio, OR = odds ratio, RCT = randomized controlled trial, ref. = reference, RR = relative risk

Several studies have examined the clinical outcome after myocardial infarction among patients receiving antidiabetic treatment.

Since the UGDP trial, a number of studies have reported an adverse clinical outcome among users of sulfonylurea following myocardial infarction.
Among 832 patients with myocardial infarction, patients treated with oral antidiabetic agents (tolbutamide, glibenclamide, or metformin) had higher mortality rates than insulin-treated patients with type 2 diabetes mellitus.[57] Others have shown that treatment with oral antidiabetic agents (sulfonylurea or metformin) and insulin was associated with increased mortality following myocardial infarction compared with diet therapy,[58,59,75,76] and early deaths were more common in the oral antidiabetic agent group compared with the insulin group.[58] In older patients with diabetes mellitus and prior myocardial infarction, treatment with sulfonylurea was associated with increased risk of a new coronary event (nonfatal or fatal myocardial infarction or sudden coronary death) compared with insulin and diet.[82]

Among patients with diabetes mellitus enrolled in the Sibrafiban versus aspirin to Yield Maximum Protection from ischemic Heart events post-acute cOroNary sYndromes (SYMPHONY) and 2nd SYMPHONY trials, users of insulin-providing therapy (sulfonylureas and/or insulin) had increased risk of death/myocardial infarction/severe recurrent ischemia compared with users of insulin-sensitizing therapy (metformin and/or glitazones) following acute coronary syndrome.[84]

Also, among patients undergoing coronary interventions, the association of sulfonylurea use and clinical outcome has been examined. Here, the use of sulfonylureas increased mortality among patients with diabetes mellitus and myocardial infarction undergoing acute revascularization therapy through coronary angioplasty.[74] In patients undergoing coronary artery bypass graft (CABG), type 2 diabetes mellitus requiring oral antidiabetic agents or insulin treatment at the time of surgery was an independent risk factor for death and myocardial infarction.[79] Patients with diabetes mellitus undergoing percutaneous coronary intervention (PCI) treated with sulfonylureas and/or insulin had markedly worse outcomes (increased rates of myocardial infarction and death) compared with patients treated with metformin.[81]

In the multicenter Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, the patients were randomized to receive either insulin or conventional therapy in the acute phase following admission with myocardial infarction. Patients in the insulin group had a lower mortality compared with the control group,[62-64] but there was no difference in the risk of reinfarction.[62,63] The effect of insulin was particularly strong among patients with a low cardiovascular risk profile not already receiving insulin at the time of hospitalization.[62,64] However, this effect could be the result of an improvement in blood glucose during the critical period following myocardial infarction and not a direct beneficial effect of insulin *per se*. The DIGAMI study did not distinguish between acute insulin infusion and continuous insulin-based metabolic control, so the DIGAMI 2 trial was planned to further explore the possible benefits of insulin treatment in patients with diabetes mellitus and myocardial infarction. However, the DIGAMI 2 trial results did not support the hypothesis that acutely introduced long-term insulin treatment improves survival in type 2 diabetic patients following myocardial infarction when compared with a conventional blood glucose management of similar intensity.[65] The DIGAMI 2 trial did, however, find that patients with type 2 diabetes mellitus should have their glucose levels closely monitored and regulated after myocardial infarction and that the metabolic treatment used to achieve this regulation did not make a difference. In a post hoc analysis of the DIGAMI-2 trial, sulfonylureas, metformin, or insulin did not influence mortality.[66] However, the risk of nonfatal myocardial infarction and stroke increased significantly with insulin treatment while metformin was protective.[66]

In a subanalysis of patients with diabetes mellitus from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial, insulin users had a higher risk of being admitted with stroke, and they also had higher 30-day and 1-year mortalities compared with non-insulin-users.[67] Similarly, in a subgroup analysis in the Survival And Ventricular Enlargement (SAVE) trial in patients with diabetes mellitus and myocardial infarction with left ventricular dysfunction, patients treated with insulin had a higher risk of subsequent mortality and cardiovascular events than patients not treated with insulin.[85]

On the other hand, many studies have found no differences among antidiabetic treatments. In a population of men who survived a first-time myocardial infarction, there were no differences in mortality rates among patients treated with diet, sulfonylurea/metformin, or insulin.[60] In addition,

use of sulfonylureas at the time of admission with myocardial infarction was not associated with increased mortality compared with insulin.[61]

Further, a large study of elderly patients with myocardial infarction did found no association between sulfonylurea therapy (glibenclamide, glipizide, chlorpropamide, tolazamide, tolbutamide, and other sulfonylurea agents) and adverse outcomes.[68] Elderly patients with type 2 diabetes mellitus hospitalized with myocardial infarction treated with either diet, oral antidiabetic agents (sulfonylurea or metformin), or insulin had similar 30-day mortality rates, but patients treated with insulin had higher 1-year mortality than patients treated with diet or oral antidiabetic agents.[70] Also, similar survival (short- and long-term) after myocardial infarction was found among patients treated with glibenclamide, gliclazide, insulin, metformin, and diet.[71]

In a German follow-up study, all patients admitted with acute myocardial infarction were evaluated retrospectively and divided into four groups; non-diabetic, patients with type 2 diabetes mellitus diagnosed on admission, patients with type 2 diabetes mellitus treated with glibenclamide, and patients with type 2 diabetes mellitus not treated with sulfonylurea. No higher in-hospital mortality was demonstrated in type 2 diabetic patients receiving a sulfonylurea drug (glibenclamide) when compared with type 2 diabetic patients not taking sulfonylureas,[78] nor were there any differences in long-term survival.[80]

Sulfonylurea use prior to admission for myocardial infarction was not associated with increased rates of either mortality or cardiovascular adverse events when compared with alternative antidiabetic therapies (diet, other oral drugs, or insulin).[77] Insulin was, however, associated with increased mortality, cardiogenic shock, reinfarction, and stroke compared with diet.[77]

There were no clear mortality benefits or risks from the prescription of metformin or glitazones (insulin sensitizers) to type 2 diabetic patients with myocardial infarction over the first year following hospital discharge compared with patients given other antihyperglycaemic agents;[83] however, prescriptions of glitazones were associated with a mildly increased risk of readmission with heart failure.[83]

Patients with diabetes mellitus on sulfonylureas at the time of admission with myocardial infarction have also been observed to have a lower in-hospital mortality rate compared with patients with diabetes mellitus not taking theses agents.[69]

Metformin (as monotherapy and in combination with sulfonylurea) has been associated with increased long-term mortality compared with patients treated with diet, whereas the use of sulfonylurea (glibenclamide, chlorpropamide, or tolbutamide) was not.[72] However, monotherapy with either glibenclamide or metformin yielded a similar outcome and was associated with a modest increase in mortality compared with diet treatment, but mortality was markedly increased when a combined glibenclamide/metformin treatment was used.[73]

In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial, a large European multicenter prospective study in male and female patients ages 35-75 years who had type 2 diabetes mellitus and a history of macrovascular disease, pioglitazone significantly reduced the risk of recurrent fatal and nonfatal myocardial infarction in a subgroup analysis of patients with type 2 diabetes mellitus and previous myocardial infarction compared with placebo.[86]

Recently, we found some indication of variation in 30-day mortality rates after myocardial infarction among users of different antidiabetic treatments.[53] In particular, gliclazide appeared to be associated with reduced mortality (9.5%).[53]

Comparison of the different studies in Table 2 is also complicated because they compare different antidiabetic treatments, use different inclusion criteria (myocardial infarction,[57-59,61-71,75-78,80,82,83,86] first-time myocardial infarction,[53,60] myocardial infarction with left ventricular dysfunction,[85] myocardial infarction and/or stable anginal syndrome,[72,73] acute coronary syndrome,[84] or coronary intervention procedures[74,79,81]), different lengths of follow-up (short-term[53,57-59,62,67-71,74,77-79,84] vs. long-term[60-64,66,67,70-73,75-77,79-83,85,86]), and different exposure times (at admission[53,57-59,61,67-71,74-79] or at discharge[60,66,71,83]), and adjust for different sets of covariates. Some of the studies had relatively small sample sizes,[53,57-60,77,78,80,82] which gave rise to statistically imprecise risk estimates and complicated the interpretation.

Because antidiabetic treatment changes over time and as the disease progresses, it is important to consider the severity of diabetes mellitus when comparing different antidiabetic treatments, but several of the existing studies did not include these data.[53,57,58,60,61,67-78,80-82,84] The lack of other important confounding factors, including other diseases[57-61,82,84] and the use of cardiovascular drugs,[57-61,68,74-76,79,82,84] also makes it difficult to interpret the results.

Finally, several studies did not distinguish between antidiabetic treatments (combined biguanides and sulfonylureas,[57-60,70,75,76,79] and combined sulfonylureas and insulin[81,83,84]) and certainly not among different sulfonylureas,[57-61,66,68,69,72,74-77,83,84] leading to previously noted possibility that the effects of one treatment may be under- or overestimated by the other.

1.3.4 Antidiabetic treatment and outcome after stroke

PubMed was searched to identify articles on the association between antidiabetic treatments and outcome after stroke, using the following search strategy:
("Stroke"[Mesh] AND ("Diabetes Mellitus, Type 2/diet therapy"[Mesh] OR "Diabetes Mellitus, Type 2/drug therapy"[Mesh] OR "Diabetes Mellitus, Type 2/therapy"[Mesh])) AND "Prognosis"[Mesh]
The search was limited to include only English- and Danish-language studies in humans. Additional studies were found by searching the reference list from the identified publications.
Only a few studies have examined the association between antidiabetic treatments and clinical outcome after stroke, and the relevant studies are shown in Table 3.

A German study found no adverse in-hospital outcome of diabetic stroke patients who used sulfonylureas (glibenclamide, glimepiride, and/or glibornuride) before stroke compared with patients treated with diet, insulin, and/or other oral antidiabetic drugs, and in-hospital mortality rate was not increased in patients who used sulfonylureas. However, there was a non-significant trend toward increased neurological improvement in the sulfonylureas group.[87]

Another German study found that treatment with sulfonylureas (glibenclamide, glimepiride, or glibornuride) at admission and maintained during the acute phase of cerebral infarction was associated with a beneficial effect on neurological and functional outcomes at the time of discharge compared with treatment with diet, insulin, and/or other oral antidiabetic drugs, preferentially in

patients with non-lacunar strokes.[88] Because the effect was independent of glucose levels,[88] the beneficial effect of sulfonylureas appeared not to be limited to the metabolic control of type 2 diabetes mellitus.

Finally, in the PROactive study, pioglitazone significantly reduced the risk of recurrent fatal and nonfatal stroke in a subgroup analysis of 984 patients with type 2 diabetes mellitus and prior stroke.[89]

Data regarding outcome in stroke patients using various types of antidiabetic treatments are sparse, and it thus remains unclear whether antidiabetic treatments have different effect on the prognosis after stroke. Pioglitazone and sulfonylureas may have beneficial effects on the prognosis after stroke in patients with type 2 diabetes mellitus, but the available studies had some limitations, including small sample sizes[87,88] and failure to adjust for a range of important prognostic factors such as severity and duration of diabetes[87,88] and concomitant treatments.[88]

Table 3. Studies on antidiabetic treatment and clinical outcome after stroke.

Author, year. country		Study design	Inclusion criteria	Outcome	Results
Wilcox *et al.* 2007, UK[89]	Pioglitazone:.486 Placebo: 498	RCT	Stroke	Cardiovascular events	All-cause mortality, nonfatal myocardial infarction, nonfatal stroke, acute coronary syndrome, cardiac intervention (including CABG or PCI), leg revascularization, or major leg amputation: Placebo: HR 1.00 (ref.) Pioglitazone: HR 0.78 (0.60-1.02) Fatal or nonfatal stroke: Placebo: HR 1.00 (ref.) Pioglitazone: HR 0.53 (0.34-0.85) Cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction: Placebo: HR 1.00 (ref.) Pioglitazone: HR 0.72 (0.53-1.00)
Weih *et al.* 2001, Germany[87]	Sulfonylurea: 60 Non-sulfonylurea: 86	Cohort	Stroke (excluding haemorrhagic stroke, subarachnoid haemorhage, transient ischemic attack, and cerebral sinus thrombosis)	Mortality, stroke severity, and in-hospital outcome	Mortality: Non-sulfonylurea: OR 1.00 (ref.) Sulfonylurea: OR 1.2 (0.4-3.5) Deteriorating stroke: Non-sulfonylurea: OR 1.00 (ref.) Sulfonylurea: OR 0.6 (0.2-21.2) Severe stroke: Non-sulfonylurea: OR 1.00 (ref.) Sulfonylurea: OR 0.9 (0.4-2.1)

Kunte *et al* 2007, Germany[88]	Sulfonylurea: 33 Non-sulfonylurea: 28	Cohort	Acute ischemic stroke	National Institute of Health Stroke Scale (NIHSS), modified Rankin scale (mRS) score ≤2	Neurological outcome (NIHSS improvement ≥4 or NIHSS=0): Sulfonylurea: 36.4% Non-sulfonylurea: 7.1% p=0.007 Functional outcome (reached mRS≤2 at the time of discharge): Sulfonylurea: 81.8% Non-sulfonylurea: 57.1% p=0.035

HR = hazard ratio, OR = odds ratio, RCT = randomized controlled trial, ref. = reference

2. AIMS OF THE THESIS

- To examine whether the risk of myocardial infarction differ according to type of antidiabetic treatment in patients with type 2 diabetes mellitus (*Study I*)

- To examine whether the clinical outcome following hospitalization with myocardial infarction differ according to type of antidiabetic treatment in patients with type 2 diabetes mellitus (*Studies II+III*)

- To examine whether the clinical outcome following hospitalization with ischemic stroke differ according to type of antidiabetic treatment in patients with type 2 diabetes mellitus (*Study IV*)

3. SUBJECTS AND METHODS

3.1 Setting

All studies were conducted within the entire Danish population (approximately 5.3 million) and were based on population-based Danish medical and administrative registries. The Danish National Health Service provides tax-supported health care for all inhabitants, guaranteeing free access to general practitioners and hospitals and refunding a variable proportion of prescription medication costs.

3.2 Data sources

3.2.1 The Danish Civil Registration System

The Danish Civil Registration System has kept electronic records on gender, date of birth, change of address, date of emigration, and changes in vital status since 1968.[90,91] The records carry a unique 10-digit civil registration number, assigned to every Danish citizen and used in all Danish registries, enabling unambiguous linkage among them.

3.2.2 The Danish National Patient Registry

This registry, established in 1977, holds data on all hospitalizations from all Danish non-psychiatric hospitals, including dates of admission and discharge, surgical procedure(s) performed, and up to 20 discharge diagnoses assigned by the treating physician and coded according to the International Classification of Diseases (ICD) (8th revision (ICD-8) until the end of 1993, and 10th revision (ICD-10) thereafter).[92] Visits to emergency departments and outpatient clinics have also been recorded since 1995.

3.2.3 The Register of Medicinal Product Statistics

This registry contains data from 1995 and onwards on all prescription drugs dispensed at all Danish pharmacies, including patient civil registration number, type of drug according to the Anatomical Therapeutic Chemical (ATC) classification system, and date of dispensing the drug.

3.2.4 The Integrated Database for Labour Market Research (IDA)

The IDA database was established in 1980 and is administered by Statistics Denmark.[93] It consists of more than 250 variables characterizing the Danish population, the population's attachment to the labour market, and the labour market. All Danish citizens are characterized by data on their family and household, education, employment, and income. The data are supplied by tax authorities, educational institutions, and employment services. The IDA database is updated annually.

3.2.5 The National Health Insurance Service Registry

This registry contains data on services in the primary healthcare (general practitioners, medical specialists, doctors on emergency duty, opticians, dentists, private laboratories, physiotherapists, occupational therapists, chiropodists, and psychologists) since 1990. The individual provider is responsible for registering any given health care service. Diabetes-related services include blood glucose measurements and diabetic foot care performed by a chiropodist. The registry does not contain information on the results of the tests.

3.2.6 The Danish National Indicator Project (DNIP)

The DNIP[94] was established in 2000 as a nationwide quality-improvement project. The project targets documentation, monitoring, and improvement of the quality of care for patients with specific diseases, including stroke. Data on quality of care and patient characteristics are collected prospectively upon hospital admission by the staff treating the patients, using a standardized registration form with strict data specifications. Participation in DNIP is mandatory for all hospitals and relevant clinical departments in Denmark treating patients with stroke.

Patients 18 years of age or older are eligible for inclusion in the DNIP stroke database if they are hospitalized with stroke according to the WHO criteria, *i.e*., rapidly developing symptoms and signs of focal or global neurological dysfunction of presumed vascular aetiology lasting more than 24 hours or leading to death.[95] A national expert panel has identified seven quality-of-care criteria covering the acute phase of stroke.[94] A time frame is defined for each criterion to capture the timeliness of the interventions. The criteria include early admission to a specialized stroke unit, early administration of antiplatelet or anticoagulant therapy, early examination with CT/MRI scan, and early assessment by a physiotherapist and occupational therapist and of nutritional risk. Patients were classified as eligible or non-eligible for the specific processes of care depending on whether

the stroke team or physician treating the patients identified contraindications, such as severe dementia in a patient with ischemic stroke and atrial fibrillation precluding oral anticoagulant therapy, or rapid spontaneous recovery of motor symptoms, making early assessment by a physiotherapist and occupational therapist irrelevant. Thus, it was left to the staff to decide whether or not contraindications to the specific criteria were present.

Data on patient characteristics include age, sex, marital status (living with partner, family, or friend, living alone), Scandinavian Stroke Scale score, history of previous stroke and myocardial infarction, previous and/or current atrial fibrillation, hypertension, diabetes mellitus, intermittent claudication, smoking habits (never, daily, occasionally, former (quit more than ½ year prior to admission)), alcohol intake (≤14/21 or >14/21 drinks per week for women and men, respectively), and body mass index (BMI) (weight in kg divided by the square of the height in meters).

3.2.7 The Laboratory Information Systems (LABKA)

All tests analyzed in hospital laboratories in Aarhus and North Jutland counties are registered in the LABKA system and thus contain information on all specimens submitted for analysis by hospitals and practitioners. The databases were initiated in 1992 in North Jutland and in 1990 in Aarhus, but data are first considered complete from 1997 in North Jutland County and 1996 in Aarhus County. Data include the patient's civil registration number, the test name, the test's International Union for Pure and Applied Chemistry code and/or a local analysis number, the result, the measuring unit, the dates of ordering and carrying out the analysis, and a code for the hospital department or the general practitioner who ordered the test.

3.3 Study designs

3.3.1 Case-control design (Study I)

Study I is a case-control study aimed at comparing the risk of hospitalization with myocardial infarction among users of different antidiabetic treatments. The source population consisted of all patients with type 2 diabetes mellitus in Denmark. Cases (*i.e.*, patients with type 2 diabetes mellitus and a first-time hospitalization with myocardial infarction between 1996 and 2004) were then identified. On the date of each case's first hospitalization with myocardial infarction, we randomly selected 10 non-myocardial infarction controls from the total population of patients with type 2 diabetes mellitus through the Danish Civil Registration System using risk set sampling,[96] *i.e.*, the

controls had to be alive and at risk of myocardial infarction at the time the corresponding case was diagnosed. The controls were matched for age and gender.

3.3.2 Cohort design (Studies II, III, and IV)

Studies II, III, and IV were all cohort studies examining the clinical outcome among users of antidiabetic treatments with a first-time myocardial infarction (studies II, and III) or ischemic stroke (study IV). In studies II and III, we identified all patients with a first-time myocardial infarction and type 2 diabetes mellitus between 1996 and 2004; in study IV, we identified all patients with an ischemic stroke and type 2 diabetes mellitus between 2003 and 2006.

3.4 Study population, exposure, outcomes, and confounding factors

3.4.1. Study population

In all studies, we started by identifying all patients with diabetes mellitus (in studies II, and III among patients with myocardial infarction, and in study IV among patients with ischemic stroke). In studies II, III, and IV, we used the Danish National Patient Registry and the Registry of Medicinal Product Statistics to identify patients with diabetes mellitus because this has proven to be of high quality and almost complete.[97] We found all hospital discharge diagnoses of type 1 and type 2 diabetes mellitus (ICD-8 codes 249, 250, ICD-10 codes E10, E11, E14, G63.2, H36.0, and N08.3), and because antidiabetic drugs are available only by prescription in Denmark, we traced all prescriptions for antidiabetic drugs (ATC-codes A10A and A10B) redeemed prior to admission for myocardial infarction (studies II and III) or prior to admission for ischemic stroke (study IV).

In study I, we further extended the definition of diabetes mellitus to include data from the National Health Service Registry to obtain a more valid estimate of the entire population with diabetes mellitus in Denmark.[98,99] We thus identified patients with diabetes mellitus either from the Danish National Patient Registry, the Registry of Medicinal Product Statistics, or the National Health Service Registry (at least one visit to a chiropodist, at least five blood glucose measurements within one year, and/or minimum two blood glucose measurements per year during five subsequent years).

We were interested only in patients with type 2 diabetes mellitus, and the patients were thus classified according to the type of diabetes mellitus. Patients with type 1 diabetes mellitus were those who were younger than 30 years by the time of the first prescription or diagnosis (or diabetes

defining service in the primary health care only in study I), and who filled prescription(s) for insulin but not for an oral antidiabetic drug. Patients with type 1 diabetes mellitus under this definition were excluded, and the remaining patients with type 2 diabetes mellitus therefore constituted the study population.

3.4.2. Exposure

In all studies the exposure was antidiabetic treatment among patients with type 2 diabetes mellitus, and patients with type 2 diabetes mellitus were thus categorized according to type of antidiabetic treatment. The patients using only one type of antidiabetic drugs in the 90 days prior to hospitalization (or index date) were categorized according to the antidiabetic drug class: sulfonylureas, metformin, other oral antidiabetic drugs (glitazones, acarbose, and repaglinide), or insulin. Patients who used more than one type of antidiabetic drug during the 90 days prior to hospitalization (or index date) were categorized as combined users. Patients not using any antidiabetic drugs during the 90 days prior to hospitalization (or index date) were categorized as patients without antidiabetic pharmacotherapy. Patients using glitazones, acarbose, and/or repaglinide were excluded from the analyses in all four studies because their limited numbers made it impossible to draw any conclusions about the clinical outcomes in the context of the study aims.

Prescriptions for antidiabetic drugs in Denmark are usually issued for three months but may be issued for up to six months. We therefore also categorized patients according to drug use within 180 days prior to hospitalization (or index date).

3.4.3. Outcome

Myocardial infarction:

In study I, the outcome was hospitalization with myocardial infarction. Data on myocardial infarction were obtained from the Danish National Patient Registry. We first constructed a hospital discharge history for all Danish patients with diabetes mellitus based on data going back to 1977, and then identified all patients who were registered with a first-time hospitalization with myocardial infarction (ICD-10 codes I21.0-I21.9) during the study period.

Mortality:

The main outcome in studies II, III, and IV was death from any cause within 30 days and at one year following the admission date. In this thesis, mortality is used as a synonym for "risk of death", "cumulative incidence of death", or "cumulative mortality". The mortality was ascertained from the Civil Registration System.

Readmissions:

Secondary outcomes in studies II, III, and IV were readmissions with myocardial infarction or heart failure (studies II and III) and myocardial infarction and ischemic stroke (study IV) within one year after hospitalization. Readmission with myocardial infarction (IDC-10 codes I21, I22) or heart failure (ICD-10-codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.6, I42.7, I42.8, I42.9, I50.0, I50.1, or I50.9) was ascertained from the Danish National Patient Registry. In studies II and III, readmission with myocardial infarction within 28 days of the original myocardial event was not considered a new event.[100] Readmission with recurrent ischemic stroke (ICD-10 codes I63, I64) was ascertained from the DNIP stroke database.

3.4.4. Confounding factors

A number of factors may have affected the choice of antidiabetic treatment. We therefore adjusted for a wide range of potential confounding factors in all studies. Data on the potential confounding factors were obtained through the different Danish registries.

Comorbidity:

To adjust for confounding by comorbidity in studies II, III, and IV, we computed for each patient the comorbidity index score developed by Charlson *et al*[101] based on discharge diagnoses from the Danish National Patient Registry. The index covers 19 major disease categories, including diabetes mellitus, myocardial infarction, heart failure, cerebrovascular diseases and cancer, weighted according to their effect on patient survival, and is widely used to control for confounding in epidemiological studies. Recently, the positive predictive values of the included disease diagnoses, as ascertained in the Danish National Patient Registry, was found to be very high.[102]

We calculated the score based on all previous discharge diagnoses recorded before the date of admission but excluded discharge diagnoses of diabetes mellitus and myocardial infarction (or

ischemic stroke in study IV). We defined three comorbidity levels on the basis of the Charlson index scores: 0 ("low"), corresponding to patients with no recorded underlying diseases according to the Charlson index; 1-2 ("medium"); and ≥3 ("high").

We also obtained information on conditions/procedures not included in the Charlson comorbidity index: previous diagnoses of hypertension, coronary revascularization procedures (PCI and CABG), alcoholism-related diseases, and diabetes complications (*i.e.*, retinopathy, nephropathy, and neuropathy). These covariates were also used in study I together with previous diagnoses of chronic bronchitis and emphysema, liver cirrhosis, stroke, and peripheral arterial disease. Data on coronary revascularization procedures performed during or after the admission for myocardial infarction were also obtained in studies II and III.

Duration of type 2 diabetes mellitus:
We estimated the duration of type 2 diabetes mellitus as the time since the first prescription for a antidiabetic drug or the first diagnosis of diabetes mellitus, (or in addition in study I, the first diabetes mellitus defining service in the primary health care system) and categorized the duration into three groups: ≤5 years, 5-10 years, and >10 years.

Socioeconomic status:
We received information about the socioeconomic status from IDA. In studies II and III, patients were classified according to socioeconomic status (employed, pensioner, or other) in the year prior to the admission. In study I, we also included marital status (single, married or co-habiting), gross income in quartiles, and educational level (university degree, short/medium-term formal education, basic vocational education, basic school, or unspecified) in the year prior to admission. Similar covariates were used in study IV, but the information on marital status was received from the DNIP stroke database.

Comedication:
We identified all prescriptions for cardiovascular drugs (antihypertensive drugs, lipid-lowering drugs, platelet inhibitors, vitamin K antagonists, nitrates), and hormone replacement therapy (HRT) filled before the date of admission. Because the use of these drugs can change following admission,

in studies II, III, and IV, we also identified all prescriptions filled within one year after the admission.

Biochemical data:

Biochemical data reflecting the intensity of the antiglycaemic treatment and the extent of myocardial damage following admission with myocardial infarction were available from the LABKA system for tests analyzed in North Jutland and Aarhus counties, covering a population of approximately 1,150,000 (~22% of the total Danish population). Data on HbA_{1c}, blood glucose, troponin T, and creatine kinase MB (CK-MB) were retrieved. We used the latest measurement of HbA_{1c} within 180 days prior to admission and seven days after the admission, and the highest level of blood glucose, troponin T, and CK-MB on the day of admission or the following day. In studies II and III, we included all four covariates, but in study I, only HbA_{1c} was included.

Lifestyle factors:

For study IV, further information on lifestyle factors came from the DNIP stroke database. We included alcohol intake, smoking habits, and BMI.

Scandinavian Stroke Scale score:

The Scandinavian Stroke Scale score is used to assess the admission stroke severity. It is a validated and widely used neurologic stroke score in Scandinavia that evaluates the level of consciousness, eye movement, power in hand, arm, and leg, orientation, aphasia, facial paresis, and gait on a total score that ranges from 0 to 58.[103] The Scandinavian Stroke Scale score can be assessed reliably either face-to-face[104] or from routine hospital admission records.[105] We defined four levels of the score: very severe (0-14), severe (15-29), moderate (30-44), and mild (45-58).

Quality of in-hospital care:

The quality of in-hospital stroke care during the acute phase, *i.e.*, fulfilment of the quality-of-care criteria (early admission to a specialized stroke unit, early administration of antiplatelet or anticoagulant therapy, early examination with CT/MRI scan, and early assessment by a physiotherapist and occupational therapist and of nutritional risk), have been linked to post-stroke mortality.[106] We computed a variable containing the percentage of fulfilled criteria for each patient in study IV as a measure for in-hospital stroke care.

3.5 Statistical analyses

All analyses were performed using Stata (StataCorp LP, College Station, TX, USA) (version 8.2 in studies II and III, and version 10.0 in studies I and IV) and using version 9.1.3 of the SAS software (SAS Institute Inc., Cary, NC, USA). The statistical significance level was set to 0.05 in all analyses.

3.5.1 Conditional logistic regression analysis (Study I)

The association between preadmission antidiabetic treatment and the risk of myocardial infarction in study I was expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and was derived from logistic regression models. Because patients were matched for age and gender, we used conditional logistic regression. Also, because we used risk set sampling of controls, these ORs were unbiased estimates of the corresponding incidence rate ratio.[96] In the logistic regression analyses, we adjusted for a previous history of hypertension, chronic bronchitis and emphysema, alcohol-related diseases, liver cirrhosis, stroke, peripheral arterial disease, and diabetes complications (*i.e.*, retinopathy, nephropathy, and neuropathy), and for use of antihypertensive drugs, statins, other lipid-lowering drugs, high-dose aspirin, platelet inhibitors, oral anticoagulants, nitrates, or HRT, and marital status, employment status, gross income, and educational level.

Differences in risk of myocardial infarction between the different combination types and between the individual sulfonylureas were assessed by likelihood ratio tests. Patients receiving sulfonylureas were used as the reference group in the primary analyses. In the subanalysis in which we compared the risk among users of different sulfonylureas, both users of tolbutamide and metformin served as the reference group.

3.5.2 Cox proportional hazards regression analysis (Studies II, III, and IV)

In the clinical outcome studies, follow-up began on the date of admission and ended on the date of readmission (only in analyses on risk of readmissions), death, emigration, or after 30 days/1 year. We constructed Kaplan-Meier mortality curves for the antidiabetic treatments and computed the cumulative 30-day and 1-year mortality.

The associations between antidiabetic treatment and mortality and readmissions were expressed as hazard ratios (HRs) and 95% CIs as estimates of the relative risks for each outcome and were

derived from a Cox proportional hazards regression analysis. We used the Efron approximation to handle tied survival times and included all measured covariates; uses of antidiabetic drugs, cardiovascular drugs, and HRT after admission were treated as time-dependent covariates. Patients receiving sulfonylureas served as the reference group; however, for estimations of the effect of individual sulfonylureas, tolbutamide served as the reference.

We assessed the assumption of proportional hazards in the Cox regression model using log(-log(survival)) plots as well as goodness-of-fit testing on the basis of Schoenfeld residuals. Differences in clinical outcome between the different combination types were assessed by likelihood ratio tests in studies II and III. In study IV, differences in clinical outcome between different combination types and between individual sulfonylureas were assessed using the Wald test.

3.5.3 "Dose-response" analysis (Study III)

In study III, we examined the association between the number of filled prescriptions (as a measure of exposure levels) and clinical outcome. Patients with the lowest level of exposure served as the reference group. Using Wald tests, we examined whether the association between numbers of filled prescriptions and the outcome followed a linear trend.

3.5.4 Subanalyses (Studies I, II, III)

To examine the effect of the intensity of glycaemic control, we further added HbA_{1c} (studies I, II, and III) and blood glucose (studies II and III) values into the regression analysis in a subanalysis among patients from North Jutland and Aarhus counties. In study II and III, we also evaluated if the treatment groups differed in the extent of myocardial infarction by assessing troponin T and CK-MB levels using the Kruskal-Wallis test.

3.5.5 Multiple imputation (Study IV)

The prevalence of patients with missing data on some of the prognostic factors range between 4.9% and 48.0% for some of the variables considered in study IV. Because exclusion of all patients with missing data would have reduced the sample size substantially and potentially also introduced a selection bias, we used multiple imputation to estimate the missing values by creating different data

sets and combining results obtained from each of them. However, for comparison, we also performed a complete subject analysis based only on patients with a complete data set. Multiple imputation was used to impute missing values for Scandinavian Stroke Scale score, smoking habits, alcohol intake, BMI, marital status, and educational level. We generated five imputed data sets, and the HRs were then averaged across the five imputations, correcting for between- and within-imputation variation.[107-109] In addition to all measured covariates, we included the event indicator and the Nelson-Aalen estimator of the cumulative hazard to the survival time in the imputation model.[110]

4. RESULTS

The main results of the four studies are summarized below.

4.1 Study I

We identified a total of 10,616 cases with myocardial infarction and 90,697 population controls among patients with type 2 diabetes mellitus. Among cases, 7,134 (67.2%) had filled a prescription for an antidiabetic drug within 90 days prior to admission for myocardial infarction. In comparison, 53,821 (59.3%) controls had filled a prescription.

4.1.1 Antidiabetic treatments and risk of hospitalization with myocardial infarction

Table 4 shows the crude and adjusted ORs for myocardial infarction according to use of antidiabetic drugs. After adjustment for possible confounding factors, use of metformin and insulin were associated with a lower risk of myocardial infarction compared with use of sulfonylureas with adjusted ORs of 0.86 (95% CI: 0.78-0.95) and 0.92 (95% CI: 0.86-0.99), respectively. The lowest risk of myocardial infarction was found among patients not receiving any antidiabetic pharmacotherapy (adjusted OR 0.75; 95% CI: 0.71-0.79). Users of any combination of antidiabetic drugs had a risk of myocardial infarction similar to that of users of sulfonylureas (adjusted OR 0.99; 95% CI: 0.92-1.06), with no differences between the various types of combinations (p=0.11).

4.1.2 Individual sulfonylureas and risk of hospitalization with myocardial infarction

We found no differences in the risk of myocardial infarction between the individual sulfonylureas (p=0.39). Thus, compared with tolbutamide, the adjusted ORs for use of glibenclamide, glipizide, gliclazide, or glimepiride were 1.01 (95% CI: 0.90-1.14), 0.94 (95% CI: 0.82-1.08), 0.89 (95% CI:

0.74-1.07) and 1.02 (95% CI: 0.90-1.16), respectively. Table 5 shows crude and adjusted ORs for myocardial infarction according to the different sulfonylureas compared with users of metformin. All sulfonylureas carried a slightly increased risk of myocardial infarction compared with metformin, but not all reached statistical significance.

Table 4. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for hospitalization with myocardial infarction according to prescription for antidiabetic drugs filled within 90 days before hospitalization or index date compared with patients who filled prescriptions for sulfonylureas

Antidiabetic medication	Cases (N=10,616)		Controls (N=90,697)		Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Sulfonylureas	3,080	(29.0)	23,698	(26.1)	1.00 (reference)	1.00 (reference)
Metformin	599	(5.6)	5,328	(5.8)	0.86 (0.79-0.95)	0.86 (0.78-0.95)
Insulin	1,972	(18.6)	13,853	(15.3)	1.09 (1.03-1.16)	0.92 (0.86-0.99)
Any combination	1,483	(14.0)	10,942	(12.1)	1.04 (0.98-1.11)	0.99 (0.92-1.06)
No pharmacotherapy	3,482	(32.8)	36,876	(40.7)	0.72 (0.69-0.76)	0.75 (0.71-0.79)

[a] Adjusted for discharge diagnoses of hypertension, bronchitis and emphysema, alcohol-related diseases, liver cirrhosis, retinopathy, nephropathy, neuropathy, stroke and peripheral arterial disease, prescriptions for antihypertensive drugs, statins, other lipid-lowering drugs, high-dose aspirin, platelet inhibitors, oral anticoagulants, HRT, nitrates, and previous use of other types of antidiabetic drugs before the hospitalization or index date, and for duration of diabetes mellitus, marital status, education, income, and employment status.

Table 5. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for hospitalization with myocardial infarction according to prescription for different sulfonylureas filled within 90 days before hospitalization or index date compared with patients who filled prescriptions for metformin

Antidiabetic medication	Cases (N=3,679)		Controls (N=29,026)		Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Metformin	599	(5.6)	5,328	(5.8)	1.00 (reference)	1.00 (reference)
Tolbutamide	461	(15.0)	3,585	(15.1)	1.15 (1.01-1.31)	1.16 (1.02-1.33)
Glibenclamide	1,013	(32.9)	7,721	(32.6)	1.17 (1.05-1.30)	1.18 (1.05-1.32)
Glipizide	496	(16.1)	4,077	(17.2)	1.09 (0.96-1.24)	1.10 (0.96-1.25)
Gliclazide	188	(6.1)	1,635	(6.9)	1.02 (0.86-1.22)	1.04 (0.87-1.24)
Glimepiride	922	(29.9)	6,680	(28.2)	1.22 (1.09-1.36)	1.19 (1.06-1.33)

[a] Adjusted for discharge diagnoses of hypertension, bronchitis and emphysema, alcohol-related diseases, liver cirrhosis, retinopathy, nephropathy, neuropathy, stroke and peripheral arterial disease, prescriptions for antihypertensive drugs, statins, other lipid-lowering drugs, high-dose aspirin, platelet inhibitors, oral anticoagulants, HRT, nitrates, and previous use of other types of antidiabetic drugs before the hospitalization or index date, and for duration of diabetes mellitus, marital status, education, income, and employment status.

4.1.3 Subanalysis including biochemical data

Data on HbA_{1c} were available on 886 cases and 1,397 controls from North Jutland and Aarhus counties. We examined the effect of the intensity of the glycaemic control among this subset of patients, although with a much weaker statistical precision. The HbA_{1c} level had only minor effects on the risk estimates, *i.e.*, further adjustment for the parameter changed the estimates by only 2.2%-6.5%.

4.1.4 180-day exposure window

All results were virtually unchanged when estimating the ORs based on drug use within 180 days prior to myocardial infarction or index date. Thus, compared with sulfonylureas, the adjusted ORs were 0.86 (95% CI: 0.78-0.95), 0.91 (95% CI: 0.85-0.98), 1.00 (95% CI: 0.94-1.07), and 0.75 (95% CI: 0.71-0.79), respectively, for use of metformin, insulin, any combination and no antidiabetic pharmacotherapy.

4.2 Study II

We identified 8,494 patients with type 2 diabetes mellitus hospitalized with a first-time myocardial infarction during the study period. This number was lower than in study I because of the inclusion of data from the National Health Service Registry in study I. Among the patients with type 2 diabetes mellitus and myocardial infarction, a total of 2,691 were treated with sulfonylureas, 511 with metformin, 1,827 with insulin, 1,333 with any combination of antidiabetic drugs, and 2,132 received no antidiabetic pharmacotherapy at the time of admission.

4.2.1 Antidiabetic treatments and mortality after hospitalization with myocardial infarction

Figure 4 shows the cumulative mortality curves for the different treatment groups. The overall cumulative 30-day and 1-year mortality rates were 22.2% and 36.6%, respectively.

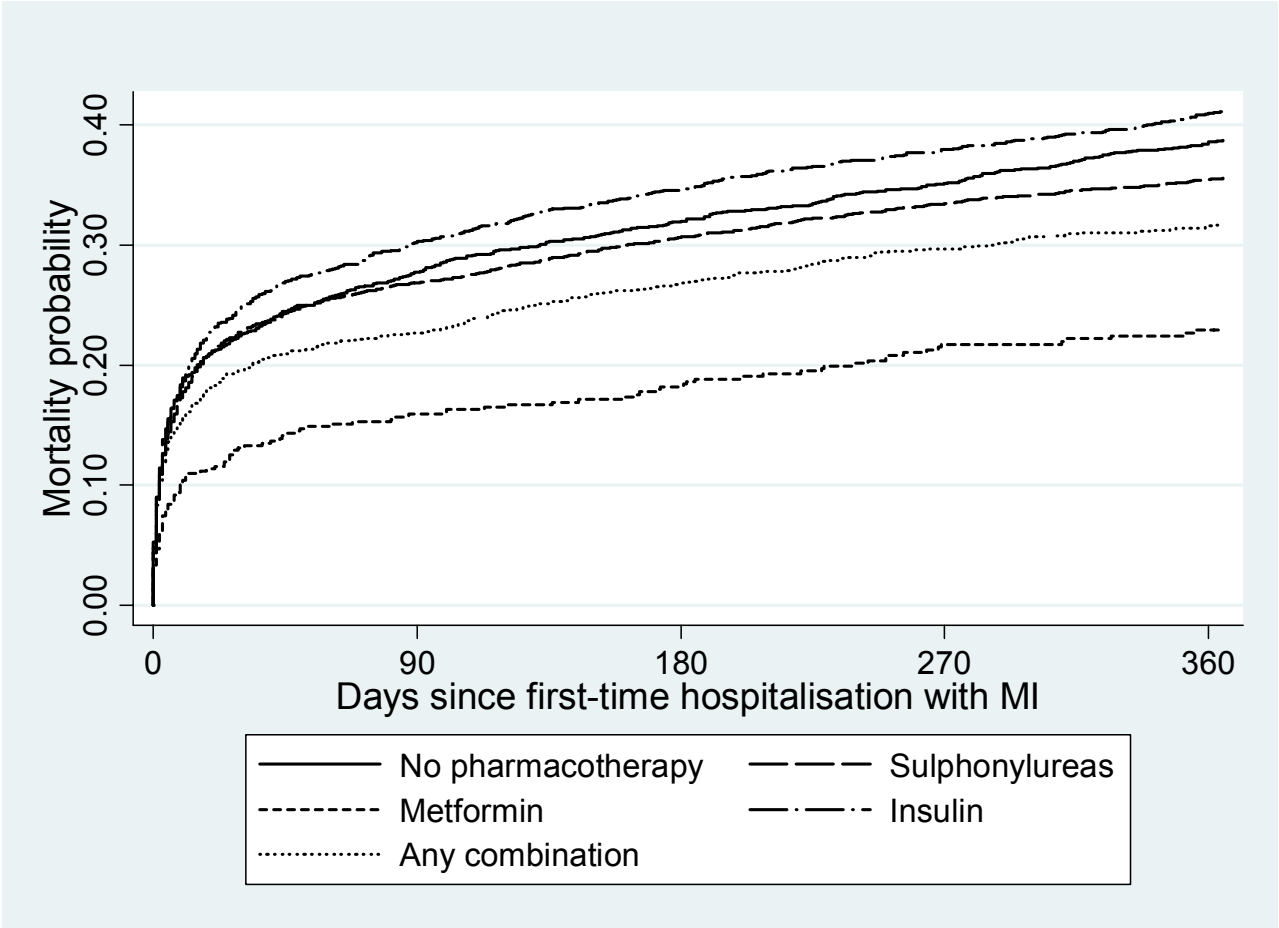

Figure 4. Kaplan-Meier curves of 1-year all-cause mortality after hospitalization with myocardial infarction (MI) according to use of antidiabetic treatments within 90 days prior to the hospitalization.

Table 6 shows the crude and adjusted HRs according to the use of antidiabetic drugs. After adjustment for differences in covariates, we found no differences between the antidiabetic treatments in monotherapy, *i.e.*, the 30-day adjusted HRs for the use of metformin and insulin were 0.85 (95% CI: 0.40-1.81) and 1.05 (95% CI: 0.63-1.76), but the use of any combination was associated with an increased risk of mortality compared with use of sulfonylureas (adjusted 30-day HR 1.43; 95% CI: 0.98-2.09). The highest risk estimate was found among users of the triple combination with sulfonylurea, metformin, and insulin (adjusted 30-day HR 1.79; 95% CI: 0.65-4.95), but we found no differences in mortality when comparing use of the different types of combinations (p=0.33). When estimating the 1-year HRs, we found similar results (Table 6).

Table 6. Crude and adjusted 30-day and 1-year hazard ratios (HRs) with 95% confidence intervals (CIs) for death after first-time hospitalization with myocardial infarction according to use of antidiabetic treatment within 90 days prior to the hospitalization

	30-day mortality				1-year mortality			
Antidiabetic treatment	Crude HR (95% CI)		Adjusted HR[a] (95% CI)		Crude HR (95% CI)		Adjusted HR[a] (95% CI)	
Sulfonylureas (SU)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
Metformin (MET)	0.55	(0.43-0.71)	0.85	(0.40-1.81)	0.58	(0.47-0.72)	0.96	(0.71-1.31)
Insulin	1.10	(0.97-1.24)	1.05	(0.63-1.76)	1.16	(1.05-1.29)	1.13	(0.91-1.40)
Any combination	0.85	(0.73-0.98)	1.43	(0.98-2.09)	0.89	(0.79-1.01)	1.43	(1.18-1.73)
SU+MET	0.86	(0.73-1.01)	1.30	(0.69-2.45)	0.89	(0.78-1.01)	1.35	(1.09-1.68)
SU+insulin	1.13	(0.79-1.61)	1.47	(0.87-2.50)	1.31	(0.98-1.75)	1.65	(1.18-2.29)
MET+insulin	0.52	(0.32-0.83)	1.03	(0.40-2.65)	0.58	(0.38-0.87)	1.06	(0.64-1.73)
SU+MET+insulin	0.87	(0.44-1.75)	1.79	(0.65-4.95)	0.84	(0.46-1.51)	1.80	(0.95-3.45)
No pharmacotherapy	0.99	(0.88-1.11)	0.79	(0.57-1.10)	1.08	(0.98-1.19)	0.85	(0.72-1.00)

[a] Adjusted for age, sex, calendar period, duration of diabetes mellitus, former use of other types of antidiabetic drugs, level of comorbidity (measured by the Charlson index), socioeconomic status, discharge diagnosis of hypertension, former and subsequent revascularization, alcoholism, retinopathy, neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, lipid-lowering agents, HRT before the date of hospitalization with myocardial infarction, and time-dependent treatment with antidiabetic drugs, cardiovascular drugs, and HRT after the date of hospitalization with myocardial infarction.

4.2.2 Antidiabetic treatments and readmissions after hospitalization with myocardial infarction

Within one year of follow-up, 8.4% and 9.6% of patients were readmitted with a new myocardial infarction and heart failure, respectively. We found no substantial differences in the risks of new myocardial infarction or heart failure between users of the different antidiabetic treatments (Table 7), nor were there any differences in risk of new myocardial infarction (p=0.75) or heart failure (p=0.28) among users of the different types of combinations.

Table 7. Crude and adjusted 1-year hazard ratios (HRs) with 95% confidence intervals (CIs) for new myocardial infarction and heart failure after first-time hospitalisation with myocardial infarction according to use of antidiabetic treatment within 90 days prior to the hospitalisation

	Myocardial infarction				Heart failure			
Antidiabetic treatment	Crude HR (95% CI)		Adjusted HR[a] (95% CI)		Crude HR (95% CI)		Adjusted HR[a] (95% CI)	
Sulfonylureas (SU)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
Metformin (MET)	0.84	(0.57-1.23)	1.21	(0.77-1.92)	0.77	(0.54-1.11)	0.81	(0.51-1.29)
Insulin	1.30	(1.05-1.60)	1.30	(0.91-1.86)	1.19	(0.98-1.45)	0.99	(0.70-1.40)
Any combination	1.11	(0.87-1.41)	1.33	(0.97-1.81)	0.97	(0.77-1.23)	0.89	(0.65-1.22)
SU+MET	1.04	(0.79-1.36)	1.24	(0.88-1.74)	0.92	(0.71-1.18)	0.82	(0.58-1.16)
SU+insulin	1.83	(1.06-3.14)	1.78	(0.98-3.22)	1.53	(0.89-2.62)	1.28	(0.71-2.32)
MET+insulin	1.06	(0.56-2.01)	1.40	(0.67-2.93)	1.19	(0.68-2.08)	0.90	(0.45-1.79)
SU+MET+insulin	1.01	(0.32-3.15)	1.32	(0.41-4.32)	0.28	(0.04-1.99)	0.27	(0.04-2.00)
No pharmacotherapy	0.96	(0.77-1.20)	0.93	(0.71-1.23)	0.95	(0.78-1.16)	0.91	(0.69-1.18)

[a] Adjusted for age, sex, calendar period, duration of diabetes mellitus, former use of other types of antidiabetic drugs, level of co-morbidity (measured by the Charlson index), socioeconomic status, discharge diagnosis of hypertension, former and subsequent revascularization, alcoholism, retinopathy, neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, lipid-lowering agents, HRT before the date of hospitalization with myocardial infarction, and time-dependent treatment with antidiabetic drugs, cardiovascular drugs, and HRT after the date of hospitalization with myocardial infarction.

4.2.3 Subanalysis including biochemical data

In the North Jutland and Aarhus counties subcohort, data on biochemical parameters were available for 1,027 patients with myocardial infarction. We examined the effect of the intensity of the glycaemic control among this subset of patients, although with a much weaker statistical precision. The HbA_{1c} and admission blood glucose levels had only minor effects on the risk estimates, *i.e.*, further adjustment for these parameters changed the estimates only 1.0-6.1%. Thus, compared to use of sulfonylureas, the adjusted HR of 30-day mortality was 1.90 (95% CI: 0.68-5.32) for use of any combination, and after further adjustment for HbA_{1c} and blood glucose, the adjusted HR of 30-day mortality was 1.83 (95% CI: 0.65-5.13). A similar pattern was found when estimating the 1-year HRs.

We found significant differences in levels of CK-MB (p=0.0001) and troponin T (p=0.0001) among users of different antidiabetic treatments. The highest levels were found among users of sulfonylureas and insulin, probably reflecting a larger infarct size in these patients.

4.2.4 180-day exposure window

All results were virtually unchanged when estimating the HRs based on drug use within 180 days prior to myocardial infarction.

4.3 Study III

We identified 72,295 patients with myocardial infarction during the study period, of which 4,005 (5.4%) had filled prescriptions for sulfonylureas within 90 days before hospitalization. We excluded 75 patients who had received prescriptions for more than one sulfonylurea drug within 90 days prior to hospitalization. Of the remaining 3,930 patients, 514 (13.1%) were treated with tolbutamide, 1,329 (33.8%) with glibenclamide, 672 (17.1%) with glipizide, 1,160 (29.5) with glimepiride, and 255 (6.5%) with gliclazide.

4.3.1 Sulfonylureas and mortality after hospitalization with myocardial infarction

Figure 5 shows the cumulative mortality curves for users of the different sulfonylureas. The overall cumulative 30-day and 1-year mortality rates were 22.0% and 35.3%, respectively.

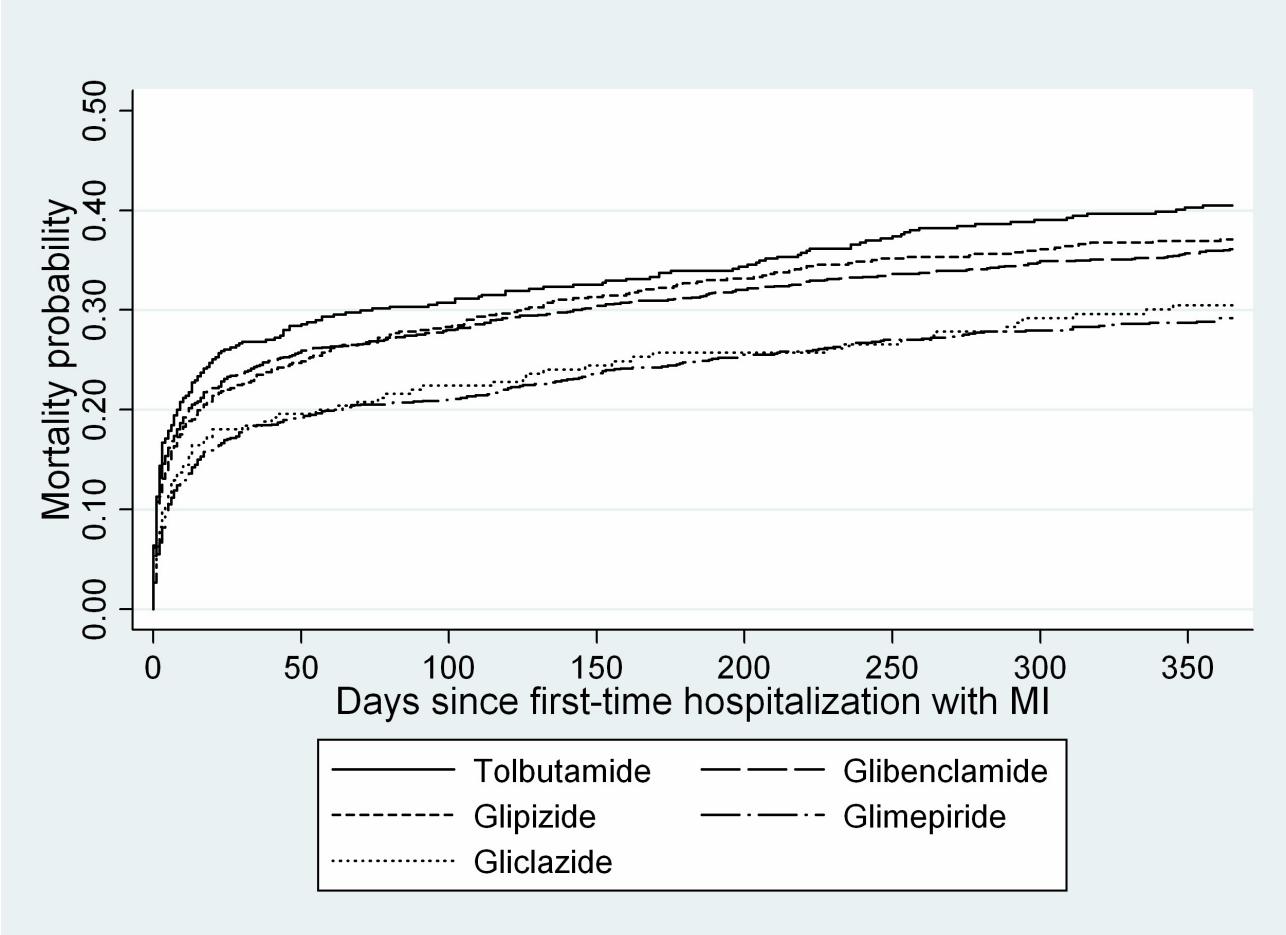

Figure 5. Kaplan-Meier curves of 1-year all-cause mortality after hospitalization with myocardial infarction (MI) according to use of different sulfonylureas within 90 days prior to the hospitalization.

Table 8 shows the 30-day and 1-year HRs among users of the different sulfonylureas compared with users of tolbutamide. After adjustment for differences in covariates, the HRs shifted towards unity, and there were no major differences between the sulfonylureas.

4.3.2 Sulfonylureas and readmissions after hospitalization with myocardial infarction

Within one year of follow-up, 285 (8.3%) of the patients were readmitted with a new myocardial infarction, and 329 (9.5%) were readmitted because of heart failure. No clear differences in the risk of new myocardial infarction or heart failure were found among the individual sulfonylureas (Table 9).

Table 8. Crude and adjusted 30-day and 1-year hazard ratios (HRs) with 95% confidence intervals (CIs) for death after first-time hospitalization with myocardial infarction according to use of sulfonylureas within 90 days prior to hospitalization

Antidiabetic treatment	30-day mortality				1-year mortality			
	Crude HR (95% CI)		Adjusted HR[a] (95% CI)		Crude HR (95% CI)		Adjusted HR[a] (95% CI)	
Tolbutamide (all)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
Glibenclamide (all)	0.88	(0.72-1.08)	0.98	(0.80-1.20)	0.87	(0.73-1.02)	0.97	(0.82-1.16)
Glipizide (all)	0.83	(0.66-1.05)	0.94	(0.74-1.19)	0.88	(0.72-1.06)	0.99	(0.82-1.20)
Glimepiride (all)	0.63	(0.50-0.78)	0.90	(0.71-1.14)	0.67	(0.56-0.81)	0.87	(0.71-1.06)
Gliclazide (all)	0.65	(0.46-0.91)	0.84	(0.60-1.18)	0.65	(0.49-0.87)	0.79	(0.59-1.05)
Tolbutamide (mono)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
Glibenclamide (mono)	0.92	(0.73-1.17)	1.03	(0.81-1.31)	0.88	(0.73-1.07)	0.99	(0.81-1.20)
Glipizide (mono)	0.99	(0.75-1.29)	1.08	(0.83-1.42)	0.98	(0.78-1.22)	1.07	(0.85-1.34)
Glimepiride (mono)	0.69	(0.53-0.88)	0.98	(0.74-1.29)	0.72	(0.59-0.90)	0.92	(0.73-1.16)
Gliclazide (mono)	0.74	(0.50-1.10)	0.97	(0.65-1.44)	0.59	(0.41-0.85)	0.70	(0.48-1.00)

[a] Adjusted for age, sex, calendar period, duration of diabetes mellitus, level of co-morbidity (measured by the Charlson index), socioeconomic status, discharge diagnosis of hypertension, former and subsequent revascularization, alcoholism, retinopathy, neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, lipid-lowering agents, HRT before the date of hospitalization for myocardial infarction, and time-dependent cardiovascular treatment and HRT after the date of hospitalization for myocardial infarction. For the analyses with sulfonylureas in combination therapy, there is also adjustment for the type of combination therapy (*i.e.*, metformin, insulin and/or other oral antidiabetic drugs).

Table 9. Crude and adjusted 1-year hazard ratios (HRs) with 95% confidence intervals (CIs) for new myocardial infarction and heart failure after first-time hospitalization with myocardial infarction according to use of sulfonylureas within 90 days prior to hospitalization

Antidiabetic treatment	Myocardial infarction				Heart failure			
	Crude HR (95% CI)		Adjusted HR[a] (95% CI)		Crude HR (95% CI)		Adjusted HR[a] (95% CI)	
Tolbutamide (all)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
Glibenclamide (all)	1.20	(0.82-1.77)	1.32	(0.89-1.95)	0.86	(0.61-1.22)	0.88	(0.62-1.25)
Glipizide (all)	1.01	(0.65-1.57)	1.07	(0.68-1.68)	0.81	(0.55-1.21)	0.87	(0.58-1.30)
Glimepiride (all)	0.95	(0.63-1.44)	1.00	(0.65-1.54)	0.93	(0.65-1.32)	0.94	(0.65-1.37)
Gliclazide (all)	1.19	(0.69-2.04)	1.26	(0.72-2.19)	1.13	(0.70-1.81)	1.12	(0.69-1.82)
Tolbutamide (mono)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
Glibenclamide (mono)	1.11	(0.72-1.70)	1.25	(0.81-1.95)	0.95	(0.64-1.43)	1.00	(0.66-1.51)
Glipizide (mono)	0.84	(0.50-1.43)	0.94	(0.55-1.61)	0.87	(0.54-1.41)	0.94	(0.58-1.53)
Glimepiride (mono)	0.89	(0.56-1.41)	0.93	(0.55-1.54)	1.06	(0.70-1.61)	1.20	(0.77-1.88)
Gliclazide (mono)	1.07	(0.55-2.05)	1.07	(0.55-2.08)	1.10	(0.61-2.00)	1.10	(0.60-2.01)

[a] Adjusted for age, sex, calendar period, duration of diabetes mellitus, former use of antidiabetic treatment, level of co-morbidity (measured by the Charlson index), socioeconomic status, discharge diagnosis of hypertension, former and subsequent revascularization, alcoholism, retinopathy, neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, lipid-lowering agents, HRT before the date of hospitalization for myocardial infarction, and time-dependent cardiovascular treatment and HRT after the date of hospitalization for myocardial infarction. For the analyses with sulfonylureas in combination therapy, there is also adjustment for the type of combination therapy (*i.e.*, metformin, insulin and/or other oral antidiabetic drugs).

4.3.3 Dose-response effect of the sulfonylureas

Except for users of gliclazide, the number of filled sulfonylurea prescriptions per patient was not associated with mortality. For users of gliclazide, a decreased mortality was observed with increasing numbers of filled prescriptions; the adjusted 30-day HRs were 0.52 (95% CI: 0.25-1.10) among patients who had filled 8-20 gliclazide prescriptions and 0.28 (95% CI: 0.12-0.68) among those with more than 20 filled gliclazide prescriptions, as compared to patients who had filled only

1-7 gliclazide prescriptions (p=0.004). The number of filled sulfonylurea prescriptions did not appear to influence the risk of developing either new myocardial infarction or heart failure.

4.3.4 Subanalysis including biochemical parameters

Data on HbA_{1c} and glucose levels were available for 456 patients in the North Jutland and Aarhus counties subcohort. Among this subset of patients, we found no substantial differences in clinical outcome between the use of different sulfonylureas, and further adjustment for HbA_{1c} and blood glucose levels yielded similar results for all sulfonylureas.

There were also no significant differences in the levels of CK-MB (p=0.98) or troponin T (p=0.98) among patients with myocardial infarction treated with different sulfonylureas, suggesting that the type of sulfonylurea did not affect infarct size.

4.3.5 180-day exposure window

Results were similar when estimating the HRs based on sulfonylurea use 180 days before myocardial infarction.

4.4 Study IV

We identified 41,398 patients hospitalized with a first-time stroke during the study period. Data for a total of 4,816 patients with type 2 diabetes mellitus and ischemic stroke were available for analysis. Of these patients, 27.1% did not receive pharmacotherapy, and 22.6% were treated with sulfonylureas, 11.7% with metformin, 18.3% with insulin, and 20.3% with a combination.

4.4.1 Antidiabetic treatment and mortality after ischemic stroke

Figure 6 shows the Kaplan-Meier mortality curves for the different treatment groups. The overall cumulative 30-day and 1-year mortality rates were 11.2% and 25.7%, respectively.

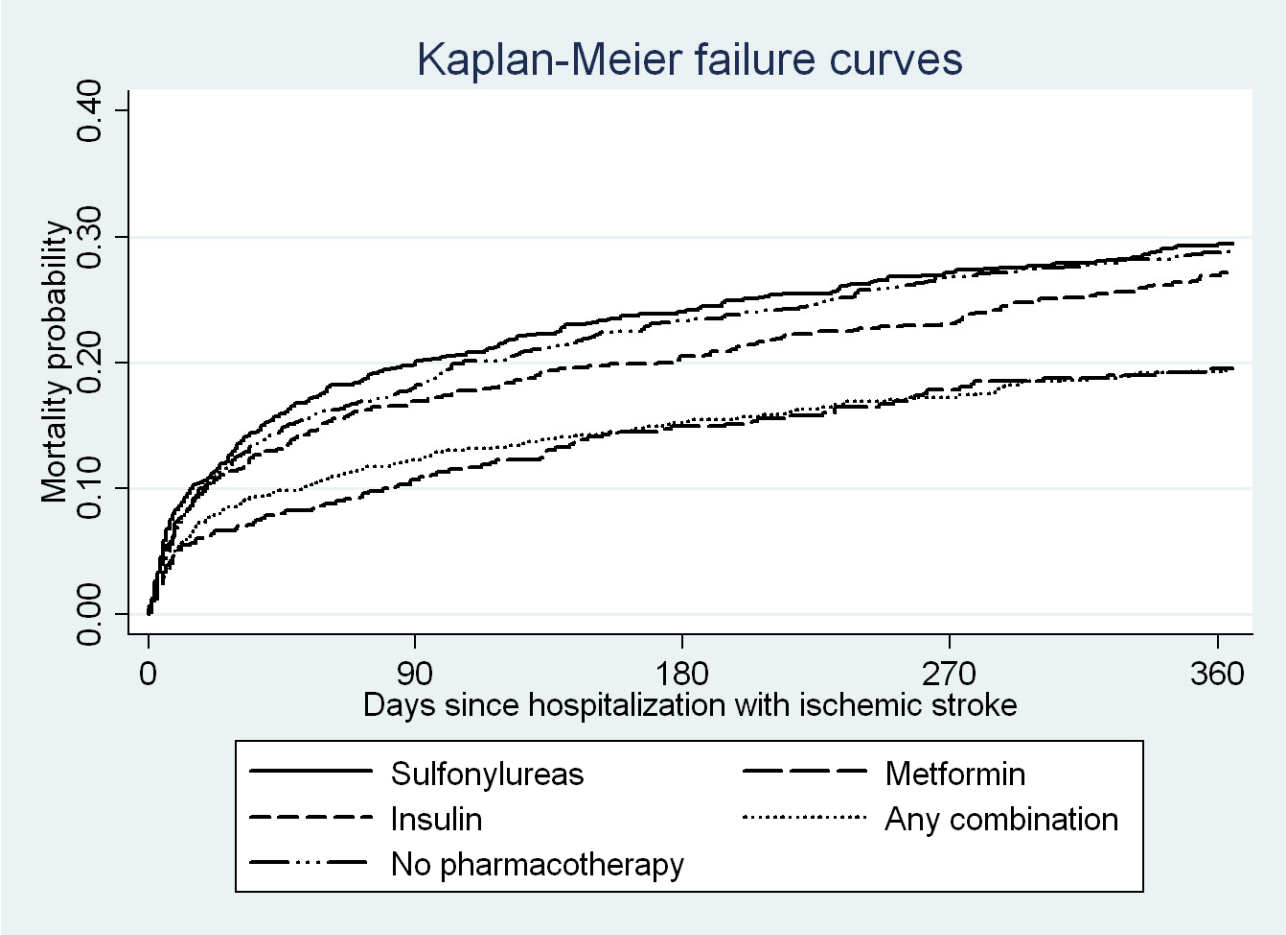

Figure 6. Kaplan-Meier curves of 1-year all-cause mortality after hospitalization with ischemic stroke according to use of antidiabetic treatments within 90 days prior to the hospitalization.

Table 10 shows the crude and adjusted HRs according to antidiabetic treatments. After adjustment for differences in covariates, we found lower 30-day mortality rates among users of the antidiabetic treatments in monotherapy and among patients not treated with antidiabetic pharmacotherapy, *i.e.*, the adjusted HRs for the use of metformin, insulin, and no antidiabetic pharmacotherapy were 0.32 (95% CI: 0.15-0.67), 0.50 (95% CI: 0.29-0.84), and 0.57 (95% CI: 0.36-0.91) compared with users of sulfonylureas. The use of any combination was also associated with a decreased risk of mortality compared with use of sulfonylureas (adjusted 30-day HR 0.63; 95% CI: 0.33-1.20), but this association did not reach statistical significance. When estimating the 1-year HRs, we found no significant differences among the antidiabetic treatments (Table 10). We also found no differences in mortality when comparing use of the different types of combinations (30-day mortality: p=0.16; 1-year mortality: p=0.87) or individual sulfonylureas (30-day mortality: 0.98; 1-year mortality: p=0.89).

Table 10. Crude and adjusted 30-day and 1-year hazard ratios (HRs) with 95% confidence intervals (CIs) for death after first-time hospitalization with ischemic stroke according to use of antidiabetic treatment within 90 days prior to the hospitalization

Antidiabetic treatment	30-day mortality				1-year mortality			
	Crude HR (95% CI)		Adjusted HR[a] (95% CI)		Crude HR (95% CI)		Adjusted HR[a] (95% CI)	
Sulfonylureas	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
Metformin	0.50	(0.35-0.71)	0.32	(0.15-0.67)	0.60	(0.48-0.76)	0.89	(0.64-1.25)
Insulin	0.84	(0.65-1.08)	0.50	(0.29-0.84)	0.89	(0.75-1.05)	0.92	(0.69-1.22)
Any combination	0.63	(0.48-0.82)	0.63	(0.33-1.20)	0.61	(0.51-0.74)	1.03	(0.78-1.35)
No pharmacotherapy	0.92	(0.73-1.14)	0.57	(0.36-0.91)	0.96	(0.83-1.12)	0.82	(0.66-1.03)

[a] Adjusted for age, sex, duration of diabetes mellitus, former use of antidiabetic treatment, level of co-morbidity (measured by the Charlson index), discharge diagnosis of hypertension, former revascularization, retinopathy, neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, statins, other lipid-lowering agents, HRT before the date of hospitalization for ischemic stroke, Scandinavian Stroke Scale score, fulfilled specific quality-of-care criteria, smoking habits, alcohol intake, BMI, marital status, gross income, educational level, employment status, and time-dependent antidiabetic treatment, cardiovascular treatment, and HRT after the date of hospitalization for ischemic stroke.

4.4.2 Antidiabetic treatment and readmissions after ischemic stroke

Within one year of follow-up, 331 (9.0%) of the patients were readmitted with a recurrent stroke or myocardial infarction. We found an increased risk of recurrent stroke or myocardial infarction in users of any antidiabetic treatments compared with users of sulfonylureas; however, this increase reached statistical significance only in patients not treated with antidiabetic pharmacotherapy (Table 11). We found no differences in risk of recurrent stroke or myocardial infarction among users of the different types of combination (p=0.54) or among users of different sulfonylureas (p=0.47).

Table 11. Crude and adjusted 1-year hazard ratios (HRs) with 95% confidence intervals (CIs) for recurrent ischemic stroke or myocardial infarction after first-time hospitalization with ischemic stroke according to the use of antidiabetic treatment within 90 days prior to the hospitalization

Antidiabetic treatment	Myocardial infarction or ischemic stroke			
	Crude HR (95% CI)		Adjusted HR[a] (95% CI)	
Sulfonylureas	1.00	(reference)	1.00	(reference)
Metformin	1.30	(0.85-1.98)	1.40	(0.79-2.48)
Insulin	1.73	(1.22-2.47)	1.61	(0.96-2.69)
Any combination	1.56	(1.09-2.22)	1.46	(0.91-2.32)
No pharmacotherapy	1.50	(1.07-2.11)	1.58	(1.04-2.42)

[a] Adjusted for age, sex, duration of diabetes mellitus, former use of antidiabetic treatment, level of comorbidity (measured by the Charlson index), discharge diagnosis of hypertension, former revascularization, retinopathy, neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, statins, other lipid-lowering agents, HRT before the date of hospitalization for ischemic stroke, Scandinavian Stroke Scale score, fulfilled specific quality-of-care criteria, smoking habits, alcohol intake, BMI, marital status, gross income, educational level, employment status, and time-dependent antidiabetic treatment, cardiovascular treatment and HRT after the date of hospitalization for ischemic stroke.

4.4.3 Complete subject analysis

Data were complete for only 1.508 (31.3%) of the patients. When estimating the mortality, we found similar results, although with a much lower statistical precision, *i.e.*, the adjusted 30-day HRs for the use of metformin, insulin, any combination, and no antidiabetic pharmacotherapy were 0.27 (95% CI: 0.04-1.90), 0.43 (95% CI: 0.09-2.06), 3.64 (95% CI: 0.70-18.93) and 0.34 (95% CI: 0.07-1.59), respectively, compared with users of sulfonylureas. The adjusted 1-year HRs for the use of metformin, insulin, any combination, and no antidiabetic pharmacotherapy were 0.83 (95% CI: 0.41-1.65), 0.80 (95% CI: 0.42-1.49), 1.55 (95% CI: 0.86-2.77) and 0.62 (95% CI: 0.37-1.03), respectively, compared with users of sulfonylureas. For estimates of the risk of readmission, the adjusted HRs for the use of metformin, insulin, any combination, and no antidiabetic pharmacotherapy were 0.70 (95% CI: 0.24-2.00), 2.00 (95% CI: 0.82-4.88), 1.82 (95% CI: 0.79-4.20) and 1.41 (95% CI: 0.66-3.04), respectively, compared with users of sulfonylureas.

4.4.4 180-days exposure window

When estimating the HRs based on drug use 180 days before ischemic stroke, we found similar patterns, although only one reached statistical significance.

5. DISCUSSION

5.1 Methodological considerations

Before deciding whether an association is causal, it is necessary to consider whether the association may be an artifact arising from bias or random variation. The association also might be indirect through another (confounding) factor. Thus, in assessing the validity of findings from observational studies, the possibility of alternative explanations must be considered, including bias (selection and measurement/information), confounding, and chance.[13] Figure 7 outlines these alternative explanations.

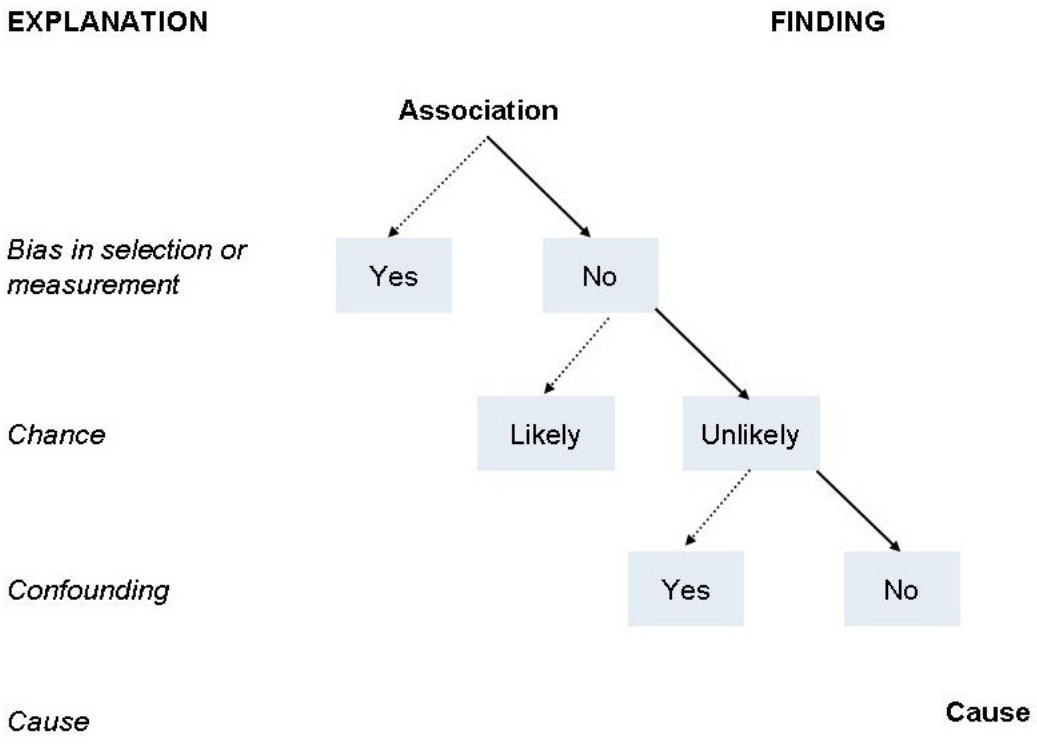

Figure 7. Association and cause. From *Clinical Epidemiology - The Essentials*.[13]

5.1.1 Selection bias

Selection bias occurs when the association between exposure and outcome differs between participants and non-participants in the study. It may occur both when identifying the patients to be included in the studies and during the follow-up period. All studies in this thesis used nationwide population-based registries that enabled valid identification of the study population independently of the study hypothesis. Study I was therefore in principle based on all patients with type 2 diabetes mellitus, while studies II, III and IV were based on all patients hospitalized with myocardial infarction or ischemic stroke, respectively.

The combined use of the Danish registries to identify patients with diabetes mellitus has proven to yield high-quality and almost complete data sets,[97-99] but it is still possible that we missed some patients with type 2 diabetes mellitus. However, the potential patients with type 2 diabetes mellitus not included in our studies were most likely never hospitalized with or treated for their diabetes mellitus, and would thus all have been part of the group with no antidiabetic pharmacotherapy. Lack of information on non-hospitalized patients with myocardial infarction (or stroke), including patients who died before reaching the hospital, might also introduce selection bias, if users of a particular antidiabetic treatment were more likely to die before reaching the hospital.

Loss to follow-up may also be a potentially important source of selection bias. Selection bias occurs when the loss to follow-up is related to both the risk of exposure and the outcome. Because we used the almost-complete population-based registries (the Danish Civil Registration system, the Danish National Patient Registry, and the DNIP stroke database) to ascertain data on the outcomes, we had virtually complete follow-up.

In the subanalyses in North Jutland and Aarhus counties, we included only patients with complete laboratory data, thus possibly introducing selection bias if the outcome among patients with different antidiabetic treatments without complete laboratory data differed from those with complete laboratory data. However, as the subanalyses (without adjustment for laboratory data) showed results similar to the main analyses, this bias does not appear to have been introduced.

5.1.2 Information bias

Information bias may occur when there is systematic error in the measurement of exposure, outcome, or confounding factors. The measurement error is often referred to as misclassification for categorical variables. Misclassification can either be non-differential with the measurement error evenly distributed between comparison groups, or differential with an uneven distribution of the error among the comparison groups. Only differential misclassifications lead to systematic error resulting in an over- or underestimation of the true association. Non-differential misclassification of a dichotomous exposure will most likely bias the association toward null. When more than two groups are compared, non-differential misclassification may lead to either an over- or underestimation of the association, depending on the categories into which the patients are misclassified.

In studies II, III, and IV, one of the outcomes was death. Information bias from errors in this outcome is unlikely because the deaths were recorded completely and independently of the antidiabetic treatment by the Danish Civil Registration System. Similarly, information bias from errors in the secondary outcomes is unlikely because of the almost-complete population-based registries used to identify the readmissions. The validity of the hospital discharge diagnoses used to identify readmissions with myocardial infarction was high,[111] and extensive efforts were made to ensure the validity of DNIP stroke data.[94] Readmissions with heart failure might be misclassified because some of these patients might have been patients with chronic obstructive pulmonary disease exacerbation misdiagnosed as heart failure. However, any misclassifications were unlikely to be related to antidiabetic treatment.

Because we used the filling of a prescription as a proxy for compliance, we may have overestimated actual exposure. However, these patients receive medication for their lifetime, so it seems reasonable to assume that the compliance was high.

We used a 90-day time window to define exposure of antidiabetic treatment. This duration could potentially have lead to misclassification because some antidiabetic prescriptions may extend up to 6 months. However, using a 180-day time window had virtually no influence on our risk estimates.

Recall bias hampers many case-control studies. We avoided any potential difficulties with this type of bias by using the medical and administrative databases with prospectively collected data.

5.1.3 Confounding

We were able to adjust for a range of potential confounding factors related to both type 2 diabetes mellitus and myocardial infarction (or stroke). Nevertheless, our estimates may still be affected by residual confounding arising from either misclassification or use of crude categories for some of the included covariates. In our studies, we might have misclassified the duration of diabetes mellitus because the definition was based on different registry data with different time frames, *i.e.*, the Danish National Patient Registry since 1977, and the Registry of Medicinal Product Statistics since 1995 (and the National Health Insurance Service Registry since 1990 in study I). The defined duration may thus not be entirely correct because some patients might have been defined as having had a longer duration of diabetes mellitus if the data on prescriptions (and diabetes-related service in study I) also had been available since 1977. The misclassification and use of crude categories for both the duration of diabetes mellitus and Charlson's comorbidity index might have led to imperfect adjustment. The estimates may also have been affected by unmeasured factors such as diet and exercise or unknown confounding factors.

It could be argued that not all covariates included in our studies could be considered true confounding factors but rather intermediate steps in the association between use of a specific antidiabetic drug and outcome (e.g., HbA_{1c}). Thus, we may in theory have underestimated the real effect by adjusting for these covariates; however, in reality, neither measures of intensity of glycaemic control, duration of diabetes mellitus, nor other possible "intermediate step covariates" had any substantial impact on the adjusted risk estimates.

Because certain antidiabetic drugs are used as second- or third-line therapies and therefore are prescribed in a more advanced or uncontrolled stage of the disease, patients treated with these drugs are at higher cardiovascular risk regardless of treatment. This confounding by indication (or prescription bias) may thus lead to a distorted estimate of the association between the use of a drug and cardiovascular outcome because the given drug(s) preferentially is/are prescribed to patients who have, *a priori*, a higher or lower cardiovascular risk. However, we made extensive efforts in all our studies to account for possible confounding, including duration and severity of the disease, but we cannot entirely exclude the possibility of confounding by indication.

5.1.4 Precision

The precision in all studies was reflected by the width of the 95% confidence interval. The large population-based studies resulted in a high statistical precision in all main analyses. However, the statistical precision was low when estimating the associations in the subanalyses, and some caution is therefore required when interpreting the findings from these subanalyses because they were more sensitive to chance.

5.2 Comparison with the existing literature

5.2.1 Study I

Our finding of a slightly increased risk of myocardial infarction among users of sulfonylureas is in agreement with several other studies showing an increased risk both in comparison with diet,[38,39] and metformin.[48,49] We found a similar risk of hospitalization with myocardial infarction in patients treated with any combination and patients treated with sulfonylureas alone, which is also in agreement with other studies finding that the combination of metformin and sulfonylurea was not associated with lower risk compared with sulfonylurea alone.[41,47,49]

Our results do not, however, agree with those of the randomized trials (UKPDS and ADOPT) finding no differences between users of sulfonylureas and diet,[40,41] sulfonylureas and insulin,[40] or sulfonylureas and metformin.[44] In fact, these authors even reported a decreased risk of myocardial infarction among users of sulfonylureas compared with diet.[42] The trials differed from our study population by including only newly diagnosed patients with type 2 diabetes mellitus.

We also could not confirm our previous finding of a particularly high risk of myocardial infarction among patients not treated with antidiabetic drugs. This lack may at least partly be explained by the use of the National Health Insurance Service Registry to identify patients with diabetes mellitus. In doing so, we might have included a not-treated population with milder diabetes mellitus than we would have had we identified only patients from the Danish National Patient Registry and the Register of Medicinal Product Statistics. Nor could we confirm our previous finding of a higher risk of hospitalization with myocardial infarction among users of glibenclamide, glipizide, and tolbutamide compared with users of glimepiride and gliclazide (p=0.01). However, the previous study was small (867 cases and 3,148 controls with diabetes mellitus, of which 361 cases and 1,626 controls were treated with sulfonylureas) with less-detailed data on confounding factors.

5.2.2 Study II

Several studies have examined the effect of antidiabetic treatments on clinical outcome in patients with myocardial infarction (and patients undergoing procedures that are often related to myocardial infarction, *i.e.*, PCI and CABG) with conflicting results. A number of these studies also found similar mortality rates among users of antidiabetic treatments after hospitalization with myocardial infarction. There were no differences in mortality rates between users of sulfonylureas and diet,[57,60,70,72,77,79,84] metformin and diet,[57,60,70,71,73] users of insulin and diet,[70] users of sulfonylureas and metformin,[71-73,84] users of sulfonylureas and insulin,[58-61,68,70,71,75-77,79,84] users of metformin and insulin,[58-60,70,75,76] users of sulfonylureas and non-sulfonylureas,[66,78,80] users of metformin and non-metformin,[66,83] and users of insulin and non-insulin.[65,66]

Further, in agreement with our findings, an increased mortality rate has previously been found among users of combination therapy (combined use of metformin and sulfonylureas) when compared with patients treated with diet.[73] Our results of similar risk of reinfarction among users of different antidiabetic drugs are also consistent with those of several other studies.[62,63,65-67,74,83]

In contrast, some studies have implied that use of a specific antidiabetic drug is associated with an adverse prognosis following myocardial infarction. Users of sulfonylureas had increased mortality compared with diet-treated patients,[58,59,73,75,76,82] users of insulin,[57,82] and users of non-sulfonylurea.[74,82] Also, users of insulin had an increased mortality compared with non-insulin[62-64,67,85] and diet,[70,77] and an increased risk of reinfarction compared with non-insulin.[66] Finally, users of metformin had increased mortality compared with diet-treated patients[58,59,72,75,76] and users of insulin.[57]

A few studies have also implied that use of specific antidiabetic drugs is associated with a better outcome following myocardial infarction. Users of sulfonylureas had decreased mortality compared with users of non-sulfonylureas in a nationwide French follow-up study.[69] Users of metformin had decreased mortality and risk of reinfarction compared with non-insulin-sensitizing therapy.[81]

Our own finding from a previous study of variation in 30-day mortality rates after myocardial infarction[53] was not confirmed. However, that study was small (867 patients with diabetes mellitus) with few data on confounding factors, making it difficult to interpret the size of the variation.

5.2.3 Study III

Few studies have examined the outcome after hospitalization with myocardial infarction among users of different sulfonylureas. Consistent with our finding, an Australian cohort study on patients with type 2 diabetes mellitus hospitalized with myocardial infarction found similar short-term (HR 0.7; 95% CI: 0.3-1.4) and long-term (HR 1.6; 95% CI: 0.8-3.2) mortality in users of gliclazide compared with glibenclamide.[71] However, our results do not agree with our earlier finding of a significantly lower mortality among users of gliclazide and glimepiride compared with glibenclamide, glipizide, and tolbutamide.[53]

5.2.4 Study IV

The mortality rate after hospitalization with ischemic stroke among the patients with type 2 diabetes mellitus was comparable to findings in a smaller German study.[87] Those authors, examining 146 patients with diabetes mellitus and acute hemispheric ischemic stroke, found similar in-hospital mortality rates among users of sulfonylureas compared with non-sulfonylurea users (OR 1.2; 95% CI: 0.4-3.5).[87] That study is, to our knowledge, the only other study examining mortality after ischemic stroke according to type of antidiabetic treatment among patients with type 2 diabetes mellitus. Because of the small sample size, the imprecision in the risk estimates hinder a clear interpretation. Our study is also, to our knowledge, the first study to examine long-term clinical outcome (mortality and subsequent readmission) after hospitalization with ischemic stroke according to antidiabetic treatment.

6. CONCLUSION

Based on the results obtained and the considerations of potential bias and confounding, and chance, the following conclusions were made.

6.1 Study I

This study provides some support for the hypothesis that sulfonylureas in general may be associated with a slightly increased risk of hospitalization with myocardial infarction.

6.2 Study II

Type of preadmission antidiabetic treatment in monotherapy is not associated with substantial differences in clinical outcome following hospitalization with myocardial infarction. However, patients treated with any combination had increased mortality rates.

6.3 Study III

There are no substantial differences in mortality and risk of recurrent myocardial infarction or heart failure among users of different sulfonylureas with a first-time hospitalization for myocardial infarction.

6.4 Study IV

Sulfonylureas may be associated with increased mortality after ischemic stroke; however, the deleterious effect seems restricted to the acute phase following the stroke.

7. PERSPECTIVES

The prevalence of type 2 diabetes mellitus is predicted to rise dramatically worldwide within the coming decade, threatening global health. The total number of people with diabetes mellitus, predominantly type 2 diabetes mellitus, is predicted to reach estimated 366 million in 2030.[2]

Type 2 diabetes mellitus is associated with increased risk of atherosclerotic disease and a poor outcome. The mortality after cardiovascular disease among patients with type 2 diabetes mellitus remains high, despite the introduction of new therapeutic modalities that have decreased the overall morbidity and mortality after myocardial infarction. It is, therefore, important to further reduce the cardiovascular risk among patients with type 2 diabetes mellitus.

The studies included in this thesis in general indicate that there were only minor or no differences in the cardiovascular safety profile of different antidiabetic treatments. However, the cardiovascular safety of the novel antidiabetic treatments not included in our study (DPP-4 inhibitors, incretin mimetic drugs) needs further evaluation. Recently, it has been suggested that there might be differences in cardiovascular risk between human insulin and insulin analogs,[112] an issue not addressed in our studies. Future studies need to confirm this hypothesis.

In addition, type 2 diabetes mellitus is associated with the development of certain types of cancer (breast, colon, liver, and pancreatic cancers) as well as increased cancer-related mortality. Recently, concerns about a possible influence of antidiabetic treatments on tumour progression have been raised. In particular, insulin and sulfonylureas have been linked with increased cancer risk, *i.e.*, increased risk of colorectal cancer,[113] pancreatic cancer,[113,114] and hepatocellular carcinoma,[115] while this has not been seen with metformin.[113-115] Patients with type 2 diabetes mellitus exposed to sulfonylureas and exogenous insulin also have shown increased cancer-related mortality compared with patients exposed to metformin.[116] However, whether and to what extent different antidiabetic treatments influence cancer progression in patients with type 2 diabetes mellitus needs to be addressed further.

The choices of treatment for type 2 diabetes mellitus are increasing, offering a wide array of drugs, both in monotherapy or in combination. Thus, it is extremely important that the effects of new drugs to treat type 2 diabetes mellitus not only are investigated for effects on glucose control and other

metabolic variables but also for effects on the cardiovascular system and cancer risk. Randomized controlled trials often are costly in time and money, and it can be difficult to follow adherent patients over a long period and to be sure that they receive the assigned treatment. The unique possibilities in Denmark for combining data from population-based registries of discharge diagnoses, prescriptions, and clinical and laboratory databases offer a great alternative with the advantage of almost ready-made large-scale population-based studies, and are often the only feasible source with which to examine long-term clinical outcomes, including the safety of antidiabetic treatments.

8. SUMMARY

The prevalence of type 2 diabetes mellitus is increasing globally, and these patients are permanently dependent on their antidiabetic treatment. Type 2 diabetes mellitus is both a well-recognized risk factor and a prognostic factor for atherosclerotic diseases, and some concerns have been raised regarding the cardiovascular safety of some antidiabetic treatments. Several potential cardiovascular effects of the different antidiabetic drugs have been postulated involving their influence on the risk and prognosis; however, it is unclear if specific antidiabetic treatments are associated with increased cardiovascular risk.

The aims of this thesis were to examine if antidiabetic treatments have different effect on (1) the risk of myocardial infarction (s*tudy I*), (2) the clinical outcome after myocardial infarction (s*tudies II and III*) and stroke (s*tudy IV*). All studies were based on Danish medical and administrative databases.

In study I, we included 10,616 cases with type 2 diabetes mellitus and myocardial infarction and 90,697 population controls. Compared with users of sulfonylureas, users of metformin (adjusted HR 0.86; 95% CI: 0.78-0.95) and insulin (adjusted HR 0.92; 95% CI: 0.86-0.99) had a lower risk of myocardial infarction. Users of any combination had a risk of myocardial infarction similar to that of users of sulfonylureas (adjusted HR 0.99; 95% CI: 0.92-1.06). We found no differences in the risk of myocardial infarction among users of individual sulfonylureas (p=0.39) or between the different combination types (p=0.11).

Study II included 8,494 patients with type 2 diabetes mellitus and myocardial infarction. The overall cumulative 30-day and 1-year mortality rates were 22.2% and 36.6%, respectively. Type of antidiabetic treatment in monotherapy had no influence on clinical outcome after myocardial infarction, but use of any combination was associated with increased mortality (30-day HR 1.43; 95% CI: 0.98-2.09, and 1-year HR 1.43; 95% CI: 1.18-1.73) compared with use of sulfonylurea. Study III included only patients with type 2 diabetes mellitus and myocardial infarction treated with sulfonylureas. There were no differences in clinical outcome after myocardial infarction among users of individual sulfonylureas.

Study IV included 4,816 patients with type 2 diabetes mellitus and ischemic stroke. The overall cumulative 30-day and 1-year mortality rates were 11.2% and 25.7%, respectively. Use of antidiabetic treatment in monotherapy was associated with decreased short-term mortality after ischemic stroke compared with use of sulfonylurea, *i.e.*, the adjusted 30-day HRs for metformin, insulin, and no antidiabetic pharmacotherapy were 0.32 (95% CI: 0.15-0.67), 0.50 (95% CI: 0.29-0.84), and 0.57 (95% CI: 0.36-0.91), respectively. Use of any combination was also associated with decreased risk compared with sulfonylureas (adjusted HR 0.63; 95% CI: 0.33-1.20), but this decrease did not reach statistical significance. When estimating the 1-year HRs, we found no differences in mortality among the antidiabetic treatments, but did find an increased risk of recurrent stroke or myocardial infarction for all antidiabetic treatments compared with sulfonylurea. This increase, however, reached statistical significance only among patients not receiving antidiabetic pharmacotherapy (adjusted HR 1.58; 95% CI: 1.04-2.42).

In conclusion, our studies indicate that there are no major differences in the cardiovascular safety profile of different antidiabetic treatments.

9. DANSK RESUME

Den globale prævalens af type 2 diabetes mellitus er stigende, og disse patienter er permanent afhængige af deres antidiabetiske behandling. Type 2 diabetes mellitus er både en velkendt risikofaktor samt en prognostisk faktor for aterosklerotiske sygdomme, og der har været usikkerhed om den kardiovaskulære risiko ved brug af nogle typer antidiabetika. Flere potentielle kardiovaskulære effekter, hvorved de forskellige antidiabetika kan påvirke risiko og prognose, er blevet postuleret. Det er dog uklart, om specifikke antidiabetika er associeret med en øget kardiovaskulær risiko.

Formålet med denne afhandling var at undersøge, om forskellige typer antidiabetika påvirker (1) risiko for myokardieinfarkt (*studie I*) og (2) prognose efter myokardieinfarkt (*studie II, III*) og iskæmisk apopleksi (*studie IV*). Alle studier var baseret på danske medicinske og administrative databaser.

I studie I blev 10.616 cases med type 2 diabetes mellitus og myokardieinfarkt og 90.697 populationskontroller inkluderet. Sammenlignet med brugere af sulfonylurinstoffer havde brugere af metformin (justeret HR 0,86; 95% CI: 0,78-0,95) og insulin (justeret HR 0,92; 95% CI: 0,86-0,99) en lavere risiko for myokardieinfarkt. Brugere af enhver kombination havde samme risiko for myokardieinfarkt som brugere af sulfonylurinstoffer (justeret HR 0,99; 95% CI: 0,92-1,06). Vi fandt ingen forskel på risiko for myokardieinfarkt blandt brugerne af specifikke sulfonylurinstoffer ($p = 0,39$) eller mellem forskellige kombinationstyper ($p = 0,11$).

Studie II inkluderede 8.494 patienter med type 2 diabetes mellitus og myokardieinfarkt. De kumulerede 30 dage og et års dødeligheder var hhv. 22,2% og 36,6%. Typen af antidiabetika i monoterapi påvirkede ikke prognosen efter myokardieinfarkt, men brug af enhver kombination var associeret med øget dødelighed (30 dages HR 1,43; 95% CI: 0,98-2,09, og et års HR 1,43; 95% CI: 1,18-1,73) sammenlignet med brug af sulfonylurinstoffer. Studie III inkluderede kun patienter med type 2 diabetes mellitus og myokardieinfarkt, der var i behandling med sulfonylurinstoffer. Der var ingen forskelle i prognosen efter myokardieinfarkt blandt brugerne af specifikke sulfonylurinstoffer.

Studie IV inkluderede 4.816 patienter med type 2 diabetes mellitus og iskæmisk apopleksi. De kumulerede 30 dage og et års dødeligheder var hhv. 11,2% og 25,7%. Brug af antidiabetika i monoterapi var associeret med bedre korttidsoverlevelse efter iskæmisk apopleksi sammenlignet med brug af sulfonylurinstoffer, dvs. de justerede 30 dages HR for metformin, insulin og ingen farmakologisk behandling var hhv. 0,32 (95% CI: 0,15-0,67), 0,50 (95% CI: 0,29-0,84) og 0,57 (95% CI: 0,36-0,91). Brug af enhver kombination var også associeret med bedre overlevelse sammenlignet med sulfonylurinstoffer (justeret 30-dages HR 0,63; 95% CI: 0,33-1,20), men det var dog ikke statistisk signifikant. Ved et års follow-up var der ingen forskel i overlevelsen mellem de forskellige antidiabetiske behandlingstyper, men vi fandt øget risiko for genindlæggelse med nyt iskæmisk apopleksi eller myokardieinfarkt ved alle behandlingstyper sammenlignet med sulfonylurinstoffer, selv om det kun var statistisk signifikant hos patienter, der ikke var i farmakologisk behandling (justeret HR 1,58; 95% CI: 1,04-2,42).

Sammenfattende viser vores undersøgelser, at forskellige antidiabetiske behandlingstyper ikke giver betydelige forskelle på de kardiovaskulære udfald.

10. REFERENCES

(1) King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414-1431.

(2) 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;27:1047-1053.

(3) The National Board of Health. Det Nationale Diabetesregister 2007. Copenhagen: The National Board of Health; 2009.

(4) Carstensen B, Kristensen JK, Ottosen P, Borch-Johnsen K. The Danish National Diabetes Register: trends in incidence, prevalence and mortality. *Diabetologia* 2008;51:2187-2196.

(5) Powers AC. Diabetes Mellitus. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. Harrison's Principles of Internal Medicine. 15th ed. The McGraw-Hill Companies, Inc, 2001:2109-2137.

(6) Danish Medicines Agency. 2009; Available at: URL: http://www.medstat.dk/MedStatDataViewer.php.

(7) Kramer W, Muller G, Girbig F, Gutjahr U, Kowalewski S, Hartz D, Summ HD. The molecular interaction of sulfonylureas with beta-cell ATP-sensitive K(+)-channels. *Diabetes Res Clin Pract* 1995;28 Suppl:S67-S80.

(8) Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. *Drugs* 2003;63:1879-1894.

(9) Balfour JA, McTavish D. Acarbose. An update of its pharmacology and therapeutic use in diabetes mellitus. *Drugs* 1993;46:1025-1054.

(10) Martens FM, Visseren FL, Lemay J, de Koning EJ, Rabelink TJ. Metabolic and additional vascular effects of thiazolidinediones. *Drugs* 2002;62:1463-1480.

(11) Fuhlendorff J, Rorsman P, Kofod H, Brand CL, Rolin B, MacKay P, Shymko R, Carr RD. Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. *Diabetes* 1998;47:345-351.

(12) Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002;287:2570-2581.

(13) Fletcher RH, Fletcher SW, Wagner EH. Clinical Epidemiology - The Essentials. Third Edition ed. Baltimore: Lippincott Williams & Wilkins, 1996.

(14) Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;241:2035-2038.

(15) Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with

myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-952.

(16) Haffner SM, Lehto S, Ronnemaa 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;339:229-234.

(17) Schramm TK, Gislason GH, Kober L, Rasmussen S, Rasmussen JN, Abildstrom SZ, Hansen ML, Folke F, Buch P, Madsen M, Vaag A, Torp-Pedersen C. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation* 2008;117:1945-1954.

(18) Abbott RD, Donahue RP, MacMahon SW, Reed DM, Yano K. Diabetes and the risk of stroke. The Honolulu Heart Program. *JAMA* 1987;257:949-952.

(19) Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, Pyorala K, Tuomilehto J. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care* 1998;21:69-75.

(20) Herlitz J, Malmberg K, Karlson BW, Ryden L, Hjalmarson A. Mortality and morbidity during a five-year follow-up of diabetics with myocardial infarction. *Acta Med Scand* 1988;224:31-38.

(21) Jørgensen H, Nakayama H, Raaschou HO, Olsen TS. Stroke in patients with diabetes. The Copenhagen Stroke Study. *Stroke* 1994;25:1977-1984.

(22) Olsson T, Viitanen M, Asplund K, Eriksson S, Hagg E. Prognosis after stroke in diabetic patients. A controlled prospective study. *Diabetologia* 1990;33:244-249.

(23) Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405-412.

(24) Seino S, Miki T. Physiological and pathophysiological roles of ATP-sensitive K+ channels. *Prog Biophys Mol Biol* 2003;81:133-176.

(25) Cleveland JC, Jr., Meldrum DR, Cain BS, Banerjee A, Harken AH. Oral sulfonylurea hypoglycemic agents prevent ischemic preconditioning in human myocardium. Two paradoxes revisited. *Circulation* 1997;96:29-32.

(26) Mocanu MM, Maddock HL, Baxter GF, Lawrence CL, Standen NB, Yellon DM. Glimepiride, a novel sulfonylurea, does not abolish myocardial protection afforded by either ischemic preconditioning or diazoxide. *Circulation* 2001;103:3111-3116.

(27) Horimoto H, Nakai Y, Mieno S, Nomura Y, Nakahara K, Sasaki S. Oral hypoglycemic sulfonylurea glimepiride preserves the myoprotective effects of ischemic preconditioning. *J Surg Res* 2002;105:181-188.

(28) Klepzig H, Kober G, Matter C, Luus H, Schneider H, Boedeker KH, Kiowski W, Amann FW, Gruber D, Harris S, Burger W. Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J* 1999;20:439-446.

(29) Lee TM, Chou TF. Impairment of myocardial protection in type 2 diabetic patients. *J Clin Endocrinol Metab* 2003;88:531-537.

(30) Tomai F, Crea F, Gaspardone A, Versaci F, De Paulis R, Penta dP, Chiariello L, Gioffre PA. Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K+ channel blocker. *Circulation* 1994;90:700-705.

(31) Maddock HL, Siedlecka SM, Yellon DM. Myocardial protection from either ischaemic preconditioning or nicorandil is not blocked by gliclazide. *Cardiovasc Drugs Ther* 2004;18:113-119.

(32) Simard JM, Chen M, Tarasov KV, Bhatta S, Ivanova S, Melnitchenko L, Tsymbalyuk N, West GA, Gerzanich V. Newly expressed SUR1-regulated NC(Ca-ATP) channel mediates cerebral edema after ischemic stroke. *Nat Med* 2006;12:433-440.

(33) Jennings PE. Vascular benefits of gliclazide beyond glycemic control. *Metabolism* 2000;49:17-20.

(34) Cacciapuoti F, Spiezia R, Bianchi U, Lama D, D'Avino M, Varricchio M. Effectiveness of glibenclamide on myocardial ischemic ventricular arrhythmias in non-insulin-dependent diabetes mellitus. *Am J Cardiol* 1991;67:843-847.

(35) Rizzo MR, Barbieri M, Grella R, Passariello N, Paolisso G. Repaglinide has more beneficial effect on cardiovascular risk factors than glimepiride: data from meal-test study. *Diabetes Metab* 2005;31:255-260.

(36) Staels B. PPARgamma and atherosclerosis. *Curr Med Res Opin* 2005;21 Suppl 1:S13-S20.

(37) Jain SK, Nagi DK, Slavin BM, Lumb PJ, Yudkin JS. Insulin therapy in type 2 diabetic subjects suppresses plasminogen activator inhibitor (PAI-1) activity and proinsulin-like molecules independently of glycaemic control. *Diabet Med* 1993;10:27-32.

(38) Boyle D, Hadden DR, Bhatia SK, Montgomery DA, Weaver JA. Ischaemic heart-disease in diabetics. A prospective study. *Lancet* 1972;1:338-339.

(39) Hadden DR, Montgomery DA, Weaver JA. Myocardial infarction in maturity-onset diabetics. A retrospective study. *Lancet* 1972;1:335-338.

(40) 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;352:837-853.

(41) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854-865.

(42) Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-1589.

(43) Belcher G, Lambert C, Goh KL, Edwards G, Valbuena M. Cardiovascular effects of treatment of type 2 diabetes with pioglitazone, metformin and gliclazide. *Int J Clin Pract* 2004;58:833-837.

(44) Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006;355:2427-2443.

(45) Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 2004;25:10-16.

(46) Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. *Diabetologia* 2006;49:930-936.

(47) McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM. Coronary heart disease outcomes in patients receiving antidiabetic agents. *Pharmacoepidemiol Drug Saf* 2007;16:711-725.

(48) Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. *Diabet Med* 2005;22:497-502.

(49) Sauer WH, Cappola AR, Berlin JA, Kimmel SE. Insulin sensitizing pharmacotherapy for prevention of myocardial infarction in patients with diabetes mellitus. *Am J Cardiol* 2006;97:651-654.

(50) Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007;298:1189-1195.

(51) Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457-2471.

(52) Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007;298:1180-1188.

(53) Johnsen SP, Monster TB, Olsen ML, Thisted H, McLaughlin JK, Sørensen HT, Lervang HH, Rungby J. Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. *Am J Ther* 2006;13:134-140.

(54) Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes* 1970;19:Suppl-830.

(55) Kilo C, Miller JP, Williamson JR. The crux of the UGDP. Spurious results and biologically inappropriate data analysis. *Diabetologia* 1980;18:179-185.

(56) Seltzer HS. A summary of criticisms of the findings and conclusions of the University Group Diabetes Program (UGDP). *Diabetes* 1972;21:976-979.

(57) Rytter L, Troelsen S, Beck-Nielsen H. Prevalence and mortality of acute myocardial infarction in patients with diabetes. *Diabetes Care* 1985;8:230-234.

(58) Soler NG, Pentecost BL, Bennett MA, FitzGerald MG, Lamb P, Malins JM. Coronary care for myocardial infarction in diabetics. *Lancet* 1974;1:475-477.

(59) Soler NG, Bennett MA, Pentecost BL, FitzGerald MG, Malins JM. Myocardial infarction in diabetics. *Q J Med* 1975;44:125-132.

(60) Ulvenstam G, Aberg A, Bergstrand R, Johansson S, Pennert K, Vedin A, Wilhelmsen L, Wilhelmsson C. Long-term prognosis after myocardial infarction in men with diabetes. *Diabetes* 1985;34:787-792.

(61) Brady PA, Al Suwaidi J, Kopecky SL, Terzic A. Sulfonylureas and mortality in diabetic patients after myocardial infarction. *Circulation* 1998;97:709-710.

(62) Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L. 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.

(63) Malmberg K, Ryden L, Hamsten A, Herlitz J, Waldenstrom A, Wedel H. Effects of insulin treatment on cause-specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction. DIGAMI Study Group. Diabetes Insulin-Glucose in Acute Myocardial Infarction. *Eur Heart J* 1996;17:1337-1344.

(64) Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ* 1997;314:1512-1515.

(65) Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J, Hildebrandt P, MacLeod K, Laakso M, Torp-Pedersen C, Waldenstrom A. 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;26:650-661.

(66) Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur Heart J* 2008;29:166-176.

(67) Mak KH, Moliterno DJ, Granger CB, Miller DP, White HD, Wilcox RG, Califf RM, Topol EJ. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol* 1997;30:171-179.

(68) Jollis JG, Simpson RJ, Jr., Cascio WE, Chowdhury MK, Crouse JR, III, Smith SC, Jr. Relation between sulfonylurea therapy, complications, and outcome for elderly patients with acute myocardial infarction. *Am Heart J* 1999;138:S376-S380.

(69) Danchin N, Charpentier G, Ledru F, Vaur L, Gueret P, Hanania G, Blanchard D, Lablanche JM, Genes N, Cambou JP. Role of previous treatment with sulfonylureas in diabetic patients with acute myocardial infarction: results from a nationwide French registry. *Diabetes Metab Res Rev* 2004;21:143-149.

(70) Berger AK, Breall JA, Gersh BJ, Johnson AE, Oetgen WJ, Marciniak TA, Schulman KA. Effect of diabetes mellitus and insulin use on survival after acute myocardial infarction in the elderly (the Cooperative Cardiovascular Project). *Am J Cardiol* 2001;87:272-277.

(71) Davis TM, Parsons RW, Broadhurst RJ, Hobbs MS, Jamrozik K. Arrhythmias and mortality after myocardial infarction in diabetic patients. Relationship to diabetes treatment. *Diabetes Care* 1998;21:637-640.

(72) Fisman EZ, Tenenbaum A, Benderly M, Goldbourt U, Behar S, Motro M. Antihyperglycemic treatment in diabetics with coronary disease: increased metformin-associated mortality over a 5-year follow-up. *Cardiology* 1999;91:195-202.

(73) Fisman EZ, Tenenbaum A, Boyko V, Benderly M, Adler Y, Friedensohn A, Kohanovski M, Rotzak R, Schneider H, Behar S, Motro M. Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. *Clin Cardiol* 2001;24:151-158.

(74) Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR, Jr. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1999;33:119-124.

(75) Gustafsson I, Hildebrandt P, Seibaek M, Melchior T, Torp-Pedersen C, Kober L, Kaiser-Nielsen P. Long-term prognosis of diabetic patients with myocardial infarction: relation to antidiabetic treatment regimen. The TRACE Study Group. *Eur Heart J* 2000;21:1937-1943.

(76) Gustafsson I, Hildebrandt P, Seibaek M, Melchior T, Torp-Pedersen C, Kober L, Kaiser-Nielsen P. Prognosis of diabetic patients with MI. *Cardiology review* 2001;18:24-27.

(77) Halkin A, Roth A, Jonas M, Behar S. Sulfonylureas are not associated with increased mortality in diabetics treated with thrombolysis for acute myocardial infarction. *J Thromb Thrombolysis* 2001;12:177-184.

(78) Klamann A, Sarfert P, Launhardt V, Schulte G, Schmiegel WH, Nauck MA. Myocardial infarction in diabetic vs non-diabetic subjects. Survival and infarct size following therapy with sulfonylureas (glibenclamide). *Eur Heart J* 2000;21:220-229.

(79) Alserius T, Hammar N, Nordqvist T, Ivert T. Risk of death or acute myocardial infarction 10 years after coronary artery bypass surgery in relation to type of diabetes. *Am Heart J* 2006;152:599-605.

(80) Meier JJ, Deifuss S, Klamann A, Schmiegel W, Nauck MA. Influence of an antidiabetic treatment with sulfonylurea drugs on long-term survival after acute myocardial infarction in patients with type 2 diabetes. The LAngendreer Myocardial infarction and Blood glucose in Diabetic patients Assessment (LAMBDA). *Exp Clin Endocrinol Diabetes* 2003;111:344-350.

(81) Kao J, Tobis J, McClelland RL, Heaton MR, Davis BR, Holmes DR, Jr., Currier JW. Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. *Am J Cardiol* 2004;93:1347-50, A5.

(82) Aronow WS, Ahn C. Incidence of new coronary events in older persons with diabetes mellitus and prior myocardial infarction treated with sulfonylureas, insulin, metformin, and diet alone. *Am J Cardiol* 2001;88:556-557.

(83) Inzucchi SE, Masoudi FA, Wang Y, Kosiborod M, Foody JM, Setaro JF, Havranek EP, Krumholz HM. Insulin-sensitizing antihyperglycemic drugs and mortality after acute myocardial infarction: insights from the National Heart Care Project. *Diabetes Care* 2005;28:1680-1689.

(84) McGuire DK, Newby LK, Bhapkar MV, Moliterno DJ, Hochman JS, Klein WW, Weaver WD, Pfisterer M, Corbalan R, Dellborg M, Granger CB, Van De WF, Topol EJ, Califf RM. Association of diabetes mellitus and glycemic control strategies with clinical outcomes after acute coronary syndromes. *Am Heart J* 2004;147:246-252.

(85) Murcia AM, Hennekens CH, Lamas GA, Jimenez-Navarro M, Rouleau JL, Flaker GC, Goldman S, Skali H, Braunwald E, Pfeffer MA. Impact of diabetes on mortality in patients with myocardial infarction and left ventricular dysfunction. *Arch Intern Med* 2004;164:2273-2279.

(86) Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol* 2007;49:1772-1780.

(87) Weih M, Amberger N, Wegener S, Dirnagl U, Reuter T, Einhaupl K. Sulfonylurea drugs do not influence initial stroke severity and in-hospital outcome in stroke patients with diabetes. *Stroke* 2001;32:2029-2032.

(88) Kunte H, Schmidt S, Eliasziw M, del Zoppo GJ, Simard JM, Masuhr F, Weih M, Dirnagl U. Sulfonylureas improve outcome in patients with type 2 diabetes and acute ischemic stroke. *Stroke* 2007;38:2526-2530.

(89) Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, Dormandy J. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007;38:865-873.

(90) Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;287:2398-2399.

(91) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441-449.

(92) Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263-268.

(93) Statistics Denmark. IDA—an integrated database for labour market research. Copenhagen, Denmark: Statistics Denmark; 1991.

(94) Mainz J, Krog BR, Bjornshave B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. *Int J Qual Health Care* 2004;16 Suppl 1:i45-i50.

(95) Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke* 1989;20:1407-1431.

(96) Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. *Am J Epidemiol* 1992;135:1019-1028.

(97) Nielsen GL, Sørensen HT, Pedersen AB, Sabroe S. Analyses of data quality in registries concerning diabetes mellitus--a comparison between a population based hospital discharge and an insulin prescription registry. *J Med Syst* 1996;20:1-10.

(98) Drivsholm TB, Frederiksen K, de Fine ON, Odegaard B, Kristensen JK. [The prevalence of diabetes in Denmark. Development of a method for a registry-based assessment]. *Ugeskr Laeger* 2003;165:2887-2891.

(99) Kristensen JK, Sandbaek A, Lassen JF, Bro F, Lauritzen T. Use and validation of public data files for identification of the diabetic population in a Danish county. *Dan Med Bull* 2001;48:33-37.

(100) Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;90:583-612.

(101) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383.

(102) Thygesen SK, Christiansen CF, Lash TL, Christensen C, Sørensen HT. The predictive value of ICD-10 diagnoses in population-based hospital registries used to assess Charlson Comorbidity Index. *Pharmacoepidemiol Drug Saf* 2009;18[S1]:189.

(103) Multicenter trial of hemodilution in ischemic stroke--background and study protocol. Scandinavian Stroke Study Group. *Stroke* 1985;16:885-890.

(104) Lindenstrøm E, Boysen G, Waage Christiansen L, á Rogvi Hansen B, Würtzen Nielsen P. Reliability of Scandinavian Neurological Stroke Scale. *Cerebrovasc Dis* 1991;1:103-107.

(105) Barber M, Fail M, Shields M, Stott DJ, Langhorne P. Validity and reliability of estimating the scandinavian stroke scale score from medical records. *Cerebrovasc Dis* 2004;17:224-227.

(106) Ingeman A, Pedersen L, Hundborg HH, Petersen P, Zielke S, Mainz J, Bartels P, Johnsen SP. Quality of care and mortality among patients with stroke: a nationwide follow-up study. *Med Care* 2008;46:63-69.

(107) Royston P. Multiple imputation of missing values. *The Stata Journal* 2004;4:227-241.

(108) Royston P. Multiple imputation of missing values: update. *The Stata Journal* 2005;5:188-201.

(109) Royston P. Multiple imputation of missing values: Update of ice. *The Stata Journal* 2005;5: 527-536.

(110) White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med* 2009;28:1982-1998.

(111) Madsen M, Balling H, Eriksen LS. [The validity of the diagnosis of acute myocardial infarction in 2 registries: the Heart Registry compared to the National Patient Registry]. *Ugeskr Laeger* 1990;152:308-314.

(112) Rhoads GG, Kosiborod M, Nesto RW, Fonseca VA, Lu SE, Zhang Q, Foody JM. Comparison of incidence of acute myocardial infarction in patients with type 2 diabetes mellitus following initiation of neutral protamine Hagedorn insulin versus insulin glargine. *Am J Cardiol* 2009;104:910-916.

(113) Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009;52:1766-1777.

(114) Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009;137:482-488.

(115) Donadon V, Balbi M, Ghersetti M, Grazioli S, Perciaccante A, Della VG, Gardenal R, Dal MM, Casarin P, Zanette G, Miranda C. Antidiabetic therapy and increased risk of hepatocellular carcinoma in chronic liver disease. *World J Gastroenterol* 2009;15:2506-2511.

(116) Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care* 2006;29:254-258.

11. APPENDICES

Springer

Diabetologia

ANTIDIABETIC TREATMENTS AND RISK OF HOSPITALISATION WITH MYOCARDIAL INFARCTION: A NATIONWIDE CASE-CONTROL STUDY.

Journal:	*Diabetologia*
Manuscript ID:	Diab-09-1689
Manuscript Type:	Article
Keywords:	3.01.01 Epidemiology, 3.06.08 Cardiac complications, 3.05.03 Insulin therapy, 3.05.04 Oral pharmacological agents

ANTIDIABETIC TREATMENTS AND RISK OF HOSPITALISATION WITH MYOCARDIAL INFARCTION: A NATIONWIDE CASE-CONTROL STUDY.

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Word count:

Abstract: 247

Main text: 3,243

Abstract

Aims/hypothesis: Data on cardiovascular risk of different types of antidiabetic treatments are sparse and conflicting. Here we examined the risk of hospitalisation with myocardial infarction (MI) among patients treated with sulphonylureas, metformin, insulin, any combination and no antidiabetic pharmacotherapy.

Methods: We conducted a population-based case-control study among all patients with type 2 diabetes mellitus in Denmark and identified all patients hospitalised with a first-time MI and age- and gender-matched non-MI controls in the period 1996-2004 using data from medical registries. We estimated odds ratios (ORs) of MI associated with use of antidiabetic treatments, adjusted for potential confounding factors using patients treated with sulphonylureas as the reference group.

Results: We identified a total of 10,616 type 2 diabetic cases hospitalised with MI and 90,697 type 2 diabetic non-MI controls, of which 7,134 (67.2%) and 53,821 (59.3%) had filled a prescription for an antidiabetic drug, respectively. We found a lower risk of hospitalisation with MI among users of metformin (adjusted OR=0.86, 95% CI: 0.78-0.95), insulin (adjusted OR=0.92, 95% CI: 0.86-0.99), and among patients not receiving any antidiabetic pharmacotherapy (adjusted OR=0.75, 95% CI: 0.71-0.79) compared with users of sulphonylureas. Users of any combination had similar risk as users of sulphonylureas (adjusted OR=0.99, 95% CI: 0.92-1.06). We found no differences between individual sulphonylureas, and glycaemic control had only minor impact on the risk estimates in a subanalysis including HbA_{1c}.

Conclusion/interpretation: Our findings provide some support for the hypothesis that sulphonylureas may be associated with an increased risk of hospitalisation with MI.

Keywords: Epidemiology, type 2 diabetes mellitus, case-control study, antidiabetic treatment, risk, myocardial infarction

Abbreviations: MI myocardial infarction, ORs odds ratios, UKPDS United Kingdom Prospective Diabetes Study, ICD international classification of diseases, ATC anatomical therapeutic chemical, OAD oral antidiabetic drug, IDA integrated database for labour market research.

Introduction

Patients with diabetes mellitus have an increased risk of cardiovascular disease [1]. Maintaining blood glucose levels as close to the normal range as possible among these patients is one way to lower the risk of macrovascular disease [2]. However, the different antidiabetic treatments lower the blood glucose levels through different mechanisms, and might possibly therefore also have different effects on cardiovascular risk. Sulphonylureas have for several years been center for concerns about cardiovascular safety as the inhibition of cardiovascular K_{ATP}-channels by sulphonylureas has been linked with adverse cardiovascular effects.

The United Kingdom Prospective Diabetes Study (UKPDS) found no differences in the rates of myocardial infarction (MI) between patients assigned sulphonylureas (chlorpropamide and glibenclamide) and insulin [3], but in an observational study on older patients with prior MI, the incidence of new coronary events was higher in patients treated with sulphonylureas than in patients treated with insulin or diet [4]. Further, in the UKPDS, use of metformin was associated with reduced risk of MI compared with diet therapy in overweight patients with type 2 diabetes mellitus [5], and metformin has also been associated with decreased rates of MI compared with insulin and/or sulphonylureas [6-8]. However, in contrast a meta-analysis of four randomised trials found similar risk of MI among users of pioglitazone, metformin and sulphonylurea (gliclazide) [9].

We have previously in a smaller study found an increased risk of MI among patients using any antidiabetic drugs compared with non-diabetic patients [10]. However, patients not using any antidiabetic pharmacotherapy had the highest risk of hospitalisation with MI, indicating that treatment with an antidiabetic drug may lower the cardiovascular risk. We also found

lower risk of hospitalisation with MI among users of gliclazide and glimepiride compared with glibenclamide, glipizide and tolbutamide [10].

Data regarding the risk of MI among patients using specific types of antidiabetic treatments are thus conflicting, and we therefore examined the risk of hospitalisation with MI among users of different antidiabetic treatments in a large Danish nationwide case-control study.

Methods

Setting and design

We conducted this case-control study within the entire Danish population (approximately 5.3 million). The Danish National Health Service provides tax-supported health care for all inhabitants, guaranteeing free access to general practitioners and hospitals, and refunding a variable proportion of the prescription medication costs. The Danish Civil Registration System keeps electronic records on gender, date of birth, change of address, date of emigration, and changes in vital status since 1968 [11,12]. The records carry a unique 10-digit civil registration number, assigned to every Danish citizen, and used in all Danish registries, enabling unambiguous linkage between them.

Patients with diabetes mellitus

We identified all patients with diabetes mellitus in Denmark through three different Danish registries. From the Danish National Patient Registry [13], we identified patients with a discharge diagnosis of diabetes mellitus (ICD-8 codes 249, 250 and/or ICD-10 codes E10, E11, E14, G63.2, H36.0, N08.3). This registry, established in 1977, collects data on all hospitalisations from non-psychiatric hospitals in the country, including dates of admission and discharge, surgical procedure(s) performed, and up to 20 discharge diagnoses assigned by

the treating physician and coded according to the International Classification of Diseases (8th revision (ICD-8) until the end of 1993, and 10th revision (ICD-10) thereafter). From the Registry of Medicinal Product Statistics, we traced all prescriptions for antidiabetic drugs (Anatomical Therapeutic Chemical (ATC) A10A, A10B). In Denmark, antidiabetic drugs are available by prescription only, and the registry contains data from 1995 onwards on all prescription drugs dispensed at all Danish pharmacies, including patients' civil registration numbers, type of drug according to the ATC classification system, and date of dispensing the drug.

Patients with diabetes mellitus were also identified in the National Health Insurance Service Registry. This registry contains data on services in the primary healthcare (general practitioners, medical specialists, doctors on emergency duty, opticians, dentists, private laboratories, physiotherapists, occupational therapists, chiropodist, and psychologists) since 1990, and the diabetes-related services include blood glucose measurements and diabetic foot care performed by a chiropodist. We identified patients with diabetes mellitus by a visit at the chiropodist, 5 blood glucose measurements within one year, or minimum 2 blood glucose measurements per year in a 5 year period. This registry does not contain information on the actual values of the glucose measurements.

We classified the diabetic patients according to their type of diabetes; type 1 if they were less than 30 years by the time of the first prescription, diagnosis or diabetes defining service in the primary healthcare and filled a prescription for insulin but not for an oral antidiabetic drug (OAD), and type 2 if they did not receive antidiabetic pharmacotherapy, or filled a prescription for an OAD, or if they were older than 30 years at the time of first prescription, diagnosis or service in the primary healthcare, regardless of treatment.

Patients with MI

Using the Danish National Patient Registry, we constructed the hospital discharge history for all Danish patients with diabetes mellitus based on the data going back to 1977, and hereafter identified all in-patients, who were registered with a first-time discharge diagnosis of MI (ICD-10 codes I21.0-I21.9) recorded between January 1, 1996 and December 31, 2004 (n=12,569). MI patients with type 1 diabetes mellitus were excluded, leaving a total of 12,397 cases.

Non-MI controls

For each MI case with type 2 diabetes mellitus, we aimed to identify 10 non-MI controls from the total population of patients with type 2 diabetes mellitus through the Civil Registration System using risk set sampling [14], *i.e.*, the controls had to be alive and at risk of MI at the time the corresponding case was diagnosed (index date). This registry, which is updated daily, keeps electronic records on vital status (dead or alive), date of death, and residence of all Danish citizens. The controls were matched on age and gender. We found no controls for 2 of the cases, and they were thus excluded from the study.

Antidiabetic treatment

Using the Registry of Medicinal Product Statistics, we categorised the cases and controls according to use of antidiabetic drugs 90 days prior to the hospitalisation or index date. Subjects using only one type of antidiabetic drugs in 90 days prior to hospitalisation or index date were categorised according to the antidiabetic drugs class: sulphonylureas, metformin, other OAD (glitazones, acarbose and repaglinide) or insulin. Subjects who used more than one type of antidiabetic drugs during the 90 days prior to hospitalisation or index date were categorised as combined users. Users of other OAD (in monotherapy or in combination

therapy) were excluded from the analyses due to the low number of treated patients (52 cases and 1,185 controls in monotherapy and 177 cases and 3,205 controls in combination therapy). Subjects not using any antidiabetic drugs during the 90 days prior to hospitalisation or index date were categorised as diabetic patients without pharmacotherapy. We excluded subjects who had filled a prescription for any antidiabetic drug prior to hospitalisation or index date, but not within 90 days before the hospitalisation or index date from the analyses (n=1,469 cases and 27,572 controls). In order to evaluate the different sulphonylureas, we also excluded patients with prescriptions for more than one sulphonylurea drug within the 90 days before hospitalisation or index date (n=79 cases and 1,184 controls).

Covariates

We obtained data on covariates from the Danish National Patient Registry, the Registry of Medicinal Product Statistics, the Integrated Database for Labour Market Research (IDA) at Statistics Denmark [15], and, for a subset, data from the laboratory information systems in North Jutland and Aarhus Counties.

We obtained information on previous hospitalisations for hypertension, chronic bronchitis and emphysema (as a proxy measure for smoking), alcohol-related diseases, liver cirrhosis, stroke, peripheral arterial disease, and diabetes complications (i.e. retinopathy, nephropathy, and neuropathy). We identified all prescriptions for cardiovascular drugs (antihypertensive drugs, statins, other lipid-lowering drugs, high-dose aspirin, platelet inhibitors, nitrates), and hormone replacement therapy filled before the date of admission for MI or index date for controls.

We estimated the duration of diabetes as the time since the earliest prescription for an antidiabetic drug or the earliest diabetes diagnosis or the earliest blood glucose measurement

or visit at the chiropodist. We then categorized the duration in three groups; ≤5 years, 5-10 years, >10 years.

Finally, based on data from the IDA, we classified the cases and controls according to their marital status (single, married or co-habiting), employment status (old-age pensioner, self-employed, salaried employed), gross income (below 25th percentile, 25th-50th, 50th-75th, above 75th percentile), and educational level (university degree, short/medium-term formal education, basic vocational education, basic school, unspecified) in the year prior to admission for MI or index date. We excluded cases and controls with missing information on these socioeconomic factors.

Biochemical data reflecting the intensity of the antiglycemic treatment were available from the clinical biochemical information system for patients from North Jutland and Aarhus Counties, covering a population of approximately 1,150,000 (~22% of the total Danish population). Data were available on laboratory tests from all hospitals and general practices in the two counties. We retrieved data on HbA_{1c}, and used the latest measurement within 180 days prior to admission or index date and seven days after the admission or index date.

Statistical analyses

We created contingency tables and used conditional logistic regression analysis to compute crude and adjusted odds ratios (ORs) of MI according to use of antidiabetic treatment. Since we used risk set sampling of controls, these ORs are unbiased estimates of the corresponding incidence rate ratio [14]. We adjusted for a previous history of hypertension, chronic bronchitis and emphysema, alcohol-related diseases, liver cirrhosis, stroke, peripheral arterial disease, and diabetes complications (i.e. retinopathy, nephropathy, and neuropathy), and for use of antihypertensive drugs, statins, other lipid-lowering drugs, high-dose aspirin, platelet

inhibitors, oral anticoagulants, nitrates, or hormone replacement therapy, and marital status, employment status, gross income, and educational level in the logistic regression analyses.

Differences in risk of MI between the different combination types and between the individual sulphonylureas were assessed by likelihood ratio tests.

Patients receiving sulphonylureas were used as the reference group in the primary analyses. In the subanalysis where we compared the risk among users of different sulphonylureas, both users of tolbutamide and metformin served as the reference group.

Prescriptions for antidiabetic drugs in Denmark are usually issued for three months, but may be issued for up to six months. We therefore also analysed the data based on drug use within 180 days prior to hospitalisation or index date.

We analysed data with Stata 8.2 (StataCorp LP, College Station, TX, USA) and with version 9.13 of the SAS software (SAS Institute Inc., Cary, NC, USA).

Results

We identified a total of 10,616 MI cases and 90,697 population controls. Characteristics of cases and controls are shown in Table 1. Among cases, 7,134 (67.2%) had filled a prescription for an antidiabetic drug within 90 days prior to admission for MI. In comparison, 53,821 (59.3%) controls filled a prescription. Hypertension, chronic bronchitis and emphysema, retinopathy, nephropathy, neuropathy, stroke, and peripheral arterial disease were more prevalent among cases than controls, and more cases than controls had filled prescriptions for antihypertensive drugs, statins, other lipid-lowering drugs, high-dose aspirin, platelet inhibitors, hormone replacement therapy, and nitrates.

Table 2 shows the crude and adjusted ORs for MI according to use of antidiabetic drugs. After adjustment for possible confounding factors, use of metformin and insulin were

associated with a lower risk of MI compared with use of sulphonylureas, adjusted ORs 0.86 (95% CI: 0.78-0.95) and 0.92 (95% CI: 0.86-0.99), respectively. The lowest risk of MI was found among the patients not receiving any antidiabetic pharmacotherapy (adjusted OR 0.75 (95% CI: 0.71-0.79). Users of any combination of the antidiabetic drugs had similar risk of MI as users of sulphonylureas, adjusted OR 0.99 (95% CI: 0.92-1.06), with no differences between the various types of combination (p=0.11).

When excluding the patients only identified in the National Health Insurance Service Registry (1,643 cases and 24,910 controls), we found no differences in the risk between patients not treated with antidiabetic pharmacotherapy and users of sulphonylureas (adjusted OR 0.98, 95% CI: 0.92-1.05), indicating that the patients only seen in the primary healthcare had a milder form of diabetes. Furthermore, use of metformin was then associated with lower risk of MI than no antidiabetic pharmacotherapy (p=0.003).

We found no differences in the risk of MI between the individual sulphonylureas (p=0.39). Thus compared with tolbutamide, the adjusted ORs for use of glibenclamide, glipizide, gliclazide and glimepiride were 1.01 (95% CI: 0.90-1.14), 0.94 (95% CI: 0.82-1.08), 0.89 (95% CI: 0.74-1.07) and 1.02 (95% CI: 0.90-1.16), respectively. Table 3 shows crude and adjusted ORs for MI according to the different sulphonylureas compared with users of metformin. All sulphonylureas had slightly increased risk of MI compared with metformin, but not all reached statistical significance.

Data on HbA_{1c} were available on 886 cases and 1,397 controls from the North Jutland and Aarhus Counties. We examined the effect of the intensity of the glycaemic control among this subset of patients, although with a much weaker statistical precision. The HbA_{1c} level had

only minor effects on the risk estimates, i.e. further adjustment for the parameter changed the estimates with only 2%-6% (data not shown).

All results were virtually unchanged when estimating the ORs based on drug use within 180 days prior to MI or index date. Thus compared with sulphonylureas, the adjusted ORs were 0.86 (95% CI: 0.78-0.95), 0.91 (95% CI: 0.85-0.98), 1.00 (95% CI: 0.94-1.07), and 0.75 (95% CI: 0.71-0.79) for use of metformin, insulin, any combination and no antidiabetic pharmacotherapy, respectively.

Discussions

We found a lower risk of hospitalisation with MI among users of metformin, insulin, and patients not treated with antidiabetic pharmacotherapy compared with users of sulphonylureas in this large nationwide case-control study on patients with type 2 diabetes mellitus. However, patients discharged with a diagnosis of diabetes mellitus but not receiving any antidiabetic drugs had similar risk as users of sulphonylureas. The increased risk associated with use of sulphonylureas appeared not to be explained by differences in the intensity of the antiglycemic treatment.

The main strengths of this study are its large size, the uniformly organised healthcare system allowing a population-based design and the ability to link different data sources with prospectively collected data. As these data sources comprise complete population data, our results reflect the daily clinical practice in Denmark. We were able to examine differences between the types of antidiabetic drugs as well as between the 5 individual sulphonylureas available in Denmark, and to adjust for a wide range of conditions and treatments associated with the development of MI. Furthermore, all data were prospectively collected, avoiding the potential difficulties with any recall bias.

The validity of our estimates depends on the comparability of the groups and the accuracy of the registries. We used three different registries to identify our study population of all Danish patients with diabetes mellitus. The combined use of the Danish National Patient Registry and the Register of Medicinal Product Statistics to identify patients with diabetes mellitus have proven to be of high quality and nearly complete [16], and further addition of information from the National Health Insurance Service Registry gives a more valid estimate of the entire Danish population with diabetes mellitus [17,18]. Finally, the validity of the hospital discharge diagnoses used to identify the cases with first-time MI patients also seems high [19,20].

A potential weakness of our study is the case definition. As the diagnosis of MI was obtained through diagnoses coded at hospital discharge, the MI-patients not reaching the hospital will remain unnoticed. We have therefore not included patients who died before reaching the hospital or patients who were not hospitalized or misdiagnosed at the hospital. Thus, if users of certain antidiabetic drugs were more likely to die before reaching the hospital, be non-hospitalized if experiencing an MI or be misdiagnosed at the hospital, this would generate a selection bias. Other limitations include the lack of data on compliance and duration of actual use of the prescribed drugs. Finally, in spite of adjusting for several potential confounding factors, our results may still be affected by potential unmeasured confounding factors (lifestyle factors such as diet, obesity, and exercise), and residual confounding due to potential misclassification of the included variables or use of crude categories for some of the included variables.

Our study is in agreement with a number of other studies. An American case-control study showed a significant reduction in the risk of MI associated with metformin (OR 0.48, 95% CI:

0.27-0.82) compared with sulphonylurea (glipizide and glibenclamide) use among patients with type 2 diabetes mellitus [7]. A follow-up study investigating the incidence of new coronary events in older patients with diabetes mellitus and prior MI treated with sulphonylureas, insulin, metformin and diet found higher incidence in patients treated with sulphonylureas than in patients treated with insulin (p=0.0003) and diet (p=0.022) [4]. There were no statistical significant difference between sulphonylurea and metformin [4], however, only 7 users of metformin were readmitted with a new coronary event hampering the statistical precision.

We found similar risk of hospitalisation with MI in patients treated with any combination and patients treated with sulphonylureas alone, which is in agreement with other studies, in which the combination of metformin and sulphonylurea was not associated with lower risk compared with sulphonylurea alone [5,7].

We were not able to confirm our previous finding of a particular high MI risk among patients not treated with antidiabetic drugs [10]. This may at least partly be explained by the use in the present study of the National Health Insurance Service Registry to identify patients with diabetes mellitus, whereby we might have included a not-treated population with milder diabetes mellitus than if only identifying patients from the Danish National Patient Registry and the Register of Medicinal Product Statistics. Nor could we confirm our previous finding of a higher risk of hospitalisation with MI among users of glibenclamide, glipizide and tolbutamide compared with users of glimepiride and gliclazide (p=0.01) [10]. However, the previous study was small (867 cases and 3,148 controls with diabetes mellitus, of which 361 cases and 1,626 controls were treated with sulphonylureas) with few data on confounding factors.

Most guidelines suggest metformin as first-line therapy, we therefore compared the different sulphonylureas (suggested alternative) with metformin, and in this comparison we found a slight increase in risk for some, but not all sulphonylureas.

Our results also to some extent disagree with the studies showing a reduced risk of metformin compared with diet therapy [5,7]. However, when excluding the patients only identified in the National Health Insurance Service Registry, we found decreased risk among users of metformin compared with patients not treated with antidiabetic pharmacotherapy.

In conclusion, our findings provide some support to the hypothesis that sulphonylureas in general may be associated with a slightly increased risk of hospitalisation with MI compared with metformin and insulin.

Acknowledgements

This study was supported by the Research Initiative of Aarhus University Hospital, the University of Aarhus, the Danish Diabetes Association, and the Danish Medical Research Council. Department of Clinical Epidemiology, Aarhus University Hospital, is a partner in Center of Cardiovascular Research, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark.

Duality of interest

S. P. Johnsen and J. Rungby have previously received an unrestricted research grant from Servier. J. Rungby and H. T. Horsdal are former consultants for Sanofi-Aventis. J. Rungby has served on advisory boards for Sanofi-Aventis and Novo Nordisk. F. Søndergaard has no duality of interest to report.

References

1. Beckman JA, Creager MA, Libby P (2002) Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 287:2570-2581

2. Stratton IM, Adler AI, Neil HA, et al (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 321:405-412

3. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837-853

4. Aronow WS, Ahn C (2001) Incidence of new coronary events in older persons with diabetes mellitus and prior myocardial infarction treated with sulfonylureas, insulin, metformin, and diet alone. Am J Cardiol 88:556-557

5. UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352:854-865

6. Kao J, Tobis J, McClelland RL, et al (2004) Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. Am J Cardiol 93:1347-50, A5

7. Sauer WH, Cappola AR, Berlin JA, Kimmel SE (2006) Insulin sensitizing pharmacotherapy for prevention of myocardial infarction in patients with diabetes mellitus. Am J Cardiol 97:651-654

8. McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM (2007) Coronary heart disease outcomes in patients receiving antidiabetic agents. Pharmacoepidemiol Drug Saf 16:711-725

9. Belcher G, Lambert C, Goh KL, Edwards G, Valbuena M (2004) Cardiovascular effects of treatment of type 2 diabetes with pioglitazone, metformin and gliclazide. Int J Clin Pract 58:833-837

10. Johnsen SP, Monster TB, Olsen ML, et al (2006) Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. Am J Ther 13:134-140

11. Frank L (2000) Epidemiology. When an entire country is a cohort. Science 287:2398-2399

12. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB (2006) The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 53:441-449

13. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH (1999) The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 46:263-268

14. Wacholder S, McLaughlin JK, Silverman DT, Mandel JS (1992) Selection of controls in case-control studies. I. Principles. Am J Epidemiol 135:1019-1028

15. Statistics Denmark (1991) IDA—an integrated database for labour market research. Statistics Denmark, Copenhagen, Denmark

16. Nielsen GL, Sørensen HT, Pedersen AB, Sabroe S (1996) Analyses of data quality in registries concerning diabetes mellitus--a comparison between a population based hospital discharge and an insulin prescription registry. J Med Syst 20:1-10

17. Drivsholm TB, Frederiksen K, de Fine ON, Odegaard B, Kristensen JK (2003) [The prevalence of diabetes in Denmark. Development of a method for a registry-based assessment]. Ugeskr Laeger 165:2887-2891

18. Kristensen JK, Sandbaek A, Lassen JF, Bro F, Lauritzen T (2001) Use and validation of public data files for identification of the diabetic population in a Danish county. Dan Med Bull 48:33-37

19. Madsen M, Balling H, Eriksen LS (1990) [The validity of the diagnosis of acute myocardial infarction in 2 registries: the Heart Registry compared to the National Patient Registry]. Ugeskr Laeger 152:308-314

20. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M (2003) The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol 56:124-130

Tables

Table 1. Descriptive characteristics of cases with type 2 diabetes mellitus and a first-time hospitalisation with myocardial infarction and controls with type 2 diabetes mellitus (matched on age and gender) in Denmark, 1996-2004.

Characteristics[a]	Cases (N=10,616)		Controls (N=90,697)		p-value
Age, median (range)	73.2	(23-100)	73.3	(23-100)	0.724
Sex (males)	6,180	(58.2)	52,253	(57.6)	0.235
Duration of diabetes mellitus (%)					<0.001
≤5 years	4,922	(46.4)	45,146	(49.8)	
5-10 years	3,238	(30.5)	27,494	(30.3)	
>10 years	2,456	(23.1)	18,057	(19.9)	
Previous discharge diagnoses (%)					
Hypertension	3,091	(29.1)	19,072	(21.0)	<0.001
Chronic bronchitis and emphysema	1,030	(9.7)	6,446	(7.1)	<0.001
Alcohol-related diseases	434	(4.1)	4,004	(4.4)	0.120

Liver cirrhosis	44	(0.4)	562	(0.6)	0.009
Retinopathy	998	(9.4)	6,241	(6.9)	<0.001
Nephropathy	650	(6.1)	2,849	(3.1)	<0.001
Neuropathy	664	(6.3)	4,314	(4.8)	<0.001
Stroke	1,377	(13.0)	9,051	(10.0)	<0.001
Peripheral arterial disease	1,622	(15.3)	7,066	(7.8)	<0.001
Prescription for (%)					
Antihypertensive drugs	8,183	(77.1)	62,740	(69.2)	<0.001
Statins	1,910	(18.0)	12,555	(13.8)	<0.001
Other lipid-lowering drugs	159	(1.5)	1,120	(1.2)	0.022
High-dose aspirin	1,372	(12.9)	8,952	(9.9)	<0.001
Platelet inhibitors	2,439	(23.0)	16,086	(17.7)	<0.001
Oral anticoagulants	397	(3.7)	3,450	(3.8)	0.743
Hormone replacement therapy	1,064	(10.0)	9,887	(10.9)	0.006
Nitrates	3,189	(30.0)	13,151	(14.5)	<0.001

Marital status (%)					0.016
Single	4,750	(44.7)	41,697	(46.0)	
Married or co-habiting	5,866	(55.3)	49,000	(54.0)	
Gross income (%)					<0.001
1. quartile	3,003	(28.3)	22,362	(24.7)	
2. quartile	2,672	(25.2)	22,615	(24.9)	
3. quartile	2,607	(24.6)	22,721	(25.1)	
4. quartile	2,329	(21.9)	22,999	(25.4)	
Educational level (%)					<0.001
University degree	142	(1.3)	1,797	(2.0)	
Short/medium-term formal education	490	(4.6)	5,487	(6.1)	
Basic vocational education	2,270	(21.4)	20,669	(22.8)	
Basic school	4,692	(44.2)	37,464	(41.3)	
Unspecified	3,022	(28.5)	25,280	(27.8)	

Employment status (%)					<0.001
Old-age pensioner	8,950	(84.3)	74,661	(82.3)	
Employed	1,360	(12.8)	13,234	(14.6)	
Other	306	(2.9)	2,802	(3.1)	
Laboratory data[b]					
HbA_{1c} (%), *median (range)*[c]	7.5	(5-19)	7.3	(4-14)	<0.001

[a] All variables are shown as number (%), except for age and HbA_{1c}, which are shown as median (range).

[b] Data only available for patients from North Jutland and Aarhus Counties (N=1,466 cases, 2,484 controls).

[c] Data on HbA_{1c} only available for 886 cases and 1,397 controls.

Table 2. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for hospitalisation with myocardial infarction according to prescription for antidiabetic drugs filled within 90 days before hospitalisation or index date compared with patients who filled prescriptions for sulphonylureas.

Antidiabetic medication	Cases (N=10,616)		Controls (N=90,697)		Crude OR (95% CI)	p-value	Adjusted OR[a] (95% CI)	p-value
Sulphonylureas	3,080	(29.0)	23,698	(26.1)	1.00 (reference)		1.00 (reference)	
Metformin	599	(5.6)	5,328	(5.8)	0.86 (0.79-0.95)	0.002	0.86 (0.78-0.95)	0.004
Insulin	1,972	(18.6)	13,853	(15.3)	1.09 (1.03-1.16)	0.004	0.92 (0.86-0.99)	0.027
Any combination	1,483	(14.0)	10,942	(12.1)	1.04 (0.98-1.11)	0.221	0.99 (0.92-1.06)	0.809
No pharmacotherapy	3,482	(32.8)	36,876	(40.7)	0.72 (0.69-0.76)	<0.001	0.75 (0.71-0.79)	<0.001

[a] Adjusted for discharge diagnoses of hypertension, bronchitis and emphysema, alcohol-related diseases, liver cirrhosis, retinopathy, nephropathy, neuropathy, stroke and peripheral arterial disease, prescriptions for antihypertensive drugs, statins, other lipid-lowering drugs, high-dose aspirin, platelet inhibitors, oral anticoagulants, hormone replacement therapy, nitrates, and previous use of other types of antidiabetic drugs before the hospitalisation or index date, duration of diabetes, marital status, education, income, and employment status.

Table 3. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for hospitalisation with myocardial infarction according to prescription for different sulphonylureas filled within 90 days before hospitalisation or index date compared with patients who filled prescriptions for metformin.

Antidiabetic medication	Cases (N=3,679)		Controls (N=29,026)		Crude OR (95% CI)	p-value	Adjusted OR[a] (95% CI)	p-value
Metformin	599	(5.6)	5,328	(5.8)	1.00 (reference)		1.00 (reference)	
Tolbutamide	461	(15.0)	3,585	(15.1)	1.15 (1.01-1.31)	0.037	1.16 (1.02-1.33)	0.029
Glibenclamide	1,013	(32.9)	7,721	(32.6)	1.17 (1.05-1.30)	0.006	1.18 (1.05-1.32)	0.005
Glipizide	496	(16.1)	4,077	(17.2)	1.09 (0.96-1.24)	0.194	1.10 (0.96-1.25)	0.177
Gliclazide	188	(6.1)	1,635	(6.9)	1.02 (0.86-1.22)	0.787	1.04 (0.87-1.24)	0.682
Glimepiride	922	(29.9)	6,680	(28.2)	1.22 (1.09-1.36)	<0.001	1.19 (1.06-1.33)	0.003

[a] Adjusted for discharge diagnoses of hypertension, bronchitis and emphysema, alcohol-related diseases, liver cirrhosis, retinopathy, nephropathy, neuropathy, stroke and peripheral arterial disease, prescriptions for antihypertensive drugs, statins, other lipid-lowering drugs, high-dose aspirin, platelet inhibitors, oral anticoagulants, hormone replacement therapy, nitrates, and previous use of other types of antidiabetic drugs before the hospitalisation or index date, duration of diabetes, marital status, education, income, and employment status.

Diabetologia (2008) 51:567–574
DOI 10.1007/s00125-008-0947-6

ARTICLE

Type of preadmission glucose-lowering treatment and prognosis among patients hospitalised with myocardial infarction: a nationwide follow-up study

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Received: 26 October 2007 / Accepted: 14 January 2008 / Published online: 19 February 2008

Abstract
Aims/hypothesis We examined whether the type of preadmission glucose-lowering treatments explained differences in mortality rate and risk of readmission with myocardial infarction (MI) and heart failure following first-time hospitalisation for MI in patients with type 2 diabetes mellitus.
Methods We conducted a nationwide population-based follow-up study among all Danish patients hospitalised with first-time MI from 1996 to 2004. Data on use of glucose-lowering drugs and other medications, comorbidities, socioeconomic status, laboratory findings, readmission with MI and heart failure, and death were obtained from medical databases. We computed mortality rates and rates of MI and heart failure readmission, according to type of glucose-lowering treatment and used Cox's proportional hazards regression analysis to compute hazard ratios (HRs) as estimates of relative risks.
Results We identified 8,494 MI patients with type 2 diabetes mellitus. The overall cumulative 30 day and 1 year mortality rates were 22.2 and 36.6%, respectively. Patients not receiving any glucose-lowering drugs (adjusted 30 day HR: 0.79, 95% CI: 0.57–1.10) and users of any combination (adjusted 30 day HR: 1.43, 95% CI: 0.98–2.09) had the lowest and highest mortality rates, respectively, when compared with users of sulfonylureas. We found that glycaemic control had no impact on the risk estimates in a subanalysis including biochemical laboratory data. We found no differences in the risk of new MI and heart failure between the different glucose-lowering agents.
Conclusions/interpretation Type of preadmission glucose-lowering treatment in monotherapy is not associated with substantial differences in prognosis following hospitalisation with MI. However, patients treated with any combination had increased mortality rates.

Keywords Epidemiology · Glucose-lowering treatment · Heart failure · Hospitalisation · MI · Mortality · Myocardial infarction · Prognosis · Readmission · Type 2 diabetes mellitus

Abbreviations

CK-MB	creatine kinase-myocardial band
HR	hazard ratio
HRT	hormone replacement therapy
ICD	International Classification of Disease
IDA	Integrated Database for Labour Market Research
MI	myocardial infarction
PCOS	polycystic ovary syndrome

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Introduction

Type 2 diabetes mellitus is a progressive disease characterised by varying degrees of insulin resistance and relative insulin deficiency. Initially, glycaemic control is achieved non-pharmacologically (i.e. by diet and exercise), but in later stages pharmacotherapy with one or more drug is required [1]. It is likely that treatments aimed to improve glycaemic control will prevent cardiovascular complications, which are often seen among patients with type 2 diabetes mellitus, but it remains uncertain whether the treatments themselves have adverse effects on the cardiovascular system.

Patients with diabetes mellitus have a poorer prognosis after myocardial infarction (MI) including increased rates of new MI, heart failure and death, when compared with their non-diabetic counterparts [2]. Data regarding outcome in cardiac patients using various types of glucose-lowering drugs are sparse and conflicting [3–14], and the existing studies have some limitations, including small and often non-representative samples and shortcomings in the data analysis.

As a large proportion of patients with type 2 diabetes mellitus suffer from cardiovascular diseases and are permanently dependent on their glucose-lowering drugs, it is important to clarify the risk associated with the different glucose-lowering drugs. Here, in a nationwide population-based follow-up study, we examine the prognosis among Danish patients with type 2 diabetes mellitus, who were admitted to hospital with a first-time MI and were using various types of glucose-lowering treatments.

Methods

Setting and design We conducted this follow-up study within the entire Danish population (approximately 5.3 million).

The Danish National Health Service provides tax-supported healthcare for all inhabitants, guaranteeing free access to general practitioners and hospitals, and refunding a variable proportion of the prescription medication costs. The Danish Civil Registration System keeps electronic records on sex, date of birth, change of address, date of emigration and changes in vital status since 1968 [15, 16]. The records carry a unique ten-digit civil registration number, assigned to every Danish citizen and used in all Danish registries, enabling unambiguous linkage between them.

Patients with MI The Danish National Patient Registry [17], established in 1977, collects data on all hospitalisations from non-psychiatric hospitals in the country, including dates of admission and discharge, surgical procedure(s) performed and up to 20 discharge diagnoses assigned by the treating physician and coded according to the International Classification of Diseases (ICD) 8th revision (ICD-8) until the end of 1993 (thereafter 10th revision [ICD-10]). From the registry, we identified all patients with a first-time primary discharge diagnosis of MI (ICD-10 codes I21.0-I21.9) among those who had been hospitalised between 1 January 1996 and 30 November 2004.

Glucose-lowering agents The Register of Medicinal Product Statistics contains data from 1995 onwards on all prescription drugs dispensed at all Danish pharmacies, including patients' civil registration numbers, type of drug according to the Anatomical Therapeutic Chemical classification system and date of drug dispensing.

In Denmark, glucose-lowering drugs are available by prescription only. Among the MI patients, we traced all prescriptions for glucose-lowering drugs redeemed prior to admission for MI. Users of glitazones (n=2), meglitinides (n=60) and α-glucosidase inhibitors (n=19) were excluded from the analyses due to the low number of treated patients.

Patients who had used only one type of glucose-lowering drug in the 90 days prior to hospitalisation were categorised according to the class of the glucose-lowering drug: sulfonylureas, metformin or insulin. Patients who had used more than one type of glucose-lowering drug during the 90 days prior to hospitalisation were categorised as combined users and divided according to the type of combination: sulfonylureas and metformin, sulfonylureas and insulin, metformin and insulin, or sulfonylureas, metformin and insulin. Patients with a diagnosis of diabetes since 1977 according to the Patient Registry (ICD-8 codes 249, 250, ICD-10 codes E10, E11, E14, G63.2, H36.0, N08.3) but not using any glucose-lowering drugs during the 90 days prior to hospitalisation were categorised as diabetic patients without pharmacotherapy. For all patients, we also received information on whether they had used other types of glucose-lowering drugs before the 90 days prior to the admission for MI, as well as on their use of glucose-lowering drugs within 1 year after the admission.

We classified the diabetic patients according to their type of diabetes: type 1 if they were less than 30 years old by the time of the first prescription or diagnosis and had never received a prescription for an oral glucose-lowering drug; type 2 if they had not received pharmacotherapy or had received a prescription for an oral glucose-lowering drug or were older than 30 years at the time of first prescription or diagnosis, regardless of treatment. Patients with type 1 diabetes mellitus (n=175) were excluded from the study.

Patients with polycystic ovary syndrome (PCOS) may also receive treatment with metformin, thus to avoid inclusion of these non-diabetic patients, we sought to identify patients with a PCOS diagnosis (ICD-10 code E28.2) among the users of metformin. No such patients were identified.

Endpoints The endpoints were 30 day and 1 year all-cause mortality (in and outside the hospital) and readmission with

new MI or heart failure within 1 year after admission with MI. Mortality was ascertained from the Civil Registration System; readmission with a new MI (ICD-10 codes I21, I22) or heart failure (ICD-10-codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.6, I42.7, I42.8, I42.9, I50.0, I50.1, I50.9) were ascertained from the Danish National Patient Registry. Readmission with MI within 28 days of the original MI was not considered a new event [18].

Covariates We obtained data on covariates from the Danish National Patient Registry, the Register of Medicinal Product Statistics, the Integrated Database for Labour Market Research (IDA) at Statistics Denmark [19] and, for a subset, from the Laboratory Information Systems in the Counties of North Jutland and Aarhus.

Based on discharge diagnoses from the Danish National Patient Registry, we computed, for each patient, the comorbidity index score developed by Charlson et al. [20]. The index covers 19 major disease categories, including diabetes mellitus, MI, heart failure, cerebrovascular diseases and cancer, weighted according to their impact on patient survival. MI and diabetes mellitus were excluded from the comorbidity index calculations. We also obtained information on previous diagnoses of hypertension, coronary revascularisation procedures (percutaneous coronary intervention and coronary artery bypass graft), alcoholism-related diseases and diabetes complications (i.e. retinopathy, nephropathy and neuropathy). Data on coronary revascularisation procedures performed during or after the admission for MI were also obtained.

We identified all prescriptions for cardiovascular drugs (antihypertensive drugs, lipid-lowering drugs, platelet inhibitors, vitamin K antagonists) and hormone replacement therapy (HRT) redeemed before the date of admission for MI or within 1 year after the admission.

We estimated the duration of diabetes as the time since the earliest prescription for a glucose-lowering drug or the earliest diabetes diagnosis and categorised the duration in three groups: ≤5 years, 5 to 10 years, >10 years. Finally, based on data from IDA, we classified the patients according to socioeconomic status (employed, pensioner or other) in the year prior to admission for MI.

Biochemical data reflecting the intensity of the antiglycaemic treatment and the extent of myocardial damage following admission with MI were available from the Laboratory Information System for tests analysed in North Jutland and Aarhus Counties, covering a population of approximately 1,150,000 (~22% of the total Danish population). Data were available on laboratory tests from all the counties' hospitals and general practices. We retrieved data on HbA_{1c}, blood glucose, troponin T and creatine kinase-myocardial band (CK-MB). We used the latest measurement of HbA_{1c} within 180 days prior to admission and 7 days after the admission and the highest level of blood glucose, troponin T and CK-MB on the day of admission or the following day.

As the proportion of users of the different glucose-lowering drugs varied during the study period, thereby creating a risk of comparing patients from different calendar periods when comparing the treatments, we also included the calendar time of admission in the analyses.

Statistical analyses Characteristics of the users of various types of glucose-lowering treatments were compared using a χ^2 analysis for the categorical variables, whereas continuous variables were compared using Kruskal–Wallis tests.

Follow-up began on the date of admission with MI and ended on the date of admission with new MI or heart failure (only in analyses on risk of new MI or heart failure, respectively), death, emigration or after 30 days or 1 year. We computed Kaplan–Meier mortality curves for the glucose-lowering treatments and computed the cumulative 30 day and 1 year mortality rates.

We used Cox's proportional hazards regression analysis (with the Efron approximation to handle tied survival times) to compute hazard ratios (HRs) as estimates of the relative risks for each outcome. We included all the measured covariates; use of glucose-lowering drugs, cardiovascular drugs, HRT and coronary revascularisation procedures after MI were treated as time-dependent covariates. The p values were estimated by Wald tests. The largest group, i.e. patients receiving sulfonylureas, served as the reference group in all analyses.

To examine possible sex-related differences in prognosis, we also analysed the HRs stratified by sex. Differences in prognosis between the different combination types were assessed by likelihood ratio tests; differences in troponin T and CK-MB levels, which may reflect infarct size [21], were assessed by Kruskal–Wallis tests.

Prescriptions for glucose-lowering drugs in Denmark are usually issued for 3 months, but may be issued for up to 6 months. We therefore also analysed the data based on drug use within 180 days prior to hospitalisation.

We analysed data with Stata 8.2 (StataCorp LP, College Station, TX, USA) and with version 9.13 of SAS software (SAS Institute, Cary, NC, USA). The statistical significance level was set to 0.05 in all analyses.

Results

Diabetes treatment groups We identified 8,494 patients with type 2 diabetes mellitus who were hospitalised with a first-time MI during the study period. Among these patients, 31.7% were being treated with sulfonylureas, 6.0% with metformin, 21.5% with insulin and 15.7% with any combination of glucose-lowering drugs, while 25.1% were not

Table 1 Descriptive characteristics according to glucose-lowering treatment of patients with type 2 diabetes mellitus hospitalised with a first-time MI in Denmark during the period 1996 to 2004

Characteristic[a]	SU		Metformin		Insulin		Combination		No pharmacotherapy		*p* value
	(*n*=2,691)		(*n*=511)		(*n*=1,827)		(*n*=1,333)		(*n*=2,132)		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Age in years, median (range)	75.4	36–100	67.5	33–96	71.9	25–96	70.1	37–97	74.1	35–100	<0.001
Sex (men)	1,583	58.8	324	63.4	932	51.0	763	57.2	1,218	57.1	<0.001
Calendar period											<0.001
1996–1998	911	33.8	73	14.3	527	28.9	336	25.2	555	26.0	
1999–2001	909	33.8	153	29.9	585	32.0	398	29.9	738	34.6	
2002–2004	871	32.4	285	55.8	715	39.1	599	44.9	839	39.4	
Duration of diabetes mellitus (years)											<0.001
≤5	1,702	63.2	346	67.7	322	17.6	522	39.2	1,198	56.2	
5–10	707	26.3	122	23.9	571	31.3	544	40.8	557	26.1	
>10	282	10.5	43	8.4	934	51.1	267	20.0	377	17.7	
Charlson's comorbidity index											<0.001
0	1,296	48.1	294	57.5	624	34.2	682	51.2	822	38.6	
1–2	1,065	39.6	186	36.4	877	48.0	522	39.1	930	43.6	
≥3	330	12.3	31	6.1	326	17.8	129	9.7	380	17.8	
Discharge diagnoses of											
Hypertension	1,999	74.3	393	76.9	1,471	80.5	1,060	79.5	1,635	76.7	<0.001
Alcoholism	71	2.6	19	3.7	102	5.6	41	3.1	111	5.2	<0.001
Former revascularisation	80	3.0	25	4.9	93	5.1	45	3.4	91	4.3	0.003
Retinopathy	135	5.0	21	4.1	594	32.5	156	11.7	194	9.1	<0.001
Nephropathy[b]	95	3.5	19	3.7	301	16.5	81	6.1	169	7.9	<0.001
Neuropathy	110	4.1	26	5.1	342	18.7	107	8.0	139	6.5	<0.001
Prescription for[c]											
Antihypertensive drugs	1,972	73.3	385	75.3	1,446	79.2	1,047	78.5	1,594	74.8	<0.001
Platelet inhibitors	562	20.9	111	21.7	424	23.2	311	23.3	401	18.8	<0.001
Vitamin K antagonists	88	3.3	16	3.1	68	3.7	60	4.5	66	3.1	0.209
Lipid-lowering drugs	316	11.7	140	27.4	352	19.3	299	22.4	273	12.8	<0.001
HRT	243	9.0	46	9.0	194	10.6	138	10.4	220	10.3	0.339
Socioeconomic status[d]											<0.001
Employed	285	10.8	114	22.7	204	11.4	184	14.0	258	12.3	
Pensioner	2,287	86.8	364	72.5	1,535	86.1	1,068	81.3	1,774	84.6	
Other	63	2.4	24	4.8	45	2.5	62	4.7	66	3.1	
Laboratory data[e]											
HbA_{1c}, % (median [range])[f]	7.5	4.7–12.5	7.2	5.4–11.3	8.5	5.4–13.9	8.1	1.0–13.8	7.1	4.7–13.1	<0.001
Blood glucose, mmol/l (median [range])[g]	12.8	3.9–48.4	10.9	5.6–26.3	14.8	2.3–61.7	14.4	4.8–36.1	10.8	3.2–33.9	<0.001
Troponin T, μg/l (median [range])[h]	1.29	0.01–64	0.96	0.01–50	1.42	0.01–48	1.2	0.01–34	1.00	0.01–43	<0.001
Creatine kinase MB, μg/l (median [range])[i]	42.4	0.8–1746	35.6	0.3–455	41.6	1.5–1000	31.1	1.9–529	29.9	0.1–1000	<0.001

[a]All variables are shown as *n* (%), except for age and laboratory data, which are shown as median (range)
[b]Also included in the Charlson index
[c]Received a prescription within 90 days (platelet inhibitors and vitamin K antagonists) or ever (all others) before admission for MI
[d]The year prior to admission for MI
[e]Data only available for patients from North Jutland and Aarhus Counties
[f]Measured within 180 days prior to admission and 7 days after admission with MI (*n*=1,189, *n*=265, *n*=352, *n*=69, *n*=323, *n*=180 for total, no pharmacotherapy, sulfonylurea, metformin, insulin, combination treatments, respectively)
[g]Highest measurement at the day of admission (*n*=1,403, *n*=345, *n*=424, *n*=76, *n*=348, *n*=210 for total, no pharmacotherapy, sulfonylurea, metformin, insulin, combination treatments, respectively)
[h]Highest measurement at the day of admission or the following day (*n*=1,043, *n*=270, *n*=307, *n*=67, *n*=246, *n*=153 for total, no pharmacotherapy, sulfonylurea, metformin, insulin, combination treatments, respectively)
[i]Highest measurement at the day of admission or the following day (*n*=770, *n*=206, *n*=214, *n*=50, *n*=188, *n*=112 for total, no pharmacotherapy, sulfonylurea, metformin, insulin, combination treatments, respectively)
SU, sulfonylurea

receiving glucose-lowering pharmacotherapy at the time of admission. The main clinical and laboratory characteristics of the patients according to glucose-lowering treatment are presented in Table 1.

All-cause mortality rate Cumulative mortality curves for the different treatment groups are shown in Fig. 1. We excluded 161 patients for whom data on socioeconomic status were missing. A total of 1,851 of the remaining 8,333 (22.2%, 95% CI: 21.3–23.1) patients died within 30 days after admission. Within 1 year, 36.6% (95% CI: 35.5–37.7) of the patients were dead.

Compared with users of sulfonylureas, we found lower crude risks of mortality among patients using metformin (30 day HR: 0.55, 95% CI: 0.43–0.71) or any combination (30 day HR: 0.85, 95% CI: 0.73–0.98). In contrast, the crude 30 day HRs were 1.10 (95% CI: 0.97–1.24) and 0.99 (95% CI: 0.88–1.11) for users of insulin and patients not receiving pharmacotherapy, respectively, compared with users of sulfonylureas. After adjustment for differences in covariates, we found no differences between the glucose-lowering drugs in monotherapy i.e. the 30 day adjusted HRs for the use of metformin and insulin were 0.85 (95% CI: 0.40–1.81) and 1.05 (95% CI: 0.63–1.76), but the use of any combination was associated with an increased risk of mortality compared with use of sulfonylureas (adjusted 30 day HR: 1.43, 95% CI: 0.98–2.09) (Table 2). The highest risk estimate was found among users of the triple combination with sulfonylurea, metformin and insulin (adjusted 30 day HR: 1.79, 95% CI: 0.65–4.95), but we found no differences in mortality rate when comparing use of the different types of combination (p=0.33). When estimating the 1 year HRs, we found similar results (Table 2).

For most treatments, the association was similar among men and women. However, among women the use of metformin was associated with a lower mortality rate than the use of sulfonylureas (adjusted 30 day HR: 0.51, 95% CI: 0.25–1.04; adjusted 1 year HR: 0.49, 95% CI: 0.30–0.79), whereas among men the risk appeared to be increased (adjusted 30 day HR: 1.80, 95% CI: 0.91–3.56; adjusted 1 year HR: 1.82, 95% CI: 1.25–2.64).

The results were similar when estimating the HRs based on drug use 180 days prior to MI.

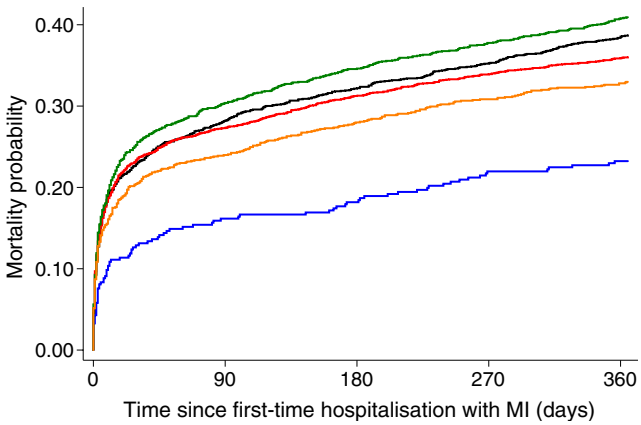

Fig. 1 Kaplan–Meier curves of 1 year all-cause mortality rate after hospitalisation with myocardial infarction (MI) according to use of glucose-lowering treatments in the 90 days prior to hospitalisation. Green line, insulin; black line, no pharmacotherapy; red line, sulfonylureas; orange line, any combination; blue line, metformin

New MI and heart failure Within 1 year of follow-up, 8.4 and 9.6% of the patients were readmitted with a new MI and heart failure, respectively. We found no substantial differences in the risks of new MI or heart failure between users of the different glucose-lowering treatments (Table 3), nor were there any differences in risk of new MI (p=0.75) or heart failure (p=0.28) among users of the different types of combination.

The results were similar when estimating the HRs based on drug use 180 days prior to MI.

Subanalysis including biochemical parameters In the North Jutland and Aarhus County subcohort, data on HbA_{1c} and admission blood glucose levels were available for 1,027 patients with MI. We examined the effect of the intensity of glycaemic control among this subset of patients, although with a much weaker statistical precision. The HbA_{1c} and admission blood glucose levels had only minor effects on the risk estimates, i.e. further adjustment for these parameters changed the estimates by only 1 to 6%. Thus compared with use of sulfonylureas, the adjusted HR of 30 day mortality rate was 1.90 (95% CI: 0.68–5.32) for use of any combination. After further adjustment for HbA_{1c} and blood glucose, the adjusted HR of 30 day mortality rate was 1.83 (95% CI: 0.65–5.13). A similar pattern was found when estimating the 1 year HRs.

We found significant differences in the levels of CK-MB (p=0.0001) and troponin T (p=0.0001) between the users of different glucose-lowering treatments (Table 1). The highest levels were found among users of sulfonylureas and insulin, probably reflecting a larger infarct size in these patients.

Discussion

In this large population-based follow-up study, we found no substantial differences in the prognosis following hospitalisation with MI among patients with type 2 diabetes mellitus using different glucose-lowering drugs in monotherapy. However, use of any combination of glucose-lowering drugs was associated with an increased mortality rate.

The main strength of this study is the use of nationwide population-based registries with complete follow-up both during and after hospitalisation. As these data sources

Table 2 Crude and adjusted 30 day and 1 year HRs for death after first-time hospitalisation with MI according to use of glucose-lowering treatment in the 90 days prior to hospitalisation

Glucose-lowering treatment	n[a]	Mortality rate within 30 days (%)	Crude HR (95% CI)	p value	Adjusted HR[b] (95% CI)	p value	n[c]	Mortality rate within 1 year (%)	Crude HR (95% CI)	p value	Adjusted HR[b] (95% CI)	p value
SU	2,635	23.0	1.00 (reference)	–	1.00 (reference)	–	2,382	36.0	1.00 (reference)	–	1.00 (reference)	–
MET	502	13.4	0.55 (0.43–0.71)	<0.001	0.85 (0.40–1.81)	0.679	396	23.2	0.58 (0.47–0.72)	<0.001	0.96 (0.71–1.31)	0.791
Insulin	1,784	24.9	1.10 (0.97–1.24)	0.141	1.05 (0.63–1.76)	0.848	1,586	40.9	1.16 (1.05–1.29)	0.004	1.13 (0.91–1.40)	0.272
Any combination	1,314	19.7	0.85 (0.73–0.98)	0.025	1.43 (0.98–2.09)	0.067	1,126	33.0	0.89 (0.79–1.01)	0.068	1.43 (1.18–1.73)	<0.001
SU + MET	1,004	20.0	0.86 (0.73–1.01)	0.065	1.30 (0.69–2.45)	0.423	881	32.8	0.89 (0.78–1.01)	0.079	1.35 (1.09–1.68)	0.007
SU + insulin	127	25.2	1.13 (0.79–1.61)	0.497	1.47 (0.87–2.50)	0.154	109	44.0	1.31 (0.98–1.75)	0.069	1.65 (1.18–2.29)	0.003
MET + insulin	144	12.5	0.52 (0.32–0.83)	0.006	1.03 (0.40–2.65)	0.948	100	23.0	0.58 (0.38–0.87)	0.009	1.06 (0.64–1.73)	0.830
SU + MET + insulin	39	20.5	0.87 (0.44–1.75)	0.703	1.79 (0.65–4.95)	0.259	36	30.6	0.84 (0.46–1.51)	0.552	1.80 (0.95–3.45)	0.073
No pharmacotherapy	2,098	22.6	0.99 (0.88–1.11)	0.828	0.79 (0.57–1.10)	0.169	1,829	38.7	1.08 (0.98–1.19)	0.137	0.85 (0.72–1.00)	0.043

[a]The total number of users is lower than in Table 1, because we excluded patients for whom information on socioeconomic status was missing (n=161, 1.9%)
[b]Adjusted for age, sex, calendar period, duration of diabetes, former use of other types of glucose-lowering drugs, level of comorbidity (measured by the Charlson index), socioeconomic status, discharge diagnoses of hypertension, former and subsequent revascularisation, alcoholism, retinopathy and neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, lipid-lowering agents and HRT before the date of hospitalisation with MI; also adjusted for time-dependent treatment with glucose-lowering drugs, cardiovascular drugs and HRT after the date of hospitalisation with MI
[c]The total number of users is lower than in Table 1, because we excluded patients with a first admission in 2004 and patients for whom information on socioeconomic status was missing
MET, metformin; SU, sulfonylurea

Table 3 Crude and adjusted 1 year HRs for new MI and heart failure after first-time hospitalisation with MI according to use of glucose-lowering treatment in the 90 days prior to hospitalisation

Glucose-lowering treatment	n[a]	New MI within 1 year (%)	Crude HR (95% CI)	p value	Adjusted HR[b] (95% CI)	p value	Heart failure within 1 year (%)	Crude HR (95% CI)	p value	Adjusted HR[b] (95% CI)	p value
SU	2,382	7.9	1.00 (reference)	–	1.00 (reference)	–	9.5	1.00 (reference)	–	1.00 (reference)	–
MET	396	7.8	0.84 (0.57–1.23)	0.370	1.21 (0.77–1.92)	0.406	8.6	0.77 0.54–1.11)	0.163	0.81 (0.51–1.29)	0.378
Insulin	1,586	9.7	1.30 (1.05–1.60)	0.017	1.30 (0.91–1.86)	0.148	10.7	1.19 (0.98–1.45)	0.085	0.99 (0.70–1.40)	0.954
Any combination	1,126	9.1	1.11 (0.87–1.41)	0.418	1.33 (0.97–1.81)	0.074	9.6	0.97 (0.77–1.23)	0.820	0.89 (0.65–1.22)	0.456
SU + MET	881	8.5	1.04 (0.79–1.36)	0.788	1.24 (0.88–1.74)	0.224	9.1	0.92 (0.71–1.18)	0.506	0.82 (0.58–1.16)	0.257
SU + insulin	109	12.8	1.83 (1.06–3.14)	0.030	1.78 (0.98–3.22)	0.057	12.8	1.53 (0.89–2.62)	0.125	1.28 (0.71–2.32)	0.409
MET + insulin	100	10.0	1.06 (0.56–2.01)	0.850	1.40 (0.67–2.93)	0.372	13.0	1.19 (0.68–2.08)	0.540	0.90 (0.45–1.79)	0.755
SU + MET + insulin	36	8.3	1.01 (0.32–3.15)	0.991	1.32 (0.41–4.32)	0.644	2.8	0.28 (0.04–1.99)	0.202	0.27 (0.04–2.00)	0.201
No pharmacotherapy	1,829	7.6	0.96 (0.77–1.20)	0.719	0.93 (0.71–1.23)	0.629	9.0	0.95 (0.78–1.16)	0.614	0.91 (0.69–1.18)	0.467

[a]The total number of users is lower than in Table 1, because we excluded patients with a first admission in 2004 and patients for whom information on socioeconomic status was missing
[b]See Table 2
MET, metformin; SU, sulfonylurea

comprise complete population data, our results reflect the daily clinical practice in Denmark. Further, the use of nationwide registries with prospectively collected data minimises the risk of both selection and information bias. Another advantage is the ability to adjust for the wide range of possible confounding factors collected independently of hospitalisation with MI through access to the different medical registries.

The validity of our estimates depends on the accuracy of the registries. However, the validity of the hospital discharge diagnoses used to identify our study population of MI patients seems high [22], and the combined use of the Danish National Patient Registry and the Register of Medicinal Product Statistics to identify patients with diabetes mellitus has proven to be of high quality and nearly complete [23].

As we used the redemption of a prescription as a proxy for compliance, we may have overestimated actual exposure. Further, the lack of information on non-hospitalised MI cases, including patients who die before reaching the hospital, might introduce selection bias, if users of one particular glucose-lowering treatment were more likely to die from MI before hospitalisation.

Finally, despite our adjustment for a wide range of confounding factors, including intensity of the antiglycaemic treatment, we cannot entirely rule out the possibility of residual or unmeasured confounding related to differences in in-hospital treatment for MI, diet, smoking and obesity. In contrast, it could be argued that not all covariates should be considered true confounding factors, but rather intermediate steps in the association between use of a specific drug and prognosis (e.g. HbA_{1c}). We may in theory have underestimated the real effect by adjusting for the covariates. However, in reality neither measures of intensity of glycaemic control, nor duration of diabetes nor other possible 'intermediate step covariates' had any substantial impact on the adjusted risk estimates.

Our results are consistent with a number of other studies on both short- and long-term mortality rate after admission with MI. Two studies found that the type of diabetes treatment in monotherapy at discharge had no significant association with 28 day [4] and 1 year mortality rate [5]. One of these also found similar risk of readmission with MI or heart failure within 1 year among MI patients discharged on metformin and non-insulin sensitisers (sulfonylureas or insulin) [5]. Another study showed no differences in long-term (>3 years) survival rate between patients treated with sulfonylureas prior to MI and those receiving any other glucose-lowering treatments (diet, insulin or metformin and/or acarbose) [6]. Further, in agreement with our finding, an increased mortality rate has also previously been found among users of combination therapy (sulfonylureas and metformin) when compared with patients treated with diet, whereas no increased mortality rate was found among users of the drugs in monotherapy [14].

Recently, we found some indications of variation in 30 day mortality rates after MI among users of different glucose-lowering treatments [7]. However, the study was small (patients with diabetes $n=867$) with few data on confounding factors, making it difficult to interpret the size of the variation.

Other studies have also implied that use of specific glucose-lowering drugs is associated with an adverse prognosis among patients with previous coronary artery disease. Both sulfonylureas [3, 8, 9], metformin [9, 10] and insulin [9, 11–13] have been associated with increased mortality rate compared with diet. However, this might reflect a longer duration of diabetes and thus a more advanced stage of diabetes and/or a poorer glycaemic control among users of these drugs, rather than actual drug effects.

The finding that metformin carried a significantly lower risk in women than in men remains unexplained and may be due to chance. However, it has recently been reported that high proinsulin levels (which are reduced by metformin [24]) are pro-atherosclerotic in women, but not in men [25], and this might provide at least some explanation for our finding.

Although this study has shown similar effects of different glucose-lowering drugs in monotherapy prior to MI on the prognosis after the MI, concerns about differences in the risk of developing cardiovascular disease, including MI, among users of different glucose-lowering drugs remain [7, 26–29].

In conclusion, the prognosis after MI does not seem to vary substantially according to the glucose-lowering drugs used in monotherapy prior to MI. However, use of any combination seems to be related to an increased mortality rate.

Acknowledgements This study was supported by the Research Initiative of Aarhus University Hospital, the University of Aarhus, the Danish Diabetes Association and the Danish Medical Research Council.

Duality of interest S. P. Johnsen and J. Rungby have previously received an unrestricted research grant from Servier. J. Rungby and H. T. Horsdal are former consultants for Sanofi-Aventis. J. Rungby has served on advisory boards for Sanofi-Aventis and Novo Nordisk. F. Søndergaard has no duality of interest to report.

References

1. Turner RC, Cull CA, Frighi V, Holman RR (1999) Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 281:2005–2012
2. Malmberg K, Yusuf S, Gerstein HC et al (2000) Impact of diabetes on long-term prognosis in patients with unstable angina

and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation 102:1014–1019
3. Meinert CL, Knatterud GL, Prout TE, Klimt CR (1970) A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 19(Suppl):789–830
4. Davis TM, Parsons RW, Broadhurst RJ, Hobbs MS, Jamrozik K (1998) Arrhythmias and mortality after myocardial infarction in diabetic patients. Relationship to diabetes treatment. Diabetes Care 21:637–640
5. Inzucchi SE, Masoudi FA, Wang Y et al (2005) Insulin-sensitizing antihyperglycemic drugs and mortality after acute myocardial infarction: insights from the National Heart Care Project. Diabetes Care 28:1680–1689
6. Meier JJ, Deifuss S, Klamann A, Schmiegel W, Nauck MA (2003) Influence of an antidiabetic treatment with sulfonylurea drugs on long-term survival after acute myocardial infarction in patients with type 2 diabetes. The LAngendreer Myocardial infarction and Blood glucose in Diabetic patients Assessment (LAMBDA). Exp Clin Endocrinol Diabetes 111:344–350
7. Johnsen SP, Monster TB, Olsen ML et al (2006) Risk and short-term prognosis of myocardial infarction among users of anti-diabetic drugs. Am J Ther 13:134–140
8. Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr (1999) Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol 33:119–124
9. Gustafsson I, Hildebrandt P, Seibaek M et al (2000) Long-term prognosis of diabetic patients with myocardial infarction: relation to antidiabetic treatment regimen. The TRACE Study Group. Eur Heart J 21:1937–1943
10. Fisman EZ, Tenenbaum A, Benderly M, Goldbourt U, Behar S, Motro M (1999) Antihyperglycemic treatment in diabetics with coronary disease: increased metformin-associated mortality over a 5-year follow-up. Cardiology 91:195–202
11. Halkin A, Roth A, Jonas M, Behar S (2001) Sulfonylureas are not associated with increased mortality in diabetics treated with thrombolysis for acute myocardial infarction. J Thromb Thrombolysis 12:177–184
12. McGuire DK, Newby LK, Bhapkar MV et al (2004) Association of diabetes mellitus and glycemic control strategies with clinical outcomes after acute coronary syndromes. Am Heart J 147:246–252
13. Murcia AM, Hennekens CH, Lamas GA et al (2004) Impact of diabetes on mortality in patients with myocardial infarction and left ventricular dysfunction. Arch Intern Med 164:2273–2279
14. Fisman EZ, Tenenbaum A, Boyko V et al (2001) Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. Clin Cardiol 24:151–158
15. Frank L (2000) Epidemiology. When an entire country is a cohort. Science 287:2398–2399
16. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB (2006) The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 53:441–449
17. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH (1999) The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 46:263–268
18. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A (1994) Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation 90:583–612
19. Statistics Denmark (1991) IDA—an integrated database for labour market research. Statistics Denmark, Copenhagen
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
21. Steen H, Giannitsis E, Futterer S, Merten C, Juenger C, Katus HA (2006) Cardiac troponin T at 96 hours after acute myocardial infarction correlates with infarct size and cardiac function. J Am Coll Cardiol 48:2192–2194
22. Madsen M, Balling H, Eriksen LS (1990) The validity of the diagnosis of acute myocardial infarction in 2 registries: the Heart Registry compared to the National Patient Registry. Ugeskr Laeger 152:308–314 (article in Danish)
23. Nielsen GL, Sørensen HT, Pedersen AB, Sabroe S (1996) Analyses of data quality in registries concerning diabetes mellitus—a comparison between a population based hospital discharge and an insulin prescription registry. J Med Syst 20:1–10
24. Lachin JM, Christophi CA, Edelstein SL et al (2007) Factors associated with diabetes onset during metformin versus placebo therapy in the diabetes prevention program. Diabetes 56:1153–1159
25. Kronborg J, Johnsen SH, Njolstad I, Toft I, Eriksen BO, Jenssen T (2007) Proinsulin:insulin and insulin:glucose ratios as predictors of carotid plaque growth: a population-based 7 year follow-up of the Tromso Study. Diabetologia 50:1607–1614
26. UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352:854–865
27. Kao J, Tobis J, McClelland RL et al (2004) Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. Am J Cardiol 93:1347–1350
28. McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM (2007) Coronary heart disease outcomes in patients receiving antidiabetic agents. Pharmacoepidemiol Drug Saf 16:711–725
29. Sauer WH, Cappola AR, Berlin JA, Kimmel SE (2006) Insulin sensitizing pharmacotherapy for prevention of myocardial infarction in patients with diabetes mellitus. Am J Cardiol 97:651–654

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2009; **25**: 515–522.
Published online 20 May 2009 in Wiley InterScience (www.interscience.wiley.com) **DOI:** 10.1002/dmrr.971

RESEARCH ARTICLE

Sulfonylureas and prognosis after myocardial infarction in patients with diabetes: a population-based follow-up study

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Received: 13 March 2009
Accepted: 2 April 2009

Abstract

Background The cardiovascular safety, including risk of myocardial infarction (MI), of individual sulfonylureas (SUs) may differ. It remains uncertain whether treatment with individual SUs influences prognosis following MI.

Methods We conducted a nationwide population-based follow-up study among all Danish patients hospitalized with first-time MI from 1996 to 2004. From the national health databases, we identified 3930 MI patients who used SUs at the time of admission. We computed mortality rates and rates of MI and heart failure readmission according to type of SU and used Cox's proportional hazards regression analysis to compute hazard ratios (HRs) as estimates of relative risk controlling for differences in prognostic covariates.

Results The 30-day and 1-year mortality after MI among SU users was 22.0% and 35.3%, respectively. We found no substantial differences in 30-day and 1-year mortality among users of different SUs. Use of gliclazide in monotherapy showed a trend towards lower mortality; adjusted HR of 1-year mortality 0.70 (95% CI: 0.48–1.00). Users of the different SUs appeared to have similar risks of new MI and heart failure following MI.

Conclusions The prognosis after MI was not substantially influenced by the choice of SU. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords sulfonylureas; myocardial infarction; epidemiology; prognosis; type 2 diabetes mellitus

Introduction

Sulfonylureas (SUs) remain a mainstay for treatment of patients with type 2 diabetes mellitus. However, the University Group Diabetes Program reported a possibly increased cardiovascular mortality after 5–8 years use of tolbutamide compared with insulin and placebo [1].

The cardiovascular safety of SUs has subsequently been examined in several trials and observational studies [2–17] with conflicting results. Thus, some studies suggest that SUs are detrimental to the heart [7–9,15,16], some suggest a decreased cardiac mortality with SUs [4] and some suggest that SUs are neutral in this respect [2,3,5,6,10–14,17]. The inconsistencies, which preclude firm conclusions about the safety of SUs, may be related to insufficient numbers of outcomes and other methodological limitations in some of the studies, but may also reflect

that differences in safety may exist when comparing individual SUs.

The different pharmacological properties of individual SUs could potentially cause differences in prognosis after myocardial infarction (MI) [18]. We have recently reported lower risk of MI among users of gliclazide and glimepiride compared with users of glibenclamide, glipizide and tolbutamide. Users of gliclazide and glimepiride also had a lower 30-day mortality rate (25.0% *vs* 33.8%) after MI compared with users of glibenclamide, glipizide and tolbutamide. In particular, gliclazide appeared to be associated with reduced mortality (9.5%) [19]. However, the study was small (Number of patients using SUs = 361) with few data on confounding factors. Since any increased cardiovascular mortality may have major clinical implications, we examined the prognosis after MI among users of different SUs in a large nationwide Danish follow-up study.

Materials and methods

Setting and design

The study drew on health care databases covering the entire Danish population (approximately 5.3 million). The tax-supported Danish National Health Service provides all inhabitants with free access to general practitioners and hospitals and refunds a variable proportion of prescription medication costs. The Danish Civil Registration System keeps records on gender, date of birth, change of address, date of emigration and changes in vital status since 1968 [20]. The records carry a 10-digit civil registration number (CRN), assigned to every Danish citizen and used in all Danish registers, enabling unambiguous record linkage between them. The CRN enabled us to establish, for each individual under study, a complete hospital and prescription history since 1995.

Patients with MI

The Danish National Patient Registry [21] collects data on all hospitalizations from Danish hospitals since 1977, including dates of admission and discharge, procedure(s) performed and up to 20 discharge diagnoses coded by physicians according to the International Classification of Diseases (8th revision [ICD-8] until the end of 1993 and 10th revision [ICD-10] thereafter). From the registry, we identified patients with a first-time primary discharge diagnosis of MI (ICD-10 codes I21.0–I21.9) hospitalized between 1 January, 1996, and 30 November, 2004.

Use of SUs

The Register of Medicinal Product Statistics contains data from 1995 on all prescription drugs dispensed at all Danish pharmacies, including patients' CRN, type of drug according to the anatomical therapeutic chemical classification system and date of dispensing the drug.

In Denmark, SUs are available by prescription only. We traced all prescriptions for SUs among MI patients before admission for MI. Patients who had filled at least one prescription for SUs within 90 days before hospitalization were classified as users of tolbutamide, glibenclamide, glipizide, glimepiride or gliclazide. Patients with prescriptions for more than one SU drug within the 90 days were excluded. Patients were also classified based on whether they received SUs exclusively (monotherapy) or used them in combination with other oral anti-diabetic treatment or insulin.

To further estimate the level of exposure, we classified the patients according to their total number of filled prescriptions for SUs before hospitalization for MI and categorized the number of filled prescriptions based on tertiles. We considered patients to be first-time SU users if they filled their first prescription within 90 days before hospitalization with MI. We also identified prescriptions for SUs filled within 1 year after the hospitalization with MI.

Endpoints

The endpoints were 30-day and 1-year all-cause mortality, readmission with new MI or heart failure within 1 year after admission with MI. Mortality was ascertained from the Civil Registration System; readmission with new MI (ICD-10 codes: I21 and I22) or heart failure (ICD-10 codes: I11.0, I13.0, I13.2, I25.5, I42.0, I42.6, I42.7, I42.8, I42.9, I50.0, I50.1 and I50.9) was ascertained from the patient registry. Readmission with MI within 28 days of the original MI was not considered a new case [22].

Covariates

We obtained data on covariates from the patient registry and the Register of Medicinal Product Statistics, the Integrated Database for Labour Market Research at Statistics Denmark [23] and, for a subset, data from the Laboratory Information System in Aarhus and North Jutland Counties.

Based on discharge diagnoses, we computed, for each patient, the Charlson co-morbidity index score [24]. The index covers 19 major disease categories, including diabetes mellitus, MI, heart failure, cerebrovascular diseases and cancer, weighted according to their impact on patient survival. We excluded MI and diabetes mellitus from the index calculations. We also obtained information on previous diagnoses of hypertension, coronary revascularization procedures (percutaneous coronary intervention and coronary artery bypass graft), alcoholism-related diseases and diabetes complications (i.e. retinopathy, nephropathy and neuropathy). Also subsequent coronary revascularization procedures were obtained.

We identified all prescriptions for cardiovascular drugs (anti-hypertensive drugs, lipid-lowering drugs, platelet

DOI: 10.1002/dmrr

inhibitors and vitamin K antagonists) and hormone replacement therapy (HRT) filled before admission for MI. As the use of these drugs may change following admission with MI, we also identified prescriptions filled within 1 year after the admission for MI.

As the proportion of users of different SUs changed during the study period thereby inducing a risk of comparing patients from different calendar periods when comparing users of different SUs, we also included the calendar time of hospitalization in the analyses.

We estimated the duration of diabetes as the period since the earliest prescription for any anti-diabetic drug or the earliest diabetes diagnosis and categorized the duration in three groups; $\leq$5 years, 5–10 years and >10 years. Finally, based on data from the Integrated Database for Labour Market Research, we classified the patients according to socioeconomic status (employed, pensioner or other) in the year before admission for MI. Of the 3930 users of SUs, 77 patients had missing data on socioeconomic status and were excluded from the analyses.

Biochemical data reflecting the intensity of hypoglycemic treatment and the extent of myocardial damage following admission with MI were available from the biochemical information system for all tests analysed in North Jutland and Aarhus Counties (covering a population of approximately 22% of the total Danish population), including data on tests from all the county's hospitals and general practices. The databases were initiated in 1992 in North Jutland and in 1990 in Aarhus, but were first complete from 1997 in North Jutland and 1996 in Aarhus. We retrieved data on hemoglobin A_{1c} (HbA_{1c}), blood glucose, troponin T and creatine kinase MB (CK-MB). We used the latest measurement of HbA_{1c} within 180 days before admission and 7 days after the admission, the highest level of blood glucose, troponin T and CK-MB on the day of admission or the following day.

Statistical analyses

Follow-up began on the date of admission with MI and ended on the date of admission with new MI or heart failure (only in analyses on risk of new MI or heart failure, respectively), death, emigration or after 30 days/1 year. We computed Kaplan-Meier curves for users of the different SUs and computed the cumulative 30-day and 1-year mortality.

We used Cox's proportional hazards regression analysis (with the Efron approximation to handle tied survival times) to compute hazard ratios (HRs) as estimates of the relative risks for each outcome. We included all the covariates in the model; use of cardiovascular drugs, HRT and coronary revascularization procedures after MI were treated as time-dependent covariates.

Furthermore, using Wald tests, we tested whether the association between numbers of filled prescription for individual SUs and the outcomes followed a linear trend. The MI patients receiving tolbutamide served as reference group in the outcome analyses comparing different SUs. When analyzing the effect of different exposure levels of the individual SU drug, patients with the lowest level of exposure served as the reference group.

Prescriptions for SUs in Denmark are usually issued for 3 months, but may be issued for up to 6 months. We therefore also analysed the data based on drug use within 180 days before hospitalization.

Differences between SU users in troponin T and CK-MB levels, which may reflect infarct size [25], were assessed by Kruskal-Wallis tests. We analysed data with Stata 8.2 (StataCorp LP, TX, USA) and with version 9.13 of the SAS software (SAS Institute Inc., Cary, NC, USA).

Results

Of the 72 295 patients with MI during the study period, 4005 (5.4%) had filled prescriptions for SUs within 90 days before hospitalization. We excluded 75 patients who had received prescriptions for more than one SU drug within 90 days before hospitalization. Of the remaining 3930 patients, 514 (13.1%) were treated with tolbutamide, 1,329 (33.8%) with glibenclamide, 672 (17.1%) with glipizide, 1,160 (29.5) with glimepiride and 255 (6.5%) received gliclazide. Users of the different SUs differed in age, duration of diabetes, the Charlson co-morbidity index score, prevalence of hypertension and former revascularization; numbers of filled prescriptions for cardiovascular drugs (anti-hypertensive drugs, platelet inhibitors, vitamin K antagonist and lipid-lowering drugs), HRT and other anti-diabetic drugs (metformin and insulin); and socioeconomic status and the intensity of glycaemic control (HbA_{1c} and blood glucose levels) (Table 1). For users of all SUs, approximately 80% of 30-day survivors continued with the same SU drug until end of follow-up.

All-cause mortality

Cumulative crude mortality curves for users of the different SUs are shown in Figure 1. Users of glimepiride and gliclazide appeared to have the lowest mortality.

Of 3853 patients with MI, 846 (22.0%; 95% CI: 20.7–23.3%) died within 30 days after admission. Mortality ranged from 17.9% among users of glimepiride to 26.7% among users of tolbutamide. Within 1 year, 35.3% (95% CI: 33.7–36.9) of the MI patients had died, ranging from 29.6% among users of gliclazide to 41.1% among users of tolbutamide.

Table 2 shows the 30-day and 1-year HRs among users of the different SUs compared with users of tolbutamide. After adjustment for differences in covariates, the HRs shifted towards unity and there were no major differences between the SUs. We found the lowest mortality among users of gliclazide: adjusted HR of 30 day and 1 year were 0.84 (95% CI: 0.60–1.18) and 0.79 (95% CI: 0.59–1.05),

DOI: 10.1002/dmrr

Table 1. Descriptive characteristics of patients with type 2 diabetes mellitus using different sulfonylureas hospitalized with a first-time myocardial infarction (MI) in Denmark during the period 1996–2004

	Tolbutamide ($N = 514$)		Glibenclamide ($N = 1329$)		Glipizide ($N = 672$)		Glimepiride ($N = 1160$)		Gliclazide ($N = 255$)	
Characteristic[a]	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Age in years, median (range)	76.9	(37–100)	73.9	(40–100)	73.8	(38–98)	73.0	(36–96)	73.8	(39–97)
Sex (males)	294	(57.2)	763	(57.4)	393	(58.5)	701	(60.4)	153	(60.0)
Calendar period										
1996–1998	239	(46.5)	578	(43.5)	281	(41.8)	85	(7.3)	63	(24.7)
1999–2001	170	(33.1)	449	(33.8)	212	(31.6)	382	(32.9)	86	(33.7)
2002–2004	105	(20.4)	302	(22.7)	179	(26.6)	693	(59.8)	106	(41.6)
Duration of diabetes mellitus										
≤5years	275	(53.5)	699	(52.6)	387	(57.6)	708	(61.0)	142	(55.7)
5–10 years	171	(33.3)	425	(32.0)	195	(29.0)	336	(29.0)	81	(31.8)
>10 years	68	(13.2)	205	(15.4)	90	(13.4)	116	(10.0)	32	(12.6)
Charlson's co-morbidity index										
0	239	(46.5)	681	(51.2)	347	(51.6)	542	(46.7)	138	(54.1)
1–2	211	(41.0)	527	(39.7)	254	(37.8)	454	(39.1)	93	(36.5)
≥3	64	(12.5)	121	(9.1)	71	(10.6)	164	(14.2)	24	(9.4)
Discharge diagnoses										
Hypertension	386	(75.1)	981	(73.8)	491	(73.1)	923	(79.6)	191	(74.9)
Alcoholism	12	(2.3)	30	(2.3)	18	(2.7)	36	(3.1)	10	(3.9)
Former revascularization	15	(2.9)	34	(2.6)	12	(1.8)	46	(4.0)	12	(4.7)
Retinopathy	38	(7.4)	101	(7.6)	47	(7.0)	59	(5.1)	20	(7.8)
Nephropathy[b]	25	(4.9)	53	(4.0)	19	(2.8)	51	(4.4)	7	(2.8)
Neuropathy	31	(6.0)	58	(4.4)	30	(4.5)	74	(6.4)	14	(5.5)
Prescription for the drug[c]										
Antihypertensive drugs	382	(74.3)	966	(72.7)	479	(71.3)	915	(78.9)	191	(74.9)
Platelet inhibitors	79	(15.4)	267	(20.1)	146	(21.7)	286	(24.7)	62	(24.3)
Vitamin K antagonists	19	(3.7)	32	(2.4)	20	(3.0)	56	(4.8)	12	(4.7)
Lipid-lowering drugs	49	(9.5)	124	(9.3)	80	(11.9)	272	(23.5)	48	(18.8)
Hormone replacement therapy	42	(8.2)	88	(6.6)	61	(9.1)	138	(11.9)	30	(11.8)
Metformin	94	(18.3)	396	(29.8)	208	(31.0)	325	(28.0)	69	(27.1)
Insulin	10	(2.0)	48	(3.6)	26	(3.9)	71	(6.1)	16	(6.3)
Other oral anti-diabetic drugs	4	(0.8)	39	(2.9)	16	(2.4)	31	(2.7)	9	(3.5)
Socioeconomic status[d]										
Employed	47	(9.4)	140	(10.8)	70	(10.6)	169	(14.8)	25	(10.0)
Pensioner	444	(88.4)	1,122	(86.4)	567	(86.0)	935	(81.7)	219	(87.6)
Other	11	(2.2)	36	(2.8)	22	(3.4)	40	(3.5)	6	(2.4)
Laboratory data[e]										
HbA_{1c} (%), median (range)[f]	7.3	(5.0–9.9)	8.1	(1.0–13.8)	7.8	(5.5–12.5)	7.4	(5.1–13.2)	7.3	(5.1–11.7)
Blood glucose (mmol/L), median (range)[g]	12.5	(5.0–29.2)	13.9	(5.1–48.4)	13.5	(4.8–34.1)	12.9	(4.7–34.4)	12.9	(3.9–29.8)
Troponin T (μg/L), median (range)[h]	1.4	(0.03–25)	1.3	(0.01–64)	1.2	(0.03–26)	1.5	(0.01–55)	1.00	(0.01–9)
Creatinkinase MB (μg/L), median (range)[i]	25.2	(0.8–771)	34.1	(2.0–556)	49.4	(3.3–500)	46.7	(1.9–1746)	57.5	(7.9–466)

[a]All variables are shown as number (%) except for age, which is shown as median (range).
[b]Also included in the Charlson index.
[c]Received a prescription within 90 days (platelet inhibitors, vitamin K antagonists, metformin, insulin and other anti-diabetic drugs) or ever (all others) before admission for MI.
[d]The year before admission for MI.
[e]Data only available for patients from North Jutland and Aarhus Counties.
[f]Measured within 180 days before admission and 7 days after the admission with MI [$N = 522$, ($N_{Tolbutamide} = 42$, $N_{Glibenclamide} = 212$, $N_{Glipizide} = 62$, $N_{Glimepiride} = 161$ and $N_{Gliclazide} = 45$)].
[g]Highest measurement at the day of admission [$N = 627$, ($N_{Tolbutamide} = 47$, $N_{Glibenclamide} = 257$, $N_{Glipizide} = 80$, $N_{Glimepiride} = 195$ and $N_{Gliclazide} = 48$)].
[h]Highest measurement at the day of admission or the following day [$N = 443$, ($N_{Tolbutamide} = 34$, $N_{Glibenclamide} = 155$, $N_{Glipizide} = 48$, $N_{Glimepiride} = 173$ and $N_{Gliclazide} = 33$)].
[i]Highest measurement at the day of admission or the following day [$N = 317$, ($n_{Tolbutamide} = 27$, $N_{Glibenclamide} = 101$, $N_{Glipizide} = 30$, $N_{Glimepiride} = 136$ and $N_{Gliclazide} = 23$)).

respectively and 0.97 (95% CI: 0.65–1.44) and 0.70 (95% CI: 0.48–1.00), when restricting to monotherapy.

Except for users of gliclazide, the number of filled SU prescriptions per patient was not associated with mortality. For users of gliclazide, a decreased mortality was observed with increasing numbers of filled prescriptions; the adjusted 30-day HRs was 0.52 (95% CI: 0.25–1.10) among patients who had filled 8–20 gliclazide prescriptions and was 0.28 (95% CI: 0.12–0.68) among those with more than 20 gliclazide prescriptions, as compared with patients who had filled 1–7 gliclazide prescriptions only ($p = 0.004$).

New MI and heart failure

Within 1 year of follow-up, 285 (8.3%) of the patients were readmitted with a new MI and 329 (9.5%) were

DOI: 10.1002/dmrr

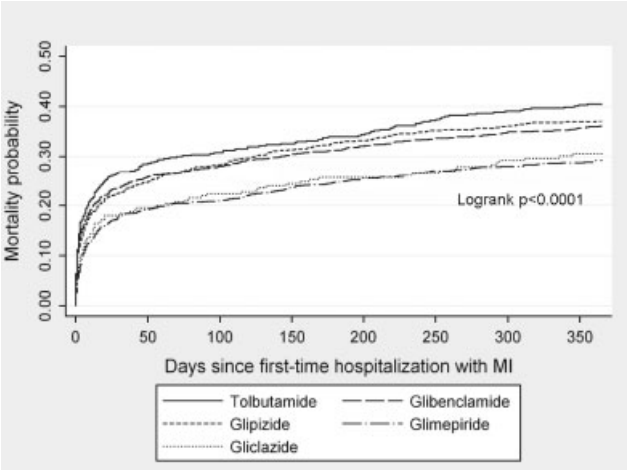

Figure 1. Kaplan-Meier curves of crude 1-year mortality after admission for myocardial infarction (MI) according to use of different sulfonylureas (SUs) within 90 days before hospitalization. 254 × 190 mm (96 × 96 DPI)

readmitted due to heart failure. No clear differences in the risk of new MI or heart failure were found between the individual SUs (Table 3). The number of filled SU prescriptions did not appear to influence the risk of developing either new MI or heart failure. Results for new MI, heart failure and all-cause mortality were similar after restricting the analyses to first-time users and when estimating the HRs based on SU use 180 days before MI.

Sub-analysis including biochemical parameters

Data on HbA_{1c} and glucose levels were available on 456 patients in the North Jutland and Aarhus Counties subcohort. Among this subset of patients, we found no substantial differences in prognosis between the use of different SUs, and further adjustment for HbA_{1c} and blood glucose levels yielded similar results for all SUs.

There were no significant differences in the levels of CK-MB ($p = 0.98$) or troponin T ($p = 0.98$) between MI patients treated with different SUs, suggesting that type of SU did not affect infarct size.

Discussion

In this large nationwide study, we found no substantial differences in mortality and risk of recurrent MI or heart failure among users of different SUs with a first-time hospitalization for MI.

The accuracy of our findings depends on the comparability of the groups and on the validity of the prescription and hospitalization data [26]. The population-based design and complete follow-up minimize selection biases. The use of prospective and routine data enables valid identification of patients with MI collected independently of the study hypothesis [27]. Furthermore, the health registries contain detailed information on diabetes, related complications, co-morbidities and co-medications, and for a sub-sample, also biochemical data. Any inaccuracy of the data will lead to residual confounding and underestimation of the real effect.

The limitations of our study include lack of information on non-hospitalized cases of MI, including patients who died before reaching the hospital. If users of some of the SUs were more likely to die from MI before hospitalization, a selection bias would ensue. Unaccounted confounding by indication (i.e. due to prescription of specific SUs according to perceived cardiovascular risk) is another possible limitation that should always be considered in pharmacoepidemiological studies. However, there are no national or international guidelines recommending use of specific SU in patients

Table 2. Crude and adjusted 30-day and 1-year hazard ratios (HRs) with 95% CI for death after first-time hospitalization with myocardial infarction (MI) according to use of sulfonylureas (SUs) within 90 days before hospitalization

Anti-diabetic medication	N[a]	Deaths within 30 days	Mortality within 30 days	Adjusted HR[b] (95% CI)		N[c]	Deaths within 1 year	Mortality within 1 year	Adjusted HR[b] (95% CI)	
Tolbutamide (all)	502	134	26.7%	1.00	(reference)	472	194	41.1%	1.00	(reference)
Glibenclamide (all)	1298	311	24.0%	0.98	(0.80–1.20)	1,238	453	36.6%	0.97	(0.82–1.16)
Glipizide (all)	659	150	22.8%	0.94	(0.74–1.19)	616	230	37.3%	0.99	(0.82–1.20)
Glimepiride (all)	1144	205	17.9%	0.90	(0.71–1.14)	906	274	30.3%	0.87	(0.71–1.06)
Gliclazide (all)	250	46	18.4%	0.84	(0.60–1.18)	216	64	29.6%	0.79	(0.59–1.05)
Tolbutamide (mono)	399	103	25.8%	1.00	(reference)	376	153	40.7%	1.00	(reference)
Glibenclamide (mono)	851	205	24.1%	1.03	(0.81–1.31)	817	300	36.7%	0.99	(0.81–1.20)
Glipizide (mono)	426	109	25.6%	1.08	(0.83–1.42)	401	159	39.7%	1.07	(0.85–1.34)
Glimepiride (mono)	752	142	18.9%	0.98	(0.74–1.29)	604	192	31.8%	0.92	(0.73–1.16)
Gliclazide (mono)	162	33	20.4%	0.97	(0.65–1.44)	140	37	26.4%	0.70	(0.48–1.00)

[a]The total number of users is lower than in Table 1, because we excluded 77 subjects with missing information on socioeconomic status.
[b]Adjusted for age, sex, calendar period, duration of diabetes, level of co-morbidity (measured by the Charlson index), socioeconomic status, discharge diagnoses of hypertension, former and subsequent revascularization, alcoholism, retinopathy and neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, lipid-lowering agents and hormone replacement therapy (HRT) before the date of hospitalization for MI, and time-dependent cardiovascular treatment and HRT after the date of hospitalization for MI. For the analyses with SU in combination therapy, there is also adjusted for the type of combination therapy (i.e. metformin, insulin and/or other oral anti-diabetic drugs).
[c]The total number of users is lower than in Table 1, because we excluded all admissions in 2004 and subjects with missing information on socioeconomic status.

DOI: 10.1002/dmrr

Table 3. Crude and adjusted 1-year hazard ratios (HRs) with 95% CI for new myocardial infarction (MI) and heart failure after first-time hospitalization with MI according to use of sulfonylureas (SUs) within 90 days before hospitalization

Anti-diabetic medication	*N*[a]	New MI within 1 year		Adjusted HR[b] (95% CI)		Heart failure within 1 year		Adjusted HR[b] (95% CI)	
Tolbutamide (all)	472	34	7.2%	1.00	(reference)	46	9.8%	1.00	(reference)
Glibenclamide (all)	1238	112	9.1%	1.32	(0.89–1.95)	111	9.0%	0.88	(0.62–1.25)
Glipizide (all)	616	47	7.6%	1.07	(0.68–1.68)	52	8.4%	0.87	(0.58–1.30)
Glimepiride (all)	906	71	7.8%	1.00	(0.65–1.54)	93	10.3%	0.94	(0.65–1.37)
Gliclazide (all)	216	21	9.7%	1.26	(0.72–2.19)	27	12.5%	1.12	(0.69–1.82)
Tolbutamide (mono)	376	29	7.7%	1.00	(reference)	34	9.0%	1.00	(reference)
Glibenclamide (mono)	817	72	8.8%	1.25	(0.81–1.95)	74	9.1%	1.00	(0.66–1.51)
Glipizide (mono)	401	26	6.5%	0.94	(0.55–1.61)	32	8.0%	0.94	(0.58–1.53)
Glimepiride (mono)	604	46	7.6%	0.93	(0.55–1.54)	64	10.6%	1.20	(0.77–1.88)
Gliclazide (mono)	140	13	9.3%	1.07	(0.55–2.08)	16	11.4%	1.10	(0.60–2.01)

[a]The total number of users is lower than in Table 1, because we excluded all admissions in 2004 and subjects with missing information on socioeconomic status.
[b]Adjusted for age, sex, calendar period, duration of diabetes, former use of anti-diabetic treatment, level of co-morbidity (measured by the Charlson index), socioeconomic status, discharge diagnoses of hypertension, former and subsequent revascularization, alcoholism, retinopathy and neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, lipid-lowering agents and hormone replacement therapy (HRT) before the date of hospitalization for MI, and time-dependent cardiovascular treatment and HRT after the date of hospitalization for MI. For the analyses with SU in combination therapy, there is also adjusted for the type of combination therapy (i.e. metformin, insulin and/or other oral antidiabetic drugs).

at high cardiovascular risk. Furthermore, extensive efforts were made in our study to account for possible confounding, which resulted in adjusted risk estimates closer to unity. This makes it unlikely that removing any possible remaining confounding would change the overall conclusion of no substantial differences in prognosis among users of different SUs. Changes in the treatment did occur during hospitalization or following discharge, which may have caused some misclassification of drug use. However, the hypoglycemic treatment was only changed in a minor proportion of the patients during the follow-up period. Thus, approximately 80% of the 30-day survivors continued with the same SU until end of follow-up. In contrast, changes in cardiovascular co-medication did occur during follow-up. We accounted for this by including the prescriptions for cardiovascular medication and HRT after hospitalization as time-dependent covariates in the Cox regression analysis.

We cannot rule out possible unmeasured confounding, including in-hospital treatment for MI, smoking or obesity. However, we have no indication that these factors should be of importance since adjustment for concomitant treatments or ailments were neutral. Finally, we did not have information on the compliance with the prescribed SUs, thereby we may have overestimated the actual exposure to these drugs.

Our results do not agree with our earlier finding of a significant lower mortality among users of gliclazide and glimepiride compared with glibenclamide, glipizide and tolbutamide [19], or the recent Italian cohort studies in which the use of gliclazide was associated with a significant lower all-cause mortality in comparison with use of glibenclamide [28,29]. Prescription patterns varied over time in our cohort and thus the increased use of glimepiride and gliclazide in later periods was accompanied by other changes in the overall care of patients, including more frequent uses of statins and anti-hypertensives and more aggressive treatment goals. However, we did find lower crude mortalities among users of gliclazide and glimepiride, but these differences were at least partly due to the fact that the patients using these drugs were younger, filled their SU prescription in the more recent calendar period (with better coronary care), had lesser co-morbidity and as stated above, they filled a higher number of prescriptions for cardiovascular drugs. After adjustment for these confounding factors, we only found a non-significant trend towards lower mortality with gliclazide.

As the pharmacological properties between the SUs differ, a potential difference in the prognosis may exist. SU sensitive(K_{ATP})-channels are present in cardiac myocytes, and blocking them inhibits ischemic preconditioning [30]. However, the pancreatic and cardiac channels are composed of different isoforms of the SU receptors, suggesting that different pharmacological effects of the individual SUs may be determined by their receptor affinities. Glibenclamide and glimepiride have a high affinity for cardiac receptors compared with tolbutamide and gliclazide [31]. Furthermore, only glibenclamide has been shown to inhibit ischemic preconditioning [32–35], whereas gliclazide [32,36], glipizide [33] and glimepiride [34,37,38] maintain it. Here, we found no consistent association between the level of receptor affinity and the prognosis after MI, however, gliclazide with the greatest selectivity for the pancreatic β-cell receptors [39,40] was associated with the lowest unadjusted mortality. Furthermore, we found lower risk estimates with increasing numbers of prescriptions among users of gliclazide. Besides the effect on ischemic preconditioning, numerous other mechanisms may be SU-dependent, including enhanced fibrinolysis and reduced platelet activity and oxidative stress [41,42].

In this population, the overall mortality rate with SUs was comparable to that seen with metformin and insulin [43], suggesting that other treatments and procedures during MI are of greater importance than the choice of anti-glycaemic drug for the prognosis. However, the

DOI: 10.1002/dmrr

mortality after MI among the diabetic patients remains high compared with the mortality among all patients admitted with MI in Denmark (28-day and 1-year mortality in 2000 were 12.3% and 20.8%, respectively) [44], though comparable to the mortality found in other studies on patients with diabetes mellitus [5,12,14]. By modern standards, the usage of lipid-lowering drugs and anti-hypertensives in this cohort is sub-standard, giving hope for a reduced mortality in the future. In contrast with previous findings on the prognosis after MI, we found no overall differences among users of different SUs.

Acknowledgement

This study was supported by the Research Initiative of Aarhus University Hospital, the University of Aarhus, Servier, the Danish Diabetes Association and the Danish Medical Research Council.

Conflict of interest

None declared.

References

1. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes* 1970; **19**(Suppl. 2): 789–830.
2. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**: 837–853.
3. Brady PA, Al Suwaidi J, Kopecky SL, Terzic A. Sulfonylureas and mortality in diabetic patients after myocardial infarction. *Circulation* 1998; **97**: 709–710.
4. Danchin N, Charpentier G, Ledru F, *et al*. Role of previous treatment with sulfonylureas in diabetic patients with acute myocardial infarction: results from a nationwide French registry. *Diabetes Metab Res Rev* 2004; **21**: 143–149.
5. Davis TM, Parsons RW, Broadhurst RJ, Hobbs MS, Jamrozik K. Arrhythmias and mortality after myocardial infarction in diabetic patients. Relationship to diabetes treatment. *Diabetes Care* 1998; **21**: 637–640.
6. Fisman EZ, Tenenbaum A, Benderly M, Goldbourt U, Behar S, Motro M. Antihyperglycemic treatment in diabetics with coronary disease: increased metformin-associated mortality over a 5-year follow-up. *Cardiology* 1999; **91**: 195–202.
7. Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1999; **33**: 119–124.
8. Gustafsson I, Hildebrandt P, Seibaek M, *et al*. Long-term prognosis of diabetic patients with myocardial infarction: relation to antidiabetic treatment regimen. The TRACE Study Group. *Eur Heart J* 2000; **21**: 1937–1943.
9. Gustafsson I, Hildebrandt P, Seibaek M, *et al*. Prognosis of diabetic patients with MI. *Cardiol Rev* 2001; **18**: 24–27.
10. Halkin A, Roth A, Jonas M, Behar S. Sulfonylureas are not associated with increased mortality in diabetics treated with thrombolysis for acute myocardial infarction. *J Thromb Thrombolysis* 2001; **12**: 177–184.
11. Jarrett RJ, McCartney P, Keen H. The Bedford survey: ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycaemic controls and risk indices for coronary heart disease in borderline diabetics. *Diabetologia* 1982; **22**: 79–84.
12. Jollis JG, Simpson RJ Jr, Cascio WE, Chowdhury MK, Crouse JR III, Smith SC Jr. Relation between sulfonylurea therapy, complications, and outcome for elderly patients with acute myocardial infarction. *Am Heart J* 1999; **138**: S376–S380.
13. Klamann A, Sarfert P, Launhardt V, Schulte G, Schmiegel WH, Nauck MA. Myocardial infarction in diabetic vs non-diabetic subjects. Survival and infarct size following therapy with sulfonylureas (glibenclamide). *Eur Heart J* 2000; **21**: 220–229.
14. Meier JJ, Deifuss S, Klamann A, Schmiegel W, Nauck MA. Influence of an antidiabetic treatment with sulfonylurea drugs on long-term survival after acute myocardial infarction in patients with type 2 diabetes. The LAngendreer Myocardial infarction and Blood glucose in Diabetic patients Assessment (LAMBDA). *Exp Clin Endocrinol Diabetes* 2003; **111**: 344–350.
15. O'Keefe JH, Blackstone EH, Sergeant P, McCallister BD. The optimal mode of coronary revascularization for diabetics. A risk-adjusted long-term study comparing coronary angioplasty and coronary bypass surgery. *Eur Heart J* 1998; **19**: 1696–1703.
16. Rytter L, Troelsen S, Beck-Nielsen H. Prevalence and mortality of acute myocardial infarction in patients with diabetes. *Diabetes Care* 1985; **8**: 230–234.
17. Ulvenstam G, Aberg A, Bergstrand R, *et al*. Long-term prognosis after myocardial infarction in men with diabetes. *Diabetes* 1985; **34**: 787–792.
18. Riveline JP, Danchin N, Ledru F, Varroud-Vial M, Charpentier G. Sulfonylureas and cardiovascular effects: from experimental data to clinical use. Available data in humans and clinical applications. *Diabetes Metab* 2003; **29**: 207–222.
19. Johnsen SP, Monster TB, Olsen ML, *et al*. Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. *Am J Ther* 2006; **13**: 134–140.
20. Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000; **287**: 2398–2399.
21. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; **46**: 263–268.
22. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994; **90**: 583–612.
23. Statistics Denmark. *IDA – An Integrated Database for Labour Market Research*. Statistics Denmark: Copenhagen, 1991.
24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–383.
25. Steen H, Giannitsis E, Futterer S, Merten C, Juenger C, Katus HA. Cardiac troponin T at 96 hours after acute myocardial infarction correlates with infarct size and cardiac function. *J Am Coll Cardiol* 2006; **48**: 2192–2194.
26. Sørensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. *Hepatology* 2006; **44**: 1075–1082.
27. Madsen M, Balling H, Eriksen LS. The validity of the diagnosis of acute myocardial infarction in 2 registries: the Heart Registry compared to the National Patient Registry. *Ugeskr Laeger* 1990; **152**: 308–314.
28. Monami M, Luzzi C, Lamanna C, *et al*. Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. *Diabetes Metab Res Rev* 2006; **22**: 477–482.
29. Monami M, Balzi D, Lamanna C, *et al*. Are sulphonylureas all the same? A cohort study on cardiovascular and cancer-related mortality. *Diabetes Metab Res Rev* 2007; **23**: 479–484.
30. Brady PA, Terzic A. The sulfonylurea controversy: more questions from the heart. *J Am Coll Cardiol* 1998; **31**: 950–956.
31. Gribble FM, Reimann F. Sulphonylurea action revisited: the post-cloning era. *Diabetologia* 2003; **46**: 875–891.
32. Loubani M, Fowler A, Standen NB, Galinanes M. The effect of gliclazide and glibenclamide on preconditioning of the human myocardium. *Eur J Pharmacol* 2005; **515**: 142–149.
33. Flynn DM, Smith AH, Treadway JL, *et al*. The sulfonylurea glipizide does not inhibit ischemic preconditioning in anesthetized rabbits. *Cardiovasc Drugs Ther* 2005; **19**: 337–346.
34. Klepzig H, Kober G, Matter C, *et al*. Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J* 1999; **20**: 439–446.

35. Tomai F, Crea F, Gaspardone A, *et al*. Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K+ channel blocker. *Circulation* 1994; **90**: 700–705.
36. Maddock HL, Siedlecka SM, Yellon DM. Myocardial protection from either ischaemic preconditioning or nicorandil is not blocked by gliclazide. *Cardiovasc Drugs Ther* 2004; **18**: 113–119.
37. Horimoto H, Nakai Y, Mieno S, Nomura Y, Nakahara K, Sasaki S. Oral hypoglycemic sulfonylurea glimepiride preserves the myoprotective effects of ischemic preconditioning. *J Surg Res* 2002; **105**: 181–188.
38. Mocanu MM, Maddock HL, Baxter GF, Lawrence CL, Standen NB, Yellon DM. Glimepiride, a novel sulfonylurea, does not abolish myocardial protection afforded by either ischemic preconditioning or diazoxide. *Circulation* 2001; **103**: 3111–3116.
39. Gribble FM, Ashcroft FM. Differential sensitivity of beta-cell and extrapancreatic K(ATP) channels to gliclazide. *Diabetologia* 1999; **42**: 845–848.
40. Meier JJ, Gallwitz B, Schmidt WE, Mugge A, Nauck MA. Is impairment of ischaemic preconditioning by sulfonylurea drugs clinically important? *Heart* 2004; **90**: 9–12.
41. Kimoto K, Suzuki K, Kizaki T, *et al*. Gliclazide protects pancreatic beta-cells from damage by hydrogen peroxide. *Biochem Biophys Res Commun* 2003; **303**: 112–119.
42. O'Brien RC, Luo M, Balazs N, Mercuri J. *In vitro* and *in vivo* antioxidant properties of gliclazide. *J Diabetes Complications* 2000; **14**: 201–206.
43. Horsdal HT, Johnsen SP, Søndergaard F, Rungby J. Type of preadmission glucose-lowering treatment and prognosis among patients hospitalised with myocardial infarction: a nationwide follow-up study. *Diabetologia* 2008; **51**: 567–574.
44. Madsen M, Rasmussen S. Myocardial infarction and angina pectoris – incidence and mortality. In *Heart Statistics 2004* (3rd edn). The Danish Heart Foundation and the National Institute of Public Health: Copenhagen, 2004; 153–176.

DOI: 10.1002/dmrr

TYPE OF PREADMISSION ANTIDIABETIC TREATMENT AND OUTCOME AMONG PATIENTS HOSPITALIZED WITH ISCHEMIC STROKE: A NATIONWIDE FOLLOW-UP STUDY

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Abstract

Background and Purpose: We examined whether type of preadmission antidiabetic treatment is associated with mortality and risk of readmission following hospitalization with ischemic stroke.

Methods: We conducted a nationwide population-based follow-up study among all Danish patients hospitalized with ischemic stroke from 2003 to 2006 and registered in the Danish National Indicator Project. We obtained data on diabetes and type of antidiabetic treatment, patient characteristics, use of other medications, comorbidities, socioeconomic status, quality of in-hospital care, readmissions and death on all patients by linking medical databases. We computed mortality rates and rates of readmission with recurrent stroke or myocardial infarction according to type of antidiabetic treatment and used Cox's proportional hazards regression analysis to compute hazard ratios (HRs) controlling for differences in prognostic covariates.

Results: We identified 4,816 stroke patients with type 2 diabetes mellitus. We found lower 30-day mortality rates among users of metformin (adjusted HR 0.32; 95% CI: 0.15-0.67), insulin (adjusted HR 0.50; 95% CI: 0.29-0.84), and among patients not receiving antidiabetic pharmacotherapy (adjusted HR 0.57; 95% CI: 0.36-0.91) compared with users of sulfonylureas. Users of any combination also had a lower mortality rate, but it did not reach statistical significance (adjusted HR 0.63; 95% CI: 0.33-1.20). In contrast, we found no significant differences when estimating the 1-year adjusted HRs. Compared with users of sulfonylureas, users of the all other types of antidiabetic treatments had increased risk of readmission, however the increased risk was only statistical significant in patients not treated with antidiabetic pharmacotherapy (adjusted HR 1.58; 95% CI: 1.04-2.42).

Conclusions: Sulfonylureas may be associated with increased mortality after ischemic stroke, however the deleterious effect seems restricted to the acute phase following stroke.

Introduction

Patients with diabetes mellitus have a higher mortality rate[1-6] and recover more slowly after stroke when compared to nondiabetic patients.[5] Patients with diabetes mellitus are also more prone to suffer a recurrent stroke and myocardial infarction.[4]

It is likely that treatments aimed to improve glycaemic control in patients with diabetes mellitus will reduce the risk of cardiovascular complications, however the cardiovascular safety profile of the different antidiabetic treatments remain uncertain, not least in relation to stroke.

Data regarding outcome in stroke patients using various types of antidiabetic treatments are in general sparse, however, the sulfonylureas (glibenclamide, glimepiride, or glibornuride) have drawn attention as use of these drugs have been linked with favorable neurological and functional outcomes compared with use of other antidiabetic treatments in two German small-scale follow-up studies.[7,8] In contrast, no clear association was found with initial stroke severity, in-hospital outcome, or mortality.[8]

Since a large proportion of patients with type 2 diabetes mellitus suffer a stroke and are permanently dependent on their antidiabetic treatments, it is of great importance to clarify the risk associated with the different antidiabetic treatments.

We therefore examined clinical outcome among patients with type 2 diabetes mellitus admitted with ischemic stroke using various types of antidiabetic treatment in a Danish nationwide population-based follow-up study.

Materials and Methods

Setting and design

This population-based follow-up study was conducted within the entire Danish population (approximately 5.3 million).

The Danish National Health Service provides tax-supported health care for all inhabitants, guaranteeing free access to general practitioners and hospitals, and refunding a variable proportion of the prescription medication costs. The Danish Civil Registration System keeps electronic records on gender, date of birth, change of address, date of emigration, and changes in vital status since 1968.[9,10] The records carry a unique 10-digit civil registration number, assigned to every Danish citizens, and used in all Danish registries, enabling unambiguous linkage between them.

Patients with stroke

The Danish National Indicator Project (DNIP)[11] was established in 2000 as a nationwide quality improvement project. The project targets documentation, monitoring, and improvement of the quality of treatment and care for patients with eight specific diseases, including stroke. Data on quality of care and patient characteristics are collected prospectively upon hospital admission by the staff treating the patients, using a standardized registration form with strict data specifications. Participation in DNIP is mandatory for all hospitals and relevant clinical departments in Denmark that treat patients with the eight diseases in question.

Patients 18 years of age or older are eligible for inclusion in the DNIP-stroke database if they are hospitalized with stroke according to the WHO criteria, *i.e*. rapidly developing symptoms and sign of focal or global neurological dysfunction of presumed vascular etiology lasting more than 24 hours or leading to death.[12] From the DNIP-stroke database, we identified

patients with a first-time discharge diagnosis of ischemic stroke (ICD-10 I63, I64) recorded between January 1, 2003 and December 31, 2006.

Antidiabetic treatment

The Register of Medicinal Product Statistics contains data from 1995 on all prescription drugs dispensed at all Danish pharmacies, including patients' civil registration numbers, type of drug according to the Anatomical Therapeutic Chemical (ATC) classification system, and date of dispensing the drug. In Denmark, antidiabetic drugs are available by prescription only. We traced all prescriptions for antidiabetic drugs among the stroke patients prior to admission for stroke. Users of glitazones, meglinitides and α-glucosidase inhibitors were excluded from the analyses due to low numbers of treated patients. Subjects who had used only one type of antidiabetic drugs in 90 days prior to hospitalization were categorised according to the antidiabetic drugs class: sulfonylureas, metformin, or insulin. Subjects who used more than one type of antidiabetic drugs during the 90 days prior to hospitalization were categorised as combined users, and divided according to the type of combination: sulfonylureas and metformin, sulfonylureas and insulin, metformin and insulin, or sulfonylureas, metformin and insulin.

The Danish National Patient Registry[13], established in 1977, collects data on all hospitalizations from non-psychiatric hospitals in the country, including dates of admission and discharge, surgical procedure(s) performed, and up to 20 discharge diagnoses assigned by the treating physician and coded according to the International Classification of Diseases (8^{th} revision (ICD-8) until the end of 1993, and 10^{th} revision (ICD-10) thereafter). Subjects with a diabetic diagnose since 1977 according to this registry (ICD-8 codes 249, 250, ICD-10 codes E10, E11, E14, G63.2, H36.0, N08.3) but not using any antidiabetic drugs during the 90 days prior to hospitalization were categorised as diabetic patients without pharmacotherapy.

For all patients, we also received information on their use of antidiabetic drugs before the 90 days prior to admission for stroke as well as their use of antidiabetic drugs within 1-year after the admission.

We classified the diabetic patients according to their type of diabetes; type 1 if they were less than 30 years by the time of the first prescription or diagnosis, received insulin monotherapy, and never had filled a prescription for an oral antidiabetic drug, and type 2 if they not received pharmacotherapy, or filled a prescription for an oral antidiabetic drug, or if they were older than 30 years at the time of first prescription or diagnosis, regardless of treatment. Patients with type 1 diabetes mellitus were excluded from the study.

Endpoints

The endpoints were 30-day and 1-year all-cause mortality, and readmission with recurrent ischemic stroke or myocardial infarction within 1-year after admission with ischemic stroke. Mortality was ascertained from the Civil Registration System; readmissions with a recurrent ischemic stroke (ICD-10 codes I63, I64) were ascertained from the DNIP-stroke, and readmissions with myocardial infarction (ICD-10 codes I21, I22) were ascertained from the Danish National Patient Registry.

Covariates

We obtained data on covariates from the DNIP-stroke, the Danish National Patient Registry, the Register of Medicinal Product Statistics, and the Integrated Database for Labour Market Research (IDA) at Statistics Denmark.[14]

Based on discharge diagnoses from the Danish National Patient Registry, we computed, for each patient, the co-morbidity index score developed by Charlson *et al*.[15] The index covers 19 major disease categories, including diabetes mellitus, myocardial infarction, heart failure,

cerebrovascular diseases and cancer, weighted according to their impact on patient survival. The index has previously been adapted for use with hospital discharge registry data, and has been reported to be useful also among patients with stroke.[16,17] Diabetes mellitus and ischemic stroke were excluded from the co-morbidity index calculations. We also obtained information on previous diagnoses of hypertension, coronary revascularization procedures (percutaneous coronary intervention and coronary artery bypass graft), alcoholism-related diseases, and diabetes complications (i.e. retinopathy, nephropathy, and neuropathy).

We identified all prescriptions for cardiovascular drugs (antihypertensive drugs, lipid-lowering drugs, platelet inhibitors, vitamin K antagonists), and hormone replacement therapy (HRT) filled before the date of admission for ischemic stroke. As the use of these drugs may change following admission with a first-time ischemic stroke, we also identified all prescriptions filled within 1-year after the admission for ischemic stroke.

We estimated the duration of diabetes as the time since the earliest prescription for an antidiabetic drug or the earliest diabetes diagnosis and categorized the duration in three groups; ≤5 years, 5-10 years, >10 years.

Based on data from IDA, we classified the patients according to gross income, educational level and employment status in the year prior to hospitalization with ischemic stroke.

Finally, we received data on patient characteristics collected at the time of hospital admission from DNIP-stroke. These data included the Scandinavian Stroke Scale score, marital status, smoking habits, alcohol intake and if the patients fulfilled the specific quality of care criteria. The Scandinavian Stroke Scale score is used to assess the admission stroke severity. It is a validated and widely used neurologic stroke score in Scandinavia that evaluates the level of consciousness, eye movement, power in hand, arm and leg, orientation, aphasia, facial paresis and gait on a total score.[18] The Scandinavian Stroke Scale score can be assessed reliably either face-to-face[19] or from routine hospital admission records.[20] A national expert panel

including physicians, nurses, physiotherapists, and occupational therapists identified 7 quality of care criteria covering the acute phase of stroke based on systematic search of the scientific literature.[11] These criteria included early admission to a specialized stroke unit, early administration of antiplatelet or anticoagulant therapy, early examination with CT/MRI scan, and early assessment by a physiotherapist, and occupational therapist and of nutritional risk. The quality of in-hospital care during the acute phase, *i.e*. fulfillment of these criteria, have been linked with mortality[21] and length of hospital stay,[22] and as a measure for the in-hospital stroke care, we computed a variable containing the percentage of fulfilled criteria for each patient. From the DNIP-stroke database, we also obtained data on lifestyle factors including body mass index (BMI), smoking habits (never, daily, occasionally, former (quit more than ½ year prior to admission)), and alcohol intake (≤14/21, >14/21 drinks per week for women and men, respectively).

Statistical analyses

Follow-up began on the date of admission with ischemic stroke and ended on the date of admission with recurrent ischemic stroke or myocardial infarction (only in analyses on risk of readmissions), death, emigration, or after 30-days/1-year. We constructed Kaplan-Meier mortality curves for the antidiabetic treatments and computed the cumulative 30-day and 1-year mortality.

We used Cox's proportional hazards regression analysis (with the Efron approximation to handle tied survival times) to compute hazard ratios (HRs) as estimates of the relative risks for each outcome. We included all the measured covariates; use of antidiabetic drugs, cardiovascular drugs, and HRT after stroke were treated as time-dependent covariates. The ischemic stroke patients receiving sulfonylureas served as the reference group in the primary

analyses. In the subanalyses, where we compared the different sulfonylureas, tolbutamide users served as the reference group.

Multiple imputation was used to impute missing values for Scandinavian Stroke Scale Score, smoking habits, alcohol intake, BMI, marital status, and educational level. We generated five imputed data sets, and the HRs were then averaged across the five imputations, correcting for between- and within-imputation variation.[23-25] Besides all measured covariates, we included the event indicator and the Nelson-Aalen estimator of the cumulative hazard to the survival time in the imputation model.[26] However, for comparison, data set consisting of only complete records was also examined.

Prescriptions for antidiabetic drugs in Denmark are usually issued for three months, but may be issued for up to six months. We therefore also analyzed the data based on drug use within 180 days prior to hospitalization.

We analyzed data with Stata 10.0 (StataCorp LP, College Station, TX, USA) and with version 9.1.3 of the SAS software (SAS Institute Inc., Cary, NC, USA).

Results

We identified 41,398 patients hospitalized with a first-time stroke during the study period. After excluding 3,174 patients with intracerebral hemorrhage, 5,020 (13.1%) of the remaining stroke patients had diabetes mellitus. We excluded all patients with type 1 diabetes mellitus (n=84), and due to low number of treated patients, users of meglitinides, glitazones and α-glucosidase inhibitors (n=44) were also excluded. A total of 4,816 patients with type 2 diabetes mellitus and ischemic stroke were available for analysis. Of these patients, 27.1% did not receive pharmacotherapy, 22.6% were treated with sulfonylureas, 11.7% with metformin, 18.3% with insulin, and 20.3% with a combination. The main clinical characteristics of the patients according to antidiabetic treatment are presented in Table 1.

Mortality

Kaplan-Meier mortality curves for the different treatment groups are shown in Figure 1.
Of the 4,816 patients, 536 (11.2%, 95% CI: 10.3-12.1%) died within 30-days, and within 1-year, 1,159 (25.7%, 95% CI: 24.5-27.0) of the patients were dead.

Table 2 shows the crude and adjusted HRs according to antidiabetic treatments.
After adjustment for differences in covariates, we found decreased 30-day mortality among users of the antidiabetic treatments in monotherapy and among patients not treated with antidiabetic pharmacotherapy, i.e. the adjusted HRs for the use of metformin, insulin, and no antidiabetic pharmacotherapy were 0.32 (95% CI: 0.15-0.67), 0.50 (95% CI: 0.29-0.84), and 0.57 (95% CI: 0.36-0.91) compared with users of sulfonylureas. The use of any combination was also associated with decreased risk of mortality compared with use of sulfonylureas (adjusted 30-day HR: 0.63 (95% CI: 0.33-1.20)), but it did not reach statistical significance.

When estimating the 1-year HRs, we found no significant differences between the antidiabetic treatments (Table 2).

We found no differences in mortality when comparing use of the different types of combination (30-day mortality: p=0.16, 1-year mortality: p=0.87) or individual sulfonylureas (30-day mortality: p=0.98, 1-year mortality: p=0.89).

Readmission with recurrent ischemic stroke or myocardial infarction

Within 1-year of follow-up, 331 (9.0%) of the patients were readmitted with recurrent ischemic stroke or a myocardial infarction.

We found increased risk of readmission in users of the all antidiabetic treatments compared with users of sulfonylureas, however, it only reached statistical significance in patients not treated with antidiabetic pharmacotherapy (Table 3).

We found no differences in risk of readmission among users of the different types of combination (p=0.54), or among users of different sulfonylureas (p=0.47).

When estimating the HRs based on drug use 180 days before hospitalization with ischemic stroke, we found similar patterns, although it not reached statistical significance.

Complete subject analysis

Data on all covariates was complete for 1.508 (31.3%) of the patients. When estimating the mortality, we found similar results, although with a much lower statistical precision, *i.e*. the adjusted 30-day HRs for the use of metformin, insulin, any combination, and no antidiabetic pharmacotherapy were 0.27 (95% CI: 0.04-1.90), 0.43 (95% CI: 0.09-2.06), 3.64 (95% CI: 0.70-18.93) and 0.34 (95% CI: 0.07-1.59) compared with users of sulfonylureas. The adjusted one year HRs for the use of metformin, insulin, any combination, and no antidiabetic

pharmacotherapy were 0.83 (95% CI: 0.41-1.65), 0.80 (95% CI: 0.42-1.49), 1.55 (95% CI: 0.86-2.77) and 0.62 (95% CI: 0.37-1.03) compared with users of sulfonylureas. When estimating the risk of readmission, the adjusted HRs for the use of metformin, insulin, any combination, and no antidiabetic pharmacotherapy were 0.70 (95% CI: 0.24-2.00), 2.00 (95% CI: 0.82-4.88), 1.82 (95% CI: 0.79-4.20) and 1.41 (95% CI: 0.66-3.04) compared with users of sulfonylureas.

Discussion

In this large population-based follow-up study, we found a lower short-term mortality among patients with type 2 diabetes mellitus using metformin, insulin, any combination, and no pharmacotherapy following hospitalization with ischemic stroke compared with patients treated with sulfonylureas. However, these patients had higher risk of being readmitted with a recurrent ischemic stroke or myocardial infarction than patients treated with sulfonylureas.

The main strength of this study was the nationwide population-based design with a large sample size and complete follow-up both during and after hospitalization. As the data sources used in our study comprise the entire Danish population, our results reflect the daily clinical practice in Denmark. Further, the use of prospectively collected data minimized the risk of both selection and information bias. Finally, detailed data on possible confounding factors were available through record linkage to the different medical databases.

The validity of our estimates depends on the accuracy of the registries. Participation in DNIP is mandatory for all departments in Denmark treating patients with stroke, and extensive efforts are made to ensure the validity of DNIP data.[11] A structured audit process is carried out regularly on a national, regional and local basis to critically assess and ensure the quality of the data. To ensure completeness of patient registration in DNIP, its enrollees are compared with local hospital discharge registries. Further, the combined use of the Danish National Patient Registry and the Register of Medicinal Product Statistics to identify patients with diabetes mellitus has proven to be of high quality and nearly complete.[27]

Use of pioglitazone was in a subanalysis from the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial associated with reduced risk of recurrent fatal and nonfatal stroke.[28] In spite of our large sample size, the number of users of glitazones was too small to be included in our analyses.

We used mortality and readmission with recurrent ischemic stroke or myocardial infarction as the clinical outcomes. Although these outcomes are clearly of major importance, they are certainly not the only outcome relevant for patients with stroke. Comparison of the association between use of different antidiabetic treatments and other clinical outcomes (e.g., functional level) is also highly relevant. Unfortunately such data were not available in our study population.

Finally, despite our adjustment for a wide range of confounding factors including lifestyle factors (BMI, smoking, alcohol), we cannot entirely rule out the possibility of residual confounding or unaccounted confounding from unmeasured factors.

To our knowledge, only one other study has examined the mortality rates among patients with type 2 diabetes mellitus and ischemic stroke according to type of antidiabetic treatment. This much smaller German study included 146 patients with diabetes mellitus and acute hemispheric ischemic stroke, of which 60 were treated with sulfonylureas. The in-hospital mortality was not statistical significant different when comparing sulfonylurea users and non-sulfonylurea users (OR 1.2; 95% CI: 0.4-3.5).[8] However, the relatively small sample size gave rise to statistically imprecise risk estimate, which hindered a clear interpretation.

Use of sulfonylureas was associated with improved neurological and functional outcomes in two German studies.[7,8] This beneficial effects may be mediated by postevent block of the $NC_{ca\text{-}ATP}$ channel, which is upregulated only under conditions of injury or ischemia.[29] In contrast, sulfonylureas might also have potentially deleterious effects in the context of stroke. Sulfonylureas might, like in the heart, impair ischemic preconditioning in the brain,[30] and they might attenuate cerebral vasodilation during hypoxia.[31] Because the extra-pancreatic receptors differ structurally from the pancreatic isoform, a potentially different pharmacological effect

of the individual sulfonylureas might exist. However, in our study, we found no difference in clinical outcome among users of different sulfonylureas.

Our study is, to our knowledge, the first study to examine long-term outcome (mortality and readmission) after hospitalization with ischemic stroke according to antidiabetic treatments.

In conclusion, our findings do not support the hypothesis that preadmission use of sulfonylureas is associated with an overall improved clinical outcome among type 2 diabetic patients admitted with stroke. In contrast, sulfonylureas may be associated with increased mortality in the early phase after ischemic stroke, whereas long-term mortality appear to be comparable with that of other types of antidiabetic treatment. However, sulfonylureas may be associated with a lower risk of admission with recurrent ischemic stroke or myocardial infarction.

References

(1) Asplund K, Hagg E, Helmers C, Lithner F, Strand T, Wester PO. The natural history of stroke in diabetic patients. *Acta Med Scand* 1980;207:417-24.

(2) Oppenheimer SM, Hoffbrand BI, Oswald GA, Yudkin JS. Diabetes mellitus and early mortality from stroke. *Br Med J (Clin Res Ed)* 1985;291:1014-5.

(3) Lithner F, Asplund K, Eriksson S, Hagg E, Strand T, Wester PO. Clinical characteristics in diabetic stroke patients. *Diabete Metab* 1988;14:15-9.

(4) Olsson T, Viitanen M, Asplund K, Eriksson S, Hagg E. Prognosis after stroke in diabetic patients. A controlled prospective study. *Diabetologia* 1990;33:244-9.

(5) Jørgensen H, Nakayama H, Raaschou HO, Olsen TS. Stroke in patients with diabetes. The Copenhagen Stroke Study. *Stroke* 1994;25:1977-84.

(6) Sprafka JM, Virnig BA, Shahar E, McGovern PG. Trends in diabetes prevalence among stroke patients and the effect of diabetes on stroke survival: the Minnesota Heart Survey. *Diabet Med* 1994;11:678-84.

(7) Kunte H, Schmidt S, Eliasziw M, del Zoppo GJ, Simard JM, Masuhr F, Weih M, Dirnagl U. Sulfonylureas improve outcome in patients with type 2 diabetes and acute ischemic stroke. *Stroke* 2007;38:2526-30.

(8) Weih M, Amberger N, Wegener S, Dirnagl U, Reuter T, Einhaupl K. Sulfonylurea drugs do not influence initial stroke severity and in-hospital outcome in stroke patients with diabetes. *Stroke* 2001;32:2029-32.

(9) Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;287:2398-9.

(10) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441-9.

(11) Mainz J, Krog BR, Bjornshave B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. *Int J Qual Health Care* 2004;16 Suppl 1:i45-i50.

(12) Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke* 1989;20:1407-31.

(13) Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263-8.

(14) Statistics Denmark. IDA—an integrated database for labour market research. Copenhagen, Denmark: Statistics Denmark; 1991.

(15) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.

(16) Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613-9.

(17) Goldstein LB, Samsa GP, Matchar DB, Horner RD. Charlson Index comorbidity adjustment for ischemic stroke outcome studies. *Stroke* 2004;35:1941-5.

(18) Multicenter trial of hemodilution in ischemic stroke--background and study protocol. Scandinavian Stroke Study Group. *Stroke* 1985;16:885-90.

(19) Lindenstrøm E, Boysen G, Waage Christiansen L, á Rogvi Hansen B, Würtzen Nielsen P. Reliability of Scandinavian Neurological Stroke Scale. *Cerebrovasc Dis* 1991;1:103-7.

(20) Barber M, Fail M, Shields M, Stott DJ, Langhorne P. Validity and reliability of estimating the scandinavian stroke scale score from medical records. *Cerebrovasc Dis* 2004;17:224-7.

(21) Ingeman A, Pedersen L, Hundborg HH, Petersen P, Zielke S, Mainz J, Bartels P, Johnsen SP. Quality of care and mortality among patients with stroke: a nationwide follow-up study. *Med Care* 2008;46:63-9.

(22) Svendsen ML, Ehlers LH, Andersen G, Johnsen SP. Quality of care and length of hospital stay among patients with stroke. *Med Care* 2009;47:575-82.

(23) Royston P. Multiple imputation of missing values. The Stata Journal 4, 227-241.

(24) Royston P. Multiple imputation of missing values: update. The Stata Journal 5, 188-201.

(25) Royston P. Multiple imputation of missing values: Update of ice. The Stata Journal 5, 527-536.

(26) White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med* 2009;28:1982-98.

(27) Nielsen GL, Sørensen HT, Pedersen AB, Sabroe S. Analyses of data quality in registries concerning diabetes mellitus--a comparison between a population based hospital discharge and an insulin prescription registry. *J Med Syst* 1996;20:1-10.

(28) Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, Dormandy J. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007;38:865-73.

(29) Simard JM, Chen M, Tarasov KV, Bhatta S, Ivanova S, Melnitchenko L, Tsymbalyuk N, West GA, Gerzanich V. Newly expressed SUR1-regulated NC(Ca-ATP) channel mediates cerebral edema after ischemic stroke. *Nat Med* 2006;12:433-40.

(30) Heurteaux C, Bertaina V, Widmann C, Lazdunski M. K+ channel openers prevent global ischemia-induced expression of c-fos, c-jun, heat shock protein, and amyloid beta-protein precursor genes and neuronal death in rat hippocampus. *Proc Natl Acad Sci U S A* 1993;90:9431-5.

Tables

Table 1. Characteristics of patients with type 2 diabetes mellitus using different antidiabetic drugs hospitalized with ischemic stroke in Denmark during the period 2003-2006

	Sulfonylureas (N=1,091)		**Metformin (N=563)**		**Insulin (N=882)**		**Any combination (N=976)**		**No pharmacotherapy (N=1,304)**	
Characteristic[a]	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Age in years, *median (range)*	78.4	(31-99)	71.2	(35-95)	71.3	(41-100)	72.0	(31-96)	76.1	(36-106)
Sex (males)	613	(56.2)	305	(54.2)	496	(56.2)	566	(58.0)	731	(56.1)
Duration of diabetes mellitus										
≤5 years	553	(50.7)	354	(62.9)	97	(11.0)	228	(23.4)	637	(48.9)
5-10 years	385	(35.3)	147	(26.1)	246	(27.9)	447	(45.8)	428	(32.8)
>10 years	153	(14.0)	62	(11.0)	539	(61.1)	301	(30.8)	239	(18.3)

Charlson's comorbidity index										
0	415	(38.0)	257	(45.6)	255	(28.9)	422	(43.2)	386	(29.6)
1-2	462	(42.4)	241	(42.8)	418	(47.4)	421	(43.2)	621	(47.6)
≥3	214	(19.6)	65	(11.6)	209	(23.7)	133	(13.6)	297	(22.8)
Discharge diagnoses of										
Hypertension	934	(85.6)	481	(85.4)	788	(89.3)	846	(86.7)	1,107	(84.9)
Former revascularization	75	(6.9)	40	(7.1)	119	(13.5)	90	(9.2)	117	(9.0)
Retinopathy	77	(7.1)	27	(4.8)	306	(34.7)	136	(13.9)	105	(8.1)
Nephropathy[b]	55	(5.0)	23	(4.1)	152	(17.2)	36	(3.7)	94	(7.2)
Neuropathy	66	(6.1)	34	(6.0)	195	(22.1)	95	(9.7)	111	(8.5)
Prescription for[c]										
Antihypertensive drugs	927	(85.0)	475	(84.4)	787	(89.2)	838	(85.9)	1,092	(83.7)
Platelet inhibitors	401	(36.8)	206	(36.6)	342	(38.8)	388	(39.8)	392	(30.1)
Vitamin K antagonists	58	(5.3)	34	(6.0)	51	(5.8)	64	(6.6)	58	(4.5)

Statins	340	(31.2)	228	(40.5)	430	(48.8)	459	(47.0)	401	(30.8)
Other lipid-lowering drugs	10	(0.9)	16	(2.8)	22	(2.5)	35	(3.6)	15	(1.2)
Hormone replacement therapy	144	(13.2)	85	(15.1)	133	(15.1)	144	(14.8)	206	(15.8)
Scandinavian Stroke Scale Score upon admission										
Mild	498	(45.6)	273	(48.5)	410	(46.5)	523	(53.6)	568	(43.6)
Moderate	228	(20.9)	96	(17.0)	165	(18.7)	159	(16.3)	239	(18.3)
Severe	103	(9.4)	55	(9.8)	83	(9.4)	73	(7.5)	145	(11.1)
Very severe	112	(10.3)	49	(8.7)	86	(9.8)	68	(6.9)	130	(10.0)
Missing	150	(13.8)	90	(16.0)	138	(15.6)	153	(15.7)	222	(17.0)
Proportion of quality of in-hospital stroke care criteria fulfilled[d]										
0-24%	171	(15.7)	71	(12.6)	156	(17.7)	120	(12.3)	197	(15.1)
25-49%	167	(15.3)	63	(11.2)	138	(15.6)	153	(15.7)	207	(15.9)

50-74%	320	(29.3)	157	(27.9)	262	(29.7)	293	(30.0)	419	(32.1)
75-100%	433	(39.7)	272	(48.3)	326	(37.0)	410	(42.0)	481	(36.9)
Smoking habits										
Never	317	(29.1)	163	(28.9)	258	(29.3)	301	(30.8)	353	(27.1)
Daily	268	(24.6)	161	(28.6)	240	(27.2)	255	(26.1)	390	(29.9)
Occasionally	15	(1.4)	10	(1.8)	14	(1.6)	17	(1.8)	14	(1.1)
Former (quit more than ½ year prior to admission)	235	(21.5)	112	(19.9)	174	(19.7)	208	(21.3)	244	(18.7)
Missing	256	(23.4)	117	(20.8)	196	(22.2)	195	(20.0)	303	(23.2)
Alcohol intake										
Less than 14/21 drinks per week for women/men	798	(73.1)	426	(75.7)	653	(74.0)	753	(77.1)	939	(72.0)
More than 14/21 drinks per week for women/men	50	(4.6)	42	(7.5)	44	(5.0)	34	(3.5)	79	(6.1)

Missing	243	(22.3)	95	(16.8)	185	(21.0)	189	(19.4)	286	(21.9)
BMI										
Underweight	14	(1.3)	3	(0.5)	15	(1.7)	2	(0.2)	37	(2.8)
Normal	206	(18.9)	75	(13.3)	174	(19.7)	147	(15.1)	276	(21.2)
Overweight	233	(21.4)	127	(22.6)	165	(18.7)	215	(22.0)	256	(19.6)
Obese	114	(10.4)	128	(22.7)	135	(15.3)	198	(20.3)	143	(11.0)
Missing	524	(48.0)	230	(40.9)	393	(44.6)	414	(42.4)	592	(45.4)
Marital status										
Living alone	509	(46.6)	220	(39.1)	318	(36.1)	377	(38.6)	613	(47.0)
Living with someone	474	(43.5)	292	(51.8)	489	(55.4)	519	(53.2)	566	(43.4)
Other form of marital status	41	(3.8)	20	(3.6)	32	(3.6)	20	(2.1)	37	(2.8)
Missing	67	(6.1)	31	(5.5)	43	(4.9)	60	(6.1)	88	(6.8)
Gross income										

1. quartile	273	(25.0)	143	(25.4)	237	(26.9)	249	(25.5)	330	(25.3)
2. quartile	317	(29.1)	128	(22.7)	205	(23.2)	205	(21.0)	321	(24.6)
3. quartile	262	(24.0)	152	(27.0)	214	(24.3)	253	(25.9)	323	(24.8)
4. quartile	239	(21.9)	140	(24.9)	226	(25.6)	269	(27.6)	330	(25.3)
Educational level										
University degree	17	(1.6)	10	(1.8)	17	(1.9)	22	(2.2)	24	(1.8)
Short/medium-term formal education	59	(5.4)	27	(4.8)	59	(6.7)	68	(7.0)	100	(7.7)
Basic vocational education	229	(21.0)	165	(29.3)	252	(28.6)	232	(23.8)	310	(23.8)
Basic school	479	(43.9)	274	(48.7)	436	(49.4)	528	(54.1)	567	(43.5)
Missing	307	(28.1)	87	(15.4)	118	(13.4)	126	(12.9)	303	(23.2)
Employment status										
Employed	88	(8.1)	80	(14.2)	114	(12.9)	158	(16.2)	159	(12.2)
Pensioner	975	(89.4)	456	(81.0)	735	(83.3)	773	(79.2)	1,093	(83.8)
Other	28	(2.5)	27	(4.8)	33	(3.8)	45	(4.6)	52	(4.0)

[a] All variables are shown as number (%), except for age, which is shown as median (range).

[b] Also included in the Charlson index.

[c] Received a prescription within 90 days (platelet inhibitors and vitamin K antagonists) or ever (all others) before admission for ischemic stroke.

[d] Admission to a stroke unit by the second day, antiplatelet therapy by the second day, anticoagulant therapy by the 14th day, CT/MRI scan by the first day, physiotherapy assessment by the second day, occupational therapy assessment by the second day, and nutritional risk assessment by the second day.

Table 2. Crude and adjusted 30-day and 1-year hazard ratios (HRs) with 95% confidence intervals (CIs) for death after hospitalization with ischemic stroke according to use of antidiabetic treatment within 90 days prior to the hospitalization

Antidiabetic treatment *	**N**	**Deaths within 30 days**	**Mortality within 30 days**	**Crude HR (95% CI)**		**Adjusted HR † (95% CI)**		**Deaths within one year**	**Mortality within one year**	**Crude HR (95% CI)**		**Adjusted HR † (95% CI)**	
Sulfonylureas	1,091	148	13.7%	1.00	(reference)	1.00	(reference)	305	29.5%	1.00	(reference)	1.00	(reference)
Metformin	563	39	7.0%	0.50	(0.35-0.71)	0.32	(0.15-0.67)	100	19.5%	0.60	(0.48-0.76)	0.89	(0.64-1.25)
Insulin	882	101	11.5%	0.84	(0.65-1.08)	0.50	(0.29-0.84)	224	27.1%	0.89	(0.75-1.05)	0.92	(0.69-1.22)
Any combination	976	85	8.8%	0.63	(0.48-0.82)	0.63	(0.33-1.20)	177	19.5%	0.61	(0.51-0.74)	1.03	(0.78-1.35)
No pharmacotherapy	1,304	163	12.6%	0.92	(0.73-1.14)	0.57	(0.36-0.91)	353	28.8%	0.96	(0.83-1.12)	0.82	(0.66-1.03)

* Antidiabetic use was measured in the 90 days prior to hospitalization for ischemic stroke.

† Adjusted for age, sex, duration of diabetes mellitus, former use of antidiabetic treatment, level of co-morbidity (measured by the Charlson index), discharge diagnoses of hypertension, former revascularization, retinopathy, neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, statins, other lipid-lowering agents, HRT before the date of hospitalization for stroke, Scandinavian stroke scale score, fulfilled specific quality of care criteria, smoking

habits, alcohol intake, BMI, marital status, gross income, educational level, employment status, and time-dependent antidiabetic treatment, cardiovascular treatment and HRT after the date of hospitalization for ischemic stroke.

Table 3. Crude and adjusted 1-year hazard ratios (HRs) with 95% confidence intervals (CIs) for admission with recurrent ischemic stroke or myocardial infarction after first-time hospitalization with ischemic stroke according to use of antidiabetic treatment within 90 days prior to the hospitalization

	N	Readmissions within one year		Crude HR (95% CI)		Adjusted HR † (95% CI)	
Antidiabetic treatment *							
Sulfonylureas	1,091	52	4.8%	1.00	(reference)	1.00	(reference)
Metformin	563	37	6.6%	1.30	(0.85-1.98)	1.40	(0.79-2.48)
Insulin	882	74	8.4%	1.73	(1.22-2.47)	1.61	(0.96-2.69)
Any combination	976	76	7.8%	1.56	(1.09-2.22)	1.46	(0.91-2.32)
No pharmacotherapy	1,304	92	7.1%	1.50	(1.07-2.11)	1.58	(1.04-2.42)

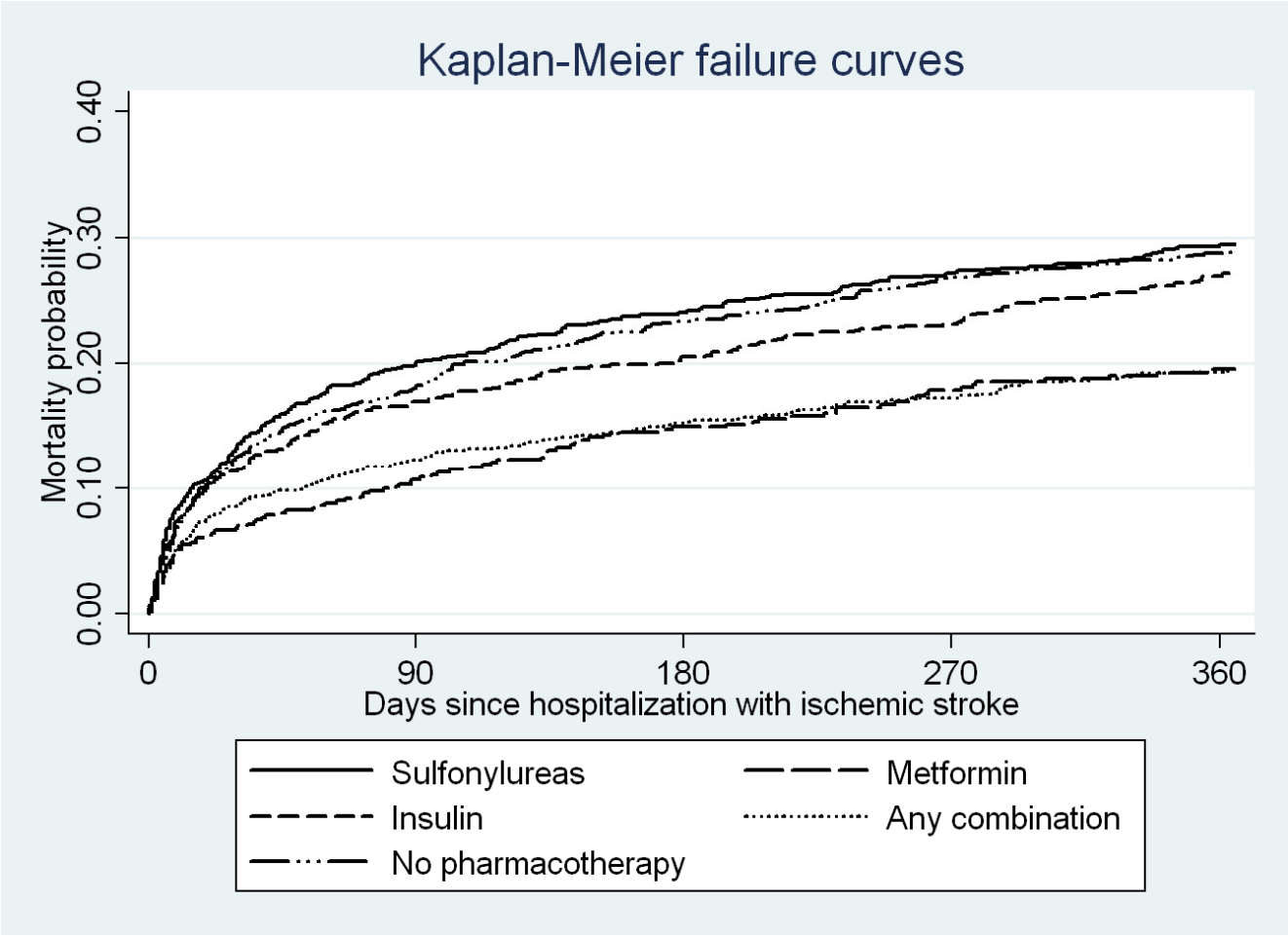
* Antidiabetic use was measured in the 90 days prior to hospitalization for ischemic stroke.

† Adjusted for age, sex, duration of diabetes mellitus, former use of antidiabetic treatment, level of co-morbidity (measured by the Charlson index), discharge diagnoses of hypertension, former revascularization, retinopathy, neuropathy, and prescriptions for platelet inhibitors, vitamin K antagonists, statins, other lipid-lowering agents, HRT before the date of hospitalization for stroke, Scandinavian stroke scale score, fulfilled specific quality of care criteria, smoking habits, alcohol intake, BMI, marital status, gross income, educational level, employment status, and time-dependent antidiabetic treatment, cardiovascular treatment and HRT after the date of hospitalization for ischemic stroke.

Figure legends

Figure 1. Kaplan-Meier curves of 1-year all-cause mortality after hospitalization with ischemic stroke according to use of antidiabetic treatments within 90 prior to the hospitalization.

Figures


Kaplan-Meier failure curves
Mortality probability
0.00
0.10
0.20
0.30
0.40
0
90
180
270
360
Days since hospitalization with ischemic stroke
Sulfonylureas
Metformin
Insulin
Any combination
No pharmacotherapy

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23. Ambulante besøg og indlæggelser for udvalgte kroniske sygdomme på somatiske hospitaler i Århus, Ringkjøbing, Viborg, og Nordjyllands amter. *2006*.

24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. *2006*.

25. Forbruget af lægemidler mod kroniske sygdomme i Århus, Viborg og Nordjyllands amter 2004-2005. *2006*.

26. Tilbagelægning af kolostomi og ileostomi i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

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